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ORIGINAL ARTICLE

Racial and ethnic differences in assisted reproduction treatment outcomes: the benefit of racial admixture

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Abstract

The goal of the present study was to determine whether racial and ethnic differences affect the outcomes of assisted reproductive technology in the Brazilian population. 1497 patients undergoing intracytoplasmic sperm injection (ICSI) cycles were split into groups according to the patient's ethnicity: Caucasian ($n = 2131$), Mestizo ($n = 358$), Asian ($n = 174$), Black ($n = 115$) and Indian ($n = 260$). ICSI outcomes were compared among the groups. Body mass index was highest in the Black group, followed by the Mestizo, Indian, Caucasian and Asian groups ($p > 0.001$). The FSH dose ($p > 0.001$) was highest among Indians, followed by Asians and Caucasians, and the dose was lowest among Blacks and Mestizos. In contrast, the oocyte yield was highest among Mestizos, followed by Indians, Blacks and Caucasians, and lowest among Asians ($p = 0.005$). The fertilisation rate was highest among Mestizos, followed by Blacks, Indians and Caucasians, whereas Asians had the lowest fertilisation rate ($p = 0.004$). Pregnancy and implantation rates were also highest among Mestizos, followed by Blacks, Indians and Caucasians, whereas the Asian patients had the lowest rates ($p = 0.008$ and $p > 0.001$, respectively). In conclusion, our evidence suggests a possible beneficial effect of racial admixture on ICSI outcomes.

Keywords: *ICSI, ethnicity, Infertility*

Introduction

Infertility affects 8–16% of reproductive-aged couples (Stephen & Chandra, 2006). Depending on the cause of infertility and patient characteristics, management options range from pharmacologic treatment to more advanced techniques. Over the past two decades, the use of assisted reproductive technology (ART) has dramatically increased worldwide and has made pregnancy possible for many infertile couples. However, certain infertile couples exhaust all forms of ART, such as in vitro fertilisation (IVF), without achieving any success.

Recent attention has been given to differences in access to care and in responses to medical therapy according to ethnicity. Among couples using ART, differences in treatment success have also been described as varying by race and ethnicity (Fujimoto et al., 2010; Bhide et al,. 2014; Iglesias et al., 2014; Jayaprakasan et al., 2014). It has been reported that White patients have the highest rates of live births, followed by Hispanic women, whereas Asian and African patients have the lowest live birth rates after ART (Seifer et al., 2008; Baker et al., 2010; Fujimoto et al.,2010; Seifer et al., 2010; Luke et al., 2011).

Many factors are known to affect ART outcomes, such as male (Hassan & Killick, 2003) and female (Lee et al., 2009) ages; male (Braga et al., 2012) and female (Hassan & Killick, 2004) lifestyle habits; and environmental and occupational factors (Younglai et al., 2005) and psychological factors, such as the patient's anxiety and depression (Smeenk et al., 2001). However, the mechanism by which ethnicity affects the IVF outcome is still under debate.

The ethnic composition of Brazilian society is the result of a confluence of people from many different ethnic backgrounds: the original indigenous people; black Africans who arrived after the arrival

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of Portuguese colonists; recent waves of immigration of Europeans, Arabs and Japanese; and other Asian and South American people (IBGE, 2000). Many different races and ethnicities are therefore observed among Brazilian people, and the frequency of interracial couples in Brazil is very high. The Brazilian population consists of nearly 200,000,000 individuals, of whom 47.7% are White; 43.1%, Mestizo; 7.61%, Black; 1.09%, Asian; and 0.50%, Indian (IBGE, 2010).

Patients undergoing IVF cycles in Brazil therefore provide an interesting model for studying the influence of race and ethnicity on ART outcomes.

The goal of the present study was to determine whether racial and ethnic differences can affect the outcome of ART in the Brazilian population.

Materials and methods

Study design

This retrospective observational study enrolled 2804 patients undergoing intracytoplasmic sperm injection (ICSI) cycles between January 2010 and December 2012. The cycles were split into groups according to the patient's ethnicity: (i) Caucasian ($n = 2131$), Mestizo ($n = 358$), Asian ($n = 174$), Black ($n = 115$) and Indian ($n = 26$). Cycle characteristics and ICSI outcomes were compared among the groups.

