Article Type: Review Article
Volume 2, Issue 1

INTERNATIONAL JOURNAL OF CLINICAL & MEDICAL CASE STUDIES

The relationship between diminished ovarian reserve and the increased cellular permeability syndrome

Abstract

Background/Objectives: The purpose of this review and perspective is to discuss the most recent reviews of causation and treatment, with the goal of conception, of women with diminished ovarian reserve and Premature Ovarian Failure (POF). The perspective part of this review will provide our opinion on the suggested etiologies and therapeutic options suggested by these reviews but will also provide in detail our experience with treatment of DOR and POF in natural cycles especially with a technique known as the FSH receptor up-regulation technique. We will also discuss the likelihood that increased inflammation related to increased cellular permeability may not only play a role in the causation of oocyte depletion, but treatment aimed at correcting the cellular permeability defect may improve the chance of a successful pregnancy with DOR or POF.

Methods: The FSH receptor upregulation technique will be described in detail. We will also discuss the use of P supplementation in the luteal phase and the use of dopaminergic drugs.

Results: The results section will emphasize the multiple studies we have conducted over 40 years evaluating the efficacy of the aforementioned techniques mentioned in the methods section.

Conclusion: In contrast to the view expressed by recent reviews and by many practicing infertility specialists, we provide data showing not only reasonable live delivered pregnancy rates with DOR, but also with POF, even with inexpensive natural cycles.

Keywords: Premature ovarian failure; Diminished ovarian reserve; Increased cellular permeability; Ethinyl estradiol; Dopaminergic drugs; Progesterone supplementation.

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Received: Feb 19, 2025

Accepted: Mar 12, 2025

Published Online: Mar 19, 2025

Journal: International Journal of Clinical & Medical Case Studies

Introduction

In 1984, we published a manuscript showing that a technique aimed at restoring sensitivity of ovarian follicles to FSH by up-regulating down-regulated FSH receptors by lowering the elevated serum FSH levels, followed by gonadotropin stimulation, was able to induce ovulation in 3 of 5 of women who were seemingly in overt menopause, and with 2 of them having a successful pregnancy [1] (Table 1).

In 1990, we reported the outcome of using this technique with some modifications to further improve and refine this treatment in 100 consecutive cases of women in apparent overt ovarian failure [2]. The results are seen in Table 2.

Table 1: Ovarian induction and pregnancy rates in 5 cases of menopause following restoration of follicular sensitivity.

Case	Age at diagnosis	No. cycles tried	No. cycles concluded	Live deliveries
1	27	2	2	yes
2	32	5	5	yes
3	26	2	2	no
4	26	2	0	no
5	22	1	0	no

Citation: Check JH, Neulander M, Check DL, O'Neil MM, Wilson CBS. The relationship between diminished ovarian reserve and the increased cellular permeability syndrome. Int J Clin Med Case Stud. 2025; 2(1): 1017.

Table 2: Outcome of the restoration of follicular sensitivity in 100 consecutive cases of premature menopause.

No. cycles attempted	No. ovulations	No. pregnancies	No. live births
354	68 (19.2%)	19	8

Over the last 40 years, we have published over 80 research publications dealing with overt ovarian failure and diminished ovarian reserve, right up to 2024 (not counting any publications involving donor oocytes) [1-6].

However, it is clear after evaluating a very large number of women over these last 40 years from all over the world, with not just Premature Ovarian Failure (POF), but diminished Ovarian Reserve (DOR), that the majority of treating physicians are not aware of these inexpensive, non-invasive treatments with the goal of achieving successful pregnancy despite DOR or POF. It was not clear as to whether the information about these treatment techniques for DOR is known, but just not utilized by the majority of reproductive endocrinologists and gynecologists, or for some reason the information somehow has not reached the treating physicians. Knowing that busy physicians tend to favor reading summary articles or meta-analyses to influence their treatment modalities, we decided to read recent reviews generally assigned to experts, or at least scientists that have significant experience in this field. We found 4 such reviews from 2021 to 2024 including Yin et al 2021 "Recent progress in the treatment of women with diminished ovarian reserve," Zhu et al 2023 "Potential factors result in diminished ovarian reserve: a comprehensive review," Zhang et al 2023 "Treatment progress in diminished ovarian reserve: western and Chinese medicine," and Zhu et al 2024 "Understanding the mechanisms of diminished oocyte reserve: insight from genetic variants and regulatory factors" [7-10].

The reviews by Yin et al had 50 references. The 1st 2023 manuscript by Zhu et al had 162 references and the 2024 manuscript by Zhu et al have 131 references, and the 2023 manuscript by Zhang et al had 56 references. However, there were not any references that included our studies [7-10]. Since our techniques of treating POF and DOR has been reasonably successful, and our technique does not seem to be well known, we chose to write a perspective on not only methods to treat DOR and POF with the intent of achieving a pregnancy, but to promote new insight as to the most likely cause of the majority of cases of DOR which may further improve the chance of success from the method that we refer to as the FSH receptor up-regulation technique. The other method that improves fecundity in this group is by reducing excessive permeability of irritants into pelvic tissues causing a reduction of an increased inflammatory state which otherwise would lead to immune destruction of the fetal semi- allograft. This type of treatment would also provide a method to slow down the rate of subsequent loss of oocytes.

The most recent reviews and perspectives that we have published on this subject were in 2022 [11,12]. The objective of this perspective is to briefly familiarize the readers with the tenets of this FSH up-regulation technique and the studies supporting its efficacy, but to add subsequent publications not included in those 2 perspectives that help to provide support of our concept as to the most likely cause of the majority of cases of DOR, and how this immunologic concept of causation of DOR may add novel treatments to further enhance the efficacy of the FSH receptor up-regulation technique to improve the chance of live delivery in women with DOR and POF.

Views of causes and treatment of DOR (and POF) as summarized in the aforementioned most recent reviews [7-10]

Introductory remarks

Before presenting our perspective, or the best method, in our opinion, to correct infertility related to DOR or POF, we wanted to evaluate other opinions as to how to treat these entities. From our experience, most of the patients that we have evaluated who have consulted other reproductive endocrinologists were generally advised of a very poor prognosis, and the patients have generally been steered toward the use of donor oocytes. If the couple did not consider donor oocytes, then the infertility specialist has generally recommended In Vitro Fertilization (IVF) using high dosage gonadotropins. Frequently they also advise the addition of Pre-implantation Genetic Testing for aneuploidy (PGT-a) because these infertility specialists inform the patients with DOR and POF that the risk of a fetal chromosome abnormality leading to the birth of a live baby with physical and mental deficiencies are similar to women of advanced reproductive age. In the succeeding pages we will present data showing why we disagree with that approach and those conclusions.

Thus, to determine how do other scientists and physicians outside of the United States treat DOR, and if their views are different, we wanted to avoid countries whose financial structure is based on capitalism. There is no question that the majority of the fertility centers in the United State are run as businesses, so suggestions for therapy are sometimes geared for what is best for the profit of the infertility center rather than the ideal therapy for the patients with consideration of their wishes and finances.

Thus, we chose these four aforementioned reviews not only because they were recent, but they came from Chinese fertility centers where capitalism is generally not a factor.

The review by Yin et al related to etiologic factors [7]

Yin et al mentioned the standard causes of DOR including advanced age, family history of early menopause, genetic factors e.g., x chromosome mosaicism or FMR1 gene mutation, endometriosis, pelvic tuberculosis, ovarian surgery, chemotherapy, radiation therapy, autoimmune disease, smoking, and environmental factors [7,13-15].

Though we do not disagree with these etiologic factors contributing to DOR, they do not leave the reader with any concept as to which of these factors are more frequent or more important, nor whether the type of etiologic factor dictates any additional treatments, other than inducing or correcting ovulation defects and possibly increasing the number of follicles.

Similar to the United States, they allude to improvement of success by improving outcome following IVF, and imply that IVF is the optimal choice. We hope to show in succeeding paragraphs that there are ways to have adequate success rates without the expense of IVF. We will show that the majority of stimulation protocols used to recruit more follicles for IVF could actually significantly reduce the patient's chance of success when they have DOR.

In succeeding paragraphs, we hope to show that "autoimmune" etiologic factors, which includes endometriosis, is the most common etiology for DOR. Furthermore, based on this concept of autoimmunity related to increased cellular permeability, there are additional immune strategies that can be added to improve the chance of pregnancy beyond achieving normal

or supranormal numbers of mature dominant follicles. Furthermore, this additional method of immunological treatment is inexpensive.

The discussion of treatment by Yin et al [7]

Human stem cells: Yin et al discuss many animal studies (mostly in mice) in which stem cells from various sources were used to try to improve ovarian function in mice with DOR. The one human study mentioned used bone marrow derived stem cells and was a prospective study [16]. The study showed that ovarian function improved in 81.3% of patients with DOR with an increase in antral follicle count of 3 or more follicles and/or two consecutive increases in AMH levels [16]. They also claimed that that this autologous stem cell ovarian transplantation increased the number of stimulable antral follicles and oocytes. However, the rate of aneuploidy was still high in these poor responders and thus no improvement in Live Delivered Pregnancy Rates (LDPRs) [16].

Yin et al conclude the discussion of the potential use of stem cells in women with DOR by stating "the in-depth analysis of the stem cell and identification of key molecules need further exploration to provide a new paradigm basis for cell-free treatment strategies." Our contention is continued research to improve medical conditions is admirable, but it is clear that autologous stem cell therapy is nowhere near the state where there will be clinical benefit as yet. It is obviously invasive, and we know that there are a few clinics around the world offering stem cell therapy which significantly increases expense for desperate patients. The shame of the matter is that there are already very effective inexpensive methods to help patients achieve pregnancies, especially for patients with DOR, but even patients with POF. These techniques will be discussed later in this manuscript. None of these methods or concepts were discussed by Yin et al [7].

The one study referred to using stem cells for humans by Herralz et al evaluated the efficacy of stem cell therapy by In Vitro Fertilization-Embryo Transfer (IVF-ET) and pre-implantation genetic analysis for aneuploidy (PGT-a) [16]. We will discuss later that not only does IVF-ET with PGT-a add a greater expense to patients with DOR (many of which could conceive naturally) but the type of controlled ovarian hyperstimulation used may actually markedly decrease the likelihood of success. We will discuss the basis for that concept later in the manuscript.

