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Inexpensive Methods to Correct Long-Term Infertility Despite Failure with Follicle Stimulating Drugs, Intrauterine Insemination, and *In Vitro* Fertilization

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Abstract

Background: Frequently, a large percentage of infertility centers have a general treatment plan that is not patient specific where most patients are treated with ovarian stimulation and intrauterine insemination (IUI). The objective of this study is to present non-invasive, non-expensive methods that resulted in live deliveries that emphasized progesterone supplementation in the luteal phase, avoided follicle maturing drugs in those attaining a mature dominant follicle, performed (IUI) only if post-coital test was inadequate or likely to be abnormal based on the spermiogram, and also considered treating some women with dopaminergic drugs (especially those with pelvic pain and/or other "autoimmune" conditions).

Method: The treatment provided to fifty consecutive patients achieving a successful pregnancy by the above methods was recorded. The couple was required to have at least two years of infertility, failure to conceive despite at least multiple treatment cycles rendered by at least two fertility specialists and failure to have a success despite a minimum of two IVF cycles.

Results: Most of these couples successfully conceived just after a few individualized non- invasive treatment cycles.

Conclusion: Based on our own studies our experience suggests that the exclusive use of progesterone in the luteal phase without follicle maturing drugs if a dominant follicle is attained naturally and perform IUI only if the post-coital test is inadequate and using dopaminergic drugs when appropriate can achieve the delivery of healthy babies even in women failing to conceive despite previous ovarian stimulation, IUI and IVF.

Keywords: Progesterone supplementation; Post-coital test; Refractory infertility; Natural conception; Immunomodulatory proteins; Dopaminergic drugs

Introduction:

Many infertility centers would consider that a couple has unexplained infertility if the female partner has regular menses with a serum progesterone (P) level >12ng/ml in mid-luteal phase, with a hysterosalpingogram demonstrating a normal uterine cavity with bilaterial fallopian tube patency, a male partner with normal semen parameters, and normal oocyte reserve as evidenced by a serum anti-mullerian hormone level >1ng/ml, and failure to conceive after at least 6 months of unprotected intercourse.

Though the infertility specialists are aware that there may be hostile cervical mucus, performing a post-coital test is considered by many infertility specialists

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as an archaic procedure. At our infertility practice, we think this test has great importance in better determining the cause of the infertility to enable the best recommendation for the most cost-effective treatment for the patient [1].

Dodson et al in 1991 published a manuscript suggesting that intrauterine insemination (IUI) is an effective treatment for infertility, not just for a male factor problem or cervical mucus problems, but for unexplained infertility [2]. Thus, the philosophy adopted by many infertility centers is why bother with the post-coital test if one is going to treat with an IUI anyhow?

Our infertility center thinks there are many factors arguing against that philosophy. For one, depending on the infertility center, IUI can be expensive, especially if it has to be repeated in many cycles. Also, some religions require procreation only using natural methods i.e., intercourse, placing an emotional strain on some couples with the desire to follow the tenets of their religion against the strong need to have a family. Even if there are no religious restrictions, and IUI is paid for by insurance carriers, there is still the inconvenience of 2 people having to interrupt their work or daily schedules to come in for an IUI that may not be needed! Our studies disagree that IUI is helpful to achieve a live delivery if there is no apparent male or cervical factor based on semen analysis and cervical mucus quality and the finding of a normal post- coital test [3]. Instead of an expensive "shot gun" approach, if there was a cervical mucus quality issue, one can correct the problem with very non-risky inexpensive treatments e.g., guaifenesin [4]. If guaifenesin fails, there are other mucus therapies that can correct the mucus defect without proceeding with IUI [5].

