



Editorial

The earlier the better: When should intrauterine insemination be done?



Intrauterine insemination (IUI) is one of the more widely used fertility treatments, and often suggested as the first choice for infertile couples with cervical infertility, mild male factor infertility, anovulation, mild or minimal endometriosis, and unexplained infertility with at least one patent fallopian tube and sufficiently motile sperm.^{1,2} Although IUI is less invasive and less expensive than *in vitro* fertilization, the conception rate of IUI is limited.³ Meta-analyses reported that IUI with controlled ovarian stimulation (COS) increases the live birth rate compared to IUI in the natural cycle.⁴ However, adverse events, including ovarian hyperstimulation syndrome and multiple pregnancy are likely increased in the stimulated IUI cycle, especially in the high dose gonadotropin cycle.^{3,5} Additionally, the success rates of IUI generally depend on various factors, including age of the women, motile sperm count, type of infertility, semen preparation, the number of mature follicles, the E2 concentration on the day of human chorionic gonadotropin (hCG) administration, luteal support, and the timing of insemination.^{2,6–10} Because oocytes and sperm have a limited survival time, correct insemination timing is imperative. However, optimal timing of the insemination is still controversial and requires further investigation.

The retrospective cohort study by Yumusak and colleagues in this issue of the *Journal of the Chinese Medical Association* indicated that different insemination timing was associated with pregnancy rate in the certain infertility group when IUI-COS cycle was applied.¹⁰ The authors observed that early insemination (24 hours following hCG trigger) achieved a superior clinical pregnancy rate than standard insemination (36 hours following hCG trigger) in unexplained infertile patients. However, the benefit was not reflected in polycystic ovarian syndrome (PCOS) patients. The authors explained that the main reason for failed pregnancy in unexplained infertile patients is fertilization defects; therefore, early insemination in unexplained infertile couples probably enhanced the fertilization potential of the inseminated sperm, leading to better pregnancy outcomes. Since anovulation is the pivotal reason for infertility in PCOS patients,¹¹ timing of insemination did not affect pregnancy outcome in PCOS couples. This explanation by the authors seemed to be reasonable. The authors supposed that early

insemination might boost the fertilization potential of the inseminated sperm, and sought to confirm their hypothesis by investigating whether or not early insemination might improve pregnancy rate in mild male infertile patients. Besides, the authors found that later ovulation triggered by hCG seemed to contribute to better pregnancy rate than earlier hCG trigger. The authors supposed that the result might stem from higher oocytes quality in later hCG trigger. However, the Cochrane review revealed that there was no difference in the pregnancy rate between early and late hCG trigger.¹² Thus, more studies are required to verify the result.

Does early insemination really improve the clinical pregnancy rate in the IUI-COS cycle? In fact, it remains a debated issue. The present study by Yumusak and colleagues provided us a useful reference,¹⁰ but the evidence supporting this proposition may still be insufficient. First, this was a retrospective cohort study with a small sample size, indicating limited evidence. Second, there have been conflicting results associated with insemination timing in previous studies.^{13,14} For example, Wang and colleagues¹³ conducted a retrospective study enrolling 135 couples undergoing IUI-COS cycles, and found that the efficacy of IUI timing did not differ at either 24 hours or 36 hours after hCG injection. Another prospective study performed by Huang et al¹⁴ recruited 210 couples with ovulatory dysfunction, unexplained infertility, and minimal to mild endometriosis. The infertile couples received an IUI-COS cycle and were treated with IUI 26–28 hours or 36–38 hours after hCG injection. The result also showed similar pregnancy rates between the two groups when IUI was performed at either 26–28 hours or 36–38 hours after hCG injection.¹⁴ By contrast, a prospective randomized trial by Rahman and colleagues¹⁵ showed the conflicted data. This study enrolled 204 couples with mild male factor, unexplained infertility, and mild endometriosis who underwent 461 IUI-COS cycles and were randomized to two groups: Group I (IUI 36 hours after hCG) and Group II (IUI 24 hours after hCG).¹⁵ The result displayed that patients who underwent IUI 36 hours after hCG had marginally better pregnancy rates than the 24 hour group, although without statistical significance.¹⁵ Moreover, the Cochrane review provided no evidence of a difference in pregnancy rates based upon varying IUI timing

ranging from 24–48 hours after hCG injection.¹² There is insufficient evidence to determine whether there is any difference in effectiveness between different synchronized approaches for IUI in subfertile couples.¹² The study by Yumusak and colleagues¹⁰ gave us a concept that couples with recognized causes of infertility possibly obtained a benefit from specific IUI timing. Taken together, the optimal IUI timing, especially for certain populations, is still unknown. Additional large-scale research is needed to determine the optimal IUI timing among different infertile patients.

In conclusion, IUI remains a popular artificial reproductive technology worldwide because it is typically less invasive and less costly than the alternatives. Since the success rates of IUI are persistently low, many factors that could optimize the success rates of IUI remain to be defined. We welcome more large-scale research to determine the optimal IUI timing among different infertile patients.

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Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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