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ASSISTED REPRODUCTION TECHNOLOGIES

Is it the egg or the endometrium? Elevated progesterone on day of trigger is not associated with embryo ploidy nor decreased success rates in subsequent embryo transfer cycles

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Abstract
Purpose The purpose of our study was to determine if progesterone (P4) values on day of trigger affect certain cycle outcome parameters, ploidy status of embryos, as well as pregnancy outcomes in the subsequent first frozen embryo transfer cycle.
Methods Two hundred thirty-eight patients undergoing pregestational screening and freeze all protocol at our fertility center from 2013 to 2014 were included. Excluded patients were those whom had cancelled cycles prior to egg retrieval as well as cycles utilizing donor eggs. Once patients were identified as eligible for this study, frozen serum from the day of trigger was identified and analyzed using the Siemens Immulite 2000. Number of eggs retrieved, number of available embryos for biopsy, and number of euploid/aneuploid embryos were analyzed. The first frozen embryo transfer cycle was linked to the initial egg retrieval and outcomes including pregnancy rates, and live birth/ongoing pregnancy rates were calculated and analyzed. A discriminatory P4 value of 1.5 ng/ml was set. Group A had P4 values of less than 1.5 ng/ml and group B had P4 values greater than or equal to 1.5 ng/ml. *T* tests and chi-squared tests were used for statistical analysis.
Results Group A had an average trigger P4 value of 0.87 +/− 0.3 and group B had an average trigger P4 of 2.1 +/− 0.8. Table 1 shows the baseline characteristics of both group A and group B. The only significant difference between the two groups was total gonadotropin dosage (IU) with a *p* value of 0.02 and estradiol (pg/ml) at trigger, also with a *p* value of 0.02 (Table 1). Number of eggs retrieved, number of embryos biopsied, number euploid/aneuploid, and non-diagnosis embryos were all non-significant. Chi-square analysis was used to compare pregnancy rates between the two groups after the first frozen embryo transfer cycle. Group A had a pregnancy rate of 72 % and Group B had a pregnancy rate of 66.7 %, which was not significant. Ongoing pregnancy/live birth rates were 65.6 % in group A and 66.67 % in group B, also not significant (Table 2).
Conclusions P4 values on day of trigger do not affect number of eggs retrieved and number of chromosomally normal embryos available for transfer in a subsequent embryo transfer cycle. Elevated P4 values (≥1.5 ng/ml) also do not affect pregnancy rates or live birth/ongoing pregnancy rates in the first subsequent frozen embryo transfer cycle.

Keywords Progesterone · HCG trigger · Ploidy · Frozen embryo transfer cycle · Single embryo transfer · Array comparative genomic hybridization

Capsule Our findings indicate that elevated progesterone on trigger day (greater than 1.5 ng/ml) is not associated with poor embryo quality or successful live births in subsequent frozen embryo transfer cycles.

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Introduction

During controlled ovarian hyperstimulation (COH), premature luteinization (and resultant elevation in serum progesterone (P4) levels is associated with elevated estrogen levels and premature luteinizing hormone (LH) surge [1]. Premature luteinization and eventual ovulation is prevented by suppression of LH secretion with a gonadotropin releasing hormone (GnRH) analogue or antagonist. Despite the use of GnRH analogues/antagonists, a subtle rise in serum P4 levels is

observed in a subgroup of women at the end of the stimulation cycle. This phenomenon has been reported with an incidence ranging from 12.3 to 46.7 % of cycles [2]. In many instances, the increase of P4 levels leads to cancellation of the in vitro fertilization (IVF) cycle [3, 4].

Since the introduction of GnRH analogues/antagonists into ART cycles, the phenomenon of elevated day-of-trigger P4 levels has been controversial [5]. Both the significance and the etiology of this phenomenon remain under debate. Many investigators have found that elevated P4 on day of human chorionic gonadotropin (HCG) trigger adversely affects pregnancy rates [2–4, 6–15]. Others have not found a correlation between P4 and pregnancy rates [16–21]. Still others have found a mixed [21, 22] or favorable effect [23, 24] on ART outcome for specific populations. Nonetheless, a recent meta-analysis of 63 studies involving over 60,000 cycles concluded that elevated P4 on day of HCG trigger lowers the pregnancy rate in fresh, but not frozen embryo transfers (FET) [2].

