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Research Article

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Geographical Variability in the Outcome of Donor egg IVF - Analysis of SART Data on 71,182 Donor egg IVF Cycles

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Abstract
An earlier analysis of abbreviated SART (Society for Reproductive Technology) data for 2007 (n=443) had identified geographical heterogeneity in live birth (LB) rates in the United States resulting from donor egg IVF (In- Vitro Fertilization), and these observations allowed for positing on ecological underpinnings to IVF success. We herein aimed to determine the validity of geographical differences in LB following donor egg IVF through use of a larger study sample of both fresh and frozen embryo transfer donor egg IVF cycles (n=71, 182), after adjusting for a number of variables that are recognized to impact cycle success. Consistent with the earlier observations, geographical location of the IVF clinic emerged as an independent predictor of LB following donor egg IVF; also, highest LB rates with donor egg IVF following both fresh ET and with FET were noted at clinics located in the W compared to centers located in NE of United States (on analyses adjusting for recipient's age, body mass index (BMI), race, number of embryos transferred (ET), and use of assisted hatching (AH) the likelihood for donor egg IVF related LB for clinics in W compared to the NE:OR 1.28, 95% CI 1.20-1.37 for fresh ET and OR: 1.18, 95% CI: 1.06 -1.30 for FET). This study reaffirms that success of donor egg IVF is susceptible to ecological influences that merit further investigation.

Keywords: Assisted reproduction, environment, SART database, ART success

Introduction
Since its advent, the use of assisted reproductive technology (ART) has steadily increased; in 2013, 66,691 infants were born utilizing ART procedures in the United States alone [1]. The constant evolution of ART has been associated with an accrual of literature for understanding and optimizing procedures and outcomes.An appreciation of both patient-specific and external factors which influence outcomes has led to universal improvements in live birth rates (LBRs) resulting from ART. A number of patient-specific characteristics (such as patient age, race, BMI, ovarian reserve status, smoking and the etiology of infertility, to name a few) as well as clinical and procedural expertise are recognized to impact on ART [2-5]. One such identified factor is the use of donor eggs, which leads consistently higher LBRs compared to infertility treatments based on use of autologous eggs. Consistently higher LBRs with in vitro fertilization (IVF) utilizing donor eggs is attributed to the youth and healthy profile of women who are accepted as donors based on standardized set of criteria proposed by the center for disease control (CDC), and adhered to by participating IVF clinics in North America [6-8]. Implications of environmental exposures such as smoking and more recently dietary components including fiber fruits and vegetables, folate and environmental toxin BPAfor ART outcomes are recognized [9-12]. More recently, emerging data have identified that in addition to egg donor and recipient characteristics, the physical environment at site of fertility clinics may be relevant for ART success; specific features, such as air quality and ART laboratory environment were noted to have statistically significant impacts on IVF treatment outcomes [13-14].

The relevance of women's vitamin D status for ART success has been investigated. Existing evidence, although observational, suggests an attenuation in treatment outcomes in the setting of vitamin D deficiency [15-20]. Given recognized ecological underpinnings to a population's vitamin D status (higher vitamin D levels are described in populations residing in regions of higher exposure to solar ultraviolet B radiation)it has been previously explored whether in the United States, live birth (LB) following donor egg in vitro fertilization (IVF) may vary by population's geographical location [21,22]. Utilizing an abbreviated version of ART cycle data

(2007) that is annually published by SART (Society for Assisted Reproductive Technology), geographical variability in LB following donor egg IVF was demonstrated; for both fresh and frozen embryo transfer, high LB rates were noted in IVF clinics located in the Western region of the United States (areas of higher regional mid-year UVB intensity); lowest LB rates were noted in the North East of United Stages (areas of lower mid-year UVB intensity) [22]. In the current study, we aim to determine the validity of our earlier observations (i.e. geographical differences in LB following donor egg IVF) in a larger sample of both fresh embryo transfer (FrET) and frozen embryo transfer (FET) donor egg IVF embryo transfer (ET) cycles (n=71,182) utilizing an expanded dataset that would allow for adjustment of a number of co-variates that are recognized to relate to ART success.

