Review Article ISSN 2639-9342

Gynecology & Reproductive Health

Maximizing Correction of Infertility with Moderate to Marked Diminished Egg Reserve in Natural Cycles by Up-Regulating Follicle Stimulating Hormone Receptors

Jerome H. Check[1,2*] and Jung K. Choe[2]

[1]*Cooper Medical School of Rowan University, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey.*

[2]*Cooper Institute for Reproductive Hormonal Disorders, P.C., Mt. Laurel, New Jersey.*

***Correspondence:**
Jerome H. Check, M.D., Ph.D, 7447 Old York Road, Melrose Park, PA 19027, Tel: 215-635-4400, Fax: 215-635-2304.

Received: 02 May 2022; **Accepted:** 30 May 2022; **Published:** 04 Jun 2022

Citation: Check JH, Choe JK. Maximizing Correction of Infertility with Moderate to Marked Diminished Egg Reserve in Natural Cycles by Up-Regulating Follicle Stimulating Hormone Receptors. Gynecol Reprod Health. 2022; 6(4): 1-7.

ABSTRACT

Many infertility specialists advise women with diminished oocyte reserve (DOR) that their remaining oocytes probably are of poor quality similar to women of advanced reproductive age. There have been studies, especially employing in vitro fertilization-embryo transfer (IVF-ET), showing very poor live delivered pregnancy rates despite the transfer of morphologically normal embryos in women even with mild DOR. However, other data suggests that the low pregnancy rates are related to the use of high dosages of follicle stimulating hormone (FSH) drugs which down-regulate some key FSH dependent enzymes, cytokines, or proteins required for proper embryo implantation. Some studies have shown that techniques that favor FSH receptor up-regulation, rather than down-regulation, can provide the chance of live delivery 80% as well in women ≤ 35 with DOR, 70% for women 36-39, and 50% for women 40-42. Though some infertility specialists will encourage women whose only infertility issue is DOR, who reject the initial suggestion to consider donor oocytes, to proceed immediately with IVF-ET to maximize success, pregnancies are quite possible with natural conception. Thus, it seems imprudent to make couples undergo the financial burden of IVF-ET in the absence of a significant tubal or male factor problem. Not only have live deliveries occurred in women with DOR, using the principle described to achieve a mature dominant follicle followed by proper luteal phase support, with serum FSH levels over 100 mIU/mL, but also serum Anti-Mullerian Hormone (AMH) levels that were undetectable. This even applies to women in overt menopause where FSH up-regulation was achieved by negative feedback to the pituitary using ethinyl estradiol inhibiting FSH release, or down-regulation of hypothalamic-pituitary stimulation of FSH production by using gonadotropin releasing hormone agonists or antagonists.

Keywords

Diminished oocyte reserve, FSH receptor up-regulation, Mild ovarian stimulation, Natural menstrual cycles, Premature menopause.

The Fetal Ovary

By 16-20 weeks gestation, related to rapid mitotic multiplication of oogonia, 6-7 million oogonia occupy the germinal ridge. This is the maximal oogonia content of the gonad. The oogonia are transformed into oocytes during the first meiotic division. They arrest in prophase.

There is a massive loss of oocytes in the fetal ovaries during the second half of pregnancy. These oocytes are not encased in follicles yet. Once the oocytes are encased in follicles, which occurs shortly after birth, the loss of follicles will be through the process of follicular growth and atresia. Prenatal oocyte depletion results in the presence of only 500,000 to 2 million oocytes at birth.

Adult Ovary

At the onset of puberty, the number of oocytes have been further reduced to 300,000 to 500,000. For the next 40 years or so, only 400-500 will be selected to ovulate. Hormonal changes occur in

the 10-15 years preceding menopause (average age 52-53). When the number of remaining follicles falls below a certain threshold one notes an increase in early follicular phase serum follicle stimulating hormone (FSH) levels, a decrease in the serum Anti-Mullerian Hormone (AMH) level, a decrease in inhibin-B, and a decrease in insulin-like growth factor-1 (IGF-1).

Inter-Relationship of FSH, AMH and Inhibin B

The release of FSH from the pituitary is inhibited by estrogen and inhibin-B. The main source of inhibin B are the smaller antral follicles. The more primary follicles that exist, the higher percentage of antral follicles present in the early follicular phase. Thus, the best time to draw a serum FSH to determine ovarian oocyte reserve is in the early follicular phase when the serum estradiol (E2) is at the lowest level.