A male may have a sub-normal spermiogram, yet that sperm could still be quite fertile even with natural intercourse [6,7]. On the other hand, if sperm were coated with an anti-sperm antibody (ASA), since the seminal plasma is devoid of complement (which is needed to immobilize the sperm), a male with ASA present on the sperm may appear to have normal motility yet the sperm die in the cervical mucus several hours after intercourse because complement is present in cervical mucus [8]. Since the manufacturer of immunobeads has stopped its production, and thus the good quality immunobead test is no longer available, the best way to be suspicious for ASA coating male sperm is finding non-motile sperm in the cervical mucus 8-12 hours after intercourse performed at the proper time [9,10]. IUI for sperm coated with ASA alone has poor success rates. A much better outcome occurs when the sperm are pre-treated with the protein digestive enzyme chymotrypsin to neutralize the ASA before preparing the sperm for IUI [11].

Studies at our infertility center more than 35 years ago found that treating women with supplemental P in the luteal phase, who appear to develop a mature dominant follicle (18-24mm with serum estradiol (E2) >200 pg/nl) and where the only infertility factor seemed to be an out of phase mid to late luteal phase endometrial biopsy, resulted in a marked superior pregnancy rate than the conventional option of treating with follicular maturation drugs, e.g., clomiphene citrate [12]. Luteal phase P supplementation was also found to produce very good live delivered pregnancy rates (LDPR) in natural cycles in women who had unexplained infertility, but yet seemed to make a mature follicle even when no endometrial biopsy was performed [13].

However, a follicle maturing drug in the follicular phase, plus P supplementation in the luteal phase, was found to be superior to P supplementation alone in women with regular menses with luteal phase defects but who did not reach the criteria of a mature follicle [12]. Vaginal or intramuscular P is preferred since the majority of oral micronized P is metabolized through first pass through the liver, and thus only a small percentage reaches the uterus to allow production of immunosuppressive proteins e.g., the progesterone induced blocking factor (PIBF) after activating membrane (M) P receptors (mPRs) in embryonic cells, mesenchymal cells, and trophoblast cells of the fetal placental unit and also circulating gamma-delta T cells. These mPR induced immunosuppressive proteins are needed to suppress the increase in cellular immune cells in the early luteal phase caused by the increased infiltration of irritants into pelvic tissues. The increase in cellular permeability was achieved by P inhibiting dopamine secretion by sympathetic nerve fibers, thus negating the effect of dopamine in suppressing cellular permeability [14-16]. The increased cellular immune activation is needed to remodel some of the thick-walled uterine arteries seen in the proliferative phase into thin-walled spiral arteries by autoimmunity to allow subsequent maternal-fetal nutrient exchange [14,16]. These mPR induced

Immunomodulatory proteins e.g., PIBF, inhibit the cytotoxic effect of the cellular immune cells e.g., inhibiting degranulation of perforin and granzymes in natural killer cells (which represent 70% of the population of the cellular immune cells in the fetal placental microenvironment) and by inhibiting prostaglandin synthesis from cytotoxic T cells [15, 16]. Inadequate neutralization of above normal increased cellular immunity in the early luteal phase by relative decreased production of mPR generated immunomodulatory proteins or relatively increased cellular permeability (either genetic or acquired) may lead to immune rejection of the fetal semi- allograft, (which may be still present despite an in phase endometrial biopsy). Thus, we abandoned the dated endometrial biopsy as the method to determine P therapy or not and just treat all women over age 30 or those under age 30 with pelvic pain with P supplementation in the luteal phase [13]. The need for more P to produce enough PIBF to neutralize the increased early luteal phase increased cellular permeability seems to increase with advancing age [13,15].

Sometimes increasing luteal phase P to increase mPR

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induced immunosuppressive proteins is insufficient, and thus it may be necessary to treat with dopaminergic drugs to decrease cellular permeability concomitant with increasing mPR immunosuppressive proteins especially when there is evidence of increased inflammation as evidenced by pelvic pain, or signs of inflammation elsewhere in the body [17-19]. The most commonly used dopaminergic drug in our practice is dextroamphetamine sulfate, though there may also be benefits from bromocriptine or cabergoline [20-22].

