Use of exogenous gonadotropins in anovulatory women: a technical bulletin

The Practice Committee of the American Society for Reproductive Medicine

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This Technical Bulletin reviews the indications for gonadotropin treatment in anovulatory women; outlines the recommended pretreatment evaluation, treatment regimens, and monitoring; describes the alternatives and adjuncts to treatment with gonadotropins; and summarizes the complications of gonadotropin treatment. (Fertil Steril® 2008;90:S7–12. ©2008 by American Society for Reproductive Medicine.)

Exogenous gonadotropins can be used for ovulation induction (OI) in women who are anovulatory and infertile, and they are indicated when OI cannot be achieved with less complex methods (1). The purpose of this document is to review the indications for gonadotropin treatment in anovulatory women; to outline the recommended pretreatment evaluation, treatment regimens, and monitoring; to describe briefly the alternatives and adjuncts to treatment with gonadotropins; and to summarize the complications of gonadotropin treatment. The use of gonadotropins to purposely induce superovulation in concert with intrauterine insemination or assisted reproductive technology (ART) is not considered or discussed in this document, because the principles, mechanisms, and goals of such treatments are distinctly different from those of OI.

INDICATIONS

Gonadotropins are used to treat infertility caused by anovulation, usually after other less complicated and costly methods have failed. Two groups of anovulatory disorders may require gonadotropin therapy: 1) hypogonadotropic amenorrhea (HA, also known as hypogonadotropic hypogonadism, hypothalamic amenorrhea, or World Health Organization [WHO] type I amenorrhea); and 2) polycystic ovary syndrome (PCOS, also known as hyperandrogenic amenorrhea or WHO type II amenorrhea) (2, 3). Premature ovarian "failure" (POF) (also known as hypergonadotropic hypogonadism or WHO type III amenorrhea) is not responsive to exogenous gonadotropins and must be excluded (2, 3).

Hypogonadotropic amenorrhea (HA)

Endogenous circulating FSH and LH concentrations are normal or low in women with HA. Although pituitary disorders, such as panhypopituitarism, can cause HA, the disorder usually results from very low or absent hypothalamic GnRH se-

cretion (2, 3). Such disorders of endogenous GnRH secretion can be congenital or acquired and may relate to severe weight loss (anorexia nervosa), excessive chronic physical exercise, severe emotional stress, or medications, or may be idiopathic (2, 3). Hyperprolactinemia resulting from a pituitary adenoma also can result in secondary or acquired HA. The possibility should be investigated specifically and treated when identified with a dopamine agonist before OI, because ovulatory function will be restored in most women after PRL levels fall into the normal range (4). Women with HA seldom respond to clomiphene citrate (CC); alternative methods for OI include pulsatile GnRH (5) and exogenous gonadotropins. However, gonadotropin treatment should include both FSH and LH activity to effectively stimulate both steroidogenesis and folliculogenesis (6).

Polycystic ovary syndrome (PCOS)

Women with PCOS generally have normal or low serum FSH and often mildly increased LH concentrations. Although most will respond to treatment with CC, many do not, particularly if obese (7). Exogenous gonadotropin treatment often is required in CC-resistant women with PCOS, but it is also associated with significantly increased risk for ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy (7, 8). Accordingly, low-dose gonadotropin treatment regimens are strongly advised (7).

PRETREATMENT EVALUATION

Gonadotropin therapy is costly and has significant risks, and should therefore be used only by clinicians having the requisite training and experience. Before treatment begins, other potential coexisting causes of infertility, such as uterine cavity abnormalities (myomas, adhesions), tubal obstruction, advanced endometriosis (ovarian endometrioma), pelvic adhesions, or poor semen quality, should be excluded. Pretreatment evaluation generally should exclude abnormalities of thyroid function and hyperprolactinemia and should include hysterosalpingography, transvaginal ultrasonography, and semen analysis. Women with POF should not be considered as candidates for OI 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 (9). Detailed information on the composition and pharmacology of gonadotropin preparations is provided in a separate document entitled "Gonadotropin Preparations: Past, Present, and Future Perspectives"(10).

GONADOTROPIN REGIMENS FOR OI

Exogenous FSH stimulates proliferation of granulosa cells and follicular growth. Luteinizing hormone stimulates the production of androgen in thecal cells that subsequently is converted to estrogen by granulosa cells via aromatization (1). The goal of treatment is to promote the growth and development of a single mature follicle.

