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## Clinical application of serum AMH in reproductive medicine

Anti-Müllerian hormone (AMH), a peptide growth factor of the transforming growth factor-β family, is a homodimer glycoprotein with a molecular weight of 140 kDa whose 2750 bp gene is on the short arm of chromosome 19. AMH was initially discovered for its role in the regression of the Mullerian ducts. Following transcription of the sex-determining region Y (SRY) region in male fetus, Sertoli cells begin to produce AMH which leads to the apoptosis of cells in the Mullerian ducts , promotes Müllerian duct regression, and initiates male phenotypic development. Given the lack of SRY in females, this series of events does not occur leading to the Mullerian ducts to develop into the uterus, oviducts, and upper two-third of the vagina.

In females, when primordial follicles are recruited, AMH is initially produced in granulosa cells. AMH expression continues to increase until primordial follicles have developed into small antral follicles approximately 4– 6 mm in size. As the pool of small growing follicles is in parallel with the total number of primordial follicles, AMH reflects ovarian reserve, and it is widely used due to its reduced intra-menstrual cycle and inter-observer variability, furthermore, AMH exhibits reduced cycle-to-cycle variability compared with antral follicles counts (AFC) and follicle-stimulating hormone (FSH) levels.

The roles of AMH in assisted reproduction include predicts oocyte yield and dosage of FSH needed for an ART, if also can help predic cycle cancellation and identify patients at high risk of OHSS. However, Quantitative decline in ovarian reserve may not be necessarily accompanied by a qualitative decline, especially in younger women with diminished ovarian reserve and poor response to ovarian stimulation.

The clinical implication of serum AMH outside assisted reproduction have included prediction of menopause in the general population, assessment of ovarian toxicity caused by surgery and chemotherapy, diagnosis of polycystic ovarian syndrome (PCOS) and others.

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## Reproductive Immune tests in infertility and recurrent miscarriage

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Immune dysfunction has been implicated in some cases of recurrent pregnancy loss, unexplained infertility and failed IVF cycles. When the immune system is over- or under-activated, implantation may be compromised resulting in infertility or recurrent miscarriage. Immunological factors involved in adverse obstetrical outcomes and infertility may include the presence of anti-thyroid antibodies (ATA), anti-phospholipid antibodies (APA) and activated natural killer cells (NKa). Other immune dysfunction may be due to an immunological mismatch in DQ-alpha and HLA genotypes or disorders called thrombophilias. Thrombophilias are a group of disorders that increase the risk of clotting in the body and closely associated with recurrent pregnancy loss. Whether thrombophilias cause infertility or result in failed IVF cycles is still controversial.

The recurrent miscarriage and implantation failures (RIF) are an important issue with more than 40% fails for patients to obtain a live birth. The rate of pregnancy chance dramatically decreases with the number of consecutive miscarriages. There is also a significantly decreased chance in a live birth with increasing maternal age. But there is no evidence of an interaction between maternal age and the number of previous miscarriages.

The immunological aspects of implantation are many and are documented extensively in basic scientific and clinical research. The decidualized stromal cells of the endometrium, critical to implantation, are able to regulate trophoblast invasion and to dampen the local maternal immune response. The failure to control that immune reaction may lead to implantation failure. Several serological immune profiles may play a role in patients with RIF. Antibodies against placenta-specific 1 (a protein expressed in the placenta and encoded by trophoblast-specific gene PLAC1) may impair implantation and have been shown in a small case-control study to be higher in patients with RIF compared with fertile controls (Matteo et al., 2013). Liang and colleagues also performed a small case-control study, and showed that proinflammatory factors (interferon-gamma [IFN-γ ], interleukin

(IL)-1β , IL-6 and IL-4) were increased, and anti-inflammatory factors (transforming growth factor-beta 1) were decreased, in the peripheral blood of RIF patients compared with control participants pregnant after IVF (Liang et al., 2015). The endometrial immune profile was also studied in patients with RIF (Ledee et al., 2016; Mariee et al., 2012). While there' s much investigation into the biological plausibility of an immunological aetiology in RIF, there is limited evidence to justify translation to clinical practice.

No immunological biomarkers have been definitively documented to cause recurrent pregnancy loss. There is quite strong evidence that presence of some autoantibodies (anticardiolipin antibodies and antithyroid antibodies) negatively affects the future live birth rate in women with or without RPL. (Nielsen and Christiansen, 2005, Thangaratinam et al., 2011). Nevertheless, the impact of other autoantibodies such as antinuclear antibodies is more controversial. At the same time, there is no sufficient documentation for the impact of natural killer abnormalities and cytokine abnormalities in the blood or endometrium in recurrent pregnancy loss. It is therefore questionable to select patients to specific treatments due to the presence or absence of specific immune biomarkers outside clinical trials.

In the overwhelming number of trials testing other treatment options: lymphocyte immunization, intravenous immunoglobulin infusions, prednisone etc. patients were not selected due to the presence of specific immune factors. A few trials have tested intravenous immunoglobulin in women with RPL with various autoantibodies or NK cell aberrations (Stricker and Winger, 2005) or NK cell/cytokine aberrations (Winger and Reed, 2008, Moraru et al., 2012) but these trials are only of moderate/low quality, primarily because they were not placebo-controlled and thus not blinded.

Serological or endometrial immune testing in these patients should be limited to research settings. More clinical studies are needed to demonstrate the efficacy of immunomodulation strategies. Despite numerous data underlying the role of immunotolerance abnormalities in the pathogenesis of recurrent miscarriage and implantation failure, further studies are required to clarify the efficacy and safety of immunomodulation strategies.

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## Long term health in children born after assisted reproductive technologies ( PGT-A included )

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自 1978 年首位試管寶寶 Louise Brown 的誕生至今，人工生殖技術已在全球蓬勃發展，幫助了許多不孕患者成功懷孕且活產生下寶寶；又隨著降低胚胎植入顆數的理念推動，已經漸漸減少了多胞胎率以及其相關的早產風險和不良周產期預後的現象。許多文獻統計都顯示，單胞胎活產的試管胎兒與自然懷孕出生的胎兒，在周產期的預後有些許差異，例如:新鮮週期植入出生的試管寶寶相較於自然受孕，有較高的早產、SGA (small for gestational age)及出生低體重(LBW, low birth weight)的風險；而冷凍胚胎植入則有較高的 LGA (large for gestational age)及子癲前症的風險。然而周產期相關風險的增加可能與患者不孕症本身的因素及人工生殖技術皆有關連性。

目前對試管嬰兒在幼兒及學齡等中長期預後的文獻探討仍有限，整體而言，認為神經心智健康的發展問題，可能是與多胞胎的因素較相關。如果是單胞胎的試管寶寶，在未來的神經發育(包括認知學習力、語言與社交行為的發展上)，或是自閉症類群障礙(Autism Spectrum Disorder, ASD)、注意力不足過動症(Attention deficit and hyperkinetic disorders, ADHD)及腦性麻痺的發生率，都與自然懷孕的兒童沒有差別。另外少數的論文發現，試管出生的孩童可能有潛在高血壓、心血管問題及代謝異常的風險，但仍需更多大型審慎的研究資料統整予以檢視。

最後，胚胎著床前染色體檢測(Preimplantation Genetic Testing, PGT)透過胚胎切片技術(cleavage stage or blastocyst stage embryo biopsy)可篩檢出染色體正常的胚胎，但是胚胎切片是侵入性的檢查，其安全性及對出生子代長期的影響，在目前有限的報告普遍認為，其出生狀況、生長發育追蹤至 5-9 年，都與自然受孕或無切片的試管嬰兒預後是差不多的，未來也需要更長期的報告來持續追蹤。

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## Mosaic Trisomy at Prenatal Diagnosis
## 產前診斷鑲嵌性三染色體異常

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1. 人類對於 mosaic trisomy at prenatal diagnosis 的經驗有限，而且很少有機會去認識這些胎兒成長的過程。所以會害怕。
2. 我們產前檢查的問題是這樣子的胎兒可以生嗎？生下來若有問題怎麼辦？
3. 所有 mosaic trisomy 的診斷都有差異：胚胎 vs 胎兒；胎兒 vs 胎盤；胎兒 vs 母血 DNA；胎盤 vs 羊水細胞；培養羊水細胞 vs 未培養羊水細胞；羊水細胞 vs 臍血；臍血 vs 新生兒體細胞；羊水細胞 vs 新生兒體細胞；新生兒體細胞 vs 幼兒兒童體細胞；幼兒體細胞 vs 成年人體細胞。
4. 人類成長從胚胎到成人是一連串複雜又漫長的過程。很少醫師可以在有生之年，完全觀察到。我有幸能看到並觀察到。鑲嵌性胚胎和鑲嵌性胎兒是很厲害的。會在新生兒或是少年成年人時看不出任何蛛絲馬跡。我在醫學文獻革命性證明許多胎兒鑲嵌性染色體異常者。出生後已經完全正常了！這就是說人類從胚胎到胎兒會不斷成長。正常的細胞最後完全超越取代異常細胞。
5. 藉由我所有診斷而生下來所有的 mosaic trisomy at amniocentesis 案例，全部都有產後血液染色體及身體細胞 FISH 驗證，並且長期追蹤。結果所有的案例均正常發展，且細胞檢查正常且全部逆轉。異常細胞終將消失。這證明一件事：胎兒時期的 mosaic trisomy 只是暫時的現象，會隨胎兒成長，出生後成長，最後正常細胞成長較快終將當家作主。所以大家不可以用兒童及成人的 mosaic trisomy 的知識來對待我們的胎兒。那是不公平的，那會導致胎兒被引產。
6. 我的觀察結果及論文是劃時代的，打破產前遺傳諮詢的迷思，修正羊水鑲嵌性染色體異常判斷的理論。我甚至證明有些是假的，是在培養箱創造的，有些高比例異常是被實驗室放大的，如此一來，我可能救全世界許多不幸被如此診斷的小孩子，這些小朋友，有些是別人的長子，或長孫，有些是試管寶寶，有些是超高齡父母的最後一次機會，所以我幫忙他們，讓父母及醫生敢讓他們出生。
7. 但是我也發現 mosaic trisomy at amniocentesis, euploid 的細胞可能併有 maternal UPD，因此對於 mosaic trisomy 6, 7, 11, 14, 15, 16, 20 要特別小心 maternal UPD 6, 7, 11, 14, 15, 16, 20。