Dehydroepiandrosterone (DHEA): Yin et al review the theoretical mechanism by which DHEA supplementation can improve ovarian function [7]. They refer to a study that showed that DHEA improved ovarian reserve and pregnancy rates in poor responders [17]. They also referenced a retrospective study that showed that DHEA increased the number of embryos created and improved cumulative pregnancy rates [18].

However, in medicine, generally not all studies agree. Yin et al refer to the meta-analysis by Qin et al that putting the positive and negative studies together the systematic review failed to show that DHEA supplementation increased the number of oocytes retrieved when considering the IVF cancellation rate [19]. Overall, the study did find an increase in the clinical pregnancy rate but without reducing the miscarriage rate [19]. However, when they evaluated the subset of randomized controlled studies (RCTs) there was no difference in the clinical pregnancy rate [19]. Thus, Yin et al state "taken together DHEA might have a beneficial effect in patients with DOR, but the method of DHEA treatment and it's in-depth mechanisms still need further research to confirm these effects" [7].

We do not prescribe DHEA supplementation for the patients we treat with DOR or POF. The selection of the eventual dominant follicle from the group of antral follicles is dependent on at least one (and usually just one) of the developing follicles to convert the follicular fluid from androgen dominance to estrogen dominance. Once the follicular fluid is estrogen dominant the follicle controls its own destiny. Since the Anti-Mullerian Hormone (AMH) functions to inhibit the FSH induced aromatase enzyme, and thus inhibits intrafollicular estradiol (E2) production, it may be that the follicle with the least amount of AMH is the one that allows the oocyte contained in the follicle to advance to the metaphase II stage without undergoing atresia [20]. The other follicles with more AMH will not make sufficient E2 in view of the decreasing levels of FSH because of negative feedback of E2 on pituitary release of FSH [20]. Thus, logically, adding more androgens by supplementing DHEA would make it more difficult to convert the androgen dominant follicular fluid to an estrogen dominant fluid. Therefore, making the follicular fluid more androgenic by supplementing DHEA could have a negative vs positive effect on fecundity.

Theoretically, if DHEA or androgens that are generated from DHEA increase the number of antral follicles able to progress to mature dominant graafian follicles, and/or increase the quality of the oocytes leading to higher LDPRs, then one should observe in poor responders a higher quantity of Metaphase II (MII) oocytes, and higher number of embryos formed, and a higher Live Delivered Pregnancy Rate (LDPR) following IVF-ET if they have higher levels of serum DHEA. Our own studies, if anything, showed an opposite finding having more oocytes and higher LDPRs with lower serum DHEA levels [21]. Our results are seen in Table 3.

Table 3: Pregnancy rates according to serum levels of DHEA following IVF-ET.

Category	Group	Mean DHEA-s levels (ng/dL)	Statistical significance
IVF-ET Cycles (<4 eggs vs. >5 eggs)	<4 eggs (Non-pregnant)	148.0±82.8	p=NS (ANOVA)
	<4 eggs (Pregnant)	143.9±47.7	
	>5 eggs (Non-pregnant)	138.5±26.4	p=NS (ANOVA)
	>5 eggs (Pregnant)	103.5±41.9	
Lowest vs. Highest DHEA-s Values	10 Lowest Values	70.4±23.2	p<0.05 (ANOVA)
	10 Highest Values	243.2±64.4	
Pregnancy Rates (PRs) - Clinical (8 weeks)	Low DHEA-s Group	40.0%	p=NS (Fisher's exact test)
	High DHEA-s Group	20.0%	
Pregnancy Rates (PRs) - Live Birth	Low DHEA-s Group	30.0%	p=NS (Fisher's exact test)
	High DHEA-s Group	20.0%	
Conception Within 3 Cycles	Conceived	140.7±57.3	p=NS (ANOVA)
	Did Not Conceive	154.1±91.4	

Human Growth Hormone (hGH): Yin et al review the potential benefit of treating patients with DOR or POF with hGH [7]. They refer to studies showing potential beneficial effects that could improve the chance for a successful pregnancy in this group. As frequently seen, some studies find a benefit, and some do not. Thus, when one analyzes all the studies as a whole, Yin et al refer to the meta-analysis by Hart et al which did not show any evidence of an increased live birth rate with hGH therapy when used with IVF-ET [22].

Our treatment philosophy for all patients, whether they have Normal Oocyte Reserve (NOR) or DOR, is, 1) to be as cost effective as possible 2) to consider the patient's wishes which may not always be the most cost effective option for them, 3) to disregard the "business" of medicine and provide the most cost effective therapy, but include the patient's desires, even if it may lower a fertility center's published success rate (and thus potentially influence a patient to seek help from another infertility center because they appear to have a highly successful program), and 4) be open minded to studies from other research centers, especially if the patients want to consider an adjunctive therapy that they either read about, was part of a treatment rendered by a previous infertility center, or a treatment that a friend was given which could have played a role in a successful pregnancy [23,24]. For example, many couples with DOR, where IVF may or may not be their only treatment option to become pregnant want to be treated by IVF despite the expense because when the most appropriate follicle maturation protocol is used, it increases their chances of success. They desire IVF with their own eggs because the option of donor gametes or adoption is not acceptable to them [25].

Because of the expense of hGH therapy, we have not conducted our own studies with hGH as yet. We considered that the data with hGH therapy was not sufficient to warrant the extra expense of hGH therapy. Though we were aware of the meta-analysis not finding improvement in LDPRs, our philosophy was to allow the patient to take the hGH if they requested it after making them aware of studies not supporting the efficacy of hGH to improve fecundity, because many of the negative studies did not use, in our opinion, the correct follicle stimulation protocol (which will be discuss later in this perspective).

We plan on performing a retrospective analysis, to be completed in time for the abstract deadline for the 2025 American Society for Reproductive Medicine (ASRM), to see if women with POF or DOR whose follicular recruitment involved the FSH receptor up regulation technique for IVF-ET, who took hGH strictly by patients' own suggestion and desire, showed any benefit in properly matched patients who did not take hGH [26].

At our medical school a Randomized control Trial (RCT) requires Institutional Review Board (IRB) approval, and it would be highly likely that the IRB would require our group to provide the hGH gratis to the patient if we requested an RCT to evaluate hGH efficacy for DOR. As a strict patient desire option this circumvents our need for IRB approval, and although not as scientifically valid, may still provide useful information.

We do allow patients with DOR and POF in non-IVF treatment cycles to use hGH, but gaining information for this group is much more time consuming since their results are not computerized. Nevertheless, if the IVF study shows potential value of hGH adjunctive therapy for IVF-ET, we will evaluate using the FSH receptor up-regulation technique and its efficacy in non-IVF cycles retrospectively also.

Melatonin treatment: Yin et al refer to some studies showing the theoretical benefit of melatonin related to its antioxidant activity, thus being able to scavenge free radicals [27]. They refer to a double-blinded placebo –controlled clinical trial by Jahroni et al [28]. Though this study showed a higher serum E2 levels following melatonin therapy in patients with DOR and a higher number of good quality embryos, there was no measure of pregnancy outcomes [28].

Many of our patients are already taking antioxidants e.g., 3 mg melatonin or 200-400 mg CO-Q-10, and we do not discourage their use with the thought that they are inexpensive and could possibly help in some instances.

Traditional Chinese medicine: Yin et al refer to studies of various Chinese herbs on improving egg quality including polysaccharides of fructose corni, yifuning, kuntai capsules, and climen that may be important in ovarian function. However, there are no studies showing clinical benefit [29-32].

Yin et al refer to studies on ovarian function concerning other naturally occurring substances including curcumin, chi to san and rapamycin [7]. As mentioned, patients with DOR and POF via the internet hear about these " natural substances," and in general, our response is that though there are no studies for which we are aware that demonstrate a higher LDPR, but it is possibly of benefit, we let them use them if they want with the exception of rapamycin because there is evidence that its long term use can be detrimental to ovarian function, and the short-term potential benefit has only been found in mice [33].

Intraovarian platelet-rich plasma (PRP): Yin et al refer to 2 studies suggesting that ovaries can be rejuvenated by injection into the ovaries with PRP [34,35]. The treatment regimen requires a laparoscopy and thus surgical risk, and an increased expense. Frequently insurance companies refuse to pay for even the laparoscopy because they consider PRP as experimental. There was limited power in these 2 studies [34,35].

The review by Zhang et al [9]

Hormonal replacement treatment: If one would ask us as to what are the 2 most common drugs or treatments that we use for POF and DOR, indeed, it would be estrogen and progesterone. However, there is a science to using them. Zhang et al did not elaborate much as to what estrogen/progesterone method constitutes the technique [9]. Were they referring to cases with POF or DOR or both? What type of estrogen? What type of progestin? Are they referring to synthetic progestins e.g., medroxyprogesterone acetate or dydrogesterone? We would not consider synthetic progestin sufficient since we have demonstrated that the only progestin that can stimulate a key immunomodulatory protein called the Progesterone Induced blocking Factor (PIBF) is progesterone itself [36]. (In the succeeding next subsection, we will be presenting a simplified working model of how successful embryo implantation occurs, and how making sufficient PIBF is needed for not only the fetal-placental semiallograft to avoid immunosurveillance, but also most, if not all, malignant tumors) [37-40].

We suspect since details were eliminated, that Zhang et al was suggesting that merely placing a woman with POF on estrogen and progesterone cyclical therapy may, overtime, lead to a fortuitous spontaneous ovulation, and thus spontaneous ovulation and pregnancy is more likely to occur than merely providing no hormonal replacement at all. We will in a later section provide specific details of a method that uses an estrogen (ethi-

nyl estradiol or EE) that allows monitoring of serum E2 (because it is not measured in the assay for serum E2). Natural vaginal P is provided, but not at a set point, as in hormonal replacement therapy, but only after ovulation has been documented. We will describe this technique in detail in a later section. However, to better understand the various nuances, we want to first describe a working model of the intricacies of this technique which is based on the principles of this model and thus could vary in different patients, and even in the same patient in different cycles.

A working model of embryo implantation [41]: Based on research in our own laboratory, we have created a model of a potential mechanism to establish proper embryo implantation. We present this model as abbreviated as possible, but with enough explanation to understand our methods for potentiating a live birth in menstruating women with DOR, or women in apparent menopause in whom we re-sensitize their follicles to FSH, allowing the development of a dominant follicle followed by ovulation. We will first concentrate on a model in normal fertile women. There are known other molecular events that we will exclude because their knowledge is not essential as yet to treat patients with DOR with the goal of achieving a normal pregnancy. We fully expect that in time our own studies and the studies of others will modify this model and will possibly disprove some of the concepts. However, at this time, this model has allowed the accomplishment of many viable deliveries in patients who were told by others that their only hope was to use donor oocytes.

