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Exploratory cohort study into underlying mechanism of differences in estrogen metabolism between Asian and Caucasian women during assisted reproductive technology treatment

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Objective: Explore whether racial differences in prevalence of CYP1A2*1F polymorphism underlies estrogen metabolism differences among Asians and Caucasians.
Design: Prospective cohort study.
Setting: University-based fertility practice.
Patient(s): Asian or Caucasian patients who underwent ovarian stimulation (OS) or programmed cycle frozen embryo transfer (FET) between October 2019 and April 2021.
Intervention(s): None.
Main Outcome Measure(s): Trigger-day serum E2 per oocyte retrieved in OS cycles, and E2 on day of lining check in FET cycles.
Result(s): Seventy-one participants were enrolled, 55 in OS group (29 Caucasian and 26 Asian) and 16 in FET group (10 Caucasian and 6 Asian). Peak E2 per oocyte retrieved in the OS group (n = 48) differed by race, with significantly lower levels in Caucasians compared with Asians (177.5 ± 64.2 vs. 261.1 ± 139.5 pg/mL). Prevalence of CYP1A2*1F polymorphism did not significantly differ by race. Compared using Kruskal–Wallis test, peak E2 per oocyte retrieved did not differ by CYP1A2*1F genotype. In multivariate linear regression model, adjusting for body mass index, caffeine intake, and self-reported race, there remained no significant correlation. In FET group, serum E2 on day of lining check was also not significantly different by CYP1A2*1F genotype.
Conclusion(s): Although a consistent difference in serum E2 between Asians and Caucasians undergoing OS was noted, the CYP1A2*1F polymorphism is unlikely the primary driver of this difference. (Fertil Steril Rep® 2023;4:396–401. ©2023 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technologies, CYP1A2*1F, estrogen metabolism, racial disparity

Racial disparities in pregnancy and live birth outcomes from assisted reproductive technologies (ART) have been demonstrated in several studies (1–5). Although there has been much focus on differences in outcomes between Black and Caucasian women, similar disparities exist for Asian women as well. In a review of Society for Assisted Reproductive Technology data from 2014 to 2016, Kotlyar et al. (6) demonstrated a significantly lower pregnancy and live birth rate among Asian and Hispanic women compared with non-Hispanic Caucasian women. In a study combining Society for Assisted Reproductive Technology data with additional data from a single fertility clinic center, Purcell et al. (1) demonstrated that Asian women had nearly 30% lower clinical pregnancy rate when compared with Caucasian women. Surprisingly, the study noted Asian participants had a significantly

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higher estradiol (E2) level on day of trigger (2,740 vs. 2,383 pg/dL; $P < .01$), despite no significant differences in baseline demographic characteristics (1). A study of over 200 oocyte donors from the same institution confirmed a pattern of significantly elevated peak E2 levels in Asian compared with Caucasian donors during ovarian stimulation (OS), both before and after adjusting for total follicle number and oocytes retrieved (7). Furthermore, in a 2011 single-center study, Asian and Caucasian women used the same dose of transdermal E2 for frozen embryo transfer (FET) preparation, but Asian women had 62% higher serum E2 levels after adjusting for age, body mass index (BMI), and cycle day of measurement ($P = .0004$). These data suggested that variations in steroid metabolism, rather than production, may underly the racial difference seen in serum E2 levels during ART treatment (8). The hormonal milieu at the time of embryo transfer is critically important to the success of an ART cycle and it is possible that endogenous hormonal differences may play a role in some of the noted racial disparities in outcomes. However, to date, the reasons for differences in E2 levels between Asian and Caucasian women has rarely been explored.

