Differences in ovarian function parameters between Chinese and Caucasian oocyte donors: do they offer an explanation for lower IVF pregnancy rates in Chinese women?

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BACKGROUND: IVF outcomes in Chinese women are inferior to those of Caucasian patients. Reflecting prematurely diminished ovarian function, women with elevated age-specific baseline (b-) FSH levels are designated to suffer from premature ovarian aging (POA). We investigated if the prevalence of POA differs between these two ethnic populations. METHODS: We compared patient characteristics and first IVF cycle outcomes in 29 consecutive, Caucasian and 17 Asian-Chinese oocyte donors. POA was diagnosed in a donor if her b-FSH levels exceeded the 95% confidence interval (CI) for her age group. RESULTS: There was no age difference between Chinese and Caucasian groups (26.2 ± 4.9 versus 25.7 ± 3.1 years, respectively). Chinese women demonstrated, however, a higher cycle cancellation rate (5/17, 29.4%) either before cycle start or during stimulation (0/29; relative risk 1.42, 95% CI 1.04–1.9; P < 0.01), fewer oocytes per initiated cycle (9.3 ± 9.7 versus 15.3 ± 7.1, respectively; P < 0.05) (difference disappeared for only cycles that reached retrieval) and higher b-FSH levels (7.5 ± 1.9 versus 5.1 ± 1.7 mIU/ml, respectively; P = 0.004). Nine out of 17 (53%) of Chinese and only 1/26 (4%) of Caucasian donors met b-FSH level criteria for a presumptive POA diagnosis. Their odds of meeting POA criteria were approximately 30-times greater (odds ratio 31.5; 95% CI 3.5–18.7; P < 0.0001). CONCLUSIONS: These data suggest a possible explanation for lower IVF pregnancy rates in Chinese women. Preceding treatment, Chinese women at all ages should be carefully investigated to detect occult POA. Ethnicity may have to be considered an additional outcome variable in fertility studies.

Keywords: fertility treatment; IVF; ethnicity; race; pregnancy rates

Introduction

In contrast to much of medicine, in infertility race and/or ethnicity have attracted only limited attention. Diagnosis and treatment outcomes have historically been evaluated independent of ethnic and/or racial considerations. This is actually somewhat surprising because considerable published evidence suggests ethnic/racial differences, which could be expected to have significant impact. For example, Asian women demonstrate a different (milder) polycystic ovary syndrome phenotype than Caucasian and African-American women (Legro et al., 2006) and the prevalence of premature ovarian failure (POF) varies with ethnicity (Luborsky et al., 2003). Menopausal status and symptoms differ, as well (Avis et al., 2001). Caucasian women with diminished ovarian reserve conceive with much higher probability than other races (Greenseid et al., 2006) and black women seem to exhibit a different level of end organ sensitivity to estrogen than white women (Montgomery et al., 2006; Alvero et al., 2006), although Caucasian women appear to produce more follicles (Montgomery et al., 2006). A genetic background to reproductive fitness was recently also reported in Hutterites (Pluzhnikov et al., 2007).

Maybe the most clinically relevant data refer, however, to IVF outcomes: three recent studies reported that women of Asian and African-American descent experience significantly lower IVF pregnancy rates than Caucasians, although the authors were unable to pinpoint causes for these findings (Grainger et al., 2004; Purcell et al., 2004, 2007). Among these studies, Grainger’s report was based on data from the national IVF registry and, therefore, involved a very large national sample (Grainger et al., 2004). Purcell’s initial study, in turn, presented a large sample size, of mostly Chinese women, from a single medical center (Purcell et al., 2004).
These two studies were alarming enough to warrant in 2006, as part of an ongoing quality assurance program at our center, a first stratified review of IVF outcomes, which was based on ethnicity/race. To our surprise, the data confirmed significantly lower clinical pregnancy rates in minority patients of Asian-Chinese and African-American descent under age 38 years (N. Gleicher and D. Barad, unpublished data).