A pregnancy test was performed 12 days after embryo transfer. All women with a positive test had a transvaginal ultrasound scan 2 weeks after the positive test. A clinical pregnancy was diagnosed when the foetal heartbeat was detected. Pregnancy rates were calculated per transfer. Miscarriage was defined as pregnancy loss before 20 weeks' gestation.

Written informed consent was obtained, in which the patients agreed to share the outcomes of their own cycles for research purposes, and the study was approved by the local institutional review board.

Ethnicity data source

Races and ethnic groups were categorised according to the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, or IBGE) (IBGE, 2006). According to the IBGE, the Brazilian population is composed of Whites, Asians, Blacks, Indians and Mestizos. Mestizos include different types of mixed races, such as Mulattos (Black/European), Caboclos (White/Indian) and Cafuzos (Indian/Black).

According to Brazilian law, before the beginning of treatment, a written informed consent form must be completed by all patients using ART, on which questions regarding ethnicity must be answered. Not only is the patient's ethnicity requested but also the origin of the father, mother, grandfather and grandmother.

Controlled ovarian stimulation and laboratory procedures

Controlled ovarian stimulation was achieved using recombinant FSH (Gonal-F; Serono, Geneva, Switzerland) at a daily dose starting on day three of the cycle. Pituitary blockage was performed using a GnRH antagonist (Cetrotide; Serono, Geneva, Switzerland), starting when at least one follicle ≥ 14 mm was visualised.

Follicular growth was followed by a transvaginal ultrasound examination that started on day four of gonadotropin administration. When adequate follicular growth and serum E2 levels were observed, recombinant hCG (Ovidrel; Serono, Geneva, Switzerland) was administered to trigger the final follicular maturation. Oocytes were collected 35 hours after hCG administration by transvaginal ultrasound-guided ovum pickup.

The nuclear status of the recovered oocytes was assessed, and those oocytes in metaphase II were submitted to ICSI using routine procedures (Palermo et al., 1997).

Embryo morphology evaluation and embryo transfer

Embryo morphology was assessed at 16–18 h post-ICSI and on the mornings of days two, three and five of embryo development using an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon, Tokyo, Japan) with a Hoffmann modulation contrast system under 400X magnification.

When assessing the cleavage-stage morphology, the following parameters were recorded: the number of blastomeres, the percentage of fragmentation, variation in blastomere symmetry and the presence of multinucleation and defects in the zona pellucida and cytoplasm. High-quality cleavage-stage embryos were defined as those having all of the following characteristics: 4 cells on day two or $8-10$ cells on day three, $<15\%$ fragmentation, symmetric blastomeres, an absence of multinucleation, colourless cytoplasm with moderate granulation and no inclusions, an absence of perivitelline space granularity and an absence of zona pellucida dysmorphism. Embryos lacking any of the above characteristics were considered to be of low quality.

When assessing blastocyst-stage morphology, the following characteristics were recorded: the size and compactness of the inner cell mass (ICM) and the cohesiveness and number of trophectoderm (TE) cells. Embryos were also given a numerical score from one to six based on their degree of expansion and hatching status, as follows: 1, an early blastocyst with a blastocoel that occupies less than half of the volume of the embryo; 2, a blastocyst with a blastocoel that is greater than half of the volume of the embryo; 3, a full blastocyst with a blastocoel completely filling the embryo; 4, an expanded blastocyst; 5, a hatching blastocyst; and 6, a hatched blastocyst. For fully formed blastocysts, the ICM was classified as follows: high-quality, tightly packed with many cells, or low-quality – loosely grouped with several cells or few cells. The TE was classified as follows: high-quality, many cells forming a cohesive epithelium,

or low-quality – few cells forming a loose epithelium or very few cells -.

One or two embryos were transferred on day five. Day three embryo transfers were only performed in special cases.

