Adjuncts for ovarian stimulation: when do we adopt "orphan indications" for approved drugs?

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Several drugs, shown to be safe for other uses, have proven to be highly effective adjuncts for ovarian stimulation. The authors evaluate these "orphan" indications and make recommendations so that more patients will benefit from their use. (Fertil Steril® 2009;92:13–8. ©2009 by American Society for Reproductive Medicine.)

Key Words: Ovarian stimulation, metformin, dexamethazone, hCG, aspirin, cabergoline, androgens

As with orphan drugs that help too few patients to make development worthwhile without financial incentives from the government, frequently manufacturers do not invest the considerable financial resources necessary to establish new indications for established drugs, particularly when they apply to a small group of patients or when the indications fall outside of the usual patient groups to which they apply, or when the drugs are already generic. A prominent example in the area of IVF is the use of leuprolide acetate (LA) to prevent premature LH release and ovulation. This contribution will make the case that there are a number of such medications that are important adjuncts to controlled ovarian hyperstimulation (COH). The decision as to when to adopt these "orphan indications" is complex. The authors will illustrate the decision-making process by using a dozen examples grouped into nine strategies ranging from widely accepted to still somewhat uncertain. Recommendations regarding use and informed consent will be made for each.

The decision-making process is influenced by the following:

A. Evidence based on well-designed, randomized, placebo-controlled trials (including meta-analysis of such trials), and corroborating evidence from other studies.
B. Basic scientific studies elucidating a logical mechanism.
C. Negative trials or meta-analysis indicating that the effect may be less than originally indicated, because only very large trials or collections of studies can establish an accu rate estimate of the treatment effect.
D. Ancillary benefits.
E. Risks of treating.

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Leuprolide Acetate (LA)

A More than 20 years ago, LA was found to effectively block premature ovulation, which otherwise resulted in the cancelation of about 20% of IVF cycles. This benefit was so clear and dramatic that one of the authors (D.M.) suggested that it should be used routinely for IVF (1).

B The mechanism has been clearly delineated.

C None.

D A subsequent meta-analysis found that the likelihood of a successful pregnancy using LA was increased almost two-fold (2), although that was likely an overestimate due to the inclusion of studies where the control group not given LA also received clomiphene citrate (CC). Also, more embryos are available for cryopreservation, resulting in more pregnancies from those additional embryos.

E Risks are minimal.

Conclusion After more than 20 years of use and clear evidence of benefit with minimal risk, use of LA continues to be "off label" as an adjunct for IVF. Use is so widespread that informed consent is not required, except as part of a comprehensive IVF consent.

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Oral Contraceptives (OCs) and Estrogen (E)

A Although GnRH agonists can be used to schedule cycles, pronounced side effects can occur during extended ovarian suppression. Biljan et al. (3) reported that OC pretreatment reduced the amount of gonadotropin required for COH and therefore appeared to improve synchronization of the follicular cohort instead of agonist alone, suggesting it as a useful adjunct for scheduling cycles and improving IVF outcome. One of the authors (D. de Z.) was first to suggest use of luteal E for scheduling of COH (4), and that adjunct has subsequently been reported to synchronize the follicles and improve the response to COH (5). Another of the authors (R.S.) has reported improved COH in poor responders with luteal E_2 (6).

B The FSH and follicular growth are suppressed by either OC or E.

C None.

D Cyst formation resulting from GnRH agonists is also reduced by OC pretreatment.

E Minimal.

Metformin

A A meta-analysis of five trials has reported a very highly significant ($P<.00001$) decrease of ovarian hyperstimulation syndrome (OHSS) with metformin (odds ratio [OR] 0.21, 95% confidence interval [CI] 0.11–0.41) in women with polycystic ovary syndrome (PCOS) having IVF (7).

B One of the authors (J.C.) was first to make the observation of elevated levels of insulin in PCOS, aside from the increase expected with the commonly associated obesity in this syndrome (8). Insulin, which is reduced by metformin, is one of the principal factors that stimulates the production of vascular endothelial growth factor by luteinized granulosa cells (GC) (9). In an editorial discussing that study, one of the authors (D.M.) suggested that various strategies, including routine use of metformin, could be used to reduce insulin levels and the incidence of OHSS in women with PCOS having IVF (10). Also, because androgens stimulate GC FSH receptors, metformin may reduce OHSS by decreasing the ovarian response to COH.

C None.

