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Original Article

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# A Comparative Analysis of Outcomes Between Two Different Intramuscular Progesterone Preparations in Women Undergoing Frozen Embryo Transfer Cycles

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## Abstract

**Background:** The purpose of the current study was to assess if luteal support with intramuscular (IM) 17 alpha-hydroxyprogesterone caproate (17-OHPC) (Lentogest, IBSA, Italy) improves the pregnancy outcome in comparison to natural intramuscular progesterone (Prontogest, AMSA, Italy) when administered to recipients in a frozen embryo transfer cycle.

**Methods:** A retrospective comparative study was performed to evaluate outcomes between two different intramuscular regimens used for luteal support in frozen embryo transfer cycles in patients underwent autologous in vitro fertilization (IVF) cycles (896 IVF cycles) and intracytoplasmic sperm injection (ICSI) who had a blastocyst transfer from February 2014 to March 2017 at the Centre for Reproductive and Genetic Health (CRGH) in London.

**Results:** The live birth rates were significantly lower for the IM natural progesterone group when compared to 17-OHPC group (41.8% *vs*. 50.9%, adjusted OR of 0.63 (0.31-0.91)). The miscarriage rates were significantly lower in the 17-OHPC group compared to the IM natural progesterone group (14.5% *vs*. 19.2%, OR of 1.5, 95% CI of 1.13-2.11). The gestational age at birth and birth weight were similar in both groups (p=0.297 and p=0.966, respectively).

**Conclusion:** It is known that both intramuscular and vaginal progesterone preparations are the standard of care for luteal phase support in women having frozen embryo transfer cycles. However, there is no clear scientific consensus regarding the optimal luteal support. In this study, it was revealed that live birth rates are significantly higher in women who received artificial progesterone compared to women who received natural progesterone in frozen embryo transfer cycles.

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## Introduction

The first live birth following a frozen embryo transfer (FET) cycle was reported more than 30 years ago (1). Since then, the number of FET cycles performed worldwide has increased dramatically. Improvements in cryopreservation technology (*i.e*., vitrification) have resulted in improved post-thaw embryo survival (2). Astoundingly, recent studies have demonstrated that compared to fresh in vitro fertilisation (IVF), FET live birth rates have improved (3-5), enabling clinicians to recommend the use of FET without compromising the chance of successful pregnancy.

Comparison of frozen and fresh embryo transfer cycles has also demonstrated improved perinatal and obstetric outcomes in FET cycles (8, 9). This has led to a substantial change in conventional clinical practice. It is now recommended that if a single embryo transfer (SET) is unsuccessful, a successive transfer with a single embryo transfer by a FET cycle will reduce the rate of multiple gestations without affecting the cumulative pregnancy rate (6, 7). Undoubtedly, it seems that favorable outcomes obtained by a FET cycle justify the recommendation of freeze-all for all cases (10, 11). However, this approach is currently being debated.

Progesterone is integral to the establishment of implantation and maintenance of early pregnancy until the placenta takes over gradually from 6 to 8 weeks of gestation. The synchrony between endometrium and embryo, *i.e*., the window of implantation is determined by progesterone (12). The requirement for progesterone support in fresh IVF cycles is due to the impairment of normal luteal function caused by pituitary suppression and follicular aspiration (13, 14). In programmed FET cycles, there is little endogenous progesterone produced. Similarly, low progesterone levels (luteal insufficiency) are associated with increased rates of pregnancy loss (15). Therefore, there is a clear need to provide exogenous progesterone in the luteal phase of assisted reproductive technology (ART) cycles.

There is wide variation in the practice of luteal phase progesterone regime used in ART cycles across the world, and it is an area of ongoing research and interest for a long time. The mainstay of progesterone administration is intramuscular (IM) progesterone and vaginal progesterone. Vaginal progesterone is well tolerated and reportedly easier to administer. However, it needs more frequent administration. In comparison, IM progesterone is self-administered after being trained by appropriate personnel, though it is poorly tolerated by patients causing pain and anxiety during injection (16). Oral progesterone is rarely used or applied as an adjunct to other progesterone medication because of its low absorption and reduced bioavailability.

