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پژوهشگاه رویان


In the name of
God

Overview of ovulation induction

INTRODUCTION

- ✓ **Ovulatory disorders:** In 18 to 25 percent of couples presenting with infertility.
- ✓ Most of these women have oligomenorrhea, arbitrarily defined as menstruation that occurs at intervals of 35 days to six months.
- ✓ This topic will review the efficacy of the different regimens used for ovulation induction in women with ovulatory disorders (clomiphene citrate, gonadotropins, pulsatile gonadotropin-releasing hormone [GnRH] therapy, aromatase inhibitors, and dopamine agonists) and provide our approach to the management of such women.

Ovulation Induction

Clomiphene citrate

- ✓ A revolutionary advance in reproductive medicine and quickly became popular for induction of ovulation because of its ease of administration and minimal side effects.
- ✓ Letrozole, an aromatase inhibitor, is also effective for ovulation induction in women with polycystic ovary syndrome (PCOS).
- ✓ Available data suggest that live birth rates are higher with letrozole than clomiphene, and many experts now suggest letrozole as first-line therapy for anovulatory women with PCOS.

Pharmacology/Mechanisms of Action

Clomiphene:

- ✓ A nonsteroidal triphenylethylene derivative distantly related to diethylstilbestrol.
- ✓ A selective estrogen receptor modulator (SERM), similar to tamoxifen and raloxifene.
- ✓ The commercially available form of clomiphene is the dihydrogen citrate salt (clomiphene citrate).
- ✓ It contains two stereoisomers: zu-clomiphene (38 percent) and en-clomiphene (62 percent)

- ✓ **En-clomiphene** is cleared rapidly, **zu-clomiphene** has a long half-life.
- ✓ The two clomiphene isomers have mixed estrogenic and antiestrogenic effects that vary among species.
- ✓ **En-clomiphene** is the more potent isomer with greater antiestrogenic activity and the one primarily responsible for inducing follicular development.
- ✓ Clomiphene is cleared through the liver and excreted in feces.
- ✓ Over 50 percent of an oral dose of clomiphene citrate is excreted after five days, but traces of radioactivity from the labeled clomiphene appear in the feces up to six weeks after administration.

Ovulation induction with letrozole

- ✓ During the past decade, aromatase inhibitors have been explored as an option for ovulation induction in women who fail to conceive with clomiphene citrate.
- ✓ Aromatase inhibitors are a class of drugs that block estrogen biosynthesis, thereby reducing negative estrogenic feedback at the pituitary.
- ✓ This topic reviews the use of letrozole, the most effective aromatase inhibitor, for ovulation induction in women with PCOS and as an adjunct to gonadotropin therapy for controlled ovarian hyperstimulation (COH) in women with ovulatory infertility.

Pharmacology and Physiology

- ✓ Aromatase is a microsomal cytochrome P450 hemoprotein-containing enzyme (P450arom, the product of the *CYP19* gene) that catalyzes the rate-limiting step in the production of estrogens:
- ✓ The conversion of androstenedione and testosterone via three hydroxylation steps to estrone and estradiol, respectively.
- ✓ Aromatase activity is present in many tissues, including the ovaries, brain, adipose tissue, muscle, liver, and breast.
- ✓ Aromatase inhibitors are widely used as adjuvant endocrine therapy for postmenopausal women with breast cancer.
- ✓ They have been used off-label in the treatment of patients with anovulatory infertility, such as polycystic ovary syndrome (PCOS).

Women with Anovulatory Infertility:

- The four most common ovulatory disorders include polycystic ovary syndrome (PCOS), hypogonadotropic hypogonadism (HA), primary ovarian insufficiency (POI), and hyperprolactinemia.

- **Premenopausal women**— Hyperprolactinemia in premenopausal women causes hypogonadism, with symptoms that include infertility, oligomenorrhea, or amenorrhea and less often galactorrhea.
- In a retrospective study of 104 patients with hyperprolactinemia ages 30 to 44 years, the most commonly reported symptoms were infertility, headache, and oligomenorrhea in 48, 39, and 29 percent, respectively.

