Original Article

Comparison Between Progesterone Rise In Fresh Cycles Versus Frozen Cycles

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Abstract

The impact of elevated progesterone levels that affects the quality of the oocyte or resulting embryo is still unclear and the increase of progesterone likely constrains the endometrium, causing an asynchrony between the developing embryo and the endometrial receptivity. So we aimed in this review to discuss the effect of high progesterone level at day of HCG injection that affect the pregnancy rate on frozen cycles undergoing the intracytoplasmic sperm injection (ICSI) treatment versus fresh cycles.

Introduction:

Over the past 6 years, evidence has increased that premature progesterone elevation decreases live birth in IVF cycles. The putative mechanism is advancing the endometrium, leading to endometrial-embryo asynchrony. This is supported by evidence suggesting that the premature progesterone elevation affects the endometrium at several detectable levels: gene expression, siRNA, implantation markers, histologic features, and ultrasonographic characteristics**.** This negative effect is summarized in a meta-analysis of observational data including over 60,000 IVF cycles and should be considered incontrovertible **(1).**

Moreover, this negative effect does not occur in oocyte donor-recipient cycles, suggesting that removing the endometrium from the negative hormonal effect resolves the problem of premature progesterone elevation. This is further supported by the absence of an association between premature progesterone elevation and oocyte or embryo quality in the available data. This leads to the logical conclusion that all embryos should be frozen and a frozen embryo transfer (FET) cycle should be performed as the appropriate treatment for premature progesterone elevation. We have published observational data supporting this hypothesis, clearly demonstrating a detrimental effect of premature progesterone elevation in fresh cycles, but not in subsequent frozen cycles **(2).**

However, only one small randomized controlled trial (RCT) has examined this hypothesis and it was underpowered to detect a difference between fresh and frozen transfer strategies**.** A study powered to detect a difference in live birth of 50% in FET cycles versus 25% fresh cycles in patients with premature progesterone elevation would only require 110 subjects to be randomized **(3, 4).**

Traditionally IVF/ICSI has involved the transfer of fresh embryos. Embryo freezing technology was originally developed to store embryos not transferred in a fresh IVF cycle. However, advances in technology have the potential to increase the attractiveness of freeze-only cycles, with cryopreservation using the vitrification technique improving embryo survival technique improving embryo survival rates compared with conventional slow freezing **(5).**

Cryopreservation of embryos allows for the avoidance of the harmful effects of high-dose hormones used for ovarian stimulation on the endometrium, and a freeze-only strategy is one method of preventing ovarian hyperstimulation syndrome (OHSS). Consequently, the use of freeze-only cycles is increasing in popularity **(6).**

Higher progesterone levels and a thinner endometrium may be associated with lower success rates after fresh embryo transfer, whereas these factors may not affect the success of freeze-only cycles or subsequent frozen cycles. A randomised clinical trial (RCT) was used to compare the outcomes of freeze-only versus fresh embryo transfer cycles in non-PCOS patients. Progesterone level and endometrial thickness could be used as biomarkers to guide the selection of a freeze-only versus fresh embryo transfer strategy **(7).**

One potential mechanism for a negative effect of higher serum progesterone levels on clinical and ongoing pregnancy rates after fresh embryo transfer is the influence of this hormone on the endometrium, which influences embryo implantation. Such an association has been reported in a number of studies **(8).**

More specifically, it has been suggested that higher serum progesterone levels could accelerate maturation of the endometrium and promote secretory transformation, resulting in a smaller window for implantation, which in turn decreases pregnancy rates in fresh transfer cycles where this occurs**.** A comprehensive meta-analysis of studies in this area, which included more than 60,000 IVF cycles, found that there was a significant negative correlation between serum progesterone level on the day of trigger ≥0.8 ng/ml and decreased pregnancy rates in fresh transfer, but not frozen–thawed, cycles**.** the negative effect of high serum progesterone levels on the LBR after fresh embryo transfer was seen at slightly higher levels than reported in the meta-analysis (1.17–1.22 versus ≥0.8 ng/ml) **(9).**

