Expert Reviews

Optimizing IVF outcomes for women with diminished oocyte reserve

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Women with diminished oocyte reserve do not have very poor oocyte quality similar to women of advanced reproductive age. The very poor pregnancy rates found in many studies of IVF-ET in this population seems to be related to the use of high-dosage FSH stimulation. The presence of significant elevated FSH levels leave many women more prone to FSH receptor downregulation. The best 'hypothesis' to fit the poor success rate found with high FSH stimulation is that FSH receptor downregulation leads to an insufficient production of a factor needed to prevent non-disjunction of chromosomes, leading to the creation of embryos with a high percentage of aneuploidy. Mild stimulation, to a reasonable degree obviates the problem with FSH receptors and results in the production of live healthy babies.

Keywords: aneuploidy • conventional/high dosage FSH stimulation • dehydroepiandrosterone sulfate • diminished oocyte reserve • ethinyl estradiol • FSH receptors • luteal phase progesterone therapy • mild FSH stimulation • reproductive aging

Though initially, natural cycles were used for *in vitro* fertilization-embryo transfer (IVF-ET), it soon became clear that improved pregnancy rates and a better chance of obtaining oocytes would be accomplished by the creation of many dominant follicles by controlled ovarian stimulation (COH) [1–2]. The pervading thought was that the creation of multiple embryos markedly improved the chance of a successful pregnancy following IVF-ET, not only for the oocyte retrieval cycle with the fresh ET, but for the future with the advent of cryopreservation. Thus, one disadvantage for women with diminished oocyte reserve would be less total number of embryos obtained from a given IVF cycle. However, it soon became clear that not only did women with diminished oocyte reserve create less embryos, but these embryos seemed to be of markedly inferior quality, leading to extremely poor pregnancy rates following ET, even when performed by some of the world's leading IVF centers [3–6]. Thus, the general conclusion was that these oocytes, from women with evidence of diminished ovarian reserve, even when obtained from younger women, have the same poor quality as women of advanced reproductive age with a similar degree of oocyte depletion [3–6].

This concept of poor oocyte quality besides quantity has been maintained in the past 35 years, and even in the modern era [3–11]. The majority of scientists and clinicians will advise the patients with diminished oocyte reserve that their prognosis is poor. Most even advise their patients to forego IVF-ET with their own oocytes, or for that matter, even avoid attempting to conceive naturally, and proceed to using donor oocytes, donor embryo or adoption. Thus, for years, most IVF centers would obtain a day 3 antral follicle count, serum follicle-stimulating hormone (FSH) and estradiol (E2), and if an increased FSH or E2 or decreased antral follicle count was found, they would cancel proceeding with COH followed by IVF-ET [4–11]. Recently, some IVF-ET centers have switched to inhibin B level or anti-Müllerian hormone (AMH) levels, hoping that low levels of these tests could better detect diminished oocyte reserve than the day 3 FSH so that the IVF center may not 'mistakenly' attempt IVF in a woman with normal day 3 FSH but still find a less than adequate follicular response to COH [12,13]. Sometimes the suggestion to use donor oocytes rather than one's own oocytes stems not from increased day 3 FSH levels but

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from exaggerated rise of FSH from a clomiphene challenge test [14–16].

There are many couples with a clear need for IVF-ET, for example, tubal occlusion, with diminished oocyte reserve whose insurance covers IVF-ET with their own oocytes but not for donor oocytes. Nevertheless, they are frequently refused by many IVF-ET centers to perform IVF-ET with their own oocytes, but encouraged to use donor oocytes. Even when these couples relate their objection for donor oocytes, sometimes even for religious beliefs, they have been refused 'for their own good'.

The purpose of this manuscript is to provide evidence that although the oocyte quality of women with diminished oocyte reserve may be inferior to age peers with normal reserve, the difference is only slight. The manuscript will provide data 'suggesting' that the extremely poor pregnancy rate with diminished oocyte reserve reported in the modern IVF era, even from the top IVF centers, is related to the excessively high dosage of gonadotropins used for COH.

The theory behind not only using conventional high dosages of FSH stimulation but even using supra high dosages of FSH for women with diminished oocyte reserve

Baart *et al.* found that only 38% of the embryos are normal when using conventional high-dosage FSH in women with normal oocyte reserve and they used FISH to evaluate only eight autosomal chromosomes plus the two sex chromosomes [17]. Thus, some embryos could have had trisomy or monosomy of the other autosomal chromosomes, so the percentage of normal embryos may even be less if one would repeat the study using techniques, for example, competitive genomic hybridization or microarray analysis with trophectoderm biopsy of the blastocyst, as is now being initiated by several centers [18].

A study published in *Fertility and Sterility* in 1999 using preimplantation genetic screening (PGD) with FISH analysis found that the embryos in younger women with diminished oocyte reserve who had received conventional high-dosage COH had a very high rate of aneuploidy more akin to women of advanced reproductive age [19]. The authors thus suggested that this high rate of aneuploidy was the explanation for the very poor IVF outcome previously reported [3–8,11]. This had led to the widespread belief by many physicians that oocytes from women with diminished oocyte reserve are of poor quality.

Thus, the tenet behind using not only conventional but supra high FSH dosages is to try to make as many oocytes as possible to maybe allow one normal embryo to develop. Clinicians with this thought process maybe thinking that there is normally no method for the body to select the best oocyte, but instead the thought is that the odds of the dominant follicle containing a normal oocyte is equal to the percentage of oocytes in a given cohort that are normal. There are varying opinions as to how many dominant follicles constitute an adequate response but it is clear that many centers will cancel the retrieval if a certain critical number is not achieved. It seems that the majority of IVF centers will forego the oocyte retrieval if there are less than five follicles.

Since the publication of the Nasseri *et al.* article, there have been many changes introduced for women undergoing IVF-ET, which has allowed a tremendous increase in pregnancy rates. Thus, the treating physician could consider that the embryo is heartier, and now in the modern era, transfer of these embryos from women with diminished oocyte reserve could result in better pregnancy rates. However, a manuscript published in the modern era by a world renowned IVF center showed that if a woman ever once in her life had a day 3 FSH level >20 mIU/ml (using a Leico assay which is normally equal to 15 MIU/ml by ELISA), their live delivered pregnancy rate was zero [11]. Thus, they strongly recommended to the readers not even to try IVF-ET with this degree of diminished oocyte reserve but to proceed directly to donor oocyte programs [11].