Some studies have found comparable pregnancy outcomes between IM and vaginal progesterone in FET cycles (17, 18). However, one study found decreased live birth rate with vaginal progesterone, compared to IM progesterone (19). Others show that the constant progesterone release provided by IM progesterone in oil suppresses uterine myometrial contractility and endometrial wave-like activity and thus improves pregnancy rate (20). These inconsistent results demonstrate that the best luteal support regime is yet to be established.

17-α hydroxyprogesterone caproate (17-OHPC) is long-acting IM progesterone in oil. 17-OHPC is currently used in the prevention of preterm birth (PTB) (21). However, recently the PROLONG (Progestin's Role in Optimizing Neonatal Gestation) trial which was designed to assess the safety and efficacy of 17-OHPC injection for reducing risk of PTB and neonatal morbidity/mortality in pregnant women with a singleton gestation who had a previous singleton spontaneous PTB showed no statistical difference in preterm birth or neonatal morbidity in the group that received 17-OHPC versus placebo.

The long half-life (7.8 to 10 days) of 17-OHPC makes it a feasible alternative to daily IM progesterone. Less frequent administration of 17-OHPC may result in better patient tolerance and compliance.

Although comparison of IM and vaginal progesterone in FET cycles has been investigated (17), the use of 17-OHPC in the luteal phase is less explored. It is approximately seventeen years ago that one comparison study performed by Costabile et al. reported comparable clinical outcomes when 17-OHPC and daily IM progesterone were used for luteal support in fresh IVF cycles (22). In this study, comparative outcomes of FET cycles were demonstrated based on our center's data when either daily intramuscular natural progesterone or thrice-weekly 17-α hydroxyprogesterone caproate was used for luteal support in women.

## Methods

***Study design:*** A retrospective comparative study of all autologous FET cycles with blastocysts (day 5 or 6) transfer performed at the Centre for Reproductive and Genetic Health (CRGH) in London from the 1st of Feb 2014 to the 31st of March 2017 was done for the type of progesterone used for luteal support. The luteal progesterone regimes were randomly assigned to the patients by their consultant. All the methods were carried out in accordance with relevant guidelines and regulations. All protocols were approved by an institutional committee. Ethical approval was obtained from the Institutional Review Board (IRB) at the Centre for Reproductive and Genetic Health

(CRGH) on 21st Feb 2018. The IRB protocol number is IRB-0004C21.02.18.

In view of the retrospective nature of the study, all the procedures being performed were part of the routine care. All the patients completed the Human Fertilisation and Embryology Authority (HFEA) forms as informed consent for non-contact research.

Patient demographic details, FET cycle parameters, embryo quality, clinical outcomes, gestational age, weight and miscarriage rates were obtained from clinical records and compared between those supported with daily (100 *mg*) natural IM progesterone (Prontogest, AMSA, Italy) and those supported with 17-OHPC (Lentogest, IBSA, Italy) three times (341 *mg*) per week. The dosing of the progesterone was based on the randomized study of Costabile et al. in 2001 (22). All the cycles were with autologous oocytes and donor cycles were not included in this study. Based on inclusion criteria, all women undergoing a FET cycle were recruited. Egg recipient cycles were regarded as exclusion criteria. In all, 896 patients were included in the study (456 patients with IM natural progesterone and 440 patients with 17 OHPC).