Anti-Mullerian Hormone is made by the cohort of all of the follicles that have a chance of becoming the dominant follicle 85 days later (i.e., the approximate 600 primary follicles that are initially recruited). Though the level of AMH increases somewhat in the late follicular phase, it is uninfluenced by estrogen, and thus can be measured throughout the menstrual cycle to evaluate diminished oocyte reserve (DOR). In contrast to serum FSH (where a high level indicates DOR), low levels of serum AMH indicate DOR.

Anti-Mullerian hormone helps to ensure that, in general there is only one follicle that becomes the dominant follicle. The one dominant follicle that occurs each menstrual cycle actually started 85 days before. Anti-Mullerian Hormone aids in causing apoptosis of most of the primary follicles that have been converted from primordial follicles. Initial follicular recruitment is a self-programmed event independent of hormonal stimulation. After 70 days a minority of the early follicles that have developed an adequate amount of FSH receptors (pre-antral follicles) will now respond to increasing bioactivity of FSH from mid-luteal phase and increasing levels of FSH levels (related to decline in inhibin B and decrease in E2 and progesterone [P]) in the late luteal phase.

Anti-Mullerian Hormone inhibits the FSH induced aromatase enzyme. A follicle to become dominant needs to be converted from an androgen dominant to an estrogen dominant follicle. Only the follicle with the least amount of AMH may respond to the decreasing levels of serum FSH related to negative feedback to the pituitary from the rising E2 levels. Thus, women with DOR, despite lower number of antral follicles in the early follicular phase, may recruit more than one dominant follicle related to increased FSH and decreased AMH.

Evidence suggests that there is some selection factor allowing better quality follicles to be selected in younger women. From the age of mid-30 on, the egg quality significantly decreases. This seems to be mostly related to meiosis II errors secondary to non-disjunction of chromosomes leading to aneuploidy. Another possibility is a decrease in mitochondrial DNA in these follicles, even if the chromosomes are normal.

Regulation of trophic peptide hormones, e.g., FSH

Follicle stimulating hormone binds to an FSH receptor on the surface of the granulosa cell membrane and through transcription and translation produces enzymes that has the effect of that hormone.

Receptor down-regulation can be accomplished by shedding of the hormone receptor complex or internalization of the receptor, where the receptor leaves the surface and goes into the cytoplasm of the cell. Follicle stimulating hormone uses the internalization mechanism. Too much hormone, i.e., prolonged FSH exposure, will cause internalization of the FSH receptor leading to insensitivity of the cell to FSH. This mechanism prevents burnout of the cell from chronically elevated FSH exposure. Pathology specimens from ovaries of women age $\geq$ 50 who were in menopause still revealed about 500-1000 follicles left. Obviously, these follicles were resistant to gonadotropin stimulation. However, even if they were still ovulating, the oocytes are of poor quality related to chromosome defects or mitochondrial defects, so that successful pregnancy would not be possible. Personally, we have never helped any woman 47 or older to have a baby with her own eggs either naturally or by in vitro fertilization (IVF).

Inducing Ovulation in Women Who Appear to Be in Overt Menopause – Scenario 1

For women in ovarian failure, but in the reproductive age range where live deliveries are quite feasible, the question arises if one could induce ovulation in these women, i.e., activate some of the FSH resistant follicles, would the egg quality be so poor that a live pregnancy would not ensue? Thus, this could be an exercise in futility!!! The only way to answer the question is to see if a live pregnancy can occur if ovulation is induced in women in apparent menopause.

We hypothesized that one could restore sensitivity of remaining follicles if we could restore FSH receptors to the granulosa cell surface that had been likely internalized by chronic high FSH exposure. In the early 1980's, when we considered this study, there were two ways to lower serum FSH: higher dose estrogen to inhibit FSH release from the pituitary or the use of chronic gonadotropin releasing hormone (GnRH) agonists to inhibit GnRH synthesis of FSH.