Since IVF protocols had always been administered uniformly, and independent of ethnic background, these findings were unexplained. We, therefore, decided to further investigate possible causes.

Purcell’s initial study of a large Chinese population (Purcell et al., 2004) and her more recent study in cooperation with Grainger, including additional data (Purcell et al., 2007), had been unable to detect differences in ovarian function between infertile Caucasian and Chinese women. We, however, in contrast to these authors, decided to investigate ovarian function in an unbiased patient population. This study, therefore, reports on the ovarian function of carefully prescreened Caucasian and Chinese oocyte donors, suggesting that inferior IVF outcomes in Chinese women may be a reflection of more frequent changes in ovarian function, which can be interpreted as premature ovarian aging (POA).

Materials and Methods

In an attempt to compare ovarian function, first oocyte donation cycles of 29 consecutive Caucasian and 17 Asian-Chinese oocyte donors, undergoing cycle stimulation during 2004–2005, were analyzed for patient parameters [baseline (b)-FSH at cycle days two-third and peak estradiol (E2) levels] and IVF cycle outcome parameters (cycle cancellations and numbers of oocytes retrieved).

Donors in both groups were also evaluated for occult evidence of POA. POA was assumed to be present if the donor’s b-FSH level exceeded the 95% confidence interval (CI) of b-FSH for her age group, as previously reported (Barad et al., 2007).

In our IVF program, selection processes and donor fees of Caucasian and Chinese oocyte donors are identical, except for the fact that many of the procedural steps for Chinese donors involve Chinese-speaking translators. All donors undergo a four-step selection process, involving a detailed medical questionnaire, two face-to-face interviews and a medical testing round.

Until early 2006, for women of all ages, the b-FSH levels for oocyte donors were considered to be normal up to a cut off value of 10 mIU/ml. Donor candidates with b-FSH levels above 9.0 mIU/ml were, nevertheless, not accepted into the program. We became aware of the significance of age-specific b-FSH levels only in 2006 (Barad et al., 2007), when we started integrating this knowledge into the selection of oocyte donors. In order to prevent selection biases, we, therefore, did not include oocyte donors selected for cycles during 2006 into the study reported here.

Oocyte donors also receive identical stimulation protocols, which involve long agonist down regulation, followed (based on age) by 150–300 IU of gonadotrophin stimulation [either all human menopausal gonadotrophin (HMG) or half HMG/FSH].

Outcomes were compared between the groups by univariate analysis, using $\chi^2$ and Fisher’s exact test, where applicable. The Statistical Package for the Social Sciences, version 15 was used for statistical calculations. Continuous variables are expressed as mean ± SD. A value of $P < 0.05$ was considered significant.

Discussion

As one would expect, mean ages of the two patient groups were statistically similar, with Chinese patients being 26.2 ± 4.9 and Caucasians 25.7 ± 3.1 years old. In comparing IVF cycle outcomes between 29 Caucasian and 17 Asian-Chinese oocyte donors, a number of issues have to be clarified in order to understand the analysis properly: among 17 Asian-Chinese oocyte donors, who were initially accepted into the donor pool, three were disqualified once their b-FSH levels had been obtained at cycle start and were found to be abnormal ($\geq 10$ mIU/ml) (Fig. 1). An additional two donors did not reach oocyte retrieval because their cycles were cancelled for poor response to stimulation. Combined, a total of 5/17 (29.4%) Asian-Chinese donors, who had initially been accepted into the donor pool and had been tentatively matched with a recipient, thus failed to reach retrieval. In contrast, all 29 Caucasian donors, tentatively matched, reached retrieval (relative risk 1.42; 95% CI 1.04–1.9; $P < 0.01$).

Univariate analysis, coding cancelled cycles with zero oocytes retrieved, demonstrated, as one would expect, significantly fewer oocytes in Chinese donors (9.3 ± 9.7 versus 15.3 ± 7.1; $P < 0.05$). However, this difference lost statistical significance when cycle outcomes were compared for cycles that reached retrieval (15.3 ± 7.1 versus 13.3 ± 8.9) (Table 1).

