TAOG 2025

台灣婦產科醫學會114年度
年會暨擴大學術研討會

The 64th Annual Congress of
Taiwan Association of Obstetrics and Gynecology

長庚 高雄

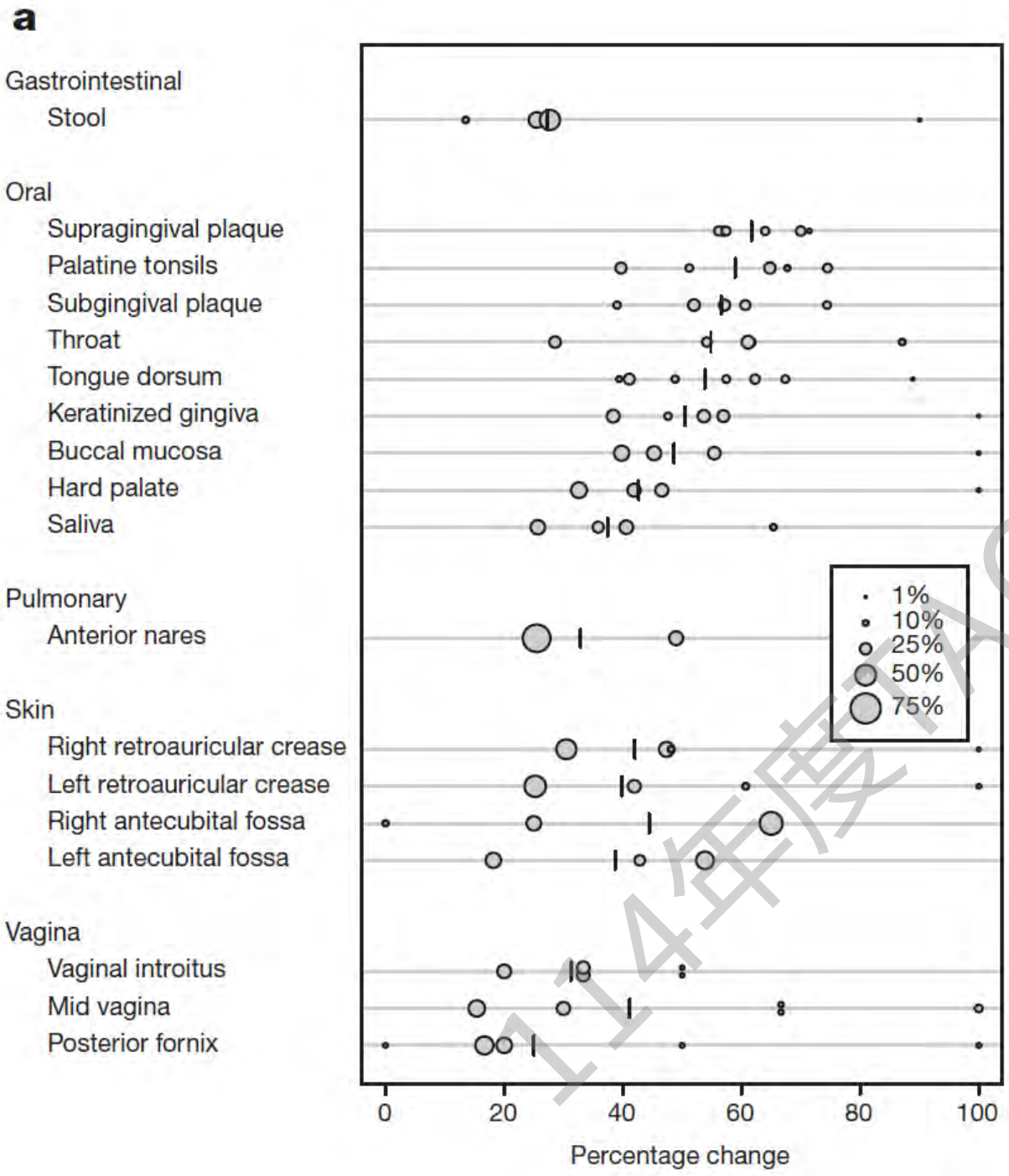
Chronic Endometritis: Diagnosis, management, and treatment efficacy

March 23, 2025 11:30-12:00

TSAI Ni-Chin, MD.
高雄長庚婦產部 生殖醫學科 蔡妮瑾

Outline

- Endometrium environment
- Dysbiosis: Chronic endometritis
- The diagnosis of chronic endometritis
- Treatment of dysbiosis
- Preliminary results of validation study



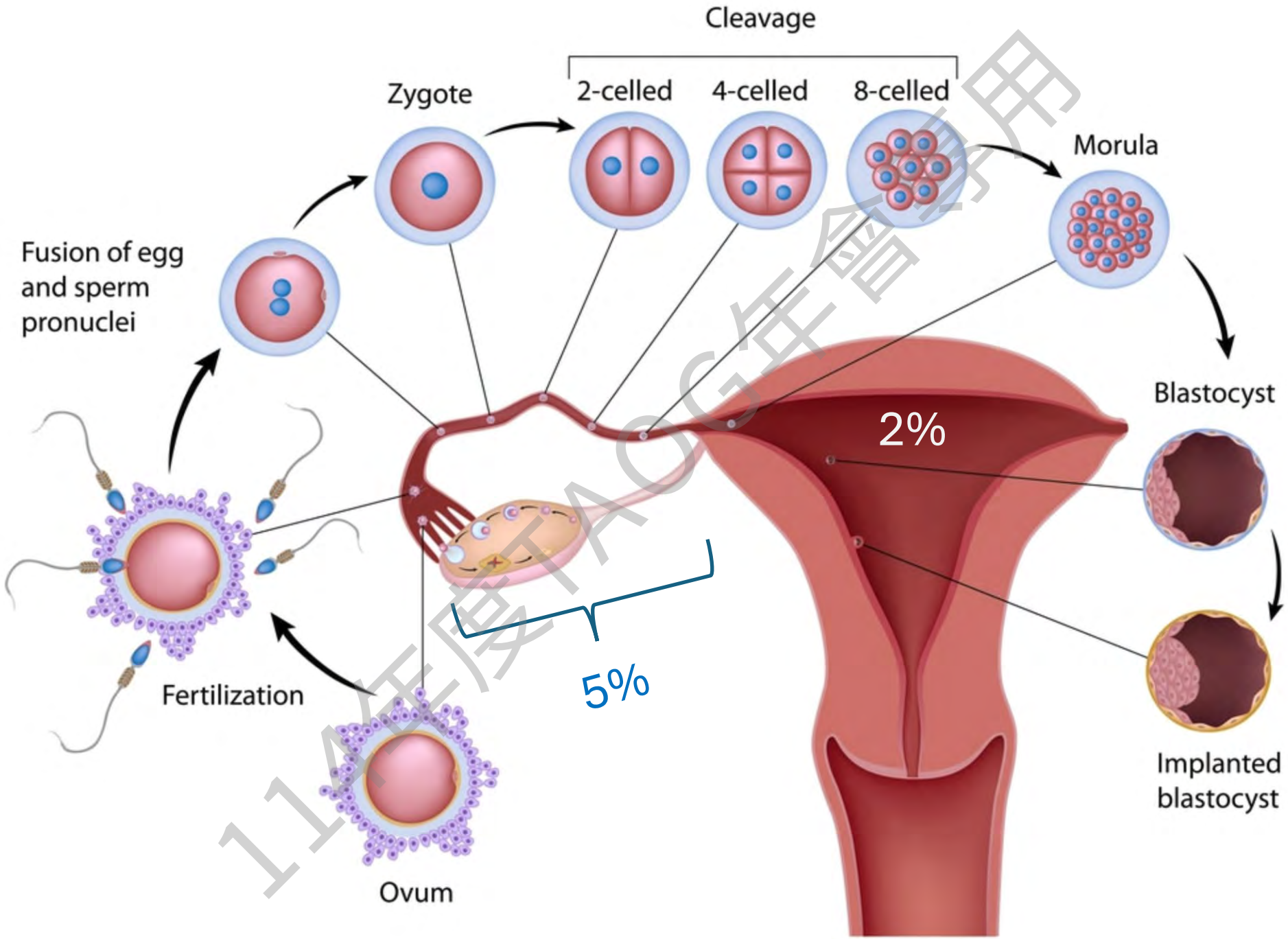
Over the course of the sampling period, the community types from sites within the oral cavity were the least stable, whereas those in the vagina and gut were the most stable.

在陰道中與在腸道中的菌相是最穩定的。

Ding, T. & Schloss, P. D. Dynamics and associations of microbial community types across the human body. Nature 509, 357–360 (2014).

子宮內膜是有細菌的嗎?

- **The endometrial cavity was considered sterile** until the second half of the 20th century.
- Reproductive tract:
  - Lactobacillus-dominant (LD, with a Lactobacillus spp. abundance percentage greater than 90%)
  - The lactic acid produced by the vaginal microbiota helps maintain a low pH of 3.5–4.5, a major factor in limiting the growth of potentially harmful bacteria.
- Upper reproductive tract 陰道菌叢的延伸



What’s the pH level within endometrium?

- The pH of the human endometrial cavity is generally considered to be **slightly acidic to neutral**, typically ranging from 6.0 to 7.3. Studies indicate that the average pH is around 6.8 to 6.98.
- **Cycle Variability**: The pH can fluctuate based on hormonal changes throughout the menstrual cycle.

Lifestyle and clinical factors associated with microbiota changes

- Age
- Phases of menstrual cycle
  - Hormone effect
- Uterine pathology: adenomyosis, endometrial cancer
  - Inflammatory cytokines

nature aging

Article

https://doi.org/10.1038/s43587-024-00692-2

Nonlinear dynamics of multi-omics profiles during human aging

Received: 9 December 2023

Accepted: 22 July 2024

Published online: 14 August 2024

Xiaotao Shen[1,2,3,7], Chuchu Wang[4,5,7], Xin Zhou[1,6], Wenyu Zhou[1], Daniel Hornburg[1], Si Wu[1] & Michael P. Snyder[1,6]

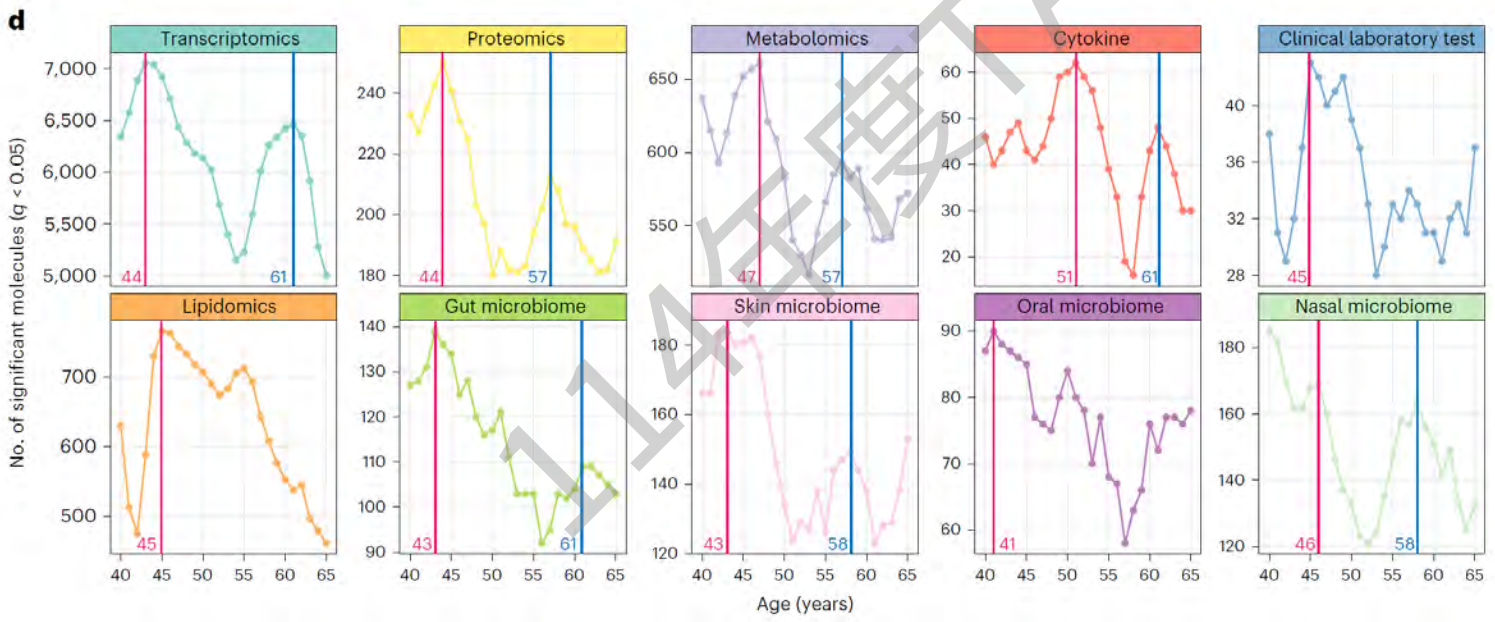
真正突然老，是幾歲?

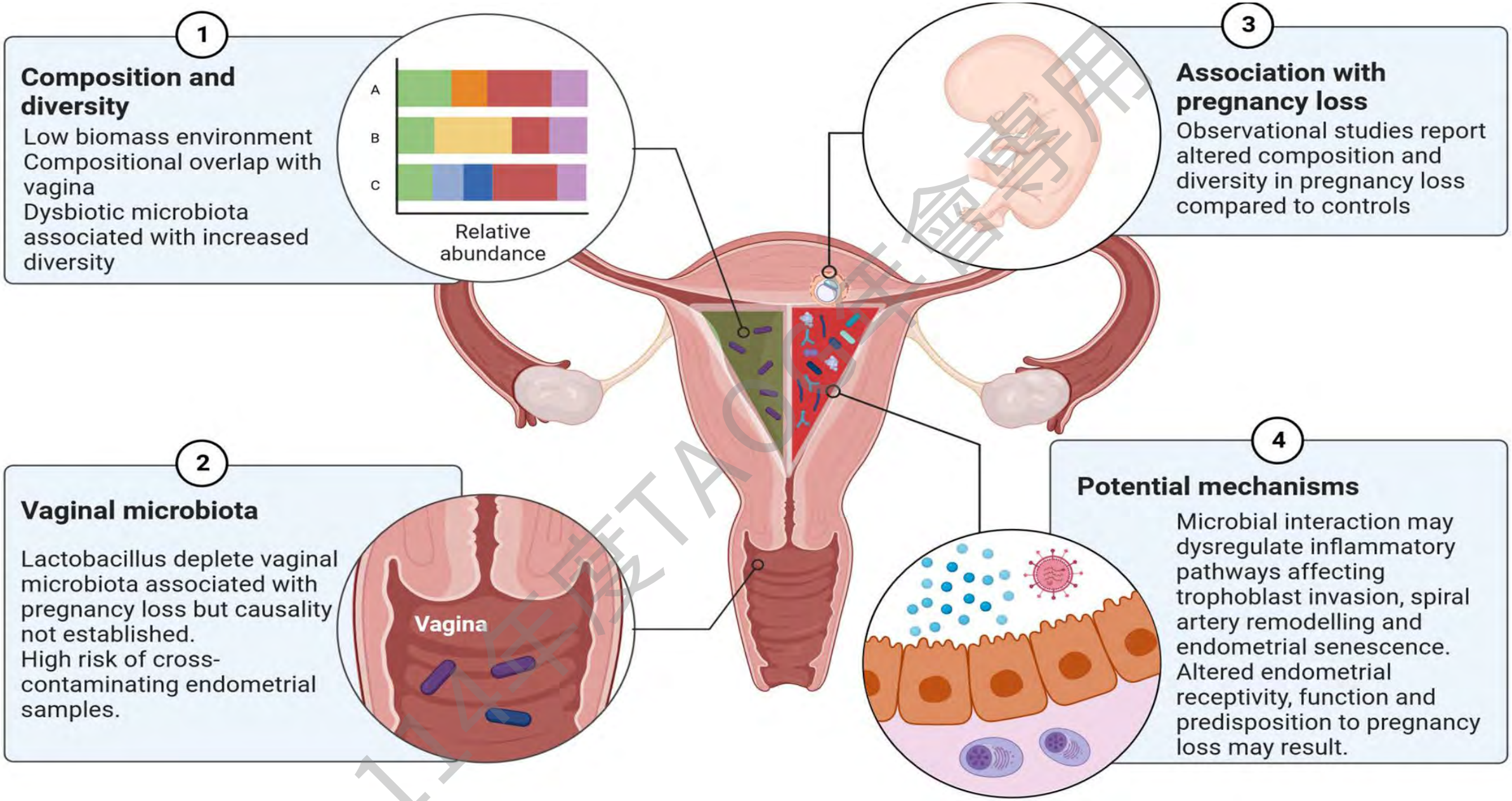
Comprehensive multi-omics profiling on a longitudinal human cohort of 108 participants, aged between 25 years and 75 years.

真正突然老，是幾歲?

- We undergo two periods of rapid change, averaging around age 44 and age 60,
- According to a Stanford Medicine study.

