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ARTICLE

Comparison of aneuploidy, pregnancy and live birth rates between day 5 and day 6 blastocysts

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Abstract Comprehensive chromosome screening is typically used for aneuploidy analysis of blastocysts. It is believed that either day of blastocyst development is acceptable. Euploidy rates and outcomes were examined between day 5 and day 6 blastocysts in two studies. First, euploidy rates of day 5 and day 6 blastocysts were examined on a per-embryo and per-patient basis. Second, outcomes were compared when only euploid day 5 or day 6 blastocysts were transferred in a cryopreserved embryo transfer cycle. In cycles ($n = 70$) that had blastocysts biopsied on both day 5 and day 6, day 5 blastocysts had a higher chance of being euploid than day 6 blastocysts (125/229 [54.6%]) and (77/180 [42.8%]), respectively ($P = 0.0231$). Similarly, euploid rates in blastocysts from patients ($n = 193$) with day 5 biopsy, day 6 biopsy, or both, were significantly higher in day 5 (235/421 [55.8%]) compared with day 6 (184/413 [44.6%]) blastocysts ($P = 0.0014$). In the second study, 50 women (36.1 ± 4.3 years) and 39 women (35.1 ± 3.8 years) with only euploid day 5 or euploid day 6 blastocysts transferred during a cryopreserved embryo transfer had similar cycle outcomes. Although underpowered, these data suggest that euploid day 6 blastocysts are as capable of positive outcomes as their euploid day 5 counterparts.

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Introduction

The relationship between chromosomal abnormalities and embryo development has been previously described (Kroener et al., 2012). Often, those embryos that are slower to progress present with chromosomal abnormalities compared with embryos that progress normally (Kroener et al., 2012; Rubio et al., 2007). Those data, however, were from chromosome analysis of cleavage stage embryos. With the advent of trophectoderm biopsy, the relationship between chromosomal abnormalities and embryos that develop to blastocysts can be more completely examined.

Trophectoderm biopsy is carried out when the embryo has become a blastocyst, either on day 5 or 6 of development. IVF clinics typically use day 5 blastocysts similarly to day 6 blastocysts, allowing them to be transferred, cryopreserved or biopsied for preimplantation genetic screening. The transfer of cryopreserved day 6 blastocysts tends to result in slightly lower pregnancy rates compared with transfer of cryopreserved day 5 blastocysts (Muthukumar et al., 2013). Similarly, those embryos that blastulate on day 6 have been shown to give a lower pregnancy rate than those that blastulate on day 5 during a fresh cycle embryo transfer (Barrenetxea et al., 2005). Campbell et al. (2013a; 2013b) used a time-lapse culture system to show that aneuploid blastocysts were slower to blastulate compared with euploid blastocysts. The lower pregnancy and implantation rates associated with day 6 blastocysts could be attributed to spindle abnormalities, mitochondrial deficiencies or gene expression (Hashimoto et al., 2013; Hsieh et al., 2004; Shapiro et al., 2013; Wood et al., 2007). These deficiencies could affect the blastocysts' ability to implant and develop *in-utero*.

Research has shown that embryos with poor progression tend to be chromosomally abnormal; it therefore stands to reason that late developed blastocysts (i.e. those that develop on day 6 compared with day 5) should have higher rates of chromosomal abnormalities. The purpose of this study was to test the hypothesis that blastocysts derived on day 6 have higher rates of chromosomal abnormalities than those derived on day 5. Regardless of chromosomal ploidy, a day 6 blastocyst is still 1 day behind in development, possibly indicating that an abnormality other than chromosomes is influencing growth. In order to control for endometrial and embryonic synchrony, only cryopreserved embryo transfers into an unstimulated uterus should be considered when examining outcomes. Therefore, in this study, pregnancy and implantation rates of blastocysts biopsied on day 5 were compared with those biopsied on day 6 in cryopreserved embryo transfer cycles.

Materials and methods

This study was deemed exempt from Institutional Review Board approval by Sterling IRB on 26 August 2013. Differences in aneuploidy rates and outcomes between day 5 and day 6 blastocysts were examined in two studies. Only patients undergoing IVF, trophectoderm biopsy, and array comparative genomic hybridization between January 2011 and April 2013 at Reproductive Endocrinology Associates of Charlotte (Charlotte, North Carolina, USA) were included in this study. Aneuploidy rates between day 5 and day 6 blastocysts were compared by two different means. First, aneuploidy rates were compared between patients that had trophectoderm biopsy on both day 5 and day 6 blastocysts in the same cycle (n = 70). If patients had trophectoderm biopsy on day 5 and not day 6, and *vice versa*, they were not included in the first calculation. Second, the overall aneuploidy rates of day 5 and day 6 blastocysts were compared among all patients who had a biopsy at the blastocyst stage (n = 193). The second study compared pregnancy, implantation and live birth rates when only euploid day 5 (group 1, n = 50) or only euploid day 6 (group 2, n = 39) blastocysts were transferred in a subsequent cryopreserved embryo transfer. All patients who had a euploid blastocyst transferred were included in this analysis.

Because our data are not normally distributed, nonparametric tests were used. For continuous variables, Wilcoxon matched pairs test and Mann–Whitney tests were used, whereas categorical variables used a chi-squared test. Significance was set at $P < 0.05$ for all tests.

Embryo culture

All oocytes were designated for ICSI. Oocytes were retrieved, trimmed of blood, and stripped of cumulus cells as described by Taylor et al. (2006). Oocytes were graded for maturity, separated, placed into a 60-mm dish (Thermo scientific, Rochester, New York, USA) containing 250 μL drops of continuous single culture (CSC; Irvine Scientific, Santa Ana, California, USA) supplemented with 10% serum substitute supplement (SSS; Irvine Scientific, Santa Ana, California, USA) and overlaid with 8 ml oil (Irvine Scientific, Santa Ana, California, USA). The dish containing the oocytes was placed into an incubator at 37°C, 6% CO_2 and 5% O_2 for 2–3 h. After 2 h, all oocytes presenting with a polar body underwent ICSI as described by Nagy et al. (1995), placed back into the same dish, and put back into the incubator.

The next morning, 16–18 h after ICSI, oocytes were evaluated for fertilization by the presence of two pronuclei. Embryos that had two pronuclei were group cultured in a fresh dish of CSC plus 10% SSS overlaid with oil and placed back into the incubator. Embryos were not viewed on day 2.

On day 3, the embryos were removed from the incubator, graded, and assisted hatching was carried out on all cleaving embryos with the aid of a laser (Zilos-tk, Hamilton Thorne, Beverly, Maine, USA). Assisted hatching facilitated the protrusion of the trophectoderm from the zona pellucida. Using a pulse of 610 μs, the zona was breached with two to three shots of the laser (Zilos-tk, Hamilton Thorne, Beverly, Maine, USA). The zona was breached where no blastomeres could be directly affected by the laser pulse. After breaching the zona with the laser, the embryos were left in the same drop and placed back into the incubator.

On the morning of day 5 (112–115 h after insemination) and day 6 (136–139 h after insemination), embryos were removed from the incubator, blastocysts were graded according to criteria by Schoolcraft et al. (1999), and those blastocysts that had a good or fair trophectoderm and which protruded from the zona pellucida, along with good or fair quality inner cell mass, were biopsied. Blastocysts were only viewed once in the morning and at no other times. If the blastocysts were not suitable for biopsy in the morning of day 5, they were re-

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