One of the articles that will be discussed subsequently is one using a modified natural cycle for women with diminished oocyte reserve from another of the world's leading IVF centers [20]. Interestingly, they state in the materials and methods section "Patients included should have a regular menstrual cycle (duration 21–35 days), FSH levels >12 IU/l on day 3 of the cycle and one or more failed IVF cycles in which 5 or fewer cumulus oocyte complexes (COCs) were retrieved using a high gonadotropin dose. Given their bad prognosis, all patients were offered oocyte donation. Patients included in the current study insisted on continuing IVF attempts in order to become parents using their own genetic material or had ethical objections to oocyte donation" [20].

Author's theory behind using mild stimulation for women with diminished oocyte reserve

The main concept for using mild, not conventional or supra-high-dose FSH regimen, is that the oocytes retrieved from women with diminished oocyte reserve treated with conventional FSH stimulation do have oocytes of poor quality comparable with their 'FSH' peers of advanced maternal age with high rates of aneuploidy, not because of an intrinsic defect, but as a result of the high-dosage FSH regimen. As will be shown in a subsequent section, the use of mild stimulation allows pregnancy rates comparable with or only slightly lower than age peers with normal FSH [21].

The pulsatile secretion of the gonadotropin-releasing hormone (GnRH) causes a pulsatile secretion of LH and FSH. There is some supporting evidence that the pulsatility inhibits downregulation and promotes upregulation of FSH and LH receptors in the pituitary [22]. With negative feedback from rising E2 from mid-follicular phase I follicle emerges from a large group of antral follicles as the one dominant follicle. There is a possibility that some mechanism exists that may allow a better chance for a follicle with a normal oocyte to develop than completely random chance (possibly the one with the most upregulated FSH receptors; the author is not aware of any definite proof to support this concept).

This author has hypothesized the following possible mechanism to explain why (as will be subsequently shown) women with diminished oocyte reserve have live delivered pregnancy rates comparable with their age peers with normal oocyte reserve when mild FSH stimulation is used but very poor pregnancy rates when high-dosage COH regimens are used. The author's speculation is that there may be an FSH-dependent factor that helps to prevent non-disjunction of chromosomes. The hypothesis continues that with high-dosage FSH, the rise in serum FSH downregulates the FSH receptor for this factor that inhibits non-disjunction leading to a reduced percentage of chromosomally normal embryos similar to women of advanced reproductive age. By contrast, mild stimulation allows the creation of a higher percentage of embryos without aneuploidy, just slightly lower than their age peers with normal oocyte reserve. It would be interesting to evaluate the percentage of embryos formed using mild ovarian hyperstimulation by pre-implantation screening in younger women with diminished oocyte reserve and compare the results with the study by Nasseri *et al.* with conventional stimulation but there have not been any such studies to date that the author could find. Without such a study this concept should be considered merely theory.

If one can provide evidence that using mild stimulation could produce pregnancy rates comparable with women with normal oocyte reserve, this would support the argument that the low pregnancy rate published by Roberts *et al.*, and the others, was iatrogenic related to high-dosage FSH, especially with the demonstration of no live pregnancies even in a small series of women with constantly increased serum FSH levels by one of the world's most successful IVF centers [11]. Evidence that seemingly supported the theory that the etiology for these low pregnancy rates are indeed from poor oocyte quality rather than the high FSH dosage was provided by the study by Kolibianakis *et al.* from another world renowned IVF center [20]. The title of their article is 'Modified natural cycle for IVF does not offer a realistic chance of parenthood in poor responders with high day 3 FSH levels as a last resort prior to oocyte donation'. There were no ongoing pregnancies in 78 modified natural cycles [20].

One criticism of the Kolibianakis study is that hCG was given to trigger advancement of meiosis when the follicular maturation reached >16 mm without measuring the serum estradiol [20]. Thus, it is quite possible that the oocytes were not quite mature, and therefore, the idea of an iatrogenic etiology for poor pregnancy rates related to meiosis errors from high-dosage FSH remains an option.

As mentioned there are studies that support the concept that the oocytes from women with diminished oocyte reserve are indeed closer in quality to their age peers and that it is the COH protocols leading to poor pregnancy rates. One study using an ELISA method for day 3 serum FSH evaluated women who had such markedly diminished oocyte reserve that they could only make one embryo [23]. Many IVF centers will only transfer embryos on day 3 that have 6–8 blastomeres. This study transferred all embryos of >4 blastomeres, irrespective of fragmentation status. With close adherence to the tenets of mild stimulation (which will be described subsequently), the clinical pregnancy rates in women <age 39.9 with 6, 7 or 8 blastomeres irrespective of fragmentation with mean serum FSH levels of 25.3, 23.3 and 18 mIU/ml showed clinical pregnancy rates of 38, 40 and 42.4%, respectively. Even more importantly, the live delivered pregnancy rate despite only 1 embryo transferred was 31.0, 25.0 and 36.4%. Even the 35% who had only a 4 or 5 cell embryo had a live delivered pregnancy rate of 3.8 and 9.5%, respectively [23].

In this study of IVF-ET in women with such diminished oocyte reserve that only a single embryo was produced combining all transfers, the clinical and live delivered pregnancy rates were 27.8 and 24.1%, respectively [23]. However, some retrievals do not result in pregnancies because of failing to obtain an oocyte, failure to fertilize or failure of the embryos to cleave until day 3. For this study, the clinical and live delivered pregnancy rates per retrieval were 14.8 and 12.8%, respectively [23]. However, most of these women were markedly depleted of oocytes and were either close to or appeared to be in menopause.

To further explore to what degree oocytes from women with diminished oocyte reserve compare qualitatively with oocytes from women with normal reserve, a matched controlled study was performed in non-IVF-ET cycles. Infertile women age <37 with day 3 serum FSH >15 mIU/ml were matched with women whose serum FSH was <10 mIU/ml [24]. The clinical pregnancy rates within a maximum of 6 months of correcting other fertility factors, for example, ovulation disorders and mild male factor, were 41.6% for those with diminished oocyte reserve versus 70.8% with normal reserve [24]. The live delivered pregnancy rates were 33.8 versus 62.5% [24]. Thus, it is possible that oocytes from women with very severe oocyte depletion are at least 50% as good as women with normal oocyte reserve. However, confounding variables in the diminished oocyte reserve group could be a higher frequency of a short follicular phase with the high FSH speeding up follicular maturation and thus leading to less progesterone receptors in the endometrium from less estrogen exposure, a higher rate of premature luteinization because of starting out with increased serum LH, possible higher percentage of not attaining a mature follicle despite apparent ovulation and possibly an increased need of progesterone supplementation in the luteal phase [25–31].

