Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion

Practice Committees of the American Society for Reproductive Medicine and Society for Reproductive Endocrinology and Infertility

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This document reviews gonadotropin treatment for ovulation induction in anovulatory women and outlines the recommended pretreatment evaluation, indications, treatment regimens, and complications of gonadotropin treatment. It replaces the document with a similar name, last published in 2008 (Fertil Steril 2008;90:S7–12). (Fertil Steril® 2020;113:66–70. ©2019 by American Society for Reproductive Medicine.)

Exogenous gonadotropins can be used for ovulation induction in infertile women who are anovulatory or when ovulation induction cannot be achieved with less complex methods (1). Gonadotropin administration can also be used in ovulatory women for ovarian stimulation with the intent of inducing the development of multiple follicles. This treatment is distinct from ovulation induction wherein the goal is the development of a single follicle. The purpose of this document is to review the use of gonadotropins for ovulation induction, including indications, patient evaluation, regimens, monitoring, and treatment complications. The use of gonadotropins for the purpose of ovarian stimulation as part of assisted reproductive technology (ART) is not considered in this document, as those goals and protocols are distinctly different from those of ovulation induction.

INDICATIONS

Gonadotropins are indicated to treat infertility caused by anovulation, either as primary treatment or after failure of other medications to induce ovulation. Gonadotropins are indicated for hypogonadotropic hypogonadism and eugonadotropic eugonadism, also defined as type I and type II amenorrhea by the World Health Organization (2, 3). Hypergonadotropic hypogonadism or primary ovarian insufficiency (WHO type III amenorrhea) is generally not responsive to exogenous gonadotropins (2, 3).

Hypogonadotropic Hypogonadism

Endogenous circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations are in the low or low-normal range in women with hypothalamic amenorrhea. Hypothalamic amenorrhea usually results from very low or absent hypothalamic gonadotropin-releasing hormone (GnRH) secretion, but pituitary disorders can lead to a similar clinical presentation (2–4). Disorders of endogenous GnRH secretion can be congenital, acquired, or idiopathic and lead to pituitary deficiency. Conditions such as anorexia nervosa, excessive chronic physical exercise, low body mass index, poor nutritional status, and severe emotional stress can result in hypothalamic amenorrhea (2, 3). Medications may also disturb the release of GnRH and gonadotropins. Hyperprolactinemia can cause hypothalamic amenorrhea. Dopamine agonist treatment will restore ovulation in most women with hyperprolactinemia (5). Behavioral modifications may be appropriate first-line treatment for many secondary causes of hypothalamic amenorrhea (6). Women with hypothalamic amenorrhea are unlikely to respond to oral agents such as clomiphene citrate and letrozole. Treatment of hypothalamic amenorrhea should include gonadotropin preparations with both FSH and LH activity to effectively stimulate steroidogenesis and folliculogenesis (7).

Eugonadotropic Eugonadism

Polycystic ovarian syndrome (PCOS) is the most common cause of eugonadotropic eugonadism. Women with PCOS generally have normal- or low-serum FSH and mildly increased LH concentrations. Women should be evaluated for other causes of anovulation prior to the diagnosis of PCOS.

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Although most women will respond to ovulation induction with oral medications, some will not. Exogenous gonadotropin treatment for ovulation induction may be indicated in women with PCOS who fail to respond to lifestyle modifications and oral agents. However, gonadotropins are associated with significantly increased risks of ovarian hyperstimulation syndrome (OHSS) and multiple-gestation pregnancy (8, 9). Accordingly, low-dose gonadotropin regimens are strongly advised (8), or considerations of other strategies such as in vitro fertilization (IVF).

PRETREATMENT EVALUATION

Pretreatment evaluation generally should exclude abnormalities of thyroid function and hyperprolactinemia and should include evaluation of the uterine cavity, fallopian tubes, and semen analysis. While evaluation for hyperprolactinemia is not indicated in the general infertility workup, it is indicated in anovulatory women (9). Women with ovarian insufficiency should generally not be considered candidates for ovulation induction with exogenous gonadotropins (2).

