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Treating Infertility without Assisted Reproduction Techniques

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ABSTRACT

Reproductive Endocrinology/Infertility, programs today emphasize in vitro fertilization-embryo transfer (IVF-ET), intracytoplasmic sperm injection, and pre-implantation genetic diagnosis. When the infertility specialist begins his/her career, unfortunately, most are not trained to solve infertility problems by non-expensive means without assisted reproductive technology. Thus, today it becomes more important for the generalist in obstetrics and gynecology to learn the principles of treating infertility using methods that are best suited for most patients which are methods generally reimbursed by third party insurance carriers that will not financially deplete the patients. Unfortunately, during OB-GYN residency the teaching of methods for treating infertility is by rotation through REI practices where the emphasis is on IVF-ET. This review is written for the purpose of providing a basis for those OB-GYN physicians who want to know more about diagnosis and treating infertility, to help their patients conceive without expensive procedures e.g., IVF-ET.

The "expert" opinion is not only based on 50 years of extensive clinical experience but will provide the published research studies by the authors that provide at least a good starting point for learning methods of treating infertility. Nevertheless, these suggestions need to be modified by the OB-GYN generalist to conform to their patient population, their findings based on their own experience, and based on the nature of their own practice to determine how much time can be dedicated to treat infertility problems themselves.

Keywords

Follicle maturing drugs, Hostile cervical mucus, Intrauterine insemination, Oligoasthenozosperma, Ovulatory dysfunction.

Introduction

I completed my fellowship in reproductive endocrinology and infertility (REI) at Thomas Jefferson School of Medicine in 1975. The entire field of medicine has changed in the last 50 years, including the REI subspeciality. One of the major changes, besides a vast increase in medical knowledge, is that medicine has become much more businesslike than 5 decades ago. This is not necessarily a "bad thing" in that business acumen may help hospitals and medical practices from closing related to insufficient funds.

One of the technological advances in the REI field was the advent of in vitro fertilization embryo transfer (IVF-ET). This allowed couples to achieve pregnancies that were precluded by damaged fallopian tubes that could not be corrected by microsurgery, infertility related to moderate degrees of oligoasthenoteratozoospermia, sperm coated with antisperm antibodies, or sperm with an abnormal hypo-osmotic swelling (HOS) test. Subsequently intracytoplasmic sperm injection (ICSI) was developed which would now enable pregnancies with sperm with rare severe oligoasthenoteratozoospermia (OAT) or azoospermia using immature sperm aspirated or obtained by testicular biopsy from men with obstructive or non-obstructive azoospermia (where there are only a few sperm in some of the seminiferous tubules).

Unfortunately, IVF-ET requires a lot of expensive equipment, expensive highly trained personnel, and very expensive gonadotropins or gonadotropin releasing hormone agonists (GnRHa) or antagonists (GnRA ant) drugs to develop multiple dominant graafian follicles. Thus, the cost of an IVF procedure is generally quite high. For many years, many insurance companies excluded fertility treatment from reimbursement. Fortunately, over the years only a minority of private insurance will restrict fertility treatment; however, the majority of private and state insurance companies will not reimburse for IVF-ET service. Even for those who do provide financial compensation, they will usually place some monetary cap on the financial amount of IVF service covered.

IVF does have some risks, e.g., the ovarian hyperstimulation syndrome. For all these reasons, it behooves the physician to solve infertility problems without IVF-ET, with or without ICSI, unless absolutely necessary, e.g., blocked fallopian tubes or extremely poor sperm quality. Unfortunately, the practice of medicine, in all areas, not restricted to, but including infertility, has become much more geared toward maximum profit. In fact, many infertility practices are owned by big "Wall Street" corporations that are governing private infertility practices still existing and, strongly encourage the infertility physician not to recommend methods that are non-expensive to the infertile couple, but instead, recommend those procedures resulting in the highest profits. This leads to a type of generic treatment before IVF that is not very likely to result in a successful pregnancy, leaving the couple with the impression that expensive IVF is their only treatment option.

Many reproductive endocrinology/infertility (REI) specialists would prefer to try more patient friendly non-invasive therapies, and be more patient with their non-IVF procedures, but the nature of their compensation is frequently based on the relative number of IVF procedures generated by the consultant subsequently performed. For these reasons, there becomes a need for generalists in OB-GYN to become non-IVF infertility specialists.

Unfortunately, if a generalist in OB-GYN wants to learn more about treating infertility through methods not involving IVF-ET, attending infertility conferences may not be the answer because the lectures and research presented are heavily geared toward IVF-ET. For these reasons, I thought for a start I would write a manuscript on our methods of treating infertility without the use of IVF-ET. I say a start because I will provide you with experience of almost 50 years of practicing REI; but you should never consider my suggested treatment as gospel. Use them as a basis, but modify these suggested treatments according to your patient population, your personnel, and your own assessment of the nature of the suggested therapies.

What characteristics of an author are important to the reader to decide that the teaching philosophy is credible. Experience should be important, but less value if the treatment of yesterday has not been updated with newer and potentially more successful treatment options. There has always been a tendency for physicians, in any field, to remember the successes, but forget the failures. Thus, it is important to carefully reevaluate data, if not with a prospective study, then at least a retrospective one to corroborate the effectiveness of a given infertility therapy.

The lead author has published over 800 peer reviewed manuscripts, and at least 75% of them involve the diagnosis or treatment of infertility. My first peer reviewed publications were published in 1971 which involved cancer immunology, and my first publications in the field of reproductive endocrinology and infertility were not until 1977 [1-8]. We are still publishing peer reviewed manuscripts in 2023 dealing with cancer research, infertility, and other medical problems [9-13]. My present academic position is a professor of OB-GYN and division head of reproductive endocrinology and infertility at Cooper Medical School of Rowen University (formerly known as Robert Wood Johnson Medical School). I am also board certified in Internal medicine and medical endocrinology. My Ph.D. is in Reproductive Biology. This background allows me a different perspective in diagnosis and treating infertility than many other REI specialists.

I do not want to leave the impression that I am an anti-IVF-ET fanatic. In fact, my first publications involving IVF-ET were from 1991 [14,15]. Though we have had no publications regarding IVF-ET in 2023 so far, (though a couple have been accepted) we did publish a couple of manuscripts regarding IVF-ET in 2022 [16,17]. Furthermore, we did have a few presentations at the 2022 American Society for Reproductive Medicine that did directly involve IVF-ET [18,19]. Thus, we try our best to help patients conceive without IVF-ET to minimize cost and to some degree, medical risk, but we are not reluctant to try IVF where absolutely needed, (obstructed fallopian tubes, very severe male factor, or the luteinized unruptured follicle syndrome, or if non-IVF methods have failed, or if IVF-ET is the patient's preference). This experience with IVF-ET, and its efficiency on various infertility situations, provides more insight as to whether treating a patient with IVF-ET is much more efficacious than non-IVF procedures.

Though the basis of my knowledge in the field of infertility was accrued by mentors during my fellowship program, fine tuning my specific treatment protocols for infertility and reproductive endocrinology are the results of attending many REI meetings over the years, reading many publications dealing with infertility to develop the "art" of my practice, it would be impossible (without writing a book) to summarize the thousands of publications related to infertility treatment that presently exist published by other scientists with infertility interests. Thus, I apologize that most of the references presented in this manuscript will relate to our own publications. This manuscript will include treating female infertility factors e.g., tubal issues, mucus abnormalities, endometrial issues, immunological abnormalities, endometriosis, and ovulation disorders, with the exception of diminished ovarian reserve which, was covered extensively in our manuscript published in Gynecol Reproductive Health in 2022 [20]. The manuscript will also cover diagnosis and treatment of male factor infertility.

Diagnosing and treating infertility without IVF

General facts about infertility

Who deserves an infertility evaluation and possible therapy? Personally, I think any couple trying for 6 months or longer; obviously earlier, if there are other issues e.g., amenorrhea, oligomenorrhea, a history of pelvic inflammatory disease, dysmenorrhea, or other types of pelvic pain, or a previous history of infertility with a previous partner.