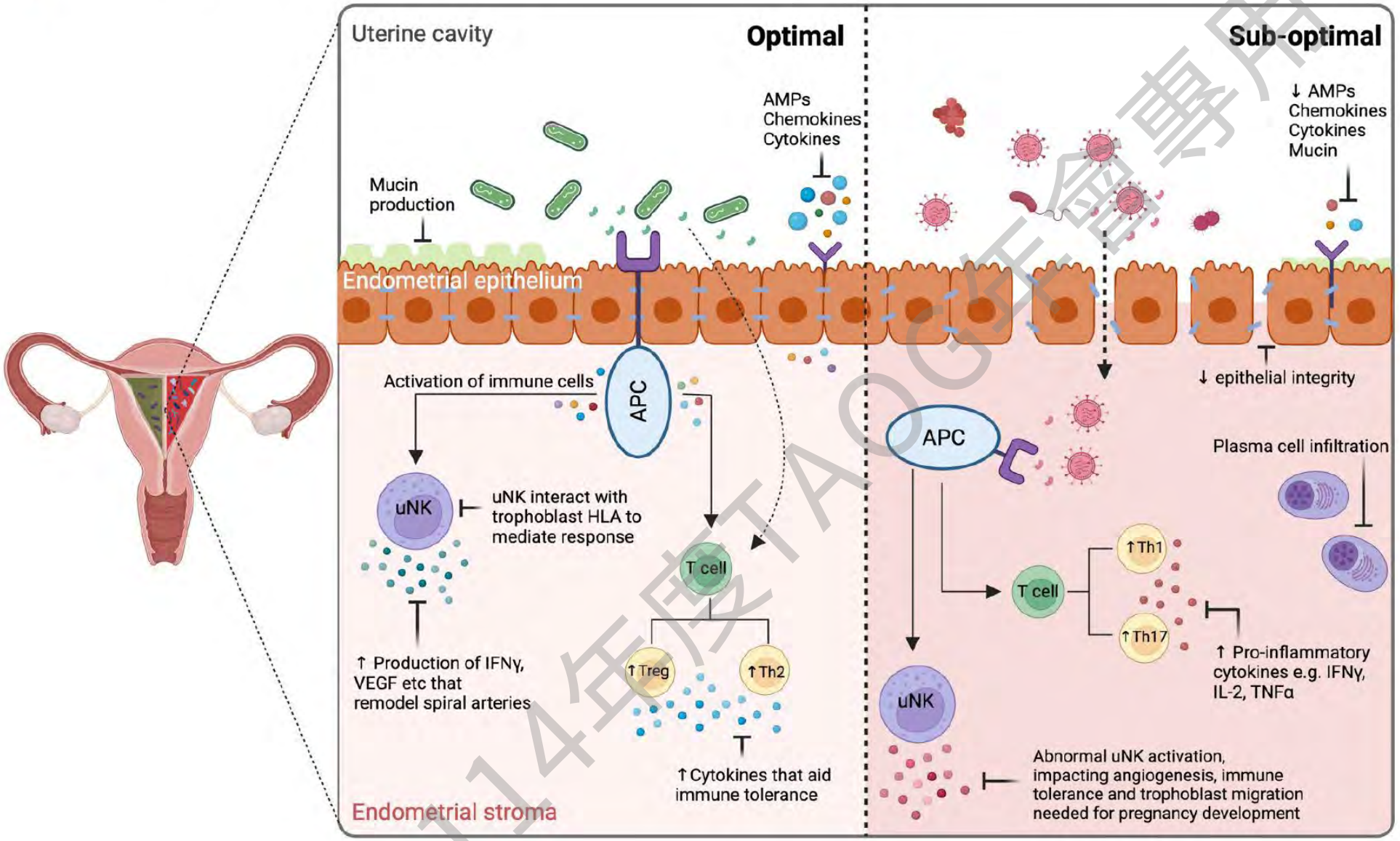
https://doi.org/10.1038/s43587-024-00692-2





The endometrial microbiota and early pregnancy loss. Human Reproduction. 2024;39(4):638-46.

Biological plausibility: the endometrial microbiota and miscarriage



The endometrial microbiota and early pregnancy loss. Human Reproduction. 2024;39(4):638-46.

nature
COMMUNICATIONS

Nat Commun 2017, 8, 875, doi:10.1038/s41467-017-00901-0.

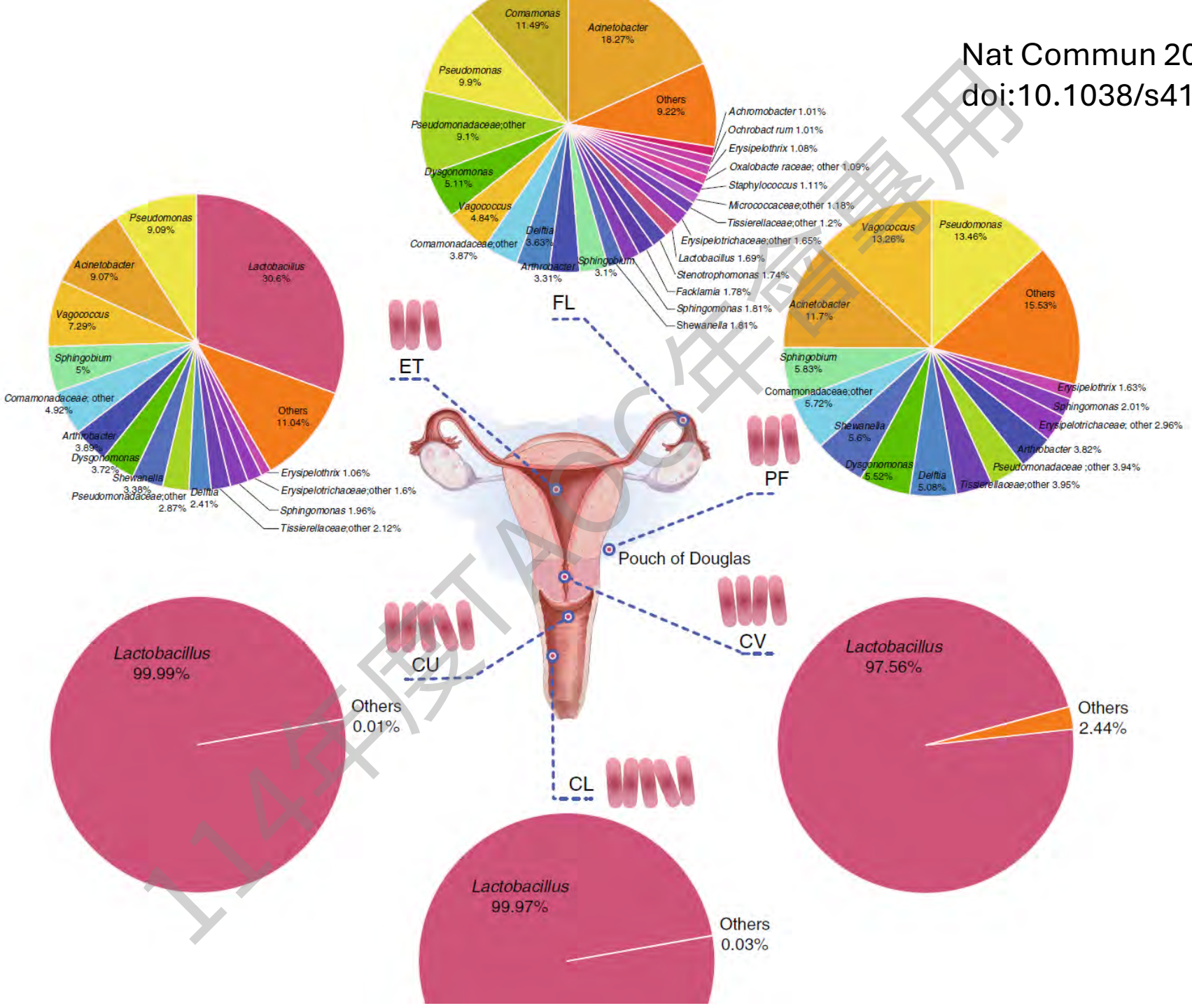
ARTICLE

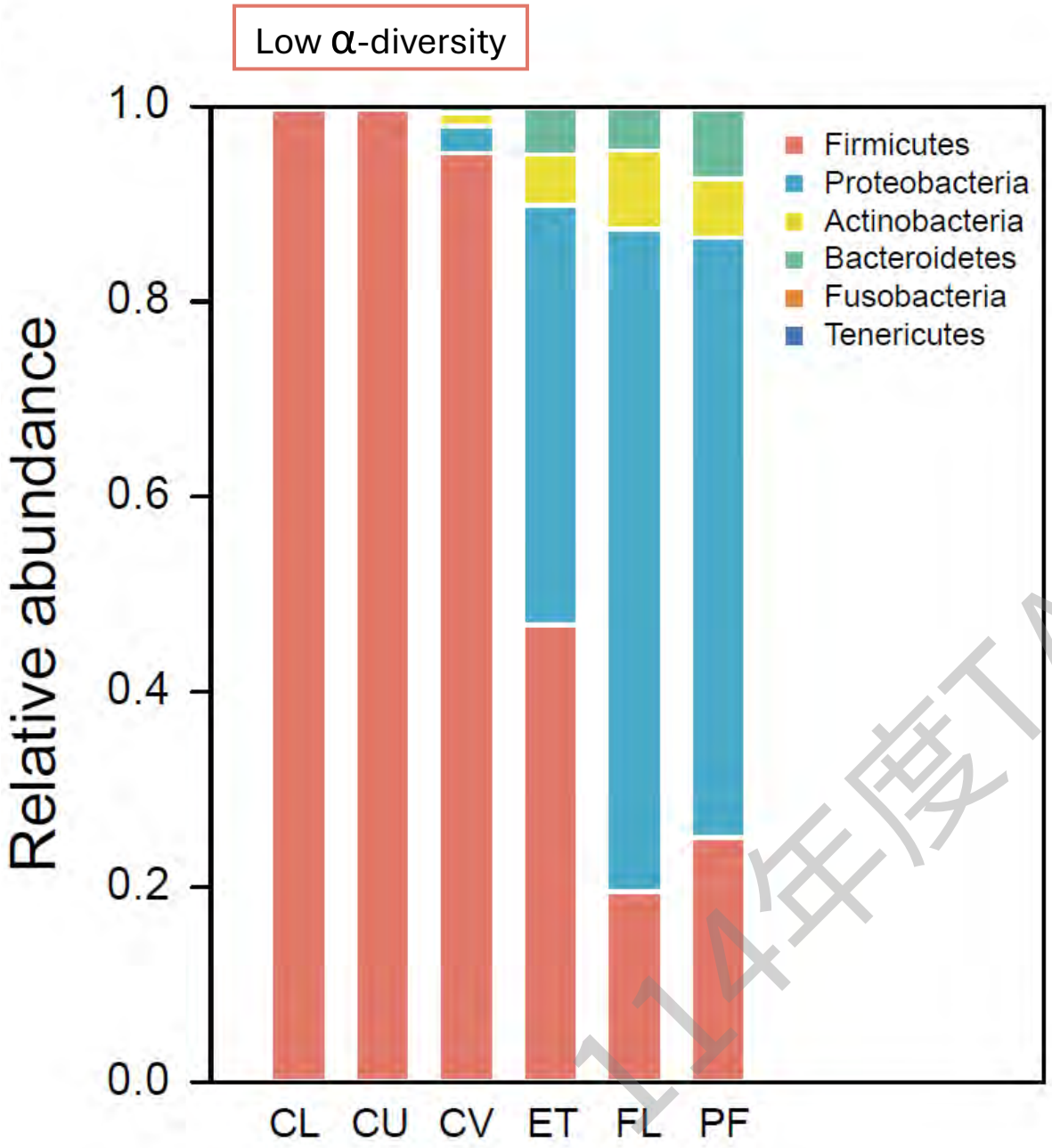
DOI: 10.1038/s41467-017-00901-0 OPEN

The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases

Here we systematically sample the microbiota within the female reproductive tract in **110** women of **reproductive age**, and examine the nature of colonisation by **16S rRNA gene** amplicon sequencing and cultivation.

Nat Commun 2017, 8, 875,
doi:10.1038/s41467-017-00901-0.



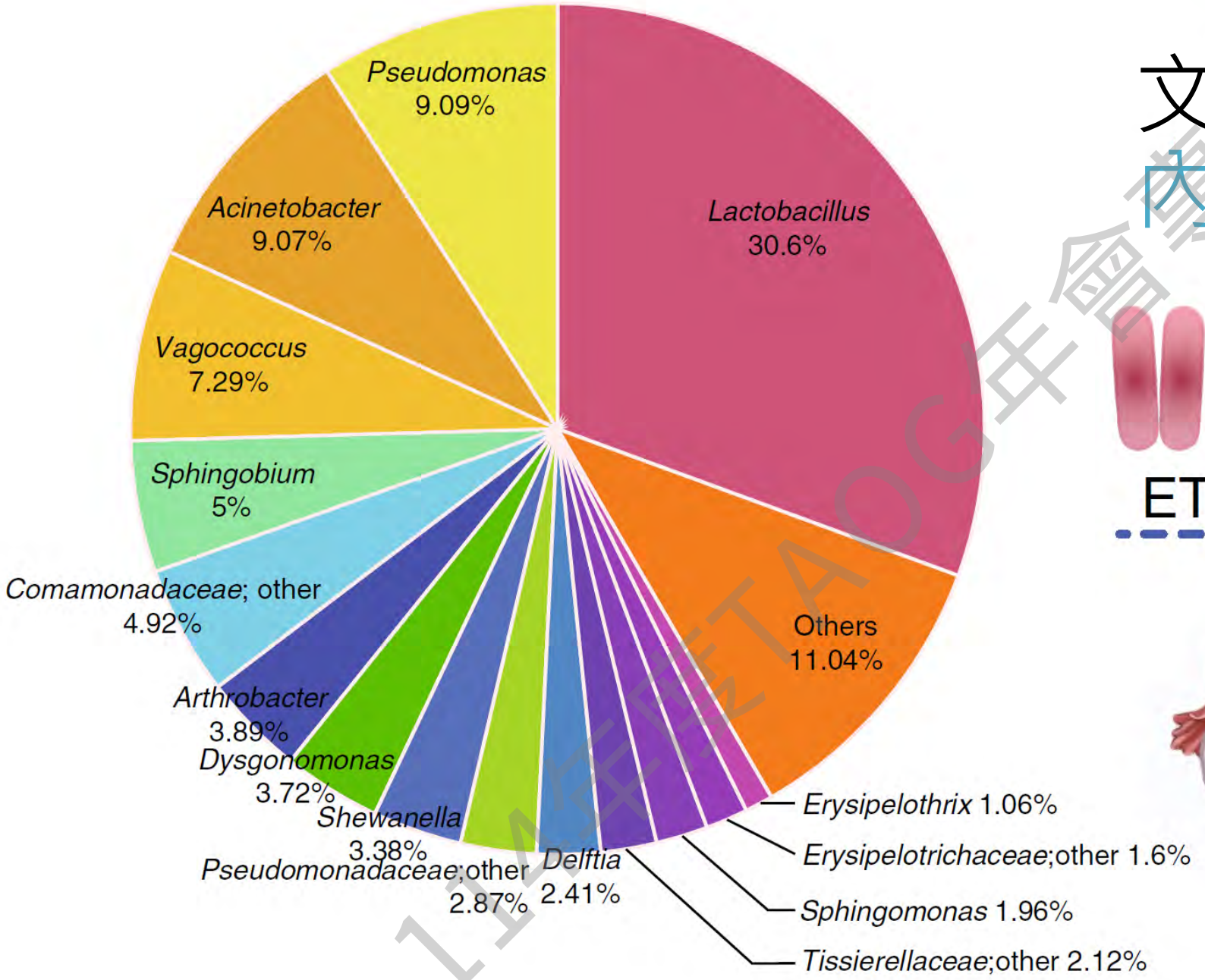


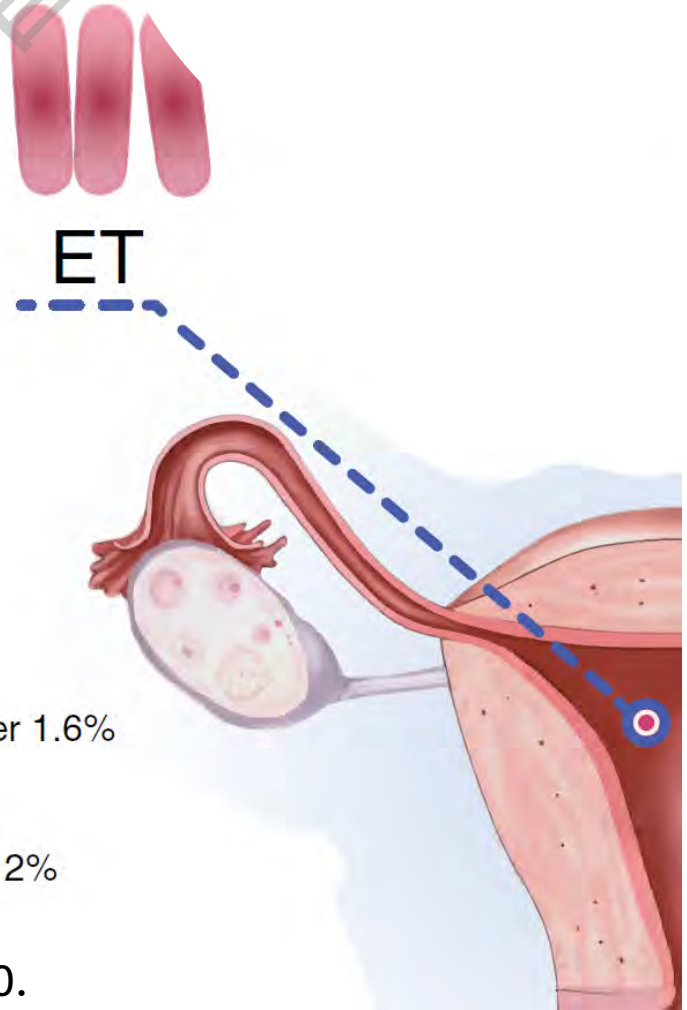
內膜菌叢

In the ET samples, **Lactobacillus no longer dominated**, and bacteria such as Pseudomonas, Acinetobacter, Vagococcus, and Sphingobium constituted a notable fraction of the microbiota.