***Statistical methods:*** Data was analyzed using SPSS Statistics V22.0 (IMB, USA). The main outcome measure was clinical pregnancy rate per embryo transfer in treatment groups. Baseline characteristics were also compared between treatment groups. Metric variables such as female age, gestational age, and weight at birth were compared by the student t-test when sample was normally distributed or Mann Whitney U test when facing lack of normal distribution. Nominal variables were analyzed by the Chi-squared test and $p<0.05$ was considered statistically significant. Blastocyst quality was categorized in three different groups based on morphologic assessment (1: average; 2: good; 3: excellent). Logistic regression analysis was performed to confirm the findings considering the covariables of age, embryo quality, and treatment protocol.

***Clinical protocols:*** Controlled ovarian hyperstimulation was achieved using one of the two protocols of GnRH-agonist long protocol or GnRH-antagonist protocol for the fresh cycles. In preparation for FET cycles, the GnRH-agonist 0.4 *mg* was started on day 21 of the prior cycle for the pituitary down-regulation. Endometrial preparation was carried out by using 2 *mg* dose of oral estradiol valerate three times a day. Transvaginal ultrasound was done between day 10 and 14 of estrogen priming. After achieving the target endometrial thickness of at least 7 *mm*, natural IM progesterone or 17-OHPC was started. The dose of the Lentogest was 341 *mg* administered intramuscularly thrice a week. Blastocysts were thawed and transferred on day 6 of progesterone supplementation. Once pregnancy was confirmed, recipients continued to receive the same doses of estrogen until the 10th week and progesterone until the 12th week of gestation. All the patients had a standardized FET preparation cycle and there were no changes in their stimulation, FET preparation, or laboratory protocols.

***Laboratory protocol:*** Embryos were frozen at the blastocyst stage. Blastocysts were frozen using blastocyst vitrification media (Cook, Ireland). Blastocysts were vitrified using established protocols. Vitrification was performed using the cryolock open carrier system (Biodiseño, Columbia). Embryos were warmed using the respective warming kits and manufacturers' protocols. Blastocysts were warmed on day 6 of progesterone supplementation. Following warming of the embryos, they were transferred after 4 *hr* of culture post warming. Embryo survival was confirmed 3 hours post thaw. Viability of trophectoderm and inner cell mass was visually evaluated under the microscope.

## Results

Patient demographics and embryo characteristics between the 1st of February 2014 and the 31 st of March 2017, 896 cycles were available for analysis (456 cycles with IM natural progesterone and 440 cycles with 17-OHPC). There was no significant difference between the primary cause of subfertility nor the proportion of patients with prior failed IVF cycles and or the number of patients with previous miscarriage between the two groups. The number of previous attempts in Prontogest group was 1.53±1.21 compared to 1.21±0.96 in Lentogest group.

The proportion of patients with day 5/day 6 blastocyst transfer in both groups was similar. The average of endometrial thickness was comparable between the two groups (9.5 *mm vs*. 8.1 *mm*; p= 0.383) for IM progesterone and 17-OHPC, respectively. Post thaw embryo quality and the average number of embryos transferred were similar between the two groups. The proportion of

patients having top, average, or poor quality embryos was not significantly different (Table 1). The number of blastocysts transferred in the Prontogest group was 1.35±0.5 *vs*. 1.46±0.5 in the Lentogest group (p=0.098).

***Clinical outcomes:*** The odds of a cryopreserved embryo transfer resulting in a clinical pregnancy were significantly lower for the IM natural progesterone in comparison to 17-OHPC group (52.6% *vs*. 59.5%, OR of 1.2 (CI of 1.12-1.68; p=0.03)). The live birth rates were also significantly lower for the IM natural progesterone group when compared to the 17-OHPC group (41.8% *vs*. 50.9%, adjusted OR of 0.63 (0.31-0.91; p<0.05)). The miscarriage rates were significantly lower in the 17-OHPC (Lentogest) group compared to the IM natural progesterone (Prontogest) group (14.5% *vs*. 19.2%, OR of 1.5, 95% CI of 1.13-2.11, p=0.03). The gestational age at birth and birth weight were similar in both groups (p= 0.297 and p=0.966, respectively) (Table 2).