Estradiol is metabolized through 2 main pathways: conjugation with sulfate or glucuronide, or hydroxylation by various cytochrome P450 (CYP) enzymes (9). Data on racial differences in E2 conjugation are limited, showing some evidence of differential expression of Arg213His polymorphism of sulfotransferase 1A1 between Asian and Caucasian women (10, 11). However, this polymorphism imparts lower enzymatic activity and had higher prevalence in Caucasian populations (11), which is the opposite relationship to that required to explain the lower serum E2 observed in Caucasian compared with Asian women during ART treatment. On the other hand, there are ample data on racial differences in prevalence of CYP polymorphisms (12–17). Specifically, CYP1A2 has been identified to have single-nucleotide polymorphisms with differential prevalence in Asian compared with Caucasian populations (13, 16, 17), and Lurie et al. (13) demonstrated that possession of the *CYP1A2*1F* genotype (A → C) was associated with 26% lower mean serum E2 levels (13).

The objective of this study was to explore whether differences in CYP1A2 may underlie differences in estrogen metabolism among Asian and Caucasian women during ART treatment. We hypothesized that Caucasians would have a higher prevalence of the CYP1A2*1F polymorphism, and those with the CYP1A2*1F variant have significantly lower serum E2 levels during ART treatment. We aimed to evaluate our hypothesis by first reproducing previously noted differences in E2 levels during ART treatment by race, then assessing for a correlation between Caucasian or Asian race and possession of CYP1A2*1F polymorphism, and finally evaluating the relationship between possession of CYP1A2*1F polymorphism and serum E2 levels during ART treatment.

MATERIAL AND METHODS

Study Design and Population

This was a prospective cohort study of patients undergoing ART treatment with OS or programmed cycle FET at the University of California, San Francisco between October 2019 and April 2021. This study was approved by the University of California, San Francisco Institutional Review Board (IRB #19-27418).

Eligible participants were self-reported Asian or Caucasian patients, starting treatment with either OS for in vitro fertilization or oocyte cryopreservation, or programmed cycle FET. All OS participants utilized a GnRH antagonist protocol with gonadotropin dosing as determined appropriate by physician on the basis of age, antral follicle count (AFC), and BMI. Exclusion criteria comprised patients taking aromatase inhibitors because of its effect on serum E2 levels, and those with diminished ovarian reserve defined as AFC <7 or anti-mullerian hormone <1.1 ng/mL. All programmed cycle FET participants utilized a standard protocol of 3 E2 transdermal patches (0.1 mg/24 h each) changed every 72 hours, starting from cycle day 1.

Participant recruitment occurred through study flyers or physician referrals within the clinic, and through in-person communication at time of baseline appointments for OS or FET start.

Participants' informed consent was obtained in person. Each subject consented to review of medical records as well as collection of blood.

Participant Cycle Data

Demographic data were obtained through review of medical records after enrollment. Data obtained included age at the time of enrollment, AFC, BMI, self-reported race, current smoking status, and daily caffeine use (cups/d).

Per clinic protocol, in the OS group, starting doses of stimulation medication were based on patient AFC, anti-mullerian hormone level, and BMI. Dosing adjustments were made per physician discretion at clinic appointments which occurred every 1–3 days. Maximum daily dosing of gonadotropin was generally 450 IU per day. Treatment cycle data including downregulation type, stimulation protocol, total gonadotropin dose used, number of follicles >13 mm on trigger day, total stimulation days, and oocytes retrieved were collected from patient charts after completion of oocyte retrieval procedure.

In the programmed cycle FET group, treatment cycle data including days of E2 use, progesterone level, and lining thickness were collected on day of lining check, before start of progesterone in oil intramuscular injections. All programmed FET participants were started on cycle day 1 with 3 (0.1 mg/24 h) E2 transdermal patches, which were exchanged every 3rd day until lining check ultrasound was completed on cycle day 12–24. For women who did not achieve an adequate endometrial thickness at the first lining check, additional measures may have been taken (e.g., additional E2 supplementation, aspirin, etc.); however, only data associated with the first lining check were used as part of this analysis.

Sample Collection

For the OS group, 1 mL peripheral blood samples were collected from participants in a sodium heparinized (green top) tube at baseline visit (stimulation day 0) and trigger day (stimulation day 9–12) appointments to complete same

day evaluation of serum E2 level. An additional 3 mL peripheral blood sample was collected from participants in an ethylenediaminetetraacetate acid (lavender top) tube on trigger day and then refrigerated at 4 °C for use in genotyping within 1 week of collection.

