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Prolactin and Reproduction

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Traditionally, hyperprolactinemia is linked to amenorrhea and infertility. Newer research suggests prolactin plays roles in normal reproduction, influencing oocyte competence, corpus luteum function, endometrial receptivity, blastocyst implantation, and sperm survival. In addition, prolactin plays dual roles as a hormone and cytokine, influencing immune modulation. It primarily affects the negative selection of autoreactive B cells, which is crucial in preventing autoimmune responses. Hyperprolactinemia—elevated PRL levels—has been linked to the development and exacerbation of autoimmune diseases. Dopamine inhibits PRL secretion by acting directly on the pituitary gland or indirectly through hypothalamic pathways. Dopamine agonists, which suppress PRL levels, have shown potential clinical benefits for autoimmune conditions, making them a promising therapeutic avenue.

During ovarian hyperstimulation in IVF, transient hyperprolactinemia is a phenomenon that has been reported. However, the timing of its occurrence remains inconsistent across various studies. This raises an important question: should transient hyperprolactinemia be treated to increase IVF pregnancy rates? Further investigation into this matter is warranted to clarify its clinical significance. Another question to consider is whether hyperprolactinemia should be continuously treated after pregnancy is achieved. Furthermore, it is crucial to investigate whether hyperprolactinemia increases the risk of miscarriage. These issues warrant further research to determine the appropriate management strategies for hyperprolactinemia in pregnancy and its potential impact on pregnancy outcomes. Elevated prolactin levels during breastfeeding disrupt the hypothalamic-pituitary-ovarian (HPO) axis, affecting ovulatory and menstrual cycles. Despite the presence of prolactin receptors in the endometrium, the effects of increased prolactin levels during breastfeeding on endometrial receptivity remain unclear. We are also wondering whether the interval between breastfeeding cessation and the initiation of a frozen embryo transfer (FET) cycle correlates with pregnancy outcomes. Clarifying this relationship may offer valuable insights into determining the optimal timing for treatment.

Prolactin (PRL), a hormone primarily known for its role in lactation, also plays a critical role in reproduction. Its functions extend beyond the postpartum period and are integral to various stages of reproductive processes.

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The Role of Prostaglandins in Follicular Maturation and the Impact of NSAIDs

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Indomethacin, a widely used non-steroidal anti-inflammatory drug (NSAID), is commonly prescribed for its anti-inflammatory, analgesic, and antipyretic properties. Its primary mechanism involves the inhibition of cyclooxygenase (COX) enzymes, leading to decreased prostaglandin synthesis. A retrospective study analyzed data from 121 patients undergoing 255 treatment cycles, including 171 cycles without Indomethacin and 84 cycles where patients received 50 mg Indomethacin three times daily until one day before oocyte retrieval. Results showed that the proportion of cycles without oocyte retrieval cancellation was 76% in the Indomethacin group, compared to 64% in the non-Indomethacin group. Moreover, the incidence of premature ovulation was significantly lower in the Indomethacin group (6%) compared to the non-Indomethacin group (16%). These findings suggest that Indomethacin may reduce premature ovulation, enhancing the success rate of oocyte retrieval procedures.

However, prostaglandins, derived from the cyclooxygenase (COX) pathway, are pivotal in reproductive processes, including follicular maturation, ovulation, and luteinization. Recent evidence has highlighted their regulatory role in granulosa cell proliferation and the cumulus-oocyte complex' s ability to undergo essential developmental changes. Transforming growth factor β 3 (TGFβ 3), identified in human follicular fluid, has been shown to modulate COX-2 expression, enhancing prostaglandin synthesis and promoting oocyte maturation. Elevated TGFβ 3 levels positively correlate with oocyte maturity in both in vivo and in vitro fertilization settings, emphasizing its biological importance.

Complementary animal studies reinforce this concept, as NSAIDs like naproxen and indomethacin, which inhibit COX enzymes, have demonstrated significant disruptions in follicular progression. Naproxen administration in murine models, for example, reduced the size of antral follicles, granulosa cell proliferation, and overall oocyte viability. These findings suggest that NSAIDs may inadvertently hinder critical prostaglandin-mediated processes essential for follicular and oocyte development.

Retrospective analyses of clinical data have indicated that the use of NSAIDs such as Indomethacin may influence ovarian physiology by modulating prostaglandin levels. In ART settings, Indomethacin has been hypothesized to reduce the risk of premature ovulation and improve oocyte retrieval success rates by delaying follicular rupture. However, the impact of Indomethacin on oocyte maturity and embryo quality remains underexplored, necessitating further investigation.

