Advantages of using a lower vs higher dosage of gonadotropins for follicular maturation including cycles of in vitro fertilization-embryo transfer

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Summary

Purpose: To demonstrate the benefits of using lower dosage FSH stimulation for follicular maturation in in vitro fertilization (IVF) cycles and in non-IVF cycles. *Methods:* Several studies are evaluated in which either high or lower dosage gonadotropins were used in IVF and non-IVF cycles. The patient population were women either with diminished or normal ovarian egg reserve. *Results:* Very poor pregnancy rates were found with high dosage gonadotropins when there was diminished egg reserve. In contrast pregnancy results per transfer were comparable to women with normal egg reserve when low dose gonadotropin regimens were used. *Conclusions:* Low dose gonadotropin regimens have the benefit of reducing costs and risks of ovarian hyperstimulation without reducing efficacy and in some cases actually increasing pregnancy rates.

Key words: Minimal stimulation; FSH; Ovarian reserve; Controlled ovarian hyperstimulation.

Introduction

As a woman ages there becomes a paucity of ovarian follicles [1]. It is well known that women aged 45 and over have markedly reduced fecundity approaching zero [2]. Thus even if women aged 45 or older are clearly ovulatory their egg quality is so poor that even achieving a pregnancy is quite rare, i.e., it is not easy to conceive but even then there is a high rate of miscarriage related to chromosome abnormalities [1].

There is evidence that one of the main reasons why the eggs from women of an older reproductive age do not result in pregnancies is related to a natural selection process where the better eggs are recruited at a younger age leaving eggs for the reproductively older women that have markedly lower quality oocytes [3]. One theory is that a mitochondrial factor that allows follicles to progress to antral stage is also responsible for inhibition of apoptosis of the cells in a given embryo beyond blastocyst stage [3]. Thus the remaining eggs in a woman of advanced reproductive age have less of this apoptosis inhibiting factor because if there had been more of this factor present it would not have taken so many years for these follicles to advance to the antral state.

When women are of advanced reproductive age they have diminished egg reserve and thus diminished number of antral follicles leading to diminished secretion of inhibin B which allows higher levels of day 3 serum FSH. Therefore if younger women have an increased day 3 serum FSH level frequently one makes the assumption that the ovarian state is similar to women of more advanced reproductive age, i.e., decreased number of follicles and it is also assumed that the eggs have poor quality.

Support for this concept was provided by publications in the late 1980s from some of the top in vitro fertilization (IVF) centers of the world demonstrating low numbers of eggs retrieved and very poor pregnancy rates following embryo transfer (ET) in women with increased day 3 serum FSH levels [4-7]. There has been much improvement in pregnancy prognosis following IVF-ET in the modern IVF era related in part to improved embryo culture media and transfer techniques. However even in the modern era some of the world's finest IVF centers report extremely poor results [8, 9]. In fact one of these IVF centers reported no live pregnancies following the transfer of the usual number of embryos with good morphology in women with diminished egg reserve [9]. Not only did all these reports use traditional controlled ovarian hyperstimulation, but they even used higher dosages of exogenous FSH to try to develop more dominant follicles [4-9].

Reports from multiple IVF centers around the world (including our own IVF center) to national and international reporting agencies all claim extremely rare successful pregnancies in women age ≥ 45 even those with normal FSH levels. Thus the very poor pregnancy rates reported by these world renowned IVF centers using traditional or even higher dosage controlled ovarian hyperstimulation (COH) regimens would certainly seem to support the concept that younger women with diminished egg reserve have an acceleration of the normal atresia process leaving them with only poor quality oocytes.

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However, if this is true it is difficult to explain how a group of women with hypergonadotropic amenorrhea and estrogen deficiency for a minimum of one year achieved a pregnancy rate of 28% (19/68) in those who ovulated and a live rate of 11.7% per ovulation cycle without any assisted reproductive procedure (ART) using a technique of gonadotropin suppression with ethinyl estradiol with low dose gonadtoropin therapy in some but not all cases [10]. The concept that these eggs from women with diminished egg reserve are of poor quality was also brought into the question by a study of euestrogenic women age ≤ 39 with a mean serum FSH of 18.9 mIU/ml who without ART achieved a clinical and ongoing six-month pregnancy rate of 46.1% and 34.6%, respectively [11]. Successful pregnancies have not only been achieved without ART in menstruating women with serum FSH levels > 100 mIU/ml [12], but successful pregnancies have been achieved in a woman in apparent menopause with serum FSH levels of 164 mIU/ml [13], and even women in apparent menopause with ovaries appearing as streaked gonads [14, 15]. A successful pregnancy was even achieved by merely lowering the elevated FSH and restoring sensitivity to endogenous FSH in a 40-year-old woman in apparent menopause with several years of amenorrhea and estrogen deficiency with a documented serum FSH of 124 mIU/ml (but a claimed level of 180 mIU/ml) who failed to conceive despite four previous transfers of fresh embryos derived from donor oocytes [16].

