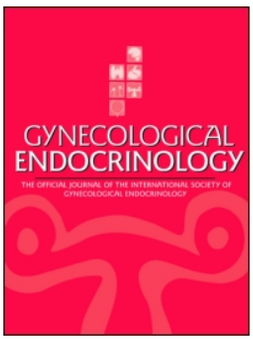

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ORIGINAL ARTICLE

Ethnicity is an independent predictor of IVF-ICSI outcome: a study of 5,549 cycles in Spain and India

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Abstract

Aim: To determine the role of ethnicity on IVF/ICSI outcomes between Indian and white Caucasian women.
Settings and design: Retrospective cohort study.
Materials and methods: White Caucasian and Indian women undergoing IVF/ICSI treatment cycles. Total 5549 self, non-donor, fresh IVF cycles conducted from January 2014 to March 2015, out of which, 4227 were white Caucasian and 1322 were Indian. Data were collected on baseline characteristics, IVF cycle parameters and outcomes. Ongoing pregnancy rate (OPR) was measured as main outcome.
Results: Indian women differed significantly from white Caucasian women in baseline characteristics like age (30.6 ± 0.2 versus 37.6 ± 0.1 years; $p < 0.001$), BMI (22.3 ± 0.2 versus 26.6 ± 1.0 kg/m^2; $p < 0.05$), duration of infertility (6.9 ± 3.0 versus 2.5 ± 0.1 years; $p < 0.001$) and antral follicle count (AFC) (8.9 ± 0.4 versus 7.5 ± 0.2; $p < 0.001$). Indian women had lower implantation rate (30.1% versus 39.6%: $p < 0.001$) and OPR (35.1% versus 41.7%: $p < 0.001$) compared with white Caucasian women. Regression analysis proved independent effect of ethnicity on OPR (OR 0.944; 95% CI 0.928–0.961: $p < 0.001$)
Conclusions: OPR was significantly lower among Indian ethnic group following IVF/ICSI suggest that ethnicity, like age, is a major and an independent predictor of IVF outcome.

Keywords

Ethnicity, ICSI, in vitro fertilization, Indian, white caucasian

History

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Introduction

The relevance of ethnicity and racial disparities are being questioned in all fields of medicine, due to differences in the epidemiology of the diseases and their response to the medical therapy [1,2].

In the field of reproduction, ethnicity has been proven to play a role in many areas like spontaneous miscarriages, preterm birth, low-birth weight [3], gestational diabetes [4], pre-eclampsia [5] and in infertility as well. In ART, basal FSH levels were found to be higher in African–American than in age matched white American women [6,7]. Anti Mullerian Hormone (AMH) levels were found lower in African–American and Hispanic women than in white American women [8]. According to ovarian reserve in infertile population, Indian women age 6 years earlier than white Caucasian women [9]. Steroid hormone production and metabolism are also different according to ethnicity [10].

Ethnicity and racial disparity influence IVF outcomes [11,12]. Being inherent and so non-modifiable, understanding its role and overcoming it by proper strategy to minimize the impact, is the only option. Many studies have found Asian ethnicity to be associated with decreased pregnancy rates and poor IVF outcomes compared to Caucasian [13–15], whereas others have found no difference [16,17]. The decreased pregnancy outcome may be attributed to differences in the ovarian reserve [9], or it may indicate fundamental biological, genetic, nutritional, lifestyle, behavioral or environmental differences in ethnicities.

Ethnicity reporting should be specific and study groups, individually should share similar cultural and environmental conditions to have clear effect of ethnicity on any outcome. Most of the studies till date have included more heterogeneous population like Asian, African–American, Black or White, which is mentioned as one of the limitations of the study [13].

The aim of our study was to determine any effect of ethnicity on IVF outcome by including more homogeneous country based study population, Indian with white Caucasian women.

Materials and methods

We conducted a retrospective cohort study from January 2014 to March 2015, including 4227 and 1322 self, non-donor and fresh stimulated IVF/ICSI cycles performed among white Caucasian and Indian women, respectively, in their respective country. This study received Institutional Review Board approval (1508-MAD-054-JG).

Treatment protocol

Among white Caucasian women, all stimulations were started after cycle scheduling with OC pills or luteal phase estradiol [18]. Among Indian women, stimulations were started on second day of menses, after TVS confirmation of baseline ovaries (no cyst or follicle of >10 mm) and endometrium (<5 mm).

