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Asian Ethnicity Associated with Reduced Pregnancy Outcomes from in vitro Fertilization

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ABSTRACT

BACKGROUND

Ethnicity is known to affect health care outcomes from disparities in access as well as from differential response to treatment. However, the role of ethnicity in patient response to infertility treatment has received little attention.

METHODS

To determine if Asian ethnicity affects outcomes of *in vitro* fertilization (IVF), we performed a comparative analysis of self-identified Asian and Caucasian infertile women. National registry data was analyzed to evaluate overall outcomes and data from an academic infertility clinic provided greater patient- and treatment-specific variables to investigate potential etiologic factors.

RESULTS

Infertile Asian women differed only minimally from their Caucasian counterparts in baseline characteristics and treatment response. However, Asian women in the registry dataset and in the clinic dataset had decreased clinical pregnancy rates (odds ratio 0.71 [0.64-0.80] and 0.69 [0.49-0.99], respectively), and live birth (odds ratio 0.69 [0.61-0.77] and 0.67 [0.46-0.98], respectively).

CONCLUSIONS

Asian women undergoing IVF have significantly fewer pregnancies than Caucasian women and this discrepancy cannot be accounted for by differences in baseline characteristics or response to current treatment protocols.

Keywords: ethnicity/ IVF/ reproductive outcomes/Asian/univariate analysis/multivariate analysis

Recent attention has been drawn to ethnic differences in health, both in access to care and in response to medical therapy[1 2, 3]. In the obstetrical field, these ethnic differences have been well-recognized. African-Americans have an increased incidence of low birth weight infants[4] while Hispanic women have an increased incidence of gestational diabetes[5, 6]. Few studies, however, have evaluated the role of ethnicity in other aspects of reproductive health, especially infertility[7]. Differences in infertility treatment success rates among women of Asian ethnicity in particular, have only minimally been studied even though infertility affects approximately 10% of women and is known to lead to a significant amount of emotional stress in Asian women[8-10]. Research has suggested that polycystic ovary syndrome may be more severe among South Asian women in the United Kingdom[11], or that HLA haplotypes may increase the prevalence of sperm-immobilizing antibody among women in Japan[12], but prior studies have been small and may not generalize well to Asian-Americans.

To determine if the response to treatment of infertility differs among Asian-American women compared to Caucasians, we analyzed data from an infertility clinic that has a high proportion of self-identified Asian patients undergoing *in vitro* fertilization (IVF) as well as data contained in a large registry in the United States. We examined potential etiologic and confounding variables to help understand how these groups may differ.

METHODS

STUDY DESIGN

Secondary data analysis was performed comparing IVF outcomes of infertile patients who identified themselves as either Asian or Caucasian from two sources: a

national registry database (SART) and a site-specific dataset (UCSF) with a high proportion of Asian patients, both described in detail below. From both datasets, oocyte donor cycles were excluded, as were any cancelled cycles due to lack of follicular response, lack of oocyte retrieval, or failed fertilization. Only patients who proceeded to embryo transfer were included in the analysis. Infertility diagnoses, treatment characteristics and outcomes were classified according to Society for Assisted Reproductive Technology (SART) guidelines[13]. Clinical pregnancy was defined as the presence of a gestational sac by ultrasound during the first trimester. Live birth was defined as birth of one or more living infants; thus the birth of twins, triplets, or higher order multiples was counted as one live birth delivery.

DATA SOURCES

In the United States, a registry database contains data collected, verified, and reported by the American Society for Reproductive Medicine (ASRM)/SART and the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Pub. L. 102-493, October 24, 1992)[13]. More than 90% of all clinics providing assisted reproductive technologies (ART) in the United States and its territories submit data according to a standardized protocol, and samples of the reported data are validated independently by medical record review. From this registry, the CDC provided a de-identified dataset from the years 1999 and 2000. These data were reported by the 187 SART member clinics that conducted 50 or more cycles of treatment in both years, and provided complete information on race (less than 5% missing). In addition to the inclusion criteria listed above, only those cycles for

which the woman reported she had not previously been treated with ART were included in order to reduce inclusion of repeat treatment cycles in the national registry dataset; these cycles are most likely to be first cycles of ART. This analysis was approved by the institutional review board of the University of Kansas School of Medicine-Wichita.

