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CORRESPONDENCE

Re: Safety and efficacy concerns of long-acting GnRH agonist trigger for ovulation induction in oncological patients undergoing oocyte cryopreservation: a call for caution and further investigation

We read with interest the Letter to the Editor by Ingold and Bedoschi,[1] raising relevant points regarding triggering ovulation with long-acting gonadotropin-releasing hormone agonist (GnRH) agonist (GnRHa) after controlled ovarian stimulation for oocyte cryopreservation, as we have proposed and reported.[2]

We wholeheartedly concur with the appeal for the need for further investigations. As we stated in our conclusions, our aim was to report preliminary data on the feasibility of the option, but, akin to any potentially transformative innovation, sustained evidence from more expansive and randomized cohorts remains imperative before introduction in clinical practice. Rationally, the use of long-acting GnRHa trigger does not entail the complete eradication of the risk of ovarian hyperstimulation syndrome (OHSS), given that this risk is not absent even with the use of short-acting GnRHa trigger alone.[3] Rather, its purpose is to reduce the increase in OHSS risk given by a second flare-up on recently stimulated ovaries, as it would happen with a long-acting GnRHa injection a few days after oocyte retrieval. Notably, the published cases of OHSS with the use of long-acting GnRHa before chemotherapy occurred under such circumstances.[4-6]

The biological rationale underlying this risk is readily apparent. A long-acting GnRHa injection after egg retrieval causes a second gonadotrophin flare-up before initiating ovarian suppression, as the pituitary regains its responsiveness not later than a week after the short-acting GnRHa trigger.[7] This flare-up stimulates recent corpora lutea: short-acting GnRHa trigger usually prompts a more rapid luteolysis than traditional human chorionic gonadotropin trigger,[8] but the literature shows variability between patients regarding luteolysis kinetics, with cases of luteolysis as far as 8 days after trigger with short-acting GnRHa.[9] Moreover, if we consider that human corpus luteum functional recovery was described as far as after 7 days of deprivation,[10] it becomes evident that the risk for a renewed surge in oestrogens and progesterone exists, prompted by the gonadotropin flare-up caused by the long-acting GnRHa injection before chemotherapy. This scenario aligns with the cases documented in the literature of OHSS in fertility-preservation patients.[4-6] In clinical practice, the risk may discourage gynaecologists and oncologists to start GnRHa before chemotherapy in cases of abundant ovarian response. These patients are those who would especially benefit from the use of long-acting GnRH trigger before oocyte retrieval.

Ingold and Bedoschi also advocate for a better understanding of the advantages of ovarian suppression with long-acting GnRHa in different patients. We wholeheartedly agree with the need to bridge this gap in our knowledge. Indeed, while we have compelling evidence for breast cancer,[11] there is still uncertainty regarding its efficacy in patients affected by other neoplasms.[12,13] Based on recent guidelines, GnRHa use during chemotherapy is a standard approach in women with cancer receiving cytotoxic therapy who wish to mitigate the risk of developing premature ovarian insufficiency.[14] However, this approach should not be considered a fertility-preservation strategy *per se* and should not replace but should follow a cryopreservation procedure.[14] Consequently, prioritizing research into the optimal methods for safely and effectively providing oocyte/embryo cryopreservation followed by the use of GnRHa during chemotherapy is paramount.

In conclusion, we concur that our proposal to trigger ovulation with long-acting GnRHa is promising, but, as we concluded in our report, further research is needed to better describe its efficacy and safety before affirming it should be the standard in clinical practice. This research should take place as a prospective, randomized controlled collaborative effort to maximize the number of patients and reduce biases.

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