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Among both ethnic groups majority were antagonist cycles, starting with using recombinant FSH (Gonal-F, Serono or Puregon, Organon) or highly purified hMG (Menopur, Ferring) ranging from 150 IU to 450 IU for follicular growth and 0.25 mg of GnRH antagonist (Orgalutran, Organon) on a daily basis was started along with gonadotropin when at least one follicle reached ≥13 mm mean diameter (usually on day 5 or 6 of stimulation). Follicular growth and number were monitored by TVS, as and when required. Recombinant hCG (Ovitrell 250 microgram; Serono) was administered when at least two follicles reached ≥17 mm mean diameter. Blood was withdrawn on the day of trigger for serum estradiol and progesterone measurement. GnRH agonist (Decapeptyl 0.2 mg; Ferring) was given to patients cryopreserving all oocytes/embryos if at risk of Ovarian Hyperstimulation Syndrome (OHSS) (≥15 follicles, ≥15 mm diameter) or in case of elevated progesterone (>1.8 ng/mL). TVS guided oocyte retrieval was performed 36 h later, under sedation. Fertilization was performed by either conventional IVF or ICSI according to semen analysis and quality. At 16 to 18 h after IVF or ICSI, the presence of two pronuclei confirmed fertilization. One or two embryos were transferred on day 3 or day 5 depending on the quantity and quality of the embryos. Luteal support was started with vaginal progesterone suppositories (400 mg) every 12 h starting from the next day of ovum pickup. It was continued till 8 weeks of pregnancy and was suspended with negative pregnancy results. Serum $\beta-$hCG level was checked between 10 and 14 days post-transfer depending on the day of transferred embryo(s) and value >10 IU/L was considered as positive result [pregnancy rate (PR)]. TVS was performed 1 week later to confirm the number, location of the G-sac [Clinical pregnancy] and for fetal cardiac activity 2–3 weeks after positive $\beta-$hCG. Pregnancies with positive $\beta-$hCG but absent G-sac on TVS were considered as biochemical pregnancies.

Comparison of main IVF outcome between white Caucasian and Indian women included ongoing pregnancy rate (OPR). Secondary outcomes included age, BMI (body mass index), type and duration of infertility, AFC, days of stimulation, total gonadotropin dose, estradiol and progesterone level on the day of trigger, total number of oocyte retrieved, number of mature oocyte, fertilization rate, number and day of embryo transfer, PR, implantation rate (IR) and miscarriage rate. IR was calculated by dividing total number of gestational sac visualized in first scan after positive $\beta-$hCG result by the total number of embryos transferred. OPR was calculated by considering all viable intrauterine pregnancy progressing beyond 12 weeks of gestation. Patients of age more than 38 years were included in advanced maternal age group.

Statistical analysis

For quantitative continuous variable *t*-test was used and for categorical variables ANOVA, chi-square test or Z-test were used. All data were reported as mean ±SD. Being a descriptive study; with this sample size we estimated 10% error to estimate the mean of the general population with confidence interval of 95%. Significance was set at p values <0.05. Univariate logistic regression was performed to assess association of ethnicity and other variables to OPR while multivariate regression was performed on all those significant variables to demonstrate independent effect of ethnicity on OPR. SPSS 20.0 (IBM Corporation, Chicago, IL) was used to analyze the data.

Results

A total of 5549 self, non-donor, stimulated IVF cycles were included; 4227 (76.2%) were white Caucasian and 1322 (23.8%) were Indian. Among white Caucasians, the proportion of the antagonist, long-agonist, and short stimulation protocol used were 92.9%, 3.3% and 3.8%, respectively, while among Indians, the proportion were 99.8%, 0.2% and 0.0%, respectively.

Table 1. Baseline characteristics of the study population.

Characteristics	White Caucasian ($n=4227$)	Indian ($n=1322$)	p
Age (years)	37.6 ± 0.1	30.6 ± 0.2	<0.001
BMI (kg/m^2)	22.3 ± 0.2	26.6 ± 1.0	<0.001
Type of infertility			
Primary	68.6 %	68.6%	NS
Secondary	16.4%	31.4%	<0.05
Others	15.1%	0.0%	<0.05
Duration of infertility (years)	2.5 ± 0.2	6.9 ± 3.0	<0.001
AFC	7.5 ± 0.2	8.9 ± 0.4	<0.001

BMI- Body Mass Index
AFC- Antral Follicle Count

Table 2. IVF treatment parameters and outcomes.