D A prospective, randomized trial in women with PCOS has reported significantly higher rates of ongoing pregnancy per cycle and per transfer with metformin versus placebo (11). This finding is supported by a case-controlled study that also reported an increase in the pregnancy rate (PR) and a highly significant increase of embryo quality with metformin (12), but in a meta-analysis of the five small randomized trials published to date (about 200 subjects total in each group), the 29% increase of the PR observed was not statistically significant (7). Very recently, a large meta-analysis of trials adding metformin or placebo to CC has reported significant increases of ovulation and pregnancy with metformin (13). Addition of metformin to FSH treatment for CC-resistant patients with PCOS has been reported to reduce the number of preovulatory follicles and the peak level of E_2 (14). Ovulation induced with metformin has been associated with decreased T levels and marked increases of glycodelin levels during the luteal phase in women with PCOS (15). Uterine blood flow is reduced in PCOS and both metformin and blockade of the effect of T by flutamide increase uterine blood flow in those women (15, 16). HOXA-10, required for implantation, is suppressed in PCOS by T, and that effect is blocked by the T antagonist, flutamide (17). Use of metformin in PCOS improves altered blood lipids and may reduce later cardiovascular disease.

E Lactic acidosis has rarely been reported. Liver and kidney disease should be excluded before use and metformin should be stopped during acute illnesses and when radiologic dye is to be used.

Conclusion Metformin appears to have benefits in women with PCOS throughout ovulation induction treatments and particularly during IVF cycles by reducing OHSS. The OHSS is the most serious complication of IVF in women with PCOS and may lead to catastrophic complications and even death. It should be noted that most clinical studies on the use of metformin in PCOS have not been based on demonstrated insulin resistance, although the criteria for the diagnosis of PCOS has varied. Use is now sufficiently widespread that a separate informed consent is not required.

Growth Hormone

A In a meta-analysis of randomized trials in poor responders, growth hormone was reported to increase the PRs and birth rates by approximately three- and fourfold, respectively, compared with placebo (18). Growth hormone was not effective in increasing ovarian response, which was the original purpose of those trials. The authors suggested that further information was needed to confirm this finding. Subsequently, a randomized trial was undertaken in poor responding women older than 40 years having IVF (19). Their poor responder status was clearly indicated by a peak level of E_2 of 912 pg/mL (SD 129), in spite of stimulation with 600 IU of gonadotropins. Approximately four- and fivefold increases of the PRs and delivery rates were noted, respectively, with a trend toward better embryo quality with growth hormone, and intrafollicular E_2 levels were significantly increased. One of the authors (W.S.), in a study of minidose LA together with growth hormone, reported a 25% rate of heartbeat per transferred embryo in poor responders with a mean of almost three failed cycles, consistent with the degree of benefit reported in those randomized trials (20).

B Increased apoptosis has been reported in the GCs of older women having IVF (16). Growth hormone and its intermediary, insulin-like growth factor I (IGF-I) are two of the most well-characterized factors known to reduce apoptosis and improve the health and proliferation of GCs (21), which are crucial to the nourishment of the maturing oocyte.

C None.

D None.

E Minimal. Use in a diabetic could adversely influence blood sugar control.

Conclusion Growth hormone has been reported to increase successful IVF outcome in low responding women. However, as its use is not widespread, a specific informed consent is advised.

Dexamethasone

A Daly et al. (22) were first to report that dexamethasone increased the response to CC in women with PCOS compared with placebo. Subsequent studies in women resistant to CC reported a high response rate, even when the levels of adrenal androgens were normal (23, 24). Dexamethasone was given in those trials as a daily dose of 0.5 mg. Subsequently, there have been two additional randomized trials in women failing to ovulate with up to 150–250 mg of CC (25, 26). The rate of ovulation increased four- to fivefold and the rate of pregnancy per cycle increased 8- to 10-fold. In these trials the dose of dexamethasone was 2 mg, but given only during the 5 days of CC and for the following 5 days (days 5–14 for women receiving CC days 5 through 9). In those trials hCG was routinely given to induce ovulation. Also, in a large randomized trial of dexamethasone during stimulation for IVF, a dramatic decrease of cancelled cycles from 12.4%–2.8 % was noted, and the implantation rates and PRs were higher, despite inclusion of those poor prognosis women going to egg retrieval (27).

