Pharmacological options in resistent ovary syndrome and premature ovarian failure

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Summary

Purpose: To present methods of treating women in apparent ovarian failure to allow them to ovulate and conceive.

Methods: Ethinyl estradiol was used to lower elevated serum follicle stimulating hormone (FSH) levels to restore down-regulated FSH receptors on the follicle. Ovulation and pregnancy rates were then determined. Aggressive progesterone (P) therapy in the luteal phase was also used. Lowering elevated serum FSH with gonadotropin releasing hormone agonists was also successful in inducing ovulation in these patients.

Results: Several anecdotal studies have demonstrated that ethinyl estradiol therapy can induce ovulation in women in apparent menopause and achieve live births.

Conclusions: The advantage of ethinyl estradiol over other estrogens to induce ovulation in hypergonadotropic women is that it does not cross-react in the assay for serum estradiol and can allow detection of estradiol secretion by the follicle. Thus estrogen therapy is by far the most effective treatment.

Key words: Resistant gonad; Ovarian failure; Ethinyl estradiol; FSH; Receptors; Progesterone.

Introduction

When women have reached an average age of 51.5 and are no longer having spontaneous menstruation, fail to get withdrawal menses after progesterone (P) administration, and fail to stimulate follicular maturation with exogenous gonadotropins, this state is considered menopause or frank ovarian follicle function [1, 2]. However, even at this time histologic study of these ovaries generally will demonstrate approximately 1,000 oocytes remaining [1]. It is considered that the remaining follicles are of extremely poor quality and thus are unresponsive to endogenous or exogenous gonadotropin stimulation. The thought process extends that because of the poor quality, these follicles had never been recruited during the menstruating years.

Many women in their 40s will have elevated day 3 serum FSH levels. The majority of women in their 20s and 30s have normal day 3 serum FSH. When a woman is ≤ age 35 and has elevated day 3 serum FSH (or a low inhibin B level) and has amenorrhea, fails to have menses following withdrawal of P therapy, and fails to respond to exogenous gonadotropin, she is considered as having premature ovarian failure. These women are the subject of this treatise, i.e., what pharmacologic methods exist to treat these women for the purpose of inducing ovulation and attaining live deliveries.

These women could theoretically have two circumstances to explain the characteristics described above: they may truly have a paucity of remaining follicles, or they may have a plethora of remaining follicles but resistance to gonadotropins so they do not reach the stage of follicular maturation where inhibin B is produced. In the former circumstance, there may be a known cause, e.g., related to previous surgery or chemotherapy or radiation therapy, or genetic, e.g., Turner's syndrome or Turner mosaicism, or may not have a known cause, e.g., presumed autoimmune destruction or genetic predetermination for more rapid atresia of follicles despite two complete X chromosomes being present. Nevertheless, in both states, there is gonadotropin resistance so in a sense it could be stated that gonadotropin resistance with a paucity or plethora of early follicles exists.

Some authors have stated that women of all ages with high day 3 serum FSH have defective oocytes and are not very likely to become pregnant even if normal appearing embryos are transferred [3-7]. One study suggested that if the serum FSH was ever elevated in a previous menstrual cycle, the prognosis is extremely poor even if the levels are now normal [8]. Very recently, a retrospective study was published by one of the foremost IVF centers in the world finding no live pregnancies in women of any age with elevation of serum FSH in three different menstrual cycles [9].

However, there are studies in disagreement with the above conclusions. One study found in women with significantly elevated day 3 serum FSH levels ongoing/delivered pregnancy rates of 27.3% in women ≤ age 35, 30.8% for age 36-39, and 21.3% for age 40-42 despite the transfer of only one embryo in most cases [10]. Only women ≥ age 43 failed

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to have a viable pregnancy [10]. Even without assisted reproductive technology, another study reported a 46.1% clinical (ultrasound evidence of pregnancy) and 34.6% ongoing/delivered (viable past 16 weeks) pregnancy rate after six months of treatment [11]. The comparable pregnancy rates for women ≥ age 40 was 10.5% and 5.3% [11]. Thus, these latter studies suggest that it is worthwhile to try to induce ovulation in younger women, especially those who are considered to be in frank or imminent ovarian failure since they may just be a further extension of their younger menstruating counterparts with diminished ovarian reserve, at least from the oocyte quality standpoint. Thus, accomplishment of ovulation in this group may produce pregnancy rates more similar to their age peer groups than women of an older reproductive age.

