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.)

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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.

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.