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Original Article

Effect of premature serum progesterone rise on embryo transfer outcomes and the role of blastocyst culture and transfer in assisted reproductive technology cycles with premature progesterone rise

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ABSTRACT

Objective: In 1991, researchers reported that a modest preovulatory increase in serum progesterone levels is associated with lower pregnancy rates and higher incidence of pregnancy loss in *in vitro* fertilization (IVF). We wonder whether embryo transfer (ET) in assisted reproductive technology (ART) cycles in patients with premature progesterone rise (PPR) have a negative impact on the clinical pregnancy rates (CPRs) and/or live birth rates (LBRs) in our series. Consequently, will blastocyst transfer reverse the negative impact?

Materials and methods: This noninterventional, retrospective, observational tertiary center study was conducted between January 2010 and December 2012. All fresh ET cycles with serum progesterone levels measured ($n = 599$) on the day of hCG administration were analyzed.

Results: Sera lutenizing hormone (LH), E2, and progesterone (P) were measured and analyzed. The CPRs of cycles in patients with $p \leq 1.5$ ng/mL (low) versus those with $p > 1.5$ ng/mL (high) were 37.04% versus 41.03% [odds ratio (OR) = 1.18, 95% confidence interval (CI): 0.728–1.920; $p = 0.50$). The LBRs of cycles in patients with low progesterone level versus those with PPR were 30.52% versus 34.62% (OR = 1.21, 95% CI: 0.729–1.992; $p = 0.47$). No statistically significant association was detected. We further analyzed the outcomes according to different stages of ET and found that blastocyst (D5) ET significantly increase the LBRs as compared with cleavage stage (D2/D3) ET in the PPR group (44.44% versus 21.43%; $p = 0.043$).

Conclusion: PPR did not significantly compromise the clinical outcomes in this series. However, shifting to blastocyst transfer probably could increase the live birth in cycles with PPR.

Introduction

Many researchers have adopted the term “premature progesterone rise (PPR)” or “premature luteinization (PL)” for patients with progesterone elevation on the day of human chorionic gonadotropin (hCG) administration for final oocyte maturation [1]. In 1991, Schoolcraft et al [2] and Silverberg et al [3] reported that a modest preovulatory increase in serum progesterone levels was associated with lower pregnancy rates and higher incidence of pregnancy loss in ovarian stimulation for *in vitro* fertilization (IVF), but the pathogenesis and effects of PPR or PL on IVF outcomes remain controversial.

Several authors have failed to demonstrate any negative impact of PPR on assisted reproductive technology (ART) outcomes [4–10] while others reported that pregnancy rates [11–13] or live birth rates [14] have been inversely related to serum progesterone levels or duration of elevation [15] on the day of hCG administration.

Furthermore, Ou et al [16] suggested that ovarian response or reserve may be of critical importance when considering PL or PPR.

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However, Xu et al [12] reported that elevated serum progesterone had no adverse effect on pregnancy rates in fresh embryo-transfer cycles within different ovarian responses.

Papanikolaou et al [17] and Ochsenkühn et al [14] concluded that blastocyst transfer (D5) was more effective than early cleavage-stage embryo transfer (D2/D3) for improving pregnancy rates and live birth rates.

The purpose of the present study is to review from our own series the impacts of premature elevated serum progesterone levels on the pregnancy outcomes of fresh embryo transfer cycles. We also wanted to find out whether the ovarian responses play a role in these phenomena. Furthermore, we retrospectively investigated whether D5 blastocyst transfer (D5-ET) could improve the clinical outcomes, both in clinical pregnancy rates (CPRs) and live birth rates (LBRs).

Materials and methods

Trial design

This noninterventional, retrospective, observational tertiary center study, which enrolled women treated for infertility, was conducted in the Center for Reproductive Medicine of Taichung Veterans General Hospital, Taichung, Taiwan between January 2010 and December 2012.

Participants

A total of 777 cycles undergoing assisted reproduction [*in vitro* fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI)] with controlled ovarian hyperstimulation (COH), suppression of premature ovulation by GnRH agonists [leuprolide acetate or triptorelin acetate (50.08%)], antagonists [cetrotide (34.06%)] or other protocols [including mild stimulation, natural cycle, or modified natural cycle (15.86%)], were included for chart review in the study period. As we did not routinely check preovulatory progesterone levels until August 2010, there were 69 cycles excluded initially. We also excluded cases (109 cycles) which did not receive fresh embryo transfers (ET). We included 27 cycles of cancelled oocyte retrieval, 24 cycles of fertilization failure, 10 cycles of very poor embryos development, 31 cycles of planned oocytes and/or embryos cryopreservation, and 17 cycles of postponement for ET due to very high serum E2 (>8000 pg/mL) and/or risk of ovarian hyperstimulation syndrome. Finally a total of 599 nonselective fresh ET cycles with serum progesterone levels measured on the day of hCG injection were analyzed.