  Galactorrhea was slightly less common (24 percent).

Menstrual cycle dysfunction

- ✓ Excluding pregnancy, hyperprolactinemia accounts for approximately 10 to 20 percent of cases of amenorrhea.
- ✓ The mechanism appears to involve inhibition of luteinizing hormone (LH), and perhaps follicle-stimulating hormone (FSH) secretion, via inhibition of the release of gonadotropin-releasing hormone (GnRH).
- ✓ As a result, serum gonadotropin concentrations are normal or low, as in other causes of secondary hypogonadism.
- ✓ The symptoms of hypogonadism due to hyperprolactinemia in premenopausal women correlate with the magnitude of the hyperprolactinemia.

Most experts have moved away from the World Health Organization (WHO) terminology which assign women to three categories of anovulation:

WHO class 1 – Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea [HA])

WHO class 2 – Normogonadotropic normoestrogenic anovulation (almost all women in this category have polycystic ovary syndrome [PCOS]), when using the Rotterdam criteria for the diagnosis of PCOS .This is the most common cause of anovulation.

WHO class 3 – Hypergonadotropic hypoestrogenic anovulation (primary ovarian insufficiency [POI; premature ovarian failure])

Hyperprolactinemia did not have a separate WHO category.

The use of serum anti-müllerian hormone (AMH) concentrations may help to further define various patient categories. AMH levels are increased in PCOS and decreased in WHO class 1 and 3.

Hypogonadotropic hypogonadism:

- ✓ Hypothalamic causes of hypogonadotropic hypogonadism include:

1. Functional hypothalamic amenorrhea (FHA)
2. Isolated gonadotropin-releasing hormone (GnRH) deficiency.

- ✓ Multiple factors may contribute to the **pathogenesis** of FHA, including eating disorders (such as anorexia nervosa), exercise, and stress.
- ✓ Women in this group, which **accounts** for 5 to 10 percent of anovulatory women, usually have amenorrhea .

Biochemical findings:

- ✓ low serum estradiol concentrations and low or low-normal serum follicle-stimulating hormone (FSH) concentrations.
- ✓ **AMH levels are low to normal**
- ✓ Reversing the lifestyle factors that contribute to the anovulation (low weight, excessive exercise, essentially any condition that leads to energy deficiency) should be attempted before considering ovulation induction with medications.
- ✓ **idiopathic hypogonadotropic hypogonadism** ,
- ✓ if it is associated with anosmia, Kallmann syndrome.

Hypogonadotropic hypogonadism (primary amenorrhea) due to complete congenital GNRH deficiency

Polycystic ovary syndrome

- ✓ Women with PCOS constitute the largest group of anovulatory women encountered in clinical practice (70 to 85% of cases).
- ✓ Serum estradiol and FSH concentrations levels are normal, luteinizing hormone (LH) concentrations may either be normal or elevated.
- ✓ The criteria for diagnosis have been referred to as the "Rotterdam criteria.
- ✓ In women with obesity and PCOS, weight loss, which may restore spontaneous ovulation in many women, should be attempted before treatment with ovulation induction agents is considered.
- ✓ impaired glucose tolerance before starting ovulation induction because of the associated risk of pregnancy complications. suboptimal perinatal outcomes, and affected cardiometabolic child health.

- ✓ There are differing opinions regarding the use of ovulation induction versus assisted reproductive technologies (ART) for the treatment of infertile women with PCOS.
- ✓ in vitro fertilization (IVF) as first-line therapy include the ability to freeze all embryos and perform single embryo transfer, thereby reducing the major complications of infertility treatment: multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).

Primary ovarian insufficiency

- ✓ POI, premature ovarian failure (POF) menopause before age 40 years, occurs in only 1 percent of all women but accounts for 5 to 10 percent of cases of anovulation.
- ✓ In most cases, unknown origin.
- ✓ Many strategies, including pretreatment suppression with exogenous estrogen, GnRH agonists, or androgens, have been proposed with the aim of improving outcomes from ovulation induction.
- ✓ An experimental approach with as yet uncertain benefits include the in vitro activation (IVA) of the patient's own ovarian tissue/oocytes. The only effective option is IVF with donor oocytes.