Statistical analyses

Dichotomous variables were evaluated by a Chi-squared test or Fisher's exact test only when the expected frequency was five or less. The data are expressed as percentages.

Continuous variables were evaluated by ANOVA, and the data are expressed as the average ± standard deviation. Additionally, binary regression models were generated to evaluate the influence of a specific ethnicity on ICSI clinical outcomes. The results of the logistic regression are presented as the odds ratio (OR), p value and 95% confidence interval (CI).

All regression analyses were adjusted for age, body mass index (BMI), the number of retrieved oocytes, endometrial thickness, sperm concentration and sperm motility, as these variables were considered to be potential confounders in the association between race and ICSI outcomes.

The results were considered to be significant at the 5% critical level ($p < 0.05$). The data analysis was performed using the statistical programme Minitab (version 16).

Results

Most of the patients evaluated were Caucasians (76%, 2131/2804), followed by Mestizos (12.7%, 358/2804), Asians (6.2%, 174/2804), Blacks (4.1%, 115/2804) and Indians (0.9%, 26/2804).

Patient and cycle characteristics

Patient and cycle characteristics are compared in Table I. The race groups were similar with respect to female age, the number of follicles, the number of retrieved oocytes, the number of retrieved MII oocytes, the MII oocyte rate and endometrial thickness.

BMI was highest in the Black group, followed by the Mestizos, Indians, Caucasians and Asians ($p > 0.001$). The FSH dose used for ovarian stimulation ($p > 0.001$) was highest amongst Indians, followed by Asians and Caucasians, and the dose was lowest among Blacks and Mestizos. The FSH dose/retrieved oocytes ratio was also highest among Indians and Blacks, followed by Caucasians, and lowest among Asians and Mestizos ($p > 0.001$). In contrast, the oocyte yield was highest among Mestizos, followed by Indians, Blacks and Caucasians, and lowest among Asians ($p = 0.005$) (TableI).

ICSI outcomes

The fertilisation rate was highest among Mestizos, followed by Blacks, Indians and Caucasians, whereas Asians had the lowest fertilisation rate ($p = 0.004$). The number of transferred embryos also differed among the groups, being highest among Asians, followed by Indians, Caucasians and Blacks, and lowest among Mestizos ($p = 0.005$, Table II).

Pregnancy and implantation rates were highest among Mestizos, followed by Blacks, Indians and Caucasians, whereas Asian patients had the lowest rate ($p = 0.018$ and $p < 0.001$, respectively) (TableII).

To confirm that the effect of race on ICSI outcomes was not mediated by differences in age, BMI or other variables, regression analysis models were generated and adjusted for possible confounding variables. These analyses confirmed our findings that whereas Mestizos had a 34% increased chance of achieving pregnancy, this was reduced by 18% among Asians. The results are given in Table III.

Discussion

Despite the increasing number of studies on the association between race/ethnicity and ART outcomes, there is no consensus regarding the impact of race on the success of treatment. Whereas several studies have suggested differences (Sharara & McClamrock, 2000; Palep-Singh et al., 2007; Purcell et al., 2007;

Table I. Comparison of patient and cycle characteristics among five different racial and ethnic groups.

Variable	Caucasian ($n = 2131$)	Mestizo ($n = 358$)	Asian ($n = 174$)	Black ($n = 115$)	Indian ($n = 26$)	p
Female age (y-old)	35.5 ± 4.4	34,7 ± 4.9	35.5 ± 4.0	34.6 ± 4.8	5.6 ± 4.7	0.543
BMI (Kg/m^2)	22.9 ± 5.8	23.2 ± 3.7	22.8 ± 6.2	23.9 ± 3.0	23.1 ± 3.2	< 0.001
FSH dose (IU)	2254.3 ± 511.5	2113.8 ± 572.7	2341.2 ± 499.4	2114.0 ± 534.6	2348.9 ± 459.7	< 0.001
FSH dose/retrieved oocytes(IU)	155.4 ± 53.1	139.0 ± 62.5	147.2 ± 53.0	166.4 ± 69.3.	183.5 ± 57.8.	< 0.001
No. of follicles	14.5 ± 9.5	15.2 ± 9.0	15.9 ± 9.3	12.7 ± 7.8	12.8 ± 7.8	0.091
No. of oocytes retrieved	9.8 ± 8.0	9.6 ± 8.2	9.8 ± 6.7	8.2 ± 7.9	9.3 ± 6.9	0.364
Oocyte yield (%)	71.2 ± 20.5	74.4 ± 20.7	65.6 ± 20.7	72.3 ± 1.3	72.9 ± 18.0	0.005
No. of MII oocytes	7.9 ± 6.9	7.5 ± 8.2	7.4 ± 5.2	7.7 ± 7.0	6.4 ± 4.9	0.605
MII oocyte rate (%)	75.8 ± 20.8	73.4 ± 3.9	74.8 ± 19.6	76.5 ± 20.3	75.2 ± 0.33	0.772
Endometrial thickness (mm)	10.4 ± 2.2	10.5 ± 2.2	10.4 ± 2.0	10.5 ± 2.1	10.3 ± 1.9	0.697