The mean age of patients was 35.21 years (range, 23–49 years). The primary or combined indications for fertility treatment were male subfertility (29.33%), tubal pathology (24.52%), endometriosis (15.63%), polycystic ovarian syndrome (PCOS; 2.40%), adenomyosis (1.68%) and other causes (0.48%), including malignancy or immunology. Detailed patient characteristics with different progesterone levels are listed in Table 1.

All patients signed a written informed consent document for the ART treatment. Institutional Review Board approval was not mandatory, because all women in the study underwent the routine IVF/ICSI-ET clinical treatment performed in our unit and no additional intervention or blood sampling was performed.

Controlled ovarian hyperstimulation protocol

Briefly, patients in the GnRH agonist group received either leuprolide acetate (Leuprolide, 0.1 mg/d; Famar L'Aigle) or triptorelin acetate (Decapeptyl SR, 0.1 mg/d; Ipsen Pharmaceuticals, Ltd.), consisting of a daily low dose of GnRHa, subcutaneously administrated for at least 10 days before the onset of ovarian stimulation. However, participants in the antagonist group received the GnRH antagonist cetrorelix acetate (Cetrotide, 0.25 mg/d SC; Merck Serono) starting flexibly on stimulation Days 5–7 by ultrasound monitoring 5 days after the onset of COH with gonadotrophins.

The types and dosages of gonadotropin administration were individualized by the attending physician for each participant according to her age, body mass index, antimullerian hormone level, follicle-stimulating hormone (FSH) level/antral follicle counts on cycle Days 2–3 and previous response to ovarian stimulation. Doses were adjusted according to ovarian response as monitored by means of vaginal ultrasound folliculometry and serum E2 level testing.

When two or more follicles reached a mean diameter of 18 mm, 10,000 IU of hCG (Pregnyl; Organon) or 500 ug of recombinant hCG (Ovidrel; Merck-Serono) was injected for the oocyte retrieval 35–36 hours later. Progesterone 25 mg/amp, 1–2 amp/d (Astar Co.), was injected intramuscularly starting from the day of oocyte retrieval and continued or shifted to topical progesterone (Crinone; Merck-Serono) 1 tube/d on the day of embryo transfer, then maintained until the day of serum β-hCG check-up (14 days after ovum pick-up) for luteal support (LS). In cases of ICSI treatment, 0.1 mg Decapetyl was also administered 6 days after ICSI as a measure of additional luteal support. If pregnancy was confirmed, LS was maintained until gestational Week 8. The embryo transfers were carried out on Day 2, Day 3, or Day 5 of culture.

Hormone assays

Sera were obtained on the day of hCG administration for oocyte retrieval; lutenizing hormone (LH), E2, and progesterone (P) were measured and analyzed by Immulite 2000 (Euro Diagnostic Products Corporation, Ltd.). The intra- and interassay coefficients of variation, respectively, were 3.71% and 6.2% for LH, 4.9% and 7.1% for

Table 1
Characteristics of patients with different serum progesterone levels on hCG day.

Progesterone level (ng/mL)[a]	≤1.5 ($N = 521$)	>1.5 ($N = 78$)	p
Age (y)	35.36 (4.61)	34.19 (3.70)	0.02*
BMI	21.98 (3.12)	21.63 (3.48)	0.27
Primary/secondary infertility	43.7/56.3	38.5/61.5	0.45/0.06
Stimulation duration (d)	9.92 (1.66)	10.26 (1.52)	0.1
rFSH dosage (IU)	3066.86 (1202.19)	3152.31 (1040.81)	0.5
LH dosage (IU)	1174.48 (583.46)	1090.71 (504.92)	0.29
rFSH/LH dosage ratio	3.44 (2.85)	3.78 (2.25)	0.004**
E2 on HCG day (pg/mL)	2169.39 (1831.45)	2194.54 (1623.21)	0.67
P/E2 ratio	0.84 (1.35)	2.78 (5.05)	<0.0001**
Number of oocytes retrieved	10.45 (7.50)	11.10 (7.22)	0.37
No. of pronucleus cells	6.60 (4.87)	10.73 (7.21)	<0.0001**
No. of embryos transferred	2.86 (0.96)	2.91 (1.00)	0.65

Data are presented as %/% or mean (standard deviation).
*$p < 0.005$.
**$p < 0.001$.
BMI = body mass index; E2 = XXX; HCG = human chorionic gonadotropin; IU = international unit; LH = lutenizing hormone; P = ; rFSH = recombinant follicle stimulating hormone.
[a] Mann–Whitney *U* test and Chi-square test (Fisher's test) were used for statistical analyses as appropriate.