
Can *in vitro* fertilization be successful in women with elevated serum FSH levels

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BACKGROUND

A woman who has amenorrhea, elevated gonadotropins and estrogen deficiency, as evidenced by failure to have withdrawal menses, is generally considered to have ovarian failure. The mechanism by which a given cycle's cohort of follicles are selected is not clear. However, it is well known from *in vitro* fertilization/embryo transfer (IVF/ET) studies that only a very small percentage of the total remaining primordial follicles are recruited.

As age advances and the total number of available primordial follicles diminishes, the number of follicles recruited for a given cycle's cohort decreases, as evidenced by reduced numbers of oocytes retrieved following IVF in older compared to younger patients¹. Logic would dictate that a certain paucity of follicles might exist where there may be no follicles recruited in some cycles, but some are selected in others. Since inhibin, which is secreted by recruited follicles, is one factor exerting a negative feedback effect on follicle stimulating hormone (FSH) secretion, incipient ovarian failure may be manifested by cycles demonstrating intermittent elevation of serum FSH in the follicular phase.

EARLY MANAGEMENT OF GONADOTROPINS

There are many centers who advise patients that if on the initial evaluation the early follicular phase serum FSH is in the postmenopausal range, the patient should immediately choose the donor oocyte programme. This is because, even if the patient does ovulate, the oocyte is likely to be defective. However, the author is not personally aware of any previous data supporting this concept. The director of the largest and most successful IVF/ET programme in the USA has been frequently quoted as stating that no IVF/ET pregnancies have ever been recorded if the early follicular phase serum FSH level was

greater than 25 mIU/ml. This statement has been extrapolated by many centers to mean that even if the patient does ovulate, an increased FSH level is indicative of a defective oocyte.

Although a high early follicular phase serum FSH level would be consistent with fewer follicles, it is not known whether this means that there are either no recruited follicles or the oocyte is defective. There have been reports of spontaneous ovulation and pregnancies in patients with hypergonadotropic amenorrhea, in those taking estrogen replacement²⁻⁵ or women on oral contraceptives⁶.

NON-IVF THERAPY FOR OVULATION INDUCTION

There have been some cases of an apparent response to gonadotropin therapy^{7,8}, but generally the patient will not respond to gonadotropins. The author has presented data demonstrating that three of five cases ovulated after estrogen therapy to suppress gonadotropins to normal levels, followed by human menopausal gonadotropin (hMG) treatment, even though he had recently failed to stimulate ovulation with hMG alone⁹; pregnancies were achieved in two cases. The hypothesis behind using high-dose estrogen was that there may be follicles present, but that they are unable to respond to endogenous or exogenous gonadotropins because of down-regulation of FSH and/or luteinizing hormone (LH) receptors in granulosa/theca (GC) cells by the elevated levels of endogenous gonadotropins¹⁰. By lowering the FSH and LH towards normal levels using higher than normal levels of estrogen, the gonadotropin receptors are restored. The estrogen used was ethinyl estradiol (EE), so that the ingested estrogen would not cross-react with the radioimmunoassay for 17 β -estradiol (E₂). However, it is possible that the estrogen therapy had no effect on the response to hMG, and that there may just have been a fortuitous follicle recruited at the time the hMG was given. It should be noted that one woman who was reported with elevated levels of gonadotropins and low E₂ formed multiple follicles and generated a serum E₂ > 800 pg/ml following EE suppression without hMG¹¹.

At first, the technique involved using EE (50 μ g) for two weeks to suppress the gonadotropins before hMG was used⁹. However, the hMG would often fail to stimulate any follicles, thus wasting much expensive medication. A modification was therefore made in which the serum E₂ was measured after only a few days of EE, and E₂ levels were monitored every few days to look for a rise; hMG would only be added if there was a rise in E₂ > 50 pg/ml. If there was no rise by three weeks, medroxyprogesterone acetate (10 mg for 14 days) would be given with the EE and the cycle repeated; a viable pregnancy was reported with this technique¹².