Materials and Methods

Data on donor egg IVF-ET cycles (FrET and FET) from the national SART Clinic Outcome Reporting System (SART CORS) database were obtained and analyzed to quantify the association between geographical location of IVF clinic and LB rate following FrET and FET cycles. Data for years 2008-2013 were included. Geographical region was categorized as Northeast (NE), South (S), Midwest (MW), and West (W) by zip code, as previously described[22]. To reduce potential for unquantified bias confounding environmental factors, an analysis was restricted to IVF cycles where the region of patient residence matched the region of the IVF clinic.

Region-specific differences in patient and IVF cycle parameters including LB rate (LBR) following FrET and FET cycles were calculated.Analysis of variance was used for assessing across-region differences in continuous variables (data presented as mean ± standard deviation [SD]) and chi-square test determined differences in frequencies of categorical data (presented as percentage). For post-hoc analyses, Tukey-Kramer tests were conducted to evaluate between-region differences in patient age and BMI. Body mass index (BMI) was considered as a both a continuous variable and as a categorical variable (<18.5, 18.5-24.9, 25-29.9, 30-39.9, and ≥40) [23]. Relationships between region (independent variable of interest) and LB (outcome variable) following donor egg FrET and FET were assessed using multivariable logistic regression analyses; adjusting for recipient age, race/ethnicity, BMI, assisted hatching (AH) and number of ET. Choice of covariates was based on evidence of statistical significance (p<0.05) to association with the outcome on univariate analyses. Sensitivity analyses were conducted in a data subset that included information on smoking status and smoking was included as an additional covariate in these sub-analyses. All analyses were performed with SAS (SAS Institute Inc., Cary, NC). Results with two tailed P<.05 were considered statistically significant.

Goodness of fit was assessed using the Akaike information criterion (AIC) and negative log likelihood, specifically to determine whether the inclusion of patient region in the adjusted analyses improved the logistic models.

Results

Of 76,296 donor egg IVF cycles reported to SART for 2008-2013, regional information was available for 71,182 (48, 887 FrET and 22,327 FET cycles). Specified regions differed significantly in the total number of donor egg IVF cycles (highest number of cycles being undertaken in the NE (n= 20,351), followed by W (n=19,804), S (n=18,786), and MW (n=12,241).

Several patient and IVF cycle characteristics were found to differ significantly across regions within the US, as shown in Table 1. Notable from the perspective of IVF cycle outcomes, regional differences in recipient's age, BMI, race, as well as per cycle number of ET, utilization of AH and day of ET were apparent, and each of these parameters was included as a covariate for adjusted analyses. Post hoc analyses suggested that age differed statistically significantly in all two-way comparisons (P = 0.0023 for comparison between Northeast and West; P < 0.001 for all other comparisons). Mean BMI differed significantly between patients in the Northeast and the West (P < 0.001), the South and the West (P < 0.001), and the Midwest and the West (P < 0.001). The highest percentage of donor egg cycles where recipients acknowledged smoking were undertaken in the NE and MW regions of US (15.06% and 11.29% respectively of donor egg IVF cycles were undertaken in smoker recipients).

The regression models including region were found to produce more favorable (i.e., lower) values of AIC and negative log likelihood, suggesting that patient region contributes information of value to the model.

Table 1: Regional differences in donor egg recipient and IVF cycle characteristics (SART 2008-2013) across the four regions of the United States

Race						
Other/Multiracial	10.27%	4.32%	6.49%	8.52%	7.18%	<0.001
Asian	6.23%	6.25%	3.62%	11.59%	7.20%	<0.001
Black/African American	6.57%	9.77%	3.26%	2.67%	5.89%	<0.001
White	72.53%	73.36%	83.84%	69.67%	74.17%	<0.001
Hispanic/Latino	4.40%	6.30%	2.80%	7.56%	5.56%	<0.001
Age (years)	42.39 ± 4.94	41.45 ± 4.98	40.89 ± 5.33	42.21 ± 4.92		<0.001
BMI (Kg/m^2)	25.41 ± 5.34	25.39 ± 5.30	25.61 ± 5.63	24.37 ± 5.02		<0.001
Smokers (%)	15.06%	9.02%	11.29%	8.50%		<0.001
Fresh ET cycles n (%)	**13, 640 (67.02)**	**13, 864 (73.80)**	**8,571 (70.02)**	**12,812 (64.69)**	**4,8887 (68.68)**	**<0.001**
Frozen ET cycles n (%)	**6719 (33.02)**	**4931 (26.25)**	**3675 (30.02)**	**7002 (35.36)**	**22327 (31.37)**	**<0.001**
Number of fresh embryos transferred per cycle	**2.24±0.69**	**2.12±0.60**	**2.17±0.59**	**2.24±0.69**	**2.20±0.67**	**<0.001**