In women with PCOS, OI usually begins after a menses induced by a brief interval of treatment with an exogenous progestogen. In women with HA, OI may begin at any convenient time. Baseline ultrasonography is prudent to exclude ovarian cysts that might be confused with new follicular growth. Among women not previously treated with exogenous gonadotropins, treatment generally should begin at a relatively low dose (e.g., 37.5–75 IU/day). 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, generally measuring 16–18 mm in mean diameter, exogenous hCG or a GnRH agonist is administered to stimulate ovum release, as described in a subsequent section (1, 7).

Monitoring of OI

The safety and efficacy of gonadotropin treatment depend on careful monitoring with serial transvaginal ultrasonography and serum E_2 measurements (1, 7). Ultrasonography provides a structural measure of follicular development and generally should be performed after the first 4–5 days of treatment and at intervals of 1–3 days thereafter according to response (1, 7). Endometrial thickness and appearance provide an indirect measure of endometrial development and maturation and have some prognostic value for implantation (1, 11). Rapid serum E_2 determinations (results available the same day and, ideally, 7 days/week) provide a functional measure of follicular maturation. Together with ultrasonography, serum E_2 levels provide an accurate gauge of response to treatment and guide the management of the OI cycle (1, 7).

Gonadotropin Regimens in HA

In women with HA, optimal clinical results are achieved by the combined administration of FSH and LH (12, 13), accomplished by administration of hMG (14) or a combination of FSH and either recombinant LH (15, 16) or low-dose hCG (17). In addition to stimulating the production of intrafollicular androgens which provide the substrate for estrogen pro-

duction that enhances oocyte development, LH activity promotes development of larger follicles (16–19). There are no established gonadotropin regimens for OI of HA patients and no prospective studies that assess treatment outcomes with different gonadotropin dosages.

Gonadotropin Regimens in PCOS

In women with PCOS, only FSH activity is required, because endogenous LH levels are adequate, although added LH does not appear to be harmful (1, 7). There is no significant advantage to using any specific gonadotropin preparation. A meta-analysis concluded that the outcomes of treatment achieved with hMG and with FSH alone were similar (20). Others have observed that treatment with rFSH or urinary FSH yields similar results (21).

The risk of OHSS and multiple pregnancy is greater among women with PCOS than among those with HA, primarily because gonadotropin treatment generally stimulates development of larger follicular cohorts in women with PCOS (22). Consequently, exogenous gonadotropins must be administered judiciously (23–29). The recommended approach in the first dose-finding cycle is to begin with a low dose of gonadotropin, typically 37.5–75 IU/day, increasing after 7 days or more if no follicle >10 mm has yet emerged, in small increments, at intervals, until evidence of progressive follicular development is observed. The maximum required daily dose of FSH/hMG seldom exceeds 225 IU/day (23).

Inducing Oocyte Release

The final stages of follicle/oocyte maturation and ovum release can be induced by administration of hCG extracted from urine, recombinant hCG, recombinant LH, or a GnRH agonist (1, 7, 30–33). Although there are no evidence-based specific guidelines for optimal timing, the ovulatory stimulus generally should be administered when at least one and, ideally, no more than two follicles greater than 16–18 mm in mean diameter are observed, so as to limit the risk for multiple pregnancy. Estradiol concentrations generally should range between approximately 150 and 300 pg/mL per dominant follicle.

Human chorionic gonadotropin is administered in a single injection of 5,000–10,000 IU IM or SC (1, 7); recombinant hCG is administered at a dose of 250 μg SC, which corresponds to approximately 6,000–7,000 IU hCG (30). Recombinant LH also is effective and potentially safer than hCG. However, the current formulation of recombinant LH (75 IU/vial) precludes its use for that purpose, because 25,000–30,000 IU recombinant LH is required to yield results similar to those achieved with 5,000 IU hCG (31). Given these considerations, hCG is the least expensive and most widely used preparation (1).

