Editorial Articles

Choosing the right stimulation protocol for in vitro fertilization-embryo transfer in poor, normal, and hyper-responders

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Summary

Purpose: To describe the advantages of low-dose stimulation for poor responders, the pros and cons of low dose vs high dose stimulation for normal responders and multiple strategies for hyper-responders especially to reduce the risk of the ovarian hyperstimulation protocol. *Methods:* Various strategies are described for these three types of responders. *Results:* Poor responders do best with mild stimulation protocols. Conventional stimulation protocols for normal responders have the advantage of providing embryos for future embryo transfers assuming the IVF center has a good cryopreservation program. Mild stimulation protocols save money for normal responders. There are many strategies for hyper-responders to prevent ovarian hyperstimulation syndrome including mild stimulation, high LH/FSH ratio for stimulation combination, GnRH agonist instead of hCG and using clomiphene citrate or aromatase inhibitors. *Conclusions:* It is important to choose the right protocol for a given patient. An infertile couple can often help in making the decision.

Key words: Mild ovarian hyperstimulation; Poor responders; Hyper-responders; In vitro fertilization; Cryopreservation.

Diminished oocyte reserve

There is an often quoted article suggesting that younger women with an elevated day 3 follicle stimulating hormone (FSH) have a very high percentage of oocytes that have chromosome abnormalities similar to women of very advanced reproductive age [1].

A study by one of the most renowned in vitro fertilization (IVF) centers in the world stated that when the serum FSH on day 3 is $\geq$ 15 mIU/ml the success rate of transferring normal appearing embryos in women of any age despite adequate response to stimulation will result in no live pregnancies [2]. Thus these two studies would agree with each other. The 2005 Fertility and Sterility article recommended and has influenced the large majority of IVF centers to immediately recommend donor oocytes with day 3 serum FSH $\geq$ 15 mIU/ml [2].

Evidence will be provided that the above conclusions are wrong. Evidence will be provided that the very poor pregnancy rates experienced by some IVF centers in women with diminished egg reserve is related to using the wrong controlled ovarian hyperstimulation (COH) regimen.

Table 1 shows the comparative pregnancy rates in younger women $\leq$ age 35 according to four ranges of FSH (mIU/ml) – normal $\leq$ 11, slightly high [12-14], moderately high with attainment of the critical level reported by Roberts *et al.* of 15-17 and extremely high of 717 mIU/ml. Tables 2, 3, and 4 compare these same parameters according to different age groups of 36-39, 40-42 and 43-44. No differences were found in women up to age 42 according to the four FSH ranges. It should be noted however that all the women with increased day 3 serum FSH were stimulated with mild stimulation protocols [3].

Tables 5 and 6 clearly show that age rather than day 3 serum FSH more relates to the attainment of live deliveries.

These data clearly do not show any adverse effect of a high day 3 serum FSH in contrast to the conclusions reached by many IVF centers including the aforementioned IVF center reporting in Fertility and Sterility, 2005 [2]. Thus we attribute the difference in conclusions to the other centers purposely using very high dosages of FSH and our use of mild ovarian stimulation in those with diminished oocyte reserve. Since frozen embryos from women hyperstimulated by high-dosage FSH regimens in women with diminished oocyte reserve fail to produce pregnancies when thawed and transferred (unpublished data), we conclude that the adverse effect of controlled ovarian hyperstimulation on pregnancy rates in women with diminished oocyte reserve seems to be on the embryo itself rather than the endometrium.

Table 7 shows the live delivered pregnancy rates according to age and serum FSH. One question that arises from looking at this table is – why do the women with normal FSH not do better than the women with diminished oocyte reserve? Though no significant differences were found there seemed to be a trend for lower pregnancy rates.

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Table 1. — *Pregnancy rates according to day 3 serum FSH following IVF-ET in women aged ≤ 35.*

	Serum FSH (mIU/ml)			
	≤ 11	12-14	15-17	> 17
# transfers	2120	111	37	88
% clinical pregnancies per transfer	33.8	32.4	40.5	44.3
% live delivered per transfer	30.8	29.7	40.5	38.6
% spontaneous abortion per clinical pregnancy	13.5	13.9	13.3	15.4

Table 2. — *Pregnancy rates according to day 3 serum FSH following IVF-ET in women aged 36-39.*

	Serum FSH (mIU/ml)			
	≤ 11	12-14	15-17	> 17
# transfers	1313	120	47	93
% clinical pregnancy per transfer	28.1	36.7	29.8	37.6
% live delivered per transfer	24.3	30.8	21.4	30.1
% spontaneous abortion per clinical pregnancy	21.1	20.5	21.4	22.9

Table 3. — *Pregnancy rates according to day 3 serum FSH following IVF-ET in women aged 40-42.*