For the programmed cycle FET group, both the 1 mL peripheral blood sample in a green top tube and 3 mL peripheral blood sample in a lavender top tube were collected from participants on lining check day (~cycle day 12–24). Samples were processed on the same day for serum E2 and refrigerated at 4 °C for genotyping, respectively.

Serum E2 Measurement. Serum E2 levels were analyzed by a commercially available, automated electrochemiluminesence immunoassay using the Roche Cobas E411 (Roche Diagnostics, Indianapolis, IN). Each assay was run with 3 controls of low, medium, and high concentrations. Serial dilutions were performed in cases where E2 levels were above the calibrated range. The inter-assay coefficient of variation was 2.12%. All serum E2 levels are reported as pg/mL.

Trigger day serum E2 levels in the OS group were normalized by the number of oocytes retrieved. Although total follicular load may account for some variation in E2 levels, most of the E2 production is expected from mature follicles. As patients were fertilized with either conventional insemination or intracytoplasmic sperm injection, not every participant had data on oocyte maturity. Thus, normalization by number of oocytes retrieved was an approximation of maturity. No normalization was necessary for the programmed cycle FET group, as the transdermal E2 reaches a steady state concentration of E2 in 12–84 hours after application (18).

Detection of CYP1A2*1F Polymorphism

Genomic DNA was isolated from blood using DNA extraction kit from Qiagen (Germantown, MD) and genotyped using single TaqMan probe for rs762551 purchased from Thermo Fisher Scientific (Waltham, MA) catalog number 4362691. The Applied Biosystems Genotyping Analysis Module hosted on Thermo Fisher Scientific cloud was used to analyze the experimental data to identify the genotypes and classify specimen in possession of the CYP1A2*1F polymorphism.

Statistics

Student's *t*-test, Mann–Whitney U test, or Chi-square test was applied, as appropriate, to compare baseline characteristics between Asian and Caucasian participants in each study group. Differences in the distributions of CYP1A2*1F polymorphism by race was determined using Chi-squared test. Association between the primary predictor variable of CYP1A2*1F polymorphism and outcome variable of serum E2 was evaluated with Kruskal–Wallis test for each of the OS and programmed cycle FET groups. CYP1A2*1F genotype relationship to phenotype of serum E2 was assessed by recessive and dominant model using Mann–Whitney U test for each of the OS and programmed cycle FET groups. Finally, a multivariate linear regression model was employed to adjust for covariates with strong biologic plausibility, including BMI, smoking status, caffeine intake, and self-reported race. Stata, version 15.1, was used for all statistical analyses.

Power Analysis

We determined our recruitment goal to be 70 women on the basis of data from the study by Lurie et al. (13). Utilizing a recessive model to define the CYP1A2*1F group, Lurie et al. (13) found a mean E2 of 97.3 pg/mL in the variant group and 129.4 pg/mL in the non-variant group. Setting a desired power of 80%, with alpha of 0.05, and effect size of 32.1 pg/mL, it was determined that at least 14 women with the CYP1A2*1F variant would be necessary to find a significant difference in serum E2 levels. To attempt and evaluate an equal number (n = 7) of Asian and Caucasian patients with the variant, utilizing the CYP1A2*1F prevalence of 22% in Caucasian women and 27% in Asian women ($P = .07$) reported in the study by Lurie et al. (13), we determined that 32 Caucasian and 26 Asian women would be needed. Accounting for an estimated 20% drop out rate, we aimed to recruit 38 Caucasian and 32 Asian participants.

RESULTS

Population Baseline Data

A total of 235 patients were screened for eligibility in the OS group and 64 were screened in the FET group. In OS group, 123 candidates were deemed ineligible on the basis of diminished ovarian reserve or use of aromatase inhibitor, 28 who were screened eligible could not be reached before cycle start, and 27 candidates declined participation after being approached. In the FET group, 38 candidates were deemed ineligible on the basis of natural cycle protocol or aromatase inhibitor use, 4 who were screened eligible could not be reached before cycle start, and 6 declined participation after being approached.