A second information source was obtained from the Center for Reproductive Health at University of California at San Francisco (UCSF) after obtaining approval by the Committee on Human Research at UCSF. The initial cycle of each eligible women treated from January 1, 2001 to December 31, 2003 was evaluated. The following variables were collected: age, ethnicity, cycle day 3 follicle stimulating hormone (FSH) and estradiol level, infertility diagnosis, specific physician involvement, treatment protocol, the starting dose of medication, the total amount of medication used, number of stimulation days, number of follicles present at the time of human chorionic gonadotropin (hCG) trigger, number of oocytes retrieved, the use of either insemination or ICSI, the number and quality of embryos, subjective and objective measures of difficulty at embryo transfer, pregnancy test results, ultrasound visualization of gestational sacs, fetal poles, fetal heartbeats, and live birth rates. Three stimulation protocols were used: a long agonist protocol with step-down gonadotropin therapy, a short microdose flare protocol, and an antagonist protocol[14]. Indications for intracytoplasmic sperm injection (ICSI) included male factor infertility, unexplained infertility, or a history of previous failed fertilization. At 16 to 18 hours after insemination, the appearance of embryos at the two pronuclei (2PN) stage was assessed. Embryo grading was performed using standard methods. In brief, a value of one was assigned when no fragmentation was seen, a value of two indicated 10% fragmentation, three indicated 10-25% fragmentation, four

indicated 25-50% fragmentation, five indicated more than 50% fragmentation but less than 100% fragmentation, and six indicated complete fragmentation.

STATISTICAL ANALYSIS

Data were analyzed using SPSS, version 11.5 (Chicago, IL) and SAS, version 8.02 (Carey, NC). For the national registry data, the treatment cycle was the unit of analysis because personal identifiers were not available, precluding analysis by individual patient. Descriptive statistics included calculation of means and standard deviations. Subgroups were compared using Chi-square analyses for categorical variables and *t*-tests for continuous variables. All statistical tests were two-tailed and used an α of 0.05.

To estimate the independent contribution of Asian ethnicity to treatment outcomes, multivariable logistic regression analyses were performed. Potential confounders found to be statistically significant in univariate analyses and others generally regarded as clinically significant were included in the models.

RESULTS

STUDY POPULATIONS

The national registry dataset contained 1,429 treatment cycles from Asian women and 25,843 cycles from Caucasian women, and women's ages ranged from 19 to 55 years. Within the national dataset, Asian women differed from the Caucasian population slightly for four characteristics (age, nulliparity, nulligravidity, and the diagnosis of diminished ovarian reserve), but had similar cycle day 3 FSH levels (Table 1).

From the UCSF database, a total of 567 cycles were analyzed, where 34.7% of the cycles were from Asian patients and 65.3% from Caucasian. Overall patient age ranged from 22-47 years within the UCSF dataset. Asian and Caucasian patients had similar mean ages (36.1y.o. vs. 36.6y.o.), day 3 FSH (7.02 vs. 7.27), as well as similar frequency and diagnostic types of male factor infertility. The female diagnosis of infertility was also equally common between the groups. However, the type of female infertility was dissimilar in that Asians were less frequently given the diagnosis of diminished ovarian reserve (0.291 vs 0.385; OR 0.66 [CI 0.45-0.95]) and more frequently given the diagnosis of ovulatory dysfunction (0.158 vs 0.088; OR 1.95 [CI 1.15-3.31]) and unexplained infertility (0.046 vs. 0.014; OR 3.46 [CI 1.14-10.46]) (Table 1).

TREATMENT CHARACTERISTICS

From the UCSF dataset, detailed information was available about treatment characteristics (Table 2). Overall, the proportion of patients undergoing the long, microflare, antagonist, and other protocols were 53.9%, 33.6%, 7.4% and 5%, respectively, and the type of protocol did not differ by ethnicity. The starting dose of gonadotropins (5.35 ampules vs 5.59 ampules) and the total dose used (47.14 ampules vs. 49.14 ampules) were similar as were the number of follicles produced during stimulation. The total number of oocytes retrieved (14.14 vs. 14.72) was also similar between the groups. Interestingly, the Asian population had a significantly higher estradiol (2740 vs. 2383; $p < 0.01$) even though the total number of follicles was similar.

