Overview of REI Clinical Trial Topic

A Three-Arm Randomized Controlled IVF Trial In Women With Diminished Ovarian Reserve

Background

Treatment with Assisted Reproductive Technologies (ART) has allowed thousands of couples to successfully build families. While the first ART cycles utilized a natural cycle, significant improvements in outcome were noted with the introduction of controlled ovarian stimulation (COS). Furthermore, the degree of responsiveness to ovarian stimulation appears to have a significant impact on final outcome with ART. The goal of stimulation protocol selection is to tailor the protocol to the individual patient so as to achieve optimal stimulation without over-response and risk for ovarian hyperstimulation syndrome. Stimulation must, however, supply an adequate number of oocytes for acceptable pregnancy rates.

Women, undergoing ART, have been considered “poor responders” only after a failed stimulation during which estradiol and/or oocyte numbers were low. Given the lower pregnancy potential in these women, biological markers of ovarian reserve prior to stimulation have been suggested. However, these are frequently utilized to counsel patients against attempted stimulation rather than to optimize stimulation protocol selection. Selection of the optimum stimulation protocol should not only eliminate cancellation for poor response, but should also improve pregnancy outcome. In

The concept of “poor response” has been studied for more than a decade. One of the problems with this term is that there appears to be no standard definition making comparison across trials difficult. This term is most often applied to patients who have already undergone stimulation but developed few mature follicles, lower maximal estradiol, and/or fewer retrieved oocytes. More recently, some have looked at prospective patient characteristics including patient age (> 40 years) or basal FSH and/or estradiol. The ability to evaluate the antral follicle count (AFC), small recruitable follicles seen on ultrasound, has lead to a new mode of evaluation and prediction of prognosis. A comparison of basal markers of ovarian reserve with AFC found the AFC provided the best prognostic information on ovarian response and risk for poor response during COH. Of the biological markers, anti-mullerian hormone (AMH) appears to have the best prognostication for oocytes retrieved. ESHRE has recently held a consensus conference to define “poor ovarian response” (POR).[Ferraretti AP, 2011] Minimal criteria for POR include: at least 2 of the following: 1) advanced maternal age (≥ 40 years) or other risk factor (e.g. prior alkylating agent, genetic abnormality); 2) a previous POR (≤ 3 oocytes with a conventional ovarian stimulation); 3) an abnormal ovarian reserve test (e.g. AFC< 5-7; AMH < 0.5-1.1ng/mL). The ESHRE document argues that prospective markers (such as AFC and AMH) have a false positive rate of 10-20% thus making them inadequate as sole markers, and that by definition, POR requires at least one stimulation attempt. They do suggest AFC, in combination with advanced age (> 40 years), would sufficient to meet the definition of POR. Given the high cost (financially and emotionally) of ART, the ability to prospectively identify women at risk for poor response would enable selection of more appropriate stimulation protocols in the first cycle rather than waiting for evidence of a poor response to stimulation.

Strategies to overcome poor response: The problem of poor response to COH is not new and many strategies have been applied to try and improve stimulation. The first of these was to apply an increased amount of gonadotropin. A randomized trial comparing two fixed dosages (although both, relatively low by some standards: 150 IU vs. 300 IU) found no improvement with the higher dosage in patients with a low AFC. Utilizing a yet higher dosage of 450IU, compared to a historical control group treated with 300 IU, a decreased cancellation rate and increased pregnancy rate was shown. However, while some studies have shown improvements in oocyte number and cycle estradiol levels, a consistent increase in pregnancy rates has not been realized with increasing gonadotropin dosages. In fact, a negative impact of higher dosages on oocyte “quality” has been shown with increased oocyte atresia rates and increased risk of triploidy with ICSI with overall decreased implantation rates. In general, dosages exceeding 450 IU have not been shown to be advantageous.

Understanding the normal dynamics of the luteal-follicular transition led to the suggestion that suppressing the late luteal phase rise of FSH, with GnRH agonist, may improve response in women at high risk for poor response. Luteal phase agonist was associated with an improved response in some women, but an increased requirement for gonadotropin. Hypothesized direct suppression of GnRH agonist on the ovary led to protocols whereby the agonist treatment was stopped early during the stimulation. Two prospective randomized trials compared these, so-called halt protocols, to standard down-regulated cycles. While neither showed a significant improvement in stimulation overall, a subset of patients for whom do have an increase in the
number of oocytes retrieved. This would suggest further investigation and patient individualization may lead to improved outcome. Several retrospective trials have also evaluated various low dose gonadotropin and/or halt protocols with mixed results.

A further alternative approach is the usage of GnRH agonists in a flare-up type protocol, taking advantage of the endogenous release of FSH when agonists are administered during the early follicular phase, and eliminating the excessive suppression of more long-term agonist exposure. These protocols were complicated by an increase in LH, in addition to the desired increase in FSH, and potential rescue of the corpus luteum. Further modifications in this protocol lead to the so-call "micro-dose" flare protocols. Only a few, small, randomized trials utilizing these flare protocols have been published. While no significant differences were seen in oocyte number and retrieval rates, there was a suggestion, in the comparison of long vs. short flare-up protocols, that the flare-up protocols may be detrimental in older patients. While this study utilized a somewhat higher agonist dosage in the flare protocol, they did find a lower number of embryos produced and lower pregnancy rates in the flare protocol.