The current literature states that mildly elevated P4 on day of HCG trigger is likely due to embryo-uterine asynchrony. We agree that this is the likely cause of the decrease in fresh IVF success rates we are observing in these instances. However, there is controversy in the literature that premature luteinization affects the quality of the egg. For example, P4 level has also been associated with poor meiosis in animal studies [25]. Studies before the use of GnRH analogues linked elevated P4 to poor oocyte maturation, lower oocyte recovery, fertilization, and reduced embryo quality [26–28]. However, the more recent studies have linked the phenomenon to endometrial receptivity or endometrial asynchrony, and this manuscript will attempt to prove this theory [21, 22, 29–31].

Pre-implantation genetic screening (PGS) cycles offer a unique opportunity to investigate this mechanism. PGS was developed to assess the chromosomal status of embryos created through in vitro fertilization. It has been shown to be a sensitive analysis for ploidy, [32] and a mechanism to improve live births and decrease spontaneous abortions in IVF cycles [33, 34]. In nearly all cases, it is followed by cryopreservation of the embryo and transfer of a single euploid embryo in a subsequent programmed cycle [35]. The ultimate goal of an IVF cycle is the live birth of a singleton. If it is true that elevated P4 (premature luteinization) during a stimulation cycle affects egg quality, then we should see a drop in the amount of euploid embryos available for transfer in this subgroup of patients. We intend to prove this is not the case.

Methods

A retrospective chart review was conducted on all embryo transfers derived from PGS in the calendar years 2013 to 2014. Inclusion criteria included patients that underwent egg retrieval with subsequent day 5/6 embryo biopsy (at least a stage 3 blastocyst), cryopreservation, and transfer in a FET cycle. Only the first subsequent frozen embryo transfer cycle was considered. Positive outcomes that were considered include clinical pregnancy rate and ongoing/live birth rate. Clinical pregnancy was defined as the presence of a gestational sac on transvaginal sonogram. Patients were excluded if they received a fresh transfer in that specific COH cycle or if the cycle involved donor eggs. Only single embryo transfer FET cycles were included in the analysis. A total of 520 patients that had undergone PGD/PGS were initially identified for the time period in question. Two hundred thirty-eight patients where frozen serum was available for analysis were ultimately included.

All patients were offered PGS screening, as is the protocol of our center. At our center, 50 % of patients have failed in vitro fertilization (IVF) in other centers and seek PGS specifically when they come for consultation. Thirty-seven percent of the patients underwent intracytoplasmic sperm injection (ICSI) and 63 % underwent standard insemination. We have shown in the past that the rates of aneuploidy achieved with both insemination technologies are similar (unpublished data).

As per our center's practice, stimulation protocols were chosen based on patient characteristics and baseline ovarian reserve lab values. The average age of our study population and the average starting follicle stimulating hormone (FSH) levels are listed in Table 1. The majority of ovarian stimulation cycles were the standard gonadotropin/antagonist cycles. Thirty-one cycles utilized micro dose Lupron flare, four were estrogen prime cycles, and three were Lupron "long protocol" cycles. As per our center protocol (in the antagonist cycles), when a lead follicle reached 13 mm or if estradiol was > 1000 pg/ml, the GnRH antagonist was initiated. When at least two lead follicles reached 18–19 mm in size, an ovulation trigger utilizing 250 mcg of recombinant HCG ×2 doses was given. Thirty-five to thirty-six hours after the trigger shot was administered, the oocytes were collected via ultrasound-guided transvaginal aspiration. Trigger, at our center, is achieved with 250 mcg of Ovidrel ×2 injections or if there is a concern for hyperstimulation, leuprolide acetate 40 units and 1000 units of human chorionic gonadotropin.

As has been described in other publications from our center, incubator conditions are set at 37 °C, 6 % CO2, and 5 % O2. We use single step Lifeglobal$^{(R)}$ (Guilford, CT) culture media and insemination was performed the same day as oocyte retrieval. If sperm appeared compromised, ICSI was performed for standard indications. Fertilization was assessed on culture day 1 via the presence of two pronuclei. On day 3 of culture, embryos were removed from the incubator and assessed for development. At this time, a small hole in the zona pellucida was created via laser assistance using a Cronus laser (Research instruments, Falmouth, UK).