Major events occurring during the proliferative phase (or follicular phase depending on reference to endometrial or follicular maturation events)

1. As estrogen increases by FSH stimulation of the granulosa-theca cells beginning with antral follicles, the estrogen allows the growth and appropriate histologic changes in the endometrium mostly through stimulation of genomic nuclear estrogen receptors.

2. The main and most physiologic estrogen is estradiol (E2).

3. Follicular phase refers to the point before the LH surge.

4. During the follicular phase stimulation of the granulosa-theca cells, mostly by FSH, is very efficient in converting the initial hormone secreted, progesterone (P), to E2 by first enzymatic cleavage of 2 carbons from the 21-carbon backbone of P to make androgens. This is followed by very efficient cleavage of one more carbon off the 19-carbon backbone of androgens by an FSH induced aromatase enzyme to make E2.

5. E2 increases the proliferation of a minority White Blood Cell (WBC) called a dendritic cell at the time of peak serum E2 level just before the LH surge.

6. During the follicular phase the serum P remains low (e.g., 0.3-0.6 ng/ml) related to efficient conversion of P to androgens e.g., testosterone, and then conversion to E2.

Major event occurring in the pre-ovulatory time (from LH surge to just prior to oocyte release)

The rise in LH inhibits some of the efficient enzymatic cleavage of 2 carbons off P thus causing the start of a rise of P.

1. The P will not exceed 2ng/ml before the egg releases.

2. This initial rise in P interacts with slow acting genomic nuclear P receptors (nPRs) leading to the secretion of various molecules needed for proper histologic development of the secretory endometrium.

3. The initial rise in P also interacts with fast acting non-genomic (epigenetic) membrane progesterone receptors (mPRs), which, as we will discuss shortly, is needed to help prevent immune destruction of the fetal-placental semi-allograft,

4. The rise in P blocks the biogenic amine dopamine to some degree. Since one of the functions of dopamine is to decrease cellular permeability, the suppression of dopamine allows the infiltration of unwanted irritants into the pelvic tissues, including the endometrium, causing inflammation and thus enhancement of cellular immune factors. Some studies find that 70% of the white blood cells in the fetal-placental microenvironment are Natural Killer (NK) cells, 20% macrophages and 10% cytotoxic T-cells [42].

5. P stimulates the secretion of a glycoprotein called mucin 1 which coats the endometrium, which thus impairs the embryo from implanting until a hole is made allowing exposure to the endometrium. (which we think is partly related to the action of the increased dendritic cells) [42].

Major events post ovulation (referred to as the luteal phase or secretory phase based on reference to follicular events vs endometrial events)

1. During the proliferative phase the large majority of uterine arteries have thick walls. Thus, to sustain a pregnancy to term one needs to develop some thin-walled arteries to allow nutrient exchange between mother and fetus. The increased cellular permeability leads to increased endometrial inflammation by infiltration of irritants, which increases cellular immunity, which facilitates the removal of the thick walls of certain designated uterine arteries to allow further conversion to thin-walled spiral arteries.

2. As mentioned, the dendritic cells that were influenced to proliferate by E2, seem to be the main WBC involved in attacking the mucin-1 barrier providing a rift to allow exposure of the endometrium to occur by day 5. Through chemokine secretion the day 5 blastocyst is attracted to the endometrium where it subsequently attaches.

3. Helped by the secretion of immunomodulatory proteins through interaction of P with mPRs (e.g., the parent 90kDa form of PIBF and the immunomodulatory protein Progesterone Receptor Membrane Component-1 protein (PGRMC-1)), the fetal placental unit invades the endometrium on day 6. The 90kDa form of PIBF and PGRMC-1 also help allow the proper depth of trophoblast invasion. These immunomodulatory proteins are also used by cancer cells to invade normal tissue [43].

4. Some of the 90 kDa parent form of PIBF is divided into small splice variants which inhibit the cellular immune cells in the fetal placental microenvironment from immunologically rejecting the fetal placental semi-allograft [44-46].

5. On day 6, with invasion of the trophoblast, cells are shed from the extra-villus trophoblast forming a single layer of trophoblast cells on the cell wall depleted arteries to form a new cell wall of the uterine arteries giving them

stability, but now having a cell wall only 1 cell thick, these newly formed spiral arteries can allow nutrient exchange between mother and fetus.

6. Though LH begins to decline after the 48-hour surge time period, it is high enough to allow continual rise of P to mid-luteal phase by the inhibition of P cleavage to androgens, and will continue to rise if there is conception with human chorionic gonadotropin rescuing the corpus luteum.

Definition of DOR and POF used in our studies

There are many definitions of what constitutes DOR. Many of our studies used a cut-off of day 3 FSH of 11 mIU/ml, i.e., >11 mIU/ml would indicate DOR and ≤11 MIU as normal as long as the FSH is not falsely lowered by a higher serum E2 from recruitment of an early follicle because of high FSH levels stimulating faster follicular development. Women with serum E2 levels over 50 pg/ml on day 3 may indeed have DOR even if the serum FSH was normal [47].

Another possibly superior way to detect DOR is by measuring serum Anti-Mullerian Hormone (AMH) levels. We have generally considered serum AMH levels under 1 ng/ml (which can be obtained anywhere in the menstrual cycle) as evidence of DOR.

Those patients closest to the cut-off for DOR, whether by day 3 serum FSH or serum AMH are more likely to have regular menstrual cycles, and those with serum levels indicative of very low oocyte reserve are more likely to have oligomenorrhea (which could be anovulatory or ovulatory) or have amenorrhea with or without estrogen deficiency.

Before proceeding with our methods and thoughts on the main cause of DOR and POF and how based on the concepts of up and down regulation of polypeptide hormones, e.g., FSH, by internalization of the receptor into the cytoplasm, we wanted to add the thoughts of Zhu et al on these issues concerning DOR and POF.

Contribution to the understanding of the potential etiology of DOR and POF and its treatment by Zhu et al [8]

One review we read to write this perspective is the manuscript by Zhu et al [8]. We recommend it to the readers if one wants to review a good summary of hormonal and molecular events that could play a role in DOR or POF [8]. The title is "Potential factors result in diminished ovarian reserve: a comprehensive review [8]. They state that ovarian reserve can be affected by many factors including hormones, metabolites, initial ovarian reserve, environmental problems, diseases, and medication among others. They also state that "attributed to its unclear mechanism and complex clinical features, it is difficult for physicians to administer targeted treatment." Their review discussed the potential influences and pathogenic factors that may explain the possible mechanism of DOR, which can be improved or built upon by subsequent researchers to verify, replicate, and establish further study findings, as well as for scientists to find new treatments."

As we commonly see in medicine, upon reading an erudite review, the physicians or scientists reading the manuscript looking for answers as to how to treat the patient seeking his/her help at present is left with "there does not appear to be any good treatment at this time, but hopefully continued research will find an answer in the near future." Indeed, scientists and researchers should also read the very erudite review by Zhu et al entitled "understanding the mechanism of diminished oocyte reserve insights from genetic variants and regulatory factors" [10]. They do a great job in discussing new ovarian research including genes that may be a factor, and thus the potential role of gene mutation, and also discuss the emerging potential effects of micro-RNA and other factors.

The abundance of studies at the molecular level led them to discuss "overview of current and emerging drug treatments." Zhu et al offer no guideline as to how to treat the condition at present. Instead, based on possible new gene or "molecular insights" and the possibility of exploring sirtuins and members of the Sirtuin family e.g., Sirt-1 and Sirt-3, they mention that resveratrol and curcumin can activate Sirt-1 and Sirt-3. This information may be useful in the future for some scientists to create a drug based on these concepts to eventually improve ovarian function in women with DOR or POF, but it is highly unlikely that these food additives would provide at present an important therapy for treating POF by their ingestion.

Our methods for treating DOR and POF

Introduction: The difference between a review and a perspective is the latter allows the authors to combine their own experience in clinical practice, combined with their own research, but to carefully consider the research and publications and views of others. The lead author of this perspective did write what would be considered a perspective on the same topic in 2022. After reviewing an invitation to write a manuscript for the journal, knowing that seeing a very large number of patients with DOR or POF (who usually had sought the experience of other infertility specialists before consulting our group), that the scientific approach that we use that has been so successful in achieving live deliveries resulting in many referrals predominately through patient to patient contact through the internet reviews, and by looking at reviews since 2022, it seemed clear that most physicians are still not aware of this FSH receptor up-regulation technique [12].

Nevertheless, before deciding to write another perspective on this subject, we wanted to see if any recent reviews on the subject, which are usually performed by scientists or physicians rendered experts in the field, use our treatment protocols or are at least aware of them. It was also clear by reading the 4 recent reviews that we found since 2022 concerning DOR or POF that even experts do not seem to be aware of our philosophy, publications, data, and treatment techniques.

The treatment methods and our adjustments of the Controlled Ovarian Hyperstimulation (COH) protocol for IVF-ET has also been provided and a review of IVF for DOR and POF has been written also in 2022 [11]. It is easier to obtain data for IVF-ET cycles since the data is computerized. However, in making the decision on what topic to write about for this invited manuscript, we attended an infertility conference whose chairman has, similar to our practice, a predominance of patients that tend to be older, have DOR, and have been unsuccessful in other tertiary infertility practices. We were not invited speakers, just attendees.

Though there were many talks and discussions concerning DOR (not so much POF), our decision to write about our long-term experience with treating DOR and POF was solidified by the failure to have any discussion at all about our approach at this meeting. Many of the invited speakers did discuss many of the potential future uses for some of the aforementioned pro-

cedures discussed by the authors of the reviews we selected. The general consensus was that none of the methods mentioned in these aforementioned 4 reviews were considered as making a significant impact on improving fertility outcome in women with DOR at this meeting. In fact, there was a consensus by the panel that some of these procedures were being used for financial gain of the infertility center, and thus most of these techniques were considered unethical if they are being used except in an approved clinical trial. We do agree with that philosophy. However, most patients with DOR and POF can achieve live deliveries without IVF-ET which obviously is much more expensive than intercourse. We asked the chairman, who treats a high percentage of women with DOR and also advanced age as to what percentage of his patients are treated with IVF, and his answer was all of them!

