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新冠肺炎對人類生殖系統的影響
The influence of COVID-19 on human infertility

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The COVID-19 pandemic is an extraordinary global situation, and all countries have adopted their own strategies to diminish and eliminate the spread of the virus. All measures are in line with the recommendations provided by the World Health Organization. Taiwan was a special place and we had relative fewer COVID-19 cases attributed to a strict border control. However, the entrance of COVID-19 might be inevitable someday due to the global pandemic situation. We had to be well-repared for the day to coexist with the virus.

The influence of COVID-19 on human infertility was an important issue whorldwide. Scientific societies, such as the ESHRE and ASRM, have provided recommendations and guidance to overcome and flatten the growing curve of infection in patients who undergo IVF treatments. Although there is as yet no evidence that the virus causing COVID-19 might have negative effects on IVF outcomes, fertility treatments have been postponed and international IVF patients were prohibited since the global pandemic. This March 1st, Taiwan govement finally allowed the foreigners applying to Taiwan for an IVF treatment and patients with previous COVID-19 infection history might enter Taiwan for help.

Coronavirus binding to cells involves the S1 domain of the spike protein to receptors present in reproductive tissues, including angiotensin-converting enzyme-2 (ACE2), CD26, Ezrin, and cyclophilins. Men showed higher vulnerability to COVID-19 and presented with depleted testosterone levels, which possibly result in compromised male reproductive health. Reports also indicated decreased sperm concentration and motility for 72– 90 days following COVID-19 infection. Besideds, gonadotropin-dependent expression of ACE2 was found in human ovaries, but it is still unclear whether COVID-19 adversely affects female gametogenesis. Although data are limited, and incomplete at this time, there is justifiable concern that negative reproductive consequences of the novel coronavirus may have lasting effects for human fertility.

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Physical and psychologic comorbidity of endometriosis

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子宮內膜異位症為一慢性發炎性疾病，對婦女長期的身心狀態有著深遠的影響。子宮內膜異位症造成婦女身體或心理合併症(comorbidity)的原因包括下列四項：(1)Altered milieu：子宮內膜異位症引起的慢性發炎可能導致體內免疫和荷爾蒙等微環境的改變而造成影響；(2) Shared risk factors：子宮內膜異位症和合併症有共同的危險因子，如基因、環境因子等；(3)Clinical presentations：疼痛和不孕為子宮內膜異位症之兩大臨床表現，其中疼痛會對婦女心理層面帶來巨大的負面影響；(4)Treatment-related comorbidity：因子宮內膜異位症之治療(藥物或手術)而延伸的問題。今天，針對子宮內膜異位症引起的身體合併症和心理合併症，各有四個面向提出向大家報告。

子宮內膜異位症導致的身體合併症主要包括下列四個面向：(1)癌症：目前最明確的證據是子宮內膜異位症會增加卵巢癌(clear cell&endometrioid type)的風險，至於是否增加子宮內膜癌和乳癌之風險，仍有爭議，其他癌症則尚需更多研究；此外，子宮肌腺症可能增加子宮內膜癌的風險，不過，併有子宮肌腺症之子宮內膜癌患者，其預後較佳。(2)心血管疾病：子宮內膜異位症之慢性發炎和高凝血狀態會破壞血管內皮，導致動脈粥狀硬化(atherosclerosis)，進而增加心血管疾病之風險。(3)免疫相關疾病：子宮內膜異位症和自體免疫疾病共有異常的基因表現、免疫環境和自體抗體，目前研究顯示，子宮內膜異位症可能會增加全身性紅斑性狼瘡(Systemic lupus erythematosus, SLE)、類風濕性關節炎(Rheumatoid arthritis, RA)、修格蘭氏症候(Sjogren's syndrome)、多發性硬化症(Multiple sclerosis, MS)、發炎性腸道疾病(Inflammatory bowel disease, IBD)等自體免疫性疾病的風險；此外，也可能會增加過敏性疾病及氣喘的風險，不過，皆需更多的研究佐證。(4)其他疾病：子宮內膜異位症可能增加大腸激躁症(Irritable bowel syndrome, IBS)、纖維肌痛症(Fibromyalgia)、間質性膀胱炎(Interstitial cystitis, IC)或膀胱疼痛症候群(Bladder pain syndrome)等疾病之風險。

