Asian ethnicity is associated with reduced pregnancy outcomes after assisted reproductive technology

Karen Purcell, M.D., Ph.D.,[a,b] *Michael Schembri, M.S.,*[b] *Linda M. Frazier, M.D.,*[c] *Martha J. Rall, M.S.,*[c,d] *Shehua Shen, M.D.,*[b] *Mary Croughan, Ph.D.,*[b] *David A. Grainger, M.D.,*[c,d] *and Victor Y. Fujimoto, M.D.*[b]

[a] Fertility Physicians of Northern California, San Jose, California; [b] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco, California; [c] Department of Obstetrics and Gynecology, University of Kansas School of Medicine–Wichita, and [d] the Women's Research Institute, Wichita, Kansas

Objective: To determine whether success rates were similar in Asian and Caucasian women undergoing infertility treatment.
Design: Secondary data analysis and multivariate modeling.
Setting: Clinics reporting to the national Society for Assisted Reproductive Technology registry and a university-based clinic.
Patient(s): Caucasian and self-identified Asian infertile women undergoing IVF. The study included 25,843 Caucasian and 1,429 Asian patients from the national registry; 370 Caucasian and 197 Asian patients were included from the site-specific clinic.
Intervention(s): In vitro fertilization.
Main Outcome Measure(s): Pregnancy rate and live-birth rate.
Result(s): Infertile Asian women differed only minimally from their Caucasian counterparts in baseline characteristics and treatment response. Yet Asian women had a decreased clinical pregnancy rate (odds ratio, 0.71; 95% confidence interval 0.64–0.80) and a decreased live-birth rate (odds ratio, 0.69; 95% confidence interval 0.61–0.77). Subsequent multivariate analysis demonstrated that Asian ethnicity was an independent predictor of poor outcome.
Conclusion(s): After treatment, infertile Asian women have significantly fewer pregnancies than do Caucasian women. Multivariate analysis indicates that this discrepancy cannot be accounted for by differences in baseline characteristics or by response to current therapeutic interventions. (Fertil Steril® 2007;87:297–302. ©2007 by American Society for Reproductive Medicine.)

Key Words: Asian, ethnicity, IVF outcomes, pregnancy rates, multivariate analysis

Recent attention has been drawn to the differences that exist by ethnicity in access to care as well as in response to medical therapy (1, 2). In the obstetrical field, these ethnic differences have been well recognized. African Americans have an increased incidence of low–birth weight infants (3), whereas Hispanic women have an increased incidence of gestational diabetes (4, 5). Few studies, however, have evaluated the role of ethnicity in other aspects of reproductive health, especially infertility (6). The paucity of information regarding infertility can, in part, be attributed to a lack of available data. Within the United States, a national registry exists to which the majority of infertility clinics contribute on a voluntary basis. However, the information gathered within this registry is limited to sparse patient demographics and particular pregnancy outcomes but does not include variables of medical treatment or the patient's response to the ascribed treatment. Therefore, this database can be used to describe general outcomes but cannot be used to analyze a number of important potential confounders or etiologic variables.

Currently, the details of each infertile patient's treatment and response can be reached only by analyzing the data present within a specific clinic. Although a majority of clinics do not have a substantial number of any particular group of ethnic minorities, the high concentration of Asian patients treated within a particular academic clinic in San Francisco provides the opportunity to evaluate demographic and treatment variables. We therefore analyzed the national registry to determine whether the response to infertility treatment differs between Asian-American women compared with Caucasians. Then, we analyzed data from the clinic containing a high proportion of self-identified Asian patients. The potential causative and confounding variables were examined to help understand how Asian and Caucasian patients differ in their response to IVF.

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Reprint requests and present address: Karen Purcell, M.D., Ph.D., Fertility Physicians of Northern California, 2581 Samaritan Drive, Suite 302, San Jose, California 95124 (FAX: 408-356-8954; E-mail: cjpurcell@pol.net).

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MATERIALS AND METHODS

Study Design and Analysis

Secondary data analysis was performed by using two different data sources described in detail in Data Sources. From both data sets, patients were included who reported their ethnicity as Asian or Caucasian, from a list provided by the Society for Assisted Reproductive Technology (SART) that included Caucasian, Asian, Hispanic, African American, Native American, or other. Any patient marking both Asian and another ethnicity were assigned to the Asian group. Oocyte-donor cycles were excluded. Cycles canceled because of lack of follicular response, lack of oocyte retrieval, or failed fertilization also were excluded to remove the potential confounding of patients who were not successful in generating embryos. Review of these cycles showed no difference in the incidence of cancelled cycles between the two groups.

