A comparison of three types of therapies for three different ovulation disorders in establishing pregnancies and evaluation of laboratory parameters that could influence the outcome

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Summary

Purpose: To evaluate the empirical use of progesterone (P) in the luteal phase for unexplained infertility. *Methods:* Clinical and live-delivered pregnancy rates in three treatment cycles were compared in women with unexplained infertility vs women taking follicle maturing drugs for women completely anovulatory or those who release the oocyte before the follicle is mature. *Results:* There was insufficient power to show a significant difference in the 19.5% live-delivered pregnancy rate found in women with a mean length of infertility duration of 2.1 years who just used P in the luteal phase vs the 30.1% rate seen in women with clear-cut ovulatory defects treated with follicle-maturing drugs in the follicular phase and P in the luteal phase. *Conclusions:* Though a larger study would possibly show a lower pregnancy rate in those women with unexplained infertility empirically treated with P vs the women with ovulation defects, the empirical use of P allows easy treatment without the side-effects of follicle-maturing drugs, e.g., hostile cervical mucus, vasomotor symptoms or ovarian cysts. The study was not designed to determine if empirical use of follicle-maturing drugs with P support for unexplained infertility would be more effective than P supplementation alone.

Key words: Progesterone; Luteal phase; Unexplained infertility; Natural cycles.

Introduction

A previous study from the 1980's found that 58 of 100 women who had at least one year of infertility that was not related to tubal, male or cervical problem issues, but who had an endometrial biopsy that was obtained in the late luteal phase and was more than two days out-of-phase, appeared to attain a mature dominant follicle (as defined as making at least an 18 mm diameter dominant follicle and a serum estradiol (E2) ≥ 200 pg/ml) [1]. Randomly treating these 58 women with either progesterone (P) vaginal suppositories in the luteal phase vs a follicle-maturing drug (clomiphene or human menopausal gonadotropin (hMG)) in the follicular phase without luteal phase support, found that out of 31 women treated with P vaginal suppositories, there were 24 clinical pregnancies (77%) in six months and only one spontaneous abortion (4.1%). In contrast 27 women were given follicle-maturing drugs, there were only three clinical pregnancies (11%) in six months and two spontaneous abortions (66.7%) [1]. Interestingly, 25 failures on follicle-maturing drugs during the first six months were now treated during the second six months with P vaginal suppositories and 16 (64%) conceived with only one spontaneous abortion (6.2%) [1].

For the 42 women who did not attain a mature follicle, there was a higher pregnancy rate with follicle-maturing drugs than with luteal phase P. The data showed that the 12 women treated with luteal phase P, there were three (25%) pregnancies and no spontaneous abortions. For the ten women treated with follicle-maturing drugs but with no luteal phase P support, seven (70%) became pregnant but four (57.1%) had spontaneous abortions. Interestingly of the 20 women treated with both follicle-maturing drugs in follicular phase and P in the luteal phase, 14 of them conceived (70% same percentage as without luteal phase support) but only one spontaneous abortion (7.1%) compared to 57.1% without P supplementation [1].

There has been great debate regarding the accuracy of the endometrial biopsy. Of more concern, some insurances refuse payment and thus there could be quite an expense for a test of debatable value. Thus at our institution a decision was made to abandon the endometrial biopsy as a diagnostic tool.

Alternatively, because it was our hypothesis that the main function of P in allowing embryos to implant and in preventing miscarriage is to induce a 34 kDa protein which inhibits natural killer cell activity at the maternal-fetal interface [2-4] (and detection of low levels of this factor is not possible as yet on a wide scale commercial basis), we decided that if we cannot detect a follicular maturation defect, the luteinized unruptured follicle syndrome, a subtle

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Table 1. — *Pregnancy outcome according to empirical use of luteal phase P support for unexplained infertility vs follicle maturing drugs plus P in women with clear-cut ovulatory defects.*

