Kung et al\textsuperscript{1} authored a valuable article entitled “Luteal phase support with decapetyl improves pregnancy outcomes in ICSI with basal FSH \textgreater 8 mIU/mL or mature oocytes \textless 3\textquotedblright. This retrospective study enrolled 240 patients who underwent intracytoplasmic sperm injection (ICSI). One hundred and forty-seven patients were in the decapetyl group and 93 patients were in the control group. The authors investigated the effect of decapetyl as an additional luteal phase support (LPS) in \textit{in vitro} fertilization (IVF) cycles and tested which subgroup would benefit from the treatment.\textsuperscript{1} We recognize the probity of this publication.

Luteal phase defect is a common problem encountered during IVF cycles. In the past, several theories have been proposed such as (1) defective corpora lutea formed from the remnants of the aspirated follicles and (2) prolonged pituitary downregulation by the gonadotropin-releasing hormone (GnRH) agonist. Both of these theories attempt to explain premature luteolysis during IVF cycles; however, there has been a lack of subsequently published studies with sufficiently reliable evidence to support these theories.\textsuperscript{2} By contrast, a new hypothesis of multiple corpora lutea has been proposed. This hypothesis is based on the effect occurring after ovarian hyperstimulation wherein more steroids are subsequently produced, which suggests that the negative feedback on the pituitary gland inhibits luteinizing hormone release. Premature luteolysis arise from the negative feedback by high concentrations of steroids caused by multiple corpora lutea.\textsuperscript{3} However, there is no doubt that LPS is essential to enhance reproductive outcomes in IVF cycles. Progesterone and human chorionic gonadotropin have served as popular and effective LPS agents.\textsuperscript{2} In addition, Tesarik et al\textsuperscript{3} described using a GnRH agonist as LPS to improve the implantation rate, pregnancy rate, and live birth rate. Several studies\textsuperscript{4–7} subsequently support the results obtained by Tesarik et al,\textsuperscript{3} whereas other studies show dissimilar conclusions.\textsuperscript{8,9} Taken together, two systemic reviews, which include meta-analyses, demonstrate that administering a luteal phase single-dose GnRH agonist can significantly ameliorate IVF outcomes.\textsuperscript{2,10} Kung et al\textsuperscript{1} confirmed in their study the beneficial effect of luteal phase single-dose decapetyl administration on the implantation rate (24.5\% vs. 17.0\%;\textit{p} = 0.023), clinical pregnancy rate (49.0\% vs. 33.3\%;\textit{p} = 0.023), and live birth rate (41.5\% vs. 28.0\%;\textit{p} = 0.039).

The precise mechanism of how a GnRH agonist exerts its effect in the luteal phase remains unclear. Some studies suggest that a GnRH agonist may have a role in regulating embryo–endometrial interactions.\textsuperscript{11,12} Metallinou et al\textsuperscript{13} however showed that GnRH agonists promote apoptosis of granulosa luteal cells and directly inhibit progesterone production in human granulosa luteal cells. Gonadotropin-releasing hormone agonists seem to have a positive effect on the embryo and endometrium, but a negative effect on the corpus luteum.

Despite controversial clinical results\textsuperscript{11–13} and possible mechanisms, the previous literature findings indicate added beneficial effects and more positive mechanisms when a GnRH agonist is administered as LPS.\textsuperscript{11,12} A GnRH agonist administered for specific groups such as LPS can supposedly generate a subsequent improved benefit.

A GnRH agonist, which can act on embryos and on the endometrium through GnRH agonist receptors,\textsuperscript{13} theoretically may fail to function properly because of prolonged and persistent downregulation of the GnRH receptors during IVF cycles with a long protocol. Therefore, the extension of the GnRH agonist through the luteal phase in IVF cycles does not enhance reproductive outcomes.\textsuperscript{14,15} In 2006, a prospective randomized study revealed that the administration of the luteal phase GnRH agonist enhances ICSI clinical outcomes in GnRH agonist-treated and GnRH antagonist-treated ovarian stimulation cycles.\textsuperscript{5} However, later studies demonstrate that luteal phase GnRH agonists mostly work within the GnRH antagonist protocol,\textsuperscript{5,10} but not in the long GnRH agonist protocol.\textsuperscript{5,9}

In the Kung et al\textsuperscript{1} study, the investigators verified that clinical pregnancy rate and live birth rate significant increased with the GnRH antagonist protocol (\textit{p} = 0.025 and \textit{p} = 0.035, respectively), but not with the long GnRH agonist protocol (\textit{p} = 0.288 and \textit{p} = 0.367, respectively). The Kung et al\textsuperscript{1} study moreover revealed that patients with higher basal FSH (>8 mIU/mL) or reduced numbers of mature oocytes (\textless 3) may have a better prognosis after using luteal phase decapetyl.\textsuperscript{1} However, because of the following reasons, Kung’s proposals may require more substantial evidence. First, the decapetyl was theoretically administered during the luteal phase, which may affect the embryo, endometrium, or corpus luteum, but not the ovarian reserve. Second, in the Tesarik et al\textsuperscript{3} study, the administration of a luteal phase GnRH agonist also was beneficial in the oocyte donation program. Thus, the patients who had diminished ovarian reserve with better reproductive outcomes may have had this as a benefit of
receiving the GnRH antagonist protocol. In the supplemental Table 3 in the Kung et al1 study, the researchers tried to clarify the impact of reduced mature oocytes. In addition, Qublan et al7 demonstrated that patients with a thin endometrium (≤7 mm) on the day of oocyte retrieval had increased implantation and pregnancy rates from the administration of a luteal phase GnRH agonist. However, it is difficult to make a conclusion from such small sample size. Additional large-scale randomized controlled trials are needed.

In conclusion, the administration of a luteal phase GnRH agonist improved IVF outcomes for the most part. To analyze the subgroups, patients with GnRH antagonist stimulation protocol seem to have a proven record of patient benefits. However, other subgroups such as women with diminished ovarian reserve or women with a thin endometrium lack strong support. The mechanism and a standard protocol are needed so that large scale, randomized controlled trials can occur.

Conflicts of interest

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

References