The younger the female partner, the sooner one should expect a pregnancy. Our data, for example show women aged 35: expect 50% pregnancy rate in three months, 70% pregnancy rate in six months, and 90% pregnancy rate in 8 months when no infertility factors exist, or all infertility factors have been corrected. Failure to conceive in 8 months drops the next 8-month pregnancy rate to only 20% maintaining the same therapy that seemingly corrected all cycles in women 35 for example. Women aged 30 should expect 65% pregnancy rate in three months and 90% by six months. Women aged 38 should expect 35% pregnancy rate by three months and 50% by six months.

Evaluation of possible tubal disorders

When evaluating the infertile couple, one option is to perform hysterosalpingography (HSG) initially, or because this procedure is frequently painful, or expensive (if not covered by insurance), it could be deferred a few months hoping pregnancy will occur first. The HSG may be considered immediately if the patient prefers (leave no stone unturned) given the option of now or deferred, history of tubal infection, history of previous pelvic surgery, or maybe earlier with a history of severe dysmenorrhea with possible adhesions from endometriosis.

As far as laparoscopy is concerned, my personal preference, because of risk with surgery for complications, or damaging blood supply to the ovary and decreasing egg reserve, is to offer this procedure if there are: ultrasound findings suggesting a possible hydrosalpinx or a sufficient number of corrected cycles without a pregnancy, hoping to find adhesions impairing tube-ovum pick-up, that could be possibly corrected following laparoscopic lysis of adhesions.

Surgical treatment of endometriosis

Should a laparoscopy be performed earlier if a woman has severe dysmenorrhea? In women with 8 months of all infertility factors seemingly corrected, randomly removing mild endometriosis vs. not, we found that 61 of 69 (88%) women whose implants of endometriosis were ablated conceived in the next 8 months going back on therapy that seemingly corrected the problem, but failed to become pregnant during the first 8 months vs 18 of 54 (33%) women whose implants were not removed [21]. Many subsequent studies support our findings from 1987, but other studies disagree [22].

In the early days of REI training before IVF-ET, fellows had extensive training in reproductive surgery, but not so today. More commonly today, the generalist in OB/GYN is a more skilled and competent surgeon for mechanical fertility issues than the younger REI specialist. This is related to the emphasis on IVF-ET during fellowship training today and much less emphasis on surgery. In fact, most REIs today would prefer to have the generalist in OB-GYN to perform the surgery because reimbursement to the surgeon is generally low and IVF-ET is more lucrative.

We no longer favor laparoscopy as first line treatment for patients with infertility or recurrent miscarriage, and dysmenorrhea. Instead, we favor treatment with drugs that release dopamine from sympathetic nerve fibers, thus negating to some degree, the increased cellular permeability of the pelvic tissues leading to excessive endometrial inflammation with subsequent implantation failure. The best drug for their problems is dextroamphetamine sulfate related to its effect on releasing dopamine from sympathetic nerve fibers [11]. A Less effective alternate, if another drug is necessary is cabergoline [10].

Medical treatment of endometriosis

Many subsequent studies support our findings from 1987, but other studies disagree Meta-analysis favors the benefit of removing endometriotic implants to improve odds of obtaining a pregnancy [22].]We have published many anecdotal case reports demonstrating the efficiency of dextroamphetamine in markedly improving pelvic pain, while not suppressing ovulation, as seen with other medical therapies, but also to improve fecundity [11,23-25].

Most women with endometriosis are positive for an inflammation marker called BCL6 obtained from endometrial tissue (marketed under the name Receptiva assay from Bruce Lessey's group in South Carolina, USA). In a study by Almquist and Lessey, Fertil Steril, 2017, 52 of 69 women having their first IVF cycles for unexplained infertility (patent fallopian tubes and normal sperm) were positive for BCL6. Their average age was 36 and they had normal egg reserve. The live delivered pregnancy rate for 17 women negative for BCL6 inflammation marker was 58%, however the live delivered pregnancy rate for majority of cases (n=52) positive for the BCL6 marker was only 11% [26].

In contrast, we showed that for women <age 39 with dysmenorrhea, who were highly likely to be positive for BCL6 marker, taking dextroamphetamine sulfate, had a slightly higher pregnancy rate than women without pelvic pain who were not treated with dextroamphetamine sulfate! The pregnancy rates were twice as high for the group receiving dextroamphetamine sulfate group vs no dextroamphetamine sulfate in women >age 40 [27]. Thus, despite publishing one of the first studies suggesting that laparoscopic removal of endometriosis can help some infertile women to achieve a pregnancy, we favor treatment with dextroamphetamine sulfate instead.

After surgical removal of endometriosis, there is frequently a return of symptoms in a short length of time suggesting return of inflammation, whether removal of endometriosis was by laser

or excision method. The excision method involves specialized training, but there is a greater risk for surgical complications such as decreasing egg reserve. Women with endometriosis, because of chronic pelvic inflammation, already are prone to diminished oocyte reserve (DOR) because of autoimmune egg depletion by excessive inflammation. Surgery may compromise egg reserve even more. Though our group is skilled in performing laparoscopic surgery, we prefer dextroamphetamine sulfate therapy over surgery.

Infertility Related to Uterine Abnormalities

The type of surgery that most REIs do is hysteroscopy. This can be performed in the office in the IVF suite, where reimbursements can be higher from insurance carriers for a "facility fee." There are many REIs that perform a hysteroscopy even if an HSG demonstrates a normal uterine cavity. Performing a hysteroscopy on a patient with a normal HSG is usually unnecessary.

What benefits can be obtained by hysteroscopic surgery? Hysteroscopic surgery is useful in the removal of endometrial polyps, intrauterine adhesions, and the removal of a uterine septum. Certainly, generalists in OB/GYN can easily perform hysteroscopic surgery, if needed. Should all patients with uterine polyps have them removed by hysteroscopic surgery [28]? Unless very large (>10mm) most uterine polyps do not impair infertility and they frequently may return in a few months [28].

Intrauterine adhesions leading to amenorrhea with no withdraw bleeding despite estradiol (E2) and progesterone (P) are a definite cause of infertility (Asherman's syndrome) and requires surgical removal by a skilled hysteroscopic surgeon. The question arises as to whether intrauterine adhesions still allowing menses could still create an infertility issue? Reduced fecundity has been found with thin endometria at peak follicular maturation. However, infertility is not a definite if there is a very thin endometrial thickness. Successful live deliveries have occurred in natural cycles with maximum endometrial thickness of 4mm [29,30].

At present, there are no good medical therapies to improve endometrial thickness when it is too thin. Studies by Wala et al. and studies by Rubenstein et al. claimed improved endometrial thickness by using low-dose aspirin [31-33]. Not only did we fail to corroborate the benefit of low dose aspirin in improving endometrial thickness or uterine blood flow, but it led to a lower live delivered pregnancy rates when used in the proliferative phase (first half of menstrual cycle before ovulation) [34].

There are many REIs that recommend low dose aspirin therapy, especially when there may be the presence of antiphospholipid antibodies. However, based on our data, aspirin, if taken during the follicular phase can adversely affect the establishment of a successful pregnancy even with the definite presence of antiphospholipid antibodies e.g., anticardiolipin antibodies, Beta 2 glycoprotein 1 or the lupus anticoagulant. If APA are present, anticoagulant therapy should not be started from the onset of pregnancy, it should not be started until later. The presence of anti-phospholipid antibodies can lead to an increased risk of thrombosis in uterine arteries that can lead to late 1st trimester or 2nd trimester miscarriage. However, during the first 2/3 of the 1st trimester, the platelets are thrombophobic and thus forming blood clots is much less likely. Thrombosis leading to diminished blood supply is much more likely to occur starting toward the end of the 1st trimester when the platelets are more thrombophobic [35]. We have made attempts to improve endometrial thickness by treating with vaginal estradiol or granulocyte colony stimulating factor (G-CSF) or low-dose aspirin, but we have not found these therapies to be effective in improving endometrial thickness [36].

Will hysteroscopic removal of adhesions improve endometrial thickness? We evaluated endometrial thickness before and after removal of intrauterine adhesions by hysteroscopic surgery. The women were divided into 3 groups: poor prognosis-endometrial thickness 4-5mm, fair prognosis-endometrial thickness 6-7mm, good prognosis endometrial thickness 8mm or more. Removal of adhesions with hysteroscopy found a 4-fold greater chance of adhesion removal to cause a thinner endometrium than a thicker one [37].