Evaluation & treatment of women in apparent premature menopause provides very good insight into oocyte quality in the oocyte depletion state

It has been estimated that in the general population the decline in fecundity accelerates between 35 and 40 years and approaches zero by age 45 [32]. Diminished oocyte quality with aging could be related to aging mitochondria leading to a high rate of chromosomal non-disjunction. Successful live deliveries have been recorded in some rare cases of women >45 but most

have been in grand multiparas [33]. However, there appear to be rare families of Orthodox Jewish couples and Bedouins studied by Laufer *et al.*, where normal fecundity is seen in very advanced age even >50 with their own oocytes, even in women who deferred child birth until the very late reproductive years [33]. There seems to be only one report in the registry of the Society of Assisted Reproductive Technology (SART) in which a live pregnancy was recorded from a women aged 47 at the time of oocyte retrieval. Some clinicians believe that younger women with marked oocyte depletion have gone through an accelerated process of the orderly use of the best oocytes first, so that the remaining oocytes have the quality of women of very advanced age. However, these data more fit the concept that some noxious factor may damage portions of the ovary but the part that has been spared has the same proportion of normal and abnormal oocytes as age peers with normal reserve just less of them. The authors further believe that these oocytes of reasonably good quality may be adversely affected by increasing serum FSH and downregulating FSH receptors.

More evidence supporting reasonable equality of oocytes despite severe depletion is the demonstration of normal babies from women with normal karyotypes with such oocyte depletion that their ovaries appear as streaked gonads by using techniques of restoration of FSH receptors in granulosa-theca cells with resulting increased sensitivity to endogenous or exogenous gonadotropins followed by ovulation and successful pregnancies [34–36]. At the 2013 Pacific Coast Reproductive Society, we presented a case of a 21-year-old young lady with secondary amenorrhea, hypergonadism and estrogen deficiency who had ovulation induction just lowering her FSH with ethinyl estradiol and we cryopreserved her oocytes. Her karyotpe was 45X.

The principles and methodology for inducing ovulation in women in apparent premature menopause will be discussed in the next section [36]. However, the fact that in a series of 100 consecutive women with amenorrhea and estrogen deficiency for at least 1 year with a mean serum FSH >35 mIU/ml and a mean serum E2 <25 pg/ml with failure to induce menses following treatment with medroxyprogesterone acetate, women could achieve a clinical pregnancy in 28% in the 68 ovulators helps favor the concept that the oocytes of younger women with marked oocyte depletion probably do not have aged mitochondria [37]. This study showed that successful pregnancies were more common in women in apparent menopause with the youngest age [37].

One could argue that the 50% miscarriage rate could be related to a tendency for non-disjunction of chromosomes, suggesting that possibly the quality of the oocytes is somewhere in between their age peers and their oocyte reserve peers of a more advanced age [37]. However, this study was published in 1990, and the dosage of progesterone vaginal suppositories was only 25 mg twice daily versus 200 mg twice daily or other potent vaginal or intramuscular preparations used today [38].

Restoration of downregulated FSH receptors leads to follicular maturation & ovulation & live pregnancies in women in apparent ovarian failure

The theory behind inducing ovulation in women with menopause is that if the FSH receptor concentration drops below a certain threshold, not only will there be not enough enzymes induced to allow separation of chromosomes adequately, but below a certain critical point, antral follicles will be thwarted from progressing.

The original technique placed women on conjugated estrogen, waited until the FSH was suppressed to a normal range, then added human menopausal gonadotropin. Ovulation occurred in three of five women and two live deliveries resulted from two ovulators in this group [39]. Later, it was modified so that instead of conjugated estrogens, the women were treated with ethinyl estradiol to lower the serum FSH [40]. The advantage of ethinyl estradiol over other estrogens is that it does not measure in the ELISA method for evaluating serum estradiol, and thus the measured estradiol is entirely coming from the recruited follicle [40]. This allows accurate determination of follicular maturation. Instead of waiting until the FSH was suppressed, the new modified technique watched for a rise in estradiol even if serum FSH is still elevated and would merely boost with a small dosage of FSH when the FSH had decreased toward normal by the rising endogenous estradiol [40]. Ethinyl estradiol, though part of most birth control pills, is not available commercially and thus must be compounded. Though occasionally a pregnancy can be achieved using an oral contraceptive, in most cases the endometrial advancement by the progestin will inhibit pregnancy [41].

In the aforementioned study of 100 consecutive women with hypergonadotropic amenorrhea, 91 were treated with ethinyl estradiol and then human menopausal gonadotropins [37]. There were 61 ovulations in 311 attempts (16% per attempt) [37]. This number is much higher than would be expected by fortuitous ovulation. For the 21 women who became pregnant, the average time from diagnosis to treatment was 2.2 years, whereas for the 65 women who did not conceive (where this interval was known), the average time from diagnosis to treatment was 4.8 years. The average FSH for those who ovulated was 70.3 mIU/ml and was 66.5 mIU/ml for those who never ovulated [37].

Nine of the 100 women used the gonadotropin-releasing hormone agonist (GnRHa) leuprolide acetate to lower the FSH [37]. Ovulation occurred in a similar percentage of attempted cycles (7 of 43, 16.2%) but there were no pregnancies in this small group [37,42]. The GnRH antagonists can also be used to induce ovulation despite menopause [43].

Some may argue that without controls, it is possible that these ovulations were fortuitous and unrelated to treatment. To reiterate, it is highly unlikely that spontaneous ovulation would occur at this frequency. Some case reports strengthen the argument that it is the technique of lowering FSH and restoring FSH receptors, and thus restoring sensitivity to both endogenous and exogenous gonadotropins, that is operational [44].

A 25-year-old woman had 1 year of amenorrhea and estrogen deficiency. She had three FSH measurements of 144.9, 145.6 and 164.2 mIU/ml. Her ovarian size was only 18 × 11 × 13 mm on the right and 15 × 12 × 17 mm on the left. She was made to ovulate 6 of 10 treatment cycles, taking ethinyl estradiol alone without any gonadotropins. She had a live delivery from cycle 10 [44]. She is an example of not adding exogenous gonadotropins if the FSH is still high but follicular maturation is progressing [44]. Similarly, a 40-year-old woman in apparent ovarian failure whose serum FSH was 123 and 185 mIU/ml was made to ovulate three of four attempts with estrogen therapy and delivered a live baby following natural intercourse and P support. Interestingly, she had previously failed to conceive at another facility, despite four previous donor oocyte cycles at a cost of US$120,000 [45].

Sometimes reversing menopause only requires stopping follicle maturing drugs, which by raising the serum FSH led to downregulation of FSH receptors and thus caused an iatrogenic menopause [46]. This adverse effect of raising serum FSH too high even applies to what may be considered 'mild' stimulation, for example, clomiphene citrate, especially if it is started at a time when the FSH is already elevated [46].

In the early days in the field of reproductive endocrinology, there was a concept that some women only appeared to be in menopause because they had gonadotropin-resistant gonads. However, it is likely that these conditions were related to pseudomenopause caused by elevated levels of biologically inactive FSH secreted by gonadotropinomas [47,48].