Body Mass Index: BMI, MII: Metaphase II.

Table II. Comparison of cycle outcomes among the five different racial and ethnic groups.

Variable	Caucasian ($n = 2131$)	Mestizo ($n = 358$)	Asian ($n = 174$)	Black ($n = 115$)	Indian ($n = 26$)	p
Fertilisation rate	70.9 ± 20.8	74.2 ± 20.6	65.3 ± 20.8	72.3 ± 21.0	71.7 ± 18.5	0.004
High-quality embryos rate	21.4 ± 24.5	25.7 ± 27.9	19.1 ± 21.7	25.2 ± 27.3	25.3 ± 34.7	0.010
Pregnancy rate	34.6 (737/2131)	45.0 (161/358)	31.6 (55/174)	38.2 (44/115)	34.6 (9/26)	0.018
Miscarriage rate	15.6 (115/737)	11.1 (18/161)	29.1 (16/55)	9.1 (4/44)	22.2 (2/9)	0.085
Implantation rate	21,0 ± 32,6	29,8 ± 38,1	19,0 ± 29,7	27,7 ± 33,8	25,3 ± 36,7	<0.001
No. of embryos transferred	1.8 ± 0.9	1.4 ± 0.9	2.0 ± 0.8	1.7 ± 1.0	1.8 ± 0.9	0.005

The values are expressed in percentage.

Seifer et al., 2008; Fujimoto et al., 2010), others have not (Bendikson et al., 2005; Feinberg et al., 2006; Matalliotakis et al., 2008; Dayal et al,. 2009). However, most of the existing literature has focussed on comparisons between White and Black women (Sharara & McClamrock, 2000; Seifer et al., 2008) or on ART outcomes among Hispanics (Bendikson et al., 2005; Fujimoto et al., 2010) and Asians (Palep-Singh et al., 2007; Purcell et al., 2007). However, racial admixture has increased markedly over time, making attempts at strict racial categorisation increasingly confusing and potentially outdated.

In the present study, the influence of the race/ethnicity on ICSI outcomes has been evaluated. As well as investigation of the classical racial classification of Caucasians, Asians and Blacks, races such as Indians and Mestizos, which are mixtures of races existing in Brazil, was also examined. Our evidence suggests disparities in ART outcomes among different races, especially when comparing Asian and Mestizos, as Mestizos had the best outcomes and Asians, the poorest. In fact, Asian women exhibited a 20% decrease in the odds of pregnancy.

An increasing number of studies have reported a decreased pregnancy rate among Asian women. Recently, a report by a SART group, involving a large sample size, confirmed this disparity (Fujimoto et al., 2010). Conversely, it has been reported that Asian women undergo oocyte loss at a slower rate than Northern European women (Scheffer et al., 1999; Ng et al., 2003). Moreover, Asian patients have a lower BMI, as observed here, than do other races, which is associated with better ART outcomes (Lintsen et al., 2005; Ferreira et al., 2010; Setti et al., 2012). The decreased pregnancy rate observed among Asians may therefore indicate fundamental biological or genetic differences between ethnicities.

