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LETTER TO EDITOR

In reply to: Christ J, Herndon CN, Yu B. Severe ovarian hyperstimulation syndrome associated with long-acting GnRH agonist in oncofertility patients. J Assist Reprod Genet. 2021;38:751–6. doi:10.1007/s10815-020-02051

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To the editor,

We read with great interest the paper by Christ and colleagues who describe three cases of severe early-onset ovarian hyperstimulation syndrome (OHSS) in oncofertility patients undergoing fertility preservation treatment [1]. All patients underwent controlled ovarian stimulation using a GnRH antagonist protocol with GnRH agonist (GnRH-a) triggering, and a depot GnRH agonist was administered immediately following oocyte retrieval for the purpose of ovarian protection.

The possibility to trigger the final stage of ovulation in GnRH antagonist cycles with a GnRH-a instead of hCG virtually eliminates the risk for OHSS [2]. However, this method of ovulation triggering induces massive luteolysis resulting in an ill luteal phase associated with reduced delivery rates [3]. Methods such as "Intensive luteal support" regimens and co-administration of low-dose hCG have been suggested to overcome this limitation but carry major drawbacks. Administration of IM and vaginal progesterone, as well as oral, transdermal, and vaginal estrogen supplementation, is rather cumbersome and far from being patient friendly. The disadvantage of using low-dose hCG is the potential risk of severe OHSS; thus, losing the safety benefit of the GnRH-a trigger [4].

Successful luteal support using solely continuous administration of intranasal (IN) GnRH-a in antagonist cycles triggered with GnRH-a have been reported in standard IVF treatments [5, 6]. One major advantage of this therapeutic approach is comfortable administration of a nasal spray compared with vaginal or intramuscular progesterone administration. In addition, GnRH-a administration is not required beyond the first two weeks of pregnancy. Furthermore, this approach has been suggested as a method to avoid OHSS in patients at high risk when patients with high ovarian response were triggered with GnRH-a and given luteal support using IN GnRH-a [7]. However, a case of severe early OHSS using IN GnRH-a for luteal support has been subsequently reported [8], and we have also encountered several such cases in our practice (unpublished data). This is not surprising, considering the effectiveness of the GnRH-a in "rescue" multiple corpora lutea following triggering of ovulation with GnRH-a.

Christ and colleagues [1] describe in fact a very similar clinical scenario where a long-acting GnRH-a was administered following oocyte retrieval for the purpose of ovarian protection. The formulation of GnRH-a with continuous release acted inadvertently as a massive "luteal support" agent, rescuing multiple corpora lutea and causing severe OHSS. The cases Christ et al. describe demonstrate that early OHSS may occur in when IM long-acting GnRH is administered, in addition to the IN route. Importantly, they point to the potentially problematic interface of fertility specialist and oncologist involved in care of oncofertility patients. We agree that both reproductive medicine specialists and oncologists should be made aware of the potential risk of developing severe OHSS following administration of short or long-acting formulations of GnRH-a for ovarian protection, in patients at high risk for OHSS following

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oocyte retrieval for fertility preservation despite GnRH-a ovulation triggering.

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