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Frozen Blastocyst Transfer Has Similar Success Rates in Asian and Caucasian Patients

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Abstract

With increasing evidence that ethnicity plays a role in health and treatment outcomes, the goal of this study was to evaluate the outcome of frozen blastocyst transfer in Asian compared to Caucasian women. In this same patient population, we previously found that fresh blastocyst transfer had a lower success rate in the Asian patients. The current study then examined 72 patients who returned and underwent subsequent frozen blastocyst transfer, of which 42 (58.3%) self-identified as Caucasian and 30 (41.7%) as Asian. With the exception of body mass index, both groups within this subset of the original study population had comparable baseline characteristics. After frozen blastocyst transfer, implantation rates (23% vs. 30%), pregnancy rates (33% vs. 33%), and live birth rates (26% vs. 27%) were not significantly different between Caucasians and Asians, respectively. Thus, we found no difference in outcomes with frozen blastocyst transfer in Asian patients compared to Caucasian patients, despite the fact that the former had lower success rates with fresh blastocyst transfer. Given this finding, further large prospective, randomized studies are necessary to determine whether race and ethnicity should prompt physicians to further individualize ART procedures.

Stanford IRB: Protocol 20102

Keywords: Caucasian; Infertility; IVF; Frozen embryo transfer; Blastocyst; Pregnancy rate; Live birth rate

Background

Recent studies have unveiled a reproductive disparity across women of various ethnicities [1-5]. Although much of the research has investigated reproductive outcomes of black women as compared to white, several studies have also included the evaluation of Asian women and their response to assisted reproductive technologies (ART) [1-5]. The largest study by Purcell, et al. examined reproductive outcomes between Asian and Caucasian patients after ART using both the national Society for Assisted Reproductive Technologies (SART) database, as well as clinical data obtained at University of California – San Francisco [5]. Despite baseline characteristics similar to Caucasian women, Asian women were found to have significantly lower pregnancy rates (PR) and live birth rates (LBR) (OR 0.71 and 0.69, respectively) [5]. Behavioral and environmental differences and elevations in estradiol with resultant endometrial dyssynchrony were suggested as possible contributors to IVF failure among Asians [5].

In efforts to further control for embryo quality, our group examined 180 fresh blastocyst transfers among Asian and Caucasian women with similar baseline characteristics [1]. Evaluating only good prognosis patients with blastocyst transfers, we found that Asian women had persistently lower implantation rates (IR), PR and LBR when compared to Caucasians. In addition to a difference in body mass index (BMI), we reported a difference in endometrial thickness between the two groups [1]. This finding, in conjunction with prior reports of higher follicular estradiol levels among Asians, led to the hypothesis that significant elevations of circulating estradiol may lead to endometrial glandular stromal dyssynchrony that may potentially contribute to a negative impact on implantation.

To examine this more carefully, we conducted a follow-up study comparing reproductive outcomes among these same Asian and Caucasian patients [1]. Since we had a well-defined patient population with good blastocyst development, we specifically examined the subset of the patients who returned for frozen embryo transfer. We hypothesized that in the absence of exogenous gonadotropins; there would be no difference in reproductive outcomes between these two groups with good embryo quality.

Methods

As a sub-analysis of our initial study in 2010, we conducted a chart review to identify outcomes of the first frozen blastocyst transfer among Asian and Caucasian patients who initially underwent oocyte retrieval and fresh blastocyst transfer from January 1, 2005, to December 31, 2006. To capture as many of the initial 180 women who underwent subsequent frozen transfer, our chart reviewed spanned from December of 2004 until December of 2009. For those with supernumary embryos allowing for multiple transfers, we included the outcomes of the first frozen blastocyst transfer for analysis. Only nondonor, nongestational carrier cycles were included. Ethnicity was obtained by patient self-reporting questionnaires, such that only women who self-reported as white/Caucasian or Asian (specifically Chinese, Japanese, Korean, Taiwanese or Vietnamese) were included. Women who self-identified as mixed ethnicity or Indian were excluded. Prior to performing this study, approval was obtained by the Stanford Institutional Review Board (Protocol 20102).