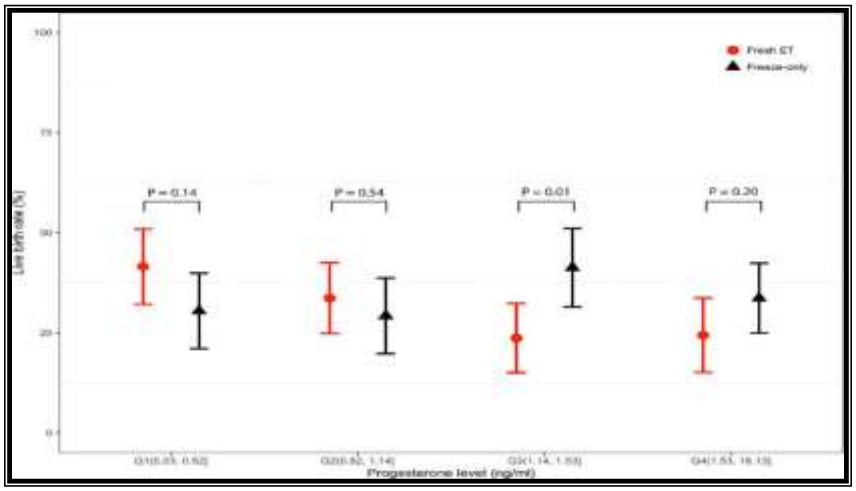

Figure (1): Live birth rate after first embryo transfer (ET) in the freeze-only and fresh embryo transfer groups by quartiles of progesterone level on the day of triggering **(6).**

Electrone Microscopy of Endometrium during Assisted Reproductive Technology:

Thin endometrium is commonly encountered in patients undergoing assisted reproduction. Endometrial thickness may impact pregnancy and live birth rates in fresh and frozen IVF cycles. There is insufficient evidence for the use of any adjuvants to increase pregnancy or live birth rates in patients with thin endometrium **(10).**

the chance of pregnancy is low in these cases. One study described two ongoing pregnancies from 12 embryo transfers for patients with endometrial thickness between 4 and 6 mm **(11).**

Another study reported no live births from 11 embryo transfers in patients with endometrial thickness between 4 and 4.9 mm, and four live births from 29 embryo transfers in patients with endometrial thickness between 5 and 5.9 mm **(12).**

Pregnancies have also been described in ovarian stimulation cycles with endometrial thickness as low as 3.8 mm on the day of HCG administration **(13).**

In IVF studies for fresh embryo transfer, the incidence of endometrial thickness < 7 mm on the day of HCG administration varies between 1% and 2.5% when large IVF retrospective and prospective cohorts (between 500 and 10,000 patients) were studied **(Al-Ghamdi et al. (14); Aydin et al. (15); Bu and Sun, (16); Shufaro et al., (17); Wu et al., (18)).(14-18)** As expected, the incidence is higher using a cut-off endometrial thickness <8 mm, and two studies have compared the incidence using <7 mm and <8 mm **(14,18)**. One study of 2000 patients found that the incidence increased from 1.5% to 9.1% when the cut-off moved from <7 mm to <8 mm; however, the other study with almost 2500 patients found that the overall incidence rates were lower at 0.7% for <7 mm and 2.5% for <8 mm.

Some of the differences between studies may be accounted for by measurement techniques and ultrasound equipment.

It should be noted that these studies only included cycles which proceeded to embryo transfer, and are likely to underestimate the incidence of thin endometrium.

A study using the Canadian ART database (BORN-CARTR+) which included 21,900 fresh IVF-embryo transfer cycles from 2012 to 2015 showed that 12.3% of fresh IVF-embryo transfer cycles occur with endometrial thickness <8 mm and 3.9% with endometrial thickness <7 mm **(19).** In 18,900 frozen-thaw embryo transfers, 14.1% occurred with endometrial thickness <8 mm and 3.1% with endometrial thickness <7 mm **(20).** As with the previous studies, this is likely to be an underestimate of the true incidence in IVF cycles as this only represents cycles which proceeded to embryo transfer.

In controlled ovarian stimulation cycles with either oral agents or gonadotropins, the incidence of thin endometrium appears to be much higher and more variable. Retrospective cohort studies found an incidence between 5.6% and 37.9% for endometrial thickness < 7 mm **(Chen et al., (20); Asante et al., (21); Wolff et al., (22)),** and between 12% and 66.2% for endometrial thickness <8 mm **(21-23).** The increased incidence of thin endometrium in ovarian stimulation cycles compared with IVF-embryo transfer cycles is likely to be due to ovarian stimulation cycles proceeding despite the thin endometrium whilst IVF cycles are more likely to be cancelled.

