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Original Research

The beneficial effect of luteal phase support on pregnancy rates in women with unexplained infertility

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Summary

Purpose: To determine what percentage of women with regular menses and unexplained infertility seem to develop a mature dominant follicle (18-24 mm average diameter and serum estradiol >200 pg/mL). Also to determine the efficacy of empirical progesterone (P) supplementation in the luteal phase for those with unexplained infertility who seem to make mature follicles. *Materials and Methods:* Serial ultrasounds and serum estradiol levels performed in cases of infertility over one year duration in patients with patent fallopian tubes, normal semen parameters, and normal post-coital test. Vaginal P of different types were given in the luteal phase as exclusive treatment. *Results:* A viable fetus past the first trimester was found in 71.7% of the 80% of women developing a mature follicle who were treated with P. *Conclusions:* For the combined effect of efficacy of therapy, cost, convenience, and lack of side effects, supplemental use of P in the luteal phase should be considered as first line therapy for unexplained infertility rather than empirical use of "fertility" drugs and intrauterine insemination or even in vitro fertilization - embryo transfer (IVF-ET). Methods of determining who needs supplemental P are not presently available.

Key words: Unexplained infertility; Follicle maturation; Progesterone supplementation; Luteal phase.

Introduction

What is unexplained infertility? The diagnosis may vary in different infertility centers according to the extent of the diagnostic work-up. "Pure vanilla" work-up: standard semen analysis with normal sperm concentration, normal motility and normal morphology, normal uterine cavity, and patent fallopian tubes by hysterosalpingogram, and normal properly timed post-coital tests. Work-up with more "exotic flavors": Semen analysis also evaluated for: subnormal hypo-osmotic swelling (HOS) test [1]. Presence of significant percentage of sperm coated with antisperm antibodies [2]. More sophisticated work-up for subtle ovulatory disorders: luteal phase defects [3], premature luteinization [4], luteinized unruptured follicle (LUF) syndrome [5-7], and short follicular phase [8, 9]. Abnormalities of the pelvis despite normal hysterosalpingogram detected by laparoscopy: presence of fimbrial adhesions or adhesions interfering with relationship of fallopian tubes and ovaries, or presence of endometriosis [10, 11]. About 25 years ago a study was conducted involving women with at least one year of infertility whose only detected infertility factor was a luteal phase defect determined by a late luteal phase endometrial biopsy [12]. Follicular maturation studies found 58 of 100 women achieved a mature follicle in a natural cycle (18-24 mm follicle with a serum E2 of > 200 pg/mL). Treating 31 of these 58 women with progesterone (P) vaginal suppositories in the luteal phase resulted in a pregnancy rate of 77% (24 of 31) in six months with only one miscarriage. In contrast only three of 27 (11.1%) achieved a pregnancy in six weeks taking either clomiphene citrate or human menopausal gonadotropin exclusively without taking P supplementation and two of three miscarried. Taking 25 of the failures who took follicle maturing drugs and now placing them on exclusive luteal phase support with P, 16 of 25 (64.0%) conceived with only one miscarriage [12]. There is a great deal of controversy concerning the importance of an endometrial biopsy and its timing in determining the presence of a luteal phase defect [13]. There are some clinicians who doubt that luteal phase deficiencies are even a cause of infertility [14].

The objective of the present study was to evaluate the efficacy of empirical luteal phase support with P in achieving live pregnancies in infertile women with unexplained infertility.

Materials and Methods

There was a prospective recruitment of women with unexplained infertility who were willing to be treated with P supplementation in the luteal phase exclusively. Unexplained infertility included evaluating all factors mentioned in "pure vanilla" and "exotic flavor" work-up with the exception that most women did not have laparoscopies. Another inclusion criteria was that the

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women either had to be age ≥ 30 or were < 30 years, but had pelvic pain.

P supplementation was given by: P vaginal suppositories 200 mg 2x/day, Crinone vaginal gel 8% 2x/day, and Endometrin vaginal tablets 100 mg 3x/day. The decision of which P to use was frequently based on insurance coverage – if no coverage for drugs then compounded P suppositories was given because they were cheaper than commercial products.

Only women attaining a mature follicle were treated with exclusive P in the luteal phase and used to determine pregnancy rates within six cycles of P therapy. In the determination of "unexplained" infertility those women with normal fallopian tubes and cervical mucus, and male partners with normal semen parameters who were excluded from the pregnancy data because they released an oocyte before the follicle was mature, were still recorded to help answer the question as to what percentage of women with unexplained infertility develop a mature follicle when an endometrial biopsy documenting a luteal phase defect is not performed.

