

Ambient Air Pollution Exposure and Fecundability in Women Undergoing In Vitro Fertilization

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Background: Limited research suggests ambient air pollution impairs fecundity but groups most susceptible have not been identified. We studied whether long-term ambient air pollution exposure before an in vitro fertilization (IVF) cycle was associated with successful livebirth, and whether associations were modified by underlying infertility diagnosis.

Methods: Data on women initiating their first autologous IVF cycle in 2012–2013 were obtained from four US clinics. Outcomes included pregnancy, pregnancy loss, and livebirth. Annual average exposure to fine particulate matter (PM_{2.5}), PM₁₀, and nitrogen dioxide (NO₂) before IVF start were estimated at residential address using a validated national spatial model incorporating land-use regression and universal kriging. We also assessed residential distance to major roadway. We calculated risk ratios (RR) using modified Poisson regression and evaluated effect modification (EM) by infertility diagnosis on additive and multiplicative scales.

Results: Among 7,463 eligible participants, 36% had a livebirth. There was a nonsignificant indication of an association between PM_{2.5} or NO₂ and decreased livebirth and increased pregnancy loss. Near-roadway residence was associated with decreased livebirth (RR = 0.96, 95% CI = 0.82, 0.99). There was evidence for EM between high exposure to air pollutants and a diagnosis of diminished ovarian reserve (DOR) or male infertility and decreased livebirth.

Conclusions: Despite suggestive but uncertain findings for the overall effect of air pollution on fecundity, we found a suggestive indication that there may be synergistic effects of air pollution and DOR or male infertility diagnosis on livebirth. This suggests two possible targets for future research and intervention.

Keywords: Air pollution; Fertility; Fecundity; Particulate matter; Nitrogen dioxide; Reproductive epidemiology; In vitro fertilization; Pregnancy

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of the article.

S.M.Q. was supported by NIH/NICHD T32-HD052462 and NIH/NIEHS T32-ES015459. A.H. was supported by R01ES023498. Portions of this study were supported by the U.S. Environmental Protection Agency (RD831697 and RD838300) and the National Institute of Environmental Health Sciences (P30ES07033). It has not been formally reviewed by EPA. The views expressed in this document are solely those of the authors and do not necessarily reflect those of the Agency. EPA does not endorse any products or commercial services mentioned in this publication.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.enviroepidem.com).

The computing code and exposure data required to replicate the results reported in this manuscript can be obtained by contacting the corresponding author. The clinical data can be obtained by making requests to the participating clinics.

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Environmental Epidemiology (2019) 3:e036

Received: 29 June 2018; Accepted: 10 December 2018

Published online 29 January 2019

DOI: 10.1097/EE9.0000000000000036

Impaired fecundity is experienced by 12% of women and 11% of women of childbearing age in the United States have used an infertility service.^{1,2} Most studies on infertility and in vitro fertilization (IVF) have focused on clinical factors, which are not easily modifiable, with little attention paid to environmental factors which can be regulated and modified.

The health effects of exposure to air pollution are well established.^{3–5} Mounting evidence indicates a consistent association between higher exposure and higher rates of preterm delivery, intrauterine growth restriction, and low birth weight.^{6–14} Recent studies found exposure to traffic-related air pollution is associated with infertility diagnoses and fertility rates.^{15,16} The use of a population undergoing IVF provides a unique opportunity to evaluate the effects of air pollution on clinical pregnancy-related outcomes before birth with well-defined exposure timelines.

Previous studies on air pollution in IVF patients assessed short-term exposure at cycle initiation, but not long-term exposure prior.^{17,18} This focus may exclude the pertinent exposure period particularly if the mechanism includes systemic maternal effects due to chronic exposure. No known studies to date have examined whether IVF success is differentially related to exposure to air pollution according to infertility diagnosis.

What this study adds

This study is one of the first to explore the role of infertility in relation to the exposure to air pollution and fecundity in the context of women undergoing IVF. Our study results suggest that two specific types of infertility, diminished ovarian reserve and male infertility, modify the association between air pollution exposure and live birth in women undergoing IVF. These findings suggest future research in this field should consider type of pre-existing infertility diagnosis when considering how air pollution, and perhaps other environmental pollutants, interplay with fecundity and pregnancy outcomes.

Differences by infertility diagnosis may provide for a better understanding of the mechanisms by which air pollution affects fertility.

This study aims to understand the association between long-term exposure to air pollution and fertilization rates, embryo quality, pregnancy, and live birth among women undergoing IVF. It takes advantage of a known date for pregnancy attempt allowing estimation of exposure before attempt. In addition, this study aims to investigate if certain types of infertility act in concert with exposure to result in decreased fecundity.

Methods

Study design and population

This retrospective cohort study used medical records from women initiating an IVF cycle at a participating fertility clinic. Clinics that are a part of Integramed, a network of private fertility clinics across the United States, were recruited. The exclusive use of Integramed clinics allowed access to medical record data that are uniformly recorded and reported and helps ensure that clinical and laboratory procedures and guidelines are relatively uniform.

Targeted clinics were located in metropolitan areas that have previously been the subject of similar research, or fine-scale pollutant monitoring and spatiotemporal modeling, by the University of Washington. Participating clinics included Seattle Reproductive Medