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Ovarian stimulation in patients with AMH excess

Anti-Mullerian hormone (AMH) is a glycoprotein of the transforming growth factor beta (TGFβ) family and is produced by granulosa cells of preantral and antral ovarian follicles. It was firstly utilized as a measurement of ovarian reserve in 2002 and is now considered the earliest and most sensitive marker among all ovarian reserve tests. It correlates strongly with the primordial follicle pool, has been reported to predict response in artificial reproductive technologies (ART), being predictive of the timing of the onset of menopause, and has potentials to help the diagnosis of polycystic ovarian syndrome (PCOS). So far there are more than 4000 published papers related to the AMH researches, and its popularity is still rapidly growing. In this section, thorough considerations and updated recommendations about ovarian stimulation in patients with AMH excess will be summarized as followed:

(1) The basics and clinical applications of AMH.
  (a) The related ovarian physiology
  (b) Considerations in AMH measurements
(2) How high is too high? What is the definition of AMH "excess"?
(3) Updated recommendations regarding to ovarian stimulation in patients with AMH excess.
  (a) To predict outcomes of ART.
  (b) To individualize ovarian stimulation protocols based on excess AMH levels.
  (c) Are there any direct or indirect causal effects of AMH excess on the outcomes of ovarian stimulation or ART?
  (d) Special considerations in the ovarian stimulation in patients with PCOS, which is a major pathological condition of AMH excess.

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Strategies in ovarian stimulation protocols to improve results in patient with diminished ovarian reserve

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Ovarian reserve (OR), which refers to the quantity and quality of residual ovarian follicles and oocytes, reflects a woman’ s reproductive potential and assisted reproductive technology (ART) outcomes . Women with diminished ovarian reserve (DOR) are associated with poor response to controlled ovarian stimulation (COS) resulting in fewer oocytes retrieval. DOR affects approximately 10% of infertile women . Women with the following two or more items such as serum follicle stimulation hormone (FSH) level 25 IU/L > FSH > 10 IU/L, serum oestradiol (E2) level >80 pg/ml, serum anti-Mullerian hormone (AMH) level <0.5-1.1 ng/ml and antral follicle count (AFC) ≤5 on day 2-3 of a spontaneous cycle are considered to have DOR . These women should be encouraged to conceive sooner due to their shorter fertility window.

It is believed that androgens could promote folliculogenesis and potentiate the effects of gonadotropin. There are some adjuvant treatments such as DHEA and androgen had been reported to improve the outcome of IVF-ET with DOR females.

Although various protocols have been used to improve pregnancy outcomes, infertility issues are still a challenge for DOR women. Many new strategies such as double stimulation, mild stimulation and cumulated embryos could provide more chance to get pregnancy to those women with diminished ovarian reserve. In this talk, I will discuss these strategies and propose a way to select an appropriate strategy

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Signal of the endometrium ready for implantation

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Embryo implantation is a complex process involving both the embryo and the maternal endometrium, whose initial steps occur over approximately a 4- to 6-day interval during the mid-luteal phase. It is estimated that embryos account for one-third of implantation failures, while suboptimal endometrial receptivity and altered embryo– endometrial dialogue are responsible for the remaining two-thirds. The aim of this speech is to systematically review the evidence from studies about various markers relevant to endometrial receptivity as prognostic factors for pregnancy outcome in women wishing to conceive, hopefully to aid clinicians in choosing the most useful signals of the endometrium ready for implantation in clinical practice.

There is no perfect endometrial receptivity marker yet so various means of evaluation have been established in the literature, including:

●by ultrasound:

1.Endometrial thickness
2.Endometrial volume
3.Endometrial pattern (Triple line)
4.Endometrial blood flow
5.Endometrial contractions

●by relatively invasive procedures:

6.Hysteroscopy inspection
7.Markers in endometrial fluid aspirate or endometrial biopsy (ex. pinopode)
8.Uterine natural killer (uNK) cells
9.Endometrial receptivity array (ERA)

In summary, endometrial receptivity seems to be multidimensional. None of the endometrial receptivity markers included in the present review has sufficient discriminatory value to act as a diagnostic test for endometrial receptivity based on their ability to predict clinical pregnancy. How to identify the signal of the endometrium ready for implantation might be the "last barrier" to ART success, wherein more prospective studies, using pregnancy outcome endpoints, are certainly needed.

