—Review—

Ovarian stimulation in *in vitro* fertilization

Yusuke Fukuda*, Yukiko Katagiri and Mineto Morita

Department of Obstetrics and Gynecology, School of Medicine, Faculty of Medicine, Toho University, Tokyo 143-8541, Japan

Abstract: In assisted reproductive technology (ART) treatments, the ovarian stimulation method is important for obtaining many good quality oocytes. The first ovarian stimulation treatments used high stimulation in long and short protocols with gonadotropin releasing hormone (GnRH) agonists. It was formulated to suppress the luteinizing hormone (LH) surge while the follicles are developing. Subsequently, a moderate stimulation with an antagonist was introduced following the development of GnRH antagonists, and low stimulation that inhibits the LH surge with continuous administration of clomiphene citrate. However, cases have been reported occurred in which estrogen replacement therapy was selected to facilitate follicular development by supplementing estrogen in ovarian insufficiency. Otherwise ART cryopreservation technology has also developed. These practices are referred to as oncofertility, and have given rise to new ovarian stimulation methods in infertility treatment. Ovarian stimulation with the random start or double stimulation methods, which are not readily affected by the menstrual cycle, and progestin-primed ovarian stimulation (PPOS) that inhibits the LH surge with a progestogen have come to be performed and are showing good outcomes. As the social and medical backgrounds change, the methods of ovarian stimulation may futher improve in the future.

Key words: *In vitro* fertilization, Ovarian stimulation, Protocol

Introduction

Ovarian stimulation is performed in the first stage of ART for pregnancy. The number of good quality oocytes that can be obtained in oocyte retrieval is important for the success of ART. In Japan, preimplantation genetic testing for aneuploidy (PGT-A) is generally not performed, and embryos are commonly evaluated by their developmental rates and morphological assessments, although there are some differences between ART centers. In data from other countries, it has been shown that, because not all blastocysts are normal, as many embryos as possible are needed [1]. Many oocytes need to be retrieved in order to obtain many embryos, therefore ovarian stimulation is normally performed. Ovarian stimulation is divided into low stimulation, moderate stimulation, and high stimulation depending on the level of ovarian reserve, but the random start method and double stimulation method have come to be used in oncofertility. The “freeze all” strategy has spread due to its stable results, prevention of ovarian hyperstimulation syndrome (OHSS) with freeze-thaw techniques [2, 3], and the disruption of endometrial synchronization due to progesterone [4]; and it has also been used as a progestin-primed ovarian stimulation (PPOS) method for ovarian stimulation in the luteal phase. The range of options for ovarian stimulation is expanding and stimulation methods suited to the patient can now be proposed. Conventional ovarian stimulation, ovarian stimulation for patients with ovarian insufficiency, and ovarian stimulation in a “freeze all” strategy are described below.

Protocol Based on Ovarian Function

Gonadotropin releasing hormone (GnRH) agonist and GnRH antagonist are in the mainstream of ovarian stimulation protocols, used worldwide. When deciding the protocol of ovarian stimulation, judgments are often made based on the FSH level, LH level, E_2 level, anti-Müllerian hormone (AMH) level, and antral follicle count (AFC) [5]. For example: when AMH is over 15 pmol/l, the high response group, the GnRH antagonist method with 150 IU FSH is selected; when AMH is 5–10 pmol/l, the normal response group, the GnRH agonist method is selected; AMH is 1–5 pmol/l,the poor response group, the GnRH antagonist method with 300 IU FSH is selected [6].

Received: August 13, 2018
Accepted: September 21, 2018
*To whom correspondence should be addressed.
E-mail:yuusuke.fukuda@med.toho-u.ac.jp

Conventional Ovarian Stimulation

The main drugs used in ovarian stimulation are oral anti-estrogen agents, recFSH and hMG preparations as injectable agents, gonadotropin releasing hormone (GnRH) antagonist preparations as injectable agents, GnRH agonist nose drops and hCG as injectable agents. Ovarian stimulation requires combinations of these drugs with consideration of their respective characteristics.

Methods for facilitating follicular development while inhibiting the start of the luteinizing hormone (LH) surge with the anti-estrogen effect from continuous oral administration of clomiphene citrate [7] are often selected for poor responders, and patients with decreased ovarian function. In addition, GnRH antagonists may also be used for the last part of ovarian stimulation in cases when follicular development with the combination of recFSH or hMG preparations is good and the LH surge is insufficiently inhibited with the anti-estrogen clomifene. For poor responders, the pregnancy rate and live birth rate with mild stimulation using clomifene can be equivalent to or higher than that of high stimulation [8]. For cases suspected of insufficient pituitary response, a dual trigger of GnRHa and hCG, 1,000 IU, injection is used to increase the oocyte collection rate [9].