Overview of Approach

Goals — The overarching goals of ovulation induction in women with anovulatory infertility are:

- Induce monofollicular rather than multifollicular development and subsequent mono-ovulation and, ultimately, a singleton pregnancy and birth of a healthy newborn. Focus on cumulative outcomes over a given period of time, rather than per cycle outcomes.
- Start with the least invasive, simplest, and cheapest treatment option; subsequent options should depend upon ovarian response (ovulation and number of follicles).
- Maximize the rate of singleton pregnancies, minimize multiple gestation rates.
- Minimize the risk of ovarian hyperstimulation syndrome (OHSS) in women undergoing gonadotropin therapy

General principles

- The method of ovulation induction selected by the clinician should be based upon the underlying cause of anovulation and the efficacy, costs, risks, patient burden, and potential complications associated with each method as they apply to the individual woman.
- Women with ovulatory disorders should undergo conventional ovulation induction strategies before considering assisted reproductive technologies (ART) because success rates are good, and if monitored by an experienced clinician, complication rates are low.
- PCOS represents a risk factor for developing OHSS following ovarian stimulation with gonadotropins.

Patient-specific approach

- **Functional hypothalamic amenorrhea (FHA)** – Women with FHA are hypoestrogenemic and are therefore unlikely to respond to clomiphene citrate, an antiestrogen.
- Because clomiphene citrate is easy to administer, it may seem reasonable to give one course of clomiphene prior to initiating pulsatile gonadotropin-releasing hormone (GnRH) or gonadotropin therapy. For those who ovulate, clomiphene citrate can then be continued.
- For those who do not ovulate, we suggest pulsatile GnRH as first-line therapy in countries where it is available. If pulsatile GnRH is unavailable, gonadotropin therapy should be initiated, with both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (these women do not respond to FSH alone).

- **Polycystic ovary syndrome (PCOS)** – The approach to women with PCOS starts with exercise and weight loss, if indicated, followed by ovulation induction.
- Weight loss should always be attempted in overweight or obese women with PCOS because ovulation can be restored with a modest amount of weight loss.
- For women with obesity and infertility who are >40 years of age, clinicians need to balance the health benefits of weight loss against the loss of fertility potential that might occur due to a delay in initiation of ovulation induction
- Fertility potential declines rapidly after 40 years of age.

- **Primary ovarian insufficiency (POI)** – All ovulation induction strategies for women with POI are unsuccessful, and we suggest against their use. Women with POI should be offered the option of IVF with donor oocytes as a successful way to fulfill their wish to have children.

- The treatment of choice for anovulatory women with hyperprolactinemia is dopamine agonists; this is reviewed in detail separately.

Metformin

- Correction of hyperinsulinemia with metformin has been shown to have a beneficial effect in anovulatory women with PCOS by increasing menstrual cyclicity and improving spontaneous ovulation.
- However, it does **not** appear to improve live-birth rates when given alone or in combination with clomiphene citrate.
- There is some experience with the use of another insulin-sensitizing drug, (myo) inositol.

Dopamine agonists

- A dopamine agonist is the treatment of choice for women with hyperprolactinemic anovulation who are pursuing pregnancy.
- In women with a lactotroph adenoma, a marked reduction in the serum prolactin concentration occurs within two to three weeks.
- Bromocriptine is still sometimes used to restore ovulation in women with hyperprolactinemia.
- drugs that bind more specifically to dopamine D2 receptors on the lactotroph cells, such as cabergoline, are associated with fewer side effects.
- The fetal safety of bromocriptine is better established than cabergoline, but cabergoline appears to be safe as well.

Pulsatile GnRH Therapy

- The pulsatile administration of gonadotropin-releasing hormone (GnRH) using an infusion pump stimulates the production of endogenous follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- The resulting serum FSH and LH concentrations remain within the normal range, so the chances of multifollicular development and ovarian hyperstimulation are low. In comparison, continuous GnRH therapy lowers gonadotropin release.

