

Can A Change In Ovulation Trigger Significantly Improve ART Outcome In Normal Responder Or Poor Responder Patients Undergoing IVF?

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Introduction

A very recent RCT by Hass J et.al. published in June 2020 has again forced us to think, whether a simple addition of GnRH agonist trigger along with hCG (dual trigger) can help in improving ART results in normal or poor responder patients undergoing IVF⁽¹⁾. Ovulation trigger is used for final oocyte maturation before IVF/IUI. Since mid 1970's exogenous hCG has been used as an ovulation trigger for final oocyte maturation both in IUI and IVF cycles because hCG acts as a surrogate for LH hence mimicking the preovulatory LH surge. The GnRH agonist trigger mimics the natural cycle more closely with both internal LH and FSH surge in comparison to hCG which is surrogate for only LH. FSH surge in a natural cycle helps in resumption of meiosis, further expansion of cumulus cells surrounding the oocyte and stimulates hyaluronic acid synthesis by oocyte cumulus cell complex for final release of oocyte^(2,3,4). The question arises, whether this apparent physiological advantage with GnRH agonist trigger translates clinically into better pregnancy rate?

Summary

GnRH agonist alone as an ovulation trigger has been very well investigated in IVF cycles since its use has been shown to decrease the incidence of OHSS remarkably^(5,6). Lamb et al in a randomized trial demonstrated that addition of FSH bolus along with hCG trigger significantly improves fertilization rate signifying better oocyte competence⁽⁷⁾. Similarly GnRHa trigger combined with hCG trigger has been shown to improve cytoplasmic maturity of oocytes with better fertilization rates⁽⁸⁾. Increasing evidence indicates that dual trigger may be better choice for final oocyte maturation in GnRH antagonist (GnRH-ant) cycles in normal or poor responder patients.

In a meta-analysis by Ding N. et.al in 2017, four eligible RCTs involving 527 women were included.⁽⁹⁾ The results of this meta-analysis indicated that the dual trigger group had a significantly higher pregnancy rate (relative risk [RR], 1.55; 95% confidence interval [CI], 1.17-2.06) than the hCG-only trigger group. No significant differences were found in the number of oocytes retrieved (weighted mean difference [WMD], 0.47; 95% CI, -0.42 to 1.37), number of mature oocytes retrieved (WMD, 0.41; 95% CI, -0.48 to 1.30), number of fertilized oocytes (WMD, 0.47; 95% CI, -0.32 to 1.26), number of good-quality embryos (WMD, 0.17; 95% CI, -0.29 to 0.64), or implantation rate (RR, 1.17; 95% CI, 0.69-2.00) between the two groups. They concluded that, GnRH-a and hCG as dual trigger was equivalent to hCG in triggering oocyte maturation and may be beneficial in improving reproductive outcomes.

Another meta-analysis published in 2018 by Chen CH et.al., not surprisingly reached the same conclusion as it involved the same trials and women (4 studies including 527 women)⁽¹⁰⁾.

A very recent randomized controlled trial published in Human reproduction, June 2020 again confirmed supremacy of dual trigger approach⁽¹⁾. In this double-blinded RCT, 150 normal responder patients were randomized either to receive hCG or dual trigger for final oocyte maturation. It was discontinued after interim analysis due to glaringly significant improvement of results with dual triggering. In the study, the age (36 years versus 35.3 years $P = NS$), BMI (24 kg/m² versus 23.7 kg/m²) and the AMH (20.1 pmol/l versus 22.4 pmol/l) were comparable between the two groups. The number of eggs retrieved (11.1 versus 13.4, $P = 0.002$), the MII oocytes (8.6 versus 10.3, $P = 0.009$), total number of blastocysts (2.9 versus 3.9, $P = 0.01$) and top-quality blastocysts transferred (44.7% versus 64.9%; $P = 0.003$) were significantly higher in the dual trigger group compared to the hCG group. The clinical pregnancy rate (24.3% versus 46.1%, OR 2.65 (1.43-1.93), $P = 0.009$) and the live birth rate per transfer (22% versus 36.2%, OR= 1.98 (1.05-3.75), $P = 0.03$) were significantly higher in the dual trigger group compared to the hCG group.

Conclusion

Based on the recent evidences, use of dual trigger in normal or poor responder patients in IVF cycles seems to improve pregnancy outcome and the simple addition of GnRH agonist does not add much to either the IVF cycle cost or stress. However, this conclusion is based on very few randomized controlled trials and more trials are the need of the hour for confirming the same.

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