A total of 71 participants were enrolled in the study, 55 in the OS group (29 Caucasian and 26 Asian) and 16 in the FET group (10 Caucasian and 6 Asian). In the OS group, 48 of 55 participants completed specimen collection. Of the 7 who did not complete collection, 6 were because of cancelled stimulation cycles and 1 was because of missed blood collection resulting from early than expected trigger. All participants in the FET group completed specimen collection. Comparison of baseline demographics for those who did and did not complete specimen collection found no significant differences in demographics. Demographic data are summarized in Table 1. Notably, in the OS group, baseline AFC was significantly higher in Caucasian (median 22, interquartile range 18–34) compared with Asian participants (median 18, interquartile range 12, 25).

In the OS group, participants' baseline E2 level was compared by type of downregulation (none, birth control, E2 patch 0.1 mg/24 h) utilizing Kruskal–Wallis test. Results showed no significant differences in participant baseline E2 level by type of downregulation (46.9 vs. 38.5 vs. 49.1 pg/mL, $P = .292$). This normalization of E2 was likely because of baseline visit occurring approximately 5 days after the last dose of birth control pills. Trigger day E2 per oocyte

TABLE 1

Participant demographic data.

Demographics	Ovarian stimulation group (n = 48) Asian (n = 23)	Ovarian stimulation group (n = 48) Caucasian (n = 25)	*P* value	Programmed FET group (n = 16) Asian (n = 7)	Programmed FET group (n = 16) Caucasian (n = 9)	*P* value
Age (y) Mean ± SD	36.0 ± 4.1	34.2 ± 3.9	.142[a]	36.9 ± 2.9	40.1 ± 3.9	.085[a]
AFC Median (IQR)	18 (12, 25)	22 (18, 34)	.042[b]	n/a	n/a	n/a
BMI (kg/m^2) Median (IQR)	21.4 (19, 23)	21.4 (20, 27)	.164[b]	23.2 ± 4.1	26.5 ± 9.1	.491[b]
Current smoker	0	0	–	0 (0%)	1 (11%)	–
Caffeine user (≥1 cup/day)	16 (70%)	21 (84%)	.171[c]	5 (71%)	7 (78%)	.771[c]

AFC = antral follicle count; BMI = body mass index; IQR = interquartile range.
[a] Student's *t*-test.
[b] Mann–Whitney U test.
[c] Chi-squared test.

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retrieved in the OS group (n = 48) differed significantly by race, with higher levels in Asians compared with Caucasian participants (261.1 ± 139.5 vs. 177.5 ± 64.2 pg/mL, *P* = .021) (Table 2). This racial difference in E2 per oocyte retrieved persisted in a multivariate linear regression adjusting for covariates of number of stimulation days, number of follicles >13 mm, total gonadotropin dose, and BMI (*P* = .032).

In the programmed FET group (n = 16), however, E2 on day of lining check was not found to differ by race (246.1 ± 134.5 vs. 230.8 ± 98.4 pg/mL, *P* = .958) (Table 2), possibly attributable to small sample size.

CYP1A2 Genotype by Race

In this study cohort, prevalence of the CYP1A2*1F polymorphism was not found to differ significantly by race (Table 2). The allelic frequency of the CYP1A2*1F polymorphism (A→C) was 32% (n = 34) in Caucasian participants and 42% (n = 30) in Asian participants (Table 2) (*P* = .2414).

Serum E2 by CYP1A2 Genotype

Treatment cycle data for the OS group are summarized by genotype in Table 3 and cycle data for the programmed FET group are summarized by genotype in Table 4. When compared using Kruskal–Wallis test, peak E2 per oocyte collected was not significantly different by CYP1A2*1F genotype (Table 3), and E2 on day of lining check was also not significantly different by CYP1A2*1F genotype (Table 4).