Comparison of IVF outcomes for Asian and Caucasian patients included both clinical pregnancy rate and live-birth rate. 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.

Initial univariate analysis was performed to determine baseline characteristic differences between the Asian population and the Caucasian population. For the national registry, available demographics included patient age; previous fertility (gravidity, parity, and history of spontaneous or therapeutic abortion); laboratory values of day 3 FSH and E_2; as well as infertility diagnosis, which was classified according to SART guidelines (7). Additional variables regarding patient-specific treatment protocols and the response to intervention were provided by the site-specific data set, as itemized in the description in Data Sources of the second data set.

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 (Table 1) and others generally regarded as clinically significant (see Treatment Outcomes) were included in the models. Backward

TABLE 1

Baseline characteristics.

	First cycles, national registry[a]			Women, UCSF clinic[a]		
Variable	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 (y)	34.7 ± 4.54	33.7 ± 4.52	<.01	36.1 ± 4.09	36.6 ± 4.08	.24
Nulliparous	85.2	78.1	<.01	85.3	83.1	.50
Nulligravid	58.9	52.9	<.01	55.8	53.9	.66
Prior spontaneous abortion	54.3	53.2	.60	16.3	21.6	.14
Prior therapeutic abortion	Not available			18.6	24.4	.11
Diagnosis[b]						
Diminished ovarian reserve	11.4	7.9	<.01	29.1	38.5	.03
Other ovulation disorders	14.5	14.7	.86	15.8	8.8	.01
Male factor	36.7	37.3	.65	43.6	42.1	.73
Unexplained	10.8	9.3	.05	4.6	1.4	.02
Cycle day 3 FSH ratio[c]			.65			.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	

Note: UCSF = University of California, San Francisco.

[a] Data are mean ± SD or are percentages (calculated vertically). The number of cycles or of women with data on each characteristic may vary because of missing values.

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

[c] FSH ratio = day 3 FSH level of patient/lab upper limit of normal.

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conditional elimination was used to generate the most parsimonious model.

Data were analyzed by using SPSS, version 11.5 (Chicago, IL), and SAS, version 8.02 (Cary, 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 SDs. Subgroups were compared by using χ^2 analyses for categorical variables and t tests for continuous variables. All statistical tests were two-tailed and used an α of 0.05.

Data Sources

The national SART registry database served as one information source. This registry contains data collected, verified, and reported by the American Society for Reproductive Medicine–SART and by the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Pub. L. 102-493, October 24, 1992) (7). 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 Centers for Disease Control and Prevention provided a deidentified data set from the years 1999 and 2000. These data were reported by the 187 SART member clinics that conducted ≥50 cycles of treatment in both years and provided complete information on race (defined as <5% of entries missing). In addition to the inclusion criteria listed above, only those cycles were included for which the woman reported she had not previously been treated with ART, to reduce inclusion of repeat treatment cycles; 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 an academic clinic at which approximately one third of the patients were noted to be Asian. This data set from the Center for Reproductive Health at the University of California, San Francisco, was analyzed after obtaining approval by the Committee on Human Research at the University of California, San Francisco. The initial cycle of each eligible woman treated from January 1, 2001 to December 31, 2003 was evaluated. The following variables were collected: age, ethnicity, cycle day 3 FSH and E_2 level, infertility diagnosis, specific physician directing care, 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 hCG trigger, number of oocytes retrieved, the use of either traditional insemination or intracytoplasmic sperm injection, 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 (8). Indications for intracytoplasmic sperm injection 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 stage was assessed. Embryo grading was performed by using standard methods to assign a value between 1 and 6. In brief, a value of 1 was assigned when no fragmentation was seen, a value of 2 indicated 10% fragmentation, a value of 3 indicated 10%–25% fragmentation, a value of 4 indicated 25%–50% fragmentation, a value of 5 indicated >50% fragmentation but <100% fragmentation, and a value of 6 indicated complete fragmentation.

RESULTS

Study Populations

The national registry data set contained 1,429 treatment cycles from Asian women and 25,843 cycles from Caucasian women. Within the national data set, Asian women differed from the Caucasian population in four characteristics (age, nulliparity, nulligravidity, and the diagnosis of diminished ovarian reserve) but had similar cycle day 3 FSH levels (Table 1).

