Parameters to predict the pregnancy in assisted reproductive technology

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There is a trend in the increasing age of women who have attempted to get pregnancy, contributing to an increasing usage of assisted reproductive technology (ART) to achieve parenthood in couples in modern society.[1–3] Although far-advanced ART in the management of various kinds of subfertile women, including tubal factor, unexplained infertility, etc., has been developed, aging process of the ovary (elder women) and poor ovarian reserve (poor ovarian responders) is still a biggest challenge for physicians to achieve the successful pregnancy.[4–6] With significant improvement of nutrition and environmental factors in adolescence, the age of menarche occurs earlier than it did before. In addition, fertility-enhancing agents are widely used for women with subfertility and infertility, regardless of the use of ART or not. Women's age with complete deprivation of oocytes and menopause is not significantly changed for recent decades.[7–9] To understand the potential of female reproductive performance, there are many biomarkers, such as basal follicle-stimulating hormone (FSH), antral follicle count, and anti-Mullerian hormone (AMH), available in hand, which help to qualify the ovarian reserve (ovarian reserve tests) and possibly to predict the response of ovulation induction.[10] However, it is still unclear whether these biomarkers could be used in the prediction of successful pregnancy and further live birth. We are glad to learn that Dr. Sckin's study published in the current issue of the *Journal of the Chinese Medical Association* attempted to use the serum level of AMH to predict pregnancy outcomes in women with unexplained infertility who had been treated with recombinant FSH stimulation and intrauterine insemination (IUI).[11]

This retrospective study investigated the correlation between the serum level of AMH and pregnancy outcomes in 84 women with unexplained infertility who were treated with recombinant FSH-stimulated IUI cycle.[11] Among these, 27% of women (n = 23) were over 35 years of age. The results showed that a total of 16 patients (19%) had achieved clinical pregnancy.[11] There were no significant differences of serum AMH levels between success or failure on pregnancy.[11] After adjusting age, the duration of the stimulation, total recombinant FSH dose used, serum estradiol levels, endometrial thickness, and number of intermediate-sized (12-15 mm) and dominant follicles (≥16 mm) on the day of human choriogonadotropin injection, there was still no difference.[11] Based on the above finding, the authors suggested that AMH was not a valuable biomarker in the prediction of clinical pregnancy.[11] Furthermore, the authors hypothesized that serum AMH concentration was not associated with oocyte and/or embryo quality and AMH concentration did not reflect the oocyte genetic competence; both might be the determinant factor for successful embryo implantation (pregnancy). The study is interesting and worthy of a further discussion.

First, the current study provided a rationale of the use of recombinant FSH-stimulated IUI cycle in the management of women with unexplained infertility. For women with unexplained infertility, all expectant therapy and ART either mediated by FSH-stimulated IUI or in vitro fertilization and intracytoplasma sperm injection have been widely acceptable in the clinical practice. However, the effectiveness or safety of FSH-stimulated IUI cycle is uncertain. A recent pragmatic, open-label, randomized, controlled two-center trial showed that the use of FSH stimulation and IUI may be a good choice compared to expectant management, because the former (FSH-stimulated IUI) had a significantly higher cumulative live birth rate (31 [31%] live births among 101 women) than the latter (expectant management) did (nine [9%] live births among 100 women), with the risk ratio of 3.41 and 95% CI of 1.71 to 6.79; p = 0·0003.[12] It suggested that the use of FSH-stimulated IUI cycles will increase at least 3.4-fold live birth rates, without an increasing risk of ovulation-induction associated complications, such as ovarian hyperstimulation syndrome or multiple pregnancies.[12] Similar to the previous study shown earlier, Dr. Sckin's study showed a relatively acceptable pregnancy rate per cycle (20%) without occurrence of ovulation induction-related complication.[11] All suggested that FSH-stimulated IUI is a safe and effective treatment for women with unexplained infertility. It could be applied to overcome an unfavorable prognosis for natural conception.

Second, it is well known that advanced age is an independent worse factor for pregnancy in women, regardless of fertile and subfertile status. When the age is more, the serum level of AMH is lower. In addition, advanced age status is also a worse factor for pregnancy, regardless of the use of ART or not. Many tools are often used to predict the ovarian reserve, including serum level of AMH and Day 3 to 5 preantral follicle counts,[9] which are also a good predictor of the adequate ovulatory response to ovulation induction agents.[5] Low AMH levels might hint the higher cancelled rate and fewer oocyte retrieval.[5] In theory,

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higher cancelled rate and few oocyte retrieval is correlated with lower pregnancy rate. It is rational to suppose that the low serum level of AMH may be correlated with less chance of successful pregnancy.

A recent large retrospective analysis of Society for Assisted Reproductive Technology Clinic Outcome Reporting System database from 2012 to 2013 showed that receiver operating characteristics curves demonstrated that the areas under the curve for AMH as predictors of live birth in fresh cycle (for selective single-embryo transfer) and thawed cycles (for selective single-embryo transfer) were only 0.631 (0.655) and 0.540 (0.533), respectively, which suggested that AMH alone is a weak independent predictor of live birth after ART.[13] Dr. Sckin's study also showed no association between serum level of AMH and pregnancy outcomes.[11]

Although there seemed to be absence of correlation between serum level of AMH and pregnancy outcome in patients treated with FSH-stimulated IUI in Dr. Sckin's study, there are still many conflicted data in this topic as shown by the authors themselves. There are some reasons, which can partly explain it.

First, there is a trend to perform a selective single-embryo transfer and avoid the hyperstimulation of ovary in the modern ART treatment, suggesting that the quality of oocyte might be much more considered than the quantity of oocytes. Second, the serum level of AMH is within the normal limits. In fact, the enrolled subjects were <40-years-old and relatively higher serum levels (ranged from 1.1-3.4 ng/mL) of AMH were noted in Dr. Sckin's study.[11] The current study attempted to assess the cycle outcomes when AMH is ultralow (≤0.16 ng/mL) and to determine which parameters contribute to the probability of outcome.[14] The results showed that cycles with ultralow AMH levels compared with age-matched normal AMH cycles demonstrated more than a 5-fold increase of preretrieval cancellation rate, a 2-fold decrease of live birth rate per cycle, and a 4.5-fold decrease of embryo cryopreservation rate.[14] The results suggested that patients with ultralow AMH levels should be counseled appropriately about the prognostic factors for cancellation and outcomes.

Based on the above-mentioned findings, the background of the enrolled patients and the original design of the study are important, because the results might be varied greatly when criteria (inclusive and exclusive) are different.[15]

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