As the table also demonstrates, Chinese donors demonstrated significantly higher baseline FSH levels (7.5 ± 1.9 versus 5.1 ± 1.7 mIU/ml; $P = 0.004$). This difference remained marginally significant ($P < 0.05$), even when two Chinese outliers with FSH levels above 15 mIU/ml (Fig. 1) were removed from the analysis. Peak E2 levels, shown in Table 1, refer only to cycles that reached retrieval. The very similar levels are, therefore, not surprising. The table also summarizes additional IVF cycle outcome data, which did not differ statistically between the groups.

A diagnosis of POA was reached in 9/17 (52.9%) Chinese and in only 1/26 (3.9%) Caucasian donors. The odds of POA diagnosis were thus approximately 30-times greater in Chinese than in Caucasian oocyte donors (odds ratio 31.5; 95% CI 3.5–187; $P < 0.0001$).

Results

Since this study involved the retrospective analysis of IVF cycles, permitted by the universal informed consent of the center, special approval by the institutional review board for this study was not required.
Their ovarian reserve appeared obviously diminished, reflected in statistically higher b-FSH levels and a higher cycle cancellation rate. Since Chinese donors did not differ in age from their Caucasian controls, these observations suggest that a statistically significantly greater proportion of Asian-Chinese oocyte donors demonstrate evidence of POA.

When we tested this hypothesis by defining POA, as recently reported, by b-FSH levels exceeding the 95% CI of age-appropriate b-FSH levels (Barad et al., 2007), this interpretation of results was confirmed in a statistically very significant way. Indeed, Chinese donors had more than 30-times the risk of POA in comparison with their Caucasian counterparts.

These data appear superficially contradictory to those of Purcell, who in routine Chinese IVF patients were unable to demonstrate differences in b-FSH levels in comparison with Caucasian controls (Purcell et al., 2004, 2007). On closer consideration, however, it becomes apparent that their data, indeed, do not contradict the interpretation of our data at all: in Purcell’s two reports, two infertile patient populations were compared. In such patients, ovarian function abnormalities can be expected. In other words, Purcell’s Chinese and Caucasian control patients represent a similarly chosen patient population, biased toward abnormal ovarian function. It, therefore, should not surprise when their ovarian function tests are similar.

In contrast, carefully prescreened oocyte donors are believed to represent young females with normal ovarian function. They inherently, like the Caucasian control group in our study so well demonstrates (Fig. 1), should include no (or an only very small number of) women with even occult diminished ovarian reserve (POA). Yet, in such patients our study demonstrates a statistically very significant increase in ovarian function abnormalities in Chinese women, suggesting that ovarian aging curves in Chinese women differ from those in average Caucasian women.

Studies in mostly Caucasian populations have suggested that POA occurs in ~10% of the female population (Nikolaou and Templeton, 2003). Whether this prevalence differs in Chinese women (and other ethnicities) has previously not been investigated, although POF is not more frequently diagnosed in Chinese and other women of Asian ethnicity. POF, indeed, appears the highest in African, Hispanic and Caucasian women (Luborsky et al., 2003). POF, however, has to be differentiated from POA and these two conditions may not be interchangeable in their etiology (Nikolaou and Templeton, 2003; Gleicher, 2005).

Considerable evidence in the literature supports that ethnicity/race, and genetics, may affect reproductive processes (Luborsky et al., 2003; Alvero et al., 2006; Greenseid et al., 2006; Legro et al., 2006; Montgomery et al., 2006; Pluzhnikov et al., 2007). This study suggests that at least part of these differences may be due to differences in the physiologic ovarian aging process. In view of Purcell’s rather convincing outcome data in Chinese women (Purcell et al., 2007), and the here presented oocyte donor data, suggesting a higher than normal POA prevalence in Chinese women, ovarian function in Chinese women, whether oocyte donors or infertility patients, should probably be assessed more carefully.

