

MILD STIMULATION IN POOR RESPONDERS

J.H. Check

Most in vitro fertilization (IVF) centers, including our own, report very poor pregnancy rates despite the transfer of seemingly normal day 3 embryos or day 5 blastocysts in women aged ≥ 45 . Considered mechanisms to explain these poor results include aneuploidy related to frequent meiosis errors in eggs from women with advanced reproductive age, and also to a lack of a mitochondrial factor that inhibits subsequent apoptosis of the embryo somewhere between day 7 and 12. Though these poor pregnancy rates include even those women \geq age 45 with normal day 3 serum FSH and a reasonable response to controlled ovarian hyperstimulation (COH), the majority of women \geq age 45 have diminished egg reserve which is associated with an increase in day 3 serum FSH.

Several IVF centers began reporting in the late 1980's that not only did women with elevated day 3 serum FSH fail to produce many oocytes, but their pregnancy rate per embryo transfer was very low. Even in the modern era of IVF one of the world's foremost IVF centers found no live pregnancies despite the transfer of normal appearing embryos in women of all ages with day 3 serum FSH of ≥ 15 mIU/mL. In fact their recommendation was that such women should not even try to conceive with their own eggs but proceed directly to donor oocyte programs. The interpretation for these poor pregnancy rates was that similar to reproductively older patients they have proceeded through an atresia process leaving them with not only less but inferior quality oocytes.

However, not all studies agree that IVF-ET results in poor pregnancy rates especially in younger women with elevated day 3 serum FSH. One study found that in women age ≤ 39.9 with such a depleted egg reserve that only a single embryo could be transferred a clinical and live delivery rate of 40.0% and 31.7%, respectively were achieved as long as they had a 6-8 cell embryo transferred. Even the minority of women (35%) who only had a 4 or 5 cell embryo transferred achieved a 3.8% and 9.5% live delivery rate, respectively, per transfer. Another study in younger women aged ≤ 35 with an elevated serum FSH ≥ 12 mIU/mL who transferred 3 embryos reported in 50 transfers a 66% clinical pregnancy rate and a 58% live delivery rate and an implantation rate of 34%. There have even been pregnancies achieved with IVF-ET in women who were actually thought to be in menopause but who were made to form a mature follicle by lowering the high serum FSH with ethinyl estradiol to allow restoration of down-regulated FSH receptors and thus restoring the sensitivity to gonadotropins of the granulosa-theca cells.

These more optimistic pregnancy rates are more consistent with the theory that the etiology for the diminished egg reserve in the majority of cases of younger women with low egg reserve is not rapid atresia of the best eggs but is more related to a process that causes destruction of a good portion of the ovaries but the remaining eggs have the same quality as their age peers.

How can one reconcile such opposite conclusions about the same study group? The only difference is that the IVF centers with the poor results used higher dosages of gonadotropins (sometimes even higher than their usual COH regimen for women with normal egg reserve) whereas the studies with good outcome used much lower dosages of gonadotropins. The possibility is that there may be an FSH dependent protein required for implantation. The use of high dose FSH regimens causes a further rise in the serum FSH because of the slow clearance of FSH leading to down-regulation of the FSH receptor in the cell that produces this hypothesized implantation protein.

The types of women with diminished egg reserve evaluated in this study using low dose FSH varied from being so low that they appeared to be in actual menopause with amenorrhea, very high serum FSH, estrogen deficiency and failure to respond with any rise in serum estradiol despite gonadotropin stimulation to those with regular menses who could still respond to high dose gonadotropins by forming several dominant follicles. Thus there is a principle used for low dose FSH stimulation rather than one exact protocol to use for everyone. With marked oocyte depletion ethinyl estradiol (this estrogen does not add to the serum estradiol (E2) measurements) is used to lower the serum FSH to restore FSH receptors in granulosa theca cells. The serum E2 is watched and ultrasound used once a rise in serum E2 is found. As long as the FSH is elevated and the serum E2 is rising one allows the endogenous FSH to develop the follicle(s). If the serum FSH gets into the normal range by the combination of ethinyl estradiol and endogenous E2 a small boost of 75 IU FSH can be used if follicular progression slows.

In contrast in women who are still getting menses the endogenous FSH can be used to develop the follicles to a certain point; then once the FSH is in the normal range, a boost of exogenous FSH can be given. For those women with only mild depletion 150 IU FSH can be given from day 5 and increased to 225 IU if cetorelix or ganirelix is given.

As mentioned by lowering serum FSH by ethinyl estradiol or by gonadotropin releasing hormone agonist or antagonist sensitivity to endogenous or exogenous FSH can be re-established in women in apparent menopause. Similar in women who are menstruating but have marked depletion of follicles a state of amenorrhea estrogen deficiency and FSH resistance in the granulosa-theca cells can be created by the increase of serum FSH related to the slow clearance of FSH when high dose gonadotropins are used. Thus in some circumstances the use of lower dose gonadotropins may produce more mature follicles than high dose FSH. Even if the responses are equal, and even if the hypothesized implantation protein is not suppressed one may question why spend more money for expensive FSH drugs?