If a woman dropped out before six cycles of P were given (unless a pregnancy was achieved) she was not included in the pregnancy data but was included in the study to determine the percentage of women with unexplained infertility achieving a mature follicle.

Two age groups were evaluated: < 39 and 40-45 years. Intrauterine insemination was not performed - only natural intercourse.

Results

Pregnancy rates in women < 39 years: the average length of infertility was 2.3 years. The average number of cycles using P was 4.5 and the average age was 32.5 years.

Pregnancies as defined as achieving a serum beta-hCG level >100 mIU/mL were achieved in 27 of 32 (84.3%) women (no hCG injections were used). A viable fetus past the first trimester was achieved in 23 (71.7%).

Pregnancy rates in women 40-45: the average age was 42.8 years. The average length of infertility was 3.1 years. Chemical pregnancies were achieved in 14 of 26 (53.3%). A viable fetus past the first trimester was achieved in five of 26 (19.2%).

Percentage of women attaining a mature follicle: age < 39 years – 32 of 40 (80%). Age 40-45 years – 26 of 33 (82.5%).

Discussion

It is very clear that exposure of the endometrium to P in the luteal phase is required for successful implantation and live delivery. However, it is not clear that a mild deficiency of P can be a cause of unexplained infertility.

It is not likely that with the average length of infertility in these women that such a high pregnancy rate in six months of treatment was fortuitous. Thus, the data are consistent with the possibility that subtle deficiencies of P during the luteal phase may be a cause of unexplained infertility that can be successfully treated by use of supplemental P in the luteal phase. Since there were no controls, an alternative hypothesis was that women with unexplained infertility may be improved by "placebo" therapy on their psyche.

As physicians we take a Hippocratic Oath to do no harm. From personal experience of consulting infertile couples who have been seen and treated by other OB/GYN specialists and infertility specialists many of these other physicians would have treated these couples empirically with clomiphene citrate plus intrauterine insemination (IUI) followed by gonadotropins with IUI sometimes with and sometimes without supplemental P therapy in the luteal phase. The problem with empirical therapy with follicle stimulating drugs for unexplained infertility: 80% of the women in the present study seemed to make mature follicles. The aforementioned study comparing follicle maturing drugs *vs*. P for luteal phase defects in those women making mature follicles (as in this study) found only a 4% live rate for those women taking follicle maturing drugs *vs*. a 74% live rate with P supplementation only. Also during the second months, 60% of the failures with follicle maturing drugs conceived with P supplementation [12]. Follicle maturing drugs can create a risk of multiple births. Clomiphene citrate frequently causes poor quality cervical mucus requiring intrauterine insemination [15]. Gonadotropins not only markedly increase the risk of multiple births but are extremely expensive. Unnecessary intrauterine insemination creates an increase in expense not to mention inconvenience of missing work for both partners. In some instances follicle maturing drugs may create a hostile uterine environment further compromising the infertility problem [16]. Follicle maturing drugs, especially gonadotropins markedly increases the expense for the couple or the insurance company (which drives up the cost of insurance premiums). Though empirical use of follicle maturing drugs may not be that effective despite being costly, some infertility specialists will bypass follicle maturing drugs and IUI and go directly to in vitro fertilization - embryo transfer (IVF-ET) with or without intracytoplasmic sperm injection (ICSI). Sometimes this option is taken after failure to conceive after only a few cycles of follicle maturing drugs and IUI. The IVF-ET option though frequently successful markedly increases the cost of achieving a pregnancy when the simple inexpensive use of P supplementation could be employed. The precise mechanism of the mechanism for the success of P supplementation in improving the chance of pregnancy in women with unexplained infertility is not known for sure; based on previous studies we suspect that there are some women who are infertile related to failure to make enough of a P induced immunosuppressive protein known as the P induced blocking factor (PIBF) that amongst other things suppress natural killer (NK) cell activity near the fetus [17-19].

Conclusions

It makes sense for all the reasons stated above to attempt empirical therapy with luteal phase P for unexplained infertility as the first line of therapy. Based on previous data (and this present study) the 20% of women who release the oocyte before adequate follicular maturation should be treated with the combination of follicle maturing drugs plus P in the luteal phase to maximize the chance of a live delivery.

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