From the University of California, San Francisco database, a total of 567 cycles were analyzed, of which 34.7% of the cycles were from Asian patients and 65.3% from Caucasian. The mean age and day 3 FSH (7.02 IU vs. 7.27 IU) values were similar for Asian and Caucasian patients, respectively. Also similar were the frequency and diagnostic types of male-factor infertility (oligospermia, asthenospermia, and/or teratospermia). The diagnosis of female infertility was equally common between the groups, although the type of female infertility was dissimilar in that Asians were less frequently given the diagnosis of diminished ovarian reserve in this patient population (0.291 vs. 0.385; odds ratio [OR], 0.66; 95% confidence interval, 0.45–0.95) and were more frequently given the diagnoses of ovulatory dysfunction (0.158 vs. 0.088; OR, 1.95; 95% confidence interval, 1.15–3.31) and unexplained infertility (0.046 vs. 0.014; OR, 3.46; 95% confidence interval, 1.14–10.46; Table 1).

Treatment Characteristics

From the University of California, San Francisco data set, detailed information was available for treatment characteristics (Table 2). Overall, the proportions 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 (5.4 ampules vs. 5.6 ampules) and the total dose used (47.5 ampules vs. 49.1 ampules) were similar, as were the number of follicles produced during stimulation. The total number of oocytes retrieved (14.1 vs. 14.7) also

TABLE 2

Treatment characteristics, UCSF clinic.

Variable	Asian (n = 197)	Caucasian (n = 370)	*P* value
Starting dose of gonadotropins (ampules)[a]	5.4 ± 1.2	5.6 ± 5.1	.39
Total dose of gonadotropins (ampules)[a]	47.5 ± 15.3	49.1 ± 16.3	.23
Days of stimulation	11.1 ± 1.6	11.4 ± 1.5	.05
Follicle count after stimulation, by size	14.1 ± 7.1	14.2 ± 8.6	.82
≥18 mm	2.7 ± 2.1	2.9 ± 2.1	.41
13–17 mm	7.4 ± 4.7	7.3 ± 5.0	.92
≥13 mm	10.1 ± 5.5	10.2 ± 5.9	.83
E_2 level on day of hCG trigger (pg/dL)	2,740.5 ± 1,376.0	2,383.2 ± 1,521.8	<.01
Endometrial thickness (mm)	10.2 ± 2.1	9.8 ± 2.0	.03
% of patients using insemination	38.1	37.0	.81
% of patients using ICSI[b]	71.6	73.2	.67
No. oocytes exposed to insemination	14.1 ± 6.8	14.7 ± 8.9	.39
No. of 2PN embryos from insemination	6.81 ± 4.27	7.27 ± 5.42	.50
No. of oocytes exposed to ICSI (MIIs)	17.21 ± 6.85	20.55 ± 8.23	.11
No. of 2PN embryos from ICSI	7.90 ± 4.79	7.68 ± 5.49	.67
Average cell no. per embryo	7.12 ± 1.35	6.98 ± 1.38	.27
Embryo fragmentation score	2.06 ± 0.80	2.24 ± 0.80	.01
No. of embryos transferred[b]			.66
1	5.1	7.0	
2	23.4	22.7	
≥3	71.6	70.3	
Ease of embryo transfer			.04
Easy	86.3	91.4	
Slightly difficult	7.1	6.5	
Difficult	5.1	1.1	
Very difficult	1.0	0.27	

Note: Data are mean ± SD or %. 2PN = two pronuclei; MII = metaphase II.

[a] One ampule contains 75 IU of FSH.

[b] Data from the national-registry data set on use of intracytoplasmic sperm injection and number of embryos transferred are given in the article. The other variables in this table were not available from the registry.

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was similar between the groups. Interestingly, the Asian population had a significantly higher E_2 level (2,740 vs. 2,383; $P<.01$), 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; $P=.01$). 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 when objective markers of transfer difficulty were used, such as blood or mucus in or on the catheter or the length of time required to accomplish the transfer.

Treatment Outcomes

In both data sets, Asian women were less likely than Caucasian women to achieve 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 Fig. 1). Regression analyses confirmed these findings. In the national-registry data set, the adjusted OR of having a live birth for Asian ethnicity was 0.76 (95% confidence interval, 0.66–0.88), controlling for the woman's age, infertility diagnosis (including diminished ovarian reserve), parity, cycle day 3 FSH ratio, use of intracytoplasmic sperm injection, and number of embryos transferred.