Thus, my philosophy is as long as the presence of intrauterine adhesions allows a normal menstrual period, one should correct other infertility factors first, and hopefully a successful pregnancy will ensue. If no successful pregnancy occurs after a reasonable period of time, and if no other infertility factor is found, then try hysteroscopic surgery to remove all of the adhesions.

If the HSG or ultrasound suggests a uterine septum, can you treat the patient for infertility or miscarriage without removing the septum first? If the fetus implants on the septal wall, there is generally insufficient blood supply to continue fetal growth and miscarriage will likely ensue. Sometimes removal of a septum can allow a live delivery in a woman with multiple miscarriages [38]. However, one study found that if a woman had only one previous miscarriage, randomly comparing septoplasty vs. no surgery found no difference in miscarriage rates in the next pregnancy [38]. Even if the space for fetal growth is cut in half by a septum, successful deliveries may occur despite a uterine cavity with a compromised size [39].

Thus, a woman with recurrent pregnancy loss and a uterine septum could be treated with supplemental P from the early luteal phase, with the possible addition of dextroamphetamine sulfate if there is pelvic pain present, without septoplasty [40,41]. But if you are skilled at septoplasty, or you know a good hysteroscopic surgeon to whom to refer your patient, it would not be wrong to have surgery first, especially, for cases where the surgery would be less complicated, and thus not likely to damage the uterus.

Unexplained infertility

Most REIs consider a couple with infertility of one year or more as "unexplained" if the female has regular menstrual cycles, the semen analysis is normal, the serum anti-mullerian hormone level

is normal, and the hysterosalpingogram shows bilateral tubal patency. When faced with "unexplained" infertility, the most common treatment rendered by REIs is a follicle stimulating drug plus IUI. Sometimes they will add some P in the luteal phase, but frequently it is at the patient's insistence. Generally, if P is given, the amount is minimal, or not nearly the dosage used in an IVF-ET cycle or frozen ET. Commonly, the REI just supplements the luteal phase with oral micronized progesterone despite the fact that 90% of the progesterone is metabolized through first pass through the liver so only 10% reaches the endometrium. Usually, if this empiric therapy is not successful after a few cycles, then the REI physician will commonly recommend IVF.

Generally, a post-coital test is not performed by most REI practices, and it is considered an archaic procedure. Many REI fellows have never seen a post-coital test in their 3 years of training. The argument given is why bother performing a post-coital test if the mucus is going to be bypassed by IUI anyhow. Most couples with infertility seeing REIs conversing with one another frequently ask what did your REI recommend IVF or IUI? The price for performing this simple IUI procedure generally ranges from $400 to $1500 per cycle. It is not just a recent trend to avoid post-coital test. It does go back over 30 years [42]! How much does an IUI correct infertility problems when the semen analysis is normal? Are treating physicians not performing IUI from the start being unfair to those patients who do not have religious reasons for avoiding this procedure or have the insurance coverage or finances to pay for this procedure, even if performed monthly? We compared in a patient choice option study, where we determined if the addition of IUI improved pregnancy rates in a first treatment cycle where some other cause of female infertility factor seemed to be corrected. Pregnancy rates were 25% with intercourse vs. 26.7% with IUI [43].

Cervical mucus abnormalities

Cervical mucus abnormalities in natural cycles are not a common cause of infertility. Most cases of cervical factor are iatrogenic in nature related to using follicle maturing drugs, e.g., clomiphene citrate or letrozole. These drugs cause adverse mucus related to their anti-estrogen effect. Clomiphene is a selective estrogen receptor modulator. Letrozole is an aromatase inhibitor. They both block the estrogen effect on the stimulation of thin watery mucus. We found in women taking clomiphene citrate for ovulation induction or oocyte maturation a good post-coital test was found in 18 of 58 (31%) women in their first treatment cycle and a poor post-coital test in 40/58 (69%) [44].

In natural cycles, if the post-coital test is normal (at least 1 sperm moving per high powered field on the microscope moving with linear progressive motion from intercourse at least 8 hours prior), it generally stays normal in succeeding cycles, and thus only has to be evaluated once. In contrast, clomiphene may cause progressively poorer post-coital tests in succeeding cycles even if the dosage in not increased [44].

Letrozole does not have as much prolonged anti-estrogen effect as clomiphene. Unfortunately, however, this drug did not decrease the frequency of adverse cervical mucus, and thus poor post-coital tests, when compared to clomiphene [45].

Empirical use of clomiphene or letrozole plus IUI for unexplained infertility

If empirical use of clomiphene or letrozole helps to correct infertility even when unexplained, what should a treating physician, who does not offer an IUI, do if these drugs adversely affect the mucus and cause a poor post-coital test? Should they then be referred to an REI as long as the couple is okay with an IUI?

To help answer this question, we must ask another: Does empirical use of anti-estrogen follicle stimulating drugs have a beneficial effect on treating unexplained infertility? Another important question is as follows: is there an inexpensive treatment option that is an equally, or an even more effective treatment option for unexplained infertility than these anti-estrogen follicle stimulating drugs?

The hypothetical basis for empirically treating with clomiphene or letrozole is based on allegedly correcting a subtle follicle maturation defect or improving luteal phase P secretion. If one would use just supplemental P (especially vaginal) in the luteal phase there would be no adverse effect on the cervical mucus, since it is being used after ovulation.

In a study of fertile women, we found the large majority of them attain an average 18-24 mm dominant follicles and attain a peak mid-cycle serum E2 level over 200 pg/mL. Using this definition, we found after evaluating 100 consecutive couples who had a minimum of 1 year infertility, patent fallopian tubes, normal semen analysis, normal post-coital test, and no luteinized unruptured follicle syndrome, but an out-of-phase endometrial biopsy taken about ten days after ovulation, we found that 58 of 100 women attained a mature follicle. For these 58 women, 27 of them were randomized to standard of care in the mid 1980's (and even today with many REI's) clomiphene citrate; but switched to gonadotropins if the post-coital test was poor. There were 31 randomized to vaginal progesterone suppositories as their only treatment. The outcome after 6 months of empiric treated with follicle maturation drugs, we found that only 3 of 27 (11.1%) conceived with fertility drugs and that 2 of 3 had miscarriages so the live birth rate only 3.7%. In contrast 24 of 31 (77.4%) conceived with P supplementation, with only 1 miscarriage with a live birth rate of 74.2% [46]. During the second 6 months patients with failure to conceive with follicle maturing drugs were offered treatment with just P in the luteal phase and 16 of 25 conceived (64%) and only one miscarried [46].

For the 42 women not attaining a mature follicle, during the first 6-month interval, despite regular menses, only 3 of 12 (25%) conceived with P only and no miscarriages. Follicle maturing drugs resulted in 7 of 10 (70%) achieving pregnancy, but there

were 4 miscarriages resulting in similar live delivered rate (30%) as P supplementation. However, combining follicle maturing drugs and supplemental P, 14 of 20 conceived (70%) with only 1 miscarriage (65% live delivered pregnancy rate). This explains why sometimes the empirical use of follicle maturing drugs plus IUI achieves a pregnancy when treated by REIs with the aforementioned empirical approach, but also explains why the majority fail, and then, with the failure, the recommendation by the REI will generally be IVF-ET [46].

In our opinion, the need for supplemental P is based on the failure of the cells of the fetal placement unit (e.g. embryonic cells, mesenchymal cells and trophoblast cells) to secrete sufficient amounts of the immunomodulatory protein, the progesterone induced blocking factor (PIBF), to neutralize natural killer (NK) cells (that are needed for creation of spiral arteries) from attacking the fetal semi-allograft [47,48]. We stopped performing the endometrial biopsy because we were concerned that an in-phase biopsy may still not detect the need for more PIBF secretion in the fetal placental microenvironment. Most of our population of patients are seeking alternative medical opinions, so we get to see REI treatment and diagnostic procedures from all over the United States and even outside the USA. Most practices do not perform the endometrial biopsy anymore for evidence of luteal phase defects.