Evaluation of the recessive genetic model (grouped wild-type AA with heterozygous AC genotype [n = 42] to compare with variant CC genotype [n = 6]), found no difference in E2 per oocyte collected (217.9 ± 110.7 vs. 207.8 ± 140.5 pg/mL, *P* = .588). There was only 1 participant in the programmed

TABLE 2

Participant genotype and cycle data by race.

	Asian	Caucasian	*P* value
CYP1A2*1F genotype	n = 30	n = 34	.490[c]
AA (n = 24)	9 (30%)	15 (44%)	
AC (n = 33)	17 (57%)	16 (47%)	
CC (n = 7)	4 (13%)	3 (9%)	
Allele frequency of "C"	25/60 (42%)	22/68 (32%)	.241[d]
OS group	n = 23	n = 25	
Days of stimulation	12.0 ± 1.7	12.2 ± 2.4	.836[a]
Follicles >13 mm	9.2 ± 6.8	9.6 ± 4.4	.818[a]
Peak E2 per oocyte	261.1 ± 139.5	177.5 ± 64.2	.021[b]
FET group	n = 7	n = 9	
Estradiol at lining check	230.8 ± 98.4	246.1 ± 134.5	.958[b]

E2 = estradiol; FET = frozen embryo transfer; OS = ovarian stimulation.
[a] Student's *t*-test.
[b] Mann–Whitney U test.
[c] Chi-squared test.
[d] Two-sample test of proportions.

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TABLE 3

Ovarian stimulation cycle data by CYP1A2*1F genotype.

	CYP1A2*1F genotypes			
Median (IQR)	**AA (n = 18)**	**AC (n = 24)**	**CC (n = 6)**	***P* value**
AFC	25.6 ± 15.5	20.9 ± 9.3	21.0 ± 8.6	.809[a]
Total gonadotropins used (IU)	2,244.4 ± 909.9	2,752.2 ± 676.9	2,500.0 ± 824.8	.097[a]
Oocytes retrieved	23.5 ± 9.0	18.4 ± 9.8	23.2 ± 6.9	.099[a]
Peak E_2 (pg/mL)	4,153.6 ± 1,897.5	3,604.1 ± 1,399.1	4,469.0 ± 2,359.9	.650[a]
Peak E_2 per oocyte	176.4 ± 67.5	250.3 ± 127.6	207.8 ± 140.5	.200[a]

AFC = antral follicle count; E2 = estradiol; IQR = interquartile range.
[a] Kruskal–Wallis test.

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FET group with the variant genotype, so comparison of E2 level at lining check was not completed.

Evaluation of the dominant genetic model (comparison of wild-type AA genotype with variant grouped CC + AC genotype), found that participants with the variant genotype (n = 30) trended toward having a higher E2 per oocyte collected (241.5 ± 128.9 pg/mL) compared with wild-type (n = 18) participants (176.5 ± 67.5 pg/mL), but was not statistically significant (P =.143). In the FET group, comparison of E2 at lining check by wild-type (n = 6) vs. variant (n = 10) in the dominant genetic model noted no significant difference (234.1 ± 85.3 vs. 242.5 ± 136.2 pg/mL, P =.914).

In a multivariate linear regression model with outcome of log transformed E2 per oocyte collected, adjusting for covariates of BMI, caffeine intake, and self-reported race, there was no significant correlation between CYP1A2*1F genotype and E2 per oocyte (P =.717). In a separate multivariate linear regression model with outcome of log transformed E2 at lining check, adjusting for the same covariates, there was again no significant correlation between CYP1A2*1F genotype and E2 at lining check (P =.569). Of note, as only 1 participant endorsed current cigarette use, smoking status was not utilized in final multivariate linear regression model.