Number of frozen embryos transferred per cycle	2.26±0.87	2.16±0.82	2.33±0.88	2.48±0.99	2.32±0.91	<0.001
Days of embryo culture	**3.85±1.07**	**4.23±1.17**	**3.99±1.34**	**4.12±1.14**	**4.05±1.18**	**<0.001**
Assisted Hatching						
None	12,208 (63.74)	13,482 (76.61)	7,521 (66.21)	13,710 (73.30)		<0.001
Any	6,946 (36.26)	4,117 (23.39)	3,839 (33.79)	4,993 (26.70)		<0.001

P-values reflect results of tests across the four geographic regions

Regional differences in LBRs following donor egg FrET and FET are presented in Table 2. Consistent with our earlier reporting, lowest LBRs following donor egg ET (for both FrET and FET) were noted for the NE (46.12% for FrET and 26.02% for FET), and highest LBRs were observed for donor egg IVF cycles undertaken in the W (54.23% for FrET and 30.12% for FET, $p< 0.001$).

Table 2: Differences in outcome of donor egg fresh and frozen embryo transfer IVF cycles (SART 2008-2013) across the four regions of the United States

Region	**Unadjusted**		**Adjusted***	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Northeast	**Reference**	**---**	**Reference**	**---**
South				
- **Fresh ET**	1.08 (1.03, 1.13)	0.002	0.98 (0.92, 1.04)	0.485
- **FET**	1.14 (1.05, 1.23)	0.003	1.15 (1.03, 1.27)	0.010
Midwest				
- **Fresh ET**	1.02 (0.96, 1.07)	0.531	0.96 (0.89, 1.03)	0.237
- **FET**	1.08 (0.99, 1.18)	0.093	1.08 (0.96, 1.21)	0.189
West				
- **Fresh ET**	1.38 (1.32, 1.45)	<0.001	1.28 (1.20, 1.37)	<0.001
- **FET**	1.23 (1.14, 1.32)	<0.001	1.18 (1.06, 1.30)	0.002

Adjusted for recipient age, race/ethnicity, BMI, number of embryos transferred, and assisted hatching. All odds ratios are calculated with the lowest performing region, the Northeast, as reference category.

On adjusted analyses, donor egg IVF cycles undertaken in clinics in the W region of the United States were significantly more likely to result in LB (28% higher likelihood for LB following FrET and 18% higher likelihood for LB following FET) compared to cycles undertaken in IVF clinics in the NE (OR for LB for cycles undertaken in clinics in the W compared to the referent NE: 1.28, 95% CI 1.2-1.37 for FrET and 1.18, 95% CI 1.06-1.30 for FET). Day of embryo transfer data for frozen embryo cycles was inconsistently reported in the database, and thus not included in the multivariate analysis.

Sensitivity analyses on data subset for which information on smoking status was available (n=22,502 for FrET and n=10,235 for FET cycles) confirmed that earlier observed regional associations with LB held after adjusting for smoking status (Supplementary table).

Supplementary Table: Differences in outcome of donor egg fresh and frozen embryo transfer IVF cycles (SART 2008-2013) across the four regions of the United States; analyses restricted to donor egg IVF cycles with available information on recipient smoking status (n=22,502)

Region	**Unadjusted**		**Adjusted***	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Northeast	**Reference**	**---**	**Reference**	**---**
South				
- **Fresh ET**	1.06 (0.99, 1.14)	0.102	1.05 (0.96, 1.15)	0.298
- **FET**	1.13 (1.00, 1.27)	0.051	1.18 (1.02, 1.37)	0.030
Midwest				
- **Fresh ET**	1.00 (0.92, 1.09)	0.980	0.96 (0.87, 1.07)	0.480
- **FET**	1.00 (0.88, 1.14)	0.960	0.99 (0.84, 1.17)	0.875
West				

- Fresh ET	1.40 (1.31, 1.51)	<0.001	1.34 (1.21, 1.48)	<0.001
- FET	1.26 (1.13, 1.40)	<0.001	1.19 (1.02, 1.37)	0.024

Adjusted for recipient age, race/ethnicity, BMI, number of embryos transferred, assisted hatching, and smoking status. All odds ratios are calculated with the lowest performing region, the Northeast, as reference category.