- **Indication** — Pulsatile GnRH administration is indicated for women with hypogonadotropic hypogonadism (hypothalamic amenorrhea [HA]) who have normal pituitary function.
- Because pulsatile GnRH therapy maintains normal feedback mechanisms, most cycles result in a single dominant follicle.
- Therefore, rates of multiple gestation are extremely low, and the risk of ovarian hyperstimulation syndrome (OHSS) in women with HA is exceedingly low.

- ✓ **Protocol** — The intravenous (IV) route appears superior to the subcutaneous route. In order to mimic the normal pulsatile release of GnRH, the pulse interval is 60 to 90 minutes.
- ✓ The most physiologic dose for IV administration is 75 ng/kg (in practice, some clinicians use 2.5 micrograms/pulse for women weighing <50 kg and 5 micrograms/pulse for women weighing >50 kg; others use doses ranging from 2.5 to 10 mcg per pulse, starting with 2.5 mcg and increasing until the minimum dose to induce ovulation is reached).

Results — Ovulation rates of 90 percent and pregnancy rates of 80 percent or higher have been reported in women treated with pulsatile GnRH Local complications such as phlebitis may occasionally occur.

Gonadotropin Therapy

There are several indications for gonadotropin therapy in anovulatory women:

- Women with polycystic ovary syndrome (PCOS) who have not ovulated or conceived with weight loss, clomiphene, or letrozole.
- Hypogonadotropic anovulatory women with hypopituitarism or women with hypothalamic amenorrhea (HA) who do not have access to pulsatile gonadotropin-releasing hormone (GnRH) therapy.

Preparations

HMG and FSH

- There were no differences in clinical pregnancy or live-birth rates for rhFSH and urinary-derived gonadotropins.
- There also were no differences between hMG preparations and urinary FSH-P.
- After pooling the data, there were no differences in the rates of ovarian hyperstimulation syndrome (OHSS) between rhFSH and urinary-derived gonadotropins.

Ovulatory triggers — hCG is used to trigger ovulation when the ovarian follicles are mature. Both urinary and recombinant hCG preparations are available.

A dose of 250 mcg of recombinant hCG appears to be equivalent to the standard doses of urinary hCG (5000 to 10,000 units).

Protocols — The aim of ovulation induction with gonadotropins, as with clomiphene, is the formation of a single dominant follicle.

In spontaneous cycles, this is achieved at the beginning of the cycle by a transient increase in serum FSH concentrations above the threshold value.

Conventional gonadotropin protocol

- ✓ The starting dose of FSH is 150 international units/day.
- ✓ This regimen is associated with a multiple pregnancy rate of up to 36 %
- ✓ Ovarian hyperstimulation occurs in up to 14 percent of treatment cycles
- ✓ In patients with PCOS, who are at particular risk for complications, this approach has been largely abandoned in favor of a **low-dose, step-up protocol**.
- ✓ In this protocol, the initial subcutaneous or intramuscular dose of FSH is 37.5 to 75 international units/day. It is recommended that the dose be increased only if, after 14 days, no response is documented on ultrasonography and serum estradiol monitoring. Increments of 37.5 international units then are given at weekly intervals up to a maximum of 225 international units/day.

- ✓ **Low-dose, step-down protocol** of ovulation induction mimics more closely the physiology of normal cycles.
- ✓ Therapy with 150 international units FSH/day is started shortly The dose is then decreased to 112.5 international units/day followed by a further decrease to 75 international units/day three days later, which is continued until hCG is administered to induce ovulation.
- ✓ The low-dose, step-up regimen should be considered the first choice treatment.

Transvaginal ultrasonography to measure follicular diameter.

- ✓ hCG is given as an ovulatory trigger on the day that at least one follicle appears to be mature.
- ✓ The criteria for follicle maturity are a follicle diameter of 18 mm and/or a serum estradiol concentration of 200 pg/mL (734 pmol/L) per dominant follicle.
- ✓ If three or more follicles larger than 15 mm are present, stimulation should be stopped, hCG withheld, and use of a barrier contraceptive advised in order to prevent multiple pregnancies and ovarian hyperstimulation.
- ✓ Measurements of serum estradiol are useful, Serum progesterone measurements are sometimes useful before administration of hCG to determine if a premature LH surge has occurred.

Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol)

Yanping Kuang, Qiuju Chen, Qingqing Hong

Abstract

Previous studies have shown that existing antral follicles in the luteal phase enable ovarian stimulation. In a pilot study, the efficacy of double stimulations during the follicular and luteal phases in women with poor ovarian response was explored (defined according to the Bologna criteria). Thirty-eight women began with mild ovarian stimulation. After the first oocyte retrieval, human menopausal gonadotrophin and letrozole were administrated to stimulate follicle development, and oocyte retrieval was carried out a second time when dominant follicles had matured. The primary outcome measured was the number of oocytes retrieved: stage one 1.7 ± 1.0; stage two 3.5 ± 3.2. From the double stimulation, 167 oocytes were collected and 26 out of 38 (68.4%) succeeded in producing one to six viable embryos cryopreserved for later transfer. Twenty-one women underwent 23 cryopreserved embryo transfers, resulting in 13 clinical pregnancies. The study shows that double ovarian stimulations in the same menstrual cycle provide more opportunities for retrieving oocytes in poor responders. The stimulation can start in the luteal phase resulting in retrieval of more oocytes in a short period of time. This offers new hope for women with poor ovarian response and newly diagnosed cancer patients needing fertility preservation.

Materials and Methods

- Patients planning to undergo IVF–ICSI treatments were eligible for participation in the study. In order to participate, patients had to meet at least two of the following criteria: age over 40 years; a history of ovarian surgery; previous treat-ment using conventional protocols that yielded less than three oocytes; antral follicle count of less than 5 on menstrual cycle day 2–3; and basal serum FSH concentration between 10 and 19 IU/l.
- Study exclusion criteria were documented ovarian failure including basal FSH above 20 IU/l or no antral follicle by ul-trasound examination; endometriosis grade 3 or higher; or any contraindications to ovarian stimulation treatment.