In young patients and patients with polycystic ovary syndrome (PCOS) with high responses, the degree to which OHSS, a side effect of ovarian stimulation, can be suppressed is a crucial point. With respect to OHSS, the use of GnRH antagonists acts as a trigger and fresh embryo transfers should be avoided, and currently, there are almost no instances of moderate or more severe disease requiring inpatient treatment. In patients with a high risk of OHSS, the occurrence of OHSS is inhibited by the use of GnRH agonists that cause an endogenous LH surge, rather than the use of exogenous hCG to stimulate the corpus luteum.

In patients with normal responses and follicular development under the age of 35, oocytes can be collected in oocyte retrieval with most ovarian stimulation methods, if ovarian function is not excessively decreased by premature ovarian insufficiency (POI) or ovarian endometrial cyst complications, and good blastocysts that will result in pregnancy can be obtained. Comparing the GnRH antagonist and GnRH agonist methods, when ovarian function is normal, the agonist method has a higher pregnancy rate, but GnRH antagonist has greater merit due to its reduction of OHSS risk [10].

Ovarian stimulation should be considered with taking account of the hospital visit schedule and other factors affecting each patient. Factors that make it difficult to choose a treatment are exceedingly decreased ovarian function due to POI or ovarian endometrial cyst complications, and an age over 40 years. In Japan, the age of patients receiving ART has risen in recent years and is now centered around the age of 40 [11]. Subsequently, an increasing number of patients suffer some distress in ovarian stimulation. As mentioned above, various drugs for use in ovarian stimulation techniques have been developed, and a number of different methods can now be considered in selecting the one that best suits the patient. Among these considerations, the most important in performing ovarian stimulation is thought to be inhibition of the LH surge before the start of the surge is induced. Typically, oocytes are retrieved before ovulation after maturity is confirmed based on follicular diameter and the estradiol (E2) level; then, a decision to retrieve oocytes is made, and the LH surge is triggered. However, in patients with ovarian insufficiency or older patients, an early LH surge is sometimes observed together with a rapid rise in E_2 levels due to excess endogenous FSH or other factors [12]. GnRH agonists used to be the most commonly used agents in ovarian stimulation, and with the long protocol using GnRH agonists to inhibit the LH surge not only endogenous LH but also FSH is inhibited, and the amount of gonadotropin used increases. As a result, the number of maturing follicles also increases, but because endogenous LH is inhibited by GnRH agonist, hCG is needed for the trigger. When ovarian reserve is high, the risk of OHSS increases. The GnRH antagonist method has, therefore, been adopted worldwide as an ovarian stimulation technique that lowers the risk of OHSS, and has become the method of choice in place of the GnRH agonist method.

The above three stimulation protocols are conventionally described as mild stimulation, moderate stimulation, and high stimulation.

Ovarian Stimulation in Ovarian Insufficiency Patients

In cases of decreased ovarian reserve, a decrease in the FSH value may be expected with Kaufman therapy for high FSH levels on the third day of menstruation. Ovarian stimulation is performed after FSH levels decrease on the third day of menstruation. However, when ovarian function is markedly decreased, there are cases in which follicular development is not seen, even with ovarian stimulation after Kaufman therapy. In other countries, donated oocytes are currently being in these patients. When follicular maturation is not seen, even with ovarian stimulation, treatment focuses on the creation of condi-

Table 1. Number of ART treatment cycles and the pregnancy rate in Japan

2015	IVF	ICSI (including split)	Frozen-thawed embryos	IVF/ICSI
No. of treatment cycles	93,614	155,979	174,740	249,593
No. of oocyte retrieval cycles	91,079	153,639		244,718
Number of "freeze all" cycles	30,498	63,660		94,158
No. of transfer cycles	28,858	41,396	171,495	70,254
No. of pregnancy cycles	6,478	8,169	56,888	14,647
No. of births	4,629	5,761	40,611	10,390
Pregnancy rate (pregnancy cycles/transfer cycles)	22.40%	19.70%	33.20%	20.80%

