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THE GNRH AGONIST/ANTAGONIST CONVERSION PROTOCOL (AACP) IN "NORMAL" AND "POOR REPONDERS"

Some form of pituitary blockade, either in the form of a GnRH agonist (e.g. Lupron, Buserelin, Nafarelin, and Synarel) or a GnRH antagonist (e.g. Cetrotide and Ganirelix) is an essential component in ovarian stimulation of "poor responders" undergoing IVF. If this is not done, a progressive rise in LH –induced ovarian androgens (mainly testosterone) may affect follicle/egg development, resulting in compromised embryo quality.

The follicles/eggs of women on GnRH-agonist "flare protocols" can be exposed to an exaggerated Lupron-induced LH release in early follicular growth. This might not be problematic in "normal responders" but could be detrimental in "poor responders" and older women where endogenous basal LH levels are often raised and the ovaries may be inordinately sensitive to LH and where excessive exposure of follicles and eggs to testosterone could severely compromise egg development and thus embryo quality. I sometimes use the analogy, that when we are young, we can be up all night and work the next day and feel fine. As we get older, we become more dependent on getting a "good night's sleep" in order to function efficiently. So too, when a woman has strong ovarian reserves, she is not nearly as sensitive to hormonal perturbations and as such, to a greater or lesser degree, her ovaries will respond appropriately, regardless of method of stimulation. However, as her ovaries become more resistant, they need "a good night's sleep" and are extremely sensitive to aberrant hormonal stimulations (e.g. excess androgen production).

With the long Lupron down regulation protocol where the pituitary gland is largely exhausted of its LH and residual minimal LH is present in the circulation by the time stimulation with gonadotropins begins, the above mentioned adverse testosterone-effect is largely negated. The down side is the fact that prolonged administration of GnRH agonists such as Lupron (such as with the GnRH agonist down-regulation protocol) could suppress subsequent ovarian response to ovarian stimulation with gonadotropins, by competitively binding with ovarian FSH receptors. The Agonist-Antagonist Conversion Protocol (AACP) has been used in an effort to counter this effect.

With the AACP, low dose Ganirelix/Cetrotide is commenced at the onset of spontaneous menstruation or following bleeding that follows initiation of GnRH agonist (e.g. Lupron) therapy using a long-down-regulation protocol arrangement. The AACP is prescribed to most of our IVF patients regardless of whether they are "normal responders" or "poor responders." Preliminary results suggest a significant improvement in egg number, egg/embryo quality as well as in implantation and viable IVF pregnancy rates. The AACP has however, proven to be most advantageous in "poor responders" where additional enhancement of ovarian response to gonadotropins may be achieved through incorporation of "estrogen priming." The addition of estradiol for a week following the initiation of the AACP, prior to commencing FSH-dominant gonadotropin stimulation, appears to further enhance ovarian response presumably by up-regulating ovarian FSH-receptors.

One potential draw back to the use of the AACP, in that the sustained use of a GnRH antagonist (Ganirelix/Cetrotide) throughout the stimulation phase of the cycle appears to compromise the predictive value of serial plasma estradiol measurements, which is a measure of follicle growth and development. Estradiol levels tend to be much lower in this type of protocol compared to agonist only (Lupron) protocols or where a "conventional" GnRH antagonist protocol is employed (i.e. antagonist administration is commenced 6-8 days following initiation of gonadotropin stimulation). Rather than being due to reduced production of estradiol by the ovary(s), the lower blood concentration of estradiol seen with prolonged exposure to GnRH-antagonist, are probably the result of a subtle, agonist-induced alteration in the configuration of the estradiol molecule, such that currently available commercial kits used to measure estradiol levels are rendered much less sensitive/specific. Thus when the AACP is employed, we rely much more heavily on ultrasound growth of follicles along with observation of the trend in the rise of estradiol levels, than on absolute estradiol values. Thus we commonly refrain from prescribing the AACP in "high responders" who are predisposed to the development of severe ovarian hyperstimulation syndrome (OHSS) and accordingly where the accurate measurement of plasma estradiol plays a very important role in the safe management of their stimulation cycles.

Conclusion: The AACP offers a different physiologic approach to stimulation. If combined with estrogen priming, patients with moderate elevations of FSH levels, indicative of ovarian resistance, can be stimulated to allow for retrieval and pregnancy initiation.

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This handout is intended as an aid to provide patients with general information. As science is rapidly evolving, some new information may not be presented here. It is not intended to replace or define evaluation and treatment by a physician.