GONADOTROPIN PREPARATIONS

Gonadotropin products for human use derive from urinary extracts or recombinant technology and all have similar effectiveness and safety (10). A systematic review found no evidence of a difference in either live-birth or OHSS rates among women with PCOS who were treated with urinary or recombinant gonadotropins (11). Detailed information on the composition and pharmacology of gonadotropin preparations is provided in a separate ASRM Practice Committee opinion entitled "Gonadotropin Preparations: Past, Present, and Future Perspectives" (12).

GONADOTROPIN REGIMENS FOR OVULATION INDUCTION

Gonadotropin therapy has more risks and is more expensive than oral ovulation induction agents and should therefore only be used by clinicians having the requisite training and experience. Exogenous FSH stimulates proliferation of granulosa cells and follicular growth and together with LH stimulates estradiol production. LH stimulates the production of androgens in thecal cells that are subsequently aromatized to estrogen by granulosa cells (1). The goal of ovulation induction is to promote the growth and development of a single mature follicle.

Women with PCOS may begin ovulation induction after a menses induced by brief treatment with an exogenous progestin. However, data suggest that progestin withdrawal bleed may decrease pregnancy rates in these women (13); ovulation induction may be induced without a withdrawal bleed when pregnancy has been excluded. Baseline ultrasonography should be performed to exclude ovarian cysts that might be confused with new follicular growth.

Exogenous FSH alone can induce ovulation in women with PCOS, because endogenous LH levels are adequate, although added LH does not appear to be harmful (1, 8). There is no significant advantage to using any specific gonadotropin preparation. A meta-analysis concluded that the outcomes of treatment achieved with human menopausal gonadotropins (hMG) and with FSH alone were similar (14). Others have observed that treatments with recombinant FSH or urinary FSH yields similar results (11, 15). The recommended approach in the first dose-finding cycle is to begin with a low dose of gonadotropin, typically 37.5–75 IU/day, and increasing in small increments after 7 days or more if no follicle >10 mm has developed. Pen devices allow more finely tuned incremental dosing. In subsequent cycles, treatment generally begins at the threshold of response previously determined. Although 7–12 total days of treatment is typical, longer durations of treatment may be required. Once a mature follicle has developed, exogenous hCG is administered to stimulate ovulation (1, 8).

In women with hypothalamic amenorrhea, optimal clinical results are achieved by administering a combination of FSH and LH (16, 17). This can be accomplished by administration of hMG (18) or a combination of FSH with either recombinant LH (19, 20) or low-dose hCG (21). In addition to stimulating the production of androgens, which provide the substrate for estrogen production that enhances oocyte and endometrial development, LH activity promotes development of larger follicles (20-24). There are no established superior gonadotropin regimens or doses for ovulation induction in patients with hypothalamic amenorrhea. Patients with profound hypothalamic dysfunction may require a prolonged period of gonadotropin treatment to achieve follicular growth; setting correct patient expectations and patience is often needed.

Monitoring of Ovulation Induction

The safety and efficacy of gonadotropin treatment depends on careful monitoring with serial transvaginal ultrasonography and estradiol measurements (1, 8). Ultrasonography provides a structural measure of follicular development and generally should be performed after the first 4–5 days of treatment and at subsequent intervals of 1–3 days according to response (1, 8). Endometrial thickness and appearance provide an indirect measure of endometrial development and have some prognostic value for implantation (1, 25). Measurement of serum estradiol in conjunction with ultrasonography provides an accurate gauge of response to treatment and informs treatment management (1, 8). The presence of multiple follicles as small as 10–12 mm at the time of ovulation can increase the risk of multiple gestation (26-28).

Inducing Ovulation

The final stages of oocyte maturation and release can be induced by injection of human chorionic gonadotropin (hCG). The trigger injection can be 5,000–10,000 IU of urinary hCG (1, 7) or 250 mg of recombinant hCG, which corresponds to approximately 6,000–7,000 IU urinary hCG (29). Ovulation is expected to occur 36-48 hours after trigger, so intercourse or intrauterine insemination should be appropriately timed to occur prior to ovulation.

Ovulation induction cycles can result in a robust multifollicular ovarian response and cycle cancellation or conversion to IVF should be considered to reduce the risk of multiple gestation and OHSS (1, 8, 22, 29-31). Gonadotropin releasing hormone (GnRH) agonists can also be used to trigger ovulation, by stimulating a sudden release of endogenous FSH and LH (32). PCOS patients who appear to be at high risk for OHSS can undergo a GnRH agonist trigger. GnRH triggers should not be used in patients with hypogonadotropic hypogonadism because those patients often lack adequate stores of endogenous LH to induce ovulation using this approach.