It is important to note that the above studies describe the incidence of thin endometrium during one assisted Summary statement Quality of evidence Justification Various factors can limit the accuracy of endometrial measurements such as fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries, uterine contractions, ultrasound machine quality, interobserver and intra-observer variability, and patient intolerance.

Recommendations Strength Quality of evidence Justification The endometrium should be measured transvaginally in the sagittal plane at the thickest portion near the fundus.

Strong: Recommendation is based on com-monly accepted practice and to ensure consistency in measurements to aid in clinical assessment, research and reporting.

Repeat any thin endometrium measurement.Weak ⨁○○○ Recommendation is based on common-ly accepted practice and intra-observer variability.

Uterine cavity assessment by hysteroscopy or sonohystero- gram may be performed in the assessment of a patient with thin endometrium to assess for pathological causes.

Weak: Consensus opinion from the Committee for Practice Guidelines: although the incidence of intrauterine adhesions in patients with thin endometrium is un-known, uterine assessment may identify patients who may benefit from surgicIn IVF studies for fresh embryo transfer, the incidence of endometrial thickness <7 mm on the day of HCG administration varies between 1% and 2.5% when large IVF retrospective and prospective cohorts (between 500 and 10,000 patients) were studied. As expected, the incidence is higher using a cut-off endometrial thickness <8 mm, and two studies have compared the incidence using <7 mm and <8 mm**.** One study of 2000 patients found that the incidence increased from 1.5% to 9.1% when the cut-off moved from <7 mm to <8 mm; however, the other study with almost 2500 patients found that the overall incidence rates were lower at 0.7% for <7 mm and 2.5% for <8 mm **(24).**

In some of the differences between studies may be accounted for by measurement techniques and ultrasound equipment. It should be noted that these studies only included cycles which proceeded to embryo transfer, and are likely to underestimate the incidence of thin endometrium **(20).**

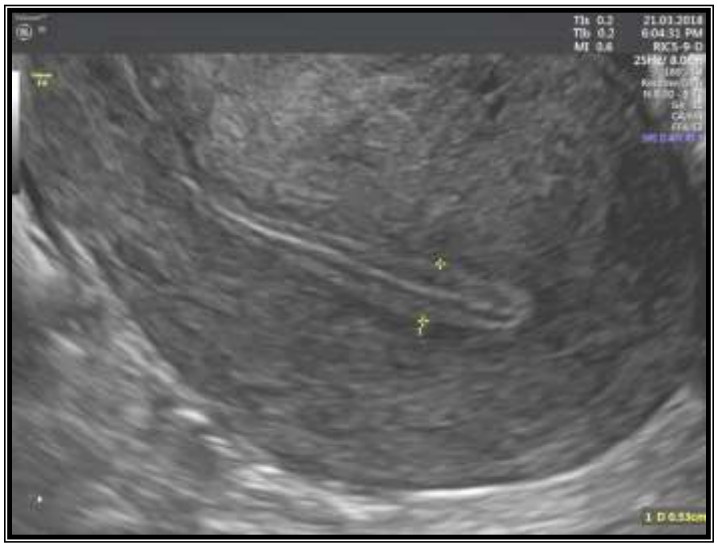

Figure (2): Measurement of endometrial thickness **(24).**

On the other hand In spite of marked improvement in assisted reproductive technology (ART), the implantation rate is 25 to 35 percent as the endometrial receptivity still remains a challenge. Endometrium is receptive for the process of implantation of the blastocyst only for a span of 3 to 4 days, which is called as window of implantation (WOI). The window of endometrial receptivity is restricted to day 16 to 22 of 28 days normal cycle. During this WOI, anatomical, morphological and molecular changes take place in the endometrium leading ultimately to enable the blastocyst to attach & finally invade the endometrial tissue **(25).**

The levels of estradiol are higher during ovarian stimulated ART cycles (supraphysiological). Higher chances of an early LH (Leuteinizing Hormone) surge that raises progesterone levels prior to ovulation are also present. The endometrium becomes distorted for the implantation process as a result of these two hormonal events, which cause the early secretary changes to appear. Even when high-quality embryos are transferred in such situations, the implantation window is preponed, which results in low implantation rates **(26, 27).**