Nat Commun 2017, 8, 875, doi:10.1038/s41467-017-00901-0.

文獻資料
內膜菌叢分布

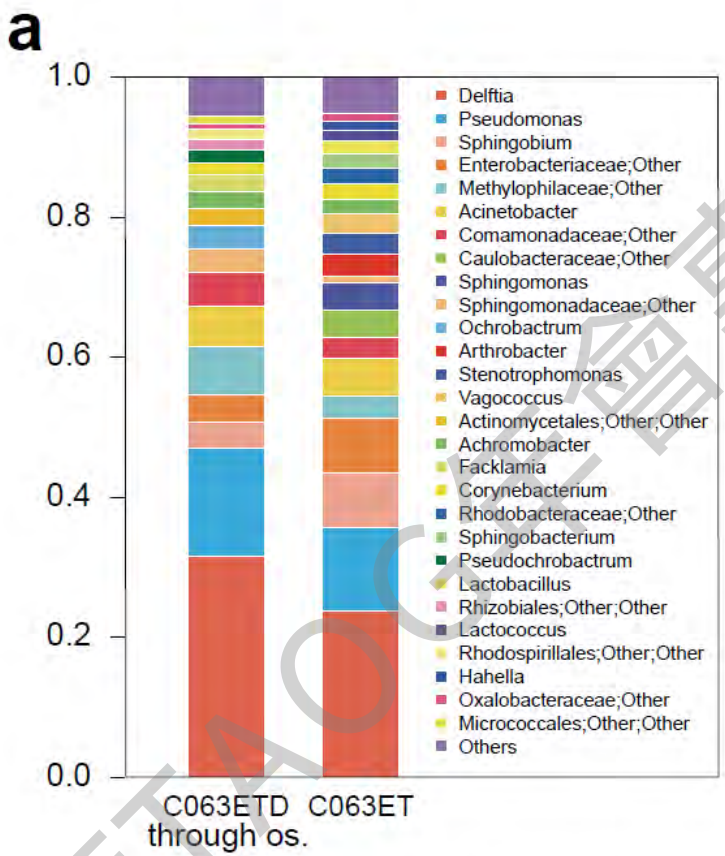




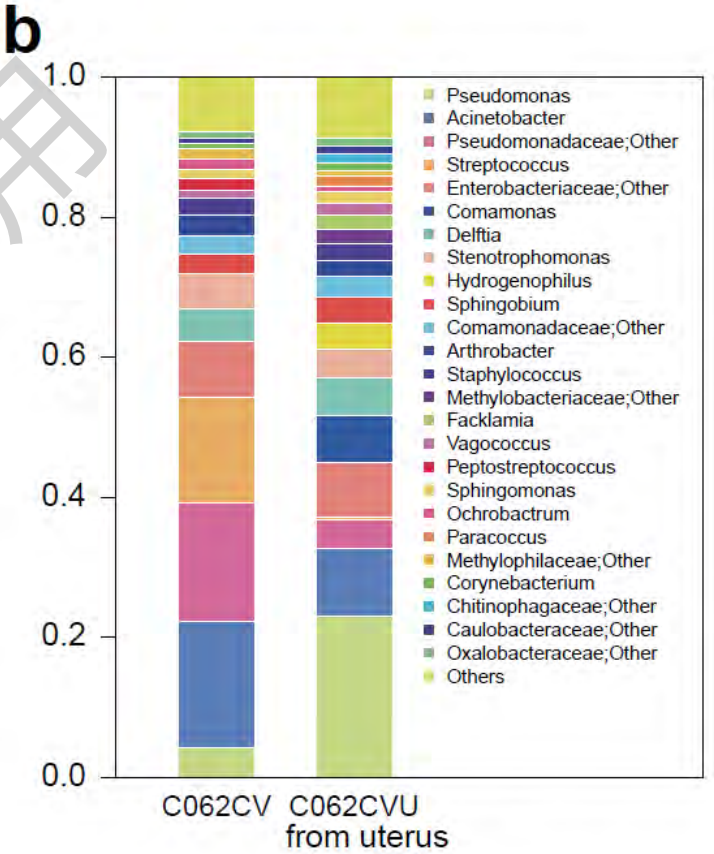
Nat Commun 2017, 8, 875, doi:10.1038/s41467-017-00901-0.

Sampling routes

- The distribution of bacteria in the samples taken through the cervical os showed high similarity to that in samples taken by opening the uterus during surgery.



C063	Pearson correlation		n (N)
	OTU	Genus	
CL-ETD	-6.39E-03	9.30E-03	7 (213)
ETD-ET	0.879	0.915	58 (155)
CL-ET	-8.98E-03	4.68E-02	3 (222)



C062	Pearson correlation		n (N)
	OTU	Genus	
CL-CV	0.350	0.473	59 (285)
CV-CVU	0.382	0.515	91 (249)
CL-CVU	4.83E-03	3.99E-03	40 (280)

Supplementary Figure 4: The relative abundance of each genus in samples taken via two sampling routes from the same individual. (a) ET samples taken directly from the uterus

Nat Commun 2017, 8, 875, doi:10.1038/s41467-017-00901-0.

The threshold of lactobacillus abundance in the Endometrium: defining normal flora for reproductive health

內膜中的lactobacillus要多少才夠?

American Journal of Obstetrics & Gynecology. 2016;215(6):684-703.

Report of Major Impact ajog.org

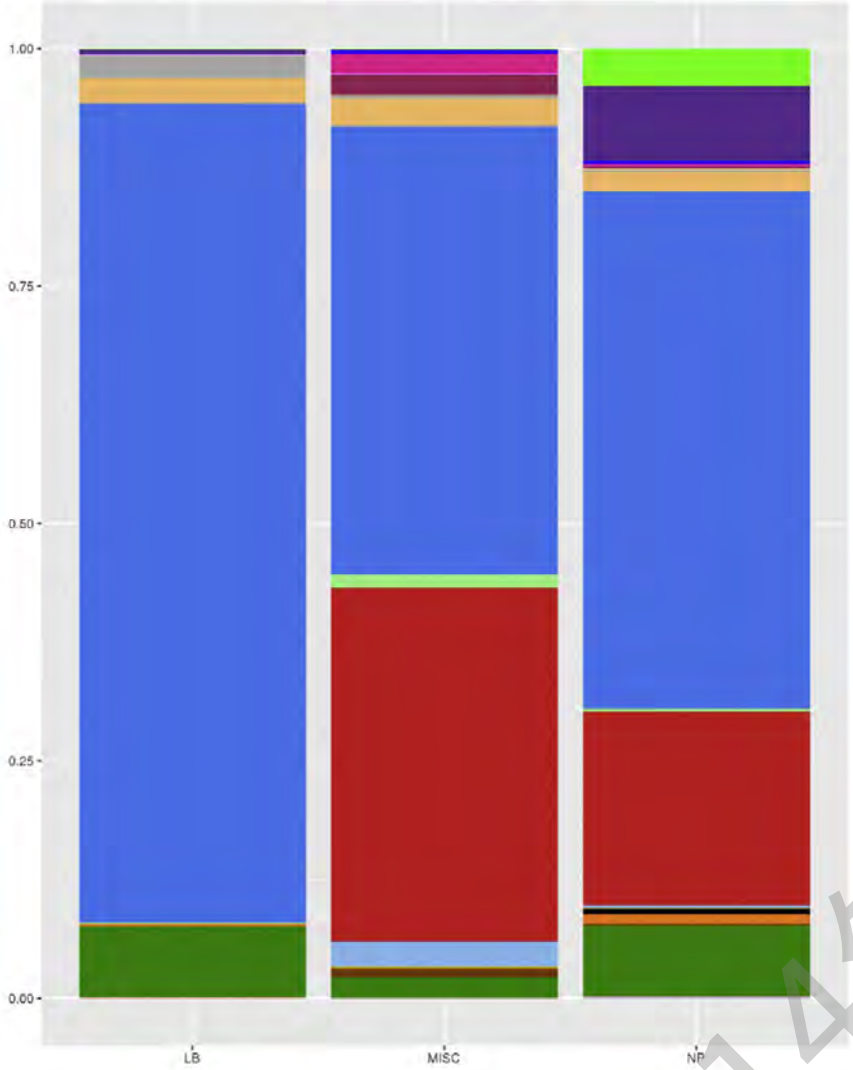
Evidence that the endometrial microbiota has an effect on implantation success or failure

Inmaculada Moreno, PhD[1]; Francisco M. Codoñer, PhD[1]; Felipe Vilella, PhD[1]; Diana Valbuena, MD, PhD; Juan F. Martinez-Blanch, PhD; Jorge Jimenez-Almazán, PhD; Roberto Alonso; Pilar Alamá, MD, PhD; Jose Remohí, MD, PhD; Antonio Pellicer, MD, PhD; Daniel Ramon, PhD[2]; Carlos Simon, MD, PhD[2]

EM 中，Lactobacillus 要多少%才夠?

- Lactobacillus-dominant: >=90%
  - Higher implantation rates, reduced miscarriage risk, and increased live birth rates in assisted reproductive technologies (ART).

FIGURE 11
Low abundance of endometrial Lactobacillus is associated with poor reproductive outcome



活產 流產 沒懷

TABLE 2
Descriptive characteristics of subjects, cycles, transfers, and outcome results

Characteristics and outcomes	LDM, n = 17	NLDM, n = 15	*P* value
Age, y	40.06 ± 3.47	39.00 ± 5.09	.49
BMI, kg/m^2	24.18 ± 5.18	22.45 ± 4.02	.30
Previous pregnancies	1.71 ± 2.44	1.53 ± 2.32	.84
Previous miscarriages	1.53 ± 2.21	1.14 ± 1.56	.58
Metaphase II oocytes/cycle	11.94 ± 4.27	10.20 ± 4.81	.28
Fertilization rate/cycle	157/203 (77.34%)	118/153 (77.12%)	.62
Transferred embryos/cycle	1.65 ± 0.49	1.73 ± 0.59	.65
Time between EF and transfer, mo	2.82 ± 2.55	1.80 ± 1.08	.16
Pregnancy rate/transfer	12/17 (70.6%)	5/15 (33.3%)	.03[a,b]
Implantation rate/transfer	17/28 (60.7%)	6/26 (23.1%)	.02[a,b]
Ongoing pregnancy/transfer	10/17 (58.8%)	2/15 (13.3%)	.02[a,b]
Miscarriage rates	2/12 (16.7%)	3/5 (60%)	.07
Live birth rate/transfer	10/17 (58.8%)	1[c]/15 (6.7%)	.002[a,b]

Values are mean ± SD unless otherwise noted.

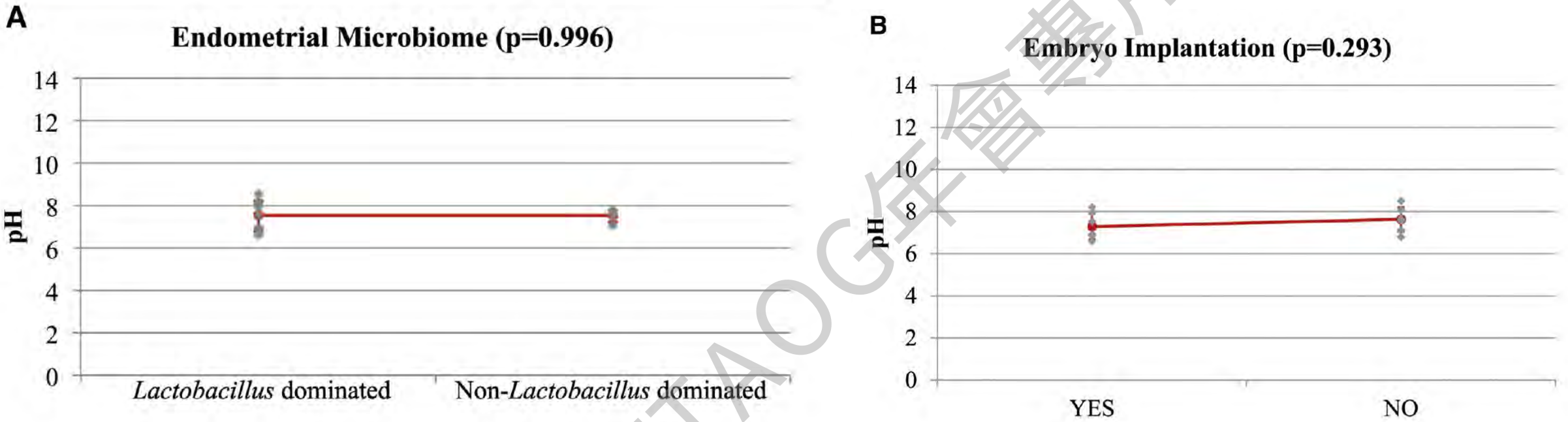
BMI, body mass index; *EF*, endometrial fluid; *LDM*, *Lactobacillus*-dominated microbiota; *NLDM*, non-*Lactobacillus*-dominated microbiota.

[a] χ^2 test and Student *t* test were performed; [b] *P* value < .05; [c] Voluntary termination of pregnancy.

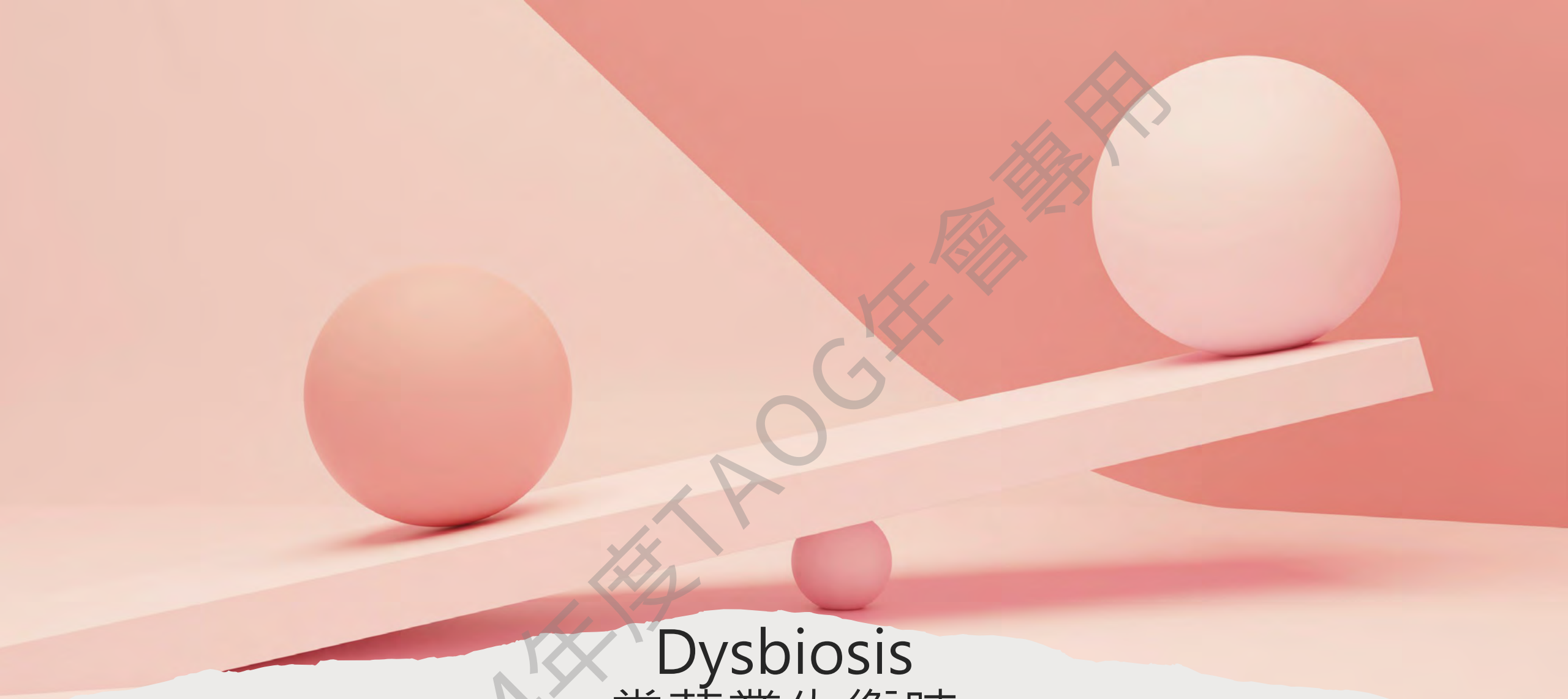
Moreno et al. Endometrial microbiota impacts reproductive potential. Am J Obstet Gynecol 2016.

Moreno et al. Endometrial microbiota impacts reproductive potential. Am J Obstet Gynecol 2016.

FIGURE 13
Endometrial pH



Moreno et al. Endometrial microbiota impacts reproductive potential. Am J Obstet Gynecol 2016.



Dysbiosis

當菌叢失衡時

Bacterial vaginitis (BV)

Chronic endometritis (CE)

Human Reproduction Open, 2023, 2023(3), hoad023
https://doi.org/10.1093/hropen/hoad023
ESHRE Pages

ESHRE good practice recommendations on recurrent implantation failure†

If RIF is suspected in the couple

Follow up with RIF-specific investigations

RECOMMENDED

- Re-assessment of lifestyle factors ♀♂
- Re-assessment of endometrial thickness ♀
- Assessment of APA and APS in case of risk factors[1] ♀

CAN BE CONSIDERED

- Karyotyping (both partners)[2] ♀♂
- 3D US/hysteroscopy ♀
- Endometrial function testing ♀
- Chronic endometritis testing ♀
- Assessment of thyroid function ♀
- Progesterone levels (late follicular/mid-luteal) ♀

Interventions for RIF

RECOMMENDED

- Review of estradiol treatment, if endometrium remains thin
- Genetic counselling and, where relevant PGT, if a chromosomal abnormality is detected
- Optimization of lifestyle factors

CAN BE CONSIDERED

- Antibiotics, if chronic endometritis is diagnosed
- PGT-A
- Blastocyst-stage embryo transfer

Chronic endometritis

The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. Am J Obstet Gynecol 2018, 218, 602 e601-602 e616, doi:10.1016/j.ajog.2018.02.012.