Maternal data collected included patient ethnicity, age at oocyte retrieval, body mass index (BMI), gravity and parity, infertility diagnosis, cycle outcome of prior fresh blastocyst transfer, cycle length, endometrial thickness, number of embryos transferred, and number of gestational sacs. Frozen cycles were either monitored natural cycles

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with HCG trigger and luteal support, or medicated using hormonal replacement. Natural cycles consisted of LH testing and follicular monitoring for development of a dominant follicle, followed by ovulation trigger using recombinant hCG at a follicular size of 16-18mm and endometrium > 8 mm. After ovulation trigger, vaginal progesterone (200 mg twice daily) was prescribed for luteal support, and the blastocyst transfer occurred 7 days after hCG trigger. A programmed cycle consisted of pituitary down regulation with GnRH agonist followed by estrogen replacement of 2 mg estradiol three times daily with the addition of progesterone (50 mg progesterone IM and 200mg twice daily vaginal) once the endometrium was > 8 mm. All embryos were blastocysts of 3BB quality or better upon freezing [6]. All freezing was performed using a slow freezing protocol.

Frozen blastocysts were thawed using Quinn's Advantage Embryo Thaw Kit (Sage Biopharma, Pasadena, CA). Once thawed, the embryos were plated and stored in a 37° incubator until just before transfer. Under ultrasound guidance, the embryos were transferred using Tefcath or Echotip Softpass catheters (Cook Ob/GYN, IN). Nine days after transfer, all patients had serum hCG performed. Clinical intrauterine pregnancy was defined as a gestational sac identified on transvaginal ultrasound between 6 and 7 weeks gestation.

Implantation rate was defined as the number of gestational sacs seen at 6 -7 weeks per number of embryos transferred per patient. Pregnancy rate was calculated as the number of clinical pregnancies (with one or more gestational sacs) divided by the total number of patients. Statistics were calculated using two-tailed Student t test, and χ^2 test. A p-value of less than or equal to 0.05 defined statistical significance.

Results

Of the 180 patients who had previously undergone fresh blastocyst transfer, and met inclusion criteria for our prior study comparing Asian and Caucasian women [1], 72 subsequently underwent frozen blastocyst transfer between December of 2004 and December of 2009. Among the 72 patients, 42 (58.3%) self-identified as Caucasian and 30 (41.7%) as Asian.

Comparing the two groups of women, there was no significant difference in maternal age at time of oocyte retrieval (p=0.44). Consistent with our previously reported findings for the fresh transfer [1], there was a significant difference in BMI among the Asians versus Caucasians (22.1 vs. 24.2 kg/m2; p=0.02). However, there was no difference in the proportion of nulligravid and nulliparous patients or in the rate of live birth after the initial fresh blastocyst transfer between the two groups (Table 1). Both Asian and Caucasian women had similar distributions of polycystic ovarian syndrome, endometriosis, diminished ovarian reserve, and unexplained infertility, as previously described (Table 1). The FET treatment protocol was similar between groups, where 83.3% of Caucasians and 80% of Asians underwent natural cycle frozen blastocyst transfer. The cycle length, endometrial thickness and number of embryos transferred between treatment groups (Table 2) were not statistically different.

Implantation rates (IR), pregnancy rates (PR), and live birth rates were similar between the two groups (Table 2).

Discussion

Disparities in many health indicators have been reported to vary by ethnicity and race. Within the reproductive life cycle, from menarche to menopause, racial and ethnic differences in reproductive potential have been described [2]. This diversity in outcomes warrants continued research, as understanding such differences may lead to improved understanding of disease mechanisms. Similarly, treatment regimens can be better individualized to improve outcomes, such as success after ART. In an effort to improve this understanding, SART has included ethnicity as a reportable outcome, and states that one of its missions is to reduce disparities in reproductive health and pregnancy outcomes among the underrepresented populations by addressing reproductive needs of various racial and ethnic populations [7].