Those clinicians and researchers concluding that even if ovulation can be induced in a woman with apparent menopause, a live pregnancy is extremely unlikely, point to the fact that normal conception in women in their late 40s and even 50s have been recorded but are extremely rare [12]. They insist that these rare women who spontaneously conceive while taking estrogen replacement [13-16] or without any therapy [13, 17] are analogous to the rare older women who conceive. Their argument continues that since premature menopause is estimated at 1% of all women during the reproductive years [18], the handful of case reports of successes are so few [13-17, 19-21] that it must conclude that the majority of remaining oocytes are defective [3-7]. Hopefully, the data presented in this chapter will convince the reader that this concept of poor quality eggs is wrong and it is very worthwhile to try to treat this group of women.

Goal of therapy

The goal of therapy of women with premature ovarian failure due to paucity of remaining follicles or gonadotropin resistance is to establish ovulation. However, it is essential that restoring ovulation can lead to successful pregnancy and live delivery.

Available compounds

1) estrogen, especially ethinyl estradiol, 2) gonadotropins, 3) progesterone, 4) gonadotropin releasing hormone (GnRH) agonists, 5) GnRH antagonists, 6) danazol, 7) corticosteroids, 8) dehydroepiandrosterone, 9) human growth hormone, and 10) aspirin.

Current best practice

A theory was proposed that the apparent resistance to endogenous and exogenous gonadotropin stimulation may be related to down-regulation of FSH receptors in granulosa-theca cells by the consistently elevated serum FSH levels [22]. Based on this theory, a higher dosage of conjugated estrogens were used to lower the serum FSH, then this was stopped, and human menopausal gonadotropins (hMG) were started. Using this technique three of five women in apparent premature menopause, who were resistant to hMG therapy, were able to ovulate and two women had live babies [22]. The authors considered that estrogen therapy was needed to restore sensitivity to the hMG because, despite the fact that there had only been a few previous case reports of spontaneous ovulation with estrogen replacement in women with premature ovarian failure, there had only been one previous case report of response to hMG [23].

Though the original idea was to lower the FSH with estrogen to restore down-regulated FSH receptors, the demonstrated response did not prove the theory. Theoretically, the estrogen could have been working in a different manner, e.g., making the pituitary more sensitive to gonadotropins. However, further support for this theory was provided by a case report showing ovulation induction in a woman with hypergonadotropic hypogonadism following suppression of elevated serum FSH levels with leuprolide acetate [24]. More support for the theory that estrogen is not needed but merely suppression of the elevated serum FSH levels is required was provided by a case report of a woman documented to have estrogen deficiency and hypergonadotropism who was able to ovulate and successfully conceive twice with exogenous gonadotropins following hypophysectomy for a macroprolactinoma [25].

It was assumed that most of these cases had a decreased number of oocytes rather than a plethora of oocytes but resistance to gonadotropins, however since there were no biopsies performed, this could not be proven. Occasionally a woman has delivered by cesarean section and then marked hypoplastic ovaries would be observed [17, 26].

The original technique would give the woman a higher dosage of estrogen (usually conjugated estrogen) for at least two weeks then start gonadotropins once the serum FSH was suppressed. Usually the starting dosage of hMG to start was 150 IU and generally it was never increased beyond 375 IU/day. Though some women ovulated, many did not; thus they were faced with high expenses for medication since frequently injectable gonadotropin drugs were not covered by insurance. It was considered that there might be a possibility that lowering the serum FSH could restore sensitivity to endogenous gonadotropins. Using conjugated estrogen, however, would not allow any distinction of whether a rise in serum E2 was related to the exogenous estrogen or if there was a contribution of endogenous E2. Though ultrasound could be performed, the woman would have to go through many ultrasound procedures and thus occupy a lot of her time and possibly markedly increase the expense. Thus, it was decided that it would be easier to monitor by measuring the serum E2 and FSH if an estrogen could be found that would suppress the E2 level without being measured in the assay for serum 17-beta E2. Ethinyl estradiol, the estrogen found in most oral contraceptives,