Regarding embryo quality, the average embryo cell number (7.12 vs 6.98) was not different between Asians and Caucasians, yet Asian patients had improved

fragmentation scores (2.06 vs 2.24; p=0.01). The number of embryos transferred (3.22 vs 3.23) in each cycle was similar. The subjective rating of the difficulty of embryo transfer was worse among Asian patients, although no difference was seen using objective markers of transfer difficulty such as blood or mucous in or on the catheter, or the length of time required to accomplish the transfer.

TREATMENT OUTCOMES

In both datasets, Asian women were less likely than Caucasian women to achieve a positive pregnancy test, a clinical pregnancy, or a live birth (Table 3). When examining treatment success rates stratified by the woman's age, poorer outcomes among Asian women persisted (e.g. live birth rates by age from the national registry, shown in Figure 1). Regression analyses confirmed these findings. In the national registry dataset, the adjusted odds ratio of having a live birth for Asian ethnicity was 0.76 (0.66-0.88), controlling for the woman's age, diagnosis, parity, cycle day 3 FSH ratio, use of ICSI and number of embryos transferred. Regression analyses of the UCSF dataset confirmed that Asian ethnicity was an independent predictor of poorer outcomes (odds ratio 0.59 [0.37-0.94]) when controlling for maternal age, diagnosis, whether infertility was primary or secondary, number of previous IVF attempts, stimulation protocol used, estradiol level, endometrial thickness, use of ICSI, embryo fragmentation score, physician who performed the embryo transfer, and subjective difficulty of embryo transfer.

DISCUSSION

This investigation reveals disparities in ART outcomes among Asian and Caucasian women with infertility in the United States. In the initial descriptive analysis comparing Asian and Caucasian patients, surprisingly few differences were found. Well-established factors known to affect IVF outcome[15], including patient age, day 3 FSH levels, primary versus secondary infertility, number of previous IVF attempts, and the number of embryos produced and transferred were similar between the two groups. To determine if the poor outcome seen in the Asian patients could be accounted for by a combination of factors, multivariate analysis was performed. However, Asian ethnicity itself was found to be an independent predictor of poor IVF outcome; even after adjusting for other variables, Asian patients had decreased pregnancy rates with an estimated odds ratio of 0.500 [CL 0.315-0.823].

The poor outcome seen in Asian women is surprising given fertile Asian women have been surmised to undergo oocyte loss at a slower rate than Northern European women[16, 17]. Additionally, Asian and Asian-American women typically have a lower body-mass index (BMI) than their Caucasian counterparts, which is associated with a higher pregnancy rate from IVF[18, 19]. The decreased pregnancy rates may indicate fundamental biological or genetic differences between the ethnicities. In this study, Asians were noted to produce more estradiol for each follicle during ovarian stimulation. This is consistent with studies showing the distribution of FSH receptor polymorphisms are different in Asians and Caucasians; the European population more frequently carries the SS variant which requires higher doses of gonadotropin stimulation and produces less estradiol than the NN variant which is more common in the Asian population[20, 21]. Alternatively, the higher estradiol levels could result from polymorphisms of the genes

involved in estrogen synthesis and metabolism, such as the *CYP19* gene, as previous research suggests these polymorphisms differ by ethnicity as well[22].

Alternatively, the poor outcome may be due to behavioral or environmental differences that are not evaluated by the variables currently used to describe IVF cycles. One speculation could be dietary factors such as increased exposure to methyl mercury, a known reproductive toxin[23-27]. The NHANES[28] has recently shown that Asians and Pacific Islanders have increased levels of this environmental toxin associated with increased consumption of seafood. Exposure of cultured animal embryos to methyl mercury has been shown to affect viability without producing any visual morphologic changes; a similar effect could exist in humans.

A limitation of this study is that in our data sources, Asian women were coded as as if they were a homogeneous group. Research on plasma hormone levels has found differences among Asian women by country of origin[29], but existing studies are small. Larger studies of breast cancer, which is hormonally-mediated, have noted that women of Chinese, Japanese, Filipino and Korean origin have different rates[30].