Our policy also has changed. In lieu of the endometrial biopsy, we treat all infertile women who attain a mature follicle with supplemental progesterone if they are age 30 or over, and if they have dysmenorrhea, dyspareunia, mittelschmerz, or chronic pelvic pain which usually, indicates excessive NK cells requiring the need for more PIBF to suppress immune attack of the fetal semi-allograft. We will prescribe P supplementation in women with pelvic pain with P even if they are younger than age 30 [48]. Using this protocol, of age and chronic pelvic pain to treat with luteal phase P in lieu of the endometrial biopsy, a higher % made a mature follicle. For women age <39, 32 of 40 (80%) made a mature follicle vs for women aged 40-45, 26 of 33 (82.5%) made a mature follicle. Did this new approach change the success with treatment solely with luteal phase support with progesterone? The six-month pregnancy rate for women aged <39- 84.3% conceived and 71.7% had a live birth. For women aged 40-45, 53.3% conceived and the live delivery ratio was 19.2% [49].

What options are available to a physician treating infertility where IUI is not an option, but where clomiphene or letrozole creates adverse cervical mucus in women with regular cycles, but not attaining a mature follicle, where improving follicular maturation is necessary? One option is to simply use a very low dose of FSH (75IU) from mid to late follicular phase to boost the follicle to maturity without adversely effecting cervical mucus, and not creating multiple follicles. Similarly for women who are anovulatory, but where clomiphene or letrozole creates adverse mucus, one can use low dose FSH drugs and monitor with blood and ultrasound. This may require a physician with a little more expertise in this type of treatment.

Therapy for poor post-coital tests including adverse cervical mucus, per se or, as a result of need for anti-estrogen follicle stimulating drugs, or anti-sperm antibodies

In performing a post-coital test, it is important that is performed at the right time. The right time is when the serum E2 has exceeded 200 pg/mL but before the LH surge [50]. It is important to perform the test at least 8 hours after intercourse to detect the possibility of anti-sperm antibodies (ASA) on the sperm (most common) or in the cervical mucus (less common). The male seminal fluid is devoid of complement, so sperm coated with ASA are not immobilized when performing a semen analysis. However, cervical mucus is loaded with complement, and thus sperm immobilization in the cervical mucus may ensue after intercourse, but the antigen-antibody-complement reaction could take 8 hours to immobilize the sperm [51]. Years ago, adverse cervical mucus was more common related to exposure to diethylstilbesterol that pregnant women once took to theoretically prevent miscarriage. Today hostile cervical mucus is less common (possibly about 3%) when properly diagnosed in women not taking anti-estrogen follicle maturing drugs.

Though IUI does not improve infertility if sperm is normal and the post-coital test is normal, it is an effective treatment for cervical mucus abnormalities occurring naturally or related to the use of anti-estrogen drugs. If the treating gynecologist does not have the facilities to perform an IUI other than referring to a REI facility, the physician could switch from clomiphene or letrozole, if they were needed for follicular maturation, to gonadotropins (follistim, gonal-F, or menopur). One can sometimes correct mucus abnormalities caused by anti-estrogen drugs by starting ethinyl estradiol (EE) after clomiphene or letrozole is stopped with ovulation or even concomitant with gonadotropins [52,53].

Simply performing an IUI for sperm washed with ASA may not result in pregnancy because these antibodies could also prevent the sperm from attaching to zona pellucida. Pregnancy rates following IUI with sperm with ASA are poor [54]. However, pregnancy rates following IUI are markedly improved by treating the sperm with the protein digestive enzyme chymotrypsin prior to IUI to neutralize the function of ASA [55]. The best mucus occurs 36 hours before ovulation, therefore the best time for intercourse is 30-36 hours before ovulation. Sperm stay alive in the crypts of the cervix and send “search parties” into the uterus and fallopian tubes until ovulation. With subnormal motile densities, however, the “troops” may be depleted before the egg is released.

At the time of ovulation, the mucus has generally dissipated or thickened, not allowing sperm to swim into the uterine cavity. Thus, if an IUI is to be performed, it should be timed when the egg releases because the egg can still be fertilized in the fallopian tube for at least 12 hours after ovulation.

Whether there is an intrinsic mucus abnormality, or iatrogenic related to using clomiphene citrate or letrozole, improvement of poor post-coital test and pregnancies have occurred following treatment with guaifenesin 1200 mg from early follicular phase to ovulation [56].

Treatment of male with subnormal sperm other than IUI

Once sperm is taken out of the seminal plasma, and suspended in media, there are no factors that inhibit capacitation, so the sperm may have fertilizing capacity for only 4 hours. Thus, the benefit of an IUI for a subnormal semen specimen is to enable the sperm to be present in the uterus closer in time to ovulation, as opposed to closer in distance to the egg. That is why IUI can be of benefit for a male factor problem that is not too severe.

So, what can a physician do to treat male factor infertility if they do not perform IUI or the couple does not want IUI? It must be noted that subnormal semen analysis does not necessarily mean a sub fertile male. We performed a study to evaluate the effect on pregnancy rates according to range of motile sperm densities where all female infertility factors did seem to have been corrected. At the time of the study, a sperm motile density of $10x10^6$/mL was considered normal. (now $8x10^6$/mL is considered normal). The following pregnancy rates were found in 6 months just with normal intercourse: <2.5 million/mL)-22%, 2.5 to <5-69%; 5 to <10-81%, 10 to <15, -78% and ≥15-81% [57]. With low motile density, one must especially avoid drugs, e.g., clomiphene or letrozole, that can adversely affect the cervical mucus. Prognosis with intercourse is even better if some live sperm are seen on post-coital test. For sperm with subnormal morphology (<4%) using Kruger's strict morphology, most REI practices usually recommend IVF with ICSI to choose the right sperm. If IVF is rejected, then they recommend at least IUI by the couple. However, except in extreme circumstance, e.g., sperm without acrosomes (globozoospermia), sperm with normal motile densities, but morphology <4% sperm do not adversely affect pregnancy rates in natural cycles [58,59]. There was no difference with only 1,2,3, or 4% having normal morphology [60]. Even if one is performing IVF for males with low % normal morphology, higher pregnancy rates are found with conventional oocyte insemination vs ICSI [61,62].

Simply stated, low sperm concentration or motility may be related to low sperm precursors in the testicles where medical treatment is generally not effective, versus inadequate stimulation from the hypothalamic/pituitary axis, where medical treatment can result in significant improvement. Diagnosing what type of male factor problem exists is needed to determine if medical therapy can be effective. This can be determined by measuring serum gonadotropins, testosterone, prolactin, and possibly estradiol [63,64]. If serum FSH is in the low normal to medium normal range, many males will respond to treatment with clomiphene citrate [3,65]. Clomiphene can be just as effective in men with varicoceles [66]. Though varicocelectomy was very popular as a treatment of male infertility, it is generally believed today that this procedure may only significantly improve the sperm in about 10% of males [67].

For males with elevated serum prolactin levels or top normal serum prolactin levels and relatively low FSH, LH, and testosterone, bromocriptine or cabergoline can be an effective therapy [68]. For males with hypogonadotropic hypogonadism, the only treatment is the combination of gonadotropins (generally 75-150 IU FSH 3x per week) with the addition of human chorionic gonadotropins 2000 IU 3x per week. One must be patient because it takes 75 days to develop sperm from spermatids to spermatozoa, and an additional 21 days to confer final maturity, so it may take several months before sperm is found in the ejaculate [64]. For some reason, it may take a lot longer before one finds sperm in the ejaculate [69].

For those physicians who do not have the facility to prepare the sperm for IUI, there are some "tricks" that can be done mechanically to improve sperm concentration for intracervical insemination. Most of the sperm is concentrated in the first portion of the ejaculate, so men may split the ejaculate followed by intracervical insemination [70]. Some men may need a "double flush" to get the sperm out of the ejaculatory ducts, and thus some men will show significant improvement of sperm concentration by a short interval second ejaculation [71]. Occasionally, males with higher serum E2 levels related to increased aromatase enzymes with subsequent low serum testosterone, can improve semen quality by treating with aromatase inhibitors e.g., inhibitors letrozole [67].