tions that make it easier for follicles to develop. In a previous investigation, we found a high oocyte retrieval rate of 96% in patients with E_2 levels of 25 pg/ml or higher on the third day of menstruation. Taking this into consideration, in cases when the E_2 level is also inhibited by Kaufman therapy, we monitor follicular development when follicular development has been made easier by supplementation of E_2. It may be that excess elevation of FSH is also inhibited by supplementation of E_2. Consequently, in cases when elevation of FSH has already started in POI or older patients, the FSH levels are lowered with EP replacement or Kaufman therapy and E_2 is supplemented. By maintaining E_2 levels at about 25–50 pg/ml, the rise in FSH can be inhibited while follicle growth is facilitated, and E_2 replacement plays a role like that of ovarian stimulation.

It has been suggested that administration of DHEA in low ovarian function may contribute to improvement of the pregnancy rate [13].

Follicular development fundamentally occurs once, as in the natural cycle; therefore stimulation by gonadotropin at the point when the follicle diameter reaches 10–12 mm should be investigated. No differences are seen in the implantation rate, pregnancy rate, or abortion rate between frozen and fresh oocytes [14].If testicular tissue has been thawed with male factor, insemination is performed after a certain number of oocytes have been stored. *In vitro* activation (IVA) and other new treatments for POI have also been established [15].

Ovarian Stimulation Generated by the "Freeze All" Strategy

With the aim of avoiding OHSS, the application of the "freeze all" strategy has spread from considerations of synchronization of fertilized oocytes and the endometrium due to the high viability of frozen-thawed embryos achieved through advances in freezing technology [16], the high pregnancy rate in frozen-thawed embryo transfer [17], and other factors. Looking at the 2015 ART data for Japan, oocyte retrieval was performed in a combined number of 246,876 IVF/ICSI cycles, of which 70,254 cycles were fresh embryo transfer and 94,158 cycles were frozen-thawed cycles. Thus, the number of frozen-thawed cycles was higher [11]. Oocyte retrieval in treatment cycles was performed in a combined total of 246,876 IVF/ICSI cycles, versus 174,740 frozen-thawed cycles. The pregnancy rate was 20.8% for fresh embryo transfer cycles and 33.2% for frozen-thawed cycles. Thus, better results were obtained in frozen-thawed cycles (Table 1). When ovarian stimulation is performed with the assumption of freeze all, there is less need to consider embryo transfer. By thinking of ovarian stimulation and embryo transfer separately, a greater range of options for ovarian stimulation appears. In a thawed embryo transfer cycle after an embryo is frozen, no difference was seen in the pregnancy rate, with an open at least one menstrual cycle before transfer, and the transfer cycle can be immediately entered [18]. In cases when there is not enough time to perform ovarian stimulation aligned with the menstrual cycle because of oncological treatment, the random start method, in which ovarian stimulation is started randomly without relation to the menstrual cycle [19], and the double stimulation method, in which ovarian stimulation is started with gonadotropin 2 or 3 days after oocyte retrieval with the aim of retrieving oocytes twice in a single menstrual cycle [20], are currently being used (Fig. 1).

With the random start method it has been shown that oocytes can be efficiently retrieved, no matter when the stimulation is started, based on the results of regular ovarian stimulation in the follicular phase, late follicular phase, and luteal phase [19]. Moreover, a good cumulative pregnancy rate is obtained by starting ovarian stimulation in the luteal phase, retrieving oocytes, and performing frozen-thawed embryo transfer [21].

In an investigation of embryos obtained with the double stimulation method, no differences were seen in the follicular development, number of oocytes retrieved, fertilization rate, number of blastocyst embryos, or euploid