An adjusted logistic regression model was performed and the odds ratios for the clinical outcomes for 17-OHPC (Lentogest) treatment type are shown in table 3. The results demonstrated the odds ratio for LBR is 0.75 (0.63-0.82, p=0.001), and for miscarriage rates is 0.21 (0.13-0.42, p= 0.02) (Table 3).

PGT-A cycles were excluded from the analysis and the findings are shown in table 4. In spite of excluding the PGT-A cycles, the LBR is consistently higher in the Lentogest group (50.29%

**Table 1.** Baseline characteristics according to the type of treatment (Means±SD)

| Parameters | Prontogest (n=456) | Lentogest (n=440) | p-value |
|---|---|---|---|
| **Female age** | | | |
| | 36.9±3.21 | 36.4±2.63 | 0.361 |
| **Insemination technique** | | | |
| IVF | 47.2% (215) | 38.6% (170) | 0.076 |
| ICSI | 52.8% (241) | 61.4% (270) | |
| **Number of blast ET** | | | |
| | 1.25±0.59 | 1.40±0.49 | 0.593 |
| **Transfer type** | | | |
| SET | 70.1% (320) | 67.7% (298) | 0.668 |
| DET | 29.9% (136) | 32.3% (142) | |
| **Blastocyst stage** | | | |
| Day 5 | 79.8% | 82.3% | 0.158 |
| Day 6 | 20.2% | 17.7% | |
| **Blastocyst quality** | | | |
| Excellent | 30.4% | 35.3% | |
| Good | 51.8% | 54.9% | 0.144 |
| Average | 17.8% | 9.8% | |
| **Endometrial thickness** | | | |
| | 9.5±1.9 | 8.1±1.8 | 0.383 |

No statistical significance was seen among these characteristics such as female age, parity, insemination technique or number of fresh blastocyst transferred

**Table 2.** Multivariate analysis of the characteristics of the cycle and different outcome measures

| Parameters | Prontogest | Lentogest | p-value | OR (CI) |
|---|---|---|---|---|
| **Implantation rate** | 58.3% (266/456) | 60.4% (266/440) | 0.268 | 0.80 (0.79-1.01) |
| **Clinical pregnancy rate** | 52.6 % (240/456) | 59.5% (262/440) | 0.026 * | 1.2 (1.11-1.68) |
| **Live birth rate** | 41.8% (191/456) | 50.9% (224/440) | 0.048 * | 0.63 (0.31-0.91) |
| **Miscarriage rate** | 19.2% (49/240) | 14.5% (38/262) | 0.028 * | 1.5 (1.13-2.11) |
| **Gestational age** | 38.6±5.2 | 38.7±3.4 | 0.297 | |
| **Weight at birth** | 3186.5±679.3 | 3216.1±706.1 | 0.966 | |

* Indicates statistical significance of p<0.05

versus 41.8% (p<0.001)) and the miscarriage rate was 10.9% in the Lentogest group versus 19.2% in the natural progesterone group.

Regarding the recent trend toward single embryo transfer (SET) to reduce the risk of multiple pregnancies, our analysis of only single embryo transfer cycles was conducted separately. There was a significant difference in the live birth rates corresponding with the above results (37% *vs.* 58%) for IM natural progesterone and 17-OHPC, respectively.

**Table 3.** Adjusted logistic regression model on 17-OHPC (Lentogest) treatment versus clinical outcomes

| Outcomes | OR (CI) | p-value |
|---|---|---|
| **Clinical pregnancy rate** | 0.72 (0.55-0.89) | 0.046 * |
| **Live birth rate** | 0.75 (0.63-0.82) | 0.001 * |
| **Miscarriage rate** | 0.21 (0.13-0.42) | 0.020 * |

* Indicates statistical significance of p<0.05

## Discussion

The main finding of this study was that luteal support with 17-OHPC was associated with higher pregnancy and live birth rates than with natural IM progesterone. This is the first study to investigate the efficacy of 17-OHPC in luteal support of FET cycles and compare the outcomes with the conventionally used natural IM progesterone. In table 5, the description of the bioavailability and pharmacokinetics of each treatment arm is indicated.