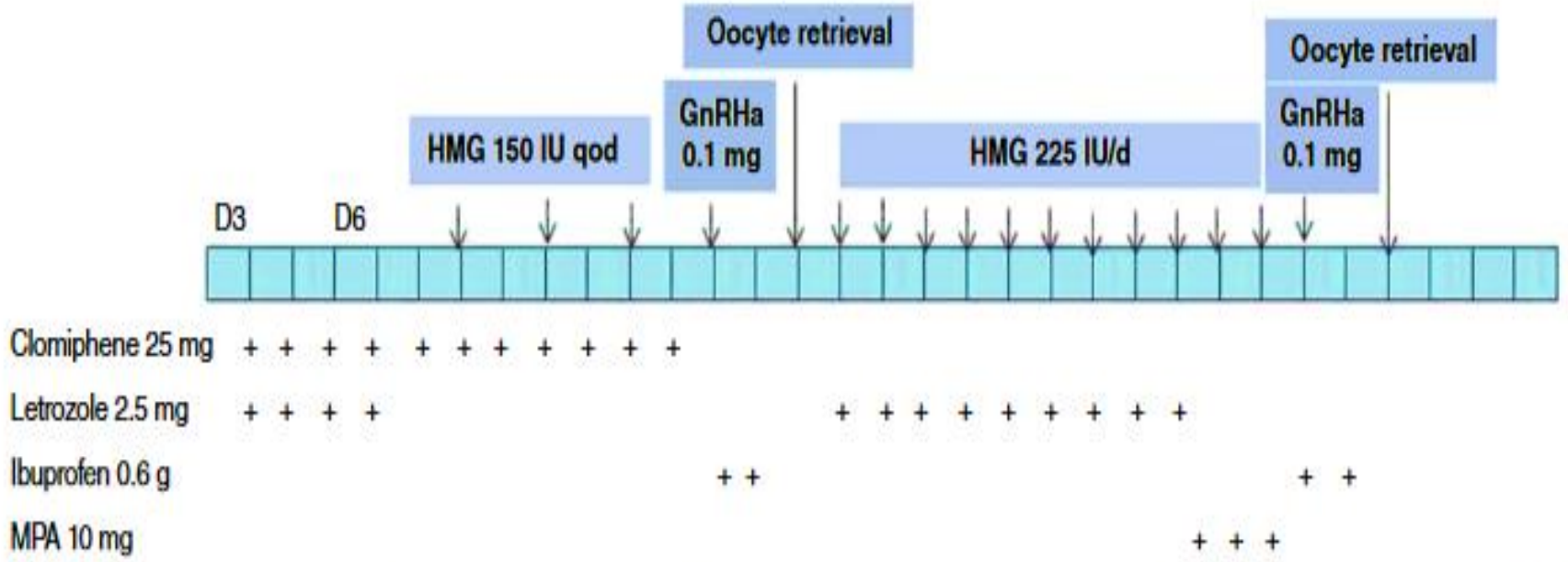

Figure 1 The protocol of double stimulation during the follicular and luteal phases in patients with poor ovarian response. GnRHa, gonadotrophin-releasing hormone agonist; HMG, human menopausal gonadotrophin; MPA, medroxyprogesterone acetate; qod, every other day.

Double mild stimulation and egg collection in the same cycle for management of poor ovarian responders

T Madani, M Hemat, A Arabipoor, S H Khodabakhshi, Z Zolfaghari

Purpose: To evaluate the effect of double stimulations during the follicular and luteal phases in women with poor ovarian response (POR) in in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles.

Basic procedures: This prospective clinical study was performed in Royan Institute from October 2014 to January 2016. 121 patients were diagnosed as POR on the basis of Bologna criteria were included. Double stimulations were performed during the follicular and luteal phases by Letrozole, Clomid, hMG and GnRH-agonist. The patients' present cycle outcomes were compared with those of the previous cycle results using appropriate statistical tests.

Main finding: The total of 104 (85.9%) patients completed the stimulation stages. The analysis revealed the number of retrieved oocytes after the first and second stimulations did not differ ($P = 0.2$); however, the fertilization rate and the number of frozen embryos after the first stimulation were significantly higher than those of in the second stimulation ($P < 0.001$ and $P = 0.03$), indicating the better quality of retrieved oocytes after the first stimulation. The mean number of MII oocytes and the fertilization rate after Shanghai protocol were higher than those of the previous antagonist protocol with a substantial trend toward significance ($P = 0.06$), which can be clinically important. The cancellation rate (33%) due to no ovarian response and no embryo formation was still high in these patients.

Principal conclusion: Since the intensity of stimulation in both stages was mild, this protocol can be considered a time-efficient and patient friendly regime; however, more studies are required with emphasis on its cost-effectiveness.

Luteal phase ovarian stimulation for poor ovarian responders

Wei Zhang, Meimei Wang, Shuang Wang, Hongchu Bao, Qinglan Qu, Ning Zhang, and Cuifang Hao

To compare the clinical outcomes of follicular versus luteal phase ovarian stimulation in women with poor ovarian response (Bologna criteria) undergoing IVF.

Methods

This retrospective study investigated 446 patients submitted to 507 cycles in three groups. First, the two larger cohorts were examined: 154 patients treated with luteal phase ovarian stimulation (Group Lu); and 231 patients administered follicular phase ovarian stimulation (Group Fo). Then the clinical outcomes of 61 patients submitted to double ovarian stimulation were analyzed. Clinical outcomes included number of retrieved oocytes, fertilization rate, cleavage rate, top-quality embryo rate, clinical pregnancy rate (CPR), and live birth rate (LBR).