This technique of reversing menopause must also take into consideration taking steps to lengthen the follicular phase if too short, block premature luteinization, check oocyte release (and if not releasing, institute measures to help release the oocyte) and use aggressive P supplementation in the luteal phase [49,50–52]. Studies in our clinic have found that elevated FSH in the follicular phase leads to luteal phase defects and that even women with regular menses but elevated day 3 serum FSH have a much better live delivery pregnancy rate if they take supplemental progesterone in the luteal phase rather than follicle maturing drugs [30,31].

Mild stimulation protocols

The basic principle of mild stimulation is to not raise the serum FSH level when it is already elevated and utilize the endogenous FSH when it is able to advance follicular maturation since it appears to be biologically active. Women with diminished oocyte reserve ranged from being in overt menopause to those with regular menses with just a decreased antral follicle count with serum FSH >12 mIU/ml.

Which protocol is used is based on degree of oocyte depletion. As mentioned for those in apparent overt menopause, the lowering of FSH is usually achieved by using ethinyl estradiol (at 20–40 µg/day – starting at 20 and less commonly increasing to 40 µg) and sometimes GnRH agonists or antagonists are used. More frequently, either 200 mg of cetrorelix or ganirelix is given subcutaneous when a follicle approaches 14 mm if IVF is considered, but sometimes it is used to prevent premature luteinization if the LH is beginning to rise with the follicle still immature. Leuprolide acetate is frequently used in the luteal phase if there is a tendency to have a short follicular phase to allow later ovulation in a succeeding cycle. Depending on the number of antral follicles that begin to develop and how low the serum FSH is suppressed, some exogenous FSH may be given usually at 75 IU to no more than 150 IU of FSH. Occasionally, if a GnRH antagonist is used when a follicle of about 14 mm is achieved usually an additional 75 IU of FSH is given when a GnRH antagonist is used.

If the FSH is suppressed below 10 mIU/ml and no rise in serum E2 or follicular advancement by ultrasound is seen then either 75–150 IU of FSH is given or sometimes clomiphene citrate 50 mg × 5 days (if FSH injection is too expensive for the patient). Generally, these drugs are only given if at least one antral follicle is seen on ultrasound.

In women with menses but a short follicular phase, ethinyl estradiol 20 µg is generally given from day 1 to suppress FSH to lengthen the follicular phase. Then it is stopped and endogenous FSH is allowed to rise to mature a dominant follicle(s). Alternatively, exogenous FSH is given in which case ethinyl estradiol may be continued because one does not have to be concerned about too much suppression of endogenous FSH.

For women with regular menses with adequate length of follicular phase FSH 75–150 IU may be added no sooner than day 5 or even as late as day 10–12 allowing the rise in serum E2 to naturally bring down the elevated serum FSH. For hCG to be given the minimum requirement is that there is at least one dominant follicle of at least an 18 mm average diameter with a serum E2 >200 pg/ml. Besides progesterone, oral micronized estradiol (not ethinyl estradiol) is given during the luteal phase at 2–4 mg (estrogen priming for next cycle).

When presenting data in various series all these protocols are lumped together so that the data include completely natural cycles, cycles using ethinyl estradiol alone, a modified natural cycle where a boost of FSH is given in the late follicular phase or mild stimulation at 75–150 IU FSH from days 5 to 8. One article that provides the relative pregnancy rate according to the protocol used (and thus degree of oocyte depletion) has been provided for severe cases providing only one embryo [23].

Sometimes patients cancel cycles and sometimes an oocyte is not retrieved or not fertilized. The study on single embryo transfer and embryo quality provides the information on cancelled cycles, for example, for failure to induce ovulation or spontaneous ovulation or premature luteinization [23].

Newer retrospective studies from our own IVF center

No randomized controlled trials (RCT) evaluating conventional or high-dosage FSH stimulation protocols versus mild stimulation for women with diminished oocyte reserve were found. Retrospective data using mild stimulation for women with diminished ovarian reserve has been published in many abstracts over the years and several publications and editorials. Many of these studies used the same data pool. Instead of

referring to these various abstracts and manuscripts, a new data set including IVF cycles from January 2002 through 31 December 2011 (Table 1) is presented. Though not published as yet, these data were presented at the 2012 American Society of Reproductive Medicine Meeting. Though the data are retrospective, it is the study with the largest power comparing outcome of women with normal oocyte reserve (day 3 FSH <12) versus diminished oocyte reserve (FSH >12 mIU/ml). The category pregnancy rate per retrieval counts a pregnancy if the fresh ET was successful or if it failed, then the frozen ET was successful. This category also lowers the pregnancy rate if no transfer occurred from a given retrieval. The data were also stratified according to age.

In contrast to the aforementioned studies using conventional or high dosage or completely natural IVF cycles, the pregnancy rates, especially in younger women with diminished oocyte reserve using mild FSH stimulation, were quite reasonable. Boosting with very low dosage of FSH in the late follicular phase, and even sometimes completely natural cycles, were employed when the highest levels of FSH were found. The live delivered pregnancy rates were quite reasonable. In fact, the live delivered pregnancy rates per transfer for women aged <39 with diminished oocyte reserve were only 20% less than the group with normal oocyte reserve (Table 1). For women aged >40, the live delivered pregnancy rates per transfer were 50% as good for diminished versus normal oocyte reserve (Table 1).

Table 1 also shows that for women aged <39 when using mild ovarian stimulation, the oocytes are, at best, only slightly more likely to result in aneuploidy as evidenced by comparable miscarriage rates. Only in women aged 40–42 were miscarriage rates 50% higher in the group with diminished oocyte reserve but becomes more comparable again in women aged >43 (Table 1).

Another publication presents the IVF data in a somewhat different way, that is, there is consideration of the impact of the degree of ovarian deficiency as manifested by progressively increasing serum FSH levels [53]. The live delivered pregnancy rates (and miscarriage rates) for the following FSH groups (mIU/ml) <11, 12–14, 15–17 and >17 mIU/ml were 45.1% (11.9%), 42.3% (13.9%), 48.6% (13.3%) and 45.5% (12.8%). For ages 36–39, the comparable values were 33.4% (17.2%), 35.0% (11.4%), 29.8% (7.1%) and 36.6% (22.9%). For ages 40–42, the live delivered pregnancy rate (miscarriage rates) were 23.1% (27.3%), 20.4% (37.3%), 30.0% (36.4%) and 27.7% (30.4%) [53]. Interestingly, the women aged 43–44 still had a reasonable live delivered pregnancy rate when the serum FSH was normal, that is, 24.0% (34.4%). Not until this age group was there a significant negative impact on pregnancy rates by diminished oocyte reserve – 10.0% (75%), 0% (100%) and 8% (75%). To reiterate, all these women were treated according to the low FSH stimulation principles that we have discussed in prior sections. It is not just using any mild stimulation approach but to be careful about not adding FSH when serum FSH is high, using ethinyl estradiol predominantly to restore downregulated FSH receptors if endogenous high levels of FSH are not causing progression of follicular maturation, using ethinyl estradiol or GnRH agonists to prevent premature luteinization, check for oocyte release and aggressively use P in the luteal phase and adjusting the dosage if there appears to be an inadequate effect as judged by sonography [51,52].

