



The relative efficacy of three types of supplemental vaginal progesterone on mid luteal sonographic echo pattern in women undergoing in vitro fertilization-embryo transfer

Abstract

A triple line sonographic endometrial echo pattern is the most common type seen in the late proliferative phase. Persistence of this pattern into the mid luteal phase is not common. However, when it occurs, there is a Lower Live Delivered Pregnancy Rate (LDPR) in natural untreated cycles or even in controlled ovarian hyperstimulation cycles with fresh embryo transfer or frozen embryo transfer cycles despite supplementation with vaginal Progesterone (P). Increasing the dosage of P at mid luteal phase when a TL pattern is found can improve the LDPR. The objective of the present study was to determine if there is any difference in failing to progress from a TL pattern at mid cycle to mid luteal phase or difference in LDPRs when comparing compounded P vaginal suppositories or commercial vaginal P, i.e., endometrin® or crinone®. The results showed the same frequency of TL patterns (which were less than 5%) comparing all 3 types. Furthermore, none showed any difference in LDPRs. The study did confirm that there is a trend for lower LDPRs with the TL pattern, but the LDPRs could be improved by increasing the dosage of P at mid luteal phase with the TL pattern by adding intramuscular P.

Keywords: Vaginal Progesterone; Mid Luteal Phase; Endometrial Echo Pattern; In Vitro Fertilization Embryo Transfer.

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Introduction

Having sufficient progesterone secretion following ovulation is essential for achieving a successful pregnancy. The secretion of progesterone is needed for proper histologic endometrial architecture developed from growth factors related to Progesterone (P) activating nuclear Progesterone (P) Receptors (R) [1]. However, it is also essential for rapid proliferation of the fetal placental cells and invasion into normal tissue and evasion of immune surveillance by interacting with rapid action Membrane Progesterone Receptors (MPRS) leading to rapid responses [2,3].

Early studies focused on the histological changes [4-6]. The finding that the endometrium was more than 2 days earlier than it should be from mid luteal phase or slightly beyond mid luteal phase was an indication that P supplementation was needed. However, even if the histological change is normal, there may be issues with insufficient suppression of immune factors that could still lead to the rejection of the fetal semi-allograft [2,3].

There are various tests that make obtaining endometrial tissue necessary to obtain if some adjustment is needed on an immunological basis, including evaluating for excessive CD 138, a cell surface proteoglycan that is part of the extra cellular matrix or the BCL6 inflammatory marker [7,8].

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Though the value of these tests has been debated because of the potential harm of an endometrial biopsy to the fetus by performing the biopsy during a cycle with possible conception and the delay in the response of the results, these tests do not help to modify or adjust the dosage of P in a given IVF-ET cycle.

There is still a great deal of debate as to whether any of these aforementioned tests can detect if the woman is making sufficient P to allow the required immunological milieu. Thus, one option is to supplement the luteal phase with vaginal or intramuscular progesterone in cases of infertility or frequent miscarriage, especially in women > age 30, or women of any age with pelvic pain e.g., dysmenorrhea, mittelschmerz, or chronic pelvic pain [9,10].

It has been known for many years that follicle stimulating drugs, despite increasing mid luteal phase serum P levels, produce other factors that impair the ability to properly create an immune environment that negates the risk of immune rejection of the fetal semi allograft [11,12]. Supplementing extra progesterone in the luteal phase can to some degree reduce the risk of immune rejection [1,9,10].

Thus, almost from its inception, the transfer of embryo's following controlled ovarian hyperstimulation i.e., (in vitro fertilization and embryo transfer IVF-ET), the egg retrieval was followed by P support in luteal phase prior to the subsequent embryo transfer [13]. IVF-ET is expensive and it would be of great benefit if there was a non-invasive test with immediate results that would indicate a need to increase the P dosage to maximize success rate rates.

There has been described sonographic features of the endometrium that changes at different parts of the menstrual cycle. There are three endometrial echo patterns as described by Gonan and Casper [14]. A Triple Line (TL) endometrial sonographic endometrial echo pattern appears multilayered with hyperechoic, outer walls and a well-defined central echogenic line [14]. Another echo pattern has been termed Isoechogenic (IS) where the endometrium has the same echo density as the myometrium with a poorly defined central echogenic line. The third sonographic echo pattern is called Homogeneous Hyperechoic (HH) which appears as an extremely dense endometrium and is more echogenic than the myometrium with no visualization of a central echogenic line [14,15].

Whereas the TL pattern would be most common at peak follicular maturation, by mid-luteal phase, one would normally find the HH pattern. Failure to attain an HH pattern mid-luteal phase did not correlate with an out of phase endometrial biopsy [16-19].

However, Check et al found that whereas women with an HH pattern in mid-luteal phase during an IVF-ET cycle had a clinical pregnancy rate of 32.8%, the clinical pregnancy rate was only 10.7% in those failing to achieve the HH pattern [20]. These data take into account previous studies showing no correlation with histological dating suggested that failure to obtain an HH endometrium echo pattern despite P supplementation may represent some other factor e.g., failure to adequately negate the increase in inflammation needed to remodel uterine arteries to create spiral arteries [1,3,21]. Possibly improved pregnancy rates could occur if the dosage of P could be increased from mid-luteal phase.

To determine if failure to attain a mid-luteal HH pattern only applied to women having controlled ovarian hyperstimulation, we determined pregnancy rates in the first evaluation cycle of women with no therapeutic intervention. In 296 patients, whereas the viable pregnancy rate was 8.5% in those reaching the HH pattern, only 2.2% had a viable pregnancy when there was a non-HH pattern in mid-luteal phase of her cycle [22].