Evaluation of the site-specific data set also showed decreased pregnancy rates with the Asian patients (adjusted OR, 0.59 [0.37–0.94]). Multivariate analysis was performed to control for the following variables that differed between the two groups: prior spontaneous or therapeutic abortion, specific diagnosis of female infertility (diminished ovarian reserve, ovulatory dysfunction, or unexplained infertility), days of stimulation, E_2 level, endometrial thickness, embryo

TABLE 3

Treatment outcomes.

Rate	Percentage of first cycles, national registry: Asian (n = 1,429)	Caucasian (n = 25,843)	Unadjusted odds ratio (95% CI)	Percentage of women, UCSF clinic: Asian (n = 197)	Caucasian (n = 370)	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)

Note: CI = confidence interval.

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fragmentation score, physician performing the embryo transfer, and subjective difficulty with the embryo transfer. In addition, controlling for variables shown to be clinically important, such as maternal age, primary or secondary infertility, number of previous IVF attempts, and stimulation protocol used also was performed. None of these variables could account for the decreased pregnancy rates seen between the two groups; Asian ethnicity remained an independent predictor of poor outcome.

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 (9), including patient age, day 3 FSH levels, primary vs. secondary infertility, number of previous IVF attempts, and the number of embryos produced and transferred were similar between the two groups. To determine whether the poor outcome seen in the Asian patients could be attributed to 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 OR of 0.59 [95% confidence interval, 0.37–0.94].

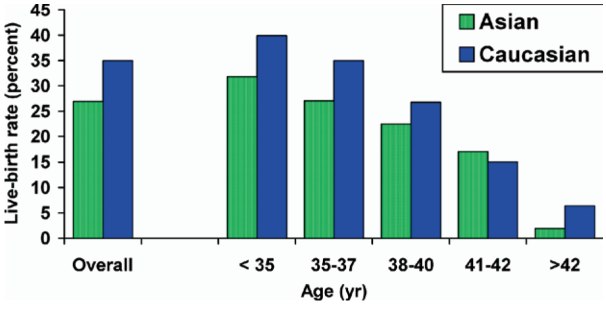
The validity of this result is supported by the large number of Asian patients studied, both in the national registry and the site-specific data set, which may explain the differing conclusion by Bendikson et al. (6), in whose study only 35 Asian patients were available for analysis.

The poor outcome seen in Asian women is surprising given that fertile Asian women have been surmised to undergo oocyte loss at a slower rate than Northern European women (10, 11). In addition, Asian and Asian-American women typically have a lower body-mass index than their Caucasian counterparts, which is associated with a higher pregnancy rate from IVF (12, 13). The decreased pregnancy rates may indicate fundamental biological or genetic differences between the ethnicities. In this study, Asians were noted to produce more E_2 for each follicle during ovarian stimulation. This is consistent with studies showing that 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 E_2 than does the NN variant, which is more common in the Asian population (14, 15). Alternatively, the higher E_2 levels could result from polymorphisms of the genes involved in estrogen synthesis and metabolism, such as the *CYP19* gene, because previous research suggests that these polymorphisms differ by ethnicity as well (16).

Alternatively, the poor outcome may be a result of 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 (17–21). The National Health and Nutrition Examination Survey (22) recently showed that Asians and Pacific Islanders have increased levels of this environmental toxicant, associated

FIGURE 1

Live-birth rate by age, national registry data. *Green bars,* Asian; *blue bars,* Caucasian.



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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 human beings.

One limitation of this study comes from the inherent difficulties in performing secondary data analysis; large surveillance data sets are prone to data-entry error and misclassifications, even when validation methods are incorporated into the design. Perhaps an even greater limitation of this study is that in our data sources, Asian women were coded as if they were a homogeneous group, although studies contradict the appropriateness of this practice. Research on plasma hormone levels has found differences among Asian women by country of origin (23). In addition, women of Chinese, Japanese, Filipino, and Korean origin have been shown to differ in the rate of breast cancer, which is hormonally mediated (24). Appropriate characterization of this heterogenous population will require clinics to deviate from the current SART data fields to ascertain the correct ethnic identifiers.

In conclusion, Asian women undergoing their first IVF treatment attempt 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 for this difference; therefore, these results promote generating hypotheses to direct future studies regarding the etiology of the disparity in outcomes. Understanding how, and if, genetic variants and related physiological differences affect oocyte maturation and embryo viability will require further investigation. It also will be important to determine whether the decreased pregnancy rate persists in successive IVF cycles. Characterization of the male partner's ethnicity and analysis by ethnic concordance or discordance may also illuminate biological differences. Physicians and patients need to be aware that infertile Asian women may have more difficulty conceiving than Caucasian women, and appropriate counseling should be made during the treatment course for Asian women.

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