These data are retrospective but have the advantage of large numbers (about 5000 cycles). It has potential bias against the group with normal FSH since the majority of that group had already failed to conceive in several previous IVF cycles in other IVF centers or they were refused IVF for other factors, for example, poor endometrial thickness. By contrast, a large majority of women with diminished oocyte reserve were denied IVF elsewhere because of high day 3 serum FSH levels or low AMH levels. Thus, a higher percentage of this group may have had less previous failed IVF cycles. If one would adjust for this confounding variable, one would probably find the normal FSH group to have somewhat better pregnancy results. However, the live delivered pregnancy rates as shown in Table 1 are only slightly less for those with decreased oocyte reserve than the normal oocyte reserve group. For that slight difference many women would prefer to use their own oocytes. If not, 35-year-old women with normal oocyte reserve would choose donor oocytes with women in their early 20s over themselves because of higher pregnancy rates even when oocyte reserve was normal.

There are data that have not been presented or published as yet that may provide more enlightenment. First, it should be recalled that the 1.8 chromosomally normal embryos reaching blastocyst per oocyte retrieval may be somewhat high since Baart *et al.* performed pre-implantation genetic sampling using FISH which only measured 8 autosomal and 2 sex chromosomes of the 24 chromosomes. Possibly if that study were to be performed again today with evaluation of all 24 chromosomes using competitive genomic hybridization or microassay analysis there could be found less than 1.8 normal embryos in women undergoing IVF-ET with normal oocyte reserve [17].

We evaluated over 1400 oocyte retrieval cycles in women with diminished oocyte reserve and evaluated the pregnancy rates per transfer. The pregnancy rate per oocyte harvest (i.e., the pregnancy rate fresh and also including frozen embryo transfer(s)) and the number of live babies born according to four age groups were determined. These data were compared with over 2500 oocyte retrieval cycles in women with normal oocyte reserve using conventional COH. The live pregnancy rate per transfer in women with normal oocyte reserve receiving full stimulation was 45.2% for ages <35 compared with 35% for women of comparable age with diminished oocyte reserve. For ages 36–39 and 40–42, these results were 36 and 24.7% versus 23.3 and 16.7%. Thus, the live pregnancy rate per transfer in women aged <35 was only 20% lower in women with diminished oocyte reserve then age peers with normal reserve and the results were comparable with women just slightly older with normal oocyte reserve in the 36- to 39-year-old category. For women aged 36–39, the pregnancy rates were about a third

Table 1. Delivery rates per retrieval for patients using their own oocytes from 2002 through 2011.

	Without diminished ovarian reserve				With diminished ovarian reserve			
Age	<35	36–39	40–42	>43	<35	36–39	40–42	>43
# Retrievals	1661	1060	784	565	296	480	425	238
# Transfers	2211	1265	860	584	316	502	430	238
# Pregnancies	1211	545	280	75	144	172	92	31
Pregnant per retrieval (+ beta-hCG >100 mIU/ml) (%)	72.9	51.4	35.7	13.3	48.6	35.8	21.6	13.0
Pregnant per transfer (%)	54.8	43.1	32.6	12.8	45.6	34.3	21.4	13.0
Clinical (n)	1086	464	228	54	126	148	71	21
Clinical pregnancy rate per retrieval (%)	**65.4**	**43.8**	**29.1**	**9.6**	**42.6**	**30.8**	**16.7**	**8.8**
Clinical pregnancy rate per transfer (%)	49.1	36.7	26.5	9.2	39.9	29.5	16.5	8.8
# Ectopic (n)	13	6	3	1	5	2	2	1
# Viable (n)	1007	404	184	34	114	122	47	12
Viable/trans (%)	45.5	31.9	21.4	5.8	36.1	24.3	10.9	5.0
Miscarriage	124	92	68	34	16	34	32	11
Miscarriage/clinical pregnancy (%)	11.4	19.8	29.8	63.0	12.7	23.0	45.1	52.4
# Deliveries (n)	962	372	160	20	110	114	39	10
Delivered per retrieval (%)	**57.9**	**35.1**	**20.4**	**3.5**	**37.2**	**23.8**	**9.2**	**4.2**
Delivered per transfer (%)	43.5	29.4	18.6	3.4	34.8	22.7	9.1	4.2
# Embryos transferred (n)	5343	3257	2214	1227	573	946	720	418
Average number of embryos transferred	2.4	2.6	2.6	2.1	1.8	1.9	1.7	1.8
Implantation rate (%)	29.8	20.9	12.9	4.9	28.4	18.5	11.0	6.0

lower for the group with diminished oocyte reserve and these data were comparable with the next age group at 40–42.

Comparing the pregnancy rate per oocyte harvest, that is, for the youngest group (age <35), the live delivered pregnancy rate was 67% for normal versus 36.5% for diminished reserve and was 42.7 versus 23.7% for the group with diminished reserve in women aged 36–39.

Interestingly, the number of live babies born per retrieval (counting multiple births and conceptions from subsequent frozen ET) was for these three age groups: 0.91, 0.55 and 0.28 for women with normal oocyte reserve versus 0.47, 0.27 and 0.10 for diminished oocyte reserve. Thus, there is approximately twice as many oocytes with normal chromosome constitution in a given oocyte harvest in women with normal versus diminished oocyte reserve if one makes the assumption that a normal embryo produces a live baby.

Many IVF enters have learned that lowering the FSH by estrogen and thus restoring downregulated FSH receptors makes the follicle less resistant to gonadotropins [54]. The term has been coined 'estrogen priming' [55,56]. However, it does not seem to make sense to suppress the FSH then use supra normal dosage of FSH as performed by many IVF centers to stimulate more follicles that may be all chromosomally abnormal because of raising the FSH and downregulating receptors again and possibly causing non-disjunction of chromosomes. It should be noted that the concept of downregulation of FSH receptors leading to meiosis errors by suppressing a key FSH-dependent factor that inhibits non-disjunction is purely speculative. It is a model that fits the observed data but there have been no studies measuring FSH receptors under various types of COH. Moreover, there are no data establishing that high-dosage FSH in women with diminished oocyte reserve decreases a factor promoting chromosome segregation. Possibly, there exists a different mechanism to explain the observed data.