One theoretical explanation of how could pregnancies be achieved naturally at reasonable rates in younger women up to age 42 with diminished egg reserve [10-16] but yet not with IVF-ET [4-9] could be that embryos derived from a diminished egg reserve for some reason cannot do without some factor provided to them by traversing the fallopian tubes. However, successful pregnancies have been recorded in women in apparent menopause with tubal factor who did achieve a pregnancy through inducing ovulation by restoring sensitivity of some of the few remaining follicles with lowering of the elevated serum FSH levels [17, 18]. One woman required a low dose of gonadotropins [17] but the other one was completely natural, i.e., without any stimulation with exogenous gonadotropins [18]. Furthermore, one woman with an elevated day 3 serum FSH who needed IVF because of male factor and was still menstruating achieved three live deliveries out of four IVF-ET cycles over an 8-year time span [19].

Even in the old era of IVF when pregnancy rates were not nearly as high as in the modern IVF era a 15% (6 of 40) pregnancy rate per cycle was recorded for women with serum FSH levels > 18 mIU/ml [20]. In the early part of the improved IVF era from 1997 to 1999 a report showed for women aged ≤ 38 with a day 3 serum FSH > 12 mIU/ml a clinical pregnancy rate of 28.6% (4/14) and an ongoing pregnancy rate past the first trimester of 21.4% per transfer [21]. These results were compared to 156 women of the same age group and with serum FSH ≤ 12 mIU/ml and the pregnancy rate was 32.0% (50/156) per cycle and an ongoing pregnancy rate of 27.6% [21].

Recently a study evaluated women who had a markedly decreased egg reserve [22]. The actual purpose of the study was to determine the relative effect of blastomere number and fragmentation indices of day 3 embryos on pregnancy and implantation rates. Thus the study consisted of women who had only one embryo to transfer and thus de-selection was eliminated [22]. Women with embryos with at least six blastomeres (which represented 65% of the transfers) had a clinical pregnancy rate per transfer of approximately 40% with a 3.8% and 9.5% pregnancy rate, respectively, for 4- and 5-cell embryos [22]. The live delivery rate with single embryo transfer of a 6-8 cell embryo on day 3 was 31.7% [22].

The study group mentioned above used as study subjects women with far less egg reserve than the recent study by Roberts *et al*. in which only those with reasonable response as far as number of mature follicles despite the high serum FSH were included [9, 22]. Many controlled ovarian hyperstimulation regimens for women with normal egg reserve began on day 2 or 3 with at least 225 mIU/ml FSH and frequently 300 mIU/ml. Most IVF centers when attempting to stimulate a woman with diminished egg reserve will increase the starting dosage of FSH hoping to get more follicles. Women with the least egg reserve will usually fail to respond to high dosage gonadotropins and their cycles are cancelled. Thus the reports are generally only in those women with greater egg reserve who demonstrate a response sufficient to obtain possibly a minimum of five oocytes [4-9].

The principal of trying to establish ovulation in a woman in apparent menopause is based on the assumption that there are some antral follicles still present but that they have acquired a resistance to exogenous and endogenous gonadotropins because the chronically high level of serum FSH causes down regulation of the FSH receptor. The theory continues that lowering the serum FSH by exogenous estrogen can allow restoration of these down-regulated FSH receptors leading to the development of a dominant follicle by stimulation with endogenous and/or exogenous gonadotropin [13-19].

It could be argued that maybe estrogen directly improves the sensitivity of the follicles to FSH without the need to suppress endogenous FSH. However, against this theory is the fact that ovulation induction in hypergonadotropic amenorrhea can also be achieved by lowering the elevated serum FSH with either gonadotropin releasing hormone (GnRH) agonists or antagonists [10, 23, 24].

If this theory is correct then it would seem possible that by using a high dosage of exogenous FSH with its slow clearance or using clomiphene citrate which would cause an exaggerated rise in endogenous FSH that a paradoxical effect with a lower number of follicles stimulated may be found because the elevated serum FSH could down-regulate FSH receptors in granulosa theca cells. In fact, it has been shown that by causing an exaggerated rise in endogenous FSH by clomiphene citrate in a woman with diminished ovarian reserve a reversible iatrogenic menopausal state could occur [25].