In our effort to not harm patients financially, our philosophy is to try to treat these patients without IVF-ET unless there is a problem e.g., damaged fallopian tubes, a significant male factor problem, or the Luteinized Unruptured Dollicle (LUF) syndrome. As we will discuss later, there may be a higher Live Delivered Pregnancy Rate (LDPR) with IVF-ET if the degree of DOR is mild to moderate, and thus we would leave the choice up to the patient considering their finances and insurance. Thus, we decided that for this perspective we would emphasize treating DOR and POF without IVF-ET. We will only refer to our own IVF studies if they provide more insight as to etiology or treatment in non-IVF-ET cycles. Perhaps, if invited to write another manuscript, we can write about treating patients with DOR or POF with IVF treatment.

DOR with regular menses

In the early days of treating infertility performing an endometrial biopsy to determine the histologic presence of sufficient progesterone was a very commonly used diagnostic tool [48]. Histologic advancement of endometrial changes from early to late luteal phase is generally a genomic function of P stimulation of nPRs leading to expression of molecules causing slower tissue changes. In contrast, non-genomic interactions with the mPRs lead to rapid changes. We had first studied a group of fertile women and found that most achieved an average sized dominant follicle of ≥18mm with a serum E2 ≥200 pg/ml in late follicular phase. Using this definition, we found that 58 of 100 women with an endometrial biopsy showing inadequate secretory changes as their only infertility factor that we could determine did make a mature follicle, and 42 did not. The 58 women making mature follicles were randomized to treatment with a follicle maturing drug (mostly clomiphene citrate) which was the standard of care at that time (and is frequently still the most commonly used treatment for women with infertility and regular menses) or the exclusive use of P supplementation in the luteal phase. The 6-month Live Delivered Pregnancy Rate (LDPR) was 23 of 31 women (74.2%) taking P exclusively vs 1 of 27 (3.9%) for those taking clomiphene or human gonadotropins [49].

However, for the 42 women who did not reach a 200 pg/ml serum E2 before the LH surge, exclusive use of progesterone vaginal suppositories had a 6-month LDPR of only 25% (3 of 12) vs 30% (3/10) with exclusive use of follicle maturing drugs vs 65% (13 of 20) with the combination of follicle maturing drugs in the follicular phase plus luteal support with P [49].

These principles also apply for women with DOR if the follicle is deemed mature, i.e., these women should be treated exclusively with vaginal P (e.g., 400mg progesterone vaginal suppositories twice daily) or commercial vaginal P in the dosages that are advised. Based on our studies of PIBF, we prefer only P rather than synthetic progestins because the latter does not increase the key immunomodulatory protein PIBF [36]. Though oral P does increase the serum PIBF made by circulating gamma/delta t cells, considering our immune model suggesting that the most important factor for conception and preventing miscarriage is the production of PIBF by rapidly proliferating cells of the fetal placental unit, we do not count on oral P because 90% of it is metabolized by the liver before reaching the endometrium [36,46]. Intramuscular P is also very effective, but it may cause moderately severe inflammation over time at the injection site.

Though we are using IVF data to make this following statement, there is reason to believe that women with DOR who make mature dominant follicles, and whose only abnormality is as an out of phase endometrial biopsy, would be 80% as likely to achieve a live delivery as women aged ≤35 with Normal Ovarian Reserve (NOR) 70% as likely as women 36-39, and 50% as likely as women aged 40-42 [50].

The histological changes in the secretory phase are mainly related to the interaction of P with the nPR, but with the knowledge that P must also interact with mPRs to allow proper depth of trophoblast invasion and allow avoidance of immune surveillance by providing non-genomic immunomodulatory proteins e.g., PIBF and PGRMC-1, one must consider that the need for supplemental P may exist even if the endometrial biopsy was in phase. We hypothesized that the decline in fecundity as a woman ages cannot be accounted for strictly by an increased rate of aneuploidy. We considered that fecundity may decline at age ≥30 related to making less or being less sensitive to P for induction of immunomodulatory proteins.

Furthermore, we considered that pelvic pain may be indicative of excessive number of cellular immune cells needed for uterine artery remodeling, so women less than age 30 with pelvic pain may also be in need of supplemental P therapy in the luteal phase to allow these rapid epigenetic actions of P with the mPR to occur.

Thus, we stopped using the luteal phase dated endometrial biopsy as a diagnostic tool to determine if supplemental P should be given. Instead, we treated all women with regular menses and absence of male, cervical or tubal factor, who were age 30 or older or had significant pelvic pain at any age with supplemental P. We found excellent results in the form of live deliveries by simply using supplemental P as seen in table 4 [51].

Table 4: Pregnancy rates according to age in women with unexplained infertility treated for a maximum of 6 months exclusively with P in luteal phase.

	Age <39.9	Age 40-45
Average length of infertility	2.3 years	3.1 years
Average age	32.5 years	42.8 years
Live pregnancy past 1st trimester	23/32 (71.7%)	5/26 (19.2%)
Ave. No. Of cycles using P	4.5	3.9

For this study only those women with unexplained infertility were treated exclusively with P. Initially, for age 39.9, 40 women were screened, but 8 eliminated for not achieving a mature follicle, and 7 of 33 women aged 40-45. Thus, the percentage of women attaining a mature follicle was similar in both age groups at 80% vs 82.5%.

From our clinical experience, the dated endometrial biopsy is not utilized by most infertility centers today. However, from our experience the patients are frequently empirically given clomiphene citrate or letrozole and intrauterine insemination by other infertility centers frequently either without supplemental P or frequently with insufficient P e.g., using 200 mg oral micronized P per day rather than vaginal or I.M. They are frequently guided toward IVF-ET where they are given proper luteal phase support with P. Thus, IVF-ET could be successful not from the procedure itself, but from the use of supplemental P. Since part of the philosophy of this perspective is to find the most effective therapy, but also to consider expense, it would make sense to try exclusive P supplementation first rather than IVF-ET with P supplementation.

Women with DOR have a good success rate with supplemental P and should not be pushed into IVF-ET or even IVF Pre-implantation Genetic Testing for aneuploidy (PGT-a) for fear of a higher risk of trisomy 13, 18, or 21 because they do not have this risk [52]. Perhaps the mild decrease in fecundity could be related to a mild increased risk of aneuploidy which cannot be fixed with PGT-a anyhow. However, they may be more prone to an excessive cellular immune response because of increased cellular permeability, and we will subsequently discuss other treatment options available. There probably is an increased risk in women with DOR in not being able to adequately negate the increased cellular immune response by supplemental P alone because an increased cellular immune response may be the etiologic factor for the DOR or POF. Thus, they may need to have additional treatment besides supplemental P to reduce their excessive cellular permeability by preventing excessive infiltration of irritants into pelvic tissues leading to a hyper immune response. This inexpensive safe way to reduce cellular permeability will be discussed later in this perspective.

One could perform a mid or late luteal phase endometrial biopsy to at least be sure that the changes related to P interacting with nPRs are sufficient, but to save money and avoid painful procedures, we do not do this as part of our routine treatment protocol. Nevertheless, this certainly could be added to "finetune" the dosage of P. We do not think there are adequate immune tests available by testing blood constituents to reflect what is happening at the fetal placental microenvironment. The serum PIBF is merely a reflection of P secretion and will increase even in menopausal women with estrogen deficiency or even men to the same levels as estrogenic women when supplemented with P [36,53]. There are differences in the PIBF made by rapidly growing cells in the fetal placental microenvironment and the PIBF made by the circulating gamma/delta T cells in the blood in that the secretion of PIBF in the former, but not the latter, can be suppressed by treatment with the PR antagonist (modulator is a better term) mifepristone [54]. We have hypothesized that circulating PIBF may be more important in preventing preterm delivery than allowing successful implantation to occur and preventing miscarriage [55].

Instead, we utilize non-invasive sonography to help us adjust the dosage of P. We have found that not attaining a mid-luteal phase endometrial echo pattern that is a homogenous hyperechogenic pattern is associated with a lower live delivered pregnancy rate [56-58]. There is evidence that increasing the dosage of P even in that cycle from mid-luteal phase to late luteal phase can improve the chance of a live delivery [59]. The mid luteal phase endometrial echo pattern is an evaluation of adequate with the nPR but not the mPR.

Women with DOR and regular menses but releasing the egg before full follicular maturation

In our aforementioned study of women who predominately had normal oocyte reserve, regular menses, an out of phase luteal phase endometrial biopsy as their only detected infertility factor there were 42 women who released their egg before attaining a 200 pg/ml serum E2. The results are seen in Table 5.

Table 5 shows that P alone was not nearly as successful in this group releasing the egg before full maturation as in the group attaining a mature follicle. Based on the aforementioned embryo implantation model, the difference in success may be related to inadequate development of both nuclear and membrane P receptors related to insufficient E2 to induce these receptors. However, another possibility is that the oocyte does not reach the metaphase II stage before its released.

Table 5: Pregnancy rates in women with luteal phase defects releasing the outcome before attaining a serum E2 according to type of treatment in 6 treatment cycles.

Type of treatment	Clinical pregnancy rate	Live delivered pregnancy rate
Clomiphene citrate		
Menopausal gonadotropins	70% (7/10)	30% (3/10)
P vaginal suppositories	75% (3/12)	25% (3/12)
Follicle maturing drugs plus P	70% (14/20)	65% (13/20)

These aforementioned women in this study had NOR. Possibly the use of the selective estrogen receptor modulator clomiphene citrate could have led to less induction of P receptors by its blocking effect on E2, but nevertheless, a reasonable 6-month live delivery rate was achieved when using clomiphene in the follicular phase and P in the luteal phase.

However, it is likely that if this same study had been conducted in women with DOR, we suspect the results with women taking clomiphene would have been worse. Before evaluating the basis of that statement, we wanted to discuss the results of a study published in Fertil Steril by scientists and clinicians from one of the top 5 IVF centers in the world at the time of publishing in 2005 [60]. They found that following a standard controlled ovarian hyperstimulation protocol, if one evaluates the outcome of women having morphologically normal appearing embryos transferred, there were no live deliveries in women who had day 3 serum levels of FSH over 18 mIU/ml [60]. This led to their conclusion (which influenced many other infertility specialists) that this very poor outcome probably was related to poor egg quality in women with DOR, even if younger [60]. Thus, many centers stopped even trying with the eggs of women with DOR and strongly advised donor eggs.