The problem of diminished oocyte reserve

When faced with diminished oocyte reserve (DOR), most REIs suggest trying to stimulate multiple eggs with aggressive gonadotropin therapy. We disagree. Most REIs suggest IVF-ET immediately, using high dosage FSH, but cancel if there is an insufficient number of eggs. We disagree. Most REIs recommend not only IVF with high dosage stimulation, but to do preimplantation genetic testing for aneuploidy (PGTa). We disagree [72]. The likelihood of live pregnancies in women with DOR compared to age peers with normal egg reserve based on IVF data are as follows: age<35-80%, age 36-39-70%, age 40-42-50% [73]. Treatment of subtle ovulation defects in women with DOR can vary according to the degree of DOR. Successful pregnancies may be achieved without IVF-ET in menstruating women, and even women in apparent premature menopause [74-77]. Last year, we published, in this journal, specific types of non-IVF treatment for women with DOR, whether they had regular menses, oligomenorrhea or amenorrhea. Though the specific type of treatment may have varied, the common thread was to realize that using higher dosage gonadotrophins or other follicle stimulating drugs e.g., clomiphene or letrozole, or both, can lead to a rise in serum FSH which may down regulate FSH receptors leading to less follicles, or to down regulate FSH receptors that are needed to produce key FSH induced enzyme or cytokines that are needed for successful embryo implantation. For more details, we refer the reader to review an article in a previous issue of Gynecol Reproductive Health [78].

Infertility related to insufficient endometrial inflammation, or excessive inflammation

Another review in Gynecol Reproductive Health discussed the experimentation that led to the hypothesis that in the luteal phase, there is a need to create an autoimmune condition leading to inflammatory cells removing some of the normally thick walls

of uterine arteries to create thin-walled spinal arteries needed for exchange of nutrients between mother and fetus. This is followed by the subsequent need to inhibit these inflammatory cells from then attacking the fetal-semi allograft causing the lack of conception or miscarriage [27].

Theoretically, infertility or miscarriage can occur related to excessive inflammation from increased cellular permeability, which could be the source of many other clinical conditions e.g., headaches, fibromyalgia, pelvic pain, interstitial cystitis, Crohn's disease, and chronic fatigue syndrome, just to name a few [79,80]. However, it is also possible that infertility can be related to insufficient inflammation leading to inadequate uterine artery remodeling [27].

The first study to purposely induce inflammation to try to improve pregnancy rates was by Barish et al. [81]. They evaluated irritating the endometrium by an endometrial biopsy in mid-luteal phase in preparation for IVF in the succeeding menstrual cycle. This biopsy without pathological interpretation has been referred to as the endometrial scratch. Though they found improved pregnancy rates per transfer, and though other REIs corroborated the value of the endometrial scratch, some other studies refuted its benefits. Our own conclusion is that the scratch seems to improve pregnancy rates in women having IVF and fresh embryo transfer, but it may lower pregnancy rates following frozen ET or in women with DOR, or advanced reproductive age [27].

There are very few studies evaluating the effect of the endometrial scratch in natural cycles. We evaluated the effect of endometrial scratch in natural cycles in women with unexplained infertility that were very refractory to previous treatments. The couple had to have minimum of 2 years of infertility (but no maximum), regular menses, with the production of a mature dominant follicle, normal sperm, normal post-coital test, and bilateral tubal patency by hysterosalpingogram. Furthermore, they had to have had a minimum (but not a maximum) in another REI center, 3 cycles of follicle drugs with IUI and/or IVF-ET.

The control group was treated for 3 cycles with vaginal and oral progesterone in the luteal phase, plus a mid-luteal phase injection of 1 mg leuprolide acetate [82]. The experimental group received an endometrial scratch in the late luteal phase prior to the first cycle of evaluation, but not before cycle 2 or 3 but otherwise received the same therapy as the controls.

In cycle 1, 4 of 40 controls conceived with 2 miscarriages compared to 20 of 40 women receiving the scratch with only 2 miscarriages [27]. The benefit of the scratch seemed to be only in the cycle after the scratch so that the live delivered pregnancy rate for the 3 cycles were 25% for the control group and 68% for the scratch group [27].

This study not only showed that irritation leading to more endometrial inflammation can be beneficial in natural cycles in a selected group of patients, but reemphasized the importance of simple progesterone treatment [27,49]. A 25% success rate in 3 cycles is very good considering some of these successes occurred in women who had spent over $100,000 dollars with IVF-ET which failed to achieve a pregnancy or controlled overran hyperstimulation without IVF [49]. We believe that the main benefits of luteal phase treatment with supplemental progesterone is to increase the secretion of the immunomodulatory protein called the progesterone induced blocking factor (PIBF) that is needed to suppress an excessive cellular immune response for uterine artery remodeling by cellular immune cells which may lead to rejection of the fetal placental semi-allograft [83]. As mentioned, the PIBF is more embryonic, mesenchymal and trophoblast cells from the fetal-placental unit and from circulating gamma-delta T-cells [47].

A sperm defect as the cause of embryo implantation defects:

A sperm abnormality, probably related to a toxic protein added to the sperm as they transverse the ejaculatory ducts that is more common in men of advanced age is known as the hypo swelling test (HOST) defect [84-86]. In fact, a low HOST better predicts by far pregnancy rates following conventional oocyte insemination compared to subnormal motile density or sperm morphology [87]. This abnormality can be treated without IVF-ET by neutralizing this toxic protein by first treating the sperm with the same protein digestive enzyme, chymotrypsin, that was used to denature antisperm antibodies, and then performing IUI. However, in contrast to ASA, one must in the case of low HOS test score <50%, to avoid unprotected intercourse since the problem is related to the sperm attaching to the zona pellucida [88]. More details about the simple, inexpensive test that for some reason is not evaluated by the large majority of REI physicians, have been summarized in great detail in a recent publication [9].

Anovulation with estrogen deficiency [89]

In the presence of amenorrhea, if the serum AMH is low, the serum FSH is high and the serum E2 is low, then the diagnosis is ovarian failure. Details as to how to sometimes achieve ovulation in this group have already been summarized [20,90]. If AMH is normal, and the serum FSH and LH, and E2 are low, then the woman has hypogonadism or hypogonadotropic hypogonadism. The preferred drug is one with LH and FSH together (menopur), but since menopur is the most expensive gonadotropin, one could treat with gonal-F or follistim with low dose HCG which provides the needed LH activity until follicular maturation is achieved when it is then necessary to trigger ovulation by using higher dosage HCG e.g., 10,000IU. One should still add supplemental progesterone in the luteal phase to decrease the risk of miscarriages [40,91].

Anovulation with normal estrogen [92]

Anovulation with normal estrogen is the most common type of secondary amenorrhea [92]. In this circumstance, one cause is related to insufficient gonadotropins which takes the follicle to the point of estrogen production, but not to the dominant follicle stage. This can be seen with mild weight loss, relative excessive exercise, or a low-calorie diet, or stress. A certain amount of adipose tissue is needed to properly modify the estrogen to allow

it to properly stimulate the gonadtropin releasing hormone from the hypothalamus which, in turn, allows adequate LH and FSH activity by the pituitary, leading to successful ovulation [93]. Thus, in cases of mild gonadotropin deficiency, follicle maturing drugs can induce follicular maturation with subsequent ovulation by raising the serum FSH level. Letrozole has a shorter half-life than clomiphene and thus it is less likely to create multiple follicles leading to multiple births. Some think if one ovulates with letrozole there is a higher pregnancy rate than with clomiphene citrate in PCOS. However, we found that clomiphene citrate has a better chance to induce ovulation in patients with PCOS [93].

For women to allow a mature follicle with clomiphene or letrozole to develop, one can add gonadotropins after stopping these drugs, which reduces the cost and reduces the risk of multiple births if clomiphene or letrozole does not seem by themselves to attain follicular maturation [93]. Adding metformin can sometimes allow ovulation without needing to add gonadotropins, but this drug frequently has gastrointestinal side effects, so we do not frequently prescribe it. Sometimes, however, elevated testosterone can inhibit FSH release from the pituitary so that clomiphene fails to induce ovulation adding a small dose of prednisone to lower the serum testosterone level in conjunction with clomiphene can achieve ovulation without adding gonadotropins [2]. Though traditionally clomiphene or letrozole had been started in day 3-5 of the menstrual cycle following induction of menses by treating with 10-14 days of progesterone, one can achieve higher pregnancy rates by starting the drugs later in the follicular phase without inducing menses in anovulatory woman [94].