子宮內膜異位症導致的心理合併症主要包括下列四個面向：(1)生活品質；(2)心理健康(如憂鬱和焦慮)；(3)社會功能(如工作生產力和日常活動能力)；(4)性生活。子宮內膜異位症對這四個面向皆造成負面影響的主要原因為疼痛，疼痛愈嚴重，負面影響愈大；除了疼痛外，睡眠障礙、慢性疲勞、憂鬱和焦慮等亦會加重此負面影響；此外，人格特質、家庭計畫、親友支持及身體共病等都是可能的影響因子，而這些因子彼此也會交互影響。子宮內膜異位症之治療，尤其是手術治療，能改善生活品質、減少憂鬱和焦慮、增加工作生產力和日常活動能力及改善性生活。

子宮內膜異位症造成婦女身體或心理的合併症，對其生命歷程(life course)會產生很大的衝擊，可能影響學校課業、職業生涯、家庭計畫、夫妻關係、人際關係、社會生活、心理健康及生活品質等。醫師的角色在於早期診斷、有效治療及長期照護，來降低子宮內膜異位症身體或心理的合併症對生命歷程的衝擊。

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Recurrent Implantation Failure: Controversy over Definition, Diagnosis, and Treatment Efficacy

反覆著床失敗：定義、診斷與治療的爭議

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反覆著床失敗是試管嬰兒治療的未解之題，首先對於定義就有諸多不同討論，除了傳統上以植入失敗的胚胎數量或次數加以定義外，近期在預測模型盛行的推波助瀾下也有了一些動態的定義，值得參考。

造成反覆著床失敗的原因目前也有諸多未知，文獻中目前持續探討的可能造成反覆著床失敗的相關原由包括：精蟲因子、卵子因素、子宮及其附屬器因素、免疫及易栓因素、內分泌因素等。這些診斷面相及其所對應的治療，是否能避免著床失敗的發生仍有爭議，在與個案的諮詢上需注意檢查的適切性。

在治療方面，近年加拿大及英國的生殖醫學會陸續推出了對於反覆著床失敗的治療建議，值得我們參考。一些被視為試管嬰兒的附加治療(Add-ons)的做法，包括：胚胎著床前染色體篩查(PGT-A)、內膜容受性檢測、免疫療法等等，雖然尚未有定論，也不建議廣泛使用於所有反覆著床失敗個案，但相關的研究及未來的發展性，是本次討論的重點。

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Revisiting add-ons for assisted reproductive technology

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Since the birth of Louis Brown in 1978, millions of children have been born following IVF, and assisted reproductive technology has become a rapidly evolving field. Despite our best efforts, IVF live birth rate is limited. While the basic steps of the IVF process are typically rather uniform, patients who are undergoing IVF are highly motivated to achieve a higher successful pregnancy, consequently new technologies are constantly developed with the intent to improve treatment outcomes. Therefore, IVF add-ons have emerged as optional extras which usually aim to increase the chance of IVF success.

What are treatment add-ons?

-optional additional treatments, also referred to as ‘supplementary’, ‘adjuvants’ or ‘embryology treatments’.

-Often claim to be effective at improving the chances of live birth rate but the evidence to support this for most fertility patients is usually missing or not very reliable.

-Likely to involve an additional cost on top of the cost of a routine cycle of proven fertility treatment.

While there is a plethora of currently available IVF add-ons, most offer rather limited convincing evidence of clinical efectiveness, and they often increase the fnancial burden of fertility care. Some existing add-ons will be perfected and become an integral part of routine practice, while others will be phased out entirely as their utility is questionable. In the meantime, both laboratories and clinical practices should take a critical eye to the add-on treatments they have incorporated to assess if they are producing true benefit to patients and are therefore justifiable interventions.