Once this new data set is published, there can now be a standard with which to compare. One can then compare pregnancy rates in similar groups with diminished reserve utilizing dehydroepiandrosterone (DHEA) supplementation (or other androgens, e.g., testosterone) or estrogen priming followed by conventional or high-dosage FSH stimulation protocols.

Use of DHEA to improve follicular response

Casson *et al.* claimed that five poor responders with normal serum FSH levels were able to increase their serum E2 from

266 to 939.8 pg/ml after 2 months of pre-treatment with DHEA [57]. Barad and Gleicher reported a case of a 43-year-old woman who had only 2 oocytes retrieved without DHEA pre-treatment but who improved to 18 oocytes following DHEA pre-treatment [58]. A subsequent series of 25 cases by the same authors suggested that poor responders with increased serum FSH could develop significant increased number of fertilized oocytes leading to an increase in day 3 embryos by taking 16 weeks of oral DHEA supplementation at 25 mg three-times per day [59]. Sonmezer *et al.* also suggested improved ovarian response and improved embryo quality leading to higher pregnancy rates in poor responders using DHEA supplementation [60]. Indeed, even live deliveries have been reported in women in apparent ovarian failure following treatment with DHEA [61,62].

Intrafollicular androgens are essential for folliculogenesis. Circulating DHEA sulfate(s) accounts for 48% of intrafollicular testosterone and 25% of DHEA (which is also converted to androstenedione) [63]. Casson *et al.* suggested that one possible explanation to explain improved response by poor responders treated with DHEA may be by increasing the follicular androgen pool [57]. After reading some of the manuscripts pertaining to the benefits of DHEA supplementation, our group considered using it for some of the patients with diminished oocyte reserve. Actually, our group had been using it in women with apparent ovarian failure for about 15 years after having listened to an oral presentation by one of Casson's fellows at the American Society for Reproductive Medicine. It was used predominantly in women who failed to induce ovulation with ethinyl estradiol or GnRH agonist or antagonists. Sometimes it was used in conjunction with ethinyl estradiol and sometimes by itself. Our group has never written a case report for its use because there has been failure to achieve a pregnancy or induce ovulation in this group of women with extremely diminished oocyte reserve. We considered that the possibility is that the DHEA is converted to E2 and the increase in E2 causes suppression of FSH leading to upregulation of FSH receptors in the follicle thus leading to ovulation in some cases as reported by Mamas and Mamas [61,62]. Admittedly, our group has never tried it in women with ovarian failure who did not take ethinyl estradiol or leuprolide acetate first because it could produce androgen side effects, it may not be as efficacious, and a delay in starting the ethinyl estradiol could allow further oocyte depletion. Also if it did work by being converted to E2 then one could lose the precision in judging follicular response of producing E2 since one would not be able to decide how much of the serum E2 was contributed by peripheral conversion of DHEA to E2 versus direct contribution of the follicle. As a reminder, ethinyl estradiol does not seem to contribute to the measured serum E2 by ELISA assay since the serum E2 generally remains <20 pg/ml with ELISA from various laboratories until a dominant follicle is detected by ultrasound.

When the reports of increasing follicular response were reported by Barad and Gleicher, we considered adding DHEA treatment to the regimen for women with diminished oocyte reserve, especially those planning on having IVF-ET. However, there was concern about increased androgens possibly casing follicular atresia. We considered that perhaps they could be best used in women with low DHEA or DHEAs levels. Interestingly, the original group described by Pisarska and collaborators (part of Casson's group) at the ASRM meeting was a group of poor responders that had low DHEA levels but normal FSH [64]. However, since we have had a reasonable good success in using mild stimulation without DHEA supplementation, we first wanted to determine if indeed women with lower DHEAs levels with diminished oocyte reserve either do not create as many follicles or have an inferior pregnancy rate. This would be the ideal group to use for a prospective RCT to determine if adding DHEA to mild stimulation improves the outcome following IVF-ET in women with diminished oocyte reserve and low serum DHEAs levels.

However before initiating an RCT, our group performed a retrospective study to determine if women who had diminished oocyte reserve undergoing IVF-ET with mild COH protocols and who also had serum DHEAs levels obtained would show less oocytes obtained and/or lower pregnancy rates in those who had the lowest DHEAs levels. Unfortunately, not only did we not find a significant difference in those with low versus top normal DHEAs levels but there was a trend for increased oocytes obtained and higher pregnancy rates the lower the serum DHEAs [65].

The concept of supplementing DHEA is that it enters the circulation from mostly secretion from the adrenal gland and this enters the follicle which is then converted to testosterone within the follicle [63,66]. A study by Li *et al.* found that whereas serum DHEAs was highly correlated with follicular fluid, serum DHEA did not correlate with follicular fluid DHEA [67]. However, intracytoplasmic follicular steroid sulfatase activity did correlate with follicular fluid DHEA, thus suggesting that follicular fluid DHEA was produced locally in the ovary [67].

Interestingly, Li *et al.* showed that follicular fluid DHEA concentrations showed significant negative correlation with the total number of oocytes retrieved, the number of metaphase II oocytes retrieved, the number of normally fertilized oocytes and the number of viable cleavage-stage embryos and the number of viable blastocyts (in the subgroup having blastocyst transfer). Though not significant there was a trend for lower follicular fluid DHEA levels (23% lower) in the pregnant versus non-pregnant group [67]. The authors suggest that if the reports of improved IVF outcome with oral DHEA supplementation are corroborated by other studies, the mechanism does not seem to be related to raising the follicular fluid level of DHEA [67].

As mentioned, probably some women with diminished oocyte reserve will respond to oral DHEA by lowering FSH by conversion of DHEA to E2. Furthermore, oral DHEA is recommended to be given for 16 weeks before another IVF cycle is started [59]. It is possible that the 'rest' from ovarian hyperstimulation rather than the DHEA is the more important factor in allowing restoration of downregulated FSH receptors in the

follicle related to previous COH with conventional or supra-conventional dosage of FSH.

Expert commentary

Though one places the most confidence in RCTs, especially if sufficiently powered, certain circumstances are not amenable to RCTs. For example, it would be almost impossible, and probably unethical, related to the short window of fecundity that remains, to compare pregnancy rates in women with ovarian failure given ethinyl estradiol to restore follicular sensitivity theoretically by restoring downregulated FSH receptors versus expectant therapy or a placebo control. In this circumstance, we must rely on a series of cases reports which may establish precedents for treatment and makes both treating physicians and patients aware that success is at least possible.