Since women need estrogen to develop nuclear nPRs required for proper histologic development of the endometrium, for women who have regular menses, but who fall shy of attaining a mature dominant follicle, we generally recommend a small boost of gonadotropins from the late follicular phase to attain follicular maturity [23]. We prefer gonadotropins over clomiphene citrate or letrozole because of the theoretical possibility that the anti-estrogen effect during the 5 days of taking these drugs may interfere with the development of adequate endometrial nPRs to form an appropriate secretory endometrium in the luteal phase.

Furthermore, the anti-estrogen effect may cause hostile cervical mucus which then requires IUI [24,25].

However, since gonadotropins are expensive, for estrogenic anovulatory women our general procedure is to achieve follicular maturation with either clomiphene or letrozole because the amount of gonadotropins required to achieve ovulation could be cost prohibitive for some couples. Furthermore, there is a greater risk of attaining multiple dominant follicles with the risk of multiple births especially with polycystic ovarian syndrome.

After many consultations with patients seeking second, third or even fourth opinions as to our recommendation as to how to correct their infertility, because they failed to have a successful pregnancy by treatment rendered by other infertility centers, we determined that many of their prior therapies were empirical rather than scientific, i.e. without investigation as to cause. A common practice is to treat with clomiphene citrate or letrozole even in women with regular menses without establishing the need for a follicular maturation drug and then perform IUI. Frequently, supplemental P in the luteal phase is not part of the therapy, and when added, is frequently at the patient's insistence (who acquires this information by the internet). When supplemental P is given, it is frequently in dosages or mode of delivery (e.g., strictly oral P) that we would deem insufficient.

The objective of this study was to determine what type of therapy that we suggested that resulted in a live delivery despite women failing to have a successful pregnancy following treatment in at least 2 previous infertility practices where they were treated not only with follicle stimulating drugs and IUI but also IVF.

Materials and Methods

The criteria for selection of patients for this study was as follows: 1) the women had to have a minimum of 2 years of primary or secondary infertility 2) they had to have been treated for a minimum of 3 cycles by each of the prior infertility specialists that they consulted 3) They had to have been treated by at least 2 previous infertility specialists without achieving a live delivery 4) They had to have at least 8 combined cycles with some type of follicle maturing drug plus IUI with previous infertility specialists and a minimum of 2 egg retrieval cycles with failure to attain a live delivery despite embryo transfer (fresh or frozen) or no embryos transferred related to failure to have proper embryo development or failure to attain a chromosomally normal embryo if preimplantation genetic diagnosis for aneuploidy (PGTa) was performed. 5) They had to be considered reasonable candidates for natural conception thus patients with severe male factor problems who want to try without IVF were excluded as were women with known compromised tubal patency e.g., unilateral or bilateral patency but with known extensive adhesions that would likely interfere with the egg reaching the fallopian tubes 6) The female partners were required to have a serum anti-mullerian hormone level of > 1ng/ml. 7) IUI would only be performed if the motile density was below normal or the post-coital test was poor despite the appearance of adequate sperm quality, and therapy to improve cervical mucus quality failing to improve the post-coital test. IUI was not performed if the sole sperm abnormality was low percentage of normal sperm morphology using strict criteria [26]. The women had at least 6 cycles of therapy with our infertility center unless conception occurred first. 8) The couple had to have a problem with infertility rather than recurrent miscarriage.

We evaluated 50 consecutive successful pregnancies achieved by some therapy rendered by our group except if it was achieved by IVF-ET. The type of therapy given was recorded. In all instances if we used dopaminergic therapy for likely excessive endometrial inflammation, the dopaminergic drug used was dextroamphetamine sulfate rather than bromocriptine or cabergoline because of more experience with the former for treating infertility or recurrent miscarriages. The dosage began at 15mg amphetamine salts tablet upon arising and at noon (equivalent to 18.8mg total dextroamphetamine sulfate) and was titrated to the maximum dosage monthly based on correction of symptoms vs side effects. The dextroamphetamine sulfate was continued throughout the 1st trimester then stopped unless it was needed to treat associated conditions that would persist and cause suffering e.g., inflammatory bowel disorders [18,19,27,28].