On the other hand in hormone replacement cycles the ovulation is suppressed and the sequential regimen of estradiol valertae for 8 to 10 days followed by addition of progesterone is administered. The endometrium in such cycle is developed in a synchronized way and the window of implantation is maintained in an ordered fashion between day 3 to day 5 of progesterone administration. Frozen embryos are transferred after throwing in this particular window. Similarly, in cases of oocyte donation and embryo donation, the procedure of embryo transfer is planned in this peculiar window. Interestingly, the implantation rates are higher in such hormone replacement cycles. Paulson et al. and Edwards et al. have shown that the clinical pregnancy rate is higher in hormone replacement therapy (HRT) cycles than in stimulated cycles, probably due to higher endometrial receptivity in HRT cycles. With this background, they have focused on the scanning electron microscopic study of the endometrium during day 2 to day 7 of progesterone administration of HRT cycle **(10).**

Earlier studies have documented the appearance of smooth, balloon like projections arising from the apical surface of the luminal epithelium of the endometrium during WOI observed by scanning electron microscopy (SEM). However, no study has been dedicatedly undertaken to study the luminal endometrium in HRT cycles. This study is the first of its kind study to evaluate the changes in all the components of luminal surface of the endometrium during WOI in HRT cycles. The understanding of these changes can be useful for the procedures of personalized embryo transfer for higher pregnancy rate in ART cycles **(10).**

The three important components of the surface luminal epithelium viz. surface epithelium, glands and vessels were studied. The stromal cells were at a deeper layer and hence could be not picked up in many cases. The surface epithelium was showing balloon like projections arising from the apical surface, called pinopodes. The biopsy on 2nd day of progesterone revealed very small pinopodes called as developing pinopodes (DP), that on 5th day of progesterone revealed fully developed pinopodes (FDP) while that on 7th day revealed regressing pinopodes (RP) the glands also showed a trend of increased number as well as diameter when followed from day 2 to day 5 of progesterone, after which they became less prominent and regressed Interestingly, the glands on day 6, were studded with pinopodes on the surface as well as throughout their depth **(28).**

The vessels also showed the phenomenon of angiogenesis evolving from day 2 to 5 and then regressing on day 7 of progesterone. Observation of the sequential development of pinopodes glands and angiogenesis were considered as positive findings while absence of such development in any one component or all three components were considered as negative findings **(29)**

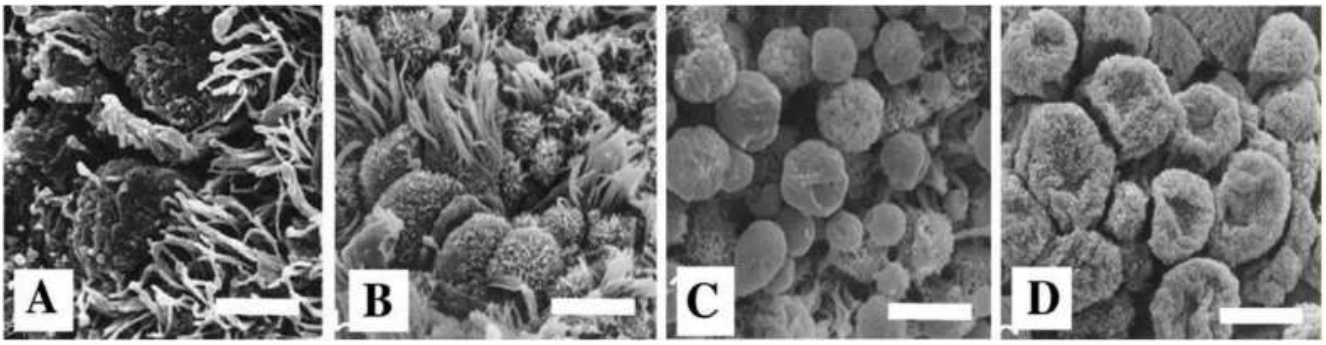

Figure (3): Scanning electron microscopy photomicrographs of luminal surface of human endometrial biopsies were taken from proliferative **(A),** early **(B),** mid- **(C)** and late luteal **(D)** phases of normal menstrual cycle to identify developmental stage of pinopodes **(10).**

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