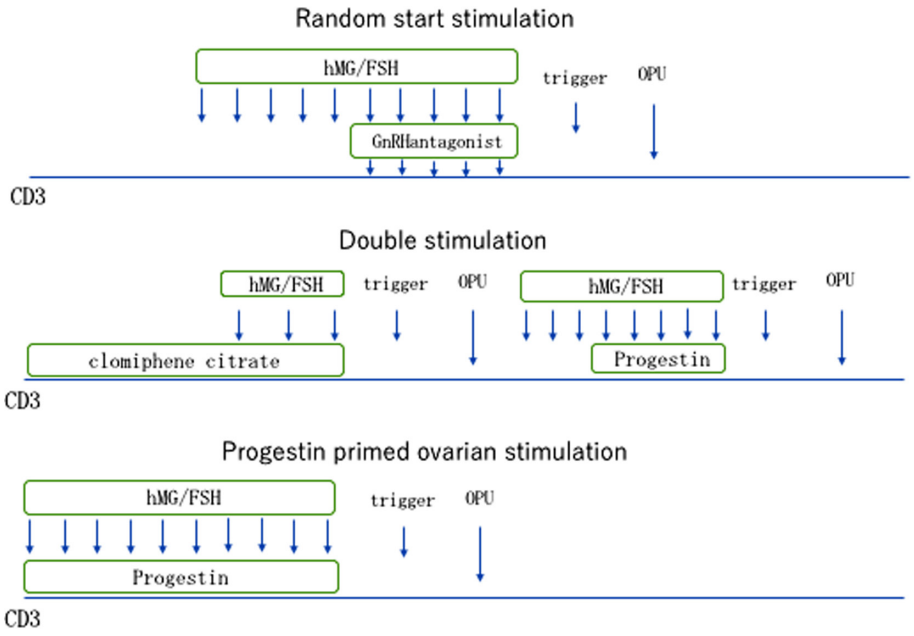

Fig. 1. Ovarian stimulation produced with freeze all strategy.

rate with PGT-A between the follicular phase and luteal phase of the same cycle [22]. The probability of obtaining good blastocysts is also thought to increase with oocyte retrieval twice in the same cycle [23].

The random start method and double stimulation method use endogenous progesterone that appears after ovulation to inhibite the LH surge, and they have the advantage of decreasing the use of GnRH antagonist. The random start method is often used in patients being treated for a current disease, such as cancer patients, and those for whom there is little time for oocyte retrieval. The double stimulation method is also used in cancer patients with the aim of retrieving as many oocytes as possible in a short time via ovarian stimulation [24]. Follicles that began growing in the latter half of the previous cycle grow and can be collected with continuous ovarian stimulation in ovarian hypofunction patients or patients in whom little ovular development is seen after stimulation in the follicular phase [20]. The method of ovarian stimulation is generally not changed after the stimulation has started, and deciding the method of ovarian stimulation in the beginning is important. When deciding the method of ovarian stimulation, judgments are often made based on the FSH level, LH level, E_2 level, AMH level, and AFC [5].

In patients with decreased ovarian reserve and patients over 40 years old, however, there are cases in which the follicles do not develop as much as expected following the start of ovarian stimulation. These are cases when the dominant follicle exceeds 14 mm in diameter, but the other follicles all remain at less than 10 mm. This is acceptable when the original plan was to retrieve oocytes from 1–2 follicles with low stimulation, but when the plan was to start stimulation with the GnRH antagonist in anticipation of the development of multiple follicles for oocyte retrieval, ovarian stimulation itself must be canceled, or retrieval from only one follicle must be considered. When continuing ovarian stimulation for oocyte retrieval, or when inhibiting the LH surge, GnRH antagonist is started and it becomes necessary to increase the dosage of gonadotropin together with the start of GnRH antagonist. As mentioned above, in cases when fresh embryo transfer is not considered for ovarian hypofunction patients, PPOS is selected. In PPOS, a progestogen preparation is administered from the start of stimulation in place of the GnRH antagonist used to inhibit the LH surge (Fig. 1). The method of inhibiting the LH surge by administering a progestogen preparation does not require attention to the LH surge. There is also no need for a close examination for a follicular diameter of 14 mm, which is the criterion for starting GnRH antagonist administration. This method is considered to be an ovarian stimulation with a low patient burden [25]. The need to increase the dose of gonadotropin together with the start of GnRH antagonist, which is necessary when the number of growing follicles is small, may also be seen as an advantage. In cases when follicular development is

Table 2. Biological activities of progestin and ovulation inhibition dose

	Progesto-genic	Anti-gonado-tropic	Anti-estrogenic	Estro-genic	Andro-genic	Anti-andro-genic	Glucocor-ticoid	Anti-mineralo-corticoid	Ovulation inhibition dose mg per day p.o.
Progesterone	+	+	+	−	−	±	+	+	300
Dydrogesterone	+	−	+	−	−	±	−	±	>30
Medroxy-progesterone-acetate	+	+	+	−	±	−	+	−	10

(+) effective; (±) weakly effective; (−) not effective. Modified from Maturitas, 46 (Suppl. 1), S7–S16.