As mentioned, since one cannot at the present time determine by testing whether women are producing enough mPR-induced immunomodulatory proteins to suppress the increased luteal cellular immune response, all women

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received P in the luteal phase. The most common type of vaginal P used in our practice is compounded vaginal suppositories 400mg upon arising and before bedtime related to the fact that this type of vaginal P is much less expensive than commercial preparations. We have no data to suggest that this type of vaginal P is superior to commercial preparations, but to keep consistency for this study, women who conceived with commercial vaginal P preparation were excluded. All women also received oral micronized P 200mg at bedtime on an empty stomach related to increasing serum PIBF by gamma delta T- cells [29]. The dosage of P could be increased especially adding intramuscular P if the mid-luteal endometrial echo pattern was not homogeneous hyperechogenic [30,31].

Egg release from the follicle was determined by ultrasound [32]. If there was failure to release the egg from the follicle before the serum P reached 2 ng/ml, this would be treated by 10,000IU human chorionic gonadotropin (hCG) in succeeding cycles at the time of peak dominant follicle maturation. If this failed, other therapies to enable egg release would be considered [33-35].

Results

The types of therapies provided that helped to achieve live deliveries in 50 consecutive patients meeting the exclusion and inclusion criteria are seen in table 1.

Different treatments rendered in 50 consecutive infertile women achieving a successful live delivery (all received luteal phase P) without in vitro fertilization-embryo transfer

There were 26 of the 50 women (52%) who attained mature follicles by the definition described in the introduction (these criteria were established for our own personal use by evaluating follicular maturation in women who were likely to be fertile based on ease of achieving a pregnancy without therapy. These data were never published). All 26 women of these women had been treated by follicle maturing drugs in other practices for many cycles.

Table 1: patients meeting the exclusion and inclusion criteria

	Group 1 – no follicular stimulation	Group 2 – FSH boost only	Group 3 – Clomid or letrozole (with or without FSH)
No. patients	26	9	15
No. IUI	8	6	10
No. dextroamphetamine sulfate	7	3	2
Avg. No. cycles to become pregnant	2.8	4.4	3.3
Avg. age	34.8	34.7	31.5
Range	27.8 – 41.1	30.5 – 38.9	25.9 – 35.7

A total of thirty-five patients (70%) were ovulating but 9 of these 35 needed a small boost of low dosage FSH injections (usually 75IU for 1-3 days) from late follicular phase to attain full maturation of the dominant follicle (E2> 200pg/nl with average size follicle diameter of > 18mm).

Only 8 women of the 26 women (30%) who did not require any follicle maturing drugs had IUI either for mild male factor problems or somewhat inadequate post-coital tests. It was not recorded as to whether the woman used guaifenesin to help mucus quality [36]. Six of 9 ovulatory women who needed a boost of FSH had IUI but 5 of the 6 was for mild male factor issues (either low motile density or lower quality motility).

There were 15 patients (30%) who were anovulatory and they were treated with either clomiphene citrate or letrozole, and some, in addition to these oral drugs, were given a boost of FSH in the latter part of the follicular phase. Ten of 15 required an IUI with 2 having been already decided to have IUIs for mild male factor problems and 8 of them for inadequate post- coital tests despite the addition of oral guaifenesin 600mg capsules twice daily from day 1 of cycle to ovulation [36].

An inadequate post-coital test (defined as none or at most 1 sperm per high powered field moving with linear progressive motion 8-12 hours after intercourse) despite a normal semen analysis was present in 8 of 13 (61.5%) anovulatory women taking an anti-estrogen drug to induce ovulation. In contrast, for women making mature follicles, 4 had IUI for mild male factor. Thus, an inadequate post-coital test was present in only 4 of 18 women (22.2%) making a mature follicle requiring those 4 women to have IUI based on some relative problem between sperm and mucus.

Dopaminergic drugs i.e., dextroamphetamine sulfate was given to 12 of the 50 women (24%). There is no way to know if this additional treatment helped them to have a successful conception or not.