According to Purcell et al. (Purcell et al., 2007), one explanation could lie in the nature of the diet. The National Health and Nutrition Examination Survey (Mahaffey et al., 2004) revealed that Asians and Pacific Islanders exhibit increased levels of environmental toxicants, which are associated with elevated consumption of seafood. However, it could be argued that Asian patients living outside Asia might not have the same dietary habits as Asians living in their homeland.

In order to discover whether the lower pregnancy rate observed among the Asian patients was mediated by differences in age, BMI, the number of retrieved oocytes, endometrial thickness or male factors, regression analysis models were generated and adjusted for possible confounding variables. It was observed that even when the analysis was adjusted for all such variables, Asian patients had an impaired outcome, demonstrating that Asian ethnicity itself is an independent predictor of decreased ART success.

Certain studies have attributed the poor outcome observed in Asian patients to a possible difference in endometrial receptivity since, in contrast to the pregnancy rate in autologous, fresh IVF cycles, Asian ethnicity was not associated with a lower pregnancy rate in recipients when anonymous donor oocytes were used. However, Asian donors exhibited significantly higher serum oestradiol levels during gonadotropin stimulation, suggesting an ethnic difference in steroid production and/or metabolism (Huddleston et al., 2010). This result is in line with our findings, which suggest an enhanced follicular response to gonadotropins among Asians compared with other ethnicities, as demonstrated by the diminished dose of FSH per retrieved oocyte in Asian patients. This evidence suggests that follicular biology, and specifically granulosa cell function, differs in Asians compared with other ethnicities.

Brazil has a population of approximately 200 million individuals, with a uniquely high degree of admixture, including individuals with different degrees of African, European, Asian and Indian ancestry. In fact, most of the Brazilian population consists of Mestizos, who originated from the free and spontaneous admixture of

Table III. Binary regression analysis of patient race/ethnicity and its effect on the chance of pregnancy and miscarriage.

Response variable	Predictor variable	P	OR	CI: Lower	CI: Upper
Pregnancy	Caucasian	0.474	0.88	0.63	1.24
	Mestizo	0.041	1.34	1.01	1.77
	Asian	0.046	0.82	0.68	0.99
	Black	0.310	1.28	0.80	2.06
	Indian	0.085	1.54	0.92	3.26
Miscarriage	Caucasian	0.900	0.97	0.60	1.58
	Mestizo	0.269	0.64	0.29	1.42
	Asian	0.085	2.11	0.99	4.36
	Black	0.472	0.59	0.14	2.51
	Indian	0.325	0.98	0.96	0.99

OR: odds ratio, CI: Confidence interval. Each race/ethnicity was considered as reference for the regression models.

native Brazilians with White Europeans and Black Africans (IBGE, 2000; Pena et al., 2009).

Our evidence demonstrates that Mestizos have more than a 30% chance of becoming pregnant compared with other ethnicities. This finding raises the question of the benefit of the mixture of races for the success of ART. Epidemiologists around the world are intrigued by such findings and while they are easy to describe, the mystery behind ethnic differences is not easily solved (Bhopal, 2007). One problem is that populations identified by current definitions of race or ethnicity do not often include within-group heterogeneity, diminishing the value of ethnic categorisation.

While considerable evidence from animal studies supports the idea that racial admixture may be beneficial for different aspects of health (Lopez-Villalobos et al., 2000; Freyer et al., 2008; Wayne & vonHoldt, 2012), human studies are rare. Although there is a growing tendency towards the mixing of races around the world, to our knowledge, this is the first report describing the influence of racial admixture on ART outcomes.

Although this study presents promising results, its findings cannot be generalised to the rest of the word. Patients from a specific race in Brazil behave differently than those from the same race in another part of the world. The retrospective design and the differing number of patents in each group are a further limitation of this study as well as the ethnicity of the male partner, which was not recorded.

In conclusion, our evidence suggests a possible beneficial effect of racial admixture on ART outcomes. Fertilisation, embryo development and implantation were increased among the Mestizos population in Brazil, whereas Asian patients exhibited impaired embryo development and clinical outcomes.

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