However, we had found many live deliveries in women with serum day 3 FSH levels over 50 mIU/ml and even way over 100 mIU/ml [12,61-74]. Case reports thus demonstrate that live deliveries are possible despite DOR, even naturally without IVF-ET and with simple treatments e.g., P in the luteal phase. However, they do not give clinicians the sense of whether there is a

reasonable likelihood of success or not. In the succeeding paragraphs we will discuss what additional treatments are needed if the egg releases before the follicle is fully mature or if there is a short follicular phase or premature luteinization. Table 6 shows the clinical and ongoing live pregnancies past the first trimester in women aged ≤39.9 where these factors were corrected. This study was performed before the extra "fine tuning" of taking measures to inhibit excessive endometrial inflammation (which is more likely in DOR or POF) as will be described [75].

Table 6: 6 month clinical and ongoing Pregnancy Rates (PR) in women aged <40 with DOR using the FSH receptor up-regulation concept (natural cycles) [76].

Clinical PR	Ongoing PR	PR with follicle maturing drugs	PR using P only
46.1% (12/26)	34.6% (9/26)	55.0% (11/20)	16.7% (1/6)

As seen in Table 6 in contrast to the aforementioned study of 100 women with out of phase endometrial biopsies where 42% released the egg before the dominant follicle was mature, women with DOR are more likely to not make a mature follicle is 17 of 26 (77%) [46,49]. In the study where we treated with P in the luteal phase just based on age or pelvic pain without an endometrial biopsy performed, only 20% of these women who predominately had NOR released an egg before the follicle was mature [51]. Data for women aged 40 or older are seen in Table 7.

Table 7: 6-month pregnancy rate in women aged >40 years with DOR using the FSH receptor up regulation technique-natural cycles.

Clinical PR	Clinical PR with follicle	PR with P only
10.5% (2/19)	Maturing drugs and P	14.3% (1/7)
	16.2% (2/12)	

Thus, it is seen that younger women with DOR are much more likely to have successful conception vs women with advanced reproductive age and DOR when it is necessary to further mature the follicle [76]. This is consistent with studies evaluating LDPRs according to age using IVF when the PRs were 80% as likely in women >age 35, 70% as likely in omen 36-39 and 50% as likely in women 40-42 than women with NOR [50].

As mentioned with the embryo implantation model, since clomiphene and letrozole are anti-estrogen drugs, they may interfere with adequate development of E2 induced nPRs and mPRs even in women with NOR. However, this adverse effect is magnified in women with DOR as seen in the study from Roberts et al from one of the top IVF centers in the world showing no live deliveries despite the transfer of morphologically normal embryos in women who we would consider as having mild DOR compared to our studies of live deliveries with and without IVF in women with much higher FSH levels, and thus a much greater degree of DOR. These data suggest that raising the FSH too high by high dosages of exogenous FSH stimulating drugs down regulate some key FSH induced cytokines or enzymes required for normal embryo implantation [61,69,71,73,76-85].

In a separate study using a different set of patients aged ≤37 evaluating 5 natural treatment cycles comparing pregnancy outcome in women with DOR vs NOR, we found the live delivered PRs to be 80% as likely with DOR vs NOR as seen in table 8 [86].

Table 8: Clinical and live delivery pregnancy rate in up to 5 natural cycles in women aged <37 with diminished vs natural oocyte reserve using the principles of the FSH receptor up-regulation technique for DOR and using follicle maturing drugs plus progesterone vs progesterone alone according to attaining a mature follicle or not [86].

	Live delivered PR per 5 cycles	Clinical PR for 5 cycles
Women with NOR	41.6% (10/24)	70.8% (17/24)
Women with DOR	33.3% (8/24)	62.5% (15/20)

For those who conceived the average number of treatment cycles until conception were similar between the group with DOR vs NOR (3.1 vs 3.2). For this study DOR was defined as having a serum FSH >15 mIU/ml. The pregnancy rate may have been higher in the DOR group if we included women with mild DOR with day 3 serum FSH >11 mIU/ml [86].

Correcting maturation defects in women with DOR who release the egg before adequate follicular maturation

In the study of 100 women with an out of phase endometrial biopsy for the 42 women who did not make a mature follicle most were treated with clomiphene citrate and P. Gonadotropins were only used when the post-coital test was poor related to the anti-estrogen effect in cervical mucus from the clomiphene [49]. Despite the theoretical negative effect of blocking the beneficial effect of E2 inducing nPRs and mPRs for the 5 days of treatment with anti-estrogen drugs, the 65% 6-month live pregnancy rates were adequate [49].

However, in view of the toxic effect of high FSH (probably suppressing its own receptor and subsequently failing to secrete an important cytokine or enzyme needed for implantation) drugs e.g., clomiphene or letrozole should probably not be used to treat women with DOR who ovulate, but do not quite reach dominant follicular maturation criteria. In fact, sometimes the rise in pituitary secretion of FSH after ingesting 5 days of a selective estrogen receptor modulator e.g., clomiphene or an aromatase inhibitor e.g., letrozole, can down regulate FSH receptors in the granulosa-theca cells leading to a more severe maturation defect, anovulation, or even failure to generate any rise in serum E2 [12]. Thus, the treatment we recommend is to add a small dosage of FSH in the late follicular phase when the serum FSH is generally suppressed into the normal range by rising serum E2 levels to boost the follicle to complete maturation [12].

DOR and the short follicular phase

The stimulation of follicles for the succeeding cycle begins in the late luteal phase following the rise of FSH after the nadir in mid luteal phase (related to maximum suppression by E2 and P) with degeneration of the corpus luteum in the absence of hCG to rescue it. Because women with DOR have higher serum FSH levels, the rate of follicular maturation may be accelerated leading to a possible mature follicle but with a short follicular phase.

Though live deliveries have been achieved even with a short follicular phase, the success rate is compromised by insufficient time of E2 exposure to develop adequate nPRs and mPRs. Though one could block the early development of the dominant follicle by using a Gonadotropin Releasing Hormone Agonist (GNRH-a) 1) e.g., leuprolide acetate, from mid luteal phase (but supplementing with both P and E2 in the luteal phase to allow

conception in that cycle), or one could use a GRNH ant e.g. cetrorelix or ganirelix from day 1 of the menstrual cycle or from a negative pregnancy test for 5 day to delay follicular maturation. These drugs are expensive. Thus, for the purpose of increasing the length of the follicular phase, we prefer ethinyl estradiol taken from either day 1 or shortly before menses until around day 5 [20,87].

Ethinyl estradiol is the estrogen in every oral contraceptive. It is well tolerated and suppresses FSH through negative feedback to the pituitary thus inhibiting FSH release. One would not, however, provide it to the patient by using the oral contraceptive itself because the progestin in it would create a pseudo decidual reaction in the endometrium and thus inhibit implantation.

Thus, the standard use of 20 micrograms per day of ethinyl estradiol must be provided by a compounding pharmacy. Ethinyl estradiol has the advantage over a GnRHa or GnRh ant not just because it is a lot less expensive, but the estrogen helps to cause better endometrial proliferation and better induction of nPRs and mPRs, not to mention improving cervical mucus, and facilitating pregnancy through natural intercourse. Intrauterine insemination is not needed where the sperm specimen is normal, and the post coital test is sufficient [88].

We have demonstrated a lower pregnancy rate even in women with apparent NOR with a short follicular phase [89]. The use of ethinyl estradiol 40micrograms per day for day 1 plus supplemental P vaginal suppositories enabled a 45-year-old woman with a 3-year history of primary infertility to successfully conceive and deliver a live baby through natural intercourse in her very 1st treatment cycle of ethinyl estradiol and P in the luteal phase [70].

Premature luteinization

One can argue that releasing the egg before full maturation of the follicle is premature luteinization because the LH rose too early. We distinguish premature luteinization from releasing an egg before complete follicular maturation by the fact that the egg does not release in premature luteinization, whereas women who we consider ovulating without attaining a mature dominant follicle do release an egg as demonstrated by vaginal sonography (shrinking by 5mm before the serum P reaches 2 ng/ml after the LH surge from the follicle. We distinguish premature luteinization from the luteinized unruptured follicle syndrome in that in the latter the egg fails to release despite attaining a 200 pg/ml serum E2 before the LH surge. With premature luteinization, the serum E2 never reaches 200 pg/ml at least before the LH surge.

A premature ruse in the LH before follicular maturation can occur especially in women with NOR who are treated with Controlled Ovarian Hyperstimulation (COH) for the purpose of creating multiple mature follicles (as with IVF) related to the positive feedback to the pituitary of E2 for LH release. This is the reason for using GnRH-ant or sometimes GnRHa in COH protocols.

Women with DOR are more prone to develop premature hyperstimulation even in natural cycles because they not only have high FSH from early follicular phase, but also LH [90]. They can be treated by using a GnRH ant when the serum E2 reaches a certain level, i.e., around 100 pg/ml in those women prone to premature luteinization. Because the GnRH ant can suppress the FSH too low sometimes, and thus retard follicular maturation, the GnRH ant is continued while sometimes adding back exogenous FSH. One may add a small dosage of gonadotropins to continue development of a dominant follicle. Sometimes while taking the GnRH ant, in some cases with higher serum FSH levels, adding FSH stimulation may not be needed since the FSH was not lowered to such an extent that follicular maturation continues while still inhibiting the rise of LH. Sometimes using a GnRH-a from mid-luteal phase and stopping in early follicular phase can inhibit a premature rise in LH and thus can be used in patients with DOR and premature luteinization.

Though a rise in serum E2 will cause a rise in LH appropriately in natural cycles in women with NOR, pharmacologic dosages of estrogen e.g., the 20 mcg of ethinyl estradiol in the oral contraceptive, can not only suppress FSH to a degree to inhibit follicular maturation when used to prevent pregnancy, but it will suppress the LH surge. Ethinyl estradiol has been used in women with DOR and premature luteinization in women needing gonadotropins to achieve full follicular maturation or even in cases of high FSH without any extra gonadotropins when the drop in FSH and LH is not too low to allow continued follicular progressions [91].

Women with hypergonadotropic amenorrhea and estrogen deficiency- premature menopause

Between 16-20 weeks gestation there are between 6-7 million oocytes that reach the germinal ridge. However, oocyte atresia occurs rapidly during the latter half of the pregnancy so that at birth an average female has only 1-2 million oocytes left. The next greatest rate of oocyte atresia occurs from birth to puberty with now only 300,000 to 500,000 oocytes left.