Table 1 Baseline characteristics of groups A and B

	Group A (P4 < 1.5 ng/ml)	Group B (P4 ≥ 1.5 ng/ml)	*p* value
Age (years)	38.4 +/− 4.1	38.4 +/− 3.7	0.89
Total gonadotropins (IU)	3795.3 +/− 1539	4395.2 +/− 1521.7	0.02*
Day 2 FSH	6.24 +/− 2.76	7.0 +/− 2.9	0.11
Baseline AMH	2.21 +/− 1.82	1.82 +/− 1.27	0.22
Estradiol at trigger (pg/ml)	2483.8 +/− 1048.1	3034.2 +/− 1495.3	0.02*
No. of eggs retrieved	14.5 +/− 7.9	15.7 +/− 7.0	0.34
No. of embryos biopsied	5.0 +/− 3.97	5.2 +/− 3.5	0.73

All *T* tests of means, * denotes significance

Days 5/6 of culture embryos were graded via our center's standard grading criteria, adapted from Gardner and Lane 1997 [36]. When embryos reached the expanded blastocyst stage, they underwent tropho-ectoderm biopsy (TE). Immediately following biopsy, embryos were cryopreserved. TE biopsy material was analyzed via array comparative hybridization technology (CGH).

Single embryo transfer was performed in the subsequent FET cycle. The protocol is described in great detail in a previous publication by our center [37]. It is not the standard of our center to obtain P4 values on the day of HCG trigger. As such, frozen serum was used that is stored for a maximum of 2 years at our center in a −80 °C freezer. The samples were de-identified, and ascension numbers were used to match the sample to the patient and also to the correct day. In our case, this involved ensuring that the current sample for the trigger day of the corresponding cycle was identified. After thawing the sample, an Immulite 2000 (Siemens Healthcare Global) was used to measure the progesterone value (ng/ml) that corresponded to that patient's trigger day. The sample was then refrozen at −80 °C for future use. Our intra-assay variation is 5.9–6.8 % and inter-assay variation is 5.4–12.3 % for our Immulite system.

The patients were divided into two groups based on the serum P4 value on day of trigger. Group A included those patients with a P4 value of <1.5 ng/ml on day of trigger. Group B included those patients with a P4 value of ≥1.5 ng/ml. A threshold P4 value of 1.5 ng/ml was chosen based on the published literature, and one of the largest series to date that reported decreased ongoing pregnancy rates if this threshold was exceeded [4].

Statistical analysis was performed using a free online epidemiologic calculator (http://www.openepi.com/v37/Menu/OE_Menu.htm). *T* tests of means where completed where appropriate. Chi-square tests were used to evaluate pregnancy outcomes between the two patient groups.

Results

Patients were initially identified via searching our database for FET cycles performed between 2013 and 2014. Retrieval cycles that involved embryo biopsy and subsequent FET were identified. Only the first FET after index retrieval was considered in our results. As stated in the "Methods," 238 patients total were included in the analysis.

Average age for group A was 38.4 years which is identical to the average age for Group B. For each FET cycle included in the analysis, baseline characteristics of the patients were collected and analyzed; these are listed in Table 1. Group A had an average trigger P4 value of 0.87 +/− 0.3 and group B had an average trigger P4 of 2.1 +/− 0.8. Significantly, estradiol in group B was 3034.2 pg/ml, which was significantly greater than group A, 2483.8 pg/ml. Total gonadotropin dosage was also found to be significantly different between the two groups (group A 3795.3 IU and group B 4395.2 IU).

The number of eggs retrieved and number of embryos biopsied (i.e., number of blastocysts that reached the stage that could be biopsied) were not different between the two groups. Number of euploid embryos available for transfer after the index retrieval cycle was not significantly different between the two groups (group A 1.87 embryos and group B 1.6 embryos). Number of aneuploid and non-diagnosis embryos was also not found to be significantly different; 32.1 % of patients in group A had no normal embryos available after the index retrieval. This is in comparison to 25.5 % of patients in group B that had no embryos available after the index retrieval, and this was not statistically significant. Group A had a pregnancy rate of 72 % and group B had a pregnancy rate of 66.7 %, which was not statistically significant (Table 2). Ongoing pregnancy/live birth rates were 65.6 % in group A and 66.67 % in group B, also not significant.

