Mild ovarian stimulation

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Abstract

Purpose To evaluate the efficacy of using only mild ovarian stimulation protocols for in vitro fertilization. Both groups with decreased and normal ovarian reserve were evaluated.

Methods Three different mild stimulation protocols were evaluated: natural with no exogenous follicle stimulating hormone (FSH) drugs at all, natural with a boost of low dose FSH to complete follicular maturation, and minimal stimulation with low dose (75–150IU) FSH from day 3–5 of the menstrual cycle. Ethinyl estradiol was sometimes used to lower high day 3 serum FSH.

Results Good pregnancy and implantation rates were found even in those women with elevated serum FSH that could only generate one follicle.

Conclusions Mild ovarian stimulation seems preferable to high dose FSH regimens in women with elevated day 3 serum FSH based on previous poor reported pregnancy rates with the latter protocols. Comparable pregnancy rates to high dose regimen were seen in women with normal egg reserve at much lower risk and cost.

Capsule Regimens using low dosage of FSH are very effective for in vitro fertilization especially but not restricted to women with diminished egg reserve.

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Background leading to minimal stimulation protocol

Over 20 years ago a concept emerged that follicles may still be present and ovulation could be achieved in women with apparent menopause (high serum follicle stimulating hormone (FSH), estrogen deficiency, and resistance to gonadotropin stimulation) by increasing sensitivity to the granulosa-theca cell by restoring down-regulated FSH receptors [1]. The concept was that chronic elevation of FSH down-regulated the FSH receptors. However, restoration of receptors could be achieved by either using pharmacologic dosages of estrogen and thus suppressing the release of FSH from the pituitary, or suppressing the gonadotropin releasing hormone (GnRH) by using the GnRH agonist leuprolide acetate [1, 2].

The original described technique involved placing the woman on 2.5–5 mg of conjugated estrogen, waiting a couple of weeks until the FSH was brought into the normal range, then starting low dose human menopausal gonadotropins (hMG) at 75–150 IU/day [1]. The conjugated estrogens were either continued when the hMG was started and the follicular monitoring based entirely on follicle size by transvaginal sonography, or the conjugated estrogens were stopped when the hMG was started and monitoring was based on both sonography and serum estradiol [1]. Ovulation and pregnancies were recorded using this technique despite apparent menopause. All of the patients had failed to respond to hMG therapy previously even when used in higher dosages.

Anecdotally, there seemed to be more success in inducing ovulation despite hypergonadotropic amenorrhea if the estrogen was continued when the hMG was started. Pelvic sonography did not have the same quality in the 80s as it does today. The fear was that a blood vessel or non-

functional cyst could be falsely interpreted as a follicle and thus, ideally, serum estradiol should be measured.

A search for an estrogen preparation that would not cross-react in the assay for 17 beta-estradiol found ethinyl estradiol which was marketed in the United States by Schering pharmaceuticals (today it needs to be compounded in the USA) [3]. The first case of ovulation induction in a menopausal woman using ethinyl estradiol was in 1989 in a 39 year old woman with estrogen deficiency and a serum FSH of 124 mIU/ml [4]. She had failed to raise her serum estradiol above 20 pg/ml despite 3,600 IU of hMG when the hMG was given without FSH suppression. When her FSH was suppressed before hMG at 150 IU was started, she ovulated in 6 consecutive cycles and conceived on cycle 6. She delivered by cesarean section. Interestingly her right ovary was identified as a streaked gonad and the left was markedly hypoplastic estimated to have an average diameter of 12–15 mm [4].

This case illustrates that this technique of suppressing FSH and then using low dose gonadotropin stimulation is effective when there is a paucity of follicles, not merely in cases where the ovaries are replete with early follicles but they are resistant to gonadotropins. Nevertheless, the basic premise of this technique is that the few remaining follicles are already or potentially resistant to gonadotropins because of suppression of FSH receptors in the granulosa theca cells. Thus one may have to restore sensitivity by lowering the serum FSH with estrogen suppression or GnRH agonists or antagonists. Furthermore, the treating physician has to be careful to keep the gonadotropin dosage low because the slow clearance of the injected FSH may lead to down-regulation again of the FSH receptors.

