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## COMMENTARY

# Dual ovarian stimulation is a new viable option for enhancing the oocyte yield when the time for assisted reproductive technology is limited

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**Abstract** Ovarian stimulation improves assisted reproductive technology outcome by increasing the number of oocytes available for insemination and in-vitro handling. A recent Duplex protocol features a dual stimulation, with the second stimulation started immediately after the first oocyte retrieval. Remarkably, the Duplex protocol is unexpectedly well tolerated by women and provides twice as many oocytes and embryos as a regular antagonist protocol in less than 30 days. 

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Ovarian stimulation was designed for improving assisted reproductive technology outcome by providing more than one oocyte to inseminate. Logically, the ovarian stimulation protocols used in assisted reproductive technology aim to modify the hormonal environment of the follicular phase to fool the natural mechanisms of single follicular dominance that normally exist in women. The therapeutic objective was to prevent the decrease in circulating FSH occurring in the mid-follicular phase, which is precisely responsible for single follicular dominance. Practically, this is achieved by enhancing the endogenous production of FSH, using clomiphene citrate or aromatase inhibitors, or by providing exogenous FSH and human menopausal gonadotrophin. Today, 3 decades later, ovarian stimulation remains the single most effective measure ever taken for improving assisted reproductive technology outcome.

The time constraints associated with emergency fertility preservation before starting oncology treatments has led to shorter ovarian stimulation protocols being used. This was notably achieved by starting stimulation at any time in the menstrual cycle (the 'random-start' protocols) rather than precisely in the early follicular phase or after down regulation (Ozkaya et al., 2012). The 'freeze all' design used in fertility preservation treatments therefore no longer required ovarian stimulation to be dependent on the physiological advancement of the endometrium to optimize the chances of embryo implantation.

The only unknown was whether the random start of stimulation might alter the size of the oocyte crop, its functionality (fertilization rates), or both. These fears were rapidly dismissed, as the oocyte yields of the 'random-start'

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protocols were found to equal those of ovarian stimulation started in the early follicular phase (Cakmak et al., 2013). These data indicate that ovarian stimulation can be totally disconnected from the cycling phases of endogenous gonadotrophins without any detrimental consequences, as long as no fresh embryo transfer takes place.

In parallel with the new challenges encountered in fertility preservation, cryopreservation has made a quantic leap forward through the improvement of oocyte and embryo vitrification. Oocyte and embryo vitrification indeed offered access to an emerging new realm of 'no-loss cryopreservation', which brings to the fore a multitude of new practical options in assisted reproductive technology.

Moreover, the achievements of oocyte and embryo vitrification dovetailed perfectly with a novel mode of triggering final stage of oocyte maturation. Indeed, the advent of antagonist stimulation protocols revived the possibility of triggering ovulation with gonadotrophin-releasing hormone (GnRH) agonist that induces an endogenous surge of LH and FSH (Gonen et al., 1990; Itskovitz et al., 1991), instead of using exogenous HCG (510,000 IU). This approach described over 2 decades ago could not be used when gonadotrophin down-regulation GnRH agonist protocols were the rule in assisted reproductive technology. The 'GnRH-trigger' option is widely used in oocyte donors (Bodri et al., 2010; Weissman et al., 2014) and for avoiding the risk of ovarian hyperstimulation syndrome (OHSS) in association with a freeze-all strategy (Weissman et al., 2014).

Kuang et al., (2014a) capitalized on the combined achievements of the random-start protocols and embryo vitrification by testing the possibility of deliberately starting ovarian stimulation during the luteal phase. The investigators showed that 'luteal-phase start' stimulation is feasible, and produces a normal number of competent oocytes and optimal pregnancy rates from cryopreserved embryo transfer cycles. In their trial, ovarian stimulation was accomplished using a combination of aromatase inhibitor (letrozole 2.5 mg/day) and human menopausal gonadotrophin (225 IU/day), starting immediately after spontaneous ovulation until three or more follicles had reached a diameter of 18 mm or wider. Final oocyte maturation was triggered using triptorelin 0.1 mg. All 242 participants underwent oocyte retrieval, which yielded 13.1 oocytes on average and achieved a clinical pregnancy rate in cryopreserved embryo transfer cycles of 48.9%. Logically, Kuang's (Kuang et al., 2014a) data further fuelled the concept that ovarian stimulation can be dissociated from the follicular phase and its hormonal environment, as long as no fresh embryo transfer takes place.

