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Editorial

The use of luteal-phase ovarian stimulation for poor ovarian responders undergoing *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer treatment

Poor ovarian response remains a tough and challenging topic encountered during *in vitro* fertilization (IVF) [1,2]. Polyzos and colleagues [3] indicated that live birth rates were only 6.0% per cycle and 9.9% per patient in poor ovarian responders (PORs) based on the Bologna criteria. The Cochrane review published in 2010 concluded that there is insufficient evidence to support the routine use of any pituitary downregulation and ovarian stimulation protocols in the management of PORs [4]. A randomized, controlled trial comparing the use of a gonadotropin-releasing hormone (GnRH) agonist long protocol, a GnRH agonist short protocol, and a GnRH antagonist protocol in PORs revealed no significant differences in pregnancy outcomes [5]. However, Kuang and colleagues [6] demonstrated a novel protocol of luteal phase ovarian stimulation (LPOS) in normal responders with optimal pregnancy outcomes and no cases of premature luteinizing hormone (LH) surge. In the luteal phase, progesterone and estradiol secreted from the corpus luteum have a negative feedback to suppress LH release [7]. Therefore, it is reasonable to suggest that LPOS may be a suitable regimen for PORs who are easy to suffer from premature LH surge during the follicular stimulation.

The study by Wei and colleagues [8] in the current issue of the *Taiwanese Journal of Obstetrics & Gynecology* attempted to compare the IVF outcomes between LPOS and GnRH antagonist regimens in PORs. The authors concluded that LPOS is a feasible and possibly better protocol for PORs when compared to the GnRH antagonist protocol [8]. The authors observed that on the human choriogonadotropin trigger day, PORs in the LPOS group achieved significantly lower serum levels of LH than those in the GnRH antagonist group. Moreover, a marked lower rate of LH $\geq$ 10 was noted in the LPOS group (0%) than in the GnRH antagonist group (9.5%). However, total gonadotropin consumption and duration of stimulation in the LPOS group were significantly greater than those in the GnRH antagonist group. Above all, the authors found that PORs in the LPOS group obtained a significantly higher pregnancy rate (46.4%) than those in the GnRH antagonist group (overall, 25.8%; $p = 0.04$) with the transfer of fresh embryos (22.9%, $p = 0.03$) and the transfer of frozen embryos (29.6%, $p = 0.15$) [8]. By contrast, the authors displayed that in the LPOS group, the retrieved oocyte numbers in the luteal phase were significantly higher than those in the follicular phase [8].

Although Wei and colleagues [8] presented promising data with regard to the use of LPOS for PORs, we have to interpret the data carefully. First, the 'LPOS' in the study actually included LPOS alone and double stimulations (combined follicular phase and luteal phase stimulations), which rendered the group heterogeneous. Furthermore, to compare double stimulations with a GnRH antagonist protocol (single stimulation) may be a bias. Second, in addition to the bias of comparison between frozen embryos and fresh embryos, the authors compared frozen embryos between LPOS and GnRH antagonist groups, which was also a bias. Generally, good embryos are usually applied in the fresh embryos transfer. The quality of the residual frozen embryos is usually poorer. Third, the authors conducted different stimulation protocols of follicular phase (mild stimulation or natural cycle) and luteal phase (standard stimulation) in the double stimulations, which may be why more oocytes were retrieved from the luteal phase stimulation than from the follicular phase stimulation. In fact, there are several biases in the retrospective study. Therefore, we must be cautious with explaining the data. Further large-scale randomized, controlled studies are required to prove the results.

Accumulated evidence showed that multiple waves of antral follicles develop during the human menstrual cycle [9]. Several studies substantiated that antral follicles at the luteal phase are able to grow to maturity under proper ovarian stimulation [10,11]. First of all, LPOS was applied for cancer patients. Von Wolff et al [12] reported that there are no significant differences in numbers of aspirated oocytes, metaphase II oocyte rates, and fertilization rates between follicular and luteal phase stimulations in cancer patients. A retrospective cohort study conducted by Cakmak and colleagues [13] disclosed that the number of total and mature oocytes retrieved, oocyte maturity rate, and fertilization rates were similar in random-start (late follicular phase or luteal phase) and conventional-start (early follicular phase) cycles in the cancer patients. Kuang and coworkers [6] first performed LPOS in normal responders and concluded that LPOS is a feasible and effective approach of ovarian stimulation with optimal pregnancy outcomes. Additionally, a prospective comparative study revealed that donor oocytes obtained after ovarian stimulation initiated on Day 2 or Day 15 of the cycle achieved similar IVF outcomes [14]. Kuang and colleagues [15] first developed double stimulations for PORs and demonstrated that double stimulations provide more opportunities for retrieving oocytes during a short period in PORs. When compared to the traditional antagonist protocol, LPOS achieved better IVF outcomes in PORs in the study of Wei et al [8]. However,

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more studies are required to validate the efficacy of LPOS in PORs and optimal stimulation protocol in LPOS.

In summary, different stimulation protocols are one of the strategies which attempt to improve clinical outcomes of PORs. However, the effective and appropriate regimen for PORs remains controversial in previous studies. A novel protocol of LPOS is regarded as a potential better one in the management of PORs. Wei and colleagues [8] indicated that the LPOS protocol enhanced IVF outcomes compared with the GnRH antagonist protocol in PORs. However, further large-scale randomized, controlled studies are required to confirm the efficacy of LPOS in PORs and to investigate an ideal stimulation protocol in LPOS.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Li-Te Lin
Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Peng-Hui Wang
Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan

Department of Biological Science, National Sun Yat-Sen University, Kaohsiung, Taiwan

Division of Gynecology, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan

Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan

Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

Immunology Center, Taipei Veterans General Hospital, Taipei, Taiwan

Infection and Immunity Research Center, National Yang-Ming University, Taipei, Taiwan

Kuan-Hao Tsui*
Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan

Department of Pharmacy and Graduate Institute of Pharmaceutical Technology, Tajen University, Pingtung County, Taiwan

* Corresponding author. Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Number 386, Dazhong 1st Road, Zuoying District, Kaohsiung City 81362, Taiwan.
E-mail address: khtsui60@gmail.com (K.-H. Tsui).