Modification of the technique for reversing ovarian failure to be more cost effective

Although the aforementioned case demonstrated ovulation in 6 consecutive cycles [3], it was clear from treating other cases that some women never ovulated with the technique, some ovulated intermittently and some ovulated all the time [5]. The hMG injections were and are still are very expensive and was not always covered by insurance. We considered that there was a possible point where FSH receptors may be restored and the woman may respond to her own endogenous FSH which could still be slightly high or now in the normal range. Thus the hMG was not initiated until there was a clear rise in serum estradiol [5]. Sometimes, in fact, the ethinyl estradiol is used exclusively as was described in the case of a 42 year old with imminent ovarian failure needing IVF because of tubal factor who was only given ethinyl estradiol during the follicular phase to achieve follicular maturation [6].

Although, some women once the FSH receptors are restored can respond to higher daily dose gonadotropins, some women seem to shut down when the FSH levels rise secondary to the medication [7]. This fact, coupled with the concept that the objective is to save money by not using more gonadotropins than necessary, led to the concept to use low dosage (75–150 IU) exogenous FSH.

Performing endometrial biopsies in these cases in the late luteal phase found a high frequency of luteal phase deficiencies. Thus during the luteal phase the women were treated with progesterone vaginal suppositories [8].

Concepts derived from the study of 100 consecutive women with hypergonadotropic amenorrhea and estrogen deficiency [5]

The age ranges of this study was 19–47 with an average of 34 years. Of the 91 women treated with ethinyl estradiol and hMG given at least 4 cycles of treatment (unless pregnancy occurred first), 34 of 91 women (32.3%) ovulated at least once, ovulation occurred in 61 of 311 (19.6%) cycles and pregnancies occurred in 19 of the 34 ovulatory women (55.8%) and live deliveries in 8 of 34 (23.2%) ovulating women and 8 of 91 (9%) of women treated for this condition. One important prognostic factor was length of time for amenorrhea to treatment; the average time was 2.2 years for those who conceived vs. 4.8 years for those who did not [5]. Ovulation inductions followed the same pattern.

Decreased egg reserve but adequate estrogen

In the circumstance of decreased egg reserve but adequate estrogen (usually accompanied by an increased day 3 serum FSH) two basic circumstances exist—the woman appears to ovulate or not. In the first instance ovulation may occur at the same time each month leading to regular cycles or may occur at irregular intervals leading to irregular menstrual cycles. For an ovulatory women there may be menses from breakthrough bleeding or the woman may have amenorrhea but does menstruate as a result of progesterone withdrawal.

A previous prospective study found that infertile women (1 year or more) who had regular menses, appeared to make an adequate dominant follicle but had out-of-phase endometrial biopsies, had a much higher pregnancy rate when randomized to luteal phase progesterone support as opposed to follicle maturing drugs [9]. Thus for infertile women who have elevated day 3 serum FSH levels but regular menses and who make a mature follicle on their own, no ethinyl estradiol is usually given nor are gonadotropins; just progesterone in the luteal phase. An

exception may be for those women who ovulate before day 11 since they seem to have lower pregnancy rates [10]. By using ethinyl estradiol from day 2 or 3 the follicular phase may be lengthened which markedly improves pregnancy rates [11].

If in vitro fertilization–embryo transfer (IVF–ET) is to be performed, when there seems to be only one follicle, no gonadotropins would be given. However if the rising endogenous estradiol levels lower the FSH into the normal range and the ultrasound shows that there may be more than one maturing follicle, a small “boost” of gonadotropins may be given to try to attain more than one mature egg on retrieval. This boost of gonadotropins may also be employed for those “ovulatory” women with luteal phase defects who release the egg from an immature follicle [9].

Sometimes even in a natural cycle there may be premature luteinization where the luteinizing hormone (LH) rises before the follicle is mature [12]. In this case a GnRH antagonist is used when the serum estradiol is approximately 100 pg/ml and FSH or hMG is added or increased by 75 IU/day.

If there are long intervals between menses, and the serum FSH is elevated, generally ethinyl estradiol 20 µg/day is given. If the serum estradiol begins to rise then either no exogenous gonadotropins are used if the follicle or follicles are developing at a normal rate or again a boost of gonadotropins are given as previously described (usually at 75 IU/day but sometimes 150 IU/day). If GnRH antagonists are started, the dosage of gonadotropins are frequently increased to 225 IU/day.

Effect of age in women with diminished egg reserve

A successful pregnancy was recorded in a 45 year old woman with amenorrhea in apparent ovarian failure with a serum FSH of 43 mIU/ml who ovulated twice in a row with just ethinyl estradiol treatment alone and intrauterine insemination for severe oligoasthenozoospermia [13]. Other cases include two other women with diminished egg reserve (one 45 with a short follicular phase and one aged 46) who successfully conceived [14, 15].

