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Pathway to Parenthood

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CONTROLLED OVARIAN HYPERSTIMULATION (COH) IN POOR RESPONDERS

BACKGROUND:

Women are born with all the eggs they will ever have. After menarche (the onset of menstruation) a monthly process of using up numerous eggs continues until the number of eggs remaining in the woman's ovaries falls below a certain critical threshold, at which time ovarian function starts to decline and the woman becomes relatively resistant to ovarian stimulation with fertility drugs. This phase of the woman's reproductive life is referred to as the climacteric. The onset of the climacteric is heralded by gradually increasing blood concentrations of follicle stimulating hormone (FSH), as measured on the 3rd day of a spontaneous menstrual cycle, and a decline in anti-müllerian hormone (AMH). This continues for a number of years (approximately 4-6 years) until virtually all remaining eggs have been used up. Reduced ovarian responsivity to fertility drugs is usually the direct consequence of a decline in ovarian function brought about by the onset of the climacteric and pending menopause.

While the onset of the climacteric rarely commences prior to age 35 yrs (usually after age 40 yrs), it can occur at any age. It is characterized by a reduction of ovarian responsivity to fertility drugs as evidenced by rising blood levels of FSH (on day 3) and falling AMH levels, along with reduced responsivity to fertility drugs. Simply, women who are in the climacteric recruit fewer eggs for each cycle and therefore produce fewer follicles/eggs even following the administration of relatively high doses of fertility drugs.

While it is true that Lupron elicits a degree of resistance to FSH (fertility drugs included), the number of follicles a woman is capable of producing is limited by the number of eggs in her ovaries. The problem is that one needs to inhibit premature luteinizing hormone (LH) release during the cycle in order to produce healthy eggs. Lupron, Cetrotide or Ganirelix may be used to achieve this.

It is possible to offset much of the FSH receptor-antagonistic effects of Lupron by priming the woman's ovaries with estrogen for 7-10 days in advance of administering gonadotropins and by reducing the Lupron dosage to a bare minimum.

Optimizing response requires a very individualized approach, not a "recipe approach". The first stimulation attempt is based on the woman's age, previous response to prior stimulation cycles, blood levels of FSH, E2, and AMH and then fine-tuning the protocol based on response to the chosen dosage and stimulation regime.

It is common practice to administer gonadotropin releasing hormone agonists (GnRHa) such as lupreulide acetate (Lupron) and GnRH-antagonists such as Ganirelix or Cetrotide, to prevent the release of LH with COH. GnRHa exert their LH-lowering effect over a number of days. They act by causing an initial outpouring and then depletion of pituitary gonadotropins. This results in the LH level falling to within negligible concentrations within 4-7 days, thereby establishing a relatively "LH-free environment". GnRH antagonists, on the other hand, act by rapidly (within 48-72 hrs) blocking pituitary LH release, so as to achieve the same effect.

CONTROLLED OVARIAN HYPERSTIMULATION (COH):

The most commonly prescribed protocol for Lupron/gonadotropin administration is the so-called **"long protocol"**. Lupron is given starting a week or so prior to menstruation. This precipitates an initial rise in FSH and LH levels, which is rapidly followed by a precipitous fall to near zero. This is followed by uterine withdrawal bleeding (menstruation), whereupon gonadotropin treatment is initiated while daily lupron injections continue, to ensure an "LH-free" environment. Lupron can be supplanted by Ganirelix or Cetrotide.

Another approach to COH, is by way of so-called **"flare protocols"**. Here, gonadotropin and GnRHa therapy are is initiated nearly simultaneously at the start of menstruation. The intent is to deliberately allow lupron to create an initial surge *("the flare effect")* in pituitary FSH release so as to augment ovarian response to the gonadotropin medication.

Estrogen priming: Patients who have demonstrated reduced ovarian response to COH, and those with significantly raised FSH and reduced AMH levels who are also likely to be *"poor responders,"* are treated by way of a ***modified long protocol,*** using estrogen to prime ovarian FSH receptors to FSH prior to initiating gonadotropin therapy. Here, GnRH agonist is administered for a number of days prior to menstruation to induce pituitary down-regulation (as with the "long protocol"). Upon menstruation and confirmation by ultrasound that blood estradiol concentration is below 70 pg/mL, (i.e. that the ovaries have been adequately suppressed), the Lupron is switched to Ganirelix/Cetrotide (GnRH antagonists) at half the regular dosage (125 mcg daily) or alternatively, the dosage of GnRH agonist (Lupron) is drastically lowered and the woman is given twice-weekly injections of estradiol valerate for a period of 7-10 days. COH is then initiated using a relatively high dosage of FSH-dominant gonadotropins such as Folistim or Gonal F for a period of 7 days. The gonadotropin dosage is then substantively reduced. The daily administration of GnRH agonist is continued until the "hCG trigger" (or can be supplanted by Ganirelix or Cetrotide daily from the initiation of COH until hCG administration). The purpose of the estrogen priming effect is to attempt to "up-regulate" FSH receptors, thereby making the ovaries more sensitive to the gonadotropins and hopefully achieving a good stimulation response.

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