Results

Longer stimulation, higher dosages of HMG, and higher MII oocyte rates were achieved in Group Lu ($p<0.001$). There were no significant differences in CPR and LBR between the two groups offered frozen-thawed embryo transfer (28.4% vs. 33.0%, $p=0.484$; 22.9% vs. 25.5%, $p=0.666$). In the double ovarian stimulation group, the number of oocytes retrieved in the luteal phase stimulation protocol was higher ($p=0.035$), although luteal phase stimulation yielded a lower rate of MII oocytes ($p=0.031$). CPR and LBR were not statistically different (13.8% vs. 21.4%, $p=0.525$; 10.3% vs. 14.3%, $p=0.706$).

Conclusion

Luteal phase ovarian stimulation may be a promising protocol to treat women with POR, particularly for patients unable to yield enough viable embryos through follicular phase ovarian stimulation or other protocols.

Double ovarian stimulation during the follicular and luteal phase in women ≥38 years: a retrospective case-control study

Conghui Liu, Hong Jiang, Wenxiang Zhang, Huiqun Yin

Abstract

Previous studies have shown that double ovarian stimulation could obtain more oocytes in women with poor ovarian response. This retrospective case-control study aimed to investigate the efficacy of double ovarian stimulation in older women. One hundred and sixteen women aged≥38 years who received double ovarian stimulation were assigned to the study, with 103 divided into four groups according to follicular-phase ovarian stimulation protocols, including gonadotrophin-releasing hormone agonist short protocol (n=27), gonadotrophin-releasing hormone antagonist protocol (n=32), mild stimulation protocol (n=21) and medrocyprogesterone acetate (MPA) pituitary down-regulation protocol (n=23). Numbers of oocytes retrieved and available embryos after double ovarian stimulation were more than double those obtained after follicular-phase ovarian stimulation alone. In total 81.90% of patients had available embryos, and the cancellation rate decreased from 37.07% to 18.10%. Forty-eight cases underwent 50 cryopreserved embryo transfer cycles, with a 22.00% clinical pregnancy rate. The implantation rate (10.53% versus 10.67%) was similar between the embryos derived from first and second stimulations. The results suggest that double ovarian stimulation could increase the chances of achieving pregnancy by accumulating more oocytes/embryos in a short time, which might serve as a useful strategy for older women.

Luteal-phase ovarian stimulation is a feasible method for poor ovarian responders undergoing in vitro fertilization/intracytoplasmic sperm injection-embryo transfer treatment compared to a GnRH antagonist protocol: A retrospective study

Li-Hong Wei, Wen-Hong Ma , Ni Tang, Ji-Hong Wei

Abstract

Objective: Poor ovarian response to ovarian hyperstimulation is one of the biggest challenges in assisted reproduction technology. Although many stimulation protocols have been established to improve clinical outcomes in poor ovarian responders (PORs), which protocol is the most effective remains controversial. Luteal-phase ovarian stimulation (LPOS) has been used in normal ovarian responders with satisfactory outcomes. However, the efficacy of LPOS in PORs is unclear. This study aimed to compare the efficacy of LPOS and GnRH antagonist (GnRH-ant) in PORs.

Materials and methods: The clinical parameters in PORs who received LPOS (50 cycles in 39 patients) or GnRH-ant (158 cycles in 123 patients) were compared.

Results: Compared with those in the GnRH-ant group, the PORs in the LPOS group showed significantly fewer basal antral follicles (3.1 ± 2.2 vs. 4.1 ± 1.6, $p < 0.001$) and a higher in vitro fertilization rate. There were no significant differences in the numbers of retrieved oocytes and D3 transferable embryos between the two groups. However, the pregnancy rate in the LPOS group (46.4%) was significantly higher than that in the GnRH-ant group (25.8% overall; 22.9% from fresh embryos and 29.6% from frozen embryos). Moreover, 23 PORs in the LPOS group underwent oocyte retrieval twice in one cycle, and the numbers of retrieved oocytes and transferable embryos from the luteal phase were significantly higher than those from the follicular phase in the same menstrual cycle.

Conclusions: Compared with the GnRH-ant protocol, the LPOS protocol may be a better regime for PORs that can increase the numbers of retrieved oocytes and transferable embryos as well as the pregnancy rate.

Multiple gestation — The risk of multiple gestation is increased with clomiphene citrate but to a much greater extent with gonadotropin therapy.