**Table 1: Univariate analysis of patient characteristics and outcomes for oocyte donors**

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th>Asian-Chinese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>29</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.7 ± 3.1</td>
<td>26.2 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline FSH (mIU/ml)</td>
<td>5.1 ± 1.7</td>
<td>7.5 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH criteria for POA (%)</td>
<td>1 (3.5)</td>
<td>9 (52.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Estradiol peak (pg/dl)b</td>
<td>3069.2 ± 1723.1</td>
<td>3192.3 ± 1643.8</td>
<td>NS</td>
</tr>
<tr>
<td>Oocytes/cycle start (mean ± SD)</td>
<td>15.3 ± 7.1</td>
<td>13.3 ± 8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Fertilization rate (%)b</td>
<td>67</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos transferredb</td>
<td>1.8 ± 0.3</td>
<td>1.9 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancies (%)b</td>
<td>15/29 (51.7)</td>
<td>6/12 (50.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Twin pregnancies (%)</td>
<td>4/15 (26.7)</td>
<td>1/6 (16.7)</td>
<td>NS</td>
</tr>
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</table>

*a* A diagnosis of POA was reached if the b-FSH level exceeded the 95% CI of b-FSH levels for the age group. Only one donor in each group had experienced a prior pregnancy. None had given birth.

*b* Includes only cycles reaching oocyte retrieval.
In our program, this now means that even young Chinese women are automatically screened with regard to age-specific b-FSH values, as previously reported (Barad et al., 2007). Studies are currently underway to assess whether the addition of age-specific anti-Müllerian hormone levels may further improve the detection of occult POA.

As part of this continuous quality improvement investigation, we have also compared the prevalence of aneuploidy in embryos from Chinese and Caucasian patients and were unable to note significant differences (N. Gleicher and D. Barad, unpublished data). This finding is supportive of the above-suggested POA etiology for poorer IVF outcomes in Chinese women, since POA patients, in general, demonstrate normal age-specific aneuploidy rates (Weghofer et al., 2007).

The observation that IVF pregnancy rates in minority populations are inferior to those in Caucasian women, initially made by Grainger and Purcell (Grainger et al., 2004; Purcell et al., 2004), may, therefore, not be IVF-specific. Instead, it may represent an inherently enhanced decrease in female fecundity with advancing age, which is also reflected in IVF outcomes. This suggestion is supported by recent data by Greensseed et al. (2006) who demonstrated that, among women with uniformly diminished ovarian reserve, Caucasian women demonstrated significantly higher IVF pregnancy rates than minority patients. Women with POA traditionally demonstrate poor IVF outcomes, if treated based on their chronological, rather than their ovarian, age (Kumbak et al., 2005; Gleicher and Barad, 2006).

Bamshad (2005) recently explained well why race matters in regards to health issues. As he noted, ‘making accurate ancestry inferences is crucial because common diseases and drug responses are sometimes influenced by gene variants that vary in frequency, or differ altogether, amongst racial groups’. Our study offers further evidence for a racially based impact on female fertility treatments. Although our data suggest that this impact may be due to differences in the prevalence of POA between minority and Caucasian women, this study does not have the statistical power to reach final conclusions. Instead, it adds to a rapidly accumulating volume of data which suggest that, like in other areas of medicine, ethnicity/race-based observations should be included in the reporting of female fertility-related studies.

An evolving consensus on race/ethnicity-based infertility outcome data, of course, raises serious questions. To begin with, it calls for a review of published data, which may turn out to be unwittingly biased, based on the patient populations they involved, or excluded. It, however, also points toward an immediate need to include ethnicity and/or race as an additional variable which may affect outcome to future fertility-based study. As Bamshad (2005) suggested, ‘race and ancestry of infertility patients should be noted in detail and with accuracy’.

Purcell et al. (2007) added to that by suggesting that this should be done for both parents.

Funding
Supported in part by the Foundation for Reproductive Medicine, a no-for-profit research foundation.

References

Submitted on May 2, 2007; resubmitted on August 2, 2007; accepted on August 15, 2007.