THEORETICAL MANAGEMENT OF OVULATION INDUCTION

Assuming that the use of estrogen improves the chance of a follicle developing (pregnancies without any therapy have only rarely been reported), two possibilities arise:

- (1) Whether administering some estrogen improves the sensitivity of the gonadotropin receptors to LH and FSH, so that even physiological replacement dosages could be used; or
- (2) Is the theory concerning the restoration of down-regulated gonadotropin receptors by pharmacological suppression of gonadotropins more likely the mechanism of action?

No randomized studies have been performed comparing physiological with pharmacological dosages of estrogen on the rate of ovulation induction.

Some support for the concept of restoration of down-regulated receptors by lowering, but not necessarily suppressing, elevated gonadotropins was provided by demonstrating ovulation induction in a patient with hypergonadotropic hypogonadism following the use of the gonadotropin-releasing hormone agonist (GnRHa) leuprolide acetate (LA) without any supplemental estrogen¹³. Of interest in this study were two cases of perimenopausal women who, in each of many cycles, came close to, but were not quite successful in making a mature follicle following hMG therapy; when LA was tried with the hMG, one patient could not be stimulated, even with hMG, while the other patient had her best response with LA alone (without hMG) reaching an E₂ level of 641 pg/ml. She ovulated twice more with E₂ levels of 315 and 377 pg/ml, without premature luteinization (as she previously demonstrated in each cycle), and conceived on the third cycle¹⁴. There were nine patients treated in 43 cycles with LH in a review of 100 consecutive cases of ovarian failure treated with EE or LH; there were seven ovulations (16.3%) with LA/hMG as compared with 61 ovulations in 311 attempts (19.6%) with EE/hMG¹⁵.

CLINICAL OBSERVATIONS

Several interesting observations were made from the study of 100 consecutive cases of hypergonadotropic amenorrhea¹⁵. There were eight viable pregnancies delivered in women given 36 cycles of therapy and an additional patient had a stillbirth at 34 weeks. In addition, 38 women ovulated at least once, and six of these (16%) ovulated in all of their first four cycles; there were 68 ovulations in 54 attempts (16%). The pregnancy rate per cycle was 5.4% (19/351) and the pregnancy rate per successful ovulation was 28% (19/68), but approximately 50% aborted. There were two spontaneous abortions despite viability at seven weeks; four with sacs but no fetal pole on ultrasound, and four with dropping β -hCG levels without ultrasound evidence of pregnancy.

For those conceiving, there was an average of 4.4 ovulatory cycles before conception. Ethinyl estradiol alone recruited a rise in E_2 prior to hMG treatment in 40/68 ovulations (58.8%). There were 26 ovulators who had previously failed to ovulate using hMG therapy in 46 cycles and another 11 who had never received gonadotropin therapy previously (19 did not show an increase serum $E_2 > 35$ pg/ml, despite being given a mean of 3400 IU of hMG).

All 19 pregnancies in these first 100 patients were achieved using EE/hMG. Only nine patients used LA/hMG; three ovulated at least once, but no pregnancies resulted. Thus, it is possible that many of these patients would have formed a mature follicle without the use of hMG. There were 21 ovulations (32%) which occurred only after sera LH and FSH levels were suppressed into the normal range and hMG was given; however, a majority of these were not observed during the EE therapy: the average amount of hMG administered was 2850 IU.

The average length of time from diagnosis of ovarian failure to time of conception in 17 patients (where this information was known) was 2.2 years, compared with an average of 4.8 years without pregnancy in 65 non-conceivers⁹. The mean age of the pregnancy group was 33.4 *versus* 34.8 years for the non-pregnancy group. The mean serum FSH level for those who conceived was 70.2 mIU/ml, and was 66.5 mIU/ml in the non-conceivers. The mean age and serum FSH level was similar in women who ovulated to those who conceived (32.9 years and 69.1 mIU/ml, respectively).

In vitro fertilization/embryo transfer has been attempted in some patients with hypergonadotropic amenorrhea and estrogen deficiency¹⁶. One patient produced oocytes in four out of five cycles and had a total of 14 oocytes, of which five fertilized (35.7%); only one transfer resulted without a pregnancy. The highest serum E_2 was 1641 pg/ml. A second patient ovulated in four out of seven cycles, with only one oocyte per cycle, of which two became fertilized. All embryos were cryopreserved; highest E_2 was 386 pg/ml. The third patient had only one follicle and it was empty. Since this publication, the author has attempted this procedure in 15 additional patients; five have gone to transfer, but there have been no clinical pregnancies (two did have β -hCG levels over 100 IU/ml).