The slowest rate of oocyte depletion occurs from puberty to menopause where only a small number of poor-quality oocytes remain, possibly only about 1% of the number present at menarche. Despite all of these oocytes still present at puberty during the 40 years from menarche to menopause the average woman not creating more oocytes per cycle by the use of follicle maturing drugs releases no more than 400 to 500 eggs from menarche to menopause. That means there is an average of 600-1000 eggs that are lost per month.

We have seen that in women who are still menstruating, but have DOR, younger women have a better chance of a successful pregnancy than women of advanced age with the same degree of oocyte depletion. In fact, the success rate may be higher in younger women with DOR than women of advanced reproductive age with NOR.

FSH binds to an FSH receptor on the surface of the granulosa cell membrane, and through transcription and translation produces enzymes or cytokines that produce the physiologic effect of the FSH. Cells try to prevent burnout. For polypeptide hormones, e.g., FSH, a high level of exposure of FSH to the FSH receptor will lead to down –regulation of the effect of FSH because of internalization into the cytoplasm of the FSH receptor. Simply, without an FSH receptor, FSH loses its physiologic effect.

Thus, we considered that some women with POF may still have follicles containing oocytes that could achieve maturation to the Metaphase II (MII) stage, and when fertilized lead to a live baby, if FSH receptor up-regulation could be achieved. We considered that we may be able to restore sensitivity to FSH by lowering serum FSH by the use of 5mg conjugated estrogen then adding human Menopausal Gonadotropins (HMG) when the serum FSH approached a level 12 mIU/ml or lower. Five women with POF ages 27, 32, 26, 26, and 22 were stimulated

with this protocol, and 3 of 5 ovulated [1]. They were given P luteal phase support. Case 1, age 27 ovulated both cycles and delivered a healthy baby. Case 2, age 32 ovulated 5 of 5 times and had a successful delivery. Case 3, age 26 also ovulated 2 of 2 attempts but failed to conceive. Both case 4 (age 26) and case 5 (age 22) failed to ovulate in 2 and 1 cycle respectively [1]. The reason they stopped treatment was because they could not afford the HMG. This publication was in 1984 [1].

The question arose as to whether these patients could have ovulated with an appropriate number of oocytes remaining but for some reason, they were either resistant to endogenous gonadotropins, but could respond to pharmacologic dosages of FSH [93]. Alternatively, could they have normal egg reserve but have a pituitary gonadotropinoma only or micro gonadotropinoma only secreting immunologically detected FSH that was biologically inactive [94,95]. Evidence to support that this concept of FSH receptor upregulation can allow ovulation with successful pregnancy to occur in women with marked oocyte depletion was accomplished by showing that one could achieve success even in women with surgically documented streaked gonads [63,65].

Probably the best proof that diminishing serum FSH to restore sensitivity to endogenous FSH rather that fortuitous follicular maturation was the demonstration of follicular maturation and egg retrieval two out of two times with oocyte cryopreservation in a 45x teenager with primary amenorrhea and sexual infantilism [66]. Unfortunately, the levels of follicular depletion may be so severe that at times there are no primary oocytes that have progressed to an antral stage follicle where the follicle can respond to gonadotropins. Therefore, some women will be spending a lot of money on expensive gonadotropins which will be wasted if we continued the original technique of suppressing the high serum FSH with the negative fixed lack of estrogen and then adding gonadotropins. Thus, we considered ways to modify the technique to be more cost effective, but also more practical and accurate by substituting ethinyl estradiol for conjugated estrogen or estradiol itself as we used earlier. Ethinyl estradiol is a potent suppressor of FSH release from the pituitary, but another major advantage over estrogen is that it does not contribute at all to the serum E2 levels [87]. This allows monitoring by serum FSH and E2 without ultrasound, saving the cost and inconvenience of pelvic sonography. Furthermore, by detecting a rise in serum E2, it would indicate to the treating physician that an antral follicle has been recruited and that a low dosage of gonadotropins can be started if the FSH has been sufficiently suppressed [87]. Once a rise in serum E2 occurs, ultrasound is added to the monitoring.

Sometimes, because the FSH started out very high, a rise in E2 and progression of follicular development occurs with restoration of down-regulated FSH receptors allowing the development of a dominant follicle without any exogenous gonadotropins [77]. In fact, sometimes when sensitivity of the granulosa theca cells has been restored, a woman may stimulate multiple follicles from the high endogenous levels of gonadotropins [96].

The basic tenet of the FSH-receptor up-regulation technique is to 1) lower high serum E2 levels by negative feedback of an estrogen e.g., ethinyl estradiol, that does not contribute to the serum E2 levels to allow various manipulations to achieve a dominant follicle (which is best determined by a serum E2 reaching 200 pg/ml) 2) Allow progression of follicular maturation by endogenous FSH alone if there is a progressive rise of E2 and the FSH is still increased 3) Add endogenous FSH if the FSH is falling into a normal range in case the level of FSH because insufficient to stimulate progression of the follicle 4) continue the ethinyl estradiol when adding gonadotropins 5) use of GnRH-ant if there seems to be a mild increase in the serum LH and/or slight rise in serum P if a serum E2 of 200 pg/ml has not been attained as yet 6) use a low dosage of FSH to continue follicular maturation if a GnRH-ant is used 7) use hCG to trigger oocyte release unless there has been a good surge of endogenous LH 8) support the luteal phase not only with P vaginal suppositories and/or ImP but add estradiol (not ethinyl estradiol to keep the hormones natural) to help prevent a short follicular phase in the succeeding cycle 9) in some cases where ethinyl estradiol produces side effects e.g. nausea or headaches or it is precluded for health reason e.g., hormone receptor positive breast cancer, leuprolide acetate or a GNRH-ant may be used to suppress the high FSH levels [2,63,97].

We treated at least 100 additional cases of POF between 1984 and 1989 and reported the outcome of the modified aforementioned technique in 100 consecutive cases and reported the outcome in Fertil Steril in 1990 [2]. The one exception is that there was no use of a GnRH-ant because they had not come to the pharmaceutical market as yet. Furthermore, we used a much lower dosage of P vaginal suppositories than we do today. For this study there were no age restrictions, nor any restriction for how many years they may have been in menopause, the results are seen in table 9.

Table 9: 6-month pregnancy rate in women aged >40 years with DOR using the FSH receptor up regulation technique-natural cycles.

No cycles attempted	354
No couples where ovulation occurred	68
No patients who ovulated	37
No patients with clinical pregnancies	19
No live deliveries	8

There were 91 treated with ethinyl estradiol with or without a boost of FSH and 9 treated with leuprolide acetate. Overall, 16.3% of the attempted cycles resulted in ovulation. A maximum of 4 treatment cycles were attempted. Interestingly 6 of the 37 women (16%) ovulated in all 4 cycles. The live pregnancy rate was 8%. The actual 1st trimester miscarriage rate was 52.6% (10/19). We attribute this high miscarriage rate possibly to an insufficient dosage of luteal phase support with P [52, 98]. One patient had a pregnancy loss at 34 weeks related to a nuchal cord [2].

There were 91 women treated with ethinyl estradiol and 9 with leuprolide. The percentage of women who ovulated at least once in 4 cycles were similar in the 2 groups- 37.4% vs 33.3% as were the percentage of treatment cycles resulting in ovulation (10.9% vs 16.3%). However, all the pregnancies occurred in the ethinyl estradiol group [2].

The mean age for the group achieving pregnancies was 33.4 vs 34.8 for the group not achieving pregnancy. The mean time from initial diagnosis of POF to treatment was 2.2 years for those conceiving vs 4.8 years for those not conceiving. The average serum FSH for those who ovulated was 70.3 mIU/ml and was 66.5 mIU/ml for those who failed to ovulate [2].

Unfortunately, we have not considered an evaluation of success rates in women with POF in natural cycles now with using much higher dosages of P vaginal suppositories (50 mg vs

800 mg) and the availability of cetrolrelix or ganirelix. All we can say is that live pregnancies are still occurring, and we suspect a higher success rate, especially in the reduction of miscarriages. We are planning on performing a 20-year review in the near future.

There is no particular advantage in performing IVF in these patients unless there is a severe male factor problem or blocked fallopian tubes [71,77]. We did publish a more recent study on IVF outcomes in women who appear to be in overt menopause in 2016 [99]. The study only involved 5 patients. There was a 20% LDPR per day 3 embryo transfer. The LDPR per retrieval was 9.3% (4/43) but not all initiated cycles led to an egg retrieval. The LDPR per initiated cycle was 6.1% [99].

Our publications involving attempts to achieve pregnancies in natural cycles in women with POF since 1990 have mostly involved case reports that illustrated certain extremes. For example, in 2004 we reported at that time, a successful pregnancy after induction of ovulation in a woman with POF with the highest serum FSH to date of 164 mIU/ml [69]. She ovulated 6 of 10 cycles and finally was successful in cycle 10.

As we will discuss later, in our opinion the main cause of POF is related to inflammatory damage to the ovaries related to increased cellular permeability leading to excessive infiltration of irritants causing an excess of cellular immune cells, especially, but not limited, to natural killer cells [41,100]. The excessive presence of cellular immune cells can attack and damage the fetal semi-allograft. Thus, we will subsequently discuss the possible role of dopaminergic drugs to diminish excessive cellular permeability thus preventing immune deduction of the fetus so early that one does not achieve a positive pregnancy test or causing a higher miscarriage rate [41,100].

Other extremes that we described in case reports was that even though advanced age plays a greater detrimental role to success with POF than the paucity of remaining oocytes, nevertheless live deliveries are possible even in women of very advanced reproductive age and POF. We reported a 45-year-old woman with 5 years of primary infertility who had secondary amenorrhea for 6 months with failure to induce menses with 10mg of medroxyprogesterone acetate for 13 days. Her serum E2 was 15 pg/ml and her serum FSH was 43 mIU/ml. She was made to ovulate 2 out of 2 times with just ethinyl estradiol. She conceived and delivered a full-term baby in cycle 2 [68]. It should be noted that we have never had a woman deliver a live baby with conception at age 47 or higher with the woman's own oocyte even with NOR. Thus, when we were able to help a 46.5-year-old woman who had 9 months of amenorrhea with a serum E2 <15 pg/ml and a serum FSH of 117 mIU/ml and a serum AMH level of <0.09 ng/ml to attain a mature dominant follicle on day 44 of ethinyl estradiol treatment, and who conceived and delivered a live baby, we thought that this should be reported [74]. She was also treated with a dopaminergic drug, dextroamphetamine sulfate.