Some of these anecdotal reports provide convincing evidence that the lowering of FSH is the responsible mechanism for ovulation in women in apparent menopause rather than a fortuitous circumstance. A 25-year-old woman with 2 years of amenorrhea and marked estrogen deficiency was observed for 3 months with serum FSH levels 1 month apart of 144.9, 145.6 and 164.2 mIU/ml [44]. Yet she ovulated 6 of 10 cycles and conceived and had a live baby from cycle 10. The only drug used to induce ovulation was ethinyl estradiol [44]. Furthermore, in a series of 100 consecutive patients with hypergonadotropic amenorrhea and estrogen deficiency with over 3 years of amenorrhea ovulation was induced 68 times in 354 cycles using the aforementioned technique of lowering FSH with ethinyl estradiol or leuprolide with possibly a small boost of gonadotropins [37].

The decision as to whether to use IVF-ET if a follicle develops or allow natural conception in women with diminished oocyte reserve depends on several factors. It is obvious that if a tubal factor exists or severe male factor, the decision is clear to do IVF-ET if the woman strongly desires a pregnancy with their own genetic material [68]. There is no question that advancing age negatively impacts fecundity. Nevertheless, the desire to have a baby with her own oocytes influenced a woman aged 42 with blocked fallopian tubes and overt menopause with a serum FSH of 61 mIU/ml to travel 800 miles by automobile several times in a given cycle to obtain free monitoring in our clinic because she was of limited financial means [69]. Obviously, if she spends her money on her own oocytes she may not have sufficient money left for donor oocytes. However, donor oocytes were not an option. In her case, she was able to reverse menopause simply by lowering her elevated serum FSH with ethinyl estradiol. She conceived and delivered a healthy baby on her second IVF cycle with a single 4-cell embryo transferred on day 3 [69].

Our IVF center is committed to catering to the couple's desires. The preference is to show them our retrospective data and provide anecdotes to help them decide on whether, despite their diminished oocyte reserve, to try to conceive naturally versus IVF-ET or use donor oocytes. They are provided with data from other studies that we published, such as the one showing that in a group of women with day 3 serum FSH over 20 mIU/ml that the live delivered pregnancy rate per cycle was only 3% for natural cycles without IVF-ET versus 15.1% for IVF-ET in one cycle. However, in 3 natural cycles 11.7% achieved a live delivery without IVF-ET [70]. For those with insurance coverage, these data would make one initiate therapy with IVF-ET but those without IVF insurance coverage, and having only limited financial means, might opt to correct ovulatory factors and hope for pregnancy.

Some women ask for predictions as to when they will go into overt menopause to help them to decide to spend more money on IVF-ET or try naturally with correction of ovulatory and other infertility factors. They are advised that there is no definite way to predict. Here is where precedents or preceding anecdotal cases can be helpful. For example, they could be made aware, that is, two women who had three babies over 8 years since the discovery of their diminished oocyte reserve [71,72]. One had natural cycles with correction of ovulatory defects and the second needed IVF-ET because of a male factor problem [71,72]. Interestingly, the woman who conceived in 3 of 4 IVF-ET cycles had only a single 4-cell embryo transferred in cycle 4, but it was successful [72]. Some IVF centers would not transfer a 4-cell embryo on day 3 but our view is that though the success rate is low what harm is there to transfer it? Some of them make normal babies!! Nevertheless, they are advised that if an active destructive process is ongoing, they could be in a rapid decline toward menopause. There is no definite way of knowing for sure.

As long as women are advised of their odds of conception as honestly as possible, the physician should grant the patients' request to help them. One infertile physician with tubal disease from Europe came to our clinic for a consult. Because of an elevated serum FSH and because she only attained a maximum endometrial thickness of 4 mm, she was advised by the European IVF center that not only did she need donor oocytes, but she also required a gestational carrier. She actually gave up her practice of medicine and came to the USA to take a research position close to our infertility center so that we could perform IVF and transfer the embryo back to her. In her second IVF-ET cycle, she transferred an 8-cell and a 4-cell embryo on day 3, and despite a maximum endometrial thickness of 3.7 mm, she delivered a live baby [73].

One may question if there is an age limit for trying to conceive with their own oocytes in women with diminished oocyte reserve. Obviously, these two factors together are associated with a very poor prognosis. However, live pregnancies are not unprecedented. One 45-year-old woman in apparent overt menopause requested that her menopause be reversed and wanted only intrauterine insemination rather than IVF with ICSI, even though her husband's sperm had a concentration of only 3×10^6/ml with 20% motility. Ovulation induction with FSH suppression and mild gonadotropin stimulation occurred in both treatment cycles and she conceived and had a healthy baby [74]. Successful pregnancies have been achieved in women with elevated serum FSH, both with and without IVF-ET at

age 46 [75,76]. To date, we do not have a pregnancy in a 47-year-old, but have tried many times. Our lack of anecdotes has reduced the frequency of women requesting IVF at this age or older.

When should a physician advise a woman against another IVF-ET cycle? Again, here is where anecdotal case reports are important. One woman with diminished oocyte reserve failed five-times to conceive with IVF-ET from ages 41 to 43. She stopped trying because of being diagnosed with amyotrophic lateral sclerosis. Apparently, this was not the correct diagnosis because she spontaneously recovered. She desired IVF with ICSI for severe oligoasthenospermia again with her own oocytes now at age 45.5. Though she was advised of the extremely poor prognosis because of her previous failures and her advanced age, and she was advised of the advantages of donor oocytes, she chose to try IVF again, despite limited finances and no third party coverage. She had a live baby following transfer of a single 7-cell embryo. Her day 3 FSH level cycle was 29 mIU/ml [77].

Many physicians have been convinced that because of certain flaws in retrospective data they will only be influenced by RCTs. However, RCTs usually need funding which limits the size of the study. Sometimes finances are provided by large pharmaceutical companies where the patient selection will favor the financial concern of the company. Thus, sometimes conclusions reached by RCTs are based on a specific favorable population with the hope by the company or the researchers trying to promulgate their research ideas that the data will be extrapolated to the general population. However, these selected patients may represent only a small minority of the population that seeks infertility treatment. Also frequently RCTs are underpowered.

Nevertheless, in general, a well-powered unbiased RCT is the ultimate study, but if one does not exist, and is unlikely to occur in the near future, the treating physician must rely on the next best type of data. This may especially apply to infertility since advancing age is beyond question a significant factor for declining fecundity. A large retrospective study that uses all patients not merely selected patients and is a comparative study can provide useful information to treating physicians and patients alike in making certain decisions. This is true especially if a new treatment modality is provided with at least a theoretical explanation such as how women with diminished oocyte reserve could have almost the same pregnancy rate as age peers with normal oocyte reserve and a theory to explain conflicting data.