Building on these insights, this study aims to evaluate the retrospective clinical impact of indomethacin administration on follicular maturation in human populations undergoing controlled ovarian hyperstimulation (COH) for assisted reproductive technologies (ART). By leveraging large-scale retrospective data, we seek to elucidate how variations in prostaglandin modulation influence follicular development, oocyte maturity, and overall reproductive outcomes. This research focuses on the potential of indomethacin to modulate prostaglandin-mediated pathways, thereby optimizing clinical strategies to enhance ART success rates while minimizing unintended reproductive effects.

Keywords: transforming growth factor; TXA2; cyclooxygenase; COX; IVF; oocyte maturation

Highlights

- Indomethacin reduces early ovulation by inhibiting prostaglandin synthesis, improving oocyte retrieval success rates during controlled ovarian hyperstimulation (COH).
- Prostaglandin modulation by NSAIDs impacts follicular maturation and oocyte quality, highlighting the delicate balance required for optimal ART outcomes.
- Retrospective analysis explores the clinical implications of indomethacin use in ART, aiming to optimize reproductive outcomes while minimizing unintended effects.

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Endometrium preparation in frozen embryo transfer: nature or artificial

近幾年來，因為冷凍保存技術的改良與進步，使得冷凍胚胎植入(frozen embryo transfer ,FET)比例迅速增長。研究指出冷凍胚胎植入比新鮮胚胎移植有相等或較高的活產率，也可以避免新鮮週期植入擔心的卵巢過度刺激症(Ovarian hyperstimulation sydrome)風險，與可能發生的新生兒低體重(low birth weight)、胎兒較小(small for gestational age)、早產的機率。

冷凍胚胎植入的內膜準備可分為自然周期-冷凍胚胎植入 nature cycle-FET (NC-FET) 及人工周期-冷凍胚胎植入 artificial cycle-FET (AC-FET):

- 自然周期-冷凍胚胎植入 (NC-FET)：對於月經規律的女性，利用患者內源性激素調控內膜成熟，需密切追蹤濾泡或抽血追蹤 LH 或 Progesterone，取消率也較高。
- 人工周期-冷凍胚胎植入 (AC-FET)：使用外源性激素（雌激素和黃體素）調節內膜，門診追蹤次數可以較少，植入時間較有彈性。外生性的雌激素會抑制濾泡的生成，不會有黃體生成，後續不會產生 relaxin，使得母體在早期懷孕時心血管的適應力較差，而可能因此增加妊娠高血壓的機會。

系統性回顧與統合分析發現 NC-FET 週期中的活產率比 AC-FET 週期高。AC-FET 可能會有較高 early pregnancy loss，而且會增加妊娠高血壓疾病和胎兒過大(Large gestational age,LGA)的風險。

我們開始思考，在冷凍胚胎植入時，如何內膜準備才是最佳方案，是否該反璞歸真，回歸自然?

Keywords: Endometrium preparation; frozen embryo transfer ; natural cycle (NC), stimulated cycle (SC), programmed cycle (PC), artificial cycle (AC)

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The Oocyte Cryopreservation: Medical vs. Social Reasons

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Oocyte cryopreservation (OC), once an experimental technique, has evolved into a cornerstone of reproductive medicine. The journey began in 1986 with the first successful birth from a frozen-thawed human oocyte, marking a breakthrough in fertility preservation. Social oocyte cryopreservation, however, emerged later, with the first documented case reported in the early 2000s as women sought to delay childbearing for personal or professional reasons. This dual application—medical and social—has fueled the widespread adoption of OC, though with varying acceptance and outcomes globally.

Medical Oocyte Cryopreservation primarily serves individuals at risk of losing fertility due to medical conditions such as cancer, autoimmune disorders, or genetic predispositions like premature ovarian failure. These patients often face urgent timelines for ovarian stimulation and egg retrieval before undergoing gonadotoxic treatments. In contrast, Social Oocyte Cryopreservation is an elective procedure undertaken by healthy women who wish to defer childbearing for reasons such as career advancement, education, or the absence of a suitable partner.