DISCUSSION

To clarify the mechanism of observed E2 differences in Asian and Caucasian women during ART treatment (1, 7, 8), this study explored the relationship between participants' race, possession of the CYP1A2*1F polymorphism, and E2 levels during OS or programmed FET cycles. This exploratory study did not observe a racial difference in prevalence of the CYP1A2*1F variant between Caucasian and Asian participants. Furthermore, although E2 level per oocyte retrieved did differ between Asian and Caucasians participants who completed OS cycles in this study, the CYP1A2 genotype did not fully explain these E2 differences when evaluated in either the recessive or dominant genetic model. Despite prior research pointing to CYP1A2 as a likely target of E2 metabolism differences between Asian and Caucasian women, the present study does not support that hypothesis.

Allelic frequency of the CYP1A2*1F polymorphism was similar to that of prior studies, with 32% frequency in the Caucasian population (22%–68%) and 42% frequency in the Asian population (27%–66%). No statistically significant differences were noted in the distribution of the polymorphism between racial groups in this population. In the OS group, significantly increased level of E2 per oocyte was noted Asian compared with Caucasian participants, consistent with prior

TABLE 4

Programmed cycle FET data by CYP1A2*1F genotype.

	CYP1A2*1F genotypes			
Mean ± SD	**AA (n = 6)**	**AC (n = 9)**	**CC (n = 1)**	***P* value**
Days of estradiol use	15.5 ± 3.1	15.8 ± 3.3	12	.419[a]
Progesterone on day of lining check (ng/mL)	0.419 ± 0.1	0.385 ± 0.1	0.267 ± 0	.357[a]
Endometrial lining thickness (mm)	7.93 ± 0.8	8.38 ± 1.5	11 ± 0	.189[a]
Estradiol on day of lining check (pg/mL)	234.1 ± 85.3	253.8 ± 139.5	141.3 ± 0	.724[a]

[a] Kruskal–Wallis test.

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research (1, 7), but this difference was not correlated to the CYP1A2*1F genotype when analyzed as gene dosage effect, in the recessive genetic model, nor in the dominant genetic model. In the limited programmed FET group, there was no association between the level of E2 at lining check and race, and furthermore there was no correlation with CYP1A2*1F genotype. The lack of E2 difference by race may be attributable to small sample size of FET group. Finally, in the multivariate linear regression models, adjusting for covariates of BMI, caffeine intake and self-reported race, there continued to be no significant correlation between CYP1A2*1F genotype and E2 level during ART.

Despite the similar CYP1A2*1F polymorphism allelic frequency to prior studies, this study was limited by the small number of participants found to have the homozygous CC genotype ($n = 7$) resulting in reduced robustness of the recessive genetic model. On the basis of genotype prevalence seen in this study, future exploration into the relationship between CYP1A2*1F polymorphism and serum E2 during ART may benefit from including an even larger population to improve assessment of CC genotype. Evaluation of the genotype to phenotype relationship was further limited by the broad inclusion of ART treatments, both OS and FET, in the study protocol. Although the diversity of participants allowed for observation of whether metabolic effects of CYP1A2*1F polymorphism on E2 levels emerged above a certain threshold, it also limited the statistical power because of lower recruitment in the FET group. Given higher variability in serum E2 during OS, secondary to variability in peak follicle size at trigger (not measured in this study), further evaluation of this polymorphism's relationship to serum E2 may be best explored using only the FET population.

This exploratory study is the first to attempt to clarify the underlying mechanism of serum E2 differences between Asian and Caucasian patients undergoing ART by assessing the relationship between serum E2 levels during treatment and possession of the CYP1A2*1F polymorphism. An improved understanding of this mechanism would inform future research on patient specific dosing of ART therapeutics in hopes of optimizing clinical outcomes and narrowing the gap between minority and Caucasian patients. The findings of this study contribute to the current data through its indication that the underlying mechanism of serum E2 differences between Asians and Caucasians undergoing ART treatment may rely on something other than the CYP1A2*1F single gene polymorphism.

CONCLUSIONS

Although differences in serum E2 levels are noted between Asian and Caucasian patients undergoing OS in this study, the CYP1A2*1F polymorphism does not emerge as the likely primary driver of this disparity.

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