Treating women with DOR or POF with granulocyte-colony stimulating factor to improve egg quality

There were other reasons why we considered that we should report her case. When she was aged 42 she did have DOR, but had regular menses and several years of primary infertility. She made a mature follicle on her own despite a day 3 FSH of 47 mIU/ml but despite a good surge of LH at midcycle, her follicle failed to collapse indicative that she did not release the egg from the dominant follicle [74]. Thus, she was diagnosed with the Luteinized Unruptured Follicle (LUF) syndrome in that cycle [101]. In succeeding cycles, she failed to release her egg despite 10,000 IU Human Chorionic Gonadotropin (hCG), then15,000 IU of hCG and 150 IU of FSH, and finally, leuprolide acetate 1 mg every 12 hours x 3 doses [102-104]. Having failed to release an egg in all 4 of her evaluation cycles despite all known treatments, we recommended IVF-ET. Indeed, the LUF syndrome would be another reason to do IVF with either DOR or POF. She stated that she could not afford IVF but would be willing to try something experimental, even if it had never been tried before to treat LUF.

We told her that the cytokine Granulocyte Colony Stimulating Factor (G-CSF) markedly increases in the follicular fluid immediately prior to the LH surge. We considered that it may help the oocyte to release from the follicle. She was given 300 mcg of G-CSF, released the egg on cycle 5, and delivered a healthy baby. We then tried this again at age 46.5, when she attained a mature follicle on day 44. She released the egg and again delivered another live healthy full-term baby [74].

Based on diminished oocyte quality with advancing the age, the odds of achieving a live delivery with DOR at age 42 and POF at age 46.5 two out of two times once the egg released is close to a miracle. We have shown that G-CSF can help other women with persistent LUF to be able to release eggs when other therapies failed [105]. Possibly G-CSF can correct some of the quality issues with eggs from women of very advanced reproductive age and make them more likely to produce babies. We are presently evaluating the use of a single injection of G-CSF in women of advanced age with or without DOR or POF in both natural and IVF-ET cycles to improve fecundity.

Autoimmune factors that may be etiologic in causing DOR or POF

Zhu et al state that autoimmune diseases are associated with reduced fertility, possibly related to causing DOR and POF [8]. Though it is true that some of the treatments for autoimmune disorders e.g., cyclophosphamide can be one reason why DOR may be seen with higher prevalence in women with autoimmune disorders, there are studies supporting the contention that autoimmune disorders without oocyte damaging therapies may be associated with DOR [106,107].

As mentioned, in our model of embryo implantation, an important step may be the role of P in suppressing dopamine to increase cellular permeability to allow irritants to infuse into pelvic tissues [41]. We have data to support that an already intrinsic defect of increased cellular permeability may be the etiologic factor in causing pelvic pain, which when exacerbated by the extra insult of P further increasing cellular permeability by blocking dopamine, results in pelvic pain symptoms in the luteal phase, e.g., premenstrual pain and dysmenorrhea, and with a more severe permeability defect, the pain may occur at other times in the menstrual cycle leading to chronic pelvic pain, backaches, dyspareunia, and mittelschmerz as evidenced by the demonstration of marked relief of the pelvic pain symptoms following treatment with dopaminergic drugs [108-115]. We will discuss more about the use of dopaminergic drugs to improve fertility and prevent miscarriage, especially, but not limited to women with DOR or POF (other term used premature ovarian insufficiency or POI). (We prefer the term POF because POI does not clearly separate DOR and POF).

When invited to write a manuscript of the lead author's choice, there were many areas of research in which we are involved which translates to being able using this information right now in actual treatment of patients. We had published a perspective on the subject of DOR and POF in non-IVF cycles in 2022. That manuscript did not include much about the association of the increased cellular permeability condition, that not only may be the most common etiologic factor, but could provide a method to further increase the chance of a successful conception after one restores FSH sensitivity leading to ovulation [12]. The final deciding factor to choose this topic when reading review articles on the subject and realizing that the "experts" who reviewed the subject are completely unaware of these very effective methods to achieve ovulation and live deliveries with them often referring to studies that suggest that there is a 5-10% chance of spontaneous pregnancy without providing methods to improve the low chance of spontaneous pregnancy without treatment [116,117].

In the review by Luisi et al nothing is mentioned of how to induce follicular maturation in women with DOR [116]. So perhaps one may argue that maybe this group was not much involved with treating women with POF with the purpose of inducing ovulation and subsequent correction of infertility. On the other hand, another review was published in Best Practice and Research Clinical Obstetrics and Gynecology by 2 British authors with the lead author Sinead Mclacken-Byrne, a clinical research fellow and Gerard Conway, a professor of Reproductive Endocrinology [118]. Indeed, in their 76 references, there are references to previous publications by Professor Conway from 1996, an update in 2010, another reference from 1998 and a reference from 2021 in the Journal of Clinical Endocrinology and Metabolas in 2021 by McGlackin-Byrne evaluating a rare genetic case of POF showing that this genetic disorder can not only cause POF, but also meiosis errors [118-122]. They refer to an old method of treating DOR popularized by Dr. Mortimer Nelson, but they state that a controlled trial failed to show benefit [118].

The systematic review by van Kasteren et al [123]

Van Kasteren et al in a study published in Human Reproduction states, "several medical therapies have been tried to induce ovulation in women with POI, however, in a systematic review all were reported to be equally effective" [123]. The title by van Kasteren manuscript is "Premature ovarian failure: a systematic review in therapeutic intervention to restore ovarian function and achieve pregnancy." It was published in 1999. One could argue that most of our publications are case reports or case series, and they lack "controls." There is no financial advantage for a pharmaceutical company to sponsor a controlled study on compounded ethinyl estradiol vs placebo to see if ethinyl estradiol induces more ovulations and successful pregnancies than placebo. One would still have to monitor the placebo group with the same blood tests and ultrasounds to see when to supplement with P in the luteal phase. What incentive could be given to a couple to "waste time" and possibly lose whatever chance they had by the delay in proper therapy while taking the placebo? Thus, meta-analysis is only as valuable as the arbitrary criteria that the authors use for selection of the manuscripts. Thus, the need for scientific proof of efficacy by a review of "properly designed research studies" will probably never happen for DOR and POF and lead to the usual recommendation of extremely expensive donor oocytes, which besides the cost, does not satisfy the woman who would want her genetics represented in a child or those couples where donor oocyte is forbidden for religious reasons. They are not losing their opportunity to get pregnant at a later age with donor eggs or donor embryos if they choose to try with their own eggs because in contrast to other animals, the uterus seems to "remain young" even when the woman is of advanced age [124-127].

Sometimes one case report may prove the efficacy of a technique better than an RCT as in the following case report. A mother brought her 13-year-old daughter with sexual infantilism and primary amenorrhea to see if we could induce follicular maturation and cryopreserve eggs for the future. Her karyotype was 45X [3]. Her serum E2 was less than 15 pg/ml and her serum FSH was 67.2 and serum AMH was undetectable. After 40 days of ethinyl estradiol she achieved a serum E2 of 251 pg/ml (remember ethinyl estradiol does not contribute to the serum E2 level) and attained a dominant follicle of 18 mm by transvaginal sonography. She was given 10,000 IU of hCG and one metaphase II oocyte was extracted and cryopreserved [3].

The family still decided that they still did not want her to take estrogen to develop secondary sexual characteristics as yet. She showed no breast development or adrenarche. At age 14 she returned with just ethinyl estradiol to lower the high serum FSH (initially her serum E2 was less than 25 pg/ml). Once again, she developed a dominant mature follicle and an oocyte was retrieved. The egg was not frozen, however, because it was degenerating [3].

Unfortunately, if one was performing a systematic review of methods to induce ovulation despite POF, if the inclusion criteria only included RCTs, none of these case reports of success would be included, and thus the conclusion by the systematic review would be that there are no effective therapies to increase the chance of inducing ovulation in women with POF [128].

Zhang- Acupuncture [9]

It has been suggested that acupuncture may have a beneficial effect on pain by activating the dopamine system and also DOR [129]. Our studies suggest that drugs that release dopamine effectively correct many severe chronic pain disorders and other organ dysfunction in both men and women [130,131]. Zhang et al refer to a prospective acupuncture cohort study with 13 acupoints in patients with DOR and found a pregnancy rate of 15.6% [132].

Acupuncture has been shown to improve pregnancy rates in patients undergoing assisted reproductive techniques if acupuncture was performed on the day of embryo transfer [133]. A study by Westguard et al found a trend for higher PRs when acupuncture was given in weekly intervals prior to IVF-ET and on the day of embryo transfer [134]. Furthermore, an RCT showed a significantly higher PR when acupuncture was performed in the luteal phase of IVF-ET cycle [135].

We performed a matched controlled study using acupuncture for women who failed to have a successful pregnancy in 2 prior IVF-ET cycles including the full use of supernumerary frozen embryos. Acupuncture was performed on day 3 of the IVF cycle and was performed twice per week until 2 weeks after oocyte retrieval [136]. There were 18 if the 32 women receiving acupuncture who had a serum FSH $\geq$12 mIU/ml with an average serum FSH of 18.2 mIU/ml. Their mean age was 37.9. The clinical and LDPRs were 40.6% and 37.5% respectively. Because this was a group with a relatively poor prognosis, and since we found many of these women conceiving now with the addition

of acupuncture, we were convinced that the acupuncture was responsible for the good outcome.

However, we were extremely surprised that the matched control group who also had 18 women with DOR and an average FSH of 16.7 mIU/ml and an average age of 36.7, that the clinical and LDPRs were 53.1% and 43.8% respectively. Thus, it is not clear if acupuncture may or may not be effective. If further studies prove it has no or has minimal benefit, it does not negate the possibility that releasing more dopamine may benefit women with DOR since the amount of dopamine released may have been insufficient.

Dopaminergic drugs to improve fecundity with DOR and POF possibly by diminishing increased cellular permeability thus preventing excessive inflammation and possible immune rejection of the embryo/fetus.