While the fundamental principles of oocyte freezing are consistent across both groups, variations in ovarian stimulation protocols and outcomes have been observed. Medical patients, particularly those with diminished ovarian reserve or under the stress of impending medical treatments, often yield fewer oocytes, with lower recovery and maturation rates compared to their counterparts undergoing elective freezing. Social OC participants, generally younger and healthier, benefit from planned stimulation cycles, resulting in higher oocyte yields and better-quality eggs. Fertilization rates and live birth outcomes also tend to favor social OC, largely due to the younger age at which the eggs are typically harvested.

Ethical considerations play a significant role in the global disparity in the acceptance of social oocyte freezing. While countries like the United States, Canada, and Spain embrace its use, others, such as Germany and China, either restrict or prohibit the practice. Opponents argue that social OC medicalizes reproduction unnecessarily and reinforces societal pressures on women to delay childbearing. Additionally, concerns about the commercialization of fertility preservation and equitable access further fuel the debate.

Despite these ethical concerns, the increasing adoption of social OC reflects shifting societal norms and advancements in reproductive autonomy. Nonetheless, significant challenges remain, including the financial burden of the procedure, the psychological impact of unused eggs, and the relatively low utilization rates among women who freeze eggs for non-medical reasons.

In conclusion, while oocyte cryopreservation provides a powerful tool for fertility preservation, its applications in medical and social contexts reveal stark differences in clinical protocols, outcomes, and ethical considerations. The ongoing evolution of this technology necessitates a balanced approach that respects individual autonomy while addressing the societal and ethical implications of its use.

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Do infertile couples or recurrent pregnancy loss would benefit from use of PGT-A

近年來，隨著試管嬰兒技術的進步，胚胎植入前遺傳學檢測技術（PGT-A）的應用比例不斷上升。根據美國生殖醫學協會（SART）資料庫的數據顯示，PGT-A 的採用率逐年增加。從學理上看，PGT-A 通過篩選染色體正常的胚胎（euploid），能夠提高懷孕率並降低流產風險。然而，這項技術並非萬能，過度或不當使用可能帶來潛在風險，例如切片過程可能損害原本能正常發育的胚胎，或將正常胚胎誤認為異常而丟棄。這種誤判可能源於內細胞團（inner cell mass, ICM）與滋養層（trophectoderm, TE）之間的染色體差異。此外，低度鑲嵌型胚胎（low-level mosaicism embryos）可能被判定為異常而丟棄，然而這些胚胎在適當條件下仍有正常發育的潛力。本演講將深入探討 PGT-A 在一般不孕症（無 RPL）及 RPL 患者中的應用，分析最新的隨機對照試驗（RCT）與大型研究結果，並探討其在不同族群中的利弊，幫助聽眾更全面地理解這項技術的價值與爭議。

首先，我們將從 PGT-A 的基礎原理與運作邏輯開始。PGT-A 是一種用於檢測胚胎染色體異常（aneuploidy）的技術，通常在胚胎發育的卵裂期（Blastomere，約第 3 天）或囊胚期（Blastocyst，第 5 天）進行切片分析。囊胚期切片因胚胎細胞數量較多且切片對胚胎的損傷較小，被認為更為準確。然而，切片本身可能影響胚胎的發育潛能，尤其在卵裂期切片時風險更高。此外，PGT-A 依賴新一代測序（NGS）等技術，雖然提高了檢測精確度，但仍可能存在誤判風險，例如將正常胚胎誤認為異常而丟棄，這一點我們將在後文詳述。

接著，我們將介紹反覆流產（RPL）的定義與診斷流程。RPL 是指連續發生兩次或更多次自然流產的情況，其病因複雜，可能涉及遺傳因素、子宮構造異常、內分泌失調、免疫問題（如抗磷脂抗體綜合症）以及凝血功能異常。診斷流程通常包括男女雙方的體染色體核型分析、子宮結構檢查、內分泌評估、免疫學檢測及凝血功能檢查，以全面評估潛在原因。對於 RPL 患者，PGT-A 的目標是篩選出染色體正常的胚胎，降低流產風險。