A GnRH agonist also can be used to induce oocyte release in OI, provided that an agonist has not been administered earlier during the course of gonadotropin treatment to prevent

a spontaneous LH surge. The GnRH agonists are not effective in HA. For purposes of inducing ovum release, the recommended dose for leuprolide is 500 μg (32) and for triptorelin is 200 μg (33); both are administered in a single SC injection. When a GnRH agonist is used to induce ovum release, progesterone supplementation during the luteal phase is required, because agonist treatment may adversely affect endogenous luteal function.

Support of Corpus Luteum Function

Routine treatment with supplemental exogenous progesterone or additional small doses of hCG (1,500–2,500 IU every 3–4 days) during the luteal phase of OI cycles is advocated by many. Luteal support after OI is most clearly indicated and recommended in women with HA whose endogenous gonadotropin secretion may be inadequate to support normal luteal function. Its necessity and effectiveness otherwise are unproven and controversial (1).

TIMING OF INTERCOURSE

Ovulation can be expected to occur between 24 and 48 h after injection of hCG or a GnRH agonist. Consequently, intercourse within that interval can help to maximize the likelihood of conception. When specifically indicated, intrauterine insemination generally should be planned for approximately 24–36 h after the injection (1).

RESULTS ACHIEVED WITH GONADOTROPIN TREATMENT FOR OI

In a 2003 systematic review of 13 studies published between 1991 and 2000 including 1,269 cycles among 881 anovulatory infertile women (2.7 cycles per patient) who received gonadotropin treatment for OI, there were 366 pregnancies; the pregnancy rate was 15% per cycle and 41% per patient (34). Women who were obese or insulin resistant required increased total amounts of gonadotropins per cycle. Insulin resistance, but not obesity, was associated with a lower pregnancy rate (odds ratio [OR] 0.24, 95% confidence interval [CI] 0.08–1.71). Another study, not included in the 2003 systematic review, reported 18 pregnancies in 28 women with HA across 72 cycles of treatment (25% per cycle), but only 16 pregnancies in 61 hyperandrogenic women with PCOS across 205 cycles of treatment (8% per cycle) (35). The type of gonadotropin did not appear to have significant influence on pregnancy rate in four trials involving 396 patients treated with FSH (12%) or hMG (10%) (OR 0.82, 95% CI 0.44–1.53) (36).

ALTERNATIVES AND ADJUNCTS TO GONADOTROPIN TREATMENT FOR OI

Clomiphene citrate (CC) is traditional first-line treatment for OI. Clomiphene citrate competes with endogenous estrogen for the estrogen receptor and, by causing a central misinterpretation of circulating estrogen levels, induces a transient but significant increase in the secretion of pituitary FSH. In

women with HA in whom the hypothalamic-pituitary-ovarian feedback axis is severely dysfunctional, CC is ineffective. Clomiphene citrate may also be used in concert with exogenous gonadotropins in a sequential regimen that begins with CC, adding gonadotropins on the last day of CC therapy or the day after. Limited evidence suggests that sequential CC/gonadotropin therapy may help to lower the total dose, duration, and cost of gonadotropin treatment required to achieve OI (37, 38).

Metformin enhances insulin actions and has been advocated for OI in women with PCOS, in whom the prevalence of insulin resistance is relatively high. Although some anovulatory women will ovulate in response to metformin treatment alone (1,500 mg/day), CC has proven to be more effective in a large randomized clinical trial (39). Metformin treatment may be effective in nonobese women with PCOS (40). Combined treatment with metformin and FSH also has been advocated. Although combined treatment may help to reduce the total dose of gonadotropins required to achieve OI (41), pregnancy rates are not increased (42). The clinical value of metformin in CC-refractory anovulatory women who require gonadotropin therapy has not been investigated thoroughly.

Ovarian drilling has been used to decrease ovarian androgen production in the ovaries of anovulatory infertile women with PCOS and can successfully induce ovulation in many such women who may prove resistant to treatment with CC (43, 44). However, the benefits that ovarian drilling may offer are usually transient and the procedure has risks, such as pelvic adhesions and potential adverse effects on ovarian reserve (43, 44). In highly selected individuals, ovarian drilling may be an alternative to gonadotropin treatment that merits consideration. However, even after ovarian drilling, OI still may be required. With the ready availability of ART in most centers, ovarian drilling has become uncommon, although the procedure can achieve good results and is associated with a lower risk for multiple pregnancy (43, 44).