Gonadotropins are expensive. Not only did our center adopt a policy to lower the dosage of gonadotropins to prevent the occasional paradoxical negative response, but the dosage was reduced to save the couple money since experience showed no better response with higher dosages of gonadotropins. The general philosophy was to allow the elevated endogenous gonadotropins to drive follicular maturation and possibly add a small dosage of exogenous FSH once the FSH has been suppressed into the normal range by the rising endogenous estradiol. In cases where the FSH remains elevated no exogenous FSH is given as long as the follicle(s) is (are) progressing. If the serum FSH remains elevated and there is failure of the serum estradiol to rise then ethinyl estradiol (20 μg per day) is started to lower the elevated FSH and hopefully restore sensitivity of follicles. How soon the serum FSH and estradiol is repeated is dependent on whether any antral follicles are seen on ultrasound (US). Thus repeat US could be performed in a few days if an antral follicle was found or possibly not for a couple of weeks if none were seen.

In women with less severity of their degree of diminished oocyte reserve a low dosage of FSH (75-150 IU) may be started as early as day 5-7 to try to attain multiple dominant follicles. Similar to high-dosage protocols a GnRH antagonist could be added when a follicle of about 14 mm is attained. Usually an additional 75 IU of FSH is added when the GnRH antagonist is started. Generally the highest dosage of FSH used on a daily basis is 225 IU, usually when the GnRH antagonist is added.

The low-dose gonadotropin stimulation protocols have been divided into three types: natural (usually for the least egg reserve cases) where no gonadotropins are used, natural with a boost of exogenous FSH where FSH is injected in small dosages usually in the late follicular phase, and minimal FSH stimulation where low dosage FSH is used earlier in the follicular phase and is used for women with less oocyte depletion [22]. Any one of these protocols may be used with ethinyl estradiol, and protocols using gonadotropins may use GnRH antagonists in the late follicular phase.

Sometimes follicular maturation is accelerated because of the elevated serum FSH. There are data showing that a short follicular phase may be associated with lower pregnancy rates [26]. Other data show that lengthening the follicular phase with ethinyl estradiol can improve pregnancy rates [27, 28]. Thus sometimes in women with short follicular phases not only is ethinyl estradiol added from the early follicular phase but natural estradiol is added during the luteal phase to help suppress the FSH levels during the luteal phase. Sometimes leuprolide acetate can be used beginning in mid-luteal phase and then it is stopped after about ten days to try to help lower the day 3 serum FSH and help delay follicular maturation. These techniques can also prevent premature luteinization by inhibiting a premature LH surge [29].

Though the study of the effect of morphology of day 3 embryos on outcome following single embryo transfer in women age < 40 showed the lowest pregnancy rate per retrieval, using the natural protocol it should be noted that this group was the closest or even appeared to be in actual menopause. Only 31.6% of the oocyte retrievals led to embryo transfers but the clinical and live delivered pregnancy rates were 21.1% and 15.8%, respectively [22]. The natural protocol with a boost of FSH resulted in 86.2% of oocyte retrievals leading to embryo transfers and the clinical and live delivered pregnancy rates were 28.8% and 23.7%, respectively [22]. The minimal FSH stimulation protocol found that 50% of the oocyte retrievals resulted in embryo transfer with a clinical and live delivered pregnancy rate of 29.4% and 23.5%, respectively [22].

If one better evaluates responders who could transfer three embryos in younger women aged ≤ 35 despite diminished egg reserve as manifested by day 3 serum FSH ≥ 12 mIU/ml, a clinical pregnancy rate of 66% (33/50) was achieved using low-dose FSH stimulation and a live delivered pregnancy rate of 58% with an implantation rate of 34% (51/150) [30]. It should be recalled that only this type of better responder despite elevated serum FSH was evaluated in the studies concluding atrocious pregnancy rates using traditional or higher dosages of FSH in their COH regimen in women of any age with elevated serum FSH [9].

Thus the data showing such good pregnancy rates with low-dose gonadotropin protocols suggest that the majority of younger women with diminished egg reserve did not go through an acceleration of the natural atresia process, leaving them with fewer and inferior oocytes, but instead favor some destructive process resulting in fewer remaining oocytes but the ones spared have the same quality as their age peers [30]. If this conclusion is correct one may wonder why some of the best IVF centers in the world find such poor pregnancy rates even in the modern IVF era [8, 9].

There is a strong possibility that it is the use of a lower dosage of gonadotropins that is responsible for the much higher pregnancy rates in these women with diminished egg reserve. A minority of women with normal day 3 serum FSH, and thus normal oocyte reserve, will even demonstrate poor pregnancy rates when hyperstimulated with high-dose gonadotropins [31-35].

One woman with polycystic ovaries and amenorrhea failed to conceive after six years of corrected ovulatory cycles with follicle maturing drugs and who also failed to conceive after ten cycles of in vitro fertilization where 92 embryos had been transferred, was successful the first time that a frozen embryo transfer was attempted on estrogen/progesterone replacement without follicle maturing drugs [36]. In fact following delivery she started to ovulate spontaneously and with one cycle of luteal phase progesterone support she conceived again at age 40 and delivered another healthy baby [37]. There are data suggesting that the adverse effect of follicle maturing drugs in women with normal ovarian reserve may be related to an endometrial factor allowing advancement of the implantation window with possible premature trophoblast invasion [33, 34].