However, despite these three pregnancies, it is difficult to achieve pregnancies in a woman this age. At our IVF center we have had only one live pregnancy in 150 embryo transfers in women aged 45 and over (a woman aged 46).

Some equate younger women with diminished egg reserve as having equivalent egg quality as women aged ≥ 45 . This does not seem likely however because of the pregnancies achieved in women < aged 45 with apparent menopause. Studies performed on women who have diminished egg reserve but adequate estrogen showed a marked difference in pregnancy rates in younger (age <40)

vs. older (≥ 40) women [16]. The 6 month clinical and ongoing pregnancy rates in non-IVF cycles was 46 and 34.6% in the younger group vs. 10.3 and 5.3% for women aged ≥ 40 [16]. This age difference was also seen with IVF–ET comparing women aged $\leq$ age 38 vs. $>$ aged 38 [17].

In a recent published study evaluating pregnancy rates according to blastomere number of day 3 single embryos transferred, the clinical pregnancy rate was 38–42% with 6–8 cell embryos (which represented 65% of the transfers [18]. The women aged ≤ 39.9 had marked elevated serum FSH levels, and were treated with either natural cycles or minimal stimulation protocols [18].

The aforementioned studies suggested that age 40 may be the cut-off for marked reduction in pregnancy rates. However, the data was diluted by including women up to the age of 50. In a study of very poor egg reserve where no or minimal stimulation with gonadotropins were used, a 21.7% live delivery rate per transfer was found in women aged 40–42 but no live pregnancies in those $\geq$ aged 43 [19].

High dose vs. low dose gonadotropins stimulation for IVF–ET in women with diminished egg reserve

In vitro fertilization has generally been used for years with the idea of retrieving many eggs to enable the creation of many embryos to allow multiple embryos to be transferred, cryopreservation of embryos for future cycles, or finding the “best embryos” by allowing natural selection by allowing them to develop to the blastocyst stage. When it comes to women with elevated day 3 serum FSH, some IVF centers will wait for a cycle when the serum FSH is normal, attempt stimulation, but cancel if there were not enough adequate sized follicles.

With incipient ovarian failure or marked decreased egg reserve, most IVF centers will recommend donor egg programs if IVF is needed for conception. For some reason the prevailing concept is that there needs to be a certain number of eggs to make IVF worthwhile. Thus in these circumstances, it is obvious that minimum stimulation protocols are the only ones that can be employed. This is because of the concept of not spending more money than needed since one cannot stimulate more follicles than what is selected for the particular cycle’s cohort of follicles not to mention the risk of down-regulating the serum FSH receptors and getting a paradoxical worse response.

Attempts to stimulate women with increased day 3 serum FSH levels have been attempted not only with traditional high dose controlled ovarian hyperstimulation (COH) regimens, but even much higher levels than normal. Studies from the early days of IVF concluded that very poor pregnancy rates ensue in women with elevated day 3

serum FSH despite the transfer of normal appearing embryos [20, 21]. Since many pregnancies had been achieved over the last 20 years, both with and without IVF–ET in women with such low egg reserve that they were considered to actually be in menopause, I just assumed that the two studies showing such poor pregnancy rates were related to inferior techniques in those early days.

However, when a study was published by one of the finest IVF centers in the world in the modern IVF era that reported a zero live delivery rate per transfer at any age in women with a serum FSH of >15 mIU/ml (and with the recommendation that this circumstance should prompt a decision to not even try IVF but offer donor oocytes), this created great confusion in my mind [22]. In fact the group that they evaluated were those who despite the increase in serum FSH were better responders [22]. One's interpretation of their study is that this should not be so surprising since not only do they have fewer eggs remaining, but they have the same poor quality as the aforementioned women aged ≥ 45 [22].

My interpretation based on our own data of why age seemed to have a much more negative prognostic effect than elevated serum FSH levels was that possibly a mitochondrial factor present in the eggs that allowed their choice for potential egg selection during a woman's younger years was also responsible for inhibiting subsequent apoptosis of the resulting embryos. Thus our data was more consistent with the concept that the reason for diminished egg reserve in younger women is not related to a more rapid rate of atresia but more related to some destructive process that results in egg quantity similar to women age ≥ 45 . However, from a quality standpoint, the eggs are similar to their age peers.