在一般不孕症的應用中，PGT-A 的證據與爭議值得深入探討。許多隨機對照試驗顯示，PGT-A 在高齡婦女（通常指 35 歲以上）中能夠提高懷孕率並降低流產率。例如，Scott et al.（2013）的研究發現，PGT-A 顯著提升了 IVF 的植入率與活產率。然而，STAR 試驗（2019 年）卻指出，使用新鮮胚胎移植時，PGT-A 並未顯著提高懷孕率，可能是因為該試驗排除了鑲嵌型胚胎（mosaicism embryos），低估了 PGT-A 的潛在益處。此外，Yan J.（2021）的另一項發表在 NEJM 的大型 RCT（N=1212，年齡 20-37 歲）發現，PGT-A 組的活產率並未高於對照組，且需要更多次植入才能成功懷孕，但該研究可能因僅切片 3 顆胚胎而低估了 PGT-A 的功能。由原理上來推論，PGT-A 並不改變胚胎的染色體狀態，而是識別異常胚胎，但切片卻可能損傷胚胎，或因假陽性診斷丟棄健康胚胎。對於年輕族群（35 歲以下），胚胎染色體異常率較低，PGT-A 反而可能因減少可用胚胎數量或延長培養時間而降低懷孕率，特別是對卵巢儲備功能下降（DOR）的患者而言，可能延長懷孕所需的時間。此外，PGT-A 的高成本也是一大考量，根據不同國家的統計，其費用可能顯著增加患者的經濟負擔。美國生殖醫學會（ASRM）指南建議，PGT-A 可作為一種選擇，但不應常規使用，尤其在年輕、低風險患者中。

對於 RPL 患者，PGT-A 的應用同樣充滿爭議，目的在挑選健康胚胎以降低流產風險。Bhatt et al.（2021 年）的研究發現，PGT-A 在 RPL 患者中與較高的活產率和臨床懷孕率相關，但流產率並未顯著下降。文獻結果不一，部分研究支持其效益，另一些則未發現顯著差異。ASRM 指南指出，PGT-A 在 RPL 患者中並非必須，但可在特定情況下考慮，例如高齡或反覆 IVF 失敗的患者。重要的是，RPL 患者應首先接受全面檢查，若確認父母一方帶有染色體平衡易位，可考慮結合 PGT-SR（針對結構重排的遺傳學檢測）與 PGT-A。

演講中還將探討 PGT-A 的新興技術與爭議。非侵入性 PGT-A（Non-invasive PGT-A）是一項前景看好的技術，通過分析胚胎培養液中的 DNA 進行遺傳學檢測，避免切片對胚胎的損傷。然而，這項技術目前仍處於研究階段，其準確性與可靠性尚待驗證。

最後，本演講將提供實用的總結與工具。我們將以表格形式概述 PGT-A 在不孕症與 RPL 中的優缺點，基於證據支持其在高齡婦女中的益處，以及在年輕族群與 RPL 患者中的侷限性。對於 RPL 患者，建議首先進行全面檢查，針對特定遺傳異常提供 PGT-SR 與 PGT-A 的聯合應用。最後，我們開發了一個互動式 Web App，供患者與臨床諮詢人員根據年齡、胚胎數量等參數，評估 PGT-A 的風險、益處與成本，促進共享決策。此工具允許自訂參數（如胚胎冷凍存活率），並邀請觀眾提供建議以進一步完善。

關鍵字：PGT-A、不孕症、反覆流產、IVF、高齡婦女、共享決策

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Chronic endometritis: diagnosis, management and treatment efficacy

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This speech will underscore the challenge of achieving a diagnostic consensus for chronic endometritis. It emphasizes the goal of dissecting various diagnostic approaches, including traditional histopathology, immunohistochemistry, hysteroscopy, and advanced molecular techniques such as PCR and Next-Generation Sequencing (NGS). It also opens the discussion for evaluating the efficacy and specificity of these methods in the context of endometrial health and immunity, setting the stage for a comprehensive exploration of how these diagnostics can impact the understanding and treatment of infertility linked to chronic endometritis. The endometrial microbiota will be disclosed in normal and chronic endometritis cases.

We aim to develop a diagnostic flow chart in chronic endometritis and infertility patients with endometrial dysbiosis. Lactobacillus-dominant (LD, with a Lactobacillus spp. abundance percentage greater than 90%) and non-Lactobacillus-dominant (non-LD, with a Lactobacillus spp. abundance percentage smaller than 90%) will be discussed in vaginal, endocervix and endometrium. The microbial colonization profiles found along the reproductive tract at each anatomical site were discussed.

Highlight:

- The microbial colonization profiles along the reproductive tract at each anatomical site.
- The microbiome correlation between endocervix samples and endometrium.
- The treatment efficacy and follow-up pregnancy outcomes.