Table 2 Comparison of groups A and B in relation to cycle outcomes

	Group A (P4 < 1.5 ng/ml)	Group B (P4 ≥ 1.5 ng/ml)	*p* value
Mean euploid embryos	1.87 +/− 2.33	1.6 +/− 1.73	0.45,* NS
Mean aneuploid embryos	2.64 +/− 2.41	3.2 +/− 2.6	0.14,* NS
Mean no diagnosis embryos	0.48 +/− 1.29	0.38 +/−0.8	0.6,* NS
% no normal embryos	32.1 % (26–38.9)	25.5 % (15.1–39.6)	0.19^{+}, NS
Clinical pregnancy rate	72 % (62.1–79.5)	66.7 % (47.7–81.5)	0.31^{+}, NS
Ongoing/live birth rate	65.6 % (56–74.2)	66.67 % (47.7–81.5)	0.46^{+}, NS

*t test of means for all rows

$^{+}$ chi-square

Discussion

Our study found that elevated P4 was associated with increased gonadotropin use and increased estradiol level on day of HCG trigger. We also found that elevated P4 had no measurable effect on the number of oocytes retrieved or the number of embryos available for biopsy. Further, there was no measurable effect on the pregnancy rate in subsequent FET cycles. Most notably, we found no correlation between P4 and the number of euploid embryos derived from the index retrieval. We can infer that elevated P4 on day of HCG trigger does not affect egg quality; instead, it likely affects the endometrium. Many researchers have hypothesized the same and have investigated the question from different perspectives, but this is the first study we are aware of that has shown that ploidy status of the embryo is not affected by serum P4 values on day of HCG trigger.

Our data revealed no difference in number of oocytes retrieved between group A and group B in our study. Other authors have found a correlation between elevated P4 and increased oocytes retrieved [12–14, 31, 38]. However, given the similarity in patient characteristics between the two groups, and the generally standard stimulation protocols our center follows, it is within reason that egg number would not vary between the two groups.

The idea that the uterine window of implantation is the main factor is supported significantly in the literature. Studies performed in oocyte donation programs suggested that pregnancy rates of recipients were not negatively influenced by progesterone levels of the donors on day of HCG trigger [17, 20, 23, 39]. Thus, we can infer that elevated P4 on day of HCG trigger is not reflecting poor egg and subsequently embryo quality, but is instead influencing the endometrium. Many other researchers have hypothesized the same and have investigated the endometrium from different perspectives. Several studies have investigated the association of P4 on the day of HCG administration during a stimulation cycle with pregnancy rates after a subsequent FET of those embryos obtained from the previous cycle [30, 31, 40–42]. In a meta-analysis, there was no difference in pregnancy rates [2]. While this finding suggests the endometrium is responsible for the drop in pregnancy seen in fresh cycles, many of these studies are not ideal. Specifically, the idea of the embryo factor cannot be discounted. The gold standard at this time is to transfer a single embryo with a normal chromosomal complement. To the best of our ability, we know that this embryo is genetically capable of producing an intrauterine gestation, and we know the accuracy of our genetic testing approaches 98 % [43].

Therefore, the mechanism by which P4 influences pregnancy rates is likely to be asynchrony between the embryo and the endometrium, whereby the implantation window is missed in patients with elevated P4. Franasiak et al. (2013) demonstrated that slower developing blastocysts have a decreased implantation rate in fresh, but not frozen, transfer cycles [44]. Due to the fact that the day of transfer is controlled in FET cycles, his finding suggests that a dyssynchronous endometrium decreases implantation rate.

Indeed, several authors have found that patients with a P4 serum concentration above 1.5 ng/ml on the day of HCG administration demonstrate a distinct difference in endometrial gene expression profile during the traditional window of implantation when compared to women with a normal P4 profile [29, 45, 46]. Our study was unique in that it conveniently assessed the influence of P4 on both the endometrium and egg quality. By combining PGS with FET, we were able to investigate embryo quality and control for the influence of P4 on the endometrium by transferring frozen-thawed embryos in subsequent cycles. Weaknesses of our study include the retrospective nature of the study, the relatively small sample size, and the older age of the PGS population, which may not be reflective of the general IVF population.

In conclusion, elevated P4 values on day of trigger have been shown to not affect egg number and ultimate number of available euploid embryos for transfer. The “freeze-all” strategy [40] in situations where the P4 value is found to be elevated can be employed safely, and patients can be reassured that the quality of these embryos is similar to those obtained in non-elevated P4 COH cycles. Rather than canceling a cycle for women with elevated P4 on day of HCG trigger, freezing embryos for transfer in subsequent cycles is a logical alternative that will be just as likely to result in a healthy pregnancy.

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