Since there is no difference in our technique of oocyte retrieval or embryo development in these women with low egg reserve from women with normal egg reserve, one interpretation as to why there is such a dichotomy of opinion about the prognosis of these two groups may be related to the stimulation protocol used [18, 22].

Sometimes the source for donated oocytes for recipients may come from infertile donors trying to also conceive [23]. Early studies showed a markedly higher pregnancy rate in the older recipients than in the younger donors [24, 25]. One explanation for the difference in pregnancy rates was that the COH regimen created an adverse uterine environment [24, 25]. Most of the infertile donors in the days of the aforementioned studies had tubal factor since intracytoplasmic sperm injection had not been introduced as yet. Subsequently with the demonstration that hydrosalpinges can have a negative effect on implantation, and that salpingectomy can correct this, it was believed that chronic tubal infection could have been a major influence on the dichotomy of pregnancy rates [26–30]. Nevertheless in the

post salpingectomy era, there still may be about a 20% lower implantation rate in donors vs. recipients [31, 32]. This may be related to premature trophoblast invasion [33, 34].

As mentioned high dose FSH regimen can suppress the follicular development to the point that it can create a pseudo-state of menopause [7]. Perhaps a certain degree of FSH receptor concentration is needed in the granulosa theca cells to allow the production of a factor that is essential for embryo implantation. Thus, the hypothesis to explain the opposite conclusions on the ability of women with elevated day 3 FSH levels to conceive following IVF–ET may be related to an adverse effect of the high dose protocol on egg quality, not effecting the embryo morphology, but effecting the ability of the embryo to implant.

Three types of minimal stimulation protocols

The three types of minimal stimulation protocols are natural, natural with a boost of FSH, and minimal FSH stimulation. The choice of which one is used usually is dependent on the number of antral follicles, the level of serum FSH and serum estradiol on day 3, and to a lesser degree the wishes of the patient. Usually the decision on whether to do a completely natural cycle or use a boost depends on how high the serum FSH levels are and how follicular maturation is progressing. If the follicle is progressing, and the FSH is elevated, one is reluctant to boost with FSH.

The more antral follicles seen on day 3, and the lower the serum FSH, the more likely that a minimal FSH protocol of 75–150 IU from earlier in the follicular phase will be tried. The choice of ethinyl estradiol would be made if the FSH remains high without a rise in estradiol, or to try to lengthen the follicular phase if the day 3 serum estradiol is >50 pg/ml. Details of these techniques have been previously published [18].

In the study of single embryo transfers in women with diminished egg reserve completely natural cycles accounted for ~25% (60/242) of the retrievals but only about 15% (19/129) of transfers. The clinical and live delivery rate per transfer was 21.1 and 15.8% respectively with the completely natural protocol, 28.8 and 23.7% with natural, with a boost of FSH and 29.4 and 23.5% with minimal FSH stimulation [18]. Thus, at least half of the retrievals led to transfer in the natural with boost and minimal FSH stimulation and about a third of the group doing natural cycles. This latter group, in general, was the one with the least follicles and was much more likely to be closer to overt ovarian failure than the other two groups. There were no cases where a single embryo transfer was intentional, just that there was only one embryo to transfer.

The outcome of IVF using minimal stimulation protocol in younger women with increased day 3 serum FSH having two or more embryos transferred

The clinical and delivered pregnancy rates and implantation rates according to day 3 serum FSH levels in women age <35 with two or more embryos transferred is seen in Table 1. In this study, 91% had at least one embryo with ≥ 6 blastomeres. In the study of single embryo transfers the percentage of transfers with an embryo ≥ 6 blastomeres was only 65% [18]. The clinical pregnancy rate/transfer in that study was 3.8 and 9.5%, respectively for 4 or 5 blastomeres vs. 38–42% for 6–8 blastomeres. Though the group with increased FSH with at least 2 embryos transferred had a better egg reserve, the most important factor for the higher pregnancy rates seem to be not as much the transfer of multiple embryos but the better chance of having an embryo with more blastomeres.

The effect of age on pregnancy rates following IVF–ET in women with serum FSH levels >12 mIU/ml using no more than 150 IU of FSH per day

These data were presented at the 2007 American Society for Reproductive Medicine. The clinical pregnancy rate per transfer for women aged ≤ 35 was 47.4% (45/95) vs. 30.7% (44/143) for women aged 36–39. The live delivered pregnancy rates were 41.0% (39/95) vs. 25.9% (27/143). Chi-square analysis showed significant differences ($p=0.014$, $p=0.02$). The implantation rates for women ≤ 35 was 27.6% (67/242) vs. 15.6% for women aged 36–39 ($p=0.0005$).