There are perimenopausal women who have elevated sera FSH levels, but are still euestrogenic—that is, they can still have menses induced by progesterone withdrawal and some may even have regular cycles. However, some IVF centers, including the one with the highest success rates in the USA, believe that if the serum FSH exceeds 25 mIU/ml in the early follicular phase, the patient cannot achieve a pregnancy and should be registered into a donor oocyte programme. It is possible that the embryos formed from these oocytes need factors secreted by the Fallopian tubes for maximum implantation, or that the uterus is still too toxic for these embryos two days after retrieval.

One study suggested that although conception with IVF is not likely when early follicular phase FSH levels are high, some patients will intermittently have

lower levels in some cycles and pregnancies following IVF/ET have been recorded¹⁷. The study presented in this chapter evaluates the efficacy of IVF/ET for hypergonadotropic euestrogenic women when the procedure was performed during a cycle where FSH was > 18 mIU/ml.

MATERIALS AND METHODS

There were 40 cycles where women presenting to the Cooper Institute for IVF/ET from January to August 1992 had a serum FSH > 18 mIU/ml on cycle day 2. There were two treatment regimens offered; the flare-up technique or clomiphene citrate (CC)/hMG. The protocol which involved administering LA/hMG throughout the luteal phase was not used because of the tendency for suppression of follicular stimulation in this type of patient when GnRH α is extensively used¹⁴.

The decision on choosing the flare-up of CC/hMG was left to the patient. The author did suggest to the patient that, based on previous data, he expected that the short-flare might be more successful, but CC/hMG would be less expensive^{13,14,18}.

The flare-up protocol employed LA beginning on day 2, after making sure that the patient's serum FSH had already been obtained. The dosage of LA was 0.75 mg/day for those weighing < 70 kg or 1.0 mg/day for those weighing \geq 70 kg. Beginning on the fifth menstrual day, 150 IU of pure (p)FSH and 150 IU of hMG (Metrodin and Pergonal, respectively; Serono Laboratories, Randolph, MA, USA) were administered intramuscularly in two divided doses. Thereafter, the pFSH was decreased in a step-down fashion, according to serum E₂ and follicular development by ultrasound (with a serum E₂ of > 300 pg/ml only, 75 IU pFSH was given with 150 IU hMG; but with E₂ > 600 pg/ml, only 150 IU hMG was given) until at least one dominant follicle attained an average of 20 mm when hCG (10 000 U intramuscularly) was given.

The CC/hMG protocol used 100 mg CC orally, from days 3–7, plus daily 75-IU doses of hMG intramuscularly from days 3–6, then 150–225 IU from day 7, until the same criteria as flare-up was reached for administration of hCG.

RESULTS

There were six pregnancies in the 40 retrieval cycles of 40 different patients (15.0% per cycle). The flare-up was chosen by 33 patients, of which five conceived (15.1%) and demonstrated fetal viability, whereas only seven chose the CC/hMG protocol and only one conceived (14.2%). Five of the six pregnant patients delivered a healthy baby, one patient had an early second trimester spontaneous abortion.

The day 2 sera FSH levels of the conceivers were 21, 23, 28, 37, 41 and 63 mIU/ml. The mean number of follicles observed and mean number of

oocytes retrieved were higher in the flare-up group (9.8 ± 6.8 and 8.9 ± 6.4 , respectively) than the CC/hMG group (5.3 ± 4.1 and 3.8 ± 3.0 , respectively). The mean number of embryos transferred was 3.1 ± 1.7 for the flare-up *versus* 2.2 ± 1.5 for CC/hMG protocol.

Interestingly, 15/40 patients had sera FSH levels > 25 mIU/ml, of which 4/15 had viable pregnancies and three successfully delivered.