Majority of researchers studying FET cycles compared luteal support with vaginal progesterone gel versus natural IM progesterone. The reported outcomes of most retrospective and prospective studies (23, 24) showed no difference in clinical pregnancy outcomes. Similarly, a recent retrospective study (17) in which vaginal and natural IM progesterone luteal support was compared

**Table 4.** Subanalysis of the outcomes of the 2 groups without PGT-A cycles

| Outcomes | Prontogest (n=456) | Lentogest (n=340) | p-values |
|---|---|---|---|
| **Live birth rate** | 191/456 (41.8%) | 171 (50.29%) | <0.001 |
| **Miscarriage rate** | 49 (19.2%) | 21 (10.9%) | <0.001 |
| **Gestational age** | 38.6±4.2 | 38.4±3.2 | 0.268 |
| **Gestational weight** | 2186.5±679.3 | 3205±698.1 | 0.869 |

**Table 5.** Description of the bioavailability and pharmacokinetics of each treatment arm

| Prontogest | Lentogest |
|---|---|
| **Mechanism of action** | |
| Progesterone binds to the progesterone and estrogen receptors. After its absorption, progesterone is extensively bound to plasma proteins, primarily albumin (50-54%) and cortisol-binding protein (43-48%) | A synthetic progestogen that works as an agonist on the progesterone receptor |
| **Biological activity** | |
| It is primarily metabolized in the liver by reduction to pregnanediol, pregnanetriol, and pregnanolone. Subsequent conjugation results in the formation of glucuronide and sulfate metabolites. The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the urine and bile. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the faeces | It has some antimineralocorticoid activity and no androgenic, antiandrogenic, estrogenic, or glucocorticoid activity. The bioavailability of OHPC with intramuscular injection is nearly 100% as established from animal studies, but its oral bioavailability is very low, than 3%. 17α-hydroxyprogesterone caproate is rapidly excreted unchanged or as metabolites. Elimination is primarily biliary (ratio of urine elimination/I=0:05 to 0:02) and is implemented consistently and with high speed. Enterohepatic circulation is unlikely |
| **Half-life** | |
| The half-life of intramuscular progesterone is significantly longer when it is injected in the gluteal area rather than the deltoid muscle of the upper arm | When given by intramuscular injection, OHPC has been found to have an elimination half-life of 7.8 days in none pregnant women and 16 or 17 days in pregnant women. The half-life was shorter at 10 days, in women pregnant with twins compared to singleton pregnancy. Due to its long half-life, OHPC can be detected in pregnant women up to 44 days after the last dose |

in 920 FET cycles using vitrified blastocysts showed no difference in clinical outcomes between the two progesterone preparations. Kaser et al. (19) reported lower odds of clinical pregnancy rates and live birth rates with 8% crinone (vaginal progesterone) luteal support compared with those with natural IM progesterone. Only one previous study (22) examined the effectiveness of natural IM progesterone and 17-OHPC for luteal support in patients undergoing fresh IVF cycles. Costabile et al. (2001) randomized patients and administered 17-OHPC for 143 patients and natural IM progesterone for 157 patients and reported no difference in clinical pregnancy rates although the results supported the use of 17-OHPC for luteal support in fresh IVF cycles. Our retrospective study included 896 FET cycles in which the use of natural and artificial IM progesterone was compared and higher live birth rates were indicated in the latter group.