Variables	White Caucasian ($n=4227$)	Indian ($n=1322$)	p
Total days of stimulation	11.4 ± 0.9	9.4 ± 0.3	<0.001
Total gonadotropin dose (IU)	1604 ± 25	1923 ± 25	<0.001
Peak Estradiol level (pg/ml)	1587 ± 50	2931 ± 870	<0.001
Progesterone level on the day of trigger (ng/ml)	0.6 ± 0.2	0.8 ± 0.1	NS
Endometrial thickness (mm)	9.9 ± 0.1	9.9 ± 0.1	NS
N° oocytes retrieved	7.9 ± 0.2	13.9 ± 0.4	<0.001
N° of Mature oocytes (MII)	6.5 ± 0.3	10.8 ± 0.4	<0.001
Fertilization rate	85.3%	77.8%	NS
N° of transferred embryos	1.6 ± 0.1	1.9 ± 0.1	<0.001
Day of embryo transfer			
Cleavage stage embryo transfer	51.2%	73.4%	<0.05
Blastocyst Transfer	48.8%	26.6%	<0.05
N° of frozen embryos	3.3 ± 0.2	2.6 ± 0.1	<0.001
Pregnancy rate (PR)	56.5%	45.8%	<0.001
Implantation rate (IR)	39.6%	30.1%	<0.001
Miscarriage rate	27.5%	25.8%	NS
Ongoing pregnancy rate (OPR)	41.7%	35.1%	0.001

Indian women were younger (30.6 ± 0.2 versus 37.6 ± 0.1; $p<0.001$) with high ovarian reserve (AFC) (8.9 ± 0.4 versus 7.5 ± 0.2; $p<0.001$), higher BMI (26.6 ± 1.0 versus 22.3 ± 0.2; $p<0.05$) and had longer duration of infertility (6.9 ± 3.0 years versus 2.5 ± 0.1; $p<0.001$) than White Caucasian women. In Spain, apart from primary and secondary infertility, 15.1% IVF cycles were performed for other reasons, such as desire to become single mother, and in homosexual couples (Table 1).

White Caucasian women were significantly more likely to have male factor infertility, poor responders/advanced maternal age and endometriosis than Indian women. Indian women were significantly more likely to have PCOS and tubal factor infertility (Supplementary Table I).

IVF treatment parameters and outcome demonstrated in Table 2. Indian women had significantly lower PR (45.8% versus 56.5%: $p<0.001$), IR (30.1% versus 39.6%: $p<0.001$) and OPR (35.1% versus 41.7%: $p<0.001$) with similar miscarriage rate (25.8% versus 27.5%; $p=0.269$) compared with white Caucasian women (Supplementary Figure I).

On logistic regression analysis after controlling age, AFC, type of infertility, number and day of the embryo transferred, ethnicity remained the significant predictor of OPR (OR 0.944; 95% CI 0.928–0.961; $p<0.001$) (Table 3).

Table 3. Logistic regression analysis.

Parameters	Odds ratio	95% CI	*p*
Univariate regression analysis			
Ethnicity	0.901	0.840–0.967	0.004
Age	0.908	0.867–0.952	<0.001
BMI (kg/m^2)	1.000	0.961–1.040	NS
Duration of infertility	0.985	0.924–1.049	NS
Type of infertility	1.405	1.035–1.097	0.029
Male etiology	0.977	0.953–1.001	NS
Female etiology	1.053	0.998–1.110	NS
Type of protocol	1.039	0.976–1.103	NS
AFC	1.026	1.006–1.046	0.010
Peak estradiol level	1.000	0.961–1.000	NS
Progesterone level on the day of trigger	0.894	0.660-1.212	NS
Oocyte retrieved	0.968	0.932–1.005	NS
N° of Transferred embryos	1.926	1.325–2.799	0.001
Day of embryo transfer	1.172	1.085–1.265	<0.001
Multivariate analysis of all the significant variables of univariate analysis			
Ethnicity	0.944	0.928-0.961	<0.001
Age	0.912	0.880-0.944	<0.001
Type of infertility	1.093	0.936-1.276	NS
AFC	1.093	0.936-1.276	NS
N° of Transferred embryos	1.521	1.165-1.985	0.002
Day of embryo transfer	1.136	1.001-1.289	0.048

BMI- Body Mass Index
AFC- Antral Follicle Count

Discussion

These results demonstrate significant ethnic disparity in IVF outcome even after controlling every possible confounder. Asian ethnicity has lower IVF outcomes as compared to Caucasian counterpart have been proven in previous publications. Jayaprakasan et al. [14] reported a lower IR, PR and LBR (live birth rate) in ethnic minority group as compared to white European women. This study included a more heterogeneous group from South-East Asians, Middle-East Asians and African-Carribeans. Purcell et al. [13] reported lower Clinical PR and LBR in Asian compared with Caucasian women. Asians had tendency to try for a longer duration of time, before presenting for IVF treatment, which resulted in lower pregnancy rates [17].