expected in patients with decreased ovarian function and patients older than 40 without consideration of a fresh embryo transfer, the PPOS method of ovarian stimulation is thought to be effective. As for the progestogen preparation used, there are reports of oral medroxyprogesterone acetate (MPA) 10 mg/day and oral utrogestan 200 mg/day [26, 27]. Biochemical activity differs depending on the progestogen preparation, and the respective doses to inhibit ovulation also differ (Table 2) [28]. In a comparison of oral MPA 10 mg/day and dydrogesterone 20 mg/day, the hMG dosage was slightly smaller with dydrogesterone 20 mg/day [29]. In a comparative investigation of oral MPA 10 mg/day and 4 mg/day, both doses inhibited the LH surge and no difference in the dosage of hMG preparation was seen [30]. The types and dosages of progestogen preparations are open to further investigation. Looking at the hMG preparation dosage, there are reports of higher dosages use with the PPOS method than with the short method [26, 29], and there is a possibility that the dosage of the hMG preparation can be decreased with combined oral administration of clomiphene citrate or other agents [31]. The PPOS method for PCOS patients is associated with a lower incidence of OHSS than the short protocol, and in an investigation of 60 patients OHSS occurred in 3.33% with the short protocol versus 0% with hMG + MPA [32]. As a result of reducing the dose of the hMG preparation with combined oral clomiphene citrate in PCOS patients, the number of developed follicles decreased but the pregnancy rate was maintained and the OHSS incidence was the same [33]. This may be considered one option to reduce the patient burden by decreasing the hMG dose for PCOS patients in combination with an oral agent.

One difference from GnRH agonist methods is that, since no GnRH agonist is administered, a GnRH agonist can be used to trigger the LH surge. When there are concerns about the risk of OHSS or other adverse events, administration of hCG can be avoided and the occurrence of late-onset OHSS can be controlled. It has also been reported that in ovarian stimulation, the gonadotropin receptor gene mutation affects ovarian stimulation [34], and it may be that the methods of ovarian stimulation will continue to change.

Conclusion

Successful ovarian stimulation plays a major role in ART treatment outcomes. Frozen-thawed embryo transfer is the mainstream practice, but as the background of reproductive medicine involving ART has changed, for example, in its application to infertility treatment due to oncofertility, ovarian stimulation methods have changed and options have increased. Ovarian stimulation that does not cause OHSS or other adverse effects and in various ways poses little burden on patients should be selected. The consideration and selection on of the most appropriate for each individual patient is important.

References

1) Ata, B., Kaplan, B., Danzer, H., Glassner, M., Opsahl, M., Tan, S.L. and Munné, S. (2012): Array CGH analysis shows that aneuploidy is not related to the number of embryos generated. Reprod. Biomed. Online, 24, 614–620. [Medline] [CrossRef]
2) Atkinson, P., Koch, J. and Ledger, W.L. (2014): GnRH agonist trigger and a freeze-all strategy to prevent ovarian hyperstimulation syndrome: a retrospective study of OHSS risk and pregnancy rates. Aust. N. Z. J. Obstet. Gynaecol., 54, 581–585. [Medline] [CrossRef]
3) Blockeel, C., Drakopoulos, P., Santos-Ribeiro, S., Polyzos, N.P. and Tournaye, H. (2016): A fresh look at the freeze-all protocol: a SWOT analysis. Hum. Reprod., 31, 491–497. [Medline] [CrossRef]
4) Santos-Ribeiro, S., Polyzos, N.P., Haentjens, P., Smitz, J., Camus, M., Tournaye, H. and Blockeel, C. (2014): Live birth rates after IVF are reduced by both low and high progesterone levels on the day of human chorionic gonadotrophin administration. Hum. Reprod., 29, 1698–1705. [Medline] [CrossRef]