The availability of GnRH antagonists, eliminating the risk of over-suppression with GnRH agonists, has led to the suggestion they be used in poor responders to prevent a premature LH surge. The study above compared the antagonist to the flare-up protocol and found the flare protocol to be superior. Other studies utilizing the antagonist have not found statistical improvement, albeit the patient numbers have been small. More recent studies comparing the antagonist protocol to either the flare-up protocol or long-agonist protocol, in the context of the poor responder patient, have yielded conflicting results.

Another protocol suggested for poor responders is the combination of aromatase-inhibitors with gonadotropin. In this small pilot study, patients with a prior poor response to gonadotropin alone, were stimulated with sequential letrozole and gonadotropin. A significantly lower FSH dosage and increased number of follicles resulted. This protocol is not dissimilar to strategy for "flare" with clomiphene citrate(CC) that was utilized prior to the development of the lupron flare discussed above. A recent, non-randomized, pilot study comparing CC and letrozole in such a combined "overlapping" manner found no differences in pregnancy rate, but higher estradiol levels and follicle numbers with CC vs. letrozole suggesting no significant improvement with letrozole when utilized in this manner.

Pre-treatment with combined oral contraceptive (COC) pills has been suggested in order to synchronize follicular development and sensitize estrogen receptors. Although concerns have been raised that COC may also suppress gonadotropins and even ovarian response, several studies have shown pre-treatment with COC to be beneficial. A recent study, evaluating specifically antagonist protocols, found no significant improvement in response with COC and a suggestion of increased risk for early loss in the COC group. Estradiol may also be utilized in the luteal phase to synchronize follicles perhaps avoiding the over-suppression of GnRH agonist or COC. The use of these luteal phase adjuvants has not be systematically evaluated.

**The importance of the endocrine milieu:** While it likely takes up to 5 months for complete maturation of a follicle following recruitment from the resting pool, the final 2 weeks of this development ("secondary recruitment") is the most investigated and understood. For some time, information has suggested an important role may be played by both the systemic and local endocrinological milieu during ovarian stimulation. In an early study levels of immunoreactive luteinizing hormone (LH), bioactive LH, and testosterone (T) were determined in women receiving human menopausal gonadotropins (hMG) with, or without, pre-treatment with GnRH agonist. In women receiving agonist, preceding hMG, there was a significant suppression of immunoreactive and bioactive LH. The characteristic increase in serum levels of bioactive LH and T were absent. Follicular fluid(FF) estradiol and T concentrations, and serum progesterone (P) were not different, however. The lower circulating levels of T may reflect reduced LH-stimulated androgen accumulation in smaller nonaspirated follicles and may account for the enhanced follicle recruitment observed with agonist pre-treatment. A recent study of FF in antagonist protocols, with or without letrozole, showed higher FF androgens (testosterone and androstenedione) in the letrozole group. This was accompanied by an increased number of follicles retrieved and implantation rates. In this scenario, the increased intraovarian androgen was suggested to enhance folliculogenesis. A study comparing agonist with flare protocols found increased androstenedione in the flare regimen and suggested this was due to the higher circulating LH levels and may have a negative impact on outcome. Unfortunately, they did not utilize the newer "micro-dose" agonist so that the conclusions may not be relevant to present stimulation strategies. The IGF system was recently evaluated comparing down-regulated and antagonist protocols in young, normal responders. While they found differences in the intrafollicular environment, they found no difference in clinical outcome.

In studying the endocrinological impact of halt-type protocols, some investigators suggested a negative impact of LH release, seen upon the cessation of the agonist, during the early follicular phase. This is
consistent with studies suggesting high exposure to LH and estradiol in the early follicular phase is associated with a reduced chance for pregnancy in antagonist cycles. While elevated levels of LH early in the cycle may have a negative impact on pregnancy rates, concern has also arisen regarding the profound suppression of LH with the addition of antagonist in the mid- to late-follicular phase. In antagonist cycles, those with the lowest LH had an improved number of oocytes retrieved and embryos available suggesting these low LH levels had no adverse impact on the final stages of folliculogenesis during these cycles. Conversely, too little LH, particularly in the early follicular phase, has been suggested, by some, to compromise estradiol production and folliculogenesis. The optimum amount of LH for folliculogenesis, especially in the poor responder patient, has yet to been determined.

As previously discussed, the reduction of agonist dosing in flare-up protocols to the “micro-dose” appeared to prevent abnormal rises of LH, P or T. For antagonist cycles, early exposure to P has been shown to have a negative impact on pregnancy rates.

Conclusions and Significance: Defining the optimum stimulation for poor responders would increase pregnancy rates in this difficult patient population. As discussed in two reviews on COH, there is a need for standardized definitions of poor response and for large-scale well-designed randomized, controlled trials to answer important questions that guide cycle management. A recent Cochran Review[Padian Z, 2010] identified only 10 trials meeting inclusion criteria and only one reported life birth as an outcome. There was insufficient evidence available to identify the use of any particular intervention to improve outcome in poor responders in IVF. The goal of protocol selection should be optimization of response for an individual patient. “Response” is more than just progression to retrieval and absolute oocyte number.

Objective: Design a study to optimize ovarian stimulation for expected poor responders.

Question:
1) What is your primary outcome?
2) Define secondary endpoints
3) Define inclusion/exclusion criteria
4) Define randomization strategy
5) Is the study blinded? If so, how?
6) Describe the selected protocols and relevant variables for treatment
7) Compare single site vs. multi-center trial
8) Calculate sample size
9) Describe planned statistical analysis
10) Are there safety concerns? How would these be addressed?
References:


