ISSN: 2755-6204

Case Report

Journal of Sexual Health and Reproductive Medicine

A Detailed Description of the FSH Receptor up Regulation Technique Employed to Develop Metaphase II Oocytes for in Vitro Fertilization Embryo Transfer in Women with Extremely Low Egg Reserve who had Successful Pregnancies

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Received: March 20, 2026; **Accepted:** March 27, 2026; **Published:** April 06, 2026

ABSTRACT

Despite the publication of a form of mild ovarian hyperstimulation over 40 years ago and continued publication of many more scientific articles right to the present time showing that follicular sensitivity can be restored in many women with such severe diminished oocyte reserve that they were considered to be in actual menopause, this knowledge is not known by most clinicians treating infertility. There are slight variations in this technique when used in natural cycles vs in vitro fertilization (IVF) cycles where attempts are made to develop more than one dominant follicle if possible. FSH receptors can be restored by up regulating granulosa theca cells thus restoring follicular sensitivity to FSH by decreasing chronically elevated levels of FSH by suppressing FSH release by estrogen or by inhibition of the gonadotropin releasing hormone (GnRH) by GnRH agonists or antagonists. The preferred estrogen is ethinyl estradiol because it does not contribute to the measurement of serum estradiol (E2). The objective of this manuscript is to present day by day details of four cases with extremely low serum AMH levels who successfully conceived following IVF-ET. The potential benefit of also using dopamine agonists is explained to prevent autoimmune rejection of the fetus. It is hoped that this publication will influence reproductive endocrinologists to try this technique in patients with very severe diminished oocyte reserve rather than steering the patient into donor egg programs, which frequently are not preferred by the patient yet.

Keywords: Premature Menopause, Marked Diminished Oocyte Reserve, In Vitro Fertilization, Dopamine Agonists, FSH Receptor Up-Regulation

Introduction

Generally, a hormone exerts its given effect in the body by first binding with a receptor. The hormone receptor complex then through transcription and translation produces enzymes, cytokines, etc. that in the end causes the desired reaction in the body. There is generally a reciprocal relationship between the concentration of the receptor and the circulatory concentration of the hormone in the circulation to limit an excessive reaction. Down-regulation of the hormone receptor is different when comparing steroid hormone receptors and receptors for polypeptides. In the former, the receptor is shed and, in the latter, it is internalized into the cytoplasm [1].

Based on this concept of down-regulation of receptors by elevated levels of a given hormone, we considered that in women with apparent premature ovarian failure, where the assumption is that there are no more oocytes left, that this assumption may be wrong. The possibility exists that there are follicles left, but they are resistant to FSH because of FSH receptor down-regulation related to chronically elevated serum FSH levels [2]. In fact, we published as early as 1984 a method of induction of ovulation despite ovarian failure. In fact, in three of five women who appeared to be in menopause, did in fact, ovulate. This was accomplished by lowering serum FSH levels by treating with a higher dosage of estrogen to inhibit FSH release from the pituitary [3]. Two of five women actually achieved pregnancies [3]. Sometimes, once the FSH receptor is restored, some of the patients would create a mature dominant follicle with exposure just to endogenous gonadotropins, and in some instances a boost of exogenous FSH was needed [3]. By 1990, we reported our own experience with 100 consecutive cases of hyper-gonadotropic hypogonadism with amenorrhea and estrogen deficiency [4]. In that study, 35 achieved ovulations at least once given a maximum of 4 months of estrogen and sometimes gonadotropins, and 20 achieved a pregnancy [4].

Citation: Jerome H Check, Sophia Covolesky, Ann DiAntonio BSMT. A Detailed Description of the FSH Receptor up Regulation Technique Employed to Develop Metaphase II Oocytes for in Vitro Fertilization Embryo Transfer in Women with Extremely Low Egg Reserve who had Successful Pregnancies. J Sex Health Reprod Med. 2026. 2(1): 1-7. DOI: doi.org/10.61440/JSHRM.2026.v2.35

Though in the very beginning we used 5mg of conjugated estrogen to suppress FSH levels, after a short time we switched to ethinyl estradiol 20 micrograms without any progestins [5]. At the time of initial use, ethinyl estradiol was commercially available. The pharmaceutical company stopped making it and just supplied it to pharmaceutical companies making oral contraceptives. However, ethinyl estradiol is available for compounding. The advantage of using ethinyl estradiol over other forms of estrogen is that its IA a potent suppressor of FSH release from the pituitary, and also important, it does not contribute to the serum estradiol (E2) measurement thus allowing better detection of a developing dominant follicule [5]. Oral contraceptives are not used because the progestin would interfere with implantation [5].

Even when there has been up-regulation of down-regulated FSH receptors allowing the formation of a dominant follicle (18-24mm average diameter with a serum E2> 200 pg/ml) the elevated gonadotropin levels can cause some complications that can impede success. A certain number of days of estrogen exposure is needed to induce adequate development of progesterone (P) receptors in the endometrium even if a dominant follicle is achieved but with a short follicular phase there may be insufficient development of adequate P receptors in pelvic tissues related to insufficient days of estrogen exposure [6]. Also, because of increased baseline LH levels, patients with severe diminished oocyte reserve are more prone to premature luteinization [7]. Thus, with the addition of gonadotropin releasing hormones (GNRH) agonists (a) or antagonists (ant) to the clinical field one can finetune this technique for follicular maturation despite severe diminished oocyte reserve (DOR) with the occasional judicious use of GNRHa or GnRH ant added to the treatment protocol.

If one uses too much exogenous FSH drug, it will raise the serum FSH levels and possibly down-regulate FSH receptors on the follicle surface thus inhibiting follicular maturation. Similarly, drugs that are selective estrogen receptor modulators e.g., clomiphene citrate or tamoxifen, or aromatase inhibitors e.g., letrozole, could cause endogenous gonadotropin levels to increase too high and thus similarly cause FSH receptor down regulation.

Thus, the protocol for natural contraception or by in vitro fertilization embryo transfer (IVF-ET) requires mild, not excessive FSH stimulation [8]. Though this technique that we use for both natural conception and for IVF-ET are mild stimulation protocols, the mild stimulation techniques used by other infertility centers do not usually follow all the basic tenets of this mild ovarian stimulation protocol known as the FSH receptor up regulation technique [10,11].

These are some slight differences between the FSH receptor up-regulation technique for natural cycles vs IVF-ET [10,11]. In the former, the goal is just to achieve one dominant follicle. In the latter, the goal is to achieve several follicles as long as the tenets of this technique are followed. The principles of this technique with different scenarios based on differences in clinical presentation have been published for natural and IVF-ET cycles [9,10].

The principles of the FSH receptor up-regulation technique for IVF has been previously published for women with extremely low egg reserve who appear to be in actual menopause and live deliveries have been recorded [11]. Both natural and IVF cycles require progesterone supplementation in the luteal phase [12]. Frequently, since the cause of POF and severe DOR is generally related to autoimmune inflammatory damage, one also may treat with dopamine agonists to diminish excessive cellular permeability leading to an excessive inflammatory response for uterine artery remodeling needed for creation of spiral arteries [13-17].

When the FSH is very high, sometimes with the decrease in the serum FSH by estrogen or other measures one achieves recruitment of a follicle that will progress to maturity without the addition of any gonadotropins [18]. In fact, the addition of exogenous FSH could increase the FSH serum level of FSH and down-regulate the FSH receptor. One difference between natural and IVF-ET cycles even in this scenario of extremely low egg reserve is that for IVF-ET one usually gives a "trigger" shot of human chorionic gonadotropins (hCG) to time the egg retrieval (usually 32 hours later). However, sometimes, even in natural cycles, women with marked DOR can attain a follicle but luteinize without the release of the egg and thus hCG must be given or a GNRH agonist e.g., leuprolide acetate to enable egg release from the follicle [19-21]. Sometimes it is necessary to even use granulocyte colony stimulating factor before hCG to correct the luteinized unruptured follicle syndrome [22,23].

For natural cycles, or IVF-ET cycles, sometimes one cannot use the ethinyl estradiol related to side effects e.g., headaches or nausea, or risk of thrombosis, or possible risk of exacerbating breast cancer in women previously treated for this condition. Thus, one can use a GNRH a or GNRH ant to lower serum FSH and restore follicular sensitivity to FSH [24,25].

Other authors have published reviews on POF and severe DOR [25-28]. In the last most recent reviews, all 4 of the authors had at least 100 references and some over 200. We have published at least 100 manuscripts related to POF and DOR. Yet not one of these 4 manuscripts referenced any of our previous publications. In fact, and in their evaluation of different proposed methods to achieve ovulation despite apparent POF or DOR none mention the FSH receptor upregulation technique. We have observed in several other manuscripts dealing with potential future methods to develop mature follicles despite severe DOR they generally introduce the subject by stating that at present, there are no methods to achieve ovulation in women with severe DOR and POF.

Thus, the purpose of this manuscript is to describe day by day what decisions were made concerning the various treatment options available e.g., ethinyl estradiol, exogenous gonadotropins, hCG, GNRHa, and GNRH ant, progesterone, and dopamine agonists that not only allowed the retrieval of at least one egg that led to the transfer of at least one embryo that resulted in a live birth following IVF-ET. These cases were not included in our previous publication of IVF pregnancies with POF [11].

Case Report

Women who had extremely low serum AMH levels who either needed IVF for tubal or male factor or just preferred IVF-ET over natural conception were chosen to provide details of their

follicular recruitment protocol leading to embryo transfers and the delivery of a healthy baby from the embryo transfer, or they were also chosen because they were told by their previous consulting reproductive endocrinologists that their only option was to use donor eggs. We tried to choose different clinical conditions and types of use of the drugs used for follicular recruitment, even though they all were similar in having extremely low serum AMH levels.

Case 1

The patient was 36.2 years. Gravida-1, para-1. Her serum AMH level was 0.003 ng/ml.

Her IVF cycle data are seen in Table 1. Despite the very low serum AMH, her serum E2 on day 3 was 35 pg/ml and her FSH was not elevated at 9.9mIU/ml. The fact that she had a serum E2 of 35pg/nl signaled that her FSH receptors were exposed on the granulosa theca cells of the follicle. Perhaps she even had more than 1 follicle secreting inhibin B thus keeping the serum FSH at a top normal level. In this circumstance we thought that she could start as high as 150 IU of FSH. When we evaluated her on day 6, the serum E2 had increased to 80 pg/nl and her LH was still suppressed at 2.2 mIU/ml. The use of FSH did not raise her serum FSH (7.0 IU/ml). An increase in the serum FSH too high could down regulate the FSH receptor.

The doses of FSH were kept at 150 IU for 2 days but on the 3rd day we added cetrorelix (a gonadotropin releasing hormone antagonist i.e., GNRH ant) at 25mg per day. This was done to prevent the LH from rising before a mature follicle was obtained causing luteinization too early. Adding a GNRH ant can lower endogenous FSH and thus inhibit follicular growth. Thus, an additional 75 IU of FSH was provided by adding 75 IU of menopur (75 IU FSH and 75 IU LH). Thus, on day 9 with the serum E2 rising to 219 pg/ml there were 2 follicles approaching the goal of 18mm average for a dominant follicle with an average diameter of a 16.6mm and 14mm.

We gave her one more day of 225 FSH and 75 IU LH while maintaining the 25mg cetrorelix.

On day 10 the serum E2 reached 359pg/nl. The serum progesterone (P) was still not approaching 2 ng/ml (above this level the oocyte and endometrium could be adversely affected) and the follicles were about the right size at 19.1mm and 17.2mm. We prefer the serum E2 to reach a level of 200pg/nl per follicle, so we debated about giving her the hCG injection to allow maturation to metaphase II eggs or giving one more day of FSH. We chose the hCG (10,000 IU) that day. The patient did have EE provided the month before but had no rise in E2, but her FSH was lowered by the EE. It was stopped with her negative Beta hCG level.

The day after the hCG injection we measured serum hCG to be sure that the injection was given properly or had the right potency. Because the beta hCG level was on the low side at 36 IUI/ml she was given another boost of 5000IU of hCG. The patient transferred 2 embryos on day 3. One had 8 blastomeres and just mild fragmentation and mild asymmetry. She delivered a fullterm healthy girl.

Case 2

The patient was age 36.8 with a serum AMH level of less than 0.015 ng/ml. In other words, undetectable AMH. She had on day 3 a serum E2 of 25.6pg/nl with a serum FSH of 9.2 mIU/nl. She had a history of oligomenorrhea, not amenorrhea, and she was not taking ethinyl estradiol when these bloods were obtained. Similar to case 1, we were able to start her recombinant FSH. We generally do not give in DOR cases more than 150 IU FSH to start. To add some LH activity without the extra expense of menopur, she took 10IU of hCG (low dosages hCG). Because she was showing possibly multiple follicles (which was quite surprising), we elected to start her FSH dosage at 225 IU.

Table 2 provides the daily medication dosages and hormone and ultrasound findings as she was proceeding with stimulation of follicular maturation with FSH and LH, and hCG. Ganirelix 25mg was added when she obtained a 13mm average diameter follicle. However, with her serum FSH mildly increased from the FSH injection, we elected not to increase the FSH dosages as we frequently do when the GNRH ant is given for fear of down regulating the FSH receptor on the granulosa theca cells.

On the day we gave her the trigger hCG injection, the serum E2 level was shockingly high at 1129 pg/nl with 4 follicles with an average diameter of at least 18mm. Three embryos made it to day 3 (one 8 cell and two 6 cells) and they were transferred. She delivered a full-term healthy boy.

Related to dysmenorrhea and other conditions that are associated with the increased cellular permeability syndrome, and thus could lead to failure for the embryo to successfully implant from immune rejection, she was treated with the dopamine agonist dextroamphetamine sulfate which was continued during the 1st trimester to reduce the risk of miscarriage.

This case is unique in that despite an undetectable serum AMH, three times over a 3-year period she was able to respond quite well to gonadotropins. A possible hypothesis to explain this extremely unusual circumstance will be more elaborated in the discussion section.

Case 3

A 42.6-year-old woman with a serum AMH of 0.03ng/ml was considered to be in overt menopause with no spontaneous menses for over a year and a serum E2 always undetectable (<15pg/nl). She was treated with 20mcg of ethinyl estradiol and on day 50 her serum E2 was still less than 15pg/nl and her, serum FSH 33.5 mIU/ml so she was advised to repeat her serum E2, FSH, LH, and P in one week.

When women appear to be in overt ovarian failure we frequently monitor by hormonal levels only until we see a rise in serum E2 because it is more convenient to get blood tests and less convenient for ultrasounds. We were both pleased and surprised to see such a quick rise in the serum E2 of 105 pg/nl (see Table 3). We were concerned that with the serum LH double the serum FSH (22.9 vs 10.8 mIU/nl) that either she was about to ovulate or have premature luteinization.

The next day her serum E2 increased to 135pg/nl but the serum P did not increase (0.32 to 0.39 pg/nl). The LH was stable (22.9 vs

24.8 mIU/nl) and the serum FSH stable (10.8 vs 11.5 mIU/ml). There was a follicle in the right ovary which measured 12.8mm. We increased her dosage of 75IU recombinant FSH to 150 IU because we decided to block a potential further rise in the LH by treating her with 25mg cetrorelix. The follicle increased in average diameter to 16.1mm and the serum E2 was 296pg/ml. The serum P still suppressed at 0.54 ng/ml. The LH had dropped to 10.9 mIU/nl and the FSH was 15.3 mIU/nl.

There were two options at this point –1) give her one more day of the same dosage of gonadotropins and GNRH ant and repeat monitoring the next day when hCG would probably be given or 2) give her the hCG that day with a very appropriate serum E2 for 1 follicle but with the average diameter, slightly small at 16.1 mm. We chose to not stimulate one more day but trigger her that same day. A 12-cell embryo without any fragmentation and mild asymmetry was transferred on day 3. She delivered a healthy full-term boy. She had also been treated with dextroamphetamine sulfate.

Case 4

The patient was age 38.2. She was similar to case 3 in that she appeared to be in premature ovarian failure with an undetectable serum AMH and hypergonadotropic amenorrhea with marked estrogen deficiency. For several months despite the lowering of serum FSH into top normal ranges, the patient failed to demonstrate a serum E2 over 15pg/ml.

Every 2nd month she was given 10mg medroxyprogesterone acetate for 13 days while continuing the 20micrograms of ethinyl estradiol. Her blood levels would be obtained on day 3. Finally, her baseline blood tests showed a serum E2 of 76.8pg/ml with a serum P of 0.8ng/ml a serum level of LH of 26.7 MIU/ml and a serum FSH of 19.5 mIU/ml.

Because her FSH was increased, we did not start any gonadotropins. We were concerned that the LH was higher than the FSH and considered adding a GNRH ant. However, we feared suppressing her FSH too much so we just had her stay on EE 20mcg/day and have the serum hormone levels repeated in 2 days and also evaluate with pelvic sonography. (see Table 4) On day 5 of her menstrual cycle the serum E2 increased to 175 pg/ml but the average diameter of one follicle in the right ovary was only 9mm. Since the serum FSH was still slightly elevated at 13 mIU/nl., we elected to just continue with EE only and see her the next day, i.e., day 6. Another option on day 6 despite a serum E2 appropriate for a single follicle of 241 pg/nl but the average follicular diameter of only 12 mm., we chose to add another 75 IU FSH with 75 IU LH (menopur) and also add the GNRH ant cetrorelix and see her in 2 days) On day 8, the serum E2 was very good at 403.6, the serum P was still suppressed at 0.7pg.nl, the LH was not increased at 11.5 and the serum FSH at 11.6 mIU/nl.