The standard of practice for luteal support after IVF and frozen embryo transfer cycles is the use of exogenous progesterone. The two most common ones used include vaginal progesterone and IM progesterone and these two preparations in women were compared in various studies (17-19). Although some studies showed similar pregnancy rates between vaginal progesterone versus IM progesterone, one study by Devine et al. (25) showed a decrease in ongoing pregnancy rates due to miscarriage in vaginal only progesterone arm in vitrified warmed blastocyst transfer. In this study, this vaginal only progesterone arm was prematurely terminated based on these findings. Sometimes, selecting the route of preparations also depends on women's preferences (26). However, one study also demonstrated that a booster injection of IM progesterone (50 *mg* once every three days) did not increase pregnancy rates of patients who received vaginal progesterone (100 *mg* three times a day) (30). Two intramuscular preparations have not been compared in FET cycles before. In our study, natural IM progesterone was compared to 17-OHPC IM preparation. Natural IM progesterone is used daily at various doses for luteal support, and this may lead to severe inflammatory reactions, sterile abscesses, significant patient discomfort, and poor compliance. The 17-OHPC is a slow release highly potent long-acting progesterone derivative which can be administered at high doses with less frequency due to its marked solubility in oil and there is minimal irritation after injection.

17-OHPC is a popular compound used in the prevention of preterm labor. It is the most commonly used synthetic progestin given intramuscularly to prevent preterm birth (PTB). Recently, a subcutaneous auto-injector for the administration of 17-OHPC was designed for patients with recurrent preterm birth (27). The safety of 17-OHPC is well documented in the NICHD trial (28) that reported on a 4 year follow up of children exposed to 17-OHPC in the uterus. There was no significant difference in health status and conditions, or physical exam, including genital anomalies between 17-OHPC and placebo children. This aids in the counseling of the patients using this luteal phase regimen in FET cycles.

The strength of this study includes the large sample size (896 FET cycles) and comparable routes of progesterone administration between natural and synthetic progestin. Since many IVF centers are moving toward vitrification of blastocysts and transfer, our study is relevant to the current practice and as a result of good clinical outcomes, more patients will accept this luteal phase regimen.

Endometrial–embryo synchrony in FET cycles is critical to successful adhesion and implantation of the blastocyst, thereby resulting in good clinical outcomes. The duration of progesterone administration before embryo transfer, length of estrogen administration, and embryonic factors such as the stage at transfer and cryopreservation methods are also important. Binding to progesterone receptors, glucocorticoid receptors, or expression of progesterone-responsive genes is not better with 17-OHPC than other forms of progesterone (29). Other mechanisms may play a role that would possibly explain the beneficial effects of 17-OHPC on preterm birth rates. Further molecular studies are necessary to investigate this mechanism and the favorable impact on preterm birth rates and luteal support in fresh IVF and FET cycles.

This study is limited by its retrospective design and by the lack of randomization of the type of luteal support. Therefore, there is a possibility that unidentified confounders may cause bias in the results. However, good clinical outcomes observed in our study cannot be ignored.

## Conclusion

The quest for an ideal luteal phase regimen to optimize the clinical outcomes (decreasing miscarriage rates and increasing live birth outcomes)

for women having FET cycles continues. From the results of this study, it can be proposed that intramuscular 17-OHPC (Lentogest) administrations resulted in better clinical outcomes in FET cycles in comparison to natural intramuscular progesterone. Further prospective randomized studies are necessary to study the efficacy and benefit of 17-OHPC administration in luteal support in women who have FET cycles. As the dosing frequency was lower in the Lentogest group, this may be adapted as a more patient friendly luteal phase protocol. A larger, well designed randomized controlled trial is required to confirm this crucial clinical observation.

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Our data was presented as an oral presentation (a comparison of outcomes with intramuscular progesterone and 17-alpha hydroxyprogesterone caproate in women undergoing frozen embryo transfer cycles) at the ASRM 2018 in Denver, Colarado (0-213) and was published in the ASRM 2018 abstract book (https://www.asrm.org/glob-alassets/asrm/asrm-content/events/2018-Congress/asrm-2018-congress-online-program.pdf).

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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