Full dataset:

Goodness of Fit Test	Fresh		Frozen	
	Without Region	**With Region**	**Without Region**	**With Region**
AIC	42092.363	41997.398	16996.360	17030.242
-2 Log L	42062.363	41961.398	16962.360	16994.242

Smoking subset:

Goodness of Fit Test	Fresh		Frozen	
	Without Region	**With Region**	**Without Region**	**With Region**
AIC	19937.057	19889.595	8237.347	8233.032
-2 Log L	19905.057	19851.595	8205.347	8195.032

Discussion

Previous analyses undertaken with data from a single year of SART reporting had suggested regional differences in donor egg IVF success, with highest LBR's resulting from both fresh and FET noticeable for clinics located in the W region of the United States, and lowest respective rates for regions in the NE of the country [22]. The current study, undertaken in a much larger representative sample of donor egg IVF cycles from across the four regions of the United States reaffirms the earlier findings. After adjusting for both donor egg recipient and donor egg IVF cycle specific parameters that are recognized to impact on donor egg IVF cycle outcome, fertility centers in the W of are seemingly outperforming, in success of donor egg IVF, clinics located in the NE of the United States.

Although the study design does not allow any understanding of the mechanisms that could explain these regional differentials in LBRs of donor egg FrET and FET cycles, given that analyses adjusted for the many known predictors of IVF cycle success, and given the consistency in directionality of these observations with our prior study, we re-posit that the recognized regional differential in mid-year UVB may be relevant to our observations. Indeed, a connection between sunlight and seasonality for both human and animal conception has previously been described and was also hypothesized as an explanation for our earlier observation of regional differences in donor egg IVF outcome [22-24].

Data on UVB index by region for the United States, provided by the United States Environmental Protection Agency and the previously published National Weather service UV index bulletins, demonstrate the highest UVB indexes in areas corresponding to the West, followed by the Southern regions of the United States [25,26]. Direct assessment of regional UVB indices and correlation with latitude and longitudinal coordinates, as undertaken in our prior work, was not possible for the current study given the logistic constraints imposed by the large sample size, as these data were not available in the SART database. We demonstrate that after adjusting for demographic differences amongst donor egg recipients and for donor egg IVF cycle related parameters that are recognized determinants of IVF cycle success, LBR following donor egg IVF ET additionally relates to the geographical location of the IVF clinic within the United States; LBR's of donor egg FrET and FET cycles were highest for IVF centers located in the Western region of the United States (areas with higher midyear UVB indices) and lowest for clinics located in the NE (regions of low UVB indices, as evident from data from the US environmental protection agency and the national weather service.

As was suggested in our prior work, the correlation between vitamin D and UVB exposure is one possible regional variance that could, in part, explain these observed correlations. Vitamin D has been shown to impact on immune modulation and endometrial receptivity, and thereby on implantation success [27,28]. Vitamin D also plays an important role in steroidogenesis, creating an indirect influence on ovarian function, and deficiency has been linked to ovarian insufficiency [29]. Decreased prevalence of vitamin D deficiency is conjectured for populations residing in areas of higher UVB exposure. Thus higher innate vitamin D levels consequent to higher UVB exposure are hypothesized for women residing in the W compared to NE of United States, and proposed as a possible mechanism to explain the higher donor egg IVF related LBR's for cycles undertaken in W compared to the NE. Based on the observed decreased LBRs following donor egg IVF in region of low UVB exposure, we hypothesize a higher prevalence of vitamin D insufficiency in donor egg recipients residing in the NE compared to those living in the W, and propose that a population differential in vitamin D status may be one of the mechanisms that could explain our findings.

We acknowledge a number of limitations to our work including the many unrecognized environmental variables that could underlie the observed regional differences in LBR's. Environmental or region specific influences, varying from water and crop pollutants, to air quality, differential regional prevalence of population health issues, genetic underpinnings, and lifestyle practices are some of the factors that may be relevant but which could not be accounted for in this study. Etiology of recipients' infertility may have implications for donor egg IVF success (e.g. uterine factor in recipient, underlying endometriosis in egg donors), and this information was not accessible in the SART database [30-32]. Notwithstanding the limitations, our current study yields information that is both interesting and hypothesis generating. These observations and conjectures are relevant to the growing narrative on both environmental underpinnings to reproductive success as well as on the relevance of vitamin D to reproductive success.

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