診斷金標準，到底在哪裡?
Diagnosis: Chronic Endometritis (CE)

- Conventional diagnosis
  - **Histology**(+- IHC CD138),
  - **Hysteroscopy**, and
  - **Bacterial culture**
- **The molecular test (RT-PCR), 16s rRNA sequencing** shows promise as a faster and more reliable tool for a **streamlined** diagnosis of CE.

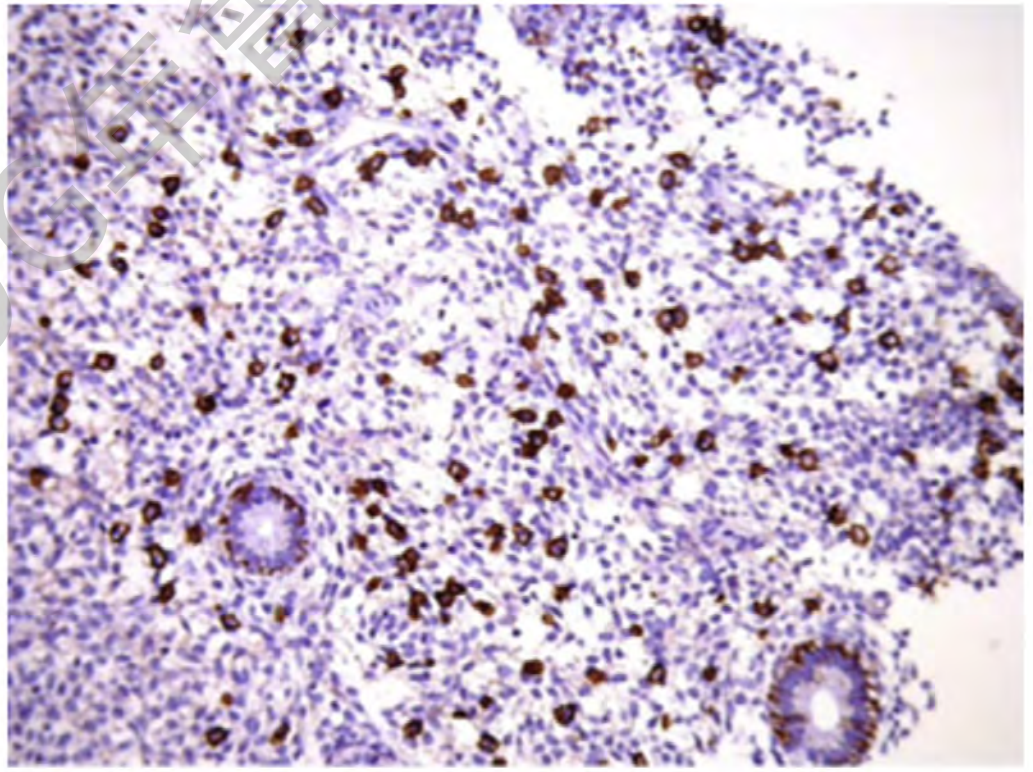
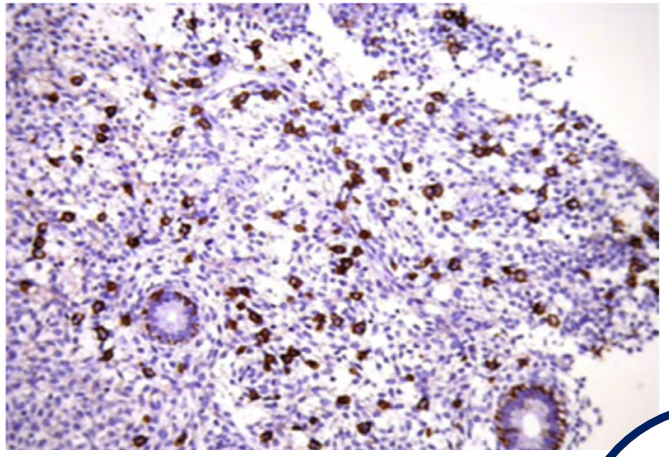
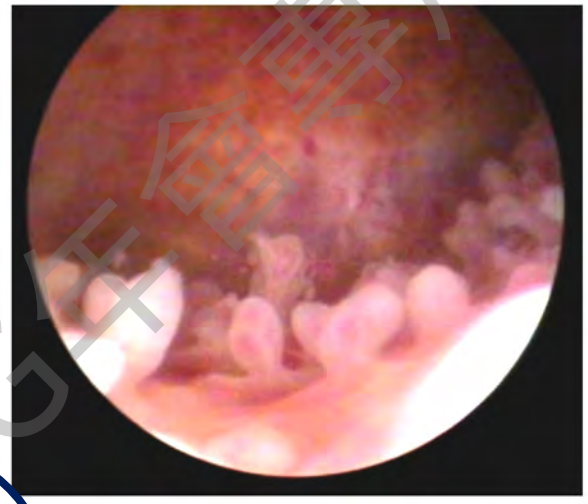


Fig. 1 Plasma cell identification (brown color) with immunostaining for syndecan-1 (CD 138) in endometrial stroma

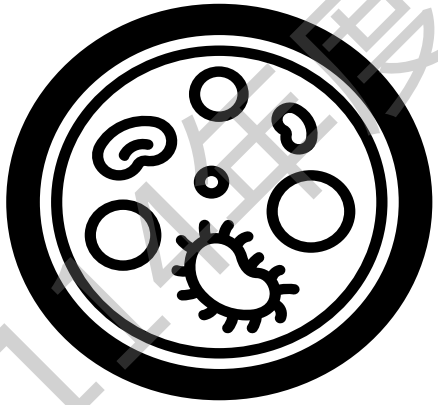
慢性內膜發炎的診斷方法

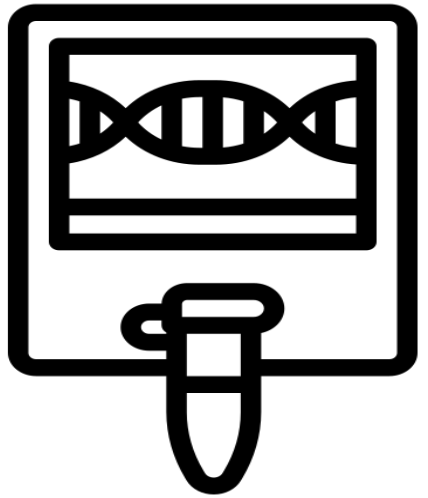




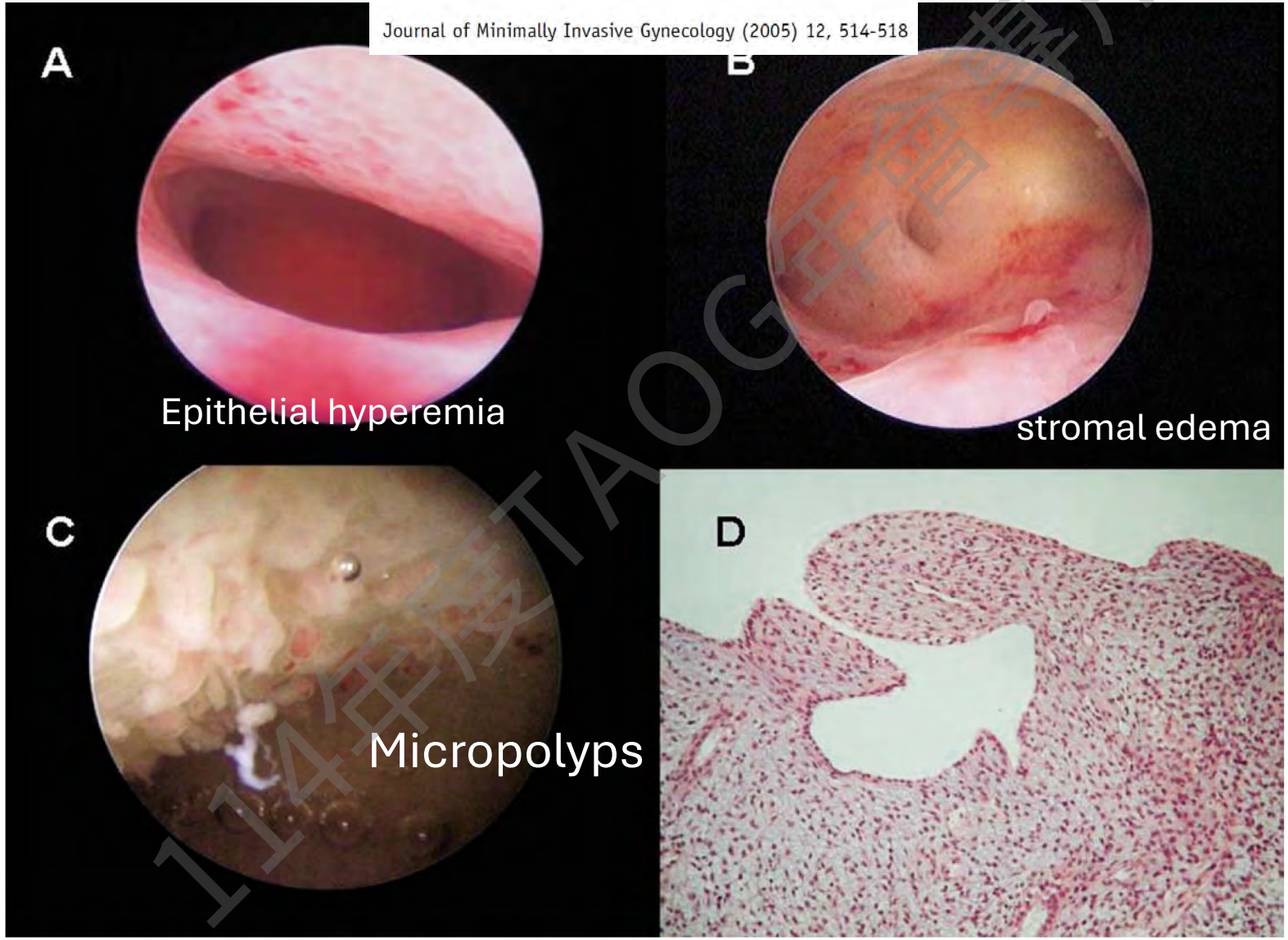
elli. Microorganisms and chronic endometritis. Fertil Steril 2008.

CE





Hysteroscopy features of CE



Different aspects of chronic endometritis at fluid hysteroscopy. (A) Endometrial mucosa appears thick, edematous,

Histology: 診斷CE的標準差異大 目前仍無共識

TABLE 1

Prevalence of chronic endometritis reported in the literature among three groups of women (infertility, recurrent miscarriage, and recurrent implantation failure) in relation to inclusion criteria, diagnostic criteria, and timing of endometrial biopsy.

Reference	Inclusion criteria	Diagnostic criteria (plasma cell count)	Timing of endometrial biopsy	Prevalence
Infertility				
Cicinelli et al., 2005	Unexplained infertility	≥1/section	Follicular phase	30% (45/150)
Kitaya and Yasuo, 2010	Unexplained infertility	≥1/10 HPFs	LH+6–8	29% (22/76)
Kasius et al., 2011	Infertility	≥1/section	Follicular phase	3% (17/606)
Kitaya et al., 2012	Infertility	≥5/20 HPFs	Follicular phase	44% (23/52)
Recurrent miscarriage				
Kitaya, 2011	≥3 miscarriages	≥1/10 HPFs	LH+6–8	9% (5/54)
Zolghadri et al., 2011	≥3 miscarriages	≥1/section	Follicular phase	43% (61/142)
Cicinelli et al., 2014	≥3 miscarriages	≥1/section	Follicular phase	53% (190/360)
McQueen et al., 2015	≥2 miscarriages	1–5/HPF or discrete clusters <20	Not mentioned	56% (60/107)
Bouet et al., 2016	≥2 unexplained miscarriages	≥5/10 HPFs	Follicular phase	27% (14/51)
Recurrent implantation failure				
Johnston-MacAnanny et al., 2010	≥2 failed ET cycles or >10 failed ETs	≥1/HPF	Not mentioned	30% (10/33)
Kitaya et al., 2017	≥3 failed ETs	ESPDI ≥0.25	Follicular phase	34% (142/421)
Cicinelli et al., 2015	≥3 failed ET cycles	≥1/section	Follicular phase	57% (61/106)
Bouet et al., 2016	≥3 failed ETs	≥5/10 HPFs	Follicular phase	14% (6/43)

Note: ESPDI = endometrial stromal plasmacyte density index; ET = embryo transfer; HPF = high-power field, ×400 magnification; LH+6–8 = 6 to 8 days after LH surge.

Liu. Prevalence of chronic endometritis. Fertil Steril 2018.

Miscarriage rate: 5/10HPFs

Biomedicines 2023, 11, 1714

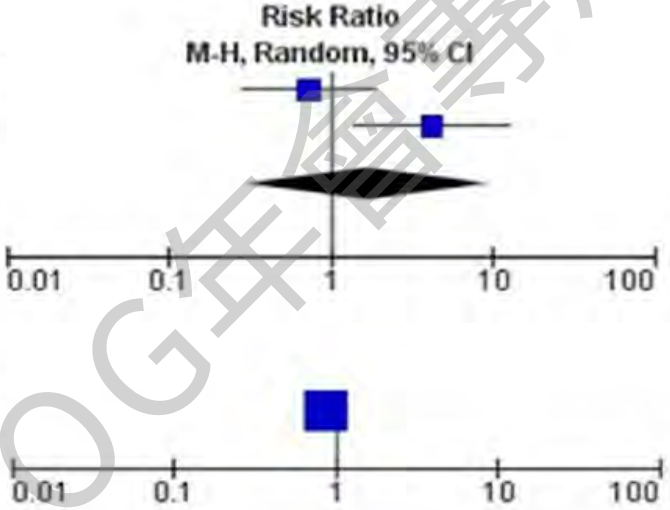
≥1/10HPF

Study or Subgroup	CE Events	CE Total	NCE Events	NCE Total	Weight	Risk Ratio M-H, Random, 95% CI
Herlihy	6	28	7	24	51.4%	0.73 [0.29, 1.89]
Hirata	6	8	3	17	48.6%	4.25 [1.41, 12.79]
Total (95% CI)		**36**		**41**	**100.0%**	**1.73 [0.31, 9.68]**
Total events	12		10			

Heterogeneity: Tau² = 1.27; Chi² = 5.65, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.62 (P = 0.54)

Song *(retrospective)*	159	378	568	1173	100.0%	0.87 [0.76, 0.99]

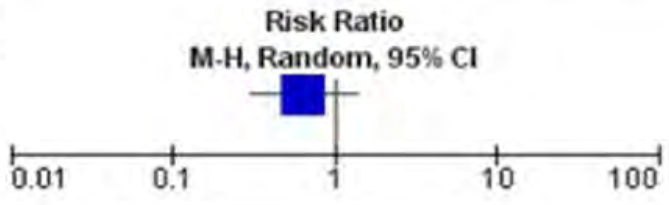
Test for overall effect: Z = 2.09 (P = 0.04)



≥2.5/10HPF

Study or Subgroup	CE Events	CE Total	NCE Events	NCE Total	Weight	Risk Ratio M-H, Random, 95% CI
Kitaya	8	53	18	77	100.0%	0.65 [0.30, 1.37]

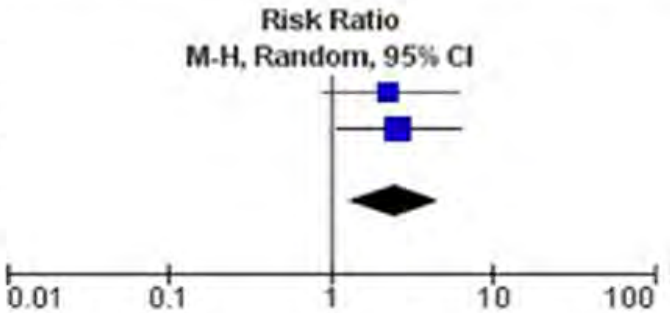
Test for overall effect: Z = 1.13 (P = 0.26)



≥5/10HPF

Study or Subgroup	CE Events	CE Total	NCE Events	NCE Total	Weight	Risk Ratio M-H, Random, 95% CI
Herlihy	3	6	10	46	45.2%	2.30 [0.87, 6.07]
Hirata	3	4	6	21	54.8%	2.63 [1.09, 6.34]
Total (95% CI)		**10**		**67**	**100.0%**	**2.47 [1.29, 4.75]**
Total events	6		16			

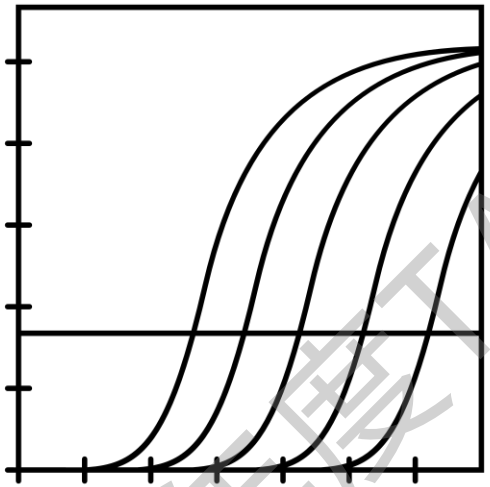
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.72 (P = 0.007)



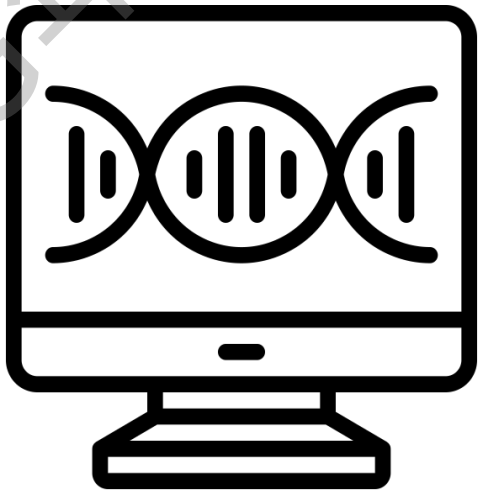
Molecular diagnosis

CE

PCR



NGS
16s rRNA



Icon from Noun Project

Am J Obstet Gynecol 2018;218:602.e1-16.