Anovulation with normal estrogen related to FSH resistance

On the other hand, in some instances, anovulation with normal estrogen can occur with relative FSH resistance [95]. During the 1st half of the follicular phase, the follicular fluid is androgen dominant. Continued maturation will not be attained unless the follicular fluid becomes estrogen dominant, in which case the follicle can now control its own destiny, and develops into the dominant graafian follicle. The Anti-Mullerian hormone (AMH) inhibits the FSH induced aromatase enzyme and thus inhibits the conversion of testosterone to estradiol [95]. There is evidence that the presence of AMH helps the body to select just one dominant follicle each month because as FSH drops during the follicular phase from negative feedback from the rising E2 levels to inhibit pituitary release of FSH, only the follicle with the least amount of AMH allowing adequate testosterone to estradiol conversion will stimulate the follicle to proceed to the dominant follicle stage. Thus, if there is too much AMH made by early follicles before advancement of follicular maturation, follicular development will stop at the stage of androgen dominance of the follicular fluid, leading to increased serum testosterone levels and inadequate serum E2, but overall increased estrogen by conversion of the increased testosterone to estrogen other than estradiol. The follicle then becomes atretic.

This may be the one of the possible mechanisms to explain the condition of polycystic ovary syndrome with the primary cause being increased AMH secretion by early follicles. This causes FSH resistance. Thus, to ovulate one needs to raise FSH higher to overcome FSH resistance, which can be by directly stimulating with FSH injection (gonal-F, follistim, menopur) or inhibiting negative feedback of estrogen to the pituitary by blocking the estrogen receptor with a selective estrogen receptor modulator e.g., clomiphene citrate or tamoxifen, or to suppress E2 production by an aromatase inhibitor e.g., letrozole [92,95].

Ovulation despite regular menses [96]

Clearly, in this manuscript, we discussed pure luteal phase defects where only progesterone (P) supplementation is required. To correct infertility when there is a luteal phase defect with insufficient follicular development, there is a need to further mature the follicle by clomiphene, letrozole, or gonadotropins then add p supplementation again in the luteal phase [96]. Adding a small boost of subcutaneous FSH from mid follicular to late follicular phase can help boost the follicle to maturity without creating adverse cervical mucus without a great increase in expense.

The luteinized unruptured follicle syndrome and premature luteinization

The key distinction between the formation of an estrogen secreting cyst vs. a luteinized unruptured follicle (LUF) is the process of luteinization. We define a luteinized unruptured follicle (LUF) as failure for a follicle to shrink by at least 5mm within 2 days of an LH surge with the serum progesterone (P) exceeding 2 ng/mL.

Sometimes the LH surge occurs before the serum estradiol(E2) has reached 200 pg/mL, and thus the serum P rises above 2 ng/mL before the E2 reaches 200 pg/mL (or sometimes never reaches 200pg/mL). Though the follicle either does not collapse by 5mm for several days after the LH surge, or sometimes it does collapse even within 2 days of the LH surge, though technically there is a LUF phenomenon, we classify this type as premature luteinization rather than LUF syndrome.

In a previous study of women with at least 18 months of infertility we found 56 of 400 women to have premature luteinization in the first cycle of evaluation (14%). In cycle 2, 52 of these 56 women also demonstrated premature luteinization [97]. This shows that premature luteinization is most likely to occur repeatedly rather than just be an isolated event.

Diagnosing LUF in women taking follicle maturing drugs may be more difficult if there are several dominant follicles developing, since some may have been obscured, and sometimes a new follicle can fill the spot vacated by one that released an egg. We evaluated whether pelvic sonography could predict egg release in gonadotropin-treated patients [98]. There were 220 patients evaluated, and egg release seemed to occur in 148 of these patients (67%), indeterminate release in 56 (25%) and non-release in 16 (7%). Pregnancies occurred in 13.5 % of those who seemed to release, 5.4% where release was questionable, and no patient without egg release. In cycle 2, egg release was seen in 134/197

(67%), indeterminate in 50/197 (25%) and 13/197 (6.6%) failed to release. Pregnancy rates were 15.7%, 4.0% and zero % [98].

Sometimes egg release is uncertain in that the follicle may shrink 3-4 mm but not over 5mm at the time of the sonography study, and the serum P level barely exceeded 2 ng/mL. As evidenced by pregnancy rates, pelvic sonography has demonstrated to be reasonably accurate in diagnosing LUF even when gonadotropins are used. Patiently rarely achieve a pregnancy in a cycle where LUF seems to be present. The indeterminant group, based on pregnancy rates, seems to be more likely to be LUF.

The question is whether LUF is an isolated phenomenon that can occur as an isolated event in any given ovulatory cycle, or does it tend to recur? We found that 91%of women releasing eggs on cycle 1 also released in cycle 2, only 30% of the group where there was a question of egg release did release in cycle 2, and only 6% of women with LUF in cycle 1, did show egg release in cycle 2. This supports the contention that LUF is a syndrome rather than an isolated phenomenon [98].

The study of factors required for oocyte release may help to create therapies for LUF syndrome. Proteolytic enzymes seem to play a role in egg rupture from the dominant follicle, e.g., plasminogen activating factor. Both LH and FSH have been demonstrated to stimulate plasminogen activating factor. Thus, theoretically, failure to release an egg from a mature dominant follicle could be related to insufficient LH and/or FSH surge or to inadequate production of sufficient biologically active LH and FSH. Since rising serum estradiol has positive feedback on LH, not attaining an adequate mid-cycle serum E2 could contribute to LUF by not attaining an adequate rise in LH or lack of creating sufficient biologically active LH and/or FSH. Since HCG has the same biological activity as LH, the method to treat LUF in a natural cycle is to start with 10,000 IU hCG when a follicle is mature whether in a normal cycle or one stimulated with gonadotropins. If treatment fails, one can try 15,000IU hCG if there seems to be LH resistance [99]. If 15,000 IU hCG fails to enable egg release, in case a rise in FSH is the necessary link, a cheaper and less risky option (and an option much easier to use by non-REI specialists and requiring much less monitoring) would be using 150 IU FSH along with 15,0000 IU hCG to enable oocyte release. One study did suggest that the addition of an FSH injection on the day of the hCG injection may enable egg release in women with LUF failing to release without treatment or with an hCG injection [99]. However, the rise in FSH at the time of peak follicular maturation could be a double-edged sword. An excess of FSH in the late follicular phase could lead to excess glycosaminoglycan, which, in turn may inhibit the production of hyaluronic acid, which is needed to thin the zona pellucida to allow rupture of the egg. High mid-cycle FSH levels can be a cause of higher frequency of LUF in some women stimulated by gonadotrophins or because of slow clearance of FSH. Women with diminished oocyte reserve, whose FSH is generally elevated even at the time of follicular maturation, may have a higher frequency of LUF [78].

A possible reason why too high of a serum FSH level at time of peak follicular maturation can cause LUF may be that the high FSH (and possibly LH) down-regulates FSH (and/or LH) receptors making the needed LH and FSH inadequate to make the essential enzymes to release eggs. Thus, one potential treatment would be raising the LH and FSH higher by releasing more endogenous LH and FSH by using a GnRH agonist. So what options are there for women treated with gonadotropins who do not release with 10,000 IU or 15,0000 IU FSH even with an extra 150 IU or FSH added at the time of the hCG injection? In fact, sometimes women who release eggs naturally fail to release the egg when hCG injection is used to time IUI [100]. Possibly an exaggerated rise in endogenous LH and FSH can be more effective than higher levels of hCG. Based on this hypothesis, we decided to try a GnRH agonist, leuprolide acetate, to enable egg release in LUF cases failing to release with hCG or hMG and hCG. In lieu of hCG, we injected the GnRH leuprolide acetate 1mg every 12 hours x3. We found in the 1st gonadotropin stimulated cycle, 20 of 24 women released their eggs with 10,000IU hCG, thus LUF occurred in 16.6%. For cycle 2, these 4 women were treated again with 10,000IU hCG, and all 4 failed to release eggs (LUF frequency 100%). Yet all 4 released their eggs in cycle 3 when leuprolide acetate was used instead of hCG (101). Pregnancy rates were equal whether using hCG or leuprolide acetate [101]. Combining cycles 1 and 2 for those releasing with hCG (no. 17) there were 7 pregnancies (41.1%). For those releasing with leuprolide there were 9 pregnancies in 24 patients (37.5%) [101]. Similar findings were focud in a study using ultra-low dose gonadotropins stimulation [102].