Luteal-Phase Progesterone Support

There is evidence to suggest that the high estradiol levels routinely produced by ovulation induction with gonadotropins are associated within adequate progesterone levels in the luteal phase (33). Therefore, some clinicians recommend progesterone luteal support in all patients undergoing ovulation induction with gonadotropins. This includes women with hypothalamic amenorrhea whose endogenous LH secretion may be inadequate to support normal luteal function. In women with unexplained infertility undergoing ovulation induction with gonadotropins, a meta-analysis of studies on luteal support with progesterone demonstrated a higher live-birth rate (34). Currently, there are insufficient data on women with PCOS to recommend luteal support with progesterone.

RESULTS ACHIEVED WITH GONADOTROPIN TREATMENT FOR OVULATION INDUCTION

A systematic review of 13 studies evaluated ovulation induction with gonadotropins in anovulatory women and found pregnancy rates of 15% per cycle and 41% per patient over an average of 2.7 cycles (35) . Women who were obese or insulin resistant required higher doses of gonadotropins. Insulin resistance, but not obesity, was associated with a lower pregnancy rate (odds ration [OR] 0.24, 95% confidence interval [CI] 0.08–1.71). A small study of women with hypothalamic amenorrhea demonstrated pregnancy rates of 25% per cycle (36). The type of gonadotropin did not appear to have significant influence on pregnancy rate in four trials involving 396 patients treated with FSH or hMG (15).

COMPLICATIONS OF OVULATION INDUCTION

Multifetal gestation is the most frequent complication of ovulation induction. Gonadotropins have been associated with risk of multiple gestation as high as 36% when strict cancellation criteria are not in place (37). The goal of ovulation induction is ovulation of a single mature oocyte, which can sometimes be difficult to achieve with gonadotropins (38). Criteria for cycle cancellation should be stringent. To minimize the risk of multifollicular ovulation and multiple pregnancy, cycle cancellation generally should be considered when more than two follicles $\geq$16 mm develop. Since intermediate-sized follicles also contribute to the risk of multiple gestation, cycle cancellation should be considered when three or more follicles $\geq$10 mm develop (39). Patients should be counseled on the risks of multifetal gestation prior to gonadotropin use. When a high risk of multifetal gestation develops, the gonadotropin cycle should be canceled, and patients counseled on abstinence or barrier contraceptives.

OHSS can occur after ovulation induction in anovulatory women and the risk cannot be eliminated, regardless of strict cancellation criteria. If OHSS is a concern, or the patient is also at an unacceptably high risk of multiple-gestation pregnancy, cycle cancellation should occur.

Concerns that ovulation induction might be associated with an increased risk for cancer of the ovary and breast (40) have not been corroborated by subsequent studies (41, 42). Although the risk for ovarian cancer may be higher for infertile women than for fertile women, there is no compelling evidence to indicate that such risk is increased by ovulation induction. A recent ASRM guideline concluded that the use of gonadotropins was not associated with an increased risk of invasive ovarian, breast, endometrial, thyroid, colon, or cervical cancer (Grade B) (43).

SUMMARY

- Gonadotropin cycles should be managed by a clinician with the requisite training and experience.
- The goal of gonadotropin treatment for ovulation induction is to promote the development of a single mature follicle. Monofollicular development sometimes can be difficult to achieve.
- Monofollicular development decreases the risk of multiple gestation and OHSS.
- The risk of multiple gestation and OHSS cannot be completely eliminated with the use of gonadotropins.
- Patients should be counseled on the risks of ovulation induction with gonadotropins prior to cycle start.
- Gonadotropins should be started at a low dose of 37.5–75 IU a day and cautiously increased as needed for monofollicular development.
- Cycle cancellation should be considered if more than two follicles $\geq$16 mm develop or if three or more intermediate-sized follicles develop.
- Luteal support is beneficial following ovulation induction with gonadotropins in women with hypothalamic amenorrhea. While luteal support also may be beneficial following ovulation induction with gonadotropins in women with PCOS, there is insufficient evidence to make a recommendation.

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