

# Enhancement of outcome in women with poor ovarian responses

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In the November issue of the *Journal of the Chinese Medical Association*, Dr. Yu et al<sup>1</sup> published an interesting research article entitled “Progestin-primed ovarian stimulation improves the outcomes of IVF/ICSI cycles in infertile women with diminished ovarian reserve.” The authors tried to resolve a tough and challenging issue encountered during assisted reproductive technology (ART)—infertile women with diminished ovarian reserve, which is also called poor ovarian response (POR), characterized by at least two of the following three features, including (1) advanced maternal age or any other risk factor for POR; (2) a previous POR; and (3) an abnormal ovarian reserve test, such as those patients who have serum follicle-stimulating hormone > 15 mIU/L, or serum anti-Müllerian hormone < 1 ng/mL, and abnormally low antral follicle counts < 4 on day 2 of their menstrual cycle.<sup>2–5</sup> Women needing ART treatment may struggle with heavy burden, such as the fear of failure, physiological harms after treatment, and heavy economic consideration.<sup>6</sup> All are much more apparent in women with POR, because regardless of the definition of POR, a poor response to controlled ovarian stimulation (COS) potentially results in high cancellation rates, reduced numbers of oocytes retrieved, decreased numbers of embryos available for transfer, and lower pregnancy rates as well as extremely low live birth rate (6% per cycles) compared with normal or higher responders.<sup>7</sup> Therefore, we are glad to learn much more efforts of the studies focusing on this topic, as shown in the current issue of the *Journal of the Chinese Medical Association*.<sup>1</sup>

To ensure patients have the greatest chance of a live birth, it is important that treatment should be individualized.<sup>8</sup> Among these, the selection of the most appropriate treatment and dosing for COS remains the keystone of successful ART treatment, aiming at achieving multi-follicular development to obtain a better chance of transferring embryos with the highest

implantation potential.<sup>9</sup> In fact, the most optimal individualized COS with efficacy, safety, and patient friendliness in conjunction with intrauterine insemination or *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) has become the mantras of modern ART,<sup>10,11</sup> because it involves the quantity and quality of retrieved oocytes (an absolute minimum without compromising live birth rates) and, of most importance, it decreases the risk of development of ovarian hyperstimulation syndrome.<sup>8–13</sup>

Although several COS protocols are reported effectively and usefully in modern ART, they can easily be classified as two categories, conventional long-protocol (downregulation) and others, both of which are based on short-term pituitary suppression, premature follicle selection prevention, and luteinized hormone rise avoidance.<sup>7</sup> Unfortunately, there is still absent of agreement on the best approach for maximizing the oocyte yield and the chances of pregnancy in POR. In 2014, Cakmak et al<sup>14</sup> developed a new COS protocol for POR and, in the next year, Kuang et al<sup>15</sup> introduced a novel protocol for POR. The former used estrogen priming in the luteal phase of the cycle preceding IVF and by seven days of gonadotropin releasing hormone (GnRH) antagonist pretreatment to start ovarian stimulation protocol and the latter used progestin-primed short ovarian stimulation protocol initially from menstrual cycle day 3.<sup>14,15</sup> A recent meta-analysis summarized 170 patients from three clinical trials showed an 18.8% clinical pregnancy rate in POR patients treated with Cakmak’s delayed start GnRH antagonist COS protocol;<sup>7</sup> by contrast, the study by Yu et al<sup>1</sup> showed a 27.5% clinical pregnancy rate in POR patients treated with progestin-primed short COS protocol and, of most importance, live-birth rate was higher up to 22.5%.<sup>1</sup> In addition, miscarriage rate seemed to be similar between Cakmak’s protocol from a meta-analysis and Kuang’s protocol in Dr. Yu’s study (18.8% vs 18.2%), but significantly lower than that of conventional COS protocols (45.5%~100%).<sup>1,7</sup> Although it may be inappropriate to compare with each other directly, the data from the study by Yu et al<sup>1</sup> study seemed to favor the use of progestin-primed ovarian stimulation protocol as a better alternative COS protocol in the management of women with POR based on its higher successful live-birth rate.

Even if the effects of progestin-primed COS protocol on the reduction of miscarriage rate and increased live-birth rate were encouraging, Dr. Yu’s study has some limitations. First, the dose of human chorionic gonadotropin was statically significantly higher in the progestin-primed COS protocol than conventional COS protocol. Second, the data on miscarriage rate from the current study with a small number of cycles (n = 18) and events

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(n = 7 miscarriage in the control group vs 2 in the intervention group). Even though the data of live-birth rate were provided, the value also limited to a small number of cycles (n = 79) and events (n = 0 live birth in the control group versus 9 in the intervention group). All potentially limited the precision of the effect size calculated. However, there is the strength of Dr. Yu's study, because the data of live birth were provided, and in fact, live-birth is currently considered as the primary outcome measure of choice in trials in ART.<sup>7</sup> Given the limitation of a small number of subjects, future large, and well-designed prospective, randomized trials are welcome to demonstrate the benefits of this relatively new protocol for COS in women with POR.

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