In conclusion, Asian women undergoing IVF treatment did not achieve the same live birth rates seen in Caucasian women. Prognostic variables currently collected to define baseline characteristics and therapeutic response could not account to this difference. Understanding how, and if, genetic variants and related physiological differences affect oocyte maturation and embryo viability will require further investigation. Physicians and patients need to be aware that infertile Asian women may have more difficulty conceiving than Caucasian women in order to define optimal treatment protocols for Asian women.

Table 1. Baseline characteristics

Variable	**National Registry**			**UCSF Clinic**		
	Mean ± SD or % of first cycles*			Mean ± SD or % of women*		
	Asian (N=1,429)	Caucasian (N=25,843)	P value	Asian (N= 197, 34.74%)	Caucasian (N= 370, 65.26%)	P value
Woman's age—yr	34.7 ± 4.54	33.7 ± 4.52	<0.001	36.1 ± 4.09	36.6 ± 4.08	0.24
Nulliparous	85.2	78.1	<0.001	55.8	53.9	0.50
Nulligravid	58.9	52.9	<0.001	85.3	83.1	0.66
Prior spontaneous abortion	54.3	53.2	0.60	21.0	33.0	0.03
Prior therapeutic abortion	Not available			23.0	37.0	0.009
Diagnosis†						
Diminished ovarian reserve	11.4	7.9	<0.001	29.1	38.5	0.03
Other ovulation disorders	14.5	14.7	0.86	15.8	8.8	0.01
Male factor	36.7	37.3	0.65	49.5	46.5	0.51
Unexplained	10.8	9.3	0.05	4.6	1.4	0.02

Cycle day 3 FSH ratio‡				0.65		0.58
Normal	>0-0.5	43.1	42.4	35.6	38.0	
	> 0.5-1.0	50.6	52.0	60.5	56.0	
Elevated	>1.0-1.5	5.2	4.5	4.0	4.8	
	>1.5-2.0	0.5	0.7	0.0	0.9	
	>2.0	0.5	0.4	0.0	0.3	

* Mean ± standard deviation. Percentages calculated vertically. The number of cycles or women with data on each characteristic may vary because of missing values.

† Categories not mutually exclusive. Other diagnoses (e.g. tubal factor, uterine factor) not shown.

‡FSH ratio = day 3 FSH level of patient/lab upper limit of normal.

Table 2. Treatment characteristics, UCSF clinic

	Asian (n=197)	**Caucasian (n=370)**	**P value**
	Mean ±SD or % of women	Mean ± or % of women	
Starting dose of gonadotropins—ampules*	5.4 ± 1.2	5.6 ± 5.1	0.39
Total dose of gonadotropins—ampules*	47.5 ± 15.3	49.1 ± 16.3	0.23
Days of stimulation	11.1 ±1.6	11.4 ±1.5	0.05
Follicle count after stimulation	14.1±7.1	14.2 ±8.6	0.82
≥ 18mm	2.7±2.1	2.9 ± 2.1	0.41
13-17mm	7.4 ± 4.7	7.3 ± 5.0	0.92
≥13mm	10.1 ±5.5	10.2 ± 5.9	0.83
Estradiol level on day of hCG trigger—pg/dL	2740.5±1376.0	2383.2 ± 1521.8	0.005
Endometrial thickness--mm	10.2±2.1	9.8 ± 2.0	0.03
% of patients using traditional insemination	38.1	37.0	0.81
% of patients using ICSI‡	71.6	73.2	0.67
No. oocytes exposed to traditional insemination	14.1±6.8	14.7 ± 9.0	0.39

No. of 2PN embryos from traditional insemination	6.81 ± 4.27	7.27 ± 5.42	0.50
No. oocytes exposed to ICSI (MIIs)	17.21 ± 6.85	20.55 ± 8.23	0.11
No. of 2PN embryos from ICSI	7.90 ±4.79	7.68 ± 5.49	0.67
Average cell number per embryo	7.12±1.35	6.98 ± 1.38	0.27
Embryo fragmentation score	2.06± 0.80	2.24 ± 0.80	0.01
No. embryos transferred‡			0.66
1	5.1	7.0	
2	23.4	22.7	
≥ 3	71.6	70.3	
Ease of embryo transfer			0.04
Easy	86.3	91.4	
Slightly difficult	7.1	6.5	
Difficult	5.1	1.1	
Very difficult	1.0	0.27	