	Treatment Group		
	Group 1 (anovulatory)	Group 2 (follicle maturation defect)	Group 3 (mature follicle) unexplained infertility
No. of treatment cycles	60	23	41
No. of clinical pregnancies (positive ultrasound at 8 weeks)	20 (33.3%)	9 (39.1%)	10 (24.4%)
Live fetus 12 weeks	18 (30.0%)	7 (30.4%)	8 (19.5%)

sperm abnormality, poor post-coital test, or tubal factor by hysterosalpingogram, we would treat this group with just P and see what outcome ensues before suggesting other measures. We realized that this group of patients with unexplained infertility is frequently recommended by other infertility centers to be treated with clomiphene and/or gonadotropins with intrauterine insemination (IUI) followed by in vitro fertilization-embryo transfer (IVF-ET). Some are recommended to proceed directly to IVF-ET.

The main objective of this study was to determine the efficacy of empirical luteal phase P therapy over a three-month treatment period for unexplained infertility. As a basis of comparison, group 3 would be compared to women who did not have regular cycles and were clearly anovulatory (group 1) and/or to women with regular menses but who did not attain a mature follicle in the cycle of investigation (group 2).

Materials and Methods

Consecutive couples limited to females aged ≤ 39.9 years with a minimum of one year of infertility who did not have a problem that required IVF-ET, were selected for evaluation. They had to demonstrate one of three types of ovulation disorders described above. Actually group 3 was just assumed to have a pure luteal phase defect based on failure to detect any other abnormality. However, one could consider this group as unexplained infertility. No exclusions were made for day 3 serum follicle stimulating hormone (FSH).

Group 1 was treated with either clomiphene citrate or low-dose FSH. Group 2 was treated with low-dose FSH beginning at day 8 or later. Group 3 was treated with luteal phase P supplementation vaginally.

No women were purposely hyperstimulated. The lowest dosages of follicle-maturing drugs were used. The median number of follicles for group 1 was 1.5 vs one for groups 2 and 3, respectively. Groups 1 and 2 also received P supplementation. Pregnancy rates were determined within three treatment cycles.

Results

There were 55 couples that were evaluated. The median age was 33 years. The mean length of infertility was 2.1 ± 0.9 years. Primary infertility was present in 44% of the women and secondary infertility in 56%. One hundred twenty-four treatment cycles were evaluated.

The pregnancy outcome according to the type of fertility defect is seen in Table 1. Combining groups 1 and 2 together, the ongoing pregnancy rate was 30.1% (25/83) which possibly related to insignificant power, was not significantly higher than group 3 receiving empirical P therapy (19.5%).

Discussion

Since the women in the group with unexplained infertility (group 3) were all treated with P without placebo controls, it cannot be stated with certainty that the treatment with P definitely helped in the establishment of the pregnancies. Nevertheless there is reason to believe that it did help since the results in clinical and ongoing pregnancies were about 70% as good as anovulatory women (group 1) where treatment was definitely necessary. Furthermore, the mean length of infertility for group 3 was 2.3 ± 1.0 years. Previous studies have suggested that the chance for spontaneous conception in a 33-year-old group of infertile women with this length of infertility in three months would be less than three percent.

These data provide certain treatment strategies. Based on these data, a treating gynecologist without proper monitoring facilities to perform IUI if hostile cervical mucus develops from treatment with clomiphene citrate should probably recommend empirical use of luteal phase P rather than empirical use of follicle-maturing drugs. Such a strategy could reduce the risk of hostile cervical mucus, ovarian cysts, side-effects from the anti-estrogen effect of clomiphene citrate, or the risk of multiple births.

These data should not be interpreted that for unexplained infertility the results would be somewhat improved by the combined use of low-dose follicle-stimulating drugs and P luteal support vs P alone. For groups 1 and 2 there was a clear-cut ovulatory problem as a contributing cause to the infertility problem, whereas P therapy alone may not have been effective in some women in group 3 who simply did not have a problem with inadequate P secretion in the luteal phase but some other occult problem.

Nevertheless, this study has stimulated us to set up a randomized controlled study to compare the efficacy of P therapy alone in the luteal phase vs mild use of FSH in the follicular phase with P in the luteal phase in women with unexplained infertility.

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