It behooves the treating physician to always seek the least risky, least expensive and most effective therapy to treat

a given illness or condition. Gonadotropins are not only very expensive but the use of high dosage can result in non-IVF cycles with the dreaded complications of ovarian hyperstimulation syndrome and/or the complications of multiple births both to the mother and to the preterm babies. Furthermore, as mentioned sometimes they can actually cause iatrogenic infertility [35]. Ovarian hyperstimulation syndrome is also a risk with IVF-ET, and although theoretically the risk of multiple births could be controlled by limiting the number of embryos transferred, in reality, this does not happen because the cost is so high the couple wants to risk multiple births so as not to pay high prices also for frozen embryo transfer. In fact some IVF centers do poorly with frozen embryo transfers and keep pushing for fresh IVF cycles as illustrated by the women described who was a hyper-responder who went through ten fresh IVF-ET cycles in another facility before we purposely froze all of her embryos [36]. Also the competition for "clients" and the public record of statistics motivates the treating physician to frequently recommend the transfer of more embryos to hopefully keep the pregnancy rates higher.

By starting later in the follicular phase and with a lower dosage of gonadotropins an excess of stimulated follicles can be prevented. This results in a marked decreased risk of OHSS. By allowing the dominant follicle to emerge before raising the serum FSH levels one can help allow the goal of monofollicular ovulation or at least to allow less eggs in certain conditions, e.g., anovulation related to polycystic ovarian syndrome where single follicular recruitment is difficult. This technique markedly reduces the cost of gonadotropins. Furthermore with fewer eggs, and thus fewer embryos, there should be a decrease in the amount of time that an embryologist has to spend per patient, thus saving money for the IVF center. This financial saving should be passed onto the infertile couple. In fact, we reduce the charge for IVF to 50% of the high-dosage COH IVF cycle price for minimal stimulation cycles.

There is constantly a quest to improve the chance of success per IVF-ET cycles. Recent research is directed to finding immune markers for the best embryo, e.g., HLA-G or metabolic by products (metabolomics) to identify the best embryos to transfer [38, 39]. Each step used to increase the success of selecting the best embryo, e.g., pre-implantation genetic diagnosis, will cause an already very expensive procedure to become even more expensive. However, starting the gonadotropins later and by using a smaller dosage of gonadotropins, allows good pregnancy rates with less risk and cost even in women who could make multiple follicles. A recent report of pregnancy outcome in women with serum FSH < 12 mIU/ml using lower dose FSH protocols found in women age ≤ 35 (n-149) a clinical pregnancy rate per transfer of 48.3%, a delivered pregnancy rate of 45.6% and an implantation rate of 31.3% [40]. For women aged 36-39 (n=117) these values were 31.6%, 29.1%, and 22.1% and for women age 40-42 these rates were 21.6%, 14.4%, and 14.0% [40]. For women ≥ 43 (n = 119) these rates were 5.9%, 3.4%, and 3.9% [40].

Interestingly the pregnancy rates for women aged ≤ 35 with serum FSH > 12 were not much different from those women with normal serum FSH, i.e., a clinical and live delivered pregnancy rate of 47.4% (45/95) and 41.0%. For women ages 36-39 these rates were 30.7% and 25.9% [40]. These data not only support the concept that low-dose gonadotropin stimulation protocols for IVF-ET are effective both for women with and without diminished egg reserve but support the concept that eggs from women with diminished egg reserve have reasonable potential to result in successful pregnancies at least when low dosage gonadotropins are used for controlled ovarian hyperstimulation.

In the aforementioned study of IVF-ET in younger women with elevated serum FSH the clinical pregnancy rates and delivered pregnancy rates were 43.7% and 39.7% for women with serum FSH ≤ 10 mIU/ml vs 52.2% and 43.5% for women with serum FSH 11-12 mIU/ml, vs 54.5% and 54.5% for ranges 13-14 and 50% and 50% for ranges 15-16 mIU/ml. Only with serum FSH levels ≥ 17 was there a reduction in pregnancy rates (33.3% and 11.1%) [40].

There are two main reasons why women with normal day 3 serum FSH levels choose low dosage gonadotropin protocols: to save money and because they have failed to conceive despite several high dosage COH regimens. One possible reason for the failure may have been related to an adverse effect of COH on implantation. In contrast, for the various reasons stated in this editorial, women with increased serum FSH are advised to use a low-dose gonadotropin regimen from the start. Thus possibly pregnancy rates per transfer in those with normal FSH levels could be somewhat biased on the low side because there may be some of them who have failed previous IVF cycles not because of the adverse effect of COH but possibly other occult tubal, oocyte, sperm, endometrial or uterine factors.

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