Ovarian hyperstimulation syndrome — OHSS is a potentially life-threatening complication of ovulation induction. Its most severe manifestations include massive ovarian enlargement and multiple cysts, hemoconcentration, and third-space accumulation of fluid; these changes may be complicated by renal failure, hypovolemic shock, thromboembolic episodes, acute respiratory distress syndrome, and death.

Adjuvant treatment

- ✓ Adjuvant GnRH agonists or antagonists are commonly used for women with ovulatory infertility undergoing "ovarian hyperstimulation" with gonadotropins in the setting of IVF.
- ✓ The goal is to suppress pituitary gonadotropins to optimize control of the cycle and prevent a premature rise of endogenous LH prior to full maturation of the cohort of ovarian follicles.
- ✓ Similar strategies have been proposed to improve outcomes in anovulatory women undergoing ovulation induction with gonadotropins.

Laparoscopic Ovarian Diathermy:

- Laparoscopic ovarian diathermy ("ovarian drilling") represents an alternative second-line therapy for women with polycystic ovarian syndrome (PCOS). In women who are still anovulatory despite an adequate trial of clomiphene citrate, another therapeutic option next to gonadotropins is laparoscopic surgery with electrocautery.

Cancer Risks:

- ✓ Ovulation-induction drugs are used in virtually all fertility treatment regimens. All result in a temporary increase in serum concentrations of estrogen and progesterone. There have been concerns that this could affect the risk of hormone-sensitive cancers.
- ✓ **Ovarian cancer** – In some early studies, it appeared that the use of fertility drugs was associated with neoplasia, particularly borderline ovarian tumors. Subsequent studies and meta-analyses have not confirmed an excess risk of ovarian cancer with infertility treatment (clomiphene or gonadotropin therapy), but in some reports, infertility itself was an independent risk factor. Thus, the initial observation that fertility drug use was linked to epithelial ovarian cancer appears to be explained by the fact that these drugs are more likely to be used in infertile women.

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- The best evidence for a lack of association comes from a systematic review of 11 case-control studies and 14 cohort studies that included a total of 182,972 women.
- In this analysis, there was no convincing evidence of an excess risk of invasive ovarian tumors with fertility drug therapy. However, there was a possible excess risk of borderline ovarian tumors in subfertile women undergoing in vitro fertilization (IVF).

- **Breast cancer** – There does **not** appear to be an increased risk of breast cancer in women treated with fertility drugs. However, interpretation of the available data is limited by several factors, such as survey information, small subgroup numbers, lack of evaluation by drug type/dose or cause of infertility, and confounding by the presence of other risk factors for breast cancer.

Other ovulation induction drugs

pulsatile gonadotropin-releasing hormone [GnRH] and dopamine agonists have not been linked to ovarian or breast cancer risk.

●**Colorectal cancer** – Sex hormones may play a role in the etiology of colon cancer. Rates are higher in men compared with women, and exogenous estrogens (oral contraceptives and menopausal hormone therapy) have been associated with a slightly lower risk of colon cancer in some studies. The impact of ovulation induction agents, which increase circulating estrogen levels, has not been well studied. However, in a population-based cohort study of nearly 150,000 women, no change in colon cancer risk was observed with the use of clomiphene citrate, exogenous gonadotropins, human chorionic gonadotropin (hCG), or GnRH agonists.

- **Other cancers** – In a retrospective, cohort study, neither clomiphene nor gonadotropin use appeared to be associated with an increased risk of melanoma, thyroid, or cervical cancers. In contrast, the same investigators reported that clomiphene use may be associated with a greater risk of endometrial cancer. However, one explanation for these findings is that infertile women who used clomiphene were more likely to have underlying chronic anovulation, which is a strong risk factor for development of endometrial cancer.
- **Risk in offspring –** A large, population-based study found that childhood tumor risk was not increased in children conceived following ovulation induction. Ongoing monitoring of the long-term effects of these drugs is warranted since the number of cases was small. However, congenital malformation risk does not appear to be increased with oral ovulation induction agents.


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Thank for you Listen