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# Mid-luteal serum progesterone concentrations govern implantation rates for cryopreserved embryo transfers conducted under hormone replacement




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Dr John L Yovich, MBBS, MD, FRANZCOG, FRCOG, CREI presented his PhD thesis 'Human Pregnancies Achieved by In-Vitro Fertilisation' following research and clinical work undertaken with Professor Ian Craft at the Royal Free Hospital and University of London (1976–1980), thereafter at the University of Western Australia Department of Obstetrics & Gynaecology based at King Edward Memorial Hospital in hometown Perth. Dr Yovich established the PIVET Medical Centre in 1980, the first private independent comprehensive fertility management facility in Australia. Current research activities are conducted with the Department of Biomedical Sciences at Curtin University with a shared Research Fellow.

**Abstract** This study explores the relevance of mid-luteal serum hormonal concentrations in cryopreserved embryo transfer cycles conducted under hormone replacement therapy (HRT) control and which involved single-embryo transfer (SET) of 529 vitrified blastocysts. Widely ranging mid-luteal oestradiol and progesterone concentrations ensued from the unique HRT regimen. Oestradiol had no influence on clinical pregnancy or live birth rates, but an optimal progesterone range between 70 and 99 nmol/l ( $P < 0.005$ ) was identified in this study. Concentrations of progesterone below 50 nmol/l and above 99 nmol/l were associated with decreased implantation rates. There was no clear interaction between oestradiol and progesterone concentrations but embryo quality grading did show a significant influence on outcomes ( $P < 0.001$  and  $P = 0.002$  for clinical pregnancy and live birth rates, respectively). Multiple comparison analysis showed that the progesterone effect was influential regardless of embryo grading, body mass index or the woman's age, either at vitrification or at cryopreserved embryo transfer. The results support the argument that careful monitoring of serum progesterone concentrations in HRT-cryopreserved embryo transfer is warranted and that further studies should explore pessary adjustments to optimize concentrations for individual women to enhance implantation rates. 

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**KEYWORDS:** blastocyst grading, clinical pregnancy rate, HRT, IVF, live birth rate, progesterone pessaries

## Introduction

Cryopreserved embryos have become an important source of pregnancies arising from IVF, particularly in current programmes, which increasingly involve elective single-embryo transfer (eSET). Early frozen embryo transfer programmes showed implantation rates much lower than those for fresh embryos, probably related to several reasons, including treatment cycle regimen, which could be a natural, stimulated or hormone replacement (HRT) cycle. Furthermore, the cryopreservation technique (slow-freeze versus vitrification) may also influence outcome. Nonetheless, there is no doubt that cryopreserved embryo transfer will have an increasingly important role in future years, mainly due to increasing interest in eSET, which has the benefit of significantly increasing the cumulative IVF productivity rate (Stanger and Yovich, 2013).

Data from the latest Australia and New Zealand Assisted Reproduction Database (ANZARD) confirms the importance of cryopreserved embryo transfer cycles (Macaldowie et al., 2014). Highlighting both safety and efficiency issues as major considerations, the report shows that the vast majority of IVF cycles are now single-embryo transfers, being 76.3% in 2012 (Macaldowie et al., 2014). This means that more embryos become cryopreserved and the resultant live birth rates per initiated cycles for cryopreserved embryo transfers has improved steadily over the preceding 5 year period (from 16.3 to 20.3%), which, for autologous cycles equates with those from fresh embryos, and exceeds fresh for donation cycles. Australia and New Zealand now share one of the lowest rates of multiple births in the world, at 6.5%. ANZARD Table 19 reports the quartile ranges from the 78 contributing IVF units and shows that the highest live birth rate per initiated cycle for autologous cryopreserved embryo transfers is 32.0% overall and 42.5% for women under 35 years, data that derives from our PIVET facility (Yovich et al., 2015a).

There are several factors that may contribute to PIVET's favourable results, but much of the methodology is shared by other infertility units. The only absolute difference relates to our specific HRT regimen, being focused on a unique combined oral tablet and vaginal pessary schedule, with monitoring of the mid-luteal concentrations of oestradiol and progesterone. A recent review (Yding Andersen and Vilbour Andersen, 2014) describes an optimal serum mid-luteal progesterone concentration in the range of 80–100 nmol/l for stimulated cycles, although those authors indicated that this had not yet been defined for cryopreserved embryo transfer cycles undertaken under HRT. The current report addresses this consideration.

## Materials and methods

### Patient selection

This is a retrospective study examining pregnancy outcomes of 529 cycles in women with an age range of 22–49 years, over a 6-year period from 1 January 2008 to 31 December 2013. Patients were selected from those who underwent a cryopreserved embryo transfer cycle with the transfer of a

single blastocyst of defined grade, whilst using an HRT regimen. At PIVET, all supernumerary/surplus embryos that reach a minimum grade of 3BB according to the Gardner grading system (Gardner and Schoolcraft, 1999) are cryopreserved; by vitrification since late 2007. During the study period 2016 women had cryopreserved embryo transfer procedures, with 1716 being performed under an HRT regimen (85%). Autologous day 3 embryo transfers were undertaken on 671 cases and day 5/6 blastocyst transfers were performed on 1006; a further 39 transfers involving donor embryos. Of the autologous blastocyst transfers, 529 cycles were single blastocysts that had been cryopreserved by vitrification.

### Embryo features

The blastocysts selected for the cryopreserved embryo transfer procedures had post-warm grading of at least 3BB or higher according to the Gardner classification. This alphanumeric code designates the number to signify the stage of blastocoele cavity expansion through to full (4), partial hatching (5) and completely hatched (6); and the letters to signify qualitative stages of development for the inner cell mass and trophectoderm, respectively, from A (high grade) to C (poorest grade). Hence the top grading embryos according to the Gardner classification were scored 4AA and 5AA. Only six of the transferred blastocyst embryos were fully hatched. Graded blastocysts were categorized into groups according to the implantation and live birth rates, namely Top, High, Medium, Modest and Low groups.

### Clinical management

The HRT regimen commenced with onset of menses (day 1) and used oestradiol valerate tablets (Progynova 2 mg three times daily (t.d.s.); Schering Plough, Australia). On day 10 of the cycle, serum oestradiol was checked along with transvaginal ultrasound scan (3D ultrasound, Voluson, General Electric) for endometrial thickness, uterine volume and sagittal area. Thereafter, 10 mg oestradiol vaginal pessaries were given for  $5 \pm 1$  days prior to the commencement of the progesterone pessary regimen, which designated the end of the artificial 'follicular' phase and onset of the artificial 'luteal' phase. This day was adjusted to avoid embryo transfer (ET) procedures on Sundays and holidays. The luteal pessary regimen was 400 mg progesterone t.d.s., with the evening pessary also containing oestradiol 2 mg.

Variations included doubling the oestradiol valerate dose to 4 mg t.d.s. times daily for oestradiol concentrations  $<1000$  pmol/l, increasing the vaginal pessaries to 20 mg oestradiol and prolonging the artificial 'follicular phase' to reach endometrial thickness  $\geq 7.5$  mm (and ideally with uterine fundal sagittal area  $\geq 15$  cm<sup>2</sup> and uterine volume  $\geq 25$  cm<sup>3</sup>).

All women had mid-luteal oestradiol and progesterone concentrations checked on day 8 or 9 of the progesterone pessary administration, a time classified as the mid-luteal point matching the post-ovulatory stage of a natural or stimulated ovarian cycle.

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