The next question we wanted to answer was whether in increasing the dosage of P at mid-luteal phase, if there was a non-HH pattern present could increase the pregnancy rate. For women aged <35 having IVF-ET, those attaining an HH pattern, 45.8% had a live delivery per cycle vs 43.4% who did not obtain a mid-luteal HH pattern, but where the dosage of P was increased [23]. For cycle 2, the Live Delivered Pregnancy Rates (LDPRs) were 41.8% vs 37.8%. For women 35-38 in cycle 1 the LDPR for HH was 33.18% for non-HH with adjustment and in cycle 2 respective LDPRs was 44.4% vs 23.5% [23].

In frozen ET cycles where there is provided both intramuscular and P vaginal suppositories during the luteal phase, LDPRs were 30.4% for HH pattern and 23.4% for non-HH [24]. This counted whether the P dosage was increased or not. If we separate those who increased their P with a non-HH pattern versus did not increase the P the LDPR was 42.4% versus 23.4% [24,25].

At our IVF institution for COH cycles with IVF-ET, the patients are given vaginal P not intramuscular P. The P used from our aforementioned studies from our institution used compounded P vaginal suppositories. Subsequently commercial vaginal P products became available in the pharmaceutical market. For the compounded P suppositories, the patient couldn't use their insurance for payment. Thus, since the P suppositories were not commercial, it is important to determine if the relative efficacy of compounded P suppositories versus crinone® vaginal P gel or endometrin® vaginal tablets has similar efficacy.

Materials and methods

Only cycles of COH with a fresh embryo transfer were included in the study. Two age groups were evaluated separately i.e., age <35 and age 36-39. No intramuscular P was given unless the mid-luteal phase endometrial echo pattern was a TL in which 100 mg was administered daily until the pregnancy test.

The dosage of vaginal P was 400 mg twice daily for P vaginal suppositories, 90 mg twice daily for crinone® vaginal gel, and 100 mg three times per day for endometrin®. The choice of vaginal P was usually influenced by insurance coverage. If the commercial vaginal P was covered by their prescription plan the choice between crinone® vs endometrin® usually depended on which of these two commercial products will be paid for by the insurance company.

Only the first IVF-ET cycle per patient was included. Statistical comparison used chi-square analysis. The embryos were transferred on their third day, and the ultrasound was performed 3-4 days after ET.

Results

For women ≤age 35 there were 1162 fresh ETs evaluated and 253 (21.4%) used endometrin® 746 (63.1%) used compounded P vaginal suppositories and 183 (15.7%) used crinone®. The percentage of a TL pattern in mid-luteal phase was 4.0% for endometrin®, 4.6% for compounded P suppositories and 1.5% for crinone®.

The LDPRs for women taking endometrin® was 46.3% for HH pattern, 52.1% for IE pattern and 35.7% for TL. The LDPRs in women taking compounded P vaginal suppositories for HH, IE, and TL pattern were 43.1%, 39.8% and 26.5%. The LDPRs for crinone® was 34.7% for HH and 36.7% for IE. There were only two patients taking crinone® vaginal gel who had a TL pattern and neither conceived. Combining all three groups there were 50 women (4.2%) who demonstrated a TL pattern in mid-luteal phase. Live delivery occurred in 14 of them (28.0%). In contrast, the LDPR was 42.6% with non-TL pattern (484 pregnancies).

For age 36-39 there was a total of 882 fresh ETs. The use of endometrin®, compounded P vaginal suppositories, and crinone® gel was 182 (21.7%) 616 (69.8%) and 74 (8.7%) respectively. The frequency of the mid-luteal TL patterns was 3.1% for endometrin®, 2.3% for compounded P, and 2.7% for crinone®.

Combining the three groups of 22 cycles with a TL pattern, there were five live deliveries (22.7%) for non-TL mid-luteal echo patterns, there were 260 live deliveries (30.2% live delivered pregnancy rate). Related to the small group with the TL pattern one could not say that the 40% higher LDPR in the non-TL group was not merely fortuitous (chi square analysis P= NS).

Discussion/Conclusion

The study found that endometrin®, compounded vaginal P suppositories, and crinone® vaginal gel are equally effective in not having a persistent TL pattern in the mid-luteal phase. Furthermore, all three seem equally effective in achieving live deliveries following IVF-ET.

Having a TL pattern in mid-luteal phase does seem to show a trend for a lower chance of a live delivery following IVF-ET. However, because it occurs so infrequently, it would be difficult to obtain a study of sufficient power to obtain a statistical difference.

The data do support the policy to increase the dosage of P by adding intramuscular P from mid-luteal phase when a mid-luteal TL pattern is present as it seems to improve LDPRs in cycles with COH followed by IVF-ET with fresh embryo consistent with previous data with frozen ETs [23,25].

If a live pregnancy was not achieved in an IVF cycle, where the dosage of P was increased by the intramuscular route, generally in the next IVF-ET cycle we add extra P usually by the intramuscular route plus the vaginal route. It would be interesting to evaluate those patients who have a TL pattern in mid-luteal phase what percentage still have the TL pattern in the next cycle despite the increase in P. One could then consider treatment options to diminish excessive inflammation related to increased cellular permeability, and thus treat with dopaminergic drugs [26]. It would be of interest to see if the addition of dopaminergic drugs could allow progression of TL pattern at the late proliferative stage to IE or HH in the mid-luteal phase. The study did not find a difference in LDPRs between IE and HH.

If a given IVF center does not evaluate the sonographic endometrial echo pattern in the mid-luteal phase, it probably would not have much effect on their LDPRs because of how infrequently it occurs. Nevertheless, with the great expense of IVF, a woman having IVF-ET would be grateful to have this painless non-invasive test, especially if the results led to a modification of therapy leading to a live delivery.

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