DISCUSSION

The incidence of women under the age of 40 having secondary ovarian failure has been estimated at approximately 1%¹⁹. Aiman and Smentek²⁰ summarized data on 14 pregnancies recorded in patients with ovarian failure, including two of their own cases. They estimate that 120 000 women have premature ovarian failure but want to establish pregnancies; from the fact that only 14 pregnancies had been reported between 1964 and 1984, they estimated that the probability of pregnancy, either spontaneously or, more likely, following hormonal replacement therapy, was less than 1 : 9200²⁰. Therefore, the author believes that considering the 19 pregnancies achieved in 100 consecutive patients, plus an additional assortment of other published and unpublished cases achieving pregnancies, the evidence indicates that therapy improves the likelihood of achieving pregnancies in this group. What is not known, is whether:

- (1) The therapy is merely identifying when spontaneous ovulation occurs by careful observation for this rare random event, so that intercourse may be properly timed;
- (2) The therapy is treating luteal phase defects with supplemental progesterone;
- (3) The therapy involves supplying the hCG required to release oocytes.

Indeed, spontaneous ovulation and pregnancies have been recorded in this population²¹.

It is highly possible that estrogen therapy, GnRHa treatment and/or the hMG therapy, is critical for the development of mature follicles. One of the proposed mechanisms for the explanation for ovulation, despite apparent ovarian failure, is the concept of autoimmune oophoritis^{22,23}. This concept involves the secretion of a trigger antigen from a very early stage follicle before it has secreted inhibin; the immune system reacts and damages the follicle before any E_2 or significant amount of androgen is produced. The original description of this condition found a high association with adrenal insufficiency, although subsequent cases having the same histopathological features have been found without adrenal insufficiency²⁴. However, to date the author has not had one case of ovarian failure associated with Addison's disease. He suspects that this condition may have been present when a woman was originally diagnosed with ovarian failure in her late teens, and confirmed in

her late twenties by elevated sera gonadotropins. She presented in her mid-thirties with a large pituitary macroadenoma and extremely low gonadotropin levels; she was able to respond to hMG and deliver two children²⁵. Although she never showed any evidence, either previously or presently, of autoimmune disease, it is assumed that she may have an autoimmune problem rather than a paucity of follicles. This was concluded because of the long length of time from diagnosis to treatment and from the many cycles where she consistently ovulated with hMG alone²⁵. In fact, this case also provides evidence against the hypothesis, in that the operational mechanism for restoration of ovulation is merely the restoration of the sensitivity of gonadotropin receptors by restoring estrogen, as this severely estrogen-deficient woman responded to hMG alone.

Down-regulation of the gonadotropin receptors, because of elevated gonadotropins, has been hypothesized as a possible mechanism for gonadotropin resistance¹⁰. The author favors this as at least one of the frequent mechanisms to explain how six women of the 100 consecutive cases with baseline FSH levels < 20 responded to high dose EE in stimulating a follicle(s), bearing in mind that they had not shown evidence of spontaneous ovulation before EE therapy and had failed to ovulate with hMG alone. The fact that two women with streaked gonads were able to ovulate and conceive supports the concept that most of the cases respond to therapy despite a paucity of follicles, rather than by spontaneous resolution of autoimmune oophoritis^{26,27}. The therapeutic concept of treating autoimmune oophoritis is to suppress follicular maturation before the trigger antigen is produced, thus eliminating the anamnestic response and so allowing ovulation before the immune system attacks the follicle again. Although the means of suppressing the gonadotropins to inhibit follicular maturation is to use GnRHa, or possibly high-dose estrogen, the E₂ response following EE or LA occurs typically after several days and seems too early to attribute the phenomenon to an autoimmune mechanism.

As for performing IVF for euestrogenic women with high early follicular sera FSH levels, these cases demonstrated that pregnancies can occur with IVF/ET, even during cycles where serum FSH is elevated during the early follicular phase. Interestingly, these women were still able to produce an average of about ten follicles using the flare-up procedure. Though a respectable pregnancy rate was found, the author doubts that the same level will be maintained with a more extensive series. The key finding, however, is that a successful pregnancy can be achieved following IVF/ET, despite elevated gonadotropins when the woman is euestrogenic. There have been successful IVF/ET pregnancies resulting from aspiration of a follicle(s) during an unstimulated cycle. These are, however, patients who would typically respond to hyperstimulation^{28,29}. It should be noted that since no pregnancies have been recorded with hypergonadotropism and estrogen deficiency, IVF/ET should not be attempted instead of a non-IVF cycle if tubal patency is established.

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