We debated as to whether to give the trigger hCG shot on day 8 or push her one more day to day 9. We decided that since the follicle was not quite the desired 18mm average diameter (was 16.5mm) coupled with continued good rise of the serum E2 showing no evidence of plateauing we decided to continue 150 IU FSH and cetrorelix one more day. Probably the deciding factor was that the hCG would have been given day 8 and thus a slightly short follicular phase. We have seen successful pregnancies by lengthening the follicular phase even in women with advanced reproductive age and DOR (6). The patient transferred a 7-cell 3-day old embryo with mild fragmentation, and she conceived and delivered a full-term healthy boy.

Discussion

It should be noted that in all 4 patients the egg retrieval was performed 32 hours after the trigger hCG injection. We have found that extending the interval longer there is a greater chance of the eggs being released. However, the eggs retrieved with the shorter time have a good percentage of metaphase II eggs. These data concerning percentage of MII eggs with a 32-hour retrieval past hCG trigger are to be submitted for consideration for presentation of the 2026 meeting of the American Society for Reproductive Medicine.

We debated to include case 2 in this small series or present her as a unique case report. The case is a "fascinoma" because she responded extremely well to exogenous gonadotropins without the need to lower her serum FSH to restore down-regulated FSH receptors despite an undetectable serum AMH.

We have seen women in apparent ovarian failure with hypergonadotropic hypergonadism and estrogen deficiency who responded well to exogenous gonadotropins. However, it was found to be related to a pseudo menopause because they had gonadotropinomas of the pituitary secreting FSH hormones immunologically identical to FSH but not biologically active thus obliterating normal FSH producing cells of the pituitary [30,31]. One possible explanation was that this is another case of pseudo menopause related to failure to produce AMH despite adequate egg reserve or making a biologically active AMH that for some reason is cloaked when performing the ELISA method for AMH measurement. Actually, because the main function of AMH in the adult is to inhibit the FSH induced aromatase enzyme which helps to allow the development of only one dominant follicle in the human, perhaps she just has some deficiency where AMH is not produced [1].

There is one other possibility to explain this interesting case 2. There is a case report showing that a 14-year-old teenager who was treated with dextroamphetamine sulfate to treat mid-epigastric pain also increased her egg reserve as evidenced by a rise of borderline low AMH to a very normal level at least for an adult female [16]. Thus, there is the possibility that the use of the dopamine agonist in case 2 inhibited autoimmune destruction of primary follicles developing from primordial follicles before the stage of development of producing AMH. We never remeasured serum AMH once she had started the amphetamines.

There is a slight difference in the methodology for non-IVF vs IVF oocyte stimulation with DOR or POF. Most patients who prefer natural cycles are trying to conceive with the least expense. Since gonadotropin injections and GnRH ant are expensive, our goal for most patients is to try to just attain one mature dominant follicle in natural cycles. In contrast, with IVF cycles, we try to intervene earlier in the follicular phase to begin FSH stimulation, and thus monitor follicular development earlier also. Nevertheless, we have evidence that the main reason for higher pregnancy rates with IVF vs natural cycles in women

with DOR is not the actual IVF process itself (unless needed for severe male or tubal factor) but the opportunity to create more embryos from a given cohort which affords a better opportunity to have a euploid embryo implant. Thus, for some patients, especially where medications are paid for by their insurance companies, we may try an FSH receptor upregulation protocol that we use for IVF cycles but without oocyte retrieval hoping to release more than one egg [9,10].

We have explained in detail our rationale for using dopamine agonists to inhibit immune rejection of the fetus and thus increase the chance of a successful pregnancy [13-15,32,33].