GYNECOLOGY

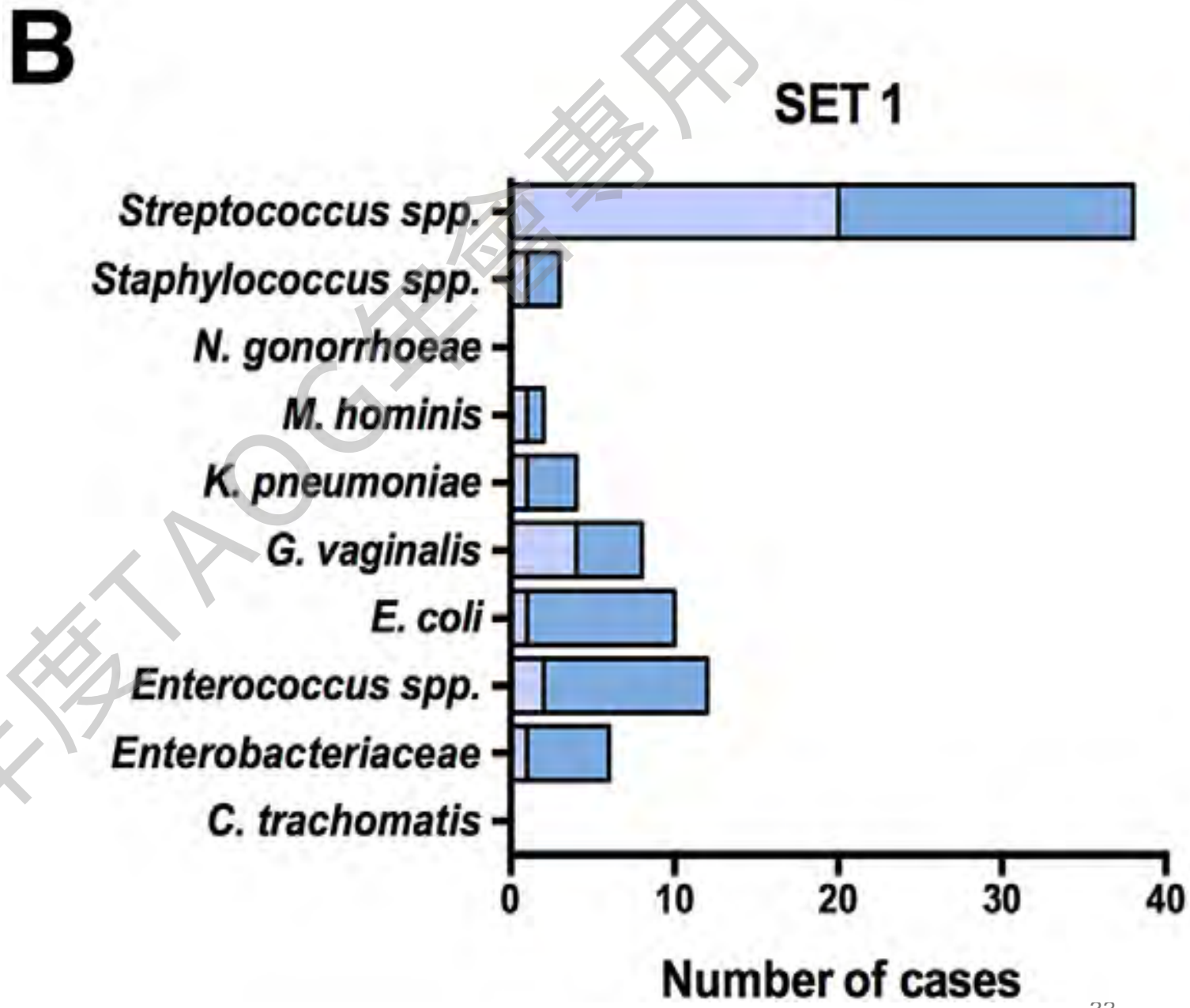
The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology

Inmaculada Moreno, PhD[1]; Ettore Cicinelli, MD[1]; Iolanda Garcia-Grau, BS[1]; Marta Gonzalez-Monfort, BS; Davide Bau, PhD; Felipe Vilella, PhD; Dominique De Ziegler, MD; Leonardo Resta, MD; Diana Valbuena, MD, PhD; Carlos Simon, MD, PhD

Endometrial samples from patients assessed for **chronic endometritis (n = 113)** using at least 1 or several conventional diagnostic methods namely **histology, hysteroscopy, and/or microbial culture**, were blindly evaluated by **real-time polymerase chain reaction** for the presence of 9 chronic endometritis pathogens: Chlamydia trachomatis, Enterococcus, Escherichia coli, Gardnerella vaginalis, Klebsiella pneumoniae, Mycoplasma hominis, Neisseria gonorrhoeae, Staphylococcus, and Streptococcus.

PCR

- Most: streptococci
- While C. trachomatis and N. gonorrhoeae were undetectable in all tested samples



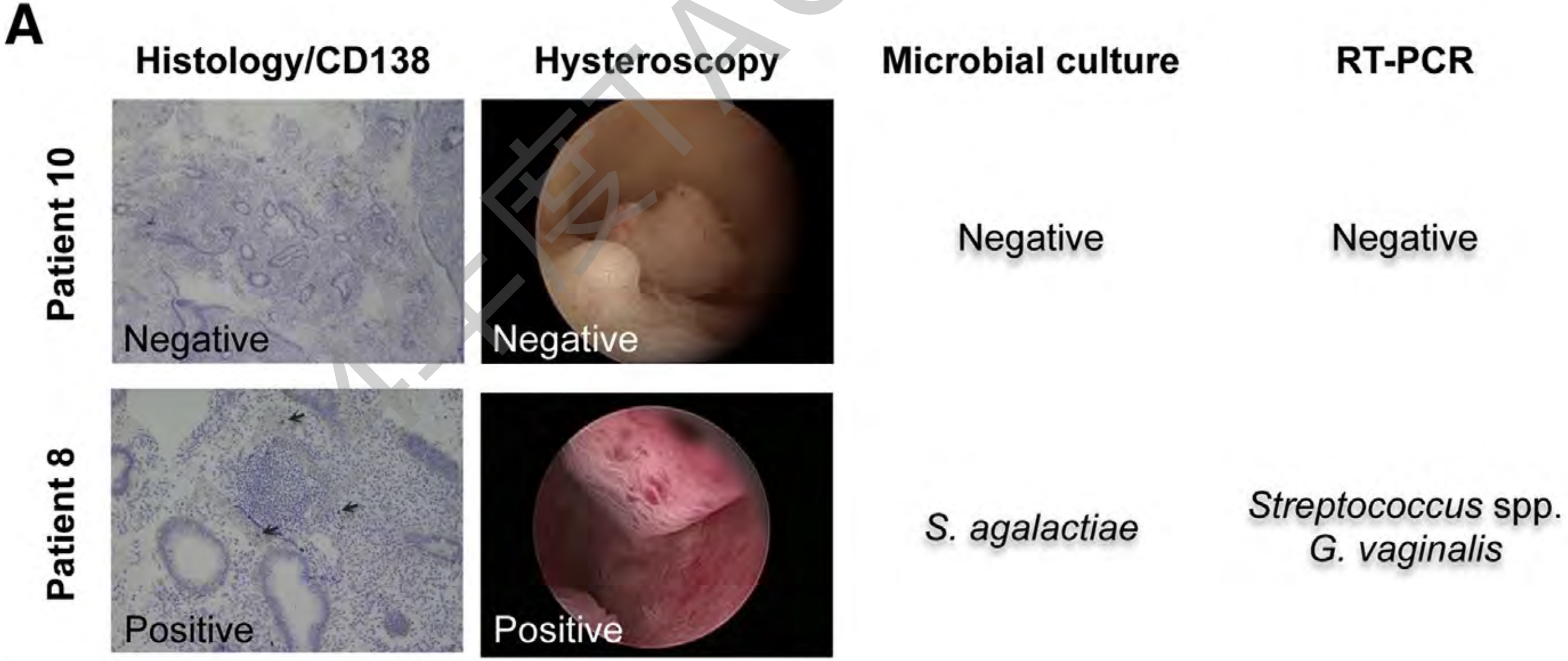
			16s rRNA sequencing													
Patient	Microbial culture	RT-PCR	*Lactobacillus*, %	*Enterococcus*, %	*Staphylococcus*, %	*Streptococcus*, %	*Mycoplasma*, %	*Enterobacteriaceae*, %	*Escherichia*, %	*Klebsiella*, %	*Gardnerella*, %	*Ureaplasma*, %	*Chlamydia*, %	*Neisseria*, %	No. of mapped reads	Alpha diversity (Shannon index)
8	*Streptococcus agalactiae*	*Streptococcus* species, *Gardnerella vaginalis*	13.75	2.52	4.46	30.87	0.00	1.00	0.00	0.00	1.48	0.00	0.00	0.00	121,624	7.32
10	Negative	Negative	99.94	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.00	218,076	2.94
15	*Escherichia coli*	*Gardnerella vaginalis*, *Escherichia coli*	74.40	0.36	1.97	0.68	0.02	1.00	0.00	0.00	1.34	0.00	0.00	0.00	96,697	6.12
17	*Enterococcus faecalis*, *Ureaplasma*	Negative	96.49	0.00	0.11	0.11	0.00	0.30	0.00	0.00	0.43	0.00	0.00	0.00	62,033	3.79

TABLE 4
Molecular diagnosis compared to classic diagnostic methods of chronic endometritis

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	FPR (%)	FNR (%)
Histology (n = 65)	56.00	40.00	46.15	36.84	59.26	60.00	44.00
Hysteroscopy (n = 65)	58.73	50.00	58.46	97.37	3.70	50.00	41.27
Microbial culture (n = 65)	71.43	56.67	66.15	65.79	62.96	43.33	28.57
Histology + hysteroscopy (concordant results, n = 27)	56.00	50.00	55.56	93.33	8.33	50.00	44.00
Histology + hysteroscopy + microbial culture (concordant results, n = 13)	75.00	100.00	76.92	100.00	25.00	0.00	25.00

FNR, false-negative rate; *FPR*, false-positive rate; *NPV*, negative predictive value; *PPV*, positive predictive value.

Moreno et al. Molecular microbiology for diagnosing chronic endometritis. Am J Obstet Gynecol 2018.



Diagnosis
小結

CE診斷

Implantation failure>= 2 times

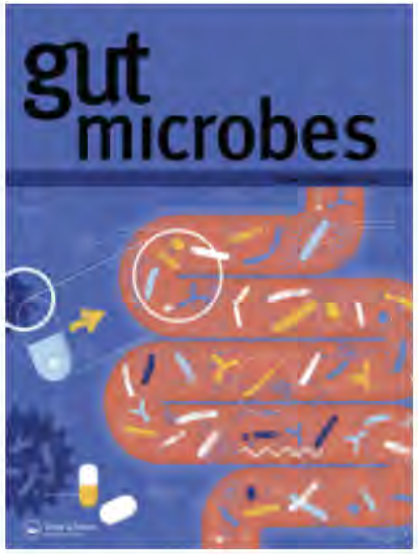
- Euploid blastocysts >= 2 times at all ages

子宮鏡 (易於追蹤，可能發現其他問題)

- + Endometium/Endocervical culture 為治療依據
  - C. trachomatis, N. gonorrhoeae, U. urealyticum, U. parvum, and Mycoplasma hominis, all of which are noncultivable strains
- +- Histology (CD138): >=5/10 HPFs

16s rRNA NGS: 貴

Treatment



Impact Factor: 12.2

Gut Microbes

Taylor & Francis
Taylor & Francis Group

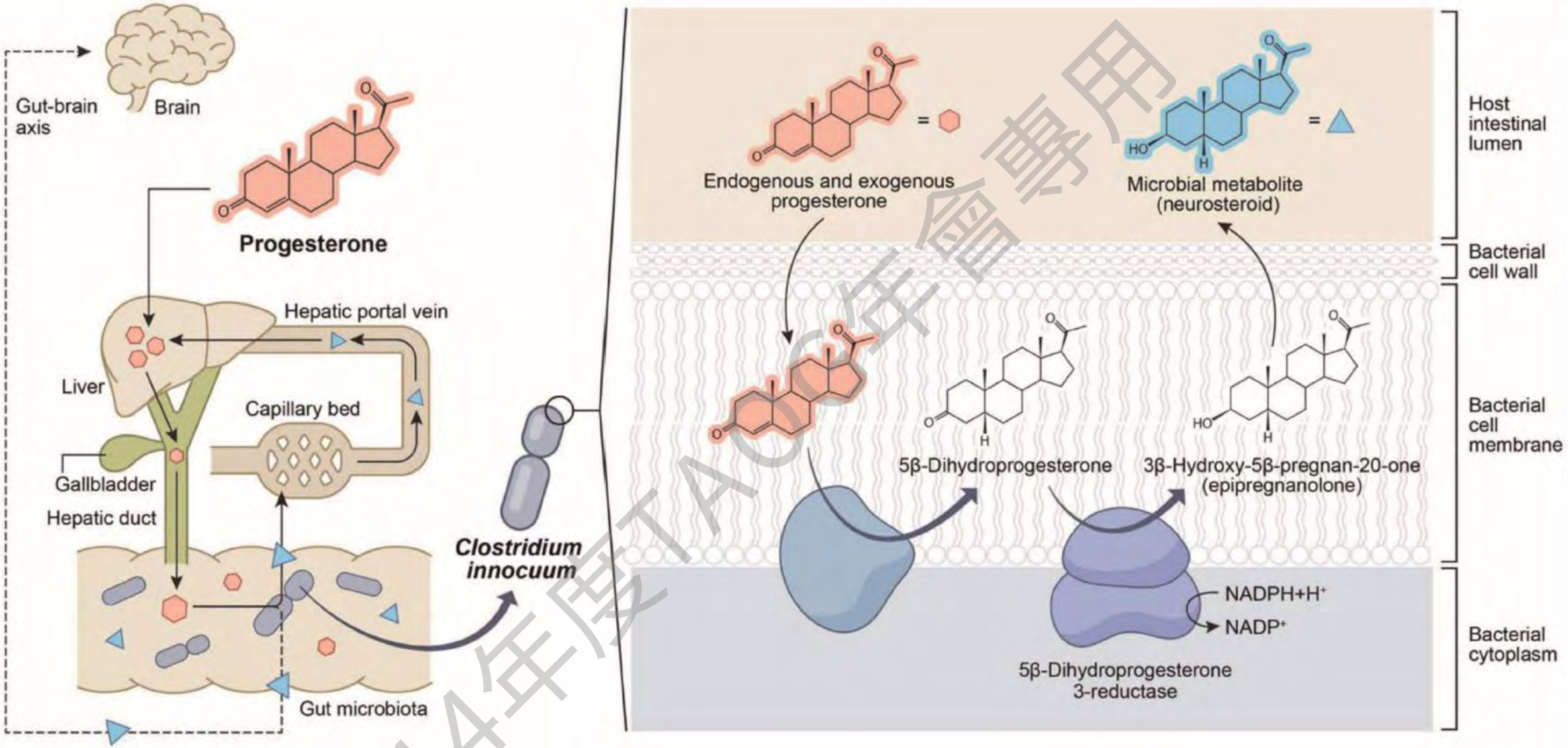
Published online: 07 Nov 2024.

https://doi.org/10.1080/19490976.2024.2424911

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/kgmi20

Clostridium innocuum, an opportunistic gut pathogen, inactivates host gut progesterone and arrests ovarian follicular development

Mei-Jou Chen, Chia-Hung Chou, Tsun-Hsien Hsiao, Tien-Yu Wu, Chi-Ying Li, Yi-Lung Chen, Kuang-Han Chao, Tzong-Huei Lee, Ronnie G. Gicana, Chao-Jen Shih, Guo-Jie Brandon-Mong, Yi-Li Lai, Po-Ting Li, Yu-Lin Tseng, Po-Hsiang Wang & Yin-Ru Chiang



Impact on host physiology:

- **decrease in serum progesterone level**
- **arrest of ovarian follicular development**

Highlights

Taylor & Francis
Taylor & Francis Group

- We identified *Clostridium innocuum* as a key player in gut progesterone metabolism.
- Progesterone is converted into epipregnanolone with negligible progestogenic activity.
- We identified the enzymes and mechanisms of microbial epipregnanolone production.
- *C. innocuum* caused decreased plasma progesterone and follicular arrest in female mice.
- *C. innocuum* is a causal factor of progesterone resistance in women taking progesterone.

https://doi.org/10.1080/19490976.2024.2424911

思考:

- 給抗生素是在殺哪裡的細菌? 腸子?陰道? 內膜?
- 想想GBS 用ampicillin Tx的道理...