Differences in the duration of infertility were found significant. The Indian women wait for a longer duration for natural conception or other infertility treatment, despite of the absolute indication of infertility. This tendency factor of Asian women has been put forward in various studies [16,17]. Hence, Indian women should be counseled, and encouraged to seek IVF treatment considering their age, ovarian reserve [9], duration and etiology of infertility.

Despite of having younger age than white Caucasian women, Indian women needed higher gonadotropin dose for ovarian stimulation, which can be explained by higher BMI. The need for higher gonadotropin dose can rarely be explained by FSH-receptor gene polymorphism, which varies in different ethnicities [19], but adequate research are still needed. High gonadotropin dose was an independent negative predictor ($p = 0.016$) of endometrial thickness and thus responsible for poor IVF outcome [20]. But we have comparable endometrial thickness between both the groups.

Despite having higher BMI among Indian women, our multivariate analysis controlled for BMI have found no impact on OPR. Bellever et al. [21], in his study of 6500 IVF cycles have found poorer IR, PR, live birth rate and cumulative PR after four IVF cycles in obese women than lower BMI women with comparable fertilization rate and embryo quality, while other investigator have found no effect of BMI on IVF outcome [22].

Comparatively higher Estradiol levels in Indian women may be explained by younger age, higher AFC (higher incidence of PCOS), higher gonadotropin dose used in present study or it may be just an ethnic difference in steroidogenesis or its metabolism. Various investigators have found higher estradiol levels in Asian women after ovarian stimulation for IVF [10,13]. Previously many studies were showing its effect on implantation rate due to detrimental effect on endometrial receptivity [23,24]. But recent publications suggest that the optimum safe level of estradiol is 3000–4000 pg/ml during stimulation, in patients <38 years [25]. So, in Indian women, in present study, higher estradiol level (2931 ± 870 pg/ml) should not have any effect on outcome.

The probability of IVF success increases by transferring more number of embryos [26]. Our results show poor outcome in Indian women, even after transferring higher number of embryos (1.9 versus 1.6; $p < 0.001$), which may be explained by more blastocysts transfer in white Caucasian women ($p < 0.05$). As blastocyst transfer has better IVF outcome compared with cleavage stage embryo transfer [27]. Though we have not included embryo quality in present study, Shahine et al. [15] concluded poor IVF outcome among Asian women even after controlling embryo quality.

The limitation of our study is that the population is strongly biased for two factors – Age, that drives all the rest of the parameters, and the lab quality, that may have an impact on the IVF results. However, both labs follow similar protocols and the regression analysis reinforces the ethnicity issue. As a drawback of retrospective study, we were unable to control unknown confounders. The recall and the collection biases would be minimal as data were entered prospectively. We have included self-IVF cycles; hence, individual patients might be counted more than once. Some facts might affect IVF outcomes are: 1) More blastocyst transfers among white Caucasian compared with Indian women (48% versus 26.6%). 2) Advanced maternal age being one of the main indications for IVF among Caucasian women, PGS (Pre-implantation Genetic Screening) was performed in higher proportion compared with Indian women (10.4% versus 6.2%).

This study has a major strength of comparing large and more homogenous ethnic groups based on their country of origin, than prior publications over ethnicity. Homogenous ethnic group have an advantage of sharing similar genetic, environmental, nutritional, cultural and behavioral factors. Though both the group had been treated in different IVF clinics, both clinics follow almost same IVF treatment protocol.

We conclude that, ethnicity, like age, is a major and an independent predictor of IVF outcome as despite of having two major factors in favor (younger age and higher antral follicle count), Indian ethnic group had poor IVF outcome. Indian women have an inherited and non-modifiable drawback of ethnicity and thus having low IVF success rate over white Caucasian women. Ethnicity and early ovarian aging cannot be changed, thus Indian women should be counseled about it and to avoid prolonging duration of infertility.

Declaration of interest

The authors declare that they have no conflicts of interest.

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Supplementary material available online