In the aforementioned proposed model of the mechanism of the events leading to embryo implantation and continual growth of the fetal semi-allograft, the model proposes that the development of thin-walled spiral arteries requires, at least in part, an autoimmune remodeling of thick-walled uterine arteries. Thin-walled spiral arteries are needed for nutrient exchange between mother and fetus. The model proposes that in order to bring more cellular immune cells into the uterus following the early secretion of P following the LH surge, P blocks dopamine. This biogenic amine is known to diminish cellular permeability and thus inhibits infiltration into the pelvic tissues of irritants leading to this inflammatory effect [41].

We have hypothesized that when the inflammatory response is at an appropriate level there are very few symptoms. However, when there is excessive cellular permeability leading to above normal infiltration of irritants, one may get various types of pelvic pain symptoms including dysmenorrhea, chronic pelvic pain, mittelschmerz, dyspareunia, vulvovaginitis, pelvic pain penetration disorder, or pelvic pain of bladder origin [108-115,137].

The increased cellular permeability of pelvic tissues could also result in endometrial cells leaking out thus explaining why frequently, but not necessarily, these pelvic pain disorders may be associated with endometriosis or adenomyosis [100]. Possibly the presence of these endometriotic implants may increase the cellular permeability or generate more irritants to infiltrate into the pelvic tissues, and thus possibly cause more pain. This would explain why laparoscopic removal of endometriosis may improve pelvic pain if the presence of these endometriotic implants provides the “straw that broke the camel’s back” to allow the critical amount of infused irritants to cause pain.

However, considering the possibility that the endometriosis is a result rather than the cause of the increased cellular permeability defect, one could explain why frequently after a short or sometimes longer period of time there is a return of the pelvic pain. In fact, even one study that removed endometriosis by excision technique in teenage girls found no evidence of any endometriosis lesions 2 years later when they were re-laparoscoped as part of the study, but half of them had a return of the pain to the same degree as before the removal of the endometriosis [138]. This supports the contention that the cellular permeability defect is the main cause of pain rather than the endometriosis per se.

There is evidence that a greater number of women with endometriosis have DOR compared to women presumably without endometriosis because of the absence of symptoms [139,140]. DOR may be further compromised by damaging ovarian blood supply or ovarian tissue directly by attempts to remove the lesions surgically [141].

There are studies suggesting improved fertility outcome following surgical treatment of endometriosis even when it is mild and without adhesions [142,143]. Because of the probable return of increased pelvic inflammation in natural cycles, it behooves the treating physician trying to achieve a successful pregnancy to follow the suggestive treatments for DOR mentioned in previous paragraphs, ee support with P in the luteal phase, making sure that the dominant follicle is mature, and if nor correct the maturation defect following the tenets of the FSH receptor up-regulation technique for natural cycles, and be sure that the sperm mucus interaction is sufficient as manifested by a normal post coital test, and to use IUI if there is the presence of subnormal post coital test related to mucus or sperm issues [143].

It should be noted that treatment with dopaminergic drugs, especially dextroamphetamine sulfate, should not be limited to women with pelvic pain but for other manifestations of the increased cellular permeability syndrome [144-146].

Consideration should also be given to treat women with dopaminergic drugs if DOR or POF is present even without symptoms of the increased cellular permeability syndrome if there was no known etiology for the problem of DOR, i.e., pelvic surgery, chemotherapy, radiation therapy, or tubal infection or family history with a known genetic defect. Because of this absence of these known etiologies in our large patient population of DOR and POF, we consider that the increased cellular permeability syndrome, with inflammatory damage of ovarian tissue, is by far the most common cause of the ovarian egg depletion. The increased cellular immune cells in the micro-environment of the fetal-semi-allograft could also lead to immune destruction of the fetus. If it is very early, infertility seems to be present despite fertilization of the egg and creation of an embryo because the loss occurs before any serum hCG can be measured in the serum, or the increased inflammatory state possibly may lead to miscarriage. Dextroamphetamine has been found to prevent miscarriage even with pregnancies achieved by IVF where aggressive P support in the luteal phase was provided [147].

Thus, in our opinion the increased cellular permeability syndrome is the cause of most chronic conditions and etiologic in auto-immune disorders, not only in women, but also in males [130,131]. However, we do not think that people with autoimmune endocrine disorders, where there may be a common antigen amongst all endocrine glands, results from evoking a humoral or cellular immune reaction against ovarian tissue. We did not find an association with DOR and adrenal insufficiency, type 1 diabetes mellitus, hypopituitarism or even hypothyroidism [148].

Concluding remarks

It is the role of the physician to save patients from death and relieve suffering both physical and mental. There is no question about the mental anguish of a couple with infertility who desperately want to have a child, preferably a child that represents the genetics of both parents.

A large percentage of our patient population are women with DOR and even POF. The majority of them have already had

at least one, but frequently many previous consultations with reproductive endocrinologists. The patients come from all over the United States and in the past from all over the world (in the last several years we have had to stop seeing patients outside the United States for economic reasons). Practically all of these consultants have told them 1) your prognosis is extremely poor and you should consider donor eggs 2) if you want to try with your own eggs, you should immediately consider IVF but with PGT-a because "you are at the same risk of women of advanced reproductive age for aneuploidy, that could lead to a baby with serious physical and mental handicaps" 3) If you were to do IVF, one should stockpile embryos from multiple IVF cycles to provide you a better chance of a live delivery 4) IVF could be attempted but would be cancelled unless there were at least 3-5 dominant follicles.

Besides trying to relieve suffering, a physician should do no harm which includes having the patients spend a large amount of money for very expensive IVF and donor egg cycles with added expense of PGT-a while at the same time inflicting a great deal of mental anguish because of making some couples financially destitute. Pushing donor eggs without giving them the proper advice on how to get pregnant naturally can create hostility between husband and wife and can lead to divorce if one party believed that this procedure was performed against their own personal desires. Severe depression has occurred in both male and female partners who were strongly guided to use an egg donor when this was clearly against their religious tenets. At least in the United States capitalism exists even in the medical field, and there is no question that some of these decisions are based on the need to compete with other infertility specialists for high priced IVF by showing superior pregnancy rates [24]. This type of advice is enhanced by the fact that many infertility practices are not owned by the physicians themselves but by business entrepreneurs and these doctor/ employees are highly encouraged to recommend the most profitable treatment option both for job security and also for financial bonus.

Even in teaching hospitals it is considered ethical to pay physicians by relative value units which means that physicians must justify their salaries by bringing in renumeration that is some multiple of their salary (e.g., 2x their salaries) or their salaries will be adjusted. We are not sufficiently familiar with what types of renumeration conditions exist in other countries.

The physicians should first understand the most effective and cost-effective way to treat DOR and POF and help the patients to make the best choice of therapy that suits their emotional and financial needs. Obviously, we advised a 42-year patient, will POF, a serum FSH >100 mIU/ml that IVF was her only option since her fallopian tubes were damaged and surgery in a previous fertility center 1500 miles away was unsuccessful. She had no insurance coverage, and she was in a financially lower-middle income class. Yet, her desire to have a baby with her own genes was so great that she kept travelling the great distance to our fertility center even for monitoring. Though we did induce follicular maturation and retrieved a mature oocyte which resulted in a single day 3 embryo transfer she failed to conceive in her first cycle. Nevertheless, she tried again which resulted in a healthy live baby [77]. Another woman with DOR with a male factor with severe asthenozoospermia was willing to do IVF not just one time, but 3 times resulting in 3 live healthy babies over 8 years [71]. LUF would be another reason to do IVF but in the aforementioned case of the 46.5-year-old in menopause she could not afford IVF but was willing to try something experimental [74].

However, for some couples with DOR or POF and another factor requiring IVF they may want to proceed with embryos derived from donor eggs or donor embryos if performing IVF would use up the remaining funds needed for donor eggs and where the female partner is comfortable with that option [125,149,150].

Considering the same ethics of not causing financial hardship for the patient, this review/ perspective emphasized methods to gain a reasonable chance of a successful live delivery in women with DOR or POF without assisted reproductive techniques. However, in women with mild to moderate POF without the need for IVF because of other infertility factors. IVF does seem to improve the chance of a live delivery per cycle if one is able to transfer more than 1 embryo and the COH is performed according to the tenets of the FSH receptor up-regulation techniques. Thus, we think that the general findings of a 2.5-fold increase in LDPRs with IVF vs natural cycles in women with mild or moderate DOR is probably related to transferring more than 1 embryo providing a better chance of having a euploid embryo at least when using the FSH receptor up-regulation techniques. It is likely that if there are several antral follicles present, but only 1 is chromosomally normal, there may not be an advantage of that chromosomally normal egg developing into the dominant follicle in a natural cycle. IVF would allow the fertilization and embryo development of the normal egg along with the aneuploidal eggs providing a better chance of a live delivery if multiple embryos are transferred.

The FSH receptor up-regulation technique is slightly different for natural vs IVF cycles since in the latter we are trying to still recruit more dominant follicles. The modified technique for IVF has been described in detail [11]. We are presently performing a study to see if using the FSH receptor up-regulation technique for modified IVF, but trying to achieve pregnancies without IVF will produce superior pregnancy rates compared to using the technique to try to allow only one follicle to develop. The reason why we do not use the techniques modified for IVF, in general, in non-IVF cycles is because we are trying to avoid the expense of using more gonadotropins and GNRH antagonists. Nevertheless, some patients that are reimbursed for these medications or could afford these drugs may prefer to try to create more than one dominant follicle even in a natural cycle.

From performing an extensive review of the literature concerning the cause and treatment of DOR and POF for treating infertility, and very recently attending a conference mostly dealing with DOR by a group of invited experts, it is clear to us that the majority of fertility specialists are not very familiar with the techniques that we employ for DOR and POF to improve fecundity in natural cycles. Thus, the main purpose of this review/perspective was to share these concepts with interested readers, and at the same time determine if there are possibly some new techniques that will improve our own success. Unfortunately, we cannot say that these other suggested treatments will lead to any real changes in our protocol at present.

Our final message is that too often a treating clinician or a scientist /physician asked to write a review may look for RCTs and meta-analyses. However, some clinical entities do not lend themselves well to RCTs, since they will not have adequate funds. Thus, one should also look for very convincing case reports to help the clinicians decide on how to treat the patient across the desk from them desperate for their help e.g., allow-

ing them to have a live baby despite DOR or POF with their own gametes without being financially depleted.

Declarations

Conflicts of interest: The authors declare no conflicts of interest.

Funding: This research involved no external funding.

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