We initiated a pilot study to determine if one could achieve ovulation, despite apparent premature ovarian failure (POF), by restoring down-regulated FSH receptors on the granulosa-theca cells by suppression of FSH release from the pituitary with pharmacologic dosages of estrogen then adding exogenous gonadotropin in the form of human menopausal gonadotropin (hMG). Human chorionic gonadotropin (hCG) 10,000 IU would then be given when a mature follicle was achieved (average diameter $\geq$18mm, serum E2 $\geq$200 pg/mL). Five cases of women with $\geq$6 months of amenorrhea with marked E2 deficiency (<20pg/mL) and increased serum FSH (>50 mIU/mL) were treated with conjugated estrogen 2.5-5mg/day. When FSH decreased to $\leq$11

mIU/mL hMG was started. The serum FSH for the 5 cases were 52, 58, 65.4, 112 and 120 mIU/mL. The woman with the serum FSH of 52 mIU/mL failed to ovulate the first cycle of treatment, but did ovulate the next two cycles. She conceived in cycle 2 and delivered a healthy baby [1].

The second woman whose FSH was 58 mIU/mL failed to ovulate. The third case where the initial FSH was 65.4 mIU/mL was diagnosed with POF at age 20 and was first treated at age 32. She failed to ovulate on the first treatment cycle but ovulated on her next 5 cycles and conceived on her fifth ovulation cycle and delivered a healthy baby [1]. Her serum FSH was 96 mIU/mL on the cycle of conception. Case 4 where FSH was 112 mIU/mL failed to ovulate. Case 5, whose POF was documented at age 17, and her first treatment was at age 26, ovulated in both treatment cycles but failed to conceive. Her FSH was 120 mIU/mL [1].

There are certain flaws of this technique. For one, hMG or FSH injections are very expensive. If there are no follicles available, one spends a lot of money on gonadotropins. In addition, one cannot continue estrogen because it precludes measuring follicle production of E2 since the oral estrogen adds to the serum E2. Finally, the stoppage of oral estrogen allows a rise of endogenous FSH, which may down-regulate the FSH receptors again. Thus, there was subsequently a refinement of this technique. First, the conjugated estrogens, or E2, to lower serum FSH was replaced with ethinyl estradiol (EE) because EE does not contribute to the serum E2 level. Ethinyl estradiol is the estrogen in almost all oral contraceptives. But oral contraceptives add progestins, and the progestins would cause abnormal endometrium preventing implantation and interference with cervical mucus. Thus, the solution was to compound EE without any P at 20 micrograms per pill. This modification of the technique was as follows: lower the FSH with EE no other estrogens, measure serum E2 levels and FSH, do not add ultrasound evaluation until one sees a rise in serum E2 (an indication of restoring sensitivity of the follicle). Furthermore, if the FSH is still elevated and E2 rising, do not add gonadotropins, but if FSH is only slightly elevated, but E2 levels are plateauing, add low dose (75 IU) FSH, but stop if E2 fails to rise. Finally, use P supplementation in the luteal phase. What option is there if the EE causes side effects or there is a possible risk of higher dose estrogen (history of breast cancer, thromboembolic disorders, etc.)? One can use leuprolide acetate to lower the serum FSH [2]. Gonadotropins are expensive. The reason why FSH injections are only given if there is some evidence of a rise in serum FSH is because if there are no antral follicles with restored FSH receptors available, there will be a lot of expense from use of gonadotropins with little chance of pushing a follicle to dominant follicle stage. Ultrasounds can be expensive, but also inconvenient, so the addition of ultrasound for monitoring is also only added when there is evidence of a responsive follicle by observing a rise in the serum E2.

A report on the first 100 cases of this modified technique was published in 1990. The range of ages for these 100 patients was 19-47 with a median of 34. There were 68 ovulations in 561 attempts (16%). The study required a minimum of 1 year of amenorrhea. The clinical pregnancy rate per successful ovulation was 28% (19/62), but about 50% miscarried [3]. The average time of treatment from initial diagnosis of POF was 2.2 years in those who conceived vs. 4.8 years for the 65 women who did conceive. The mean serum FSH was 70.5 mIU/mL for those who ovulated vs. 66.5 mIU/mL for those who failed to ovulate [3]. Since this published series of 100 cases of women with POF treated by this FSH receptor up-regulation technique, there have been no other series that have been published with natural conception. There has been one series with patients who needed IVF-ET with a 20% live delivered pregnancy rate per transfer [4].