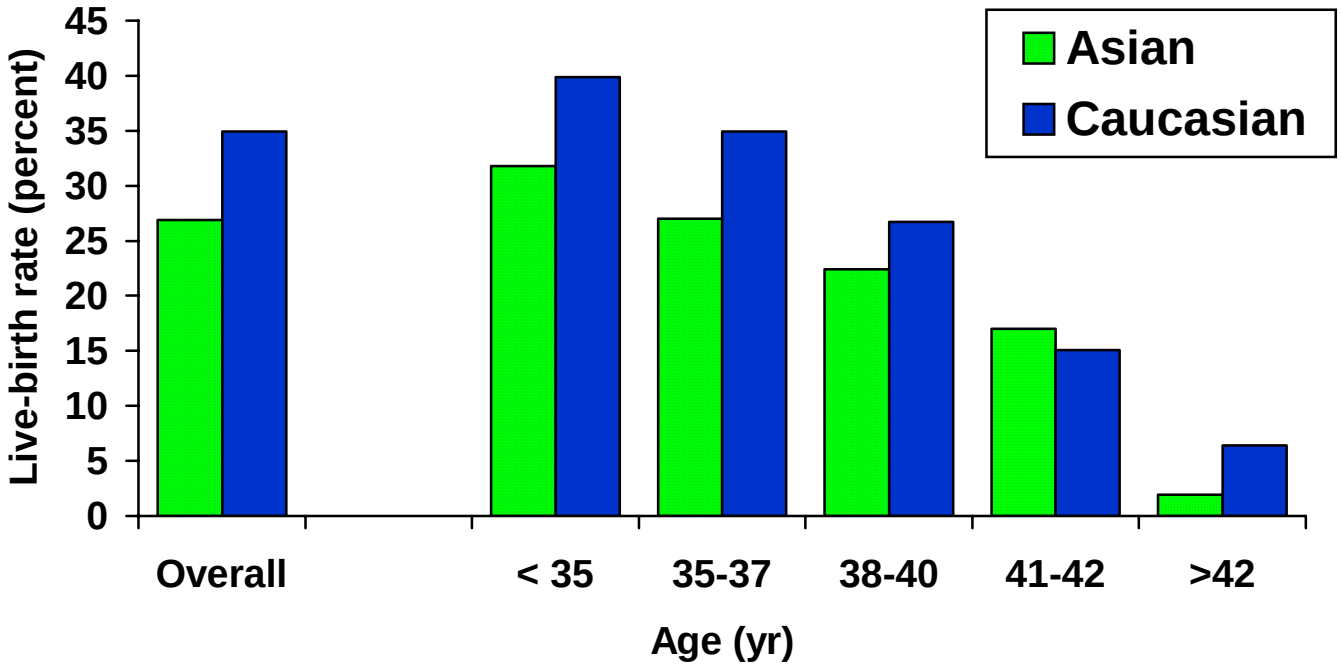
* One ampule contains 75 IU of follicle stimulating hormone.

‡ See text for data on use of intracytoplasmic sperm injection and number of embryos transferred from the national registry dataset. The other variables on this table were not available from the registry.

Table 3. Treatment outcomes

Variable	**National Registry**			**UCSF Clinic**		
	% of first cycles			% of women		
	Asian (N=1,429)	Caucasian (N=25,843)	Unadjusted odds ratio (95% CI)	Asian (N=_197, 34.74%)	Caucasian (N=370, 63.26%)	Unadjusted odds ratio (95% CI)
Clinical pregnancy	33.3	41.3	0.71 (0.64-0.80)	37.1	45.9	0.69 (0.49-0.99)
Live birth	26.9	34.9	0.69 (0.61-0.77)	28.6	37.5	0.67 (0.46-0.98)

Figure 1. Live birth rate by age, national registry data



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