B The role of glucocorticoids in the follicle is not well defined, although it is certainly of interest that the ratio of cortisol (F) to cortisone in follicular fluid (FF) has been reported to strongly correlate with IVF success (28, 29). Although the major increase of androgens during ovarian stimulation results from FSH stimulation, supression of adrenal production of androgens by dexamethasone may contribute to maximizing uterine receptivity by lowering total androgen levels and resulting in the benefits discussed previously (15–17).

C None.

D None.

E Minimal. Glucocorticoids should not be used with peptic ulcer disease, infection, diabetes, or latent tuberculosis. With its use before IVF, the authors did not use any steroid boost for oocyte retrieval, nor did they describe any tapering of the dose after retrieval (27).

Conclusion Dexamethasone has been reported to be a highly effective adjunct to CC. However, it is not yet known whether its benefits will accrue in women failing CC and metformin therapy. Dexamethasone has been widely used in PCOS, but a center may wish to have separate informed consent because the higher dose, short duration regimen has not yet been used extensively.

Human Chorionic Gonadotropin

A Human chorionic gonadotropin has been routinely used and is approved as an LH surrogate to induce ovulation. With the increasing use of recombinant FSH for ovarian stimulation, one of the authors (D.M.) proposed that small doses of hCG would be effective adjuncts for ovarian stimulation, therfore the use of hMG would be unnecessary (30). Most of the LH activity in hMG is from the approximately 10 units of hCG in each 75 IU vial, but the amount of hCG and LH bioactivity varies from batch to batch and among suppliers. Dilute hCG has the advantage of providing a consistent LH-like effect, as long as a sufficient volume is used. Various compounding pharmacies are making up these small doses.

B One of the authors (D. M.) showed that a single dose of 50 IU of hCG increased the level of bioactive LH/hCG to normal in the mid-to-late follicular phase in women suppressed with a potent GnRH antagonist (30). Because of its long half-life, we suggested that a daily dose of 20–30 IU would provide similar LH-like activity. A dose of 50 IU of hCG was subsequently used successfully in a patient with hypogonadotropic hypogonadism treated with pure FSH (31).

C–E None.

Conclusion Use of 10–30 IU daily of hCG may be logically used as an alternative to substituting 75–225 IU of hMG for the same dose of pure FSH when addition of LH activity is desired. A separate consent is not suggested.

Low Dose Aspirin

A Rubinstein et al., in 1999 in this journal (32), published a large, well-designed trial that found increases of ovarian response, pregnancy outcome, and ovarian and uterine blood flow with 100 mg of aspirin compared with placebo in a population residing in a large metropolis. The aspirin was begun with the onset of midluteal agonist and was continued through early pregnancy.

B Low dose aspirin is thought to increase blood flow by changing the balance of vasoconstricting thromboxane relative to vasodilating prostacyclin. Ovarian blood flow has been reported to correlate with ovarian response and uterine blood flow has been implicated in implantation, which is a highly vascular phenomenon. It is not known how long ovarian blood flow must be increased to potentially influence ovarian response. The most important time for maximal blood flow may be between hCG and egg retrieval, during which meiosis resumes.

C Subsequently a meta-analysis has been published, also in this journal, combining seven remarkably heterogeneous trials with the conclusion that the ovarian response and PR are not increased (33). In two of these trials the aspirin was started on the same day as ovarian stimulation was begun and in one trial the aspirin was stopped at the time of hCG administration. The patient populations varied widely from a small city in Scandinavia to environments closer to that of the original trial. Two studies were in frozen embryo

cycles and egg donation recipients, where an effect on embryo quality would not be seen, and the hormone levels are entirely different from the original trial. One trial was in poor responders and one trial was in women with an endometrium refractory to usual doses of E. In a very large trial not included in the meta-analysis, presumably due to the randomization method, the aspirin was started only with embryo transfer, yet a significant increase in the PR was observed (34). However, a reanalysis of published trials by the Division of Epidemiology of the National Institutes of Health (35) concluded that the clinical PR was increased and "there is no reason to change clinical management and discontinue the use of aspirin."

D Ovarian stimulation is accompanied by increases of clotting factors. The platelet-inhibiting effect of aspirin may reduce the chance of a thrombotic event with COH and OHSS.

E The anticoagulant effect could increase the chance of bleeding with egg retrieval.