These data further support the benefit of the use of minimal stimulation protocols in women with elevated day 3 serum FSH. They also support the contention that the eggs of younger women with elevated FSH have a much

higher quality than eggs from older women with similar FSH levels. This supports a different mechanism of diminished egg reserve for this group rather than the mechanism present in women of advanced reproductive age but with similar ovarian egg reserve. A mere acceleration of the rate of atresia in younger women with diminished egg reserve does not seem to be likely to be a common etiology.

Minimal stimulation for women with normal egg reserve as manifested by normal day 3 serum FSH levels

If adequate pregnancy rates are found with minimal stimulation protocols in women with diminished egg reserve, it seems likely that a sufficient outcome should also be found in women with normal egg reserve using minimal stimulation protocol.

The most common reasons why minimal stimulation protocols have been used in this group at our IVF facility has been because of failing to conceive after several embryo transfers using normal COH protocols with the possibility that the high dose gonadotropins caused an abnormal uterine environment inhibiting implantation.

Table 2 Pregnancy rates following IVF–ET using minimal stimulation protocols in patients with normal day 3 serum FSH

	Age ≤ 35	Age 36–39	Age 40–42	Age ≥ 43
# Retrievals	205	166	198	250
# Transfers	149	117	97	119
# Follicles	2,626	988	815	603
# Eggs retrieved	1,795	739	574	414
# M retrieved	1,391	538	483	344
# Insemination	1,521	612	512	378
# Fertilized	1,023	406	349	238
% Fertilized	67.3	66.3	68.2	63.0
# Cryopreserved	578	129	128	43
# Pregnancies	79	44	28	12
% Pregnant/trans	53.0	37.6	28.9	10.1
# Clinical	72	37	21	7
% Clinical/trans	48.3	31.6	21.6	5.9
# Chemical	6	6	5	5
# Ectopic	1	1	2	0
# Delivered	68	34	14	4
% Delivered/trans	45.6	29.1	14.4	3.4
# SAB/TAB/FD	7	5	7	4
% SAB/clin. preg	9.7	13.5	33.3	57.1
# Deliveries/ongoing	65	32	14	3
% Delivered/ongoing	43.6	27.4	14.4	2.5
# Embryos transferred	336	231	193	180
Average # ET	2.3	2.0	2.0	1.5
# Sacs implanted	105	51	27	7
Implantation rate (%)	31.3	22.1	14.0	3.9

Table 1 Clinical and delivered pregnancy and implantation rates in younger women with increased day 3 serum FSH having 2 or more embryos transferred

Groups	Serum FSH (mIU/ml)				
	1 ≤ 10	2 11–12	3 13–14	4 15–16	5 ≥ 17
Clin. preg. rate/transfer (%)	43.7	52.2	54.5	50.0	33.3
Delivered preg. rate/transfer	39.7	43.5	54.5	50.0	11.1
Implantation rate (%)	22.6	26.1	27.3	16.7	14.8
Number of transfers	355	23	11	2	9

The implantation rates were significantly lower ($p<0.05$, chi-square) in groups 4 and 5 compared to 1–3.

The next most common reason is for women trying to save money not only because the cost for gonadotropins is markedly reduced, but since there is less work for the embryologist we charge only half the price for the IVF procedure. Frequently the group preferring this protocol for financial reasons has already either used up their insurance options or finances from failing to have success with previous standard COH, IVF–ET cycles. The pregnancy rate according to age is seen in Table 2.

Conclusion

The objective of practicing good medicine is to provide a treatment for a particular condition that is the most effective treatment with the least risk and expense to the patient. The biggest risk of IVF is the development of the ovarian hyperstimulation protocol. This risk is markedly reduced by using lower dose FSH stimulation.

Similarly the risk of bleeding from follicular puncture is a lot less with less stimulated ovaries. Risk of torsion or persistent ovarian cysts are also reduced.

As mentioned expenses can be markedly reduced using minimal stimulation protocols. For all of these reasons it may be that in the near future not only will minimal stimulation protocols be preferred for women with decreased egg reserve but this may be the first choice even for women with normal egg reserve undergoing their first IVF cycle (not merely those failing to conceive from previous standard higher dose protocols).

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