	Caucasian Ethnicity (n = 42)	Asian Ethnicity (n = 30)	p value
Age at retrieval (years)	35.78 (SD 3.42)	36.40 (SD 3.23)	0.44 *
BMI (kg/m^2)	24.45 (SD 4.46)	22.09 (SD 3.71)	0.02 *
Nulligravid	0.19 (8/42)	0.2 (6/30)	0.92 °
Nulliparous	0.55 (23/42)	0.67 (20/30)	0.44 °
Live birth after intial fresh cycle	0.29 (12/42)	0.17 (5/30)	0.37 °
PCOS[a]	0.24 (10/42)	0.13 (4/30)	0.42 °
Endometriosis	0.17 (7/42)	0.17 (5/30)	1 °
Male Factor	0.21 (9/42)	0.17 (5/30)	0.84 °
DOR[b]	0.07 (3/42)	0.1 (3/30)	0.67 °
Unexplained infertility	0.48 (20/42)	0.57 (17/30)	0.60 °

a = Polycystic Ovarian Syndrome, b = Diminished Ovarian Reserve

SD = standard deviation, *calculated by student t test, ° calculated with χ^2

Table 1: Comparing Baseline Characteristics Between Asian and Caucasian Ethnicity

	Caucasian Ethnicity (n = 42)	Asian Ethnicity (n = 30)	p value
Cycle length (days)	29.87 (SD 9.09)	31.27 (SD 11.46)	0.57 *
Endometrium (mm)	8.51 (SD 1.75)	8.70 (SD 1.90)	0.67 *
Embryos transferred	2.14 (SD 0.81)	1.87 (SD 0.63)	0.12 *
Implantation rate	0.23	0.3	0.43 *
Pregnancy rate	33% (14/42)	33% (10/30)	1 °
Live birth rate	26% (11/42) 27% (8/30) 1 o	27% (8/30)	1 °

SD = standard deviation, *calculated by student t test, ° calculated with χ^2

Table 2: Comparing FET outcomes between Asian and Caucasian Ethnicity.

To date, the exact etiology for the discrepancy in reproductive outcomes between Asian and Caucasian women has yet to be defined. Prior studies examining ART outcomes have shown significant differences despite controlling for confounders such as embryo quality and ovarian reserve [1,4]. It has been postulated that alterations in the endometrium may be a contributing factor. Sampling endometrium 7-8 days postovulation in patients undergoing IVF, Basir, et al. reported dyssynchronous development of endometrial glands and stroma in patients who responded excessively after stimulation (estradiol concentrations of ≥ 20,000 pmol/l or 5448pg/ml) [8]. Since this corresponds to the time of maximum uterine receptivity, they attributed the lower IR and PR among those undergoing IVF to discordant glandular and stromal development [8].

When comparing IVF success rates in Caucasians versus Asians, Purcell, et al. found that despite similar total and starting doses of gonadotropins, number of follicles produced, and oocytes retrieved, Asian patients had significantly higher levels of estradiol levels (2,740 vs. 2,383 pg/dL, $p<0.01$) [5]. These women also had reduced IR and PR compared to their Caucasian counterparts [5]. Avoiding these high levels of estradiol in frozen blastocyst transfers, we found no statistically significant difference in pregnancy outcomes (IR, PR, LBR) in our current study. These findings suggest that if an endometrial factor related to ovarian stimulation is responsible for the difference in fresh IVF cycle outcomes, it may not persist in FET cycles.

When transferring cryopreserved blastocysts, we found no difference in reproductive outcomes between our two groups, supporting the hypothesis that a difference exists within the uterine environment between fresh and frozen cycles. In this study, we cannot determine the exact nature of the negative endometrial effect in Asian patients; however we feel that these findings justify further study of the endometrium in this population in both natural and stimulated cycles [1].

Future studies examining differences in uterine receptivity within fresh and frozen cycles may help to elucidate the mechanisms behind aberrations in endometrial glandular development and receptivity, ultimately allowing for improved treatment protocols and ART success. Our preliminary data show similar success rates between two groups that had previously demonstrated a disparity in IR, PR and LBR at the time of fresh blastocyst transfer [1]. Given the size of our study population, we are insufficiently powered to detect subtle differences that may exist within a larger population, thus increasing the likelihood of type II error. A post hoc power analysis was performed (3.1%), indicating that our current sample size is insufficient to detect statistically significant differences between the two groups. We chose to study a subset of previously well-characterized women, in efforts to reduce confounding, but this limited the sample size.

Despite limitations, our study offers new insight into the possible benefit of frozen blastocyst transfer in some patient populations. Our findings in a well-defined patient population show a potential ethnic difference in fresh and frozen transfers and this warrants further investigation. A large, multicenter study would contribute valuable information, allowing for the investigation of disparities across many ethnicities, including Asian women.

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