Conclusion A meta-analysis would negate the findings of a previous large, well-designed trial only if the subjects are similar and the study medication is applied as in the original trial. For the full effect to be seen, it may be necessary to start treatment well before the onset of stimulation, and to continue therapy uninterrupted until well after embryo transfer. Furthermore, the data have been reanalyzed with the conclusion that there is indeed an increase of the PR. The presumed benefit of aspirin must stand until refuted by a valid meta-analysis of similar trials. Because of the extremely low risk of low dose aspirin and because it is widely used, a separate consent is not required.

Dopamine Agonists

A One of the authors (A.P.) has published a study reporting that 0.5 mg of cabergoline given daily for 8 days to egg donors at high risk of OHSS starting at the time of hCG administration decreased hemoconcentration, ascites, and vascular permeability compared with placebo (36). These authors also have done a pilot study in women having embryo transfer with no adverse effects on fertilization, implantation, and PRs (37).

B Cabergoline and other dopamine agonists decrease expression of the receptor for vascular endothelial growth factor and therefore the actions of vascular endothelial growth factor in causing OHSS (38).

C and D None.

E Cabergoline is used in women with hyperprolactinemia at up to 1.0 mg twice weekly. The most common side effects are headache, nausea, and dizziness. With long-term treatment valvular heart disease has rarely been observed (3/1,000), generally with doses much higher than 0.5 mg. No cases were observed with less than 6 months of use. It is difficult to ascribe any significant risk to administration for 8 days at this very low dose (39).

Conclusion The pathophysiology of OHSS and the benefit of cabergoline have been extensively worked out, and a well-designed study reported that it successfully reduced vascular permeability, hemoconcentration, and ascites in donors at high risk. With careful informed consent, the benefits warrant use in certain high risk situations. Further experience is advised before suggesting routine use in all egg donors at risk for OHSS or in women having IVF with embryo transfer.

Androgens and Androgenic Drugs

A Balasch et al. (40) reported the use of transdermal T for 5 days preceding ovarian stimulation in poor responders, with a marked increase in the number of follicles and peak E_2, and an increase of circulating IGF-I. Although the patients' prior cycles were used as the control, therefore potentially biasing the study by regression to the mean, their inclusion of a second control cycle with an identical poor response would argue for a true treatment effect. One of the authors (A.P.) reported in a pilot study that letrozole, which increases intraovarian androgen by blocking conversion to E, was associated with an increased ovarian response to gonadotropins, increased FF T, and a marked increase of implantation compared with women not given letrozole (41). Barad et al. (42) have reported that giving DHEA (a precursor for T in the ovary) before and during IVF in poor responders was associated with an increase in the number of oocytes, embryos, and the rate of clinical pregnancy compared with retrospective controls.

B Androgens increase FSH receptor activity, and well-controlled studies in the primate have reported increased ovarian response using a comparable amount of T to that used in the study by Balash et al. Granulosa cell androgen receptor messenger RNA (mRNA) in the primate has been reported to correlate positively with proliferation and negatively with apoptosis of GCs (43). Androgens increase IGF-I and therefore may act on GCs in a way similar to growth hormone.

C Testosterone gel did not increase ovarian response, but the circulating levels of T were lower than with the T patch (44).

D None.

E Although letrozole causes fetal abnormalities in animals, such an effect has not been demonstrated in humans when the drug is stopped 10–12 days before embryo transfer (45).

Conclusion Androgens and drugs that increase ovarian androgens, such as letrozole, may become important adjuncts for patients with low prognosis IVF. Well-designed prospective, placebo-controlled studies will be necessary to definitively characterize them in enhancing ovarian response and oocyte quality.

DISCUSSION

It is the authors' opinion that there are many important adjuncts to ovarian stimulation that likely will never receive

official indications for optimizing the outcomes of COH. In the absence of involvement of regulatory agencies and the pharmaceutical industry in development and promotion of these "orphan indications," clinicians, researchers, and medical societies and their journals must assume those roles. Physician organizations, such as American Society for Reproductive Medicine (ASRM), and national patient advocacy groups, such as Resolve, should lobby the Food and Drug Administration to offer similar incentives for "orphan indications" to those in the Orphan Drug Act and to include well-designed trials, regardless of country of origin, in the approval process. Otherwise, new drug treatments will be limited to expensive new medications while ignoring major benefits of drugs already established as safe for other uses. The authors have illustrated the factors to be taken into account for physicians to consider adopting these "orphan indications." We have made suggestions for use of those adjuncts that are well established, and have discussed some new adjuncts that may be important in the near future.

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