Treatment of CE

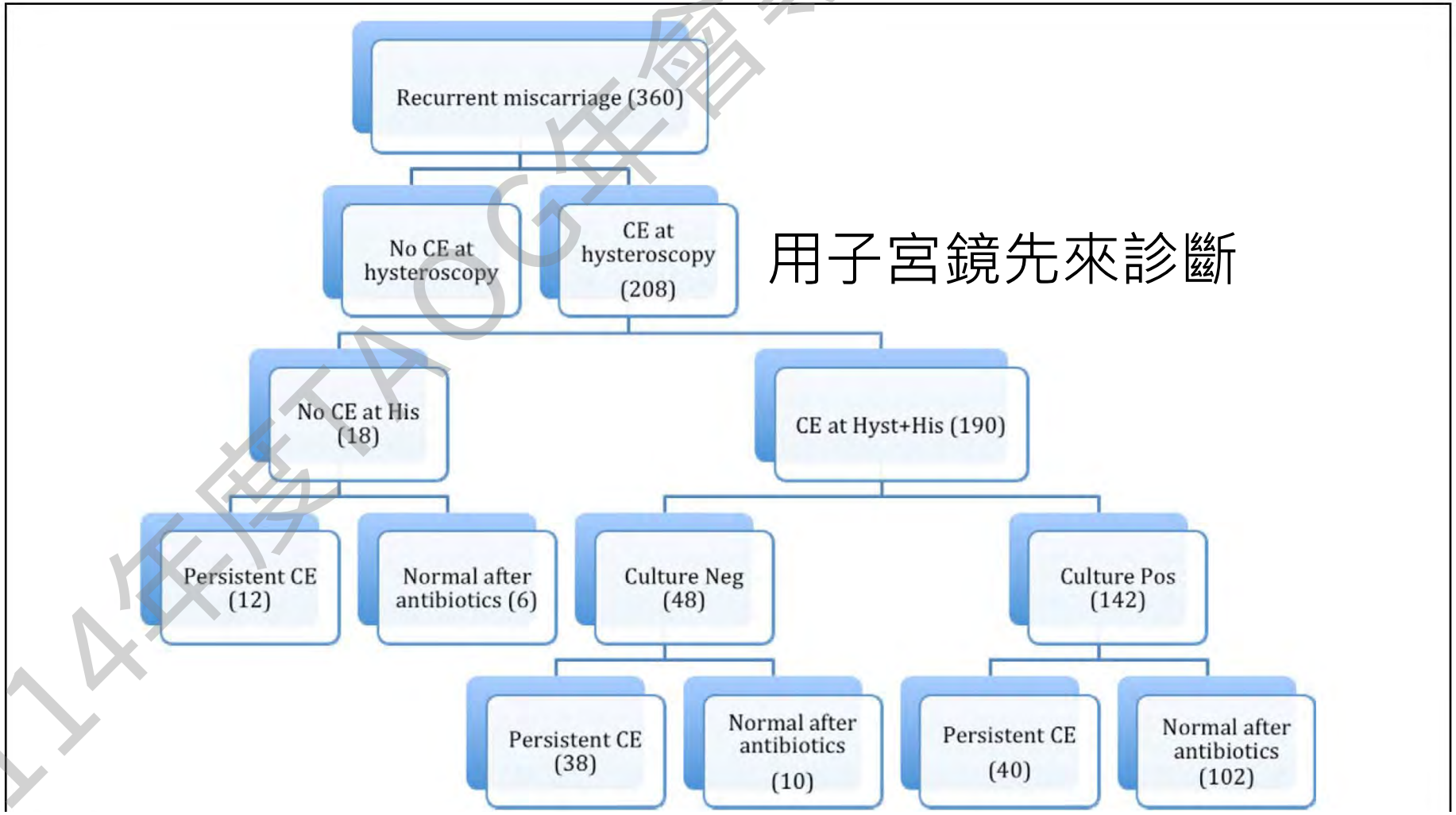
- 1. Based on antibiogram, for 7-10 days
  - Gram-negative bacteria, ciprofloxacin 500 mg twice a day for 10 days
  - Gram-positive bacteria, amoxicillin + clavulanate 1 g twice a day for 8 days was prescribed.
  - Mycoplasma and U urealyticum: josamicine 1 g twice a day for 12 days, (Azithromycin in Taiwan) while minocycline 100 mg twice a day for 12 days was used in cases of persistence.
- 2. In women with negative cultures, a treatment based on the CDC guidelines, for 14 days
  - Ceftriaxone 250 mg intramuscularly in a single dose plus doxycycline 100 mg orally twice a day for 14 days with metronidazole 500 mg orally twice a day for 14 days

Chronic Endometritis Due to Common Bacteria Is Prevalent in Women With Recurrent Miscarriage as Confirmed by Improved Pregnancy Outcome After Antibiotic Treatment

Reproductive Sciences
2014, Vol. 21(5) 640-647

DOI: 10.1177/1933719113508817
rs.sagepub.com
SAGE

208 (57.8%) women with RM showed CE at hysteroscopy; 190 (91.3%) positive at hysteroscopy+ positive at histology, and 142 (68.3%) had positive cultures.



用子宮鏡先來診斷

G2 最差　　G1 最佳

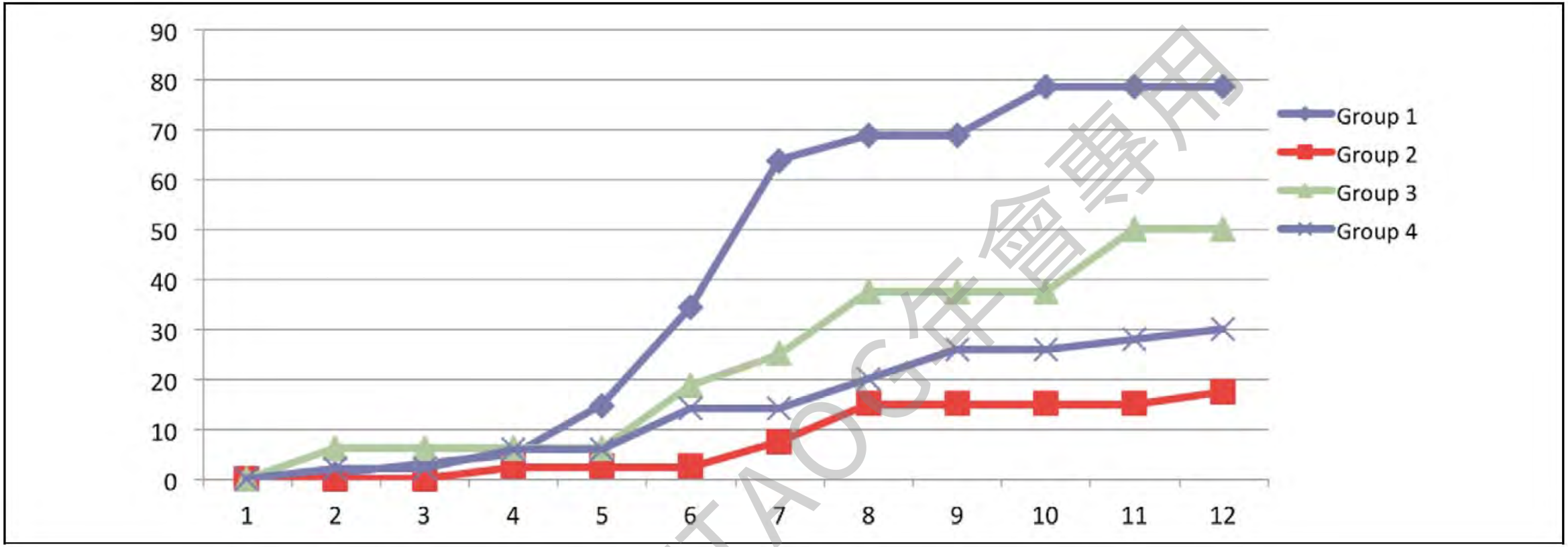


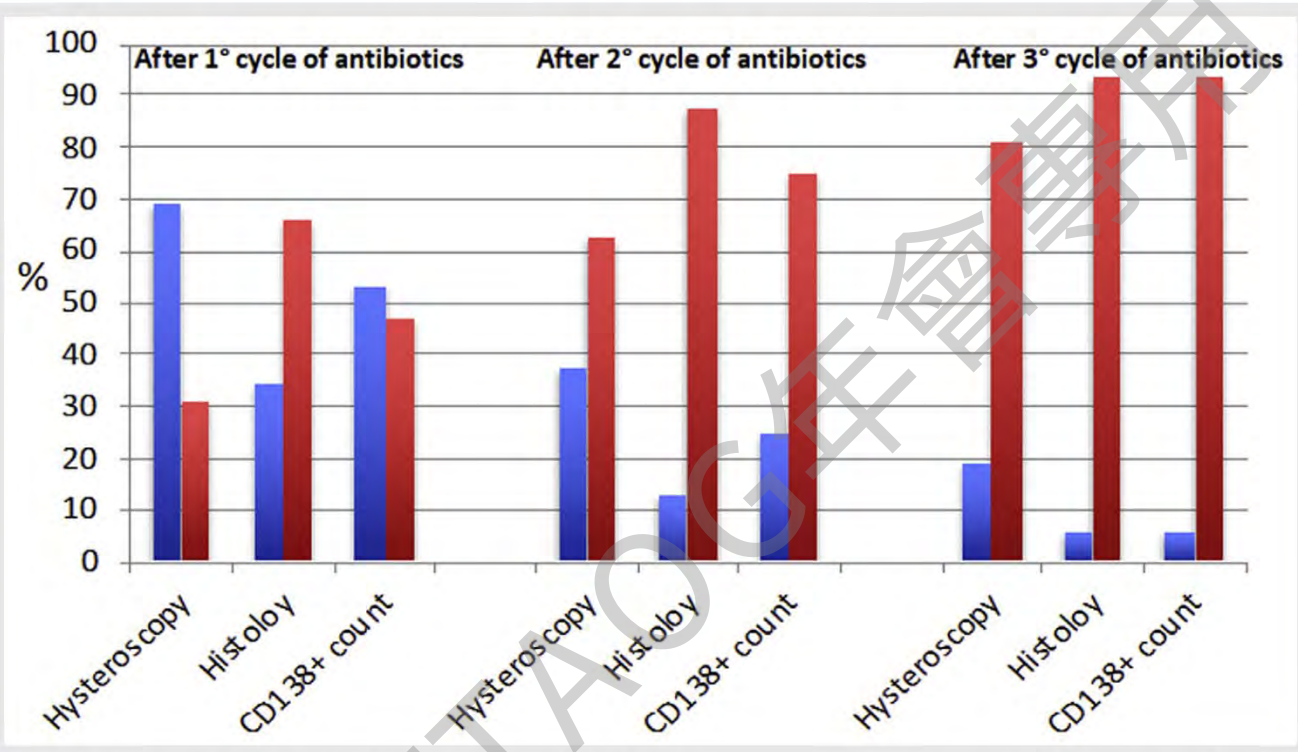
Figure 2. The percentage distribution of time, in months, in the beginning of the first successful pregnancy with live birth in the 4 groups of women with recurrent miscarriage and diagnosed with CE. CE indicates chronic endometritis.

G1: 子宮鏡有異常，culture/PCR也有菌，抗生素治療後子宮鏡**正常** 102/208=49%

G2: 子宮鏡有異常，culture/PCR也有菌，抗生素治療後子宮鏡**異常** 40/208=19%

Reprod Sci 2014, 21, 640-647, doi:10.1177/1933719113508817.

FIGURE 1



Women from Group A (receiving antibiotic therapy) diagnosed with CE at hysteroscopy, histology, and immunohistochemistry for CD138 during 3 courses of antibiotic treatment. Red bars represent cured cases, whereas blue bars represent cases with persistent CE. Data are presented as percentages.

Cicinelli. Antibiotic treatment of CE. Fertil Steril 2021.

Fertil Steril 2021;115:1541–8.

在經過一個抗生素療程後，發現仍有將近7成的病人子宮鏡仍異常。
The study surprisingly found higher persistence of CE signs after antibiotic therapy at hysteroscopy compared with histology and immunohistochemistry.

TABLE 4 Pregnancy outcomes after personalized embryo transfer

	Non-CE group $n = 27$	CE group $n = 18$	Cured-CE group $n = 29$	p Value
First personalized ET				
No of transferred embryos, mean ± *SD*	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.2	.512
ET with morphologically good blastocysts, *n* (%)	23 (85.2)	17 (94.4)	25 (86.2)	.736
Pregnancy outcomes, *n* (%)				
hCG positive rate	23 (85.2)	6 (33.3)	17 (58.6)	**.002**
Clinical pregnancy rate	21 (77.8)	4 (22.2)	15 (51.7)	**<.001**
Miscarriage rate	3 (14.3)	1 (25.0)	4 (26.7)	.521
Ongoing pregnancy rate	18 (66.7)	3 (16.7)	11 (37.9)	**.003**
	$n = 9$	**$n = 10$**	**$n = 12$**	**p Value**
Second personalized ET				
No of transferred embryos, mean ± *SD*	1.1 ± 0.3	1.0 ± 0	1.3 ± 0.5	.102
ET with morphologically good embryos[a], *n* (%)	8 (88.9)	9 (90.0)	9 (75.0)	.703

在患有子宮內膜異位症的女性中，有效的抗生素治療慢性子宮內膜炎可以降低血清CA-125水平

In women with endometriosis, effective treatment of chronic endometritis with antibiotics lowers serum CA-125 levels

高雄長庚婦產部 生殖醫學科 主治醫師 蔡妮瑾

VOL. 121 NO. 6 / JUNE 2024

Ettore Cicinelli, M.D., Ph.D.[a]
Dominique de Ziegler, M.D., Ph.D.[b]
Amerigo Vitagliano, M.D., Ph.D.[a]
[a] 1st Unit of Gynecology and Obstetrics, Department of Interdisciplinary Medicine (DIM), University of Bari (BA), Bari, Italy; and [b] Department of Obstetrics, Gynecology, and Reproductive Medicine, Foch Hospital, 92150, Suresnes, France.

Demographic characteristics of included patients and changes in serum CA-125 values and cyst sizes before and after antibiotic therapy for chronic endometritis.

Variable		N=36 Group A	N=15 Group B	*P* value
Age (y)		30.36 (±3.05)	28.93 (±3.35)	.14
Body mass index (kg/h^2)		23.41 (±2.74)	23.20 (±2.99)	.80
Previous live births (%)	0	28 (77.8)	12 (80)	.81
	1	7 (19.4)	3 (20)	
	2	1 (2.8)	0	
Infertile (%)		7 (19.4)	5 (33.3)	.30
Previous IVF (%)		5 (13.8)	3 (20)	.68
Chronic endometritis features at hysteroscopy (%)	Micropolyps dominated	28 (77.8)	11 (73.3)	.73
	Other signs	8 (22.2)	4 (26.6)	
Nonsteroidal anti-inflammatory drugs assumption (%)		21 (58.3)	9 (60)	1.00
Folic acid assumption (%)		32 (88.9)	11 (73.3)	.21
Cyst size before treatment (mm)		35.81 (±12.98)	39.80 (±12.95)	.32
Cyst number (%)	1	25 (69.4)	10 (66.7)	.76
	2	10 (27.8)	5 (33.3)	
	3	1 (2.8)	0	
Serum CA-125 before treatment (μ/mL)		58.56 (±32.45)	69.60 (±27.42)	.25
Serum CA-125 ≥ 35 (μ/mL) before treatment (%)		26 (72.2)	14 (93.3)	.14
Serum CA-125 after treatment (μ/mL)		38.25 (±17.31)	67.47 (±25.42)	< .001
Serum CA-125 < 35 (μ/mL) after treatment (%)		21 (58.3)	2 (13.3)	.005
Absolute CA-125 change from before to after treatment (μ/mL)		−20.31 (±27.09)	−2.13 (±12.51)	.02
Proportional CA-125 change from before to after treatment (%)		−21.99 (±42.27)	−0.43 (±19.37)	
Cyst size before treatment (mm)		35.81 (±12.98)	39.80 (±12.95)	.32
Cyst size after treatment (mm)		35.50 (±12.22)	39.87 (±12.01)	.25
Absolute cyst size change from before to after treatment (mm)		−0.31 (±2.93)	0.07 (±1.62)	.65
Proportional cyst size change from before to after treatment (%)		−0.87 (±9.93)	0.17 (±4.05)	

Note: The data are presented as mean (±SD) or as absolute numbers (relative percentages for each group). The *P* value was calculated using the Student's *t* test or contingency tables, as appropriate. Group A = women with cured chronic endometritis; group B = women with persistent chronic endometritis.

Cicinelli. CA-125 decreases after endometritis cure. Fertil Steril 2024.

Probiotics!!!

深水區

diagnostics

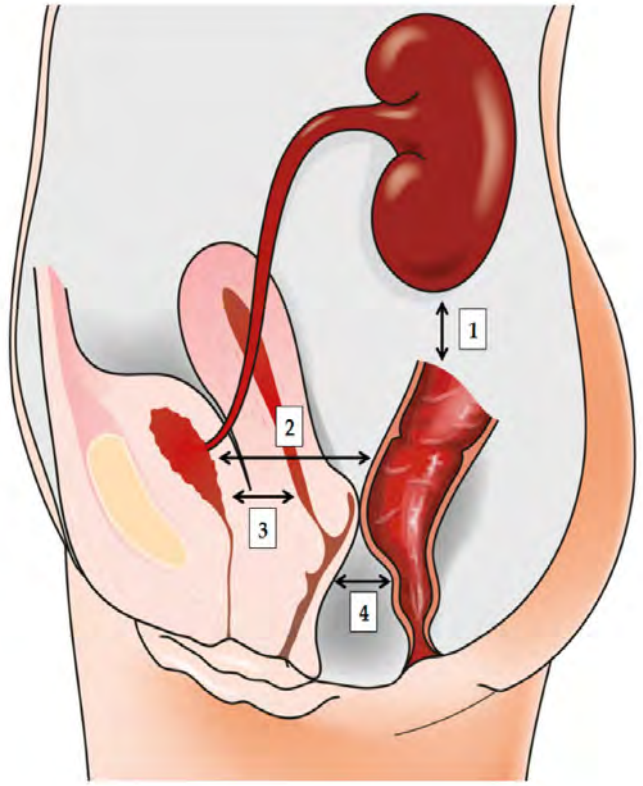
MDPI

Review

The Role of Gut, Vaginal, and Urinary Microbiome in Urinary Tract Infections: From Bench to Bedside

Tomislav Meštrović [1,2,†], Mario Matijašić [3,*,†], Mihaela Perić [3], Hana Čipčić Paljetak [3], Anja Barešić [4] and Donatella Verbanac [5]

- 腸子的細菌的確會跑到陰道 泌尿道
- the uterine peristaltic pump that aids in sperm transport from the cervical canal to the endometrium might also play a role in seeding the endometrium with bacteria.