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Emerging technologies in mitochondrial research implications for assisted reproductive technologies

Aged oocytes display increased chromosomal abnormalities. Among, mitochondrial dysfunction is responsible for depicts of ATP production, misalignment of spindle, chromosomal mis- segregation, and increasing aneuploidy rate in aged oocytes. Recently, efforts have been made to investigate the possibility of improving mitochondrial capacity by transferring healthy mitochondria. On the other hand, along with the production of ATP in mitochondria, surplus amount of cellular reactive oxygen species (ROS) are likely involved in genomic and mitochondrial DNA injury and metabolic alteration of granulose cells. In addition, growing evidence have shown that cryopreservation have posed adverse effects of spermatozoa. Overall modulation of mitochondrial bioactivity and control the ROS level in whole IVF system might be a solution for better ART outcome.

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The science of what embryo(s) to transfer in ART: fresh or frozen, cleavage or blastocyst, preimplantation genetic testing or not

胚胎植入的科學：新鮮植入或全胚冷凍？第三天植入或囊胚植入？要不要做著床前基因篩檢？

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隨著冷凍技術的進步，全胚冷凍(freeze all)可以大幅降低卵巢過度刺激症候群(OHSS)的風險。近年的研究也顯示全胚冷凍對卵巢反應很好(hyperresponder)的病人，懷孕率要比新鮮植入要好。全胚冷凍也提供更彈性的卵巢刺激方案和胚胎植入的時間。然而對於正常卵巢反應者(normal responder)或卵巢反應不良(poor responder)者，進行全胚冷凍是不是比新鮮植入要好，仍有討論的空間。另外要注意的是，冷凍胚胎雖然呈現不錯的懷孕率，但是否會增加週產期的風險，例如妊娠高血壓或胎兒過大等問題，也需要更多研究來討論。

隨著培養技術的進步，囊胚培養是所有胚胎實驗室努力的方向。囊胚期植入提供進一步選擇胚胎的機會，可以降低植入胚胎數，甚至實現選擇單一胚胎植入(eSET)，達到降低多胞胎妊娠的目標。但對於胚胎數較少的病人，必須要考慮是否會有無胚可植的風險。另外，囊胚期植入可能會增加一些同卵雙胞胎(monozygotic twin)的機率。最近關心的話題是囊胚期植入也可能會增加小部份週產期風險。

隨著基因檢測技術的進步，使用著床前基因檢查非整倍體(preimplantation genetic testing for aneuploidy, PGT-A)篩檢出染色體正常的胚胎，也成為近幾年來各胚胎實驗室努力的方向。PGT-A 能選出最有潛力的胚胎，大大提高植入著床率。文獻證據顯示確實有助於施行選擇單一胚胎植入(eSET)。PGT-A 對於因染色體異常所致的反覆性流產可能也有益處。但對於高齡婦女或試管嬰兒反覆性著床失敗的婦女，文獻對於 PGT-A 是否有益處則尚無定論。胚胎切片會不會反而傷害到原本健康的胚胎，PGT-A 後鑲嵌體(mosaic)的胚胎要如何處理，也都是很有爭議的問題。

以上這些技術，代表了胚胎實驗室近二十年來的進步；另外一方面同時增加了實驗室工作的負擔，增加了病人的花費。慎選真正有幫忙的病人，是我們在追求進步和精準時應該注意的。

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Uterine cavity evaluation in preclinical loss and implantation failure

Successful implantation requires synchronized coordination between a competent blastocyst and a receptive endometrium. Repeated implantation failure (RIF) or recurrent pregnancy loss (RPL) is frustrating to both the patients and the clinicians. Maternal causes of RIF include endometriosis, hydrosalpinx, PCOS, and uterine factors. Abnormality in the uterine cavity, such as submucous leiomyomas, endometrial polyps, intra-uterine adhesions, Müllerian duct anomalies contributed to 18%-27% of RIF.

Imaging studies of uterine cavity include hysterosalpingography, ultrasound scans (2D, 3D, saline infusion sonography), and hysteroscopy (HSC). Hysteroscopy is the gold standard to evaluate uterine cavity. The incidence of abnormal HSC findings varies between 25%-50%. Several studies showed that HSC increased the clinical pregnancy rate on the subsequent IVF cycle.

One of the etiologies of RIF or RPL is chronic endometritis, which is defined as a chronic inflammation of the endometrial lining. Successful treatment increases subsequent live birth. The diagnosis depends on endometrial biopsy. HSC has a 93.4% accuracy rate. Most of the etiological pathogens are normal flora in the genital tract, and endometrial culture has low concordance rate.

"Out-of-phase" endometrium is a cause of RIF. An endometrial receptivity array (ERA) is a novel diagnostic tool that helps evaluate the endometrial receptivity of a woman, from a molecular point of view. ERA was shown to be more accurate than endometrial histology. In patients with RIF in whom HSC showed no abnormality, ERA is another option to identify the problem.