LUF seems to be more likely to occur when women are using high FSH dosages vs very low FSH dosage. Thus, another advantage of leuprolide over hCG in hyperstimulated cycles is that GnRHa will reduce the risk of ovarian hyperstimulation syndrome. Incidentally, especially with polycystic ovarian syndrome, using gonadotropin medication with LH added to FSH rather than FSH alone can reduce the risk of OHSS [103]. Are there any other solutions other than egg retrieval if all these other options fail to enable egg release? The granulocyte colony stimulating factor (G-CSF) increases in the follicular fluid of the dominant follicle immediately preceding the LH surge. We hypothesized that G-CSF may be needed for egg release, and possibly some women may be deficient. Indeed, we found that treating with G-CSF the day before hCG could enable egg release in women previously refractory to other treatments [104]. We recently published a case report on a 46.5-year-old woman in who we reversed menopause and she conceived naturally. This is a good article to read because she illustrates so many of fertility therapies we use. We illustrate step wise therapies when we helped her to conceive at age 42 with regular menses, but very high day 3 serum FSH. Four cycles in a row, she failed to release the egg, but she was the first case we tried granulocyte colony stimulating factor and she conceived with luteal phase support with P, a mid-level phase injection of leuprolide acetate, and she was treated with dextroamphetamine. These measures were used again at age 46.5, but this time we had to use the FSH receptor-upregulation technique to allow her to ovulate despite overt ovarian failure [75].

Purpose of writing this manuscript

With the vast amount of knowledge that is available in the medical field, there has been a tendency for physicians to not only specialize, but to sub-specialize (e.g., orthopedists specializing in hand versus knee versus back surgery or oncologists specializing in hematological cancer, vs lung cancer vs bone cancer etc.). These sub-specialists are found mostly in large cities and frequently associated with medical schools or large communities. Many times, these subdivisions are made to have better experts in one particular area, but also for economic reasons.

A family physician or generalist in internal medicine may not have anywhere near the knowledge as an oncologist, but knows his/her patient for years, the family finances, and enough knowledge to know that expensive medication or clinical trials are not going to provide a cure but instead will result in suffering from side effects or financial depletion, and time away from the family. Thus, the patient's trusted family physician may opt to take care of the patient himself/herself without referral to a specialist.

The same situation now exists for patients suffering with infertility. Some of these suggested infertility treatments, discussed in this article, which are usually not expensive, will frequently not be offered by the REI. Thus, it becomes more important now for the generalist in OB-GYN to become familiar with methods to diagnose and treat infertility. Unfortunately, most reproductive endocrine/infertility practices are mostly geared toward performing IVF cycles.

I wrote this article to provide a basis for generalists in OB-GYN to become more familiar with non-IVF techniques, and hopefully utilize them to help patients conceive without financial depletion. This can be instituted from the start of their OB-GYN practice, or possibly an OB-GYN, a little older now, and wanting to stop the grueling obstetrical side of the practice, may consider specializing in non-IVF infertility.

In medicine, the truth of today may be tomorrow's fallacy. Possibly you may find better medical treatments than described in this manuscript or find new ways to diagnose infertility issues. Perhaps you need to modify these suggestions related to your patient population and personnel. As physicians, we tend to remember our successes and forget our failures. It is important that whatever treatment you render, find some method to keep track of whether your treatment is successful or not. If you deem that the problem is not correctable by non-IVF means, e.g., very damaged fallopian tubes that cannot be surgically corrected, or very severe male factor problems, then an immediate referral to an infertility specialist performing IVF is appropriate. If you are confident that you have corrected the cause of infertility, and enough treatment cycles have been rendered, so that now there appears to be truly unexplained infertility, then referral for IVF-ET therapy seems reasonable.

I completed my fellowship in reproductive endocrinology and infertility in 1975 at Thomas Jefferson University School of Medicine and stayed there for several years teaching medical students, OB-GYN residents, and fellows in REI. I switched to Robert Wood Johnson Medical School (now Cooper Medical School of Rowan University) over 35 years ago where my title was professor of OBGYN and division head of reproductive endocrinology and infertilty. I still maintain that position. We have been running an REI practice, and performing research, but also providing education, in the REI field, to students, residents, and fellows.

Thus, to conclude this manuscript, I wanted to post some questions to the new generation of REIs of the future to get their views on how OB-GYNs should be trained in diagnosing and treating infertility. I purposely chose an OB-GYN resident who has completed her second-year residency in OB-GYN at another institution, who is interested in becoming an REI specialist, but who has also not taken any clinical rotations with our practice. Her name is Brooke Neumann, DO. I have also posed questions to a medical student at Cooper Medical School of Rowan University who has completed her 1st year of medical school, but has not had any clinical rotations in our practice. Nevertheless, she has expressed great interest in the REI field. Her name is Ava Therese Karnish.

Questions to Dr. Brooke Neumann, OB-GYN resident

1. You are finishing your 2nd year of OB-GYN Residency. Have you had an REI rotation, and if so, how many weeks?

Answer

I have not had my core REI rotation, but I was fortunate to spend my elective 4-week rotation at the National Institute of Health on an REI rotation.

2. You have expressed interest in pursuing an REI fellowship when you complete your residency. Did you have interest in REI before your REI rotation or before?

Answer

During my last rotation, while I was a student in medical school, I had the opportunity to rotate with an REI group. While in the first two didactic years, I developed an interest in the REI topics, but I truly fell in love with the specialty when I gained clinical experience.

3. Before your rotation, what interested you in the field of REI? Did your clinical exposure solidify your interest or make you question whether this is the right career for you?

Answer

As I stated earlier, I found that I have a passion for learning about the physiology of REI. I find it fascinating how far this field has come in only 60 years, but I am truly amazed by the advances in technology which will continue to flourish and change the field and the way we practice it. My clinical exposure solidified my aspirations for perusing REI.

4. If no exposure to REI, what piqued your interest, and did this present article increase your desire to be an REI specialist or dampen it?

Answer
As I stated before, my interest has already piqued. After reading this article, I have gained perspective, and I am eager to read more literature and learn about new topics and concepts within the REI specialty.

5. If you do not get into an REI fellowship, which as you know is quite difficult, would you be interested in learning more as to how to treat infertility without necessarily being able to perform IVF?
Answer
I am still interested in learning how to treat infertility. It is a medical problem. However, I do find it valuable to learn IVF as it will be another tool in my toolbox to help patients accomplish their dreams of beginning and/or growing their family. I also find it valuable to learn other methods to treat infertility for I am also learning that IVF-ET is not for every patient and having another option that could lead to a successful pregnancy would be beneficial for myself in order to help my future patients.

6. Having completed 2 years of OB-GYN training, and even having an interest in REI, do you think the suggestions in this publication of treating infertility without IVF could be implemented by generalists in OB-GYN or would the demands of general OB-GYN practice preclude the more scientific approach expressed in this manuscript?
Answer
I believe that generalists could implement some of the suggestions in this article especially if our training started early, beginning with the rotations in residency with the goal of training generalists. I think it would be very helpful because REI can be a confusing topic and generalists might immediately refer to sub-specialists for evaluation and treatment if they are not comfortable. From my point of view, feeling comfortable practicing fertility starts in residency and I believe integrating a curriculum nation-wide is the first step in that process.

7. If you did not get into an REI fellowship, and if OB-GYN demands would preclude you from performing a proper infertility investigation, leading to a proper patient friendly treatment plan, would you consider limiting your practice to gynecology with an emphasis in reproductive disorders and infertility?
Answer
If I do not match into a fellowship program initially, I intend to work at an infertility practice. I will take that time to learn and grow while continuing to do research with the goal of matching in the next few years.

8. Do you think practicing non-IVF types of infertility treatment would appeal to physicians wanting to retire from the obstetrics side of OB-GYN, but practice infertility and reproductive endocrinology, and possible reproductive surgery?
Answer
Even though it sounds appealing to me, I do not believe that OB/GYNs at the end of their career would practice only REI. From my perspective, if they were not doing infertility treatments during their career, why would they want to begin as they are getting ready to hang their coat up? I do believe it does depend on the individual physician, but if I had to guess, I would assume they would choose more of a generalist GYN role since that is what they are most comfortable practicing.