Gonadotropin-releasing hormone analogs (agonists and antagonists) are most commonly used in conjunction with gonadotropin treatment in ART stimulation cycles, primarily to prevent premature luteinization and ovulation (1). Although seldom used in OI, they may have some utility for individuals in whom those phenomena are observed during gonadotropin treatment. When used in OI cycles, treatment with supplemental progesterone during the luteal phase generally is recommended because endogenous pituitary LH secretion remains suppressed for some time after treatment with a GnRH agonist (45) or antagonist (46, 47).

Aromatase inhibitors block conversion of androgens to estrogens. When normally operating, the feedback relationship between circulating estrogen levels and gonadotropin secretion results in an increase in pituitary FSH secretion (48). No trials have evaluated aromatase inhibitors as an alternative to gonadotropin treatment in CC-resistant women. When used in sequence or in conjunction with exogenous

gonadotropins, aromatase inhibitors may reduce the amount and duration of gonadotropins required to achieve OI, but E_2 levels are more difficult to interpret confidently, and the evidence to support their use is meager (49). Aromatase inhibitors are not approved for use in OI. Experience with the off-label use of aromatase inhibitors for OI is limited (50), their safety has been questioned (51, 52), and studies of their efficacy and clinical utility are ongoing.

COMPLICATIONS IN OI

Multifetal gestation is the most frequent complication of OI. The goal of OI is ovulation of a single mature oocyte, and although that objective can sometimes be difficult to achieve (53), the criteria for cycle cancellation should nonetheless be stringent. To minimize the risk of multifollicular ovulation and multiple pregnancy, cycle cancellation generally should be seriously considered when three or more mature follicles (>16–17 mm) or large numbers of intermediate-sized follicles (10–15 mm) are observed or when the serum E_2 concentration exceeds 1,000–1,500 pg/mL (1). However, the increased risk for multiple pregnancy associated with gonadotropin treatment cannot be eliminated entirely, and even the low-dose gonadotropin regimens advocated here are associated with five- to 10-fold increased risk (54). Although multifetal pregnancy reduction can be offered when treatment results in a high-order multiple pregnancy (triplets or greater), the risk is easier to avoid than to manage (55).

Ovarian hyperstimulation syndrome (OHSS) can occur after OI in anovulatory women, and the risk cannot be eliminated completely. To minimize the risk for developing OHSS, a lower dose of hCG (5,000 IU) or a GnRH agonist is recommended for inducing ovum release when E_2 levels have risen rapidly or are markedly elevated (>2,500 pg/mL) and/or a large number of intermediate-sized follicles (10–14 mm) are observed (56).

Earlier concerns that OI might be associated with an increased risk for cancer of the ovary and breast (57) have not been corroborated by subsequent studies (58, 59). 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 OI.

SUMMARY AND RECOMMENDATIONS

- Gonadotropin treatment for OI is indicated for anovulatory infertile women with HA and for those with PCOS who fail to respond to less complicated OI treatment regimens.
- Before treatment with gonadotropins, evaluation generally should exclude abnormalities of thyroid function and hyperprolactinemia, and should include hysterosalpingography, transvaginal ultrasonography, and evaluation of the male partner by semen analysis.
- Although sometimes difficult to achieve, the goal of gonadotropin treatment is to promote the growth and development of a single mature follicle.

- Among women not previously treated with exogenous gonadotropins, treatment generally should begin at a relatively low dose (e.g., 37.5–75 IU/day). In subsequent cycles, treatment generally begins at the threshold of response previously determined.
- Ovulation of a mature ovarian follicle may be triggered with either purified (5,000–10,000 IU IM or SC) or recombinant (250 μg SC) hCG. A GnRH agonist (leuprolide 500 μg SC; triptorelin 200 μg SC) also may be used to trigger ovulation, except in women with HA and those who have received GnRH agonist treatment earlier during the course of gonadotropin treatment.
- Luteal support after OI is most clearly indicated and recommended in women with HA and those who receive treatment with a GnRH agonist, because, in these cases, endogenous gonadotropin secretion may be inadequate to support normal luteal function.
- The increased risk of multiple pregnancy associated with gonadotropin treatment can be limited by judicious treatment and careful monitoring, but it cannot be eliminated entirely.
- Despite careful monitoring, OHSS can occur after OI in anovulatory women.

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