	Serum FSH (mIU/ml)			
	≤ 11	12-14	15-17	> 17
# transfers	737	103	30	05
% clinical pregnancy per transfer	23.4	30.1	36.7	35.4
% live delivered per transfer	18.5	18.4	23.0	23.1
% spontaneous abortion per clinical pregnancy	31.8	45.2	36.4	39.1

Table 4. — *Pregnancy rates according to day 3 serum FSH following IVF-ET in women aged 43-44.*

	Serum FSH (mIU/ml)			
	≤ 11	12-14	15-17	> 17
# transfers	121	30	18	25
% clinical pregnancy per transfer	26.4	26.7	16.7	32.0
% live delivered per transfer	21.5	16.0	6.0	8.0
% spontaneous abortion per clinical pregnancy	40.6	75.0	100	87.5

Table 5. — *Pregnancy rates according to age following IVF-ET in women with normal FSH ≤ 11 mIU/ml.*

	Age			
Serum FSH ≤ 11	≤ 35	36-39	40-42	43-44
# transfers	2120	1313	737	121
% clinical pregnancy rate per transfer	33.8	28.1	23.9	26.4
% delivered pregnancy rate per transfer	30.8	24.3	18.5	21.5
% spontaneous abortion	13.5	21.1	31.8	40.6

There are several possible explanations for the relatively lower pregnancy rates in the group with normal reserve. For one, there is a greater likelihood of previous failed IVF cycles in other IVF centers. Our IVF center has a reputation for finding solutions when others have failed such as the woman who had two successful deliveries at our infertility center, once with IVF-ET and once naturally despite failing six years of ovulation induction with intrauterine insemination and ten IVF-ET cycles with the transfer of 92 fresh embryos [4, 5]. These cases support larger studies suggesting that one additional possible explanation for not finding higher pregnancy rates in those with normal oocyte reserve is that high-dose gonadotropin stimulation may adversely effect embryo implantation in some cases even with normal day 3 serum FSH [6, 7].

De-selection of embryos is another possible explanation for lower pregnancy rates in the first fresh embryo transfer. We have developed a simplified slow cool embryo freezing technique that avoids the programmable freezer which we believe is the weak part of the standard slow cool procedure [8]. This modified technique allows good success rates in all stages of embryo development, e.g., 2 pronuclear, multicell and blastocyst but produces the highest survival rates and subsequent pregnancy rates when embryos are frozen at the 2 pronuclear phase [8].

We previously published an article bringing up the concept of pregnancy rate per oocyte harvest, i.e., the pregnancy rate following a given oocyte retrieval before another oocyte retrieval has to be performed [9]. Thus this allows all the cryopreserved embryos to be used before doing another expensive IVF-ET cycle and expensive controlled ovarian hyperstimulation. Table 8 shows that the chance of a live delivery before going to another IVF-ET cycle was 65% for women ≤ 35 and 45.6% for women 36-39 [9].

We have published data using women with diminished oocyte reserve showing that the clinical pregnancy rate per transfer ranged from 38-42% with day 3 embryos having six to eight cells but only 3.8 and 9.5%, respectively for embryos with four or five blastomeres [10]. Because our frozen protocol gives us a better pregnancy rate when frozen at the 2 pronuclear stage we typically will allow only twice as many embryos to develop to day 3 as the woman intends to transfer and freeze the rest at the 2 pronuclear stage. If we allowed all the embryos to be developed on day 3 we would have a better chance of transferring the best morphologic day 3 embryos during the fresh transfer but perhaps at the sacrifice of subsequent frozen embryo transfer success. Nevertheless this policy could somewhat reduce our pregnancy rate per transfer in women with normal day 3 FSH level using the standard higher dose-controlled ovarian hyperstimulation protocols to possibly explain why the pregnancy rates following fresh embryo transfer in women with normal oocyte reserve was similar to those with diminished oocyte reserve.

If other centers can show that the pregnancy rates following frozen or fresh embryo transfer are similar, it can not be known whether our policy of limiting the number of embryos to cleave is the better way. However the pregnancy rates shown in Table 8 do not include the remaining frozen embryos that can result in pregnancies at a later time.