In this issue of *Reproductive Medicine Online*, the same team of investigators recount their experience, venturing one step further by adapting ovarian stimulation to the needs of certain groups of patients (Kuang et al., 2014b). In their current study, Kuang et al. (2014b) conducted two successive ovarian stimulations in the follicular and ensuing luteal phase. The trial was conducted in 38 patients who all fulfilled the Bologna criteria for poor responders, based on prior ovarian stimulation outcome, baseline hormonal levels and age. The first and second stimulations used two different regimens as follows: the first stimulation was conducted using a combination of clomiphene citrate 25 mg per day starting on day 3 of the cycle until the triggering of ovulation; letrozole 2.5 mg per day starting on day 3, for a total of 4 days; and

human menopausal gonadotrophin 150 IU every other day, starting on day 6 until the triggering of ovulation. The second stimulation was started after the first oocyte retrieval, provided that two or more antral follicles were identified. This stimulation regimen, which differed from the first stimulation, consisted of letrozole 2.5 mg and human menopausal gonadotrophin (225 IU/day), which were both started from the day of retrieval until the second triggering of ovulation.

For both the first and second stimulations, final oocyte maturation was induced with triptorelin 0.1 mg administered when three or more follicles measured 18 mm or more in diameter. Furthermore, premature ovulation was prevented using ibuprofen (600 mg/day) on the day of triggering ovulation and the day after. Notably, no GnRH antagonist was used in either stimulation. Ultimately, 30 out of 38 patients underwent two consecutive oocyte retrievals, with the second ovarian stimulation yielding a larger number of oocytes and embryos than the first.

The magnitude of the ovarian response to the first and second ovarian stimulation cannot be directly compared in Kuang's data because of the marked difference in the stimulation regimens used in each of them. It remains, however, that Kuang's study (2014b) provides clear evidence that a second ovarian stimulation can be conducted immediately after a first stimulation and oocyte retrieval, leading to a valuable improvement in the overall number of oocytes and embryos obtained.

Kuang et al. presented their data on luteal phase stimulation presented at the fifth Asia Pacific Congress on Building Consensus out of Controversies in Gynecology and Infertility, November 21–24, 2013. A year later, the same group presented the double stimulation at the Controversies in Gynecology and Infertility meeting in Barcelona (COG-IMSRR April 25–26, 2014). Following on from these findings, we similarly offered a dual stimulation, the 'Duplex protocol' (DPX), to patients whose response to ovarian stimulation was bound to be weak. We feel that it is appropriate to provide some of our preliminary data here, as a conventional dual FSH-antagonist ovarian stimulation approach was used in the DPX protocol. Hence, our data expand the interest for the dual ovarian stimulation strategy, indicating that it is not limited to the specific protocol but rather the complex protocol used by Kuang et al. (2014b). Our preliminary data tend to confirm Kuang's findings. In our study, a second ovarian stimulation started immediately after a first oocyte retrieval was well tolerated and provided as many oocytes and blastocysts, as obtained in the first ovarian stimulation. In our DPX protocol, both the first and second stimulations used a similar regimen consisting of a classical antagonist protocol using 300 IU of FSH per day, cetrorelix 0.25 mg starting on ovarian stimulation day 6 and GnRH trigger (triptorelin 0.2 mg) when follicular maturation was reached. The first and second stimulations provided a similar number of oocytes, zygotes and blastocysts. The DPX protocol thus doubled the final blastocyst yield, compared with a classical single-ovarian stimulation assisted reproductive technology cycle. Data from our DPX protocol that used conventional ovarian stimulation regimens, identical for the first and second stimulations, support the findings of Kuang's report published in this issue of *Reproductive Medicine Online* (Kuang et al., 2014b). A striking finding in our DPX experience, also reported by Kuang, is the good general tolerance of the second ovarian stimulation

started immediately after a first oocyte retrieval. No cyst, undue pain, or both, were encountered by any of our DPX participants.

Kuang's data (2014b) and our findings indicate that a dual back-to-back ovarian stimulation protocol is a viable option for coping with the insufficient ovarian responses that are sometimes encountered in ART. Moreover, the short overall duration of these approaches (<30 days) is valuable for cases of fertility preservation. Indeed, the DPX approach permits coping with the time constraints of fertility preservation and the desire to accumulate the largest number of oocytes possible.

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