Here we attempt to provide an overview of the evidence, potential benefits and risks associated with several common IVF add-ons, and discuss future directions for managing add-ons in assisted reproductive technology.

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Epigenetics in assisted reproductive technology: how much the evidence?

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Perinatal outcomes and life-long health of the offspring.

More than 8 million individuals have been conceived by Assisted Reproductive Technologies (ART) and there is clear evidence that ART is associated with a range of adverse short term health outcomes, including rare imprinting disorders. Despite of contradictive data, accumulating evidences also linked ART with potentially increased risks of neurodevelopmental disorders, cardiovascular dysfunction and metabolic abnormity in offspring. A major challenge for research into these adverse outcomes is the difficulty in separating the contribution of infertility *per se* from the ART treatment. Pregnancies resulting from ART are generally associated with adverse obstetric and perinatal outcomes when compared to spontaneously conceived pregnancies mainly related to the higher rate of multiple gestations. Although the decline in multiple birth rates resulting from adoption single embryo transfer has considerably reduced perinatal risks for ART children, singletons born after ART still carry a 2- to 3-fold increased risk of adverse perinatal outcomes, which in turn increase the odds of life-long health problems.

Both fertility status and fertility treatment are associated with epigenetic alterations.

Epigenetic modifications are heritable alterations that do not result from changes in the DNA sequence. They are affected by the genetic variability and environmental
influences in disease. These noncoding mechanisms of gene regulation include DNA methylation and noncoding regulatory elements. They alter DNA accessibility and chromatin structure, thereby regulating patterns of gene expression. The noncoding transcriptome, which includes long noncoding RNAs and miRNAs, also affects overall gene expression. Changes in the levels of DNA methylation, histone modifications and changes in non-coding RNA (ncRNA) function are common
in various non-communicable diseases, including male and female infertility.

The periconception period and early embryogenesis are associated with widespread epigenetic remodeling of gametes and early embryos, which can be influenced by ART, with effects on the pregnancy course as well as developmental trajectory in utero, and

potentially on health throughout life. ART-related epigenetic alterations is a "chicken or egg" issue given epigenetic defects in gametes also have been documented in infertile men and women. There epigenetic defects can be transmitted to the offspring via gametes.

Summary

1.Epigenetic defects in gametes also have been documented in infertile men and women. However, there does not seem to have recurrent patterns of epimutations.

2.Fertility treatment is associated with increased incidence of rare imprinting disorders. Whether

3.The rates of epigenetic defects in gametes, early embryos, and placenta are increased by various modes of fertility treatment, including superovulation, ICSI, and *in vitro* culture of embryos. However, most evidence came from animals. Whether findings of animal experiments could be translated to humans is still an open question.

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Vaginal Microbiome in Reproductive Health

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The human vaginal microbiome is an important determinant of female reproductive health, which is a dynamic ecosystem composed of more than 200 microbial species. Although the vaginal microbiome can vary considerably between individuals and over time. Accumulated pieces of evidence have well documented that the vaginal communities are often dominated by *Lactobacillus species* in the majority of healthy reproductive age women, which is also composed of a mixed group of facultative and obligate anaerobes.

Many epidemiological and clinical studies have carried out that vaginal dysbiosis is associated with obesity, congenital diseases, gynaecological cancers, and even female infertility. However, due to the limitations of technology in the past, there are very few studies to determine the causative relationships between the vaginal microbiota and these diseases. Since recent decades have seen a dramatically accelerating pace in the development of new sequencing technologies, which have revolutionized our understanding of microbial communities.

Here, we summarize the current understanding of the vaginal microbiome and its connection with host reproductive health. We also discuss the state-of-art for investigating the human microbial communities, providing an overview of the main approaches including targeted and shotgun metagenomics and metatranscriptomics, together with an outlook on the major challenges and perspectives over the use of these technologies for vaginal microbial studies.