was found to meet these qualifications. Thus, the technique was modified so that 50 μg of ethinyl estradiol was initiated and after only one week the serum E2 and FSH would be measured [27]. Sonography was only performed if the serum E2 was rising above 50 pg/ml [27]. It may be given at 75 IU to 150 IU only when a follicle of at least 8 mm is found with a serum E2 > 50 pg/ml [27]. Since some patients had financial problems paying for the expensive gonadotropins, some cases were watched to see if they could reach a mature follicle (defined as attaining an 18 mm average diameter and a serum E2 of ~ 200 pg/ml) with endogenous gonadotropins alone once the sensitivity to gonadotropins was restored [27]. If a woman developed a follicle, but it did not fully reach maturity, the next time a minimal dosage of hMG of 75 IU was given to boost the follicle to maturity. Some women did attain mature follicles and conceived without using any, or merely minimal boosting, with gonadotropins [27]. Initially, these women were started on P vaginal suppositories (25 mg) twice daily once the follicle collapsed by ultrasound indicating egg release and the dosage was increased in a subsequent cycle if the mid-luteal phase endometrial biopsy was out of phase [27]. Today we find it more effective to use 200 mg twice daily of P vaginal suppositories. This dosage is increased if the woman fails to attain a homogeneous hyperechogenic pattern by vaginal sonography of her endometrium at mid-luteal phase [28, 29].

The dosage of gonadotropins should be kept low, not only for economic reasons, but if the serum FSH rises too high – because of the follicle maturing drugs themselves – they could down-regulate the FSH receptors and make the follicle unresponsive to gonadotropins again [30]. Maintaining the ethinyl estradiol while taking exogenous gonadotropins helps keep the endogenous secretion of FSH from the pituitary suppressed. Today we also stop the ethinyl estradiol once human chorionic gonadotropins are given or there has been a spontaneous luteinizing hormone (LH) surge but oral E2 replacement is given in the luteal phase because the corpus luteum sometimes fails to make sufficient E2 and the extra E2 helps keep the FSH suppressed to facilitate ovulation in the next cycle. Furthermore, today the dosage is usually 20 μg of ethinyl estradiol rather than 50 μg. This dosage has fewer side-effects and does not oversuppress endogenous gonadotropins as much as the 50 μg dosage.

A review was published on 100 consecutive women with hypergonadotropic amenorrhea treated with the technique described above for at least four cycles [27]. This study not only evaluated patients with premature ovarian failure but older patients with apparent menopause. There were 91 cycles where women were given ethinyl estradiol to suppress FSH and nine used leuprolide acetate. The 91 women had 311 cycles attempted. Thirty-four (37.3%) of the women ovulated at least one time. Ovulation was achieved in 61 of 311 cycles (19.5%). Clinical pregnancies (ultrasound evidence) were achieved in 19 women (20.8%) and live births occurred in eight women (8.8%) [27].

Using leuprolide to lower FSH, nine women had 43 cycles. Three (33.3%) women ovulated, and ovulation occurred in seven of 43 (16.2%) cycles. There were no pregnancies in this small group [27]. Combining both groups, there were six women who ovulated in all cycles. The clinical pregnancy rate was 5.2% per cycle (19/361) and was 28% (19/68) per successful ovulation. The miscarriage rate was about 50%. For those conceiving there was an average of 4.4 ovulatory cycles before conception. Three patients required nine, eight, and seven treatment cycles before conception [27].

Forty of the 68 ovulations (58.8%) used hMG after a follicle was recruited by lowering the serum FSH and 28 (41.2%) ovulations occurred just with ethinyl estradiol or leuprolide acetate. The average amount of hMG used was 1,050 units [27].

When the date of going into ovarian failure was known, the length of time from ovarian failure to treatment was 2.2 years in those who conceived vs 4.8 years in those who did not conceive [27]. The mean age for the group who became pregnant was 33.4 vs 34.8 for the non-pregnant group. Actually the oldest patient in apparent menopause to conceive using this technique was not in this group of 100 but she was aged 45 [31]. The oldest patient to conceive with documented elevated FSH was age 46 but she was still menstruating [32].

The mean FSH for those who ovulated was 70.3 mIU/ml vs 66.5 mIU/ml in those who did not ovulate [27]. The highest serum FSH in a woman with premature ovarian failure to successfully deliver was 164 mIU/ml and was not in the group of 100 consecutive patients [33].

All the patients in the series of 100 had patent fallopian tubes and male partners with relatively normal or mildly subnormal semen parameters and thus no assisted reproductive technology procedures were used. There have been subsequent reports of live deliveries following IVF-ET in women with premature ovarian failure [34] and even in a 42-year-old woman who would not be considered as having premature ovarian failure [35].

None of the aforementioned studies were controlled so how can one be sure that treatment effected ovulation rather than just spontaneous resumption of ovulation? There have been case reports of patients with documented resumption of spontaneous ovulation who conceived and delivered a normal healthy baby despite the diagnosis of premature ovarian failure (POF) of several years before [15, 36, 37]. The only controlled study of using estrogen replacement vs no therapy did not find that estrogen improved the frequency of ovulation induction [38]. However, this study was only estrogen replacement not FSH suppression.

Though I cannot prove it, my own bias is that therapy of suppressing FSH levels is important in improving the chance for ovulation. First of all, some studies define POF as amenorrhea for at least four months [39]. The shorter the interval the more likely one may see spontaneous ovulation. In the study of 100 consecutive patients treated with high-dose estrogen the minimum requirement was at least one year of amenorrhea [6].

Furthermore, though spontaneous pregnancies have occurred, based on the estimate that 1% of women age ≤ 40 have POF (1/250 for age ≤ 35 and 1/1,000 for ≤ 30) and considering the number of publications of actual pregnancies, the calculated chance of pregnancy spontaneously would be less than one in 6,000. In contrast we found a 20.8% pregnancy rate after just four cycles of therapy in a more difficult group [27].

Also, there is one theory that estrogen itself may activate FSH receptors on granulosa cells and then respond to the high endogenous FSH levels. However, one theory is that it is not the estrogen per se but the suppression of the high FSH leading to restoration of down-regulated FSH receptors. This theory is supported by ovulation induction using gonadotropin releasing hormone analogues [27, 40]. Thus another reason why Taylor *et al.* may not have found any advantage of estrogen therapy to induce ovulation may have been too low of a dosage to lower serum FSH sufficiently. Furthermore, it appears that the use of supplemented progesterone in the luteal phase significantly improves pregnancy rates [41].

Other factors

Other therapies have been tried. Some investigators have used corticosteroids in an attempt to suppress theoretical anti-ovarian antibodies [42-44]. Pregnancies have been recorded but are very few and are generally considered unrelated to therapy. Because of the risk of severe side-effects, a controlled study is needed before widespread use should be suggested whether anti-ovarian antibodies are found or not.

Similarly danazol was not found effective to induce ovulation in this group [45]. However, there may have been a trend for improvement in the minority of those women showing some evidence of autoimmune disease [45]. Actually, since danazol can also suppress elevated gonadotropins, and theoretically restore down-regulated FSH receptors in granulosa cells, perhaps such a drug could have been more effective if the authors had also supplemented the luteal phase with extra progesterone. Furthermore, there was no meticulous evaluation of each patient but merely that the patient was placed on danazol vs estrogen and pregnancies were recorded in a 4-month period without careful monitoring. Our preference is to watch the patient for a rise in serum estradiol (which using a drug like danazol would allow as opposed to replacement estrogen with the exception of ethinyl estradiol) and then start watching follicle growth with ultrasounds. This allows advising the patient when to have intercourse, allows intrauterine insemination if post-coital tests are poor, allows intervention of boosting with small doses of exogenous gonadotropin if the follicle is not progressing rapidly enough, allows giving human chorionic gonadotropin to help ensure oocyte release from the follicle once follicular maturity is established, and allows the use of a gonadotropin releasing hormone antagonist if the luteinizing hormone begins to rise before follicular maturation occurs. This lack of aggressive monitoring could also explain the failure of estrogen therapy to achieve successful pregnancy even in those who appear to ovulate [38].

Dehydroepiandrosterone (DHEA) supplementation has been found to augment serum insulin-like growth factor (IGF) concentrations [46-48]. Lower concentrations of androgens seem to favor progression of pre-antral follicles to antral follicles. One report suggested that DHEA supplementation augments ovarian stimulation in poor responders [49]. However, in that aforementioned study the controls were merely historical, the improved response was modest at best, and there was failure to regress to the mean [49]. Nevertheless, there are reports over the internet of anecdotal marked improvement in gonadotropin response following pretreatment with DHEA. Therapy with DHEA deserves at least a trial in some women with premature ovarian failure to see if it will increase the likelihood of attaining a mature follicle.

Other potential therapies that could possibly augment the response to endogenous or exogenous gonadotropins include growth hormone therapy [50]. Response has been moderate at best and growth hormone therapy is extremely expensive. A very inexpensive treatment is low-dose aspirin. One study suggested it increases ovarian blood supply and can improve responsiveness to gonadotropins [51]. This study has never been corroborated. Furthermore, allowing the stimulation of more follicles with exogenous gonadotropins does not mean necessarily that it can enhance ovulation in a woman in apparent menopause. Nevertheless, the very low cost and minimal side-effects certainly warrant a trial as at least an adjunctive therapy.

Conclusions

The data favor as the most effective therapy the use of ethinyl estradiol to lower elevated serum FSH while concomitantly allowing measurement of endogenous production of estradiol by the dominant follicle. Ethinyl therapy can be augmented if necessary by boosting with small dosages of exogenous gonadotropins once a follicle has been established. If a follicle is not established but FSH is lowered, one may try low dose gonadotropins and/or clomiphene citrate but this will prove less effective in establishing ovulation so the patient's financial status should be kept in mind.

Once ovulation has been established, the luteal phase should be supplemented with adequate progesterone. Also to keep FSH low for subsequent cycles the estrogen should be maintained in the luteal phase. However, to keep the environment more physiological in case conception occurred the ethinyl estradiol should be changed to estradiol in the luteal phase.

Expert opinion

Table 1 summarizes some pertinent publications related to reversing apparent menopause and Table 2 lists pertinent articles related to elevated day 3 serum FSH. Though it has never been proven by prospective controlled studies, the author favors the concept that lowering serum FSH restores down-regulated FSH receptors making follicles that had previously been resistant to gonadotropins to now become responsive. Many of the women in the first 100 cases we described had several years of amenorrhea but following treatment were made to ovulate every or almost every cycle [27]. In fact my group recently described ovulation induction in seven of ten cycles in a 25-year-old woman with two years of amenorrhea and estrogen deficiency with a serum FSH of 164 mIU/ml by suppressing gonadotropins with ethinyl estradiol and then boosting with gonadotropins. She ovulated seven of ten cycles, conceived on her 4th treatment cycle but miscarried, but then conceived and delivered following her 10th cycle of treatment [33].

Table 1. — *Ovarian Failure - Summary of Personal Publications.*

Ref. no. (year)	Importance
22 (1984)	First article describing the technique of lowering FSH by estrogen to restore down-regulated FSH receptor thus restoring sensitivity to exogenous gonadotropins.
24 (1988)	Demonstrates that lowering the serum FSH (using leuprolide acetate) is important factor in ovulation induction rather than some other effect of estrogen.
26 (1989)	Demonstrates that ovulation with ovarian failure is possible with very few
17 (1992)	follicles left – proving at least in some instances the cases are not associated with a plethora of very early follicles not making inhibin B as yet and resistant to gonadotropins.
53 (1991)	Presentation of modification of technique to evaluate serum E2 even while the FSH is elevated but coming down following ethinyl estradiol and add low dose gonadotropin if FSH close to normal range.
27 (1990)	Largest series of treating with gonadotropin suppression with or without exogenous gonadotropins for ovarian failure. Demonstrates better prognosis with younger age and shorter known duration of ovarian failure.
25 (1990)	Showed that reversal of apparent menopause is possible even after 20 years – longest duration case.
30 (1992)	Demonstrates that inducing menopause is possible by raising the endogenous gonadotropin levels by using fertility drugs and reversing the process by merely stopping the drugs.
31 (2000)	Showed even women age 45 can reverse ovarian failure and deliver a live baby.
34 (2000)	First reported case of successful IVF-ET in women with imminent ovarian failure.
35 (2002)	Oldest woman (age 42) with imminent ovarian failure to conceive with IVF-ET.
54 (2004)	Pregnancy with ovarian failure and highest recorded FSH to date (164 mIU/ml).
52 (2005)	A 38-year-old woman in imminent ovarian failure with serum FSH 120 mIU/ml who has successfully completed the first trimester with her own eggs after failing to conceive with four donor egg embryo transfers.

Table 2. — *Elevated Day 3 Serum FSH Without Estrogen Deficiency.*

Ref. no. (year)	Importance
55 (1995)	Demonstrates that pregnancies were possible with IVF-ET despite serum FSH > 18. There were 6/40 (15%) viable pregnancies with one woman with an FSH of 62.8 mIU/ml.
11 (1997)	Demonstrates that in non-IVF cycles the prognosis is much better for younger women with elevated FSH than older ones with similar FSH levels
56 (2001)	Demonstrates that in IVF cycles the prognosis is much better for younger vs older women with similar FSH levels.
32 (2000)	Oldest woman (age 46) to have a live delivery despite elevated day 3 FSH (non-IVF) who took 14 cycles of progesterone support and IUI.
10 (2004)	Demonstration of a relatively good outcome in women up to age 42 with increased day 3 FSH following single embryo transfer supportes improved outcome by using minimal or no gonadotropin stimulation.
57, 58	Though rare, demonstrates that live pregnancy is possible in a 45-year-old
(2005, 2003)	with elevated day 3 FSH (non-IVF) and shows importance of using ethinyl estradiol to lengthen follicular phase.
59 (2005)	Demonstration of the importance of perseverance – after 8 single embryo transfers a reward of monochorionic diamniotic twins.

The advantage of using ethinyl estradiol to suppress release of gonadotropins as opposed to suppressing FSH production by GnRH antagonists or agonists is that the estrogen helps stimulate cervical mucus and endometrial proliferation. Furthermore though ovulations have been recorded in women with ovarian failure with GnRH agonists, I am not aware of any recorded successful pregnancies [24, 27].

Even if the use of estrogen to suppress gonadotgropins is not the mechanism for follicular recruitment, but related to just spontaneous follicular development, careful observation allows optimizing intercourse, provides the opportunity to boost follicular maturation with gonadotropins, and provides the right timing for administration of human chorionic gonadotropin injection, and finally the appropriate time to provide luteal phase support with supplemental progesterone.

Despite using this treatment protocol for over 20 years my team has never performed a controlled study. The reason for this is that these women make appointments based on a literature study, an internet search or referral from a successful patient with a similar problem. Thus, especially with the knowledge that they might be down to their last few follicles, this group of patients would not be amenable to a placebo control. However other physicians who believe that these eggs are poor quality could prospectively compare expectant management that they mostly give to this estrogen therapy with a gonadotropin boost and progesterone supplementation in the luteal phase to see if this therapy is effective.

One important question is whether there is a prediction model as to who will respond to therapy. The study on the 100 consecutive cases of ovarian failure showed a greater chance of success, the younger the patient and the shorter the time from diagnosis to treatment [27]. The age factor was corroborated by showing that women with decreased egg reserve as manifested by elevated day 3 serum FSH levels (but still producing estrogen) were more likely to conceive at age ≤ 39 than 40 or above despite similar baseline serum FSH in both groups [10, 11]. Obviously the longer from

diagnosis to treatment the less likely there would be any remaining follicles. However, all couples deserve an attempt at therapy but should be given the option of donor oocytes.

One never knows for sure, and that is the purpose of publishing anecdotal cases so one could determine if there were any precedents. The good prognostic feature for the 25-year-old in apparent premature ovarian failure who was made to ovulate seven of ten cycles and finally successfully pregnant on her 10th was her young age [33]. The fact that her serum FSH was 164 mIU/ml, and women with estrogen production but with serum FSH over 100 mIU/ml have quickly conceived with this therapy, suggests that the level of serum FSH should not be a deterrent [31, 33]. This is important because many infertility centers immediately push couples into donor-oocyte cycles if their baseline serum FSH is increased or even if it rises only after clomiphene challenge [3-9]. In fact recently a 38-year-woman with amenorrhea, estrogen deficiency and a serum FSH of 120 mIU/ml who failed to conceive in another IVF center after four donor oocyte cycles ovulated three of four times on estrogen suppression of gonadotropin and has successfully completed her first trimester [52].

However, a 45-year-old woman in apparent menopause who ovulated both cycles with estrogen therapy and successfully delivered was close to a miracle since even women at age 45 who can transfer at least two embryos only have a 2.2% live delivery rate per transfer [31]. In her case the only good prognostic factor was that the apparent menopause was only of six month's duration. One other good prognostic factor is the demonstration by ultrasound of any antral follicles of 5 mm or more and the next best would be pre-antral ones of 2-3 mm. Nevertheless even with no follicles seen, ovulation and pregnancy have been achieved though these are the women who may ovulate less frequently.

I believe that simple inexpensive relatively innocuous treatment, e.g., DHEA alone or in combination with ethinyl estradiol therapy, bears watching [49]. Some patients who are poor responders may improve response to gonadotropins after two or more months of treatment. There have been no case reports to date of apparent ovulation induction in a woman who appears to be in ovarian failure. Even the use of low-dose aspirin by improving ovarian blood supply, might be useful as an ancillary measure in combination with other therapies [51]. Danazol could be considered in lieu of estrogen if women do not tolerate the latter. The clinician should probably stay away from expensive non-proven therapies, e.g., hGH or long-term GnRH agonists, high dose gonadotropins or therapies that have potential risky side-effects with minimal benefits, e.g., glucocorticoids.

Obviously, if pharmacologic therapy has failed to induce ovulation, or despite ovulation induction pregnancies have not ensued, the couple could however choose the highly successful option of using donor oocytes.

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