European Journal of Obstetrics & Gynecology and Reproductive Biology 163 (2012) 210–215

Contents lists available at SciVerse ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Studies on the effects of probiotic *Lactobacillus* mixture given orally on vaginal and rectal colonization and on parameters of vaginal health in women with intermediate vaginal flora

Magdalena Strus [a], Agnieszka Chmielarczyk [a], Piotr Kochan [a], Paweł Adamski [b], Zbigniew Chełmicki [c], Artur Chełmicki [c], Andrzej Pałucha [d], Piotr B. Heczko [a,*]

Table 3

Presence of the applied *Lactobacillus* strains in the studied women.

Visit	No. of women with vaginal colonization by at least one species from applied mixture/visit	No. of women with rectal colonization by at least one species from applied mixture/visit
I	0/25	0/25
II	0/25	0/25
III (day 10)	2/25	4/25
IV (day 20)	6/25	8/25
V (day 31)	15/25	17/25
VI (day 50)	9/25	11/25
VII (day 62)	13/25	11/25
VIII (day 70)	5/25	3/25

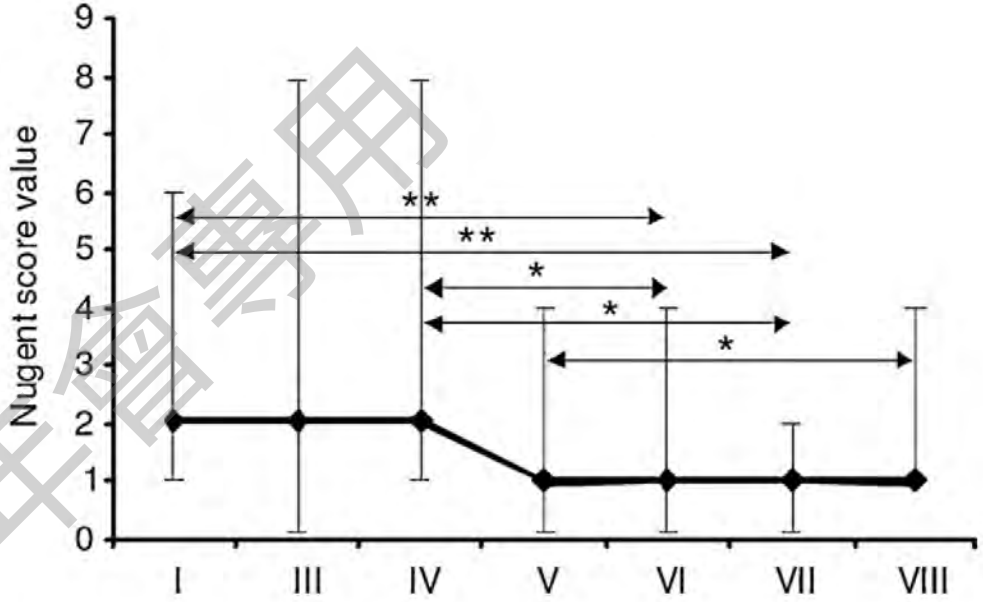
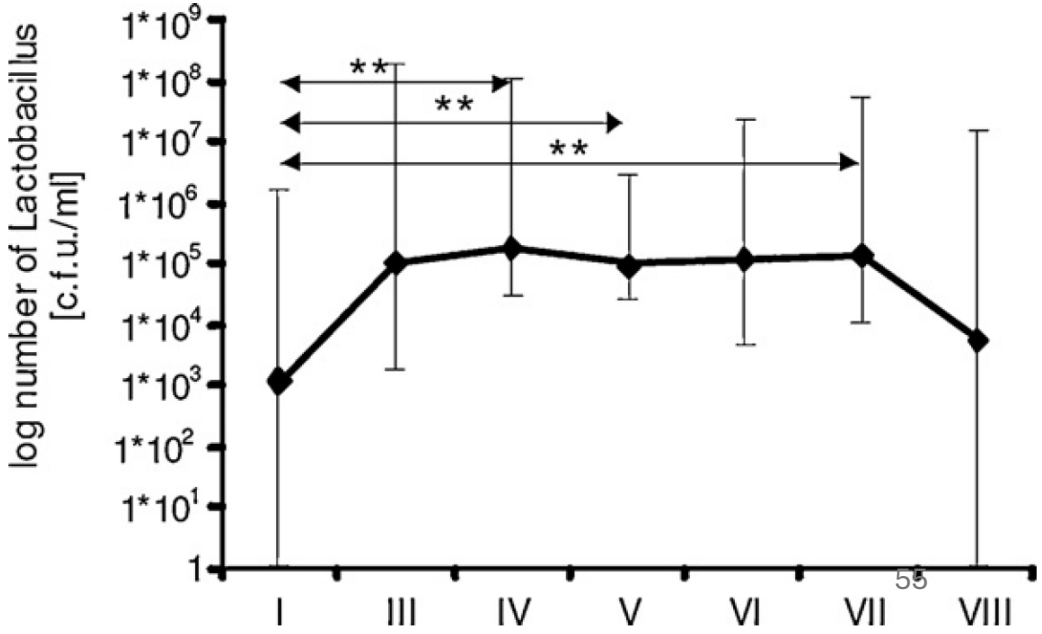


Fig. 4. Effect of oral application of the *Lactobacillus* mixture on Nugent score values during consecutive visits. Symbols in the chart the same as in Fig. 3.



Contents lists available at SciVerse ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Studies on the effects of probiotic *Lactobacillus* mixture given orally on vaginal and rectal colonization and on parameters of vaginal health in women with intermediate vaginal flora

Magdalena Strus [a], Agnieszka Chmielarczyk [a], Piotr Kochan [a], Paweł Adamski [b], Zbigniew Chełmicki [c], Artur Chełmicki [c], Andrzej Pałucha [d], Piotr B. Heczko [a,*]

Colonization of the Rectum by *Lactobacillus* Species and Decreased Risk of Bacterial Vaginosis

May A. D. Antonio,[1] Lorna K. Rabe,[1] and Sharon L. Hillier[1,2]

[1]Magee-Womens Research Institute, and [2]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania

Lactobacillus Rectal Colonization and BV • JID 2005:192 (1 August)

- Lactobacilli colonizing the rectum may be a reservoir for vaginal lactobacilli.
- Lactobacillus crispatus (16%), L. jensenii (10%), and L. gasseri (10%) were the prevalent lactobacilli colonizing the rectums of 290 females.
- Cocolonization of the vagina and rectum by H2O2-producing lactobacilli was associated with the lowest prevalence of BV (5%), whereas females colonized only vaginally, only rectally, or at neither site had a successively increased risk of BV (P<.001).

Table 4. Prevalence of bacterial vaginosis (BV) among females with vaginal vs. rectal colonization by facultative H_2O_2-producing lactobacilli.

Site(s) positive for H_2O_2-producing lactobacilli	Females with BV present, no. (%)	RR (95% CI)[a]
Vagina and rectum ($n = 198$)	9 (5)	Referent
Vagina alone ($n = 126$)	25 (20)	4.4 (2.1–9.0)
Rectum alone ($n = 32$)	15 (47)	10.3 (4.9–21.6)
Neither vagina nor rectum ($n = 175$)	123 (70)	15.5 (8.1–29.5)

NOTE. RR, relative risk; CI, confidence interval.

[a] $P < .001$, Fisher's exact test for each comparison with the referent group.

Journal of Clinical Medicine

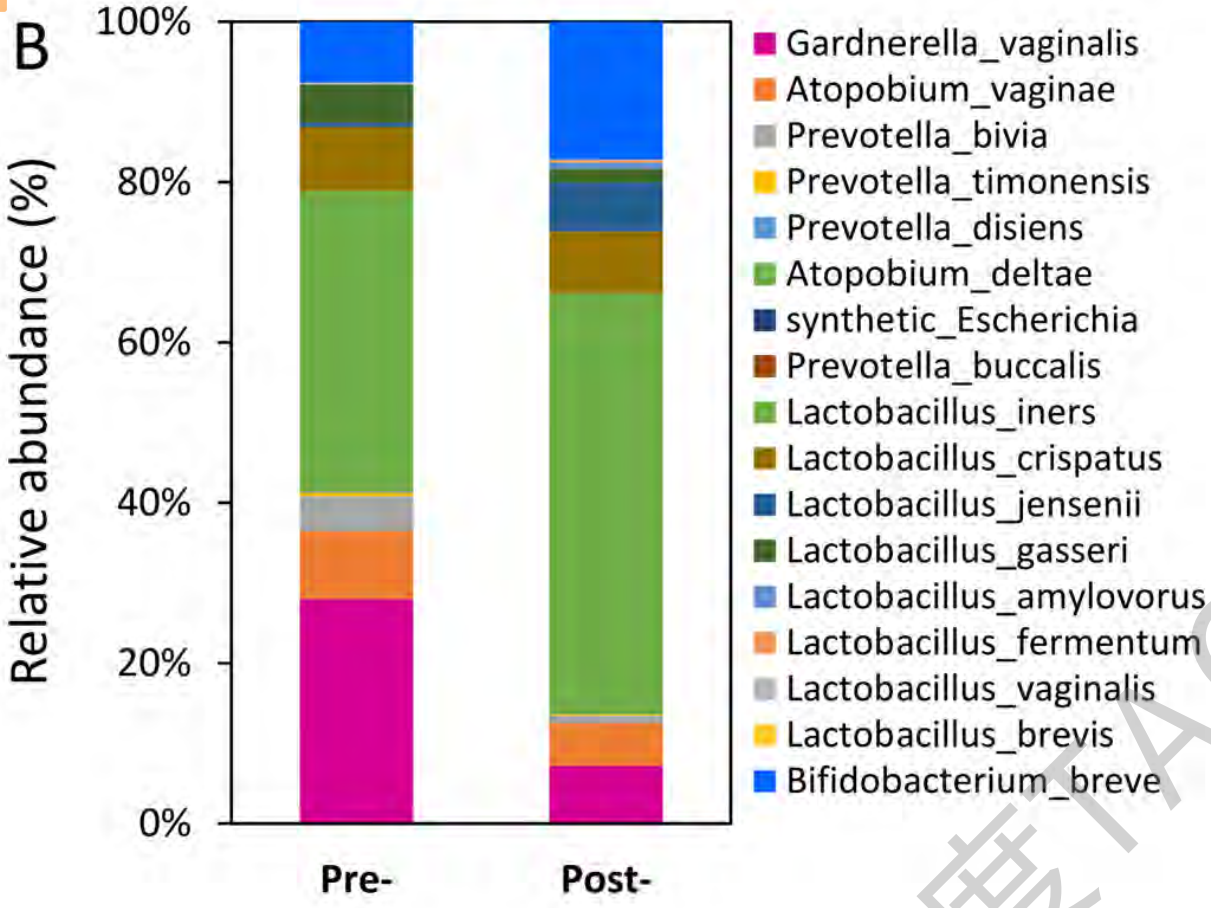
MDPI

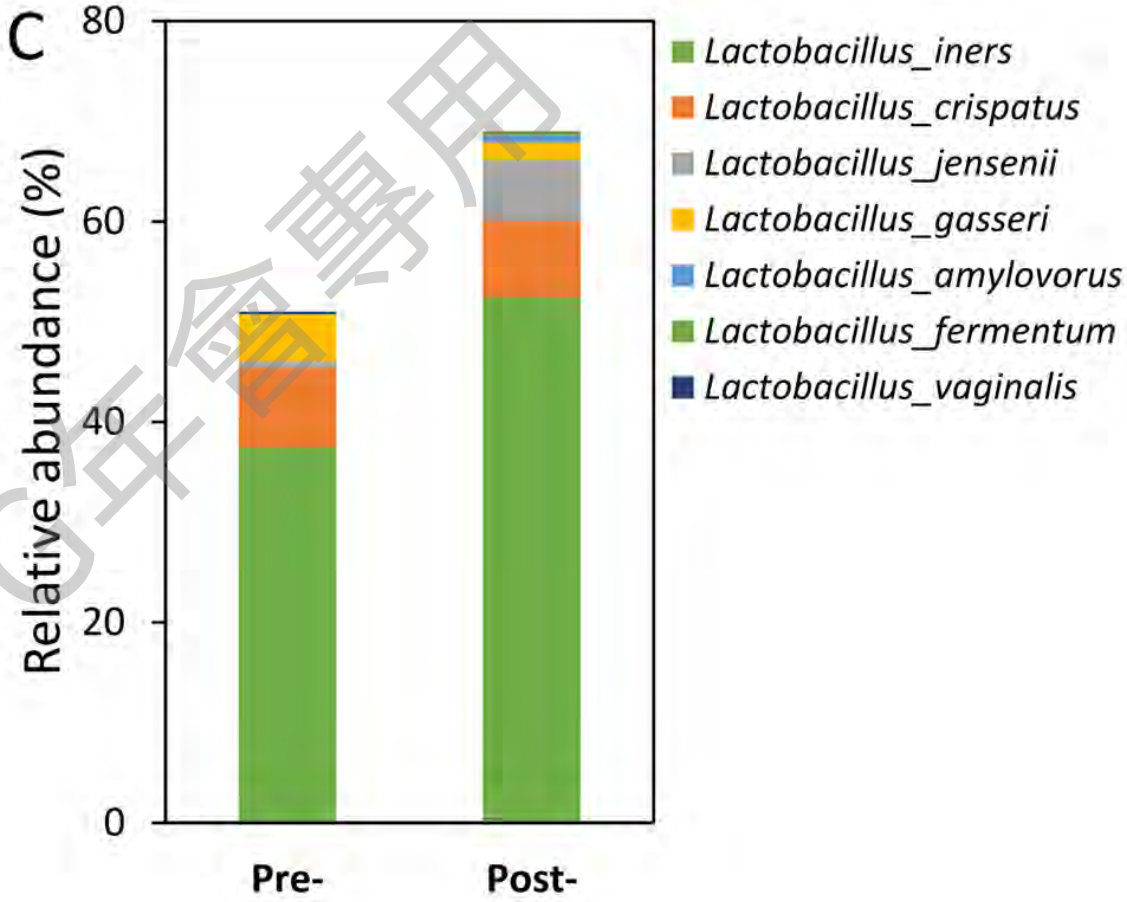
Article

Pilot Study on Next-Generation Sequencing Analysis of Vaginal Microbiota in Clinically Infertile Patients Treated with Probiotics

Li-Te Lin [1,2,3], Chia-Jung Li [1,2], Chia-Chun Wu [1], Li-Fei Pan [4,5] and Kuan-Hao Tsui [1,2,3,6,7,*]

- 30 women, averaging 37 y/o, who were scheduled to undergo ART, pre- and post- probiotics treatment for about 8 weeks.
- 16S ribosomal RNA (rRNA) sequencing
- There was a decrease in Gardnerella abundance by approximately 20%, and increases in Lactobacillus and Bifidobacterium by 10% and 15%, respectively.