Even if all the embryos are allowed to cleave to day 3 and a transfer of all day 3 embryos having eight blastomeres with little fragmentation can be achieved, one cannot be sure that the "best embryo" has been selected. The FSH recep-

Table 6. — *Pregnancy rates according to age following IVF-ET in women with serum FSH > 11 mIU/ml.*

	Age			
Serum FSH ≥ 11	≤ 35	36-39	40-42	43-44
# transfers	88	93	65	25
% clinical pregnancy per transfer	94.3	37.6	35.4	32.0
% delivered pregnancy per transfer	38.6	30.1	23.1	8.0
% spontaneous abortion	15.4	22.9	39.1	87.5

Table 7. — *Live delivered pregnancy rates according to age and day 3 serum FSH levels.*

	Day 3 FSH (mIU/ml)			
Age	≤ 11	12-14	15-17	> 17
≤ 35	30.8	29.7	40.5	38.6
36-39	24.3	30.8	23.4	30.1
40-42	18.5	18.4	30.0	23.1
43-44	21.5	10.0	0.0	8.0

Table 8. — *Pregnancy rate per oocyte harvest according to age in women with normal serum FSH.*

	Age			
	≤ 35	36-39	40-42	≥ 43
# transfers	408	239	135	16
% clinical pregnancy per transfer	73.8	59.8	34.1	37.5
% viable per transfer	65.0	45.6	25.2	25.0

tor is especially susceptible to down regulation [11]. The concept is that the main purpose of the down-regulation process is to allow the one best oocyte in the cohort to develop each menstrual cycle [3]. This supposedly will produce the best embryo. Thus one other explanation for similar results with women with normal vs diminished oocyte reserve when minimal stimulation protocols are used for the latter and traditional high-dose regimen used for the majority of women with normal day 3 serum FSH levels is that the minimal stimulation protocol better allows the natural selection of the best oocyte.

One may question so why do some very good IVF centers claim such low pregnancy rates when doing IVF with higher dosage protocols in women with diminished oocyte reserve [2, 12-16]. Our theory to explain the poor results of those IVF centers using traditional high-dose or superhigh dose use of exogenous FSH relates to the marked sensitivity of the FSH receptor to suppression. It could be hypothesized that there is an FSH dependent implantation factor that is attached to the embryo that is not adequately produced because its receptor is down-regulated. Thus in contrast to the minority of women with normal oocyte reserve where controlled ovarian hyperstimulation may create an adverse endometrial environment possibly related to premature trophoblast invasion (where one strategy would be to freeze all the embryos and defer transfer to a later time) with diminished oocyte reserve this strategy will not work because it is the embryo itself that is affected [17-18]. Also with diminished oocyte reserve the adverse effect of controlled ovarian hyperstimulation affects the majority of cases rather than a minority with normal oocyte reserve [19-22]. Diminished oocyte reserve groups are more likely to include the "best oocyte", i.e., the one that was destined to be the dominant follicle [22].

High versus low-dose gonadotropin stimulation protocols for normal responders

One of the advantages of the traditional high-dosage controlled ovarian hyperstimulation protocol for women with normal oocyte reserve is that the pregnancy rate per oocyte harvest would be higher than mild stimulation because of more embryos (however, this requires a good embryo cryopreservation program).

Another advantage of traditional high-dosage controlled ovarian hyperstimulation protocol for women with normal oocyte is that it provides embryos for a future pregnancy with pregnancy rates consistent with the younger age when frozen. For those with insurance that pays for a limited number of IVF-ET cycles stockpiling embryos for the future will reduce costs since if third party payments have expired a frozen embryo transfer is generally a lot cheaper than controlled ovarian hyperstimulation followed by IVF-ET.

One advantage of the low-dosage controlled ovarian hyperstimulation protocol for women with normal oocyte reserve is that the chance of pregnancy in the first IVF-ET cycle is probably higher using a low stimulation protocol than a high-dose one since it eliminates the adverse effects of controlled ovarian hyperstimulation on the endometrium and allows a greater chance for the embryo that would have resulted from the best oocyte that would have been selected in the absence of controlled ovarian hyperstimulation.

Another advantage of the low-dose protocol is much less risk of ovarian hyperstimulation syndrome. Not only is mild ovarian hyperstimulation less expensive because of lower cost of medication but also because of less work for the embryologist (we cut the price in half).

Even for those with adequate financial means or insurance coverage the choice of the traditional controlled ovarian hyperstimulation should only be made if one has a good cryopreservation program.

Some early studies suggested GnRH antagonists were more convenient but lowered pregnancy rates a bit [23]. Most recent studies show no difference in outcome [23]. We found no difference in outcome in those who were taking it for a longer vs shorter interval [23].

We typically use the GnRH antagonist in the late follicular phase. Some protocols use the GnRH antagonist earlier than late follicular phase when the follicle attains an average diameter of 14 mm and still claim good pregnancy rates. More oocytes are frequently found with GnRH antagonists vs GnRH agonists [23].

There are some disadvantages of GnRH agonists. Using GnRH agonists in the mid-luteal phase can interfere with a possible pregnancy achieved that cycle without IVF-ET. They can sometimes cause a "flare" effect and advance a single follicle ahead of the rest of the cohort in the follicular phase. Furthermore the use of a GnRH agonist precludes the use of a GnRH agonist to induce the LH surge and advance meiosis and avoid exposure to hCG injection in case of a risk of ovarian hyperstimulation syndrome (OHSS). Finally it can sometimes blunt the response to exogenous FSH.