5) Tomas, C., Nuojua-Huttunen, S. and Martikainen, H. (1997): Pretreatment transvaginal ultrasound examination predicts ovarian responsiveness to gonadotrophins in in-vitro fertilization. Hum. Reprod., 12, 220–223. [Medline] [CrossRef]
6) La Marca, A., and Sunkara, S.K. (2014): Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum. Reprod. Update, 20, 124–140. [Medline] [CrossRef]
7) Kato, K., Takehara, Y., Segawa, T., Kawachiya, S., Okuno, T., Kobayashi, T., Bodri, D. and Kato, O. (2012): Minimal ovarian stimulation combined with elective single embryo transfer policy: age-specific results of a large, single-centre, Japanese cohort. Reprod. Biol. Endocrinol., 10, 35. [Medline] [CrossRef]
8) Nargund, G., Datta, A.K. and Fauser, B.C.J.M. (2017): Mild stimulation for in vitro fertilization. Fertil. Steril., 108, 558–567. [Medline] [CrossRef]
9) Lu, X., Hong, Q., Sun, L., Chen, Q., Fu, Y., Ai, A., Lyu, Q. and Kuang, Y. (2016): Dual trigger for final oocyte maturation improves the oocyte retrieval rate of suboptimal responders to gonadotropin-releasing hormone agonist. Fertil. Steril., 106, 1356–1362. [Medline] [CrossRef]
10) Lambalk, C.B., Banga, F.R., Huirne, J.A., Toftager, M., Pinborg, A., Homburg, R., van der Veen, F. and van Wely, M. (2017): GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum. Reprod. Update, 23, 560–579. [Medline] [CrossRef]
11) https://plaza.umin.ac.jp/~jsog-art/2015data_201709. pdf.
12) Messinis, I.E., and Templeton, A. (1986): The effect of pulsatile follicle stimulating hormone on the endogenous luteinizing hormone surge in women. Clin. Endocrinol. (Oxf.), 25, 633–640. [Medline] [CrossRef]
13) Nagels, H.E., Rishworth, J.R., Siristatidis, C.S. and Kroon, B. (2015): Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst. Rev., 26, CD009749. [Medline]
14) Crawford, S., Boulet, S.L., Kawwass, J.F., Jamieson, D.J. and Kissin, D.M. (2017): Cryopreserved oocyte versus fresh oocyte assisted reproductive technology cycles, United States, 2013. Fertil. Steril., 107, 110–118. [Medline] [CrossRef]
15) Zhai, J., Yao, G., Dong, F., Bu, Z., Cheng, Y., Sato, Y., Hu, L., Zhang, Y., Wang, J., Dai, S., Li, J., Sun, J., Hsueh, A.J., Kawamura, K. and Sun, Y. (2016): In vitro activation of follicles and fresh tissue auto-transplantation in primary ovarian insufficiency patients. J. Clin. Endocrinol. Metab., 101, 4405–4412. [Medline] [CrossRef]
16) Roque, M., Valle, M., Guimarães, F., Sampaio, M. and Geber, S. (2015): Freeze-all policy: fresh vs. frozen-thawed embryo transfer. Fertil. Steril., 103, 1190–1193. [Medline] [CrossRef]
17) Braga, D.P., Setti, A.S., Figueira, R.C., Azevedo, M.C., Iaconelli, A. Jr., Lo Turco, E.G. and Borges, E. Jr. (2016): Freeze-all, oocyte vitrification, or fresh embryo transfer? Lessons from an egg-sharing donation program. Fertil. Steril., 106, 615–622. [Medline] [CrossRef]
18) Santos-Ribeiro, S., Polyzos, N.P., Lan, V.T., Siffain, J., Mackens, S., Van Landuyt, L., Tournaye, H. and Blockeel, C. (2016): The effect of an immediate frozen embryo transfer following a freeze-all protocol: a retrospective analysis from two centres. Hum. Reprod., 31, 2541–2548. [Medline] [CrossRef]
19) Qin, N., Chen, Q., Hong, Q., Cai, R., Gao, H., Wang, Y., Sun, L., Zhang, S., Guo, H., Fu, Y., Ai, A., Tian, H., Lyu, Q., Daya, S. and Kuang, Y. (2016): Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection. Fertil. Steril., 106, 334–341.e1. [Medline] [CrossRef]
20) Kuang, Y., Chen, Q., Hong, Q., Lyu, Q., Ai, A., Fu, Y. and Shoham, Z. (2014): Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). Reprod. Biomed. Online, 29, 684–691. [Medline] [CrossRef]
21) Kuang, Y., Hong, Q., Chen, Q., Lyu, Q., Ai, A., Fu, Y. and Shoham, Z. (2014): Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles. Fertil. Steril., 101, 105–111. [Medline] [CrossRef]
22) Cimadomo, D., Vaiarelli, A., Colamaria, S., Trabucco, E., Alviggi, C., Venturella, R., Alviggi, E., Carmelo, R., Rienzi, L. and Ubaldi, F.M. (2018): Luteal phase anovulatory follicles result in the production of competent oocytes: intra-patient paired case-control study comparing follicular versus luteal phase stimulations in the same ovarian cycle. Hum. Reprod., 33, 1442–1448. [Medline] [CrossRef]
23) Ubaldi, F.M., Capalbo, A., Vaiarelli, A., Cimadomo, D., Colamaria, S., Alviggi, C., Trabucco, E., Venturella, R., Vajta, G. and Rienzi, L. (2016): Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation. Fertil. Steril., 105, 1488–1495.e1. [Medline] [CrossRef]
24) von Wolff, M., Thaler, C.J., Frambach, T., Zeeb, C., Lawrenz, B., Popovici, R.M. and Strowitzki, T. (2009): Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil. Steril., 92, 1360–1365. [Medline] [CrossRef]
25) Huang, C.Y., Chen, G.Y., Shieh, M.L. and Li, H.Y. (2018): An extremely patient-friendly and efficient stimulation protocol for assisted reproductive technology in normal and high responders. Reprod. Biol. Endocrinol., 16, 18. [Medline] [CrossRef]
26) Kuang, Y., Chen, Q., Fu, Y., Wang, Y., Hong, Q., Lyu, Q., Ai, A. and Shoham, Z. (2015): Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Fertil. Steril., 104, 62–70.e3. [Medline] [CrossRef]
27) Zhu, X., Zhang, X. and Fu, Y. (2015): Utrogestan as an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian

hyperstimulation for in vitro fertilization. Medicine (Baltimore), 94, e909. [Medline] [CrossRef]
28) Schindler, A.E., Campagnoli, C., Druckmann, R., Huber, J., Pasqualini, J.R., Schweppe, K.W. and Thijssen, J.H. (2003): Classification and pharmacology of progestins. Maturitas, 46,(Suppl 1): S7–S16. [Medline] [CrossRef]
29) Yu, S., Long, H., Chang, H.Y., Liu, Y., Gao, H., Zhu, J., Quan, X., Lyu, Q., Kuang, Y. and Ai, A. (2018): New application of dydrogesterone as a part of a progestin-primed ovarian stimulation protocol for IVF: a randomized controlled trial including 516 first IVF/ICSI cycles. Hum. Reprod., 33, 229–237. [Medline] [CrossRef]
30) Dong, J., Wang, Y., Chai, W.R., Hong, Q.Q., Wang, N.L., Sun, L.H., Long, H., Wang, L., Tian, H., Lyu, Q.F., Lu, X.F., Chen, Q.J. and Kuang, Y.P. (2017): The pregnancy outcome of progestin-primed ovarian stimulation using 4 versus 10 mg of medroxyprogesterone acetate per day in infertile women undergoing in vitro fertilisation: a randomised controlled trial. BJOG, 124, 1048–1055. [Medline] [CrossRef]
31) Liu, Y., Chen, Q., Yu, S., Wang, Y., He, W., Chang, H.Y., Wang, B., Gao, H., Long, H., Wang, L., Lyu, Q., Ai, A. and Kuang, Y. (2018): Progestin-primed ovarian stimulation with or without clomiphene citrate supplementation in normal ovulatory women undergoing in vitro fertilization/intracytoplasmic sperm injection: A prospective randomized controlled trial. Clin. Endocrinol. (Oxf.), 88, 442–452. [Medline] [CrossRef]
32) Wang, Y., Chen, Q., Wang, N., Chen, H., Lyu, Q. and Kuang, Y. (2016): Controlled ovarian stimulation using medroxyprogesterone acetate and hMG in patients with polycystic ovary syndrome treated for IVF: a double-blind randomized crossover clinical trial. Medicine (Baltimore), 95, e2939. [Medline] [CrossRef]
33) Ye, H., Tian, H., He, W., Lyu, Q., Kuang, Y., Chen, Q. and Sun, L. (2018): Progestin-primed milder stimulation with clomiphene citrate yields fewer oocytes and suboptimal pregnancy outcomes compared with the standard progestin-primed ovarian stimulation in infertile women with polycystic ovarian syndrome. Reprod. Biol. Endocrinol., 16, 53. [Medline] [CrossRef]
34) Alviggi, C., Conforti, A., Santi, D., Esteves, S.C., Andersen, C.Y., Humaidan, P., Chiodini, P., De Placido, G. and Simoni, M. (2018): Clinical relevance of genetic variants of gonadotrophins and their receptors in controlled ovarian stimulation: a systematic review and meta-analysis. Hum. Reprod. Update, 24, 599–614. [Medline] [CrossRef]