Gardnerella levels showed a significant decrease from 28% to 7.2%,

Lactobacillus iners increased from 37.5% to 52.5%,

子宮內膜菌叢檢測計畫

May 2023 ~ April 2024

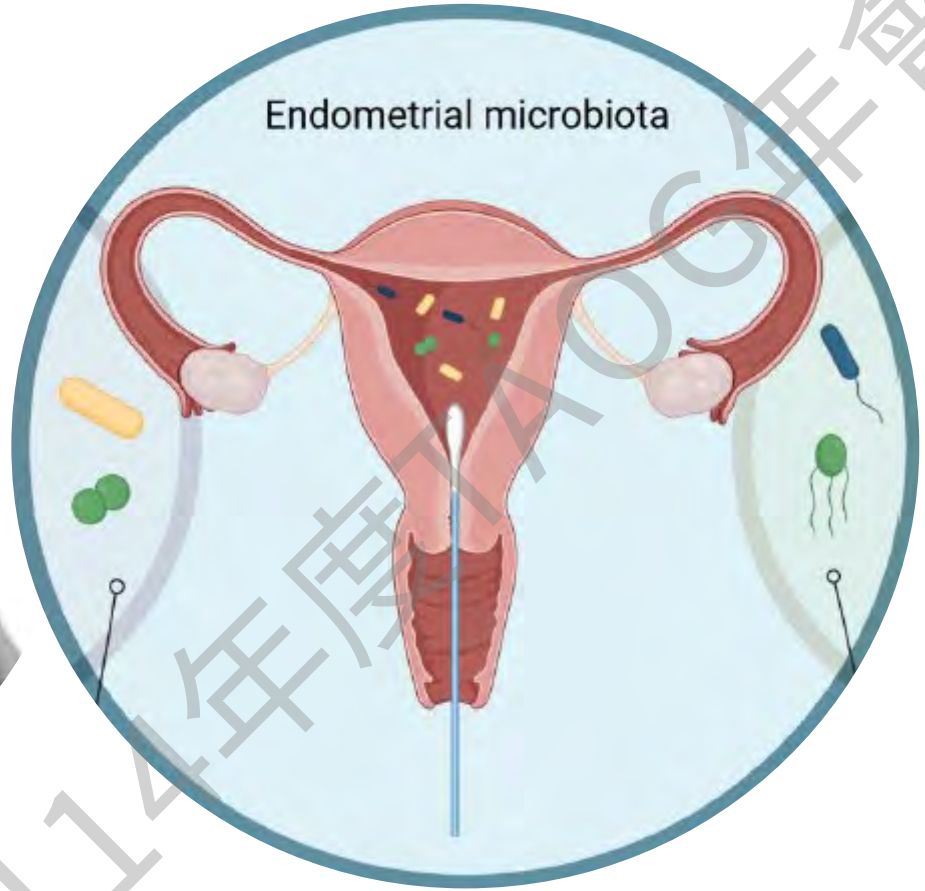
高雄長庚婦產部

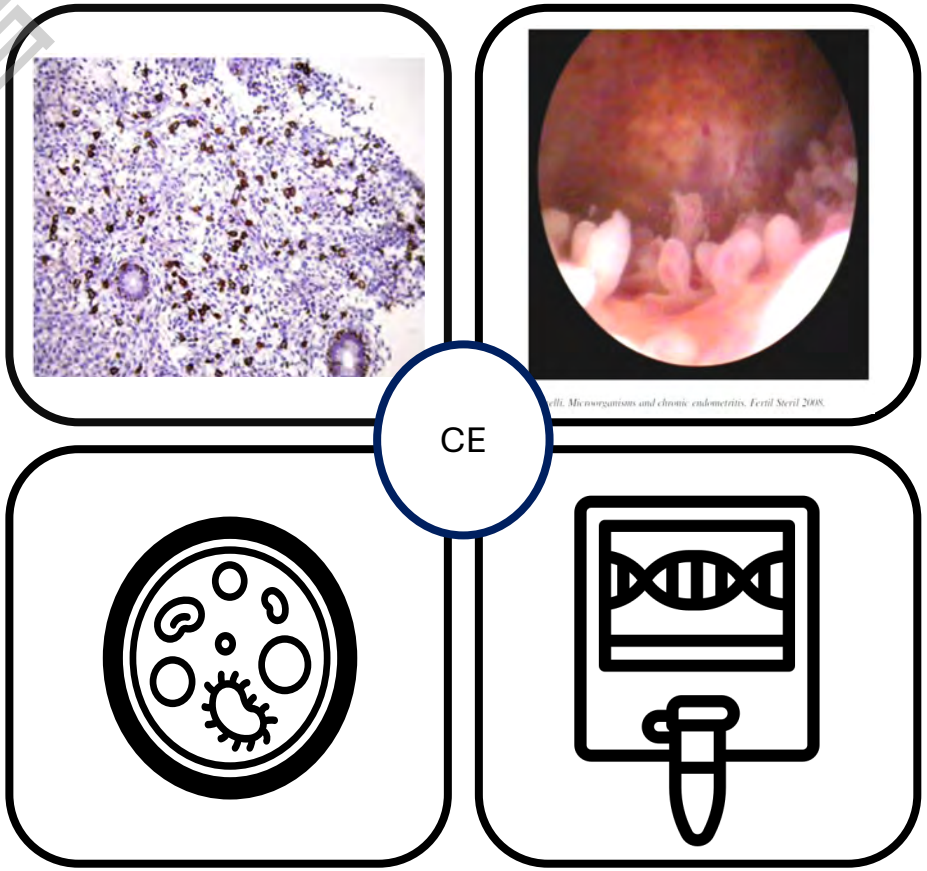
高雄長庚檢驗醫學部

合作案

Women undergoing infertility survey, indication for hysteroscopy exam.

- Hysteroscopy
- EM sampling, for histology, culture, and 16s rRNA sequencing.





The endometrial microbiota and early pregnancy loss. Human Reproduction. 2024;39(4):638-46.

Results-1 Endometrial culture

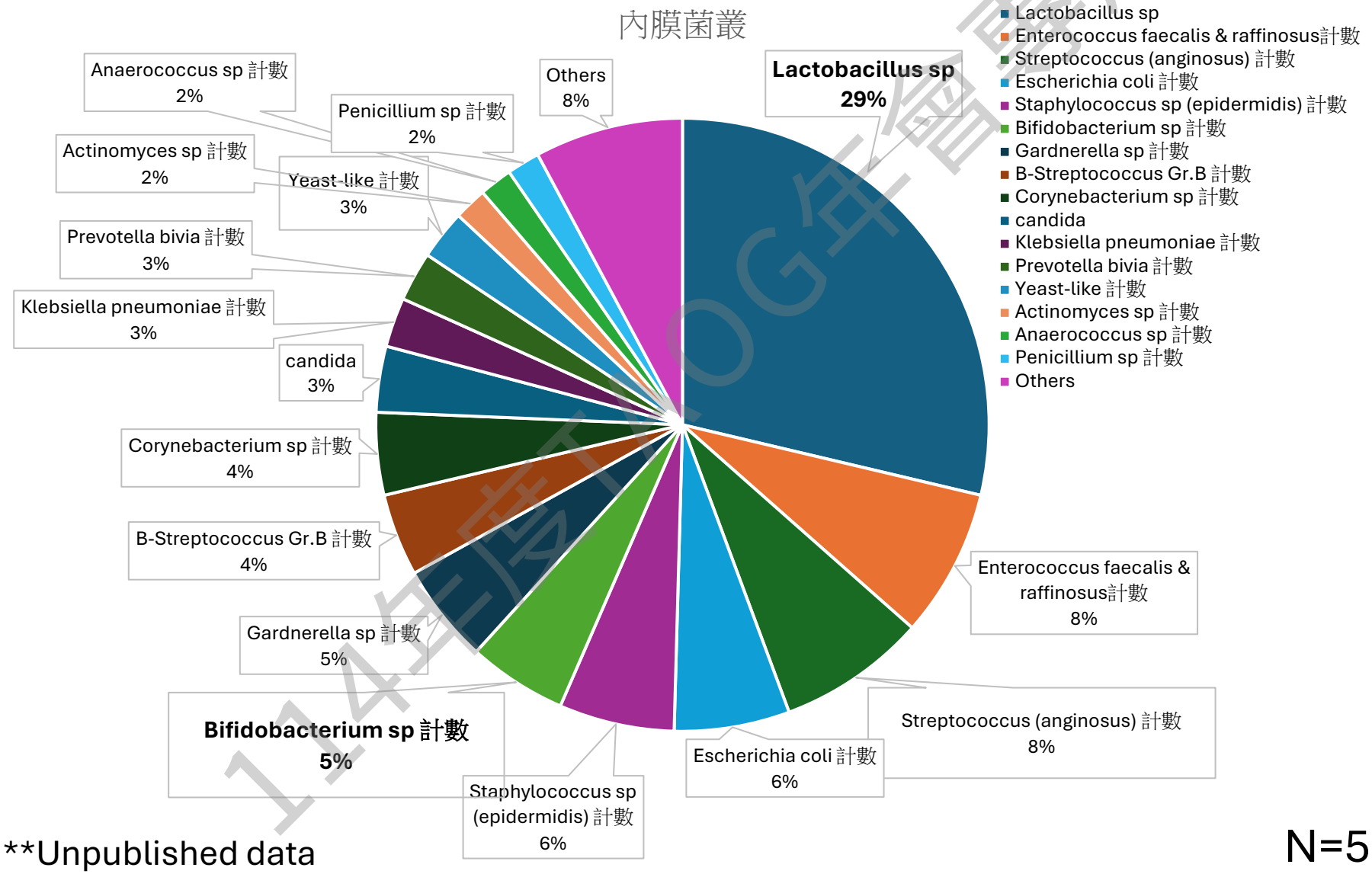
- Positive culture rate: 58/89=65.2%
  - Negative Culture: 31/89
- Positive pathogen: 34/89=38.2%
- Positive Lactobacillus sp: 24/89=27.0%
  - 18/24 from aerobic culture
- Most of them (21/34) were multiflora instead of single pathogens.

Result-1 內膜菌叢培養排名

1	Lactobacillus sp 29%
2	Enterococcus faecalis & raffinosus
3	Streptococcus (anginosus)
4	Escherichia coli
5	Staphylococcus sp (epidermidis) 6%
6	Bifidobacterium sp
7	Gardnerella sp

From bacterial culture
**Unpublished data

Result-1 內膜菌叢分布



**Unpublished data

N=58

Endocervix culture

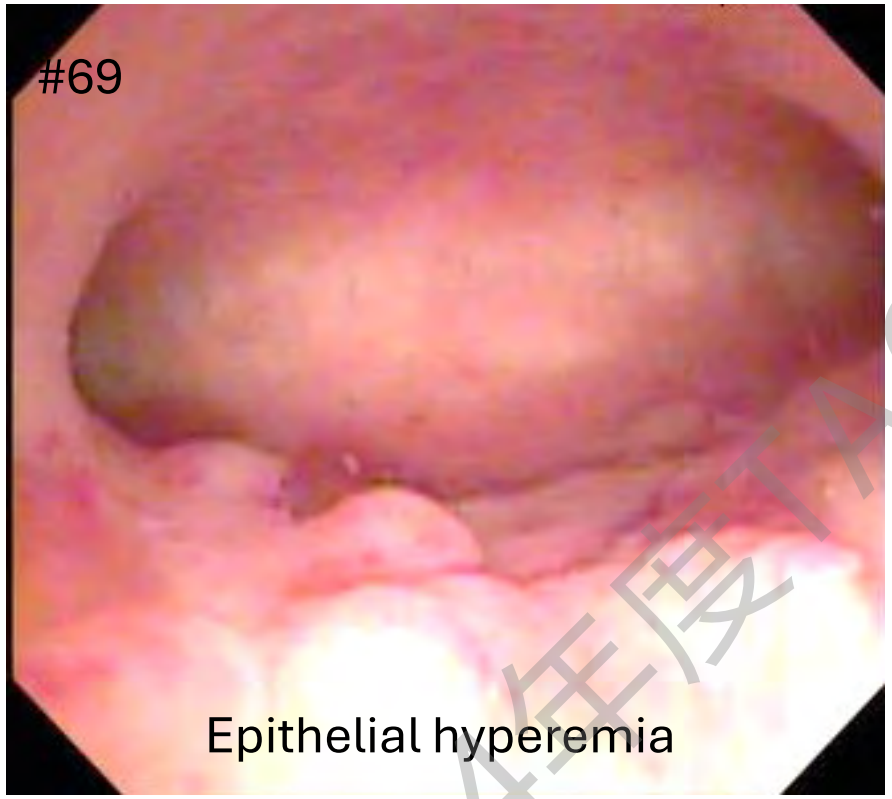
- Positive culture rate: 30+8/89= 42.7%
- Positive Lactobacillus sp: 8/89

- Endocervical swabs and EM culture had a concordance rate of 76.4% (68/89).

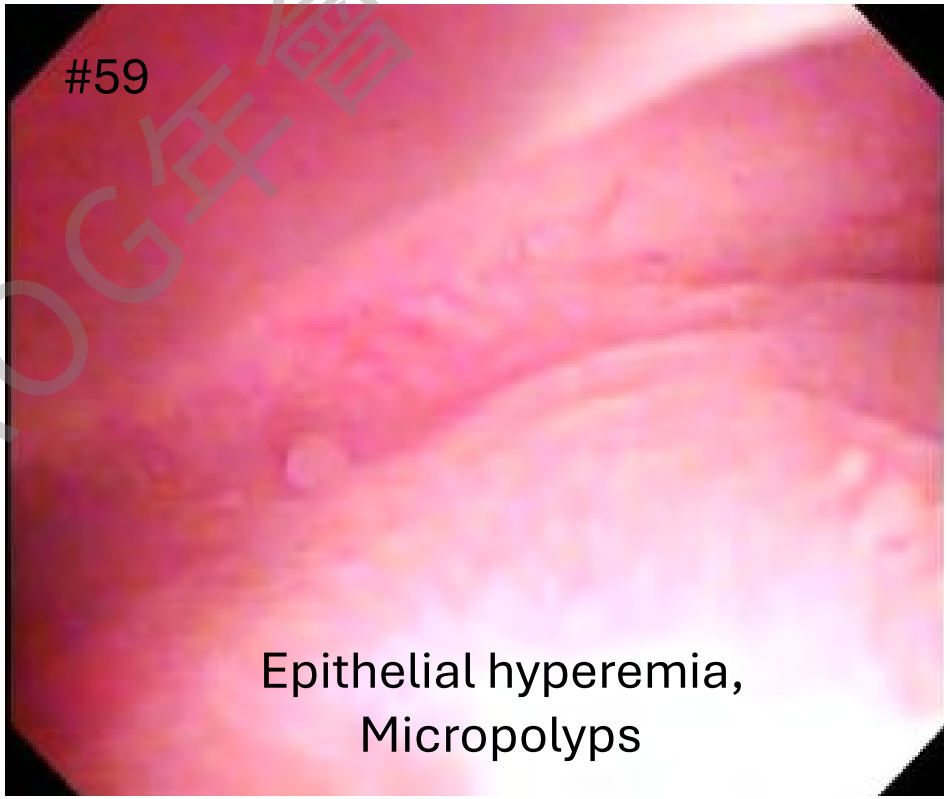
子宮鏡診斷CE

**Unpublished data

- Positive rate: 31.1 %
  - Most positive finding:
  - Hyperemia 21/28



Culture: Bifidobacterium sp.
Histology (CD138): negative



Culture: Enterococcus Faecalis
Histology (CD138): negative

Lactobacillus sp. 探討(1)

- Belong to the Firmicutes Phylum(門), Lactobacillus Genus(屬).
- Lactobacillus is an anaerobic 厭氧菌, Gram(+), rod-shaped bacteria.
  - **oxygen-tolerant anaerobes**
- Normal **vaginal** microbiota
  - They contribute to the acidic environment of the vagina by producing lactic acid, which inhibits the growth of pathogenic bacteria.
- Account for 29% of cultured EM. (與文獻不謀而合)

TABLE 1 PATIENT CHARACTERISTICS AND CLINICAL PARAMETERS

Variables	Normal Endometrium Culture (n=55)	Pathologic Endometrium Culture (n=34)	P-value
Female age, years	36.6 ± 3.5	36.8 ± 4.1	0.76
Body mass index, kg/m^2	23.1 ± 3.6	22.3 ± 3.3	0.35
Number of para, n	0.2 ± 0.4	0.2 ± 0.5	0.57
Number of abortion history, n	0.8 ± 1.0	0.9 ± 1.0	0.69
AMH, ng/ml	2.9 ± 2.3	3.9 ± 3.4	0.12
Endometriosis, %	34.6%	26.7%	0.46
Recurrent miscarriage, %	23.6%	26.5%	0.76
ET failure times, n	**1.0 ± 1.3**	**1.8 ± 1.5**	**<0.01***
RIF, %	**30.9%**	**52.9%**	**0.04***
Hysteroscopy positive CE findings, n (%)	16 (29.1%)	11 (32.4%)	0.75

Unless otherwise stated, all data are presented as mean± SD or n (%). **Unpublished data

TABLE 1 PATIENT CHARACTERISTICS AND CLINICAL PARAMETERS

Variables	Normal Endometrium Culture (n=55)	Pathologic Endometrium Culture (n=34)	P-value
ET failure times, n	1.0 ± 1.3	1.8 ± 1.5	<0.01*
RIF, %	30.9%	52.9%	0.04*
Hysteroscopy positive CE findings, n (%)	16 (29.1%)	11 (32.4%)	0.75

Unless otherwise stated, all data are presented as mean± SD or n (%).

**Unpublished data

TABLE 2 IHC stain results

Variables	Normal Endometrium Culture (n=55)	Pathologic Endometrium Culture (n=34)	P-value
CD138 numbers/ 10 HPF	1.1 ± 1.6	1.0 ± 1.3	0.79
CD138 numbers/ HPF	1.2 ± 1.7	0.6 ± 1.1	0.08

**Unpublished data

NGS實驗結果比對

姓名	EM		NGS (EM) 阿拉伯數字代表NGS排名
	Aerobic culture	Anaerobic culture	
鍾OO	Enterococcus faecalis B-Streptococcus Gr.B Corynebacterium glucuronolyticum Lactobacillus crispatus	Aerobes(+), Anaerobe no Growth to date	1.Gardnerella leopoldii 2.Lactobacillus crispatus 3.Gardnerella vaginalis 5.Fannyhessea vaginae 11.Lactobacillus iners
林OO	Escherichia coli Enterococcus faecalis Streptococcus mitis Klebsiella pneumoniae Gemella haemolysans	Actinomyces neuii	1.Streptococcus mitis 2.Streptococcus pneumoniae 3.Lancefieldella rimae 4.Escherichia coli 5.Prevotella bivia 9. Gemella haemolysans

Conclusion

- The most accurate diagnosis of this study: Culture
  - 傳統的細菌培養 目前還是最準
- The interobserver variations of hysteroscopy
  - 子宮鏡診斷標準可能不夠客觀，且因人而異
  - 可能不適合用子宮鏡追蹤治療成效
- The poor AUC of CD138
  - 染IHC來診斷CE,在此試驗中不準

Take home message

- Lactobacillus is the signature genus along the female reproductive tract.
- Chronic endometritis can be diagnosed with conventional culture. Treatment can be based on antibiogram.
- Further studies could explore the additional effects of 16S rRNA sequencing and microbiome supplements.

感謝指教

高雄長庚 蔡妮瑾 醫師 TSAI Ni-Chin, MD. Email: ninytsai@cgmh.org.tw