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## A new class of oral GnRH antagonists for the treatment of endometriosis and uterine leiomyomas

To advance the development of more effective GnRH analogs for clinical application, feasible cloning of the GnRH receptor and high-throughput screening of small molecules targeting the GnRH receptor have been continuously conducted. Recently, orally bioavailable nonpeptide GnRH receptor antagonists have been developed to improve the compliance of patients using GnRH analogs for clinical treatment. Several orally-active small molecule GnRH antagonists targeting the GnRH receptor have been synthesized by high-throughput screening and biochemical processing. Elagolix, an orally bioactive nonpeptide GnRH receptor antagonist, has been approved by the FDA for the clinical treatment of endometriosis-related pelvic pain. Additionally, elagolix was recently applied for the management of abnormal uterine bleeding related to uterine fibroids. For these estrogen-related diseases, elagolix inhibits gonadotropin and estrogen synthesis in a dose-dependent manner, adjusting serum estrogen concentrations through partial to complete inhibition of estrogen at low to high doses. Data obtained from clinical studies indicate that elagolix inhibits the production of gonadotropins and estrogen as well as ovulation in a dose-dependent manner and decreases average endometrial thickness but does not affect the serum AMH level. Other oral non-peptide GnRH receptor antagonists, including relugolix and linzagolix, are currently in phase III clinical trials for the treatment of hormone-related diseases.

As a newer treatment option, clinicians may be unfamiliar with oral GnRH antagonists and their application in clinical practice. Therefore, to provide a practical guide for use of oral GnRH antagonists based on available evidence and clinical experience is a new class. It is anticipated that with ongoing experience, expertise will continue to develop regarding the best use of oral GnRH antagonists for the management of endometriosis and uterine leiomyomas symptomatology.

**References**

1.Conn PM, Janovick JA. 2014. A phenotypic high throughput screening assay for the identification of pharmacoperones for the GnRH receptor. Assay Drug. Dev. Technol. 12,238– 246.

2.Lamb YN. 2018. Elagolix: first global approval. Drugs 78, 1501– 1508.

3.Schlaff WD, Watts NB, Muneyyirci-Delale O. 2020. Elagolix for heavy menstrual bleeding in women with uterine fibroids. N Engl. J. Med. 382, 328– 340.

4.Archer DF, Klein CE. 2020. Elagolix suppresses ovulation in a dose-dependent manner: results from a 3-month, randomized study in ovulatory women. J. Clin. Endocrinol. Metabol.105.

5.Osuga Y, Hoshiai H. 2019.Relugolix, a novel oral GnRH antagonist, in the treatment of pain symptoms associated with uterine fibroids: a randomized, placebo-controlled, phase 3 study in Japanese women.Fertil Steril 112,922– 929.

6.Pohl O, Gotteland JP. 2020. Effects of combined GnRH receptor antagonist linzagolix and hormonal add-back therapy on vaginal bleeding-delayed add-back onset does not improve bleeding pattern. Reprod Sci 27, 988– 995.

7.Wu HM, Chang HM, Leung PC. Gonadotropin-releasing hormone analogs: Mechanisms of action and clinical applications in female reproduction. Frontiers in Neuroendocrinology 2021 Jan;60:100876. doi: 10.1016.

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## Strategies of couples with azoospermia

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Around 1 in 7 couples present with infertility, and male factor accounts for up to 50% of these couples. Azoospermia, defined as a complete lack of spermatozoa in the ejaculate, is identified in about 1% among all men and 10~15% of infertile men. Azoospermia can be classified as obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). About 40% of azoospermia cases are OA, which is resulted from mechanical blockage to the male reproductive tract and typically presents normal serum hormone profile, testicular volume and spermatogenesis. On the other hand, the spematogenesis in NOA cases is impaired, and men with NOA are the most difficult to management. Possible etiologies of NOA include genetic disorders (sexual chromosome abnormalities or Y-chromosome microdeletions), hypogonadotropic hypogonadism, cryptorchidism, testicular torsion, radiation, and chemotherapy. Microdissection testicular sperm extraction (micro-TESE) is the gold standard for surgical sperm retrieval, but a successful pregnancy also requires adequate number of oocytes, reliable protocol of oocyte cryopreservation, meticulous skills of sperm identification and intracytoplasmic sperm injection, and tacit cooperation between gynecologists and urologists. The strategies to achieve these requirements in Taipei Veterans General Hospital will be discussed here.