9. What do you think about a new OB-GYN sub-specialty of infertility (non-IVF) reproductive endocrinology, pelvic pain, and minimally evasive surgery?
Answer
I believe this is a fascinating idea, although my initial thought is if you propose this idea versus the traditional REI fellowship training, most trainees will choose to learn IVF simply to have that extra skill in their toolbox.

10. Do you think an extra training program for 1 year would appeal to those OB-GYNs ready to retire from OB, but wanting to limit their practice to gynecology, do you think that they would they be interested in taking an extra year of REI training without IVF-ET?
Answer
I do not believe it would appeal to generalists. My thought is that they are ready to retire and would not likely want to go back to train for the last few years of their career in a sub-specialty.

11. Do you think that OB-GYN residents completing their 4-year residency but not accepted to an official REI fellowship, would be interested in taking an extra year of training as I stated above?
Answer
I truly believe that this could be an excellent opportunity. I know that some residents that do not initially match will join an REI practice as a generalist to not only learn on the job but also being able to practice the medicine they love with the hopes of matching in the next few cycles. I would assume they are not doing the retrievals and transfers but will gain experience learning about the process of IVF while they are working at the practice. The extra year of training, in my opinion, would be beneficial for the residents interested in becoming REIs and I think other residents with the same interests as me would agree.

12. Would you, if you were not successful in being accepted to an official REI fellowship think about taking this extra year of training, if it would enable you, if joining a larger OB-GYN practice, other than sharing some of the general OB-GYN duties, to be the primary physician in that practice to evaluate and treat infertility patients and those with endocrine issues?
Answer
I would consider this extra year of training. I hope to pursue a fellowship in REI, but if I did not have that opportunity, I would want to learn as much as I can before practicing on my own. I also believe that the extra year of training would show my dedication to the field which will hopefully help me toward my goal of matching into a fellowship.

13. Assuming that this extra training would not gain acceptance as a board recognized subspeciality, what means could be taken so

that certification of completion of 1-2 years of this type of program could be officially recognized, so that patients have the option of seeking the opinion of an OB-GYN more knowledge than other generalists in OB-GYN for infertility treatment, in lieu of an OB-GYN who has completed a board certified REI fellowship where there will be a general emphasis in IVF-ET, and thus without as much expertise as an OB-GYN completing this type of extra training.

Answer

I believe that there might be too many politics involved and it would be rather difficult to have this approved. It would be interesting to know what the majority of currently practicing REIs feel about this type of training and how comfortable they would feel if this 1-year fellowship became an official board-certified fellowship.

Questions to Ava Therese Karnish, medical student

1. You have just completed your 1st year of medical school and have had little or no exposure to reproductive endocrinology and infertility, yet you have already expressed a great interest in becoming an REI. How did you become interested in this subspeciality?

Answer

There are various factors that have captivated my interest in this ever-growing field aimed at the goal of family completion. Perhaps the initial spark came from my personal background in that my mother had an exceedingly difficult journey conceiving my brothers and me. I have seen how her experience has framed her role as a mother and how it still impacts her even today. Careful to understand her relationship with her own OB-GYN, from a young age, I was very aware of the gratitude and trust she placed in their hands. This example of a strong centered Doctor-Patient rapport set the stage for how I wish to serve others throughout my career. I find that there is truly something special about caring for women during this exceedingly difficult time in their lives. Infertility is a topic that is only newly brought to the forefront of discussions and has historically been a silent battle for many. Embracing this concept, I seek to devote my medical career to assisting those on the front line of this battle and maintaining a spotlight on this prevalent topic.

2. After reading this manuscript, and the questions posed to the OB-GYN resident Brooke Neumann, and her responses, are you now even more convinced that you want to become an REI, less convinced of pursuing this field, or this manuscript and Brooke Neumann's responses, have had no influences, pro or con, on your desire to become an REI?

Answer

At this point, I am now even more confident that I want to become an REI. In reading through the manuscript, I became increasingly intrigued as it caused me to question how I would handle certain circumstances as an REI. I am truly amazed by how this field has progressed through time and I am excited to be a part of its future. After reading Dr. Neumann's responses, I am reassured by how her passion has been strengthened through her clinical experience and how she aims to continue pursuing an REI fellowship despite its challenges. Though I am only at the beginning of my own journey, I feel as though I am looking at one clear path straight ahead.

3. At this stage, are you enamored with the surgical side of REI, the medical side of REI, or both? Is your fascination with REI actually related to the IVF-ET side of REI?

Answer

After working as a clinical assistant at a fertility care practice in New York City, I recognize that I am most drawn to the medical side of REI. I believe there is something special about the personally curated approach to each patient. I enjoy being there every step of the journey for the patient, paying careful attention to each monitoring appointment and meticulously altering their protocol considering each subtle change in their progress. I have never encountered another medical specialty that is so intimate and allows for such a real, substantive relationship between physician and patient. This aspect allows for the end goal of achieving pregnancy to be such a spectacular moment for not only the patient but the physician as well. Perhaps I cherish the most, however, when pregnancy seems unattainable even after many tried attempts, there is seemingly always another option at the physician's disposal. I have found that it is very rare to have to tell a patient that there is nothing that can be done. There is almost always another path to what they want, even if it is one that has never been tried before.

That being said, I understand that one of the most frequent options posed to a patient struggling to conceive is IVF-ET. However, from my perspective thus far, this physically and financially invasive treatment is not to be recommended until more natural approaches have been attempted, unless at the patient's request. IVF-ET is not only expensive but emotionally taxing and so time-consuming that it is often disruptive to the life of the patient. I feel grateful, however, to be practicing at a time in which this option is often at an REIs disposal when indicated.

4. Most medical endocrinologists are not needed to treat the majority of endocrine problems since they can usually be treated by family medicine and internal medicine specialists, What do you think about offering an extra year of reproductive endocrinology and non-IVF fertility training to medical endocrinologists, and to provide them some means to be distinguished from medial endocrinologists without extra training in this field? Do you think that there would be an interest in medical students, more interested in the medical side of reproductive endocrinology, rather than the surgical side, to consider a path of internal medicine first then a fellowship in reproductive and medical endocrinology rather than an OB-GYN residency followed by a 3-year REI fellowship? In answering this question consider the great difficulty in being accepted to an REI fellowship (at least in the United States) and much less problem being accepted to a medical endocrine fellowship?

Answer

At this stage, I do not see the full benefit of adding reproductive training to medical endocrinologists so that they may assist patients with REI needs. Achieving pregnancy through endocrinology is only the first half of the battle for infertility patients. Once

a patient achieves a positive HCG value, they are still to be monitored weekly for the progress of their growing fetus. In my opinion, I think that OB-GYN training is a critical strength for REI doctors. I am not sure that medical endocrinologists would be able to effectively assist patients once they are in this stage of their journey, especially since OB-GYN referrals are typically not sought until approximately 6-8 weeks after confirmed pregnancy. In my experience, a lot can happen before that 6-8 week "graduation" date, and I feel that it is best for the REI physician to be equipped in handling those circumstances.

When it comes to medical students' interest, I have found among my peers that not many of them know much about this specialty. I do know, however, that medical students are often deterred from pursuing certain paths due to the length of training time. If a new path to REI meant less time, I do believe that those who are exposed to REI and interested would consider it as an option rather than going through OB-GYN residency.

I would, however, like to pose an alternative option that I believe could alleviate some of the hurdles of being accepted into the competitive REI fellowship. Being that REI is unique in that it maintains surgical and medical components, is becoming heavily involved in genetics, and is such a growing field, I wonder if it would be possible to have a residency program all in itself. This program could be mainly aimed at endocrinology training but also include a year of OB-GYN training that is pertinent to the first weeks of pregnancy.

5. Feel free to add any of your thoughts to the questions posed to Dr. Neumann or to her responses, or comments about this discussion on how to correct infertility issues without IVF-ET.

Answer

In response to some of the questions posed to Dr. Neumann, I am also intrigued by the idea of an extra year of training in lieu of the ability to complete an REI fellowship. Being that this fellowship is exceedingly competitive, I feel that more avenues to sharing this information and skill is a great opportunity for all who are interested.

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