Table 1: Response to follicular stimulation in IVF cycle
Patient 1

Day of cycle	3	4	5	6	7	8	9	10	11	12	13
E2(pg/ml)	35			80			219		359	766	
P(ng/ml)	1.4			0.8			0.7		1.1	0.71	
LH(mIU/ml)	3.0			2.2			1.1		2.5	8.7	
FSH(mIU/ml)	9.9			7.7			4.4		5.0	7.1	
EE											
Gonal- f	150 iu	150i u	150i u	150i u	150i u	150 iu	150 iu	150 iu	150 iu		
Menopur						75 iu	75 iu	75 iu	75 iu		
GNRH a						.25	.25	.25	.25		
Follicle size	<10	11.9 9.6					16.61 4		19. 1 17.2		
HCG trigger									hCg		

Table 2: Response to follicular stimulation in IVF cycle
Patient 2

Day of cycle	3	4	5	6	7	8	9	10	11	12	13	14	15
E2(pg/ml)	25.6			75.56		472.9		377.4		1129.9	1249.1		
P(ng/ml)	0.6			0.2		0.3		0.6		0.7	0.54		
LH(mIU/ml)	3.4			1.3		1.1		1.4		1.4	0.4		
FSH(mIU/ml)	9.2			12.0		16.2		19.4		18.7	17.5		
EE													
Follistim	150iu	150iu	150 iu	225 iu	225 iu	225 iu	225 iu	225 iu	225 iu	225 iu	225 iu		
LDHCG		10 iu	10 iu	10 iu	10 iu	10 iu	15 iu	15 iu	15 iu	15 iu	15 iu		
GnRHa							.25	.25	.25	.25	.25		
Follicle size				1 <10		11 13 11 10 10		14 13 13 11 11 11 6<10		18 15 14 12 12 10 18 11 11	19 21 18.3 8<10 19		
hCG trigger											hCG trigger		

There is reason to consider that the most common cause of DOR is excessive cellular permeability leading to an excess of cellular immune cells (that are normally needed for spiral artery formation from remodeling of thick-walled uterine arteries) allowing infiltration into pelvic tissue of irritants leading to autoimmune damage and also the increased risk of immune rejection of the fetal semi-allograft [13]. There were 2 cases of the 4 where because they lived in a state of the United States that has a law against using a drug with a class II narcotic restriction off-label so that they were not prescribed amphetamines. Thus, successful pregnancies can occur even without the addition of dopamine agonists. However, if possible, we do encourage the use of dextroamphetamine sulfate, a drug that we have extensively used safely during pregnancies. However, where amphetamine treatment is not possible or patient or doctor has reservations with using this particular dopamine agonist, lately we have used other dopamine agonists, e.g., cabergoline or carbidopa levodopa [34-36].

The basic tenet of the FSH receptor up regulation technique is not to significantly increase the serum FSH level because we have observed many times that the increase in serum FSH will lead to down regulation of FSH receptors on granulosa theca cells leading

to a paradoxical lower response. Furthermore, since one of the top IVF centers reported no live deliveries in women with only mild DOR following transfer of normal appearing embryos using conventional controlled ovarian hyperstimulation, the possibility exists that raising the serum FSH too high may cause down-regulation of a key FSH receptor responsible for making a protein critical for successful embryo implantation [37].

Table 3: Response to follicular stimulation in IVF cycle
Patient 3

Day of cycle	57	58	59	60	61	62
E2(pg/ml)	105	135		296	279	
P(ng/ml)	0.32	0.39		0.364	0.54	
LH(mIU/ml)	22.9	24.8		10.9	10.8	
FSH(mIU/ml)	10.8	11.5		15.3	14.2	
EE	0.2mg	0.2mg	0.2mg	0.2mg		
Gonal-f	75iu	150iu	150iu	150iu		
GnRHa		.25	.25	.25		
Follicle Size		12.8		16.1		
hCG trigger					hCG trigger	

Table 4: Response to follicular stimulation in IVF cycle
Patient 4

Day of cycle	3	5	6	7	8	9	10	11
E2(pg/ml)	76.8	175	241		403.6	628	716.1	
P(ng/ml)	0.8	0.8	0.6		0.7	0.7	0.8	
LH(mIU/ml)	26.7	17.9	18.4		11.5	Not done	41.4	
FSH(mIU/ml)	19.5	13	11.5		11.6	Not done	12.3	
EE								
Gonal-f			75iu	75iu	75iu	75iu		
menopur				75iu	75iu	75iu		
GNRHa				.25	.25	.25		
Follicle Size		9	12		16.5	19		
hCG trigger						hCG trigger		

Declaration
The authors have nothing to declare. They receive no outside funding from pharmaceutical companies or other agencies.

The authors would like to apologize for so many self-references. These concepts have not become standard dogma as yet, so we tried to share the studies we have performed leading to this concept. Nevertheless, there have been many studies performed by other researchers and clinicians that helped us formulate these concepts. For those interested in these other studies many are used as references in references 12 and 17.

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