However there are several advantages of GnRH agonists. The main advantage of a GnRH agonist is that it is cheaper than a GnRH antagonist. We find it easier to use when coordinating donors and recipients. Finally it is less likely to cancel an IVF-ET cycle because of premature luteinization when using a GnRH agonist vs GnRH antagonist.

Ways to reduce the risk of ovarian hyperstimulation syndrome in women with polycystic ovarian syndrome

There are several ways to reduce the risk of OHSS. One method is to use less FSH but sometimes even low dosage leads to excessive numbers of follicles. One can use a higher LH:FSH ratio [24]. Another option is to use the GnRH agonist (e.g., 1 mg leuprolide acetate x 2 doses 12 hours apart) instead of hCG [25-27]. Another method is to coast by stopping the gonadotropin for one to two days (frequently lose follicle if go beyond 2 days) [28, 29]. Finally one can use LH only when follicles ~12-14 mm (we have not found this very successful but others, e.g., Filicori *et al.* have had success [30, 31].

There are other ways to reduce ovarian hyperstimulation syndrome in polycystic ovarian syndrome (POS). One can use clomiphene citrate alone or follow it by low-dose hMG. Alternatively one can use an aromatase inhibitor alone, e.g., letrozol or followed by low-dose gonadotropins.

There are other options. One can perform in vitro maturation (only applies to a few experienced centers). Another option is to freeze all the embryos and defer transfer to a later cycle (pregnancy worsens OHSS).

There are even more ways to reduce risk of ovarian hyperstimulation syndrome in POS. One can add bromocryptine or cabergoline near the time of follicular maturation and continue it in the luteal phase in the hope of inhibiting vascular endothelial growth factor (VEGF) receptor [32]. Some have tried IV albumin but it is probably not effective despite early positive reports. Another way to reduce the risk of ovarian hyperstimulation syndrome is to use sympathomimetic amines, e.g., dextroamphetamine sulfate (diminishes vascular permeability – very effective but not well known) [33].

There are more ways to reduce the risk of ovarian hyperstimulation syndrome in POS hyper-responders. One can continue the GnRH agonist or GnRH antagonist into the luteal phase for at least a week after retrieval (especially in cycles where all embryos are cryopreserved) or one can pretreat with two to three months of oral contraceptives to lower androgens or one can pretreat with metformin to restore down regulated insulin receptors and thus lower androgens.

Finally for the women with POS who are oligovulatory instead of anovulatory one can wait until a dominant follicle emerges as established by careful monitoring without gonadotropin and then use mild ovarian stimulation.

Sometimes IVF-ET is used as a backup for women with increased androgens and polycystic ovaries who do not need IVF-ET per se for tubal damage, male factor problems, luteinized unruptured follicle syndrome or unexplained infertility but merely because they fail to respond to conventional ovulation induction with either clomiphene citrate or conventional dosages of gonadotropins. Though drugs, e.g., metformin can restore down-regulated insulin receptors occasionally work after three months of treatment frequently they fail or the patient is unwilling to wait so long with no guarantee.

Another option for this group of patients to avoid higher dosage gonadotropin (using a high LH to FSH ratio but still risking severe ovarian hyperstimulation syndrome) and thus avoiding IVF-ET.together is to try to reduce the adverse effects of the androgens. Increased androgens are responsible for the increase in preantral follicles developing into the antral stage where they can be stimulated to form mature follicles containing metaphase II oocytes but is also responsible for follicular atresia in the presence of a normal amount of FSH stimulation. In 1977 we showed that using a low-dose of glucocorticoids before bedtime which will not only reduce the inhibitors of adrenal androgens but also ovarian androgens and can allow ovulation to clomiphene citrate in lower dosage even in women who failed to ovulate with higher dosages [34].

Not only is free testosterone elevated in POS but so is dihydrotestosterone (DHT) [35]. The conversion to DHT could be blocked by adding a 5 alpha reductase inhibitor, e.g., finasteride prior to ovulation but this would only be effective if DHT plays a role in inhibiting folliculogenesis. Indeed a recent a study has found that the use of finasteride 5 mg from day 1 of the cycle until the injection of human chorionic gonadotropin can help some women who have previously failed to ovulate with conventional lower dosage gonadotropin to now respond [35].

Of course the use of these anti-androgens could also be used in women who hyper-respond and who need IVF-ET to respond to a mild ovarian stimulation protocol. It would be interesting to see if anti-androgens could also help to reduce the hyper-response that some women with POS have even when given low-dose stimulation.

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