RCTs do not always provide definitive answers. For example, the aforementioned RCT trial by Baart *et al.* was extremely interesting [17]. As a reminder they concluded that there were a higher percentage of embryos with aneuploidy using conventional versus milder ovarian stimulation suggesting that there is some natural selection of oocytes with normal chromosomal constitution. Thus in the end, despite more embryos they found that there were the same number of normal blastocysts produced with conventional or mild stimulation, that is, 1.8 [17]. There were 111 patients in the RCT by Baart *et al.*, which employed a seemingly unbiased patient selection with no apparent motivation other than trying to answer an important scientific question [17].

However, a new RCT study was just published in 2013 which had reached opposite conclusions, that is, there is no greater frequency of aneuploidy in cycles using conventional COH than even natural cycles [78]. The prospective study by LaBarta *et al.* employed 59 patients. So which RCT does the reader decide makes the right conclusion? What does this author think? Can they both be right? The answer is yes. The study by Baart *et al.* used infertile patients who were older than the 25-year-old oocyte donors used in the study by LaBarta *et al.* [17,78]. Could the difference in these two studies be explained using the FSH receptor up- and downregulation theory? A theoretical model can be proved. Young donors with multiple antral follicles present have lower serum FSH and are theoretically much less susceptible to downregulation of FSH receptors with rising serum FSH levels from conventional COH protocol. This prevents downregulation of the 'hypothesized' FSH-dependent factor needed to enable chromosome separation during meiosis. We would suspect that if Baart *et al.* would perform the same study on women with diminished oocyte reserve they may find an even wider disparity on the percentage of embryos with normal chromosomes with conventional versus mild stimulation and thus reach the same conclusion as did Nasseri *et al.* that even younger women with elevated FSH created an extremely high percentage of embryos with aneuploidy when conventional COH protocols are used [19].

Ethically, it does not seem appropriate on a personal basis to conduct an RCT to better prove that women with diminished oocyte reserve depending on age can get a 75–80% as good of a chance to achieve a live pregnancy as age peers with normal reserve by simply using low FSH COH protocols rather than conventional ones. However, this manuscript may stimulate others who already use a high-dosage FSH regimen for this group with or without estrogen priming to be convinced to perform an RCT. Until that time hopefully these very large retrospective comparative studies and anecdotes of extreme cases will stimulate others to try this technique, and hopefully corroborate (but possibly refute) some of these conclusions.

Five-year view

Though knowledge that when treatment is initiated with the proper COH protocol women with diminished oocyte reserve may fare almost as well as women with normal reserve has been known for about 30 years, only recently have there been requests to write editorials or review articles on this subject. With this information better promulgated, there should be a trend for more infertility centers to try to help women conceive with their own oocytes, even if they have marked oocyte depletion, instead of automatically steering them in the direction of donor oocyte programs. This would help immensely if some modification of national reporting is made so as not to penalize

the pregnancy rate statistics from those centers willing to accommodate their patient's wishes, despite the risk of lowering their pregnancy rates.

There has been a recent trend toward using mild stimulation protocols for women with normal oocyte reserve using mild versus conventional FSH dosage COH with findings of comparable pregnancy rates with a significant reduction in the cost of expensive medication and a marked reduction in the risk of ovarian hyperstimulation [79–83]. The policy would logically trickle down to their patients with diminished oocyte reserve who refuse the advice of a donor oocyte program. Finding successful pregnancies now using mild stimulation, despite previous failure with high-dose FSH regimens, may encourage more IVF centers to try mild stimulation techniques for women with diminished oocyte reserve having witnessed successful outcome in their own IVF department.

With improvement in cryopreservation with vitrification, some IVF centers may be willing to put the patient through several retrievals, stockpile the embryos, then do one frozen ET with several embryos. This makes no sense. Why should couples pay for multiple cycles when cycle 1 IVF-ET could be the one producing the normal embryo? Furthermore, up until now, a frozen-thawed embryo has not been as likely as a fresh one to achieve a pregnancy so transferring one fresh and two frozen embryos may still be less likely to result in a pregnancy than the three transfers of one fresh embryo each, though possibly with the resurgence of vitrification this disparity may change [84,85]. Finally, transferring several embryos places a woman at risk for multiple births. The best option is to transfer fresh embryos, even if only one embryo is formed [23].

Genomics has led to a great deal of new information concerning the pathology of various medical disorders. The gene that encodes the follicle-stimulating hormone receptor is located on the short arm of chromosome 2. It consists of 10 exons spanning 54 kB of genomic DNA [86]. Over the last 15 years, there have been a variety of FSH receptor mutations detected leading to various problems with folliculogenesis and ovarian reserve including premature ovarian failure [87–91]. Though there are several mutations detected they appear to be uncommon and are inherited as a recessive gene [92].

Similarly, there have been a large number of LH receptor mutations seen in infertile women especially involving the beta-subunits [93–94]. Over the past 5 years, there has hardly been any new publications concerning LH and FSH mutations; and thus it does not seem likely that there will be any breakthroughs concerning FSH or LH receptor mutations. It may not matter because the treatment would be similar no matter what the etiology. Actually, there have been a couple of anecdotal reports of successful pregnancies by another group using a similar technique as has been described by lowering elevated gonadotropin with a GnRH analog and estrogen followed by progesterone in two women with LH beta-subunit mutations [95,96]. One of these women was in premature ovarian failure [95] and the other with a luteal phase defect [96]. Thus, the knowledge of chromosomal abnormalities associated with premature ovarian failure may help us to better understand the etiology of some cases of this disorder, it does not seem likely that any new knowledge in this area will occur in the next 5 years to better enable the treating physician to optimize outcome for IVF in women with diminished oocyte reserve [97].

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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Key issues

- Higher dosage of follicle-stimulating hormone (FSH) drugs leads to a much greater expense for *in vitro* fertilization (IVF).
- Higher dosage of FSH may lead to the creation of more embryos but a lower percentage of chromosomally normal embryos especially in women with diminished oocyte reserve.
- Conventional or supra high dosage of FSH markedly decreases the pregnancy rate per embryo transfer in women with decreased oocyte reserve.
- The adverse effect of conventional FSH controlled ovarian stimulation (COH) in women with diminished oocyte reserve seems to be on the embryo itself, rather than the uterus.
- Freezing embryos to avoid the adverse effect of COH may be useful in a minority of cases with normal oocyte reserve, but not those with diminished oocyte reserve.
- Age rather than degree of oocyte reserve is a much more important determinant of successful pregnancy.
- Even women with apparent premature menopause can be made to ovulate by restoring downregulated FSH receptors and they actually have a reasonable live delivered pregnancy rate especially if younger.
- Some recent data question a possible adverse effect of dehydroepiandrosterone (DHEA) supplementation in women with diminished oocyte reserve.

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