Discussion

The patients sought another opinion as to their clinical management because they were not happy with the suggested plan by their last infertility specialist that was at that time managing their care. Suggestions included performing in vitro fertilization embryo transfer (IVF- ET) again without any change in protocol, deferring fresh ET in favor of freezing all embryos and then performing a subsequent frozen ET (FET) either with or without PGT-a performed with a trophectoderm biopsy on the fresh embryos prior to freezing or, the possible use of donor eggs or, the possible consideration of transfer of the embryos into a gestational carrier, or going back to ovarian stimulation with a milder form of gonadotrophins with a subsequent IUI instead of IVF to take a financial respite.

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This study shows that using a scientific approach, but with a lot less financial expenditure than assisted reproductive techniques, successful correction of infertility is possible despite failure with many previous commonly used expensive infertility therapies. The experimental design was not intended to determine if achieving these pregnancies with this treatment was possible, but rare, or were they more the rule than the exception? Since our practice is a tertiary type of care facility with many infertility specialists in close geographical proximity, and the majority of our infertile patient population have successful outcomes in our practice without the need to perform IVF-ET, and a large percentage of our patient population have failed to have success in other infertility practices, it is this author's opinion that these non-invasive inexpensive infertility therapies that were described will provide a high success rate for the majority of seemingly refractile infertility cases.

As mentioned, the majority of the patients in this study, when seen by their previous infertility centers, have been treated with a generic approach used for all patients rather than a more patient specific approach to determining the cause of infertility leading to individualized best therapy for that given person. A common generic non-IVF approach is to treat with clomiphene or letrazole for 3-6 cycles with IUI, sometimes switching to FSH injection with IUI, then recommending IVF-ET. Many of these treatment cycles do not include supplemental P in the luteal phase. Frequently, when P supplementation is used, the dosage or mode of delivery falls below what we typically use. We have recently provided an even more in-depth description of how we treat patients with infertility without the use of assisted reproductive techniques and the studies that we have performed to influence this treatment philosophy [37].

For women with diminished oocyte reserve (DOR) these same treatment principles also apply. However, we have additional recommended non-IVF treatment options for women with DOR which have been summarized previously [38].

Unfortunately, many infertility centers are owned by large corporations, and IVF-ET is not only the most profitable procedure to perform, but recently, charges for an IVF procedure have skyrocketed. These corporations put pressure on their physicians based on salary structure (and even some hospital or university owned infertility centers) to use a generic therapy to satisfy the couple seeking fertility help but to try to convince the couple that IVF-ET or other assisted-reproductive procedures are the best way to proceed, even when much less expensive therapies may exist. Today at infertility conferences or journals more emphasis is placed on improving IVF success than finding non-IVF solutions. Perhaps there is a need for generalists in obstetrics/gynecology to learn more about helping couples to conceive naturally, and only refer to an infertility specialist when the generalist thinks that all non-IVF options have been explored, and the next best option would be IVF. Alternatively, understanding options of non-IVF treatment therapies that exist, the generalist, in obstetrics/gynecology will look to refer their patient to an infertility specialist more cognizant of these techniques rather than refer to the infertility center with the "highest pregnancy rate per embryo transfer."

There may be many other non-IVF infertility treatments practiced by either other fertility specialists or generalists in OB-GYN. Hopefully, this manuscript may encourage letters to the editor of this journal, or the publication of their treatment modalities (with at least some scientific support of that therapy) but without the need for a randomized controlled trial (RCT). Generally, RCTs are pharmaceutical company supported. Thus, the pharmaceutical company usually will only provide funding for RCTs, which if demonstrating efficacy of a new drug, will provide great financial benefit to the pharmaceutical company. Without RCTs, very informative credible studies could still provide beneficial information for other treating physicians to help better enable those physicians to help couples solve infertility problems. These studies could be retrospective, matched-controlled, or case series or even convincing case reports.

Conflict of Interest/Funding

I declare there was no conflict of interest and no funding for this study.

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