There was a concept more than 40 years ago that one cause of apparent ovarian failure was FSH resistance, even though the ovaries had normal oocyte reserve, i.e., the follicles were resistant to endogenous gonadotropins. The thought was that this might be overcome by high dosage exogenous gonadotropins. There is, indeed, FSH resistance, but this is not related to ovaries that are replete with oocytes, but instead with follicle depletion related to the chronically high serum FSH levels which down-regulate the FSH receptors on the granulosa theca cells [5]. Using high dose gonadotropins will make matters worse because the serum FSH levels will increase even more. The question arises however, whether there are a certain minimal number of oocytes that are needed to induce ovulation and achieve pregnancies with DOR. In fact, there have been cases of ovulation induction and successful pregnancies in women with streaked gonads [6,7]. Ovulation and oocyte freezing has been accomplished even in a young teenager with primary amenorrhea and sexual infantilism (Turner's syndrome) using the FSH receptor up-regulation technique (unpublished).

There are circumstances where there appears to be FSH resistance despite what appears to be adequate oocyte reserve by pelvic sonography, who do respond to exogenous gonadotropins. However, these cases seem to be related to gonadotropinomas producing immunologically detected FSH that is biologically inactive [8,9]. Studies comparing IVF-ET outcome according to egg reserve status found that women $\leq$ age 35 with DOR were 80% as likely to have a live delivery compared to women aged $\leq$35 with normal egg reserve, whereas women age 36-39 were 70% as likely, and women 40-42, 50% as likely as long as this FSH receptor uptake stimulation technique was used [10].

Thus, it is likely that women with overt ovarian failure are less likely to achieve a live delivery even if ovulation induction is successful especially if they are of advanced reproductive age. Nevertheless, there is a published case report of a woman 45 years old who used the FSH receptor up-regulation technique and had a successful delivery despite appearing to be in overt menopause [11]. Furthermore, a case of a woman with a similar success using EE only without gonadotropins to induce ovulation who was 46.5 was also successful [12].

There does not seem to be any ceiling to how high the serum FSH can be to prevent a successful pregnancy. The highest level of FSH in the published literature was 164 mIU/mL in a 25 year old woman with POF [13]. There was, however, a very interesting case of a woman with POF who failed to conceive despite four fresh donor oocyte cycles in an IVF center on the west coast of the United States. She consulted our facility to consider whether there may be an immunological cause of her infertility so she could continue to try to deliver the baby herself, rather than use a gestational carrier, as suggested by the other clinic. We had suggested the use of dextroamphetamine sulfate (this topic will be discussed later) but told her to wait until she selected another donor. Despite her amenorrhea of 6 years' duration and her serum FSH of 143 mIU/mL with a serum E2 <15 pg/mL, we attempted to induce ovulation with the FSH receptor up-regulation technique. Ovulation was achieved by merely using EE alone [14,15]. Progesterone vaginal suppositories 800mg were supplemented in the luteal phase [16]. The FSH level that we published was the one we had obtained in our infertility center. We subsequently learned that while in the California IVF center her serum FSH had been as high as 185 mIU/mL. There have been many cases of successful pregnancies with serum AMH levels undetectable with both POF and DOR.

There is one other option to lower FSH and up-regulate FSH receptors in granulosa-theca cells, and that is to use a GnRH antagonist, if one cannot use the EE [17]. However, this is the most expensive option. The other advantage of EE over GnRH agonists, e.g., leuprolide acetate, or GnRH antagonists, e.g., ganirelix or cetrorelix, other than being less expensive, is that it helps create better endometrial thickness. Furthermore, EE also stimulates fertile cervical mucus to allow natural conception vs. intrauterine insemination (IUI).

Using the FSH Receptor Up-Regulation Technique for Women with Diminished Oocyte Reserve

A study published in the journal Fertility and Sterility in 2005 out of Cornell University (which at that time was considered one of the foremost IVF centers in the world) published their data that there were no live deliveries in women who even one time in their life on day 3 had a serum FSH ≥18 mIU/mL despite the transfer of embryos that appeared morphologically normal [18].

The question would naturally arise as to how live deliveries were possible in women with apparent menopause conceiving naturally even with serum FSH levels exceeding 100 IU/mL, yet no live deliveries following IVF-ET from a top IVF facility. One hypothesis is that the high dosage of FSH down-regulated a key FSH receptor that produces some enzyme or protein that is required for successful embryo implantation. Thus, the main principal of the FSH up-regulation technique in those women with DOR, who still menstruate, is not to raise the serum FSH even higher to prevent potential down-regulation of a key FSH receptor required for embryo implantation.

The specific methodology varies according to several factors including the degree of DOR, the interval length between menses, and the serum E2 and serum FSH levels in the early follicular phase. The general principle for treating women with DOR trying to conceive according to their particular circumstances will be described from various scenarios involving DOR.

Scenario number 1, i.e., women with amenorrhea with marked estrogen deficiency, i.e., POF, has been previously described in the preceding pages. In the 5 tables to follow, specific nuances are described how to most effectively treat women that have DOR but are not markedly estrogen deficient. For scenario 2, i.e., women with a short follicular phase one must remember that FSH starts stimulating the follicle from mid-luteal phase. Thus, with higher serum FSH levels the follicle may be driven faster. Therefore, a more advanced follicle may be found on day 3 with higher serum E2 levels. Estradiol inhibits FSH release from the pituitary. Thus, in evaluating oocyte reserve one should always measure the serum E2 along with the FSH since a higher E2 level could suppress the FSH level giving the false impression that some women with DOR have normal egg reserve [23]. There are some women with normal egg reserve who have elevated serum FSH related to a gonadotropinoma [8,9]. They can be separated from those with DOR by the demonstration of a serum AMH >1ng/mL.

As seen in scenarios 1-4, EE is useful in inducing ovulation by up-regulating down-regulated FSH receptors on granulosa theca cells, lengthening a short follicular phase, and prevention of premature luteinization [15]. Ethinyl estradiol has also been used to counteract the adverse effect of clomiphene citrate or letrozole to allow monitoring by serum E2 along with ultrasound monitoring of follicular size since EE does not measure in the E2 assay [15,24,25]. It can also be used to treat hostile mucus in various protocols even when anti-estrogen drugs are not used for those patients who prefer not to perform IUI [26].

With scenario 6, it has been previously demonstrated that for women with at least 1 year of infertility, where the only abnormality found in their infertility investigation was a luteal phase defect (as evidenced by an out-of-phase biopsy in the late luteal phase), 24 of 31 women conceived with just vaginal P in the luteal phase vs. those treated with clomiphene citrate or hMG where only 3 of 27 conceived and 2 miscarried [27,28]. Interestingly, 16 of 25 of the follicle maturing drug group, who failed to conceive in their first 6 months, were successful in conceiving with only 1 miscarriage when treated with luteal phase vaginal P without follicle stimulating drugs during the ensuing 6 months [27,28]. Thus, though it may vary from patient to patient, or even cycle to cycle, in women with mild, moderate, and severe diminished oocyte reserve, Table 6 provides the usual medications that are required to treat this group.

One other medication may be needed to maximize pregnancy success rates: drugs that release dopamine to diminish excessive uterine permeability leading to excessive inflammatory cells, especially natural killer cells [29]. The most common cause of DOR may be excessive inflammation of pelvic tissues, including

ovaries that may damage existing follicles over time. This condition usually is responsible for various types of pelvic pain including vulvodynia, mittelschmerz, dyspareunia, dysmenorrhea, and chronic pelvic pain [30-34]. The increased permeability may lead to menstrual tissue escaping the uterus and implanting ectopically in other areas of the pelvis, which may exacerbate the pain, but is not the cause of the pain. When the woman has pelvic pain and there is the presence of ectopic endometrial implants it is called endometriosis or adenomyosis, but without the presence of these modalities, it is just called the increased cellular permeability syndrome with pelvic pain [35]. Whether endometriosis is present or not, the increase in inflammatory cells may lead to rejection of the fetal semi-allograft, and not only cause DOR or POF, but infertility even in the presence of normal oocyte reserve [29].

One study evaluated by endometrial biopsy a marker for pelvic inflammation (BCL6) which is highly associated with the presence of endometriosis [36]. This study found the BCL6 marker in 52 of 69 women with unexplained infertility and normal egg reserve with a mean age of 36. Following their first IVF-ET cycle, the live delivered pregnancy rate per transfer was 58% for 17 women negative for the BCL6 marker vs. only 11% for the large majority of women (n=52) who were positive for the BCL6 marker [36].

A recent study found that 17 of 25 women with pelvic pain not effectively treated with standard medication (oral contraceptives, progestins, P or leuprolide acetate) reported marked improvement in pelvic pain at the 3-month mark of dextroamphetamine sulfate treatment. Two reported moderate relief so 76% after 3 months of a small non-addicting dosage of dextroamphetamine sulfate had moderate to marked relief of pain [37]. There is evidence that the use of dextroamphetamine sulfate with its release of dopamine from sympathetic nerve fibers can not only relieve pelvic pain, but markedly improve pregnancy rates in women with pelvic pain whether they have normal or diminished oocyte reserve as seen in Tables 7 and 8 [29].

This article also provides interesting anecdotal cases strongly suggesting a marked beneficial role of dextroamphetamine sulfate improving fecundity [29]. The mechanism is thought to be increased release of dopamine from sympathetic nerve fibers, thus diminishing excessive permeability of pelvic tissues, which led to a pathological increase in the normal inflammatory process that is needed, amongst other things, for the creation of spiral arteries [29]. Thus, the list of medication to help women to have babies naturally despite DOR should include dextroamphetamine sulfate, especially for those with pelvic pain, but not necessarily limited to them, especially if they have any of the other clinical manifestations of the increased cellular permeability syndrome, or an unknown cause of the DOR [35]. Dextroamphetamine sulfate may even be used to help with recurrent miscarriage [38].

Table 1: Scenario 2 – Oligomenorrhea with elevated FSH and/or low serum AMH.

1. Obtain baseline hormone levels and possibly ultrasound.
2. If E2 <20 pg/mL and FSH elevated observe by bloods alone for a week or two.
3. If no rise in E2 treat as a woman in ovarian failure as above by adding EE (or GnRHa or GnRHant if estrogen contradicted).

Table 2: Scenario 3 – Regular menses with short follicular phase and elevated FSH or decreased AMH.

1. One needs to attain a minimum level of serum E2 to develop adequate P receptors in the endometrium but also enough days of estrogen exposure is also needed.
2. As previously mentioned, increased FSH related to decreased negative feedback of inhibin B on pituitary cells can lead to higher FSH from mid-luteal phase and thus speed up follicular recruitment.
3. A short follicular phase can lower fecundity even if a mature follicle is achieved [19,20].
4. The easiest way to lengthen the follicular phase is by using estrogen in higher dosages (especially EE) to lower FSH in the early follicular phase.
5. E2 can be used in the preceding luteal phase to keep the FSH lower from mid-luteal phase.
6. Higher levels of E2, e.g., 4mg can be used from day 1 and then stopped after day 7 or 8.
7. Alternatively, EE can be continued the whole follicular phase with mild gonadotropins given toward the mid-follicular phase.

Table 3: Scenario 4 - Regular menses with premature luteinization [21].

1. Though premature luteinization, where a premature LH surge causes the P to rise above 2 ng/mL before a serum E2 of 200 pg/mL is reached, can occur in women with normal oocyte reserve or DOR, but it is much more common with DOR.
2. In some instances, the egg does release from the follicle and a 200 pg/mL E2 level is achieved but infertility occurs by extending the window of implantation too far by too many days of P before embryo implantation. Frequently, however, the egg fails to release from the dominant follicle.
3. Frequently the E2 level never gets to 200 pg/mL.
4. The least expensive treatment is to use EE to inhibit the premature rise in LH.
5. If the E2 is rising because FSH has only been lowered, but not suppressed, one can have a completely natural follicular phase with 10,000 IU hCG given when the follicle is mature.
6. Sometimes once the FSH is top normal or just slightly elevated low dose gonadotropins can be used to complete follicular maturation.

Table 4: Scenario 5 - Women with DOR, regular menses, adequate follicular phase length but follicle does not reach full maturity (E2 <200 pg/mL).

1. This is best treated by giving a boost of gonadotropins from middle to late follicular phase while the FSH is decreasing related to rising E2 levels with negative feedback to the pituitary.
2. This should be followed by extra P in the luteal phase [16,22].

Table 5: Scenario 6 - Women with DOR, adequate length to follicular phase, slightly decreased egg reserve, who appear to make a mature follicle:

1. Best treatment is just luteal phase vaginal P supplementation [16,22].

Table 6: The medication that may be needed to treat infertile women with DOR include:

1. EE
2. Vaginal P, oral P, and possibly IM P
3. Gonadotropins
4. GnRH antagonist
5. GnRH agonist
6. hCG
7. E2 in luteal phase

Table 7: Clinical and live delivered pregnancy rates in women aged ≤39 per fresh embryo transfer in women with pelvic pain taking dextroamphetamine sulfate vs. women not taking sympathomimetic amines who did not have pelvic pain.

	Taking Dex	Not taking Dex
Number	23	197
Number of clinical pregnancies (%)	13 (56.5%)	93 (47.2%)
Number of live delivered pregnancies (%)	10 (43.5%)	74 (37.6%)

Table 8: Clinical and live delivered pregnancy rates in women 40-42 having IVF-ET according to taking dextroamphetamine or not [27].

	Taking Dex	Not taking Dex
Number	11	77
Number of clinical pregnancies (%)	3 (27.3%)	17 (18.2%)
Number of live delivered pregnancies (%)	3 (27.3%)	9 (11.7%)

References

1. Check JH, Chase J. Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy. Fertil Steril. 1984; 42: 919-922.
2. Check JH, Wu CH, Check M. The effect of leuprolide acetate in aiding induction of ovulation in hypergonadotropic hypogonadism: A case report. Fertil Steril. 1988; 49: 542-543.
3. Check JH, Nowroozi K, Chase JS, et al. Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea. Fertil Steril. 1990; 53: 811-816.
4. Check JH, Wilson C, DiAntonio G, et al. In vitro fertilization (IVF) outcome in women in overt menopause attempting to induce follicular maturation by follicle stimulating hormone (FSH) receptor down-regulation. Clin Exp Obst Gynecol. 2016; 43: 181-183.
5. Check JH. Pharmacological options in resistant ovary syndrome and premature ovarian failure. Clin Exp Obst Gyn. 2006; 33: 71-77.
6. Check JH, Chase JS, Wu CH, et al. Case Report: Ovulation induction and pregnancy with an estrogen gonadotropin stimulation technique in a menopausal woman with marked hypoplastic ovaries. Am J Ob Gyn. 1989; 160: 405-406.
7. Shanis BS, Check JH. Spontaneous ovulation and successful pregnancy despite bilateral streaked ovaries. Infertility. 1992; 15: 70-77.
8. Check JH. Gonadotropinoma presenting as a case of pseudo-ovarian failure changing to macroprolactinoma. Clin Exp Obst Gyn. 2013; 40: 295-296.
9. Check JH, Dowland W. Detection of a microgonadotropinoma by magnetic resonance imaging performed because of excellent response to controlled ovarian hyperstimulation despite elevated day 3 FSH. Clin Exp Obst Gyn. 2015; 42: 279-281.
10. Check JH, Wilson C. The younger the patients the less adverse effect of diminished oocyte reserve on outcome following in vitro fertilization-embryo transfer as long as the proper ovarian stimulation protocol is used. J Reprod Contracep. 2013; 24: 221-227.
11. Check JH, Check ML, Katsoff D. Three pregnancies despite elevated serum FSH and advanced age: Case report. Hum Reprod. 2000; 15: 1709-1712.
12. Check JH, Check DL, Richardson K. Live delivery in a 46.5-year-old woman in overt menopause by restoring follicular sensitivity to follicle stimulating hormone (FSH). Gynecol Reprod Health. 2022, 6: 1-3.
13. Check ML, Check JH, Kaplan H. Pregnancy despite imminent ovarian failure and extremely high endogenous gonadotropins and therapeutic strategies: Case report and review. Clin Exp Obst Gyn. 2004; 31: 299-301.
14. Check JH, Katsoff B. Successful pregnancy with spontaneous ovulation in a woman with apparent premature ovarian failure who failed to conceive despite four transfers of embryos derived from donated oocytes. Clin Exp Obst Gyn. 2006; 33: 13-15.
15. Check JH. The multiple uses of ethinyl estradiol for treating infertility. Clin Exp Obst Gyn. 2010; 37: 249-251.
16. Check JH, Liss J, Check D. The beneficial effect of luteal phase support on pregnancy rates in women with unexplained infertility. Clin Exp Obstet Gynecol. 2019; 46: 447-449.
17. Check JH, Katsoff B. Ovulation induction and pregnancy in a woman with premature menopause following gonadotropin suppression with the gonadotropin releasing hormone antagonist, cetrorelix – a case report. Clin Exp Obstet Gynecol. 2008; 35: 10-12.
18. Roberts JE, Spandorfer S, Fasouliotis SJ, et al. Taking a basal follicle-stimulating hormone history is essential before initiating in vitro fertilization. Fertil Steril. 2005; 83: 37-41.
19. Check JH, Adelson H, Lurie D, et al. The effect of the short follicular phase on subsequent conception. Gynecol Obstet Invest. 1992; 34: 180-183.
20. Katsoff B, Check MD. Successful pregnancy in a 45-year-old woman with elevated day 3 serum follicle stimulating hormone and a short follicular phase. Clin Exp Obstet Gynecol. 2005; 32: 97-98.
21. Check JH, Chase JS, Nowroozi K, et al. Premature luteinization Treatment and incidence in natural cycles. Hum Reprod. 1991; 6: 190-193.
22. Check JH, Cohen R. The role of progesterone and the progesterone receptor in human reproduction and cancer. Exp Rev Endocrinol Metab. 2013; 8: 469-484.
23. Check JH, Chern R, Amui J. Successful pregnancy following in vitro fertilization embryo transfer in a 46-year-old woman with diminished oocyte reserve as evidenced by a high day 3 serum estradiol. Clin Exp Obst Gyn. 2011; 38: 209-210.
24. Check JH, Adelson HG, Davies E. Effect of clomiphene citrate therapy on post coital tests in successive treatment cycles including response to supplemental estrogen therapy. Arch Androl. 1994; 32: 69-76.
25. Check JH, Liss JR, Vaniver J. The effect of clomiphene citrate vs. letrozole on post-coital tests. Clin Exp Obst Gynecol. 2016; 43: 184-185.
26. Check JH. Diagnosis and treatment of cervical mucus abnormalities. Clin Exp Obst Gyn. 2006; 33: 140-142.
27. Check JH, Adelson HG. The efficacy of progesterone in achieving successful pregnancy: II, in women with pure luteal phase defects. Int J Fertil. 1987; 32: 139-141.
28. Check JH, Nowroozi K, Wu CH, et al. Ovulation inducing drugs versus progesterone therapy for infertility in patients

with luteal phase defects. Int J Fertil. 1988; 33: 252-256.

29. Check DL, Check JH. Novel methods of improving fecundity and various pathological disorders based on a hypothetical model of embryo implantation. Gynecol Reprod Health. 2020; 4: 1-15.
30. Check JH. Sympathomimetic amines are a safe, highly effective therapy for several female chronic disorders that do not respond well to conventional therapy. Clin Exp Obst Gyn. 2015; 42: 267-278.
31. Check JH, Wilson C. Dramatic relief of chronic pelvic pain with treatment with sympathomimetic amines – case report. Clin Exp Obstet Gynecol. 2007; 34: 55-56.
32. Check JH, Cohen R. The triad of luteal phase ocular migraines, interstitial cystitis, and dyspareunia as a result of sympathetic nervous system hypofunction. Clin Exp Obst Gyn. 2014; 41: 575-577.
33. Check JH, Jaffe A. Resolution of pelvic pain related to adenomyosis following treatment with dextroamphetamine sulfate. Clin Exp Obstet Gynecol. 2015; 42: 671-672.
34. Check JH. Increased tissue permeability and sympathetic nervous system hypofunction may be the common link between dysmenorrhea, chronic pelvic pain, Mittelschmerz, and Crohn's disease. Clin Exp Obst Gynecol. 2016; 43: 112-113.
35. Check JH. Changing the name of a syndrome: Sympathetic neural hyperalgesia edema syndrome becomes – the increased cellular permeability syndrome. Clin Exp Obst Gyn. 2017; 44: 819-823.
36. Almquist LD, Likes CE, Stone B, et al. Endometrial BCL6 testing for the prediction of in vitro fertilization outcomes: a cohort study. Fertil Steril. 2017; 108: 1063-1069.
37. Carpentier P, Meier B, Check JH, et al. Sympathomimetic amine treatment very effective for relieving pelvic pain in women even when hormonal therapy and surgery were not sufficient. 2020 American Society for Reproductive Medicine Virtual Meeting, October 17-21, 2020. Fertil Steril. 2020; 114: e203.
38. Check JH, Chern R, Katsoff B. Prevention of first-trimester miscarriage with dextroamphetamine sulfate treatment in women with recurrent miscarriage following embryo transfer – case report. Clin Exp Obstet Gynecol. 2014; 40: 471-472.