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台灣實施人工生殖生育補助之成果與現況

The Ministry of Health and Welfare expanded the IVF subsidy program since July, 2021. The criteria to apply the subsidy are 1) either partner is citizen of Taiwan and 2) the wife is under 45 years of age. For first time application, infertility couples can apply for up to NT\$100,000. For subsequent applications, they can apply up to NT\$60,000 per treatment. For a female below 40 years of age, they can apply up to 6 times subsidy. For a female 40-44 years of age, they can apply up to 3 times.

In this subsidy program, there are restrictions for the number of embryo transfer. For females below the age of 36, only one embryo is allowed to transfer each time.

After the subsidy program, there is a growth of 70% in the number of treatments. More than 90% of the treatments have transferred less than 2 embryos. The multiple pregnancy rate after IVF was reduced from 24% to 15%.

The greatest achievement of this expended subsidy program is to decrease multiple pregnancy rate and increase our national maternal and neonatal health.

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ICSI for male vs non-male infertility

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Intracytoplasmic sperm injection (ICSI) involves the injection of a single spermatozoon into an oocyte cytoplasm using a glass micropipette. Since the introduction of ICSI in the clinical practice in 1992, ICSI has been applied in male and non-male infertility. For male infertility use includes azoospermia, oligo-astheno-teratozoospermia (OAT), globozoospermia, antisperm Ab and those with sperm DNA fragmentation. ICSI was used in non-male infertility, such as unexplained infertility, poor quality oocytes, low oocyte yield, advanced maternal age, prior failed IVF history, routine use, PGT, IVM, and cryopreserved oocytes. The high utilization rate of ICSI is for fear of fertilization failure and myth of high pregnancy rate for ICSI. In Taiwan, ICSI becomes popular, even reaches more than 90% utilization among some ART centers. The most consideration is to increase the fertilization rate and pregnancy rate. But, more than 30 unnecessary ICSI is performed for decreasing unexpected fertilization failure. Increasing evidence shows although fertilization rate would be increased by ICSI, it does not improve the live birth for advanced maternal age and in routine use. Pregnancy rate was reported to be even worse in routine use of ICSI in comparison with conventional IVF.

ICSI should be reserved for male factor infertility. ICSI is mandatory for azoospermia, absolute asthenozoospermia, globozoospermia, severe OAT, globozoospermia, and sperm DNA fragmentation. ICSI may be highly recommended for PGT or cryopreserved oocytes. Some raise the concern of offspring well-being in ICSI group. According to our study, ICSI does not increase the pregnancy rate, and we found ICSI had unfavorable implications for the neurodevelopmental health of offspring, in terms of increased risks of autism spectrum disorder and developmental delay. Our study concurs with the opinion we should select ICSI with cautious indication.

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Fertility preservation after diagnosis of breast cancer

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處於生育期之癌症病患在確診時往往只專注在如何治療疾病，而忽略了癌症治療對生育能力保存的影響，因此治療癌症的醫療團隊應當主動說明提醒生育能力保存之重要性。癌症本身若不是直接起源於生殖器官，未必對生殖器官有直接侵犯，但治療對生殖能力的間接影響往往不可逆，所以生育能力保存的提示和說明，應該主動向生育年齡之癌症病患提出，不宜應因病患年齡、婚姻狀態、伴侶有無、以及是否已育有小孩而省略，如此方能了解病患在治療開始前對生育能力保存議題的回饋，並予以尊重，同時成為治療計畫的一部分。

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Ovarian function after COVID-19 infection

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The COVID-19 pandemic has not only challenged global health systems but also sparked an intense debate about its potential effects on human fertility. Among these concerns is the impact of COVID-19 on female reproductive health, specifically ovarian function and fertility. This presentation will critically examine the emerging body of research exploring the potential effects of COVID-19 on ovarian function.

Initial observations during the pandemic indicated changes in menstrual cycle patterns among women who had recovered from COVID-19. These alterations, ranging from cycle irregularity to changes in menstrual flow, suggested a potential disruption in normal ovarian function. Subsequent studies endeavored to understand these changes more deeply, exploring whether they were transient phenomena or indicative of longer-term reproductive health issues. A crucial aspect of this investigation is the analysis of ovarian reserve markers, particularly Anti-Müllerian Hormone (AMH) and antral follicle count (AFC). These markers are pivotal in assessing a woman's ovarian reserve and, by extension, her fertility potential. Research in this area has produced mixed results. Some studies, such as those conducted by Yang et al. (2023), have reported a temporary impact of COVID-19 on these markers, suggesting a possible transient effect on ovarian reserve. However, other studies have not found significant long-term impacts, indicating the need for further research to clarify these findings. Another dimension of this issue is the impact of COVID-19 on ovarian follicular function. Research, including a notable study by Bentov et al. (2021), has explored whether the virus directly affects the functionality of ovarian follicles. Their findings suggest that, in most cases, follicular function remains unaffected in women who have recovered from COVID-19, providing some reassurance regarding the virus's long-term impact on fertility.

Beyond the direct effects on ovarian function, this presentation will address the implications of COVID-19 for women undergoing assisted reproductive technologies (ART), including in vitro fertilization (IVF). The potential impact of a past COVID-19 infection on ART outcomes is a subject of considerable interest and concern. Lomova's (2022) study, among others, underscores the need for heightened vigilance and tailored management for women with a history of COVID-19 undergoing these treatments.

Of particular concern is the intersection of COVID-19 with polycystic ovary syndrome (PCOS). Women with PCOS may increase susceptibility to COVID-19 infection and increase the severity of COVID-19, necessitating specific management strategies. Additionally, the potential association between COVID-19 and premature ovarian insufficiency (POI) is explored. While some research points to a possible link, the evidence remains inconclusive, highlighting the need for continued investigation.

There are some contradictory findings in the literature. For instance, studies by Madendag et al. (2022) and Kolanska et al. (2021) suggest that COVID-19 may not have a significant long-term impact on ovarian function. These divergent views underscore the complexity of the subject and the necessity for ongoing research to fully understand the implications of COVID-19 on female reproductive health.

In summary, while some studies point to a possible transient effect of COVID-19 on ovarian function, others suggest no significant long-term impacts. This variability in findings emphasizes the need for further research and a cautious approach in interpreting these results.

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Rethink of “add-ons” in Assisted Reproductive Technology

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受限於輔助生殖治療技術及試管嬰兒治療長久以來無法向上突破的成功率，加上難孕症患者的高度期待，催生了各種生殖治療的「附加選項 (add-ons)」。這些「附加選項」包括各種檢測、藥物、設備、補充品或替代療法、實驗室程序、醫療處置甚至於手術，均被歸類為標準輔助生殖治療技術之外的額外選擇，使用的宗旨是提高懷孕或活產率，降低流產風險，或縮短實現懷孕的時間。然而，這些「附加選項」通常會產生額外甚至是昂貴的費用，但換得的臨床效益卻常受到實證醫學的質疑。

關於這些「附加選項」是否應該使用，持續困擾著生殖醫學界。英國官方的「人類受孕及胚胎學管理局 (Human Fertilisation and Embryology Authority, HFEA)」自 2013 年起就成立了一個顧問委員會，定期每年舉辦三次會議，有系統的討論各種 add-ons 的實證發展，並自 2017 年創建了一個紅綠燈標示系統，將各種 add-ons 賦予紅、橙、綠三種燈號，用以代表不同的 add-ons 是否有足夠的臨床證據支持使用，這個燈號辨識系統也在 2023 年 10 月做了更細的翻新分類，協助臨床從業人員快速了解不同 add-ons 的實證等級。大約同時，歐洲生殖醫學會 (ESHRE) 也在 2023 年 11 月，首次針對 add-ons 提出了官方版本的建議：“ Good practice recommendations on add-ons in reproductive medicine ”，期望能從實證的角度評估各種附加選項的安全性和有效性。這些更新資料及實證建議，可以做為生殖治療臨床從業人員在使用或諮詢 add-ons 時的基本指引，非常值得與婦產科醫學會會員分享。

本次演講，便是依循著 HFEA 及 ESHRE 的專家所檢視審批各種 add-ons 的實證結果加以延伸，並對不同附加選項做一個概括性的介紹，期望會員們能藉由本演講，學習到各種生殖治療附加選項目前的實證現況及未來的可能發展、體認目前各種附加選項都還在滾動式發展，並了解使用實證不足的附加選項可能帶來的倫理或法律問題。

醫學仍在進展，臨床從業人員應持續追蹤這些附加選項在臨床研究上的進展，並給予不孕症個案正確的醫療資訊、共享決策，才能最佳化不孕症個案之預後。

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亞臨床性甲狀腺低能症和懷孕

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Pregnancy has a huge impact on the thyroid. Placental human chorionic gonadotropin stimulates thyroid hormone production and leads to suppressed maternal thyrotropin concentrations. The concentration of the thyroxine-binding globulin (TBG) is also increased in pregnancy causing total T4 and total T3 levels to be elevated. This makes normal thyroid function reference values different in the pregnant and non-pregnant population. Correct diagnosis and prompt treatment of thyroid dysfunction in pregnancy is of crucial importance and could only be achieved using a reliable gestation specific reference standard, which differ largely among ethnicities and iodine status.

Subclinical hypothyroidism which is usually tolerable in non-pregnancy conditions has been shown to be associated with increased risk of miscarriage, pre-term labor, gestational hypertension, and low birth weight. Unlike overt hypothyroidism, which should be treated promptly before conception, during pregnancy or lactation, controversies exist in treatment for subclinical hypothyroidism and the decision should be weighted for the risks and benefits for the mother and the fetus. It is reasonable to treat subclinical hypothyroidism with levothyroxine when the TSH level is high or in the presence of thyroperoxidase antibodies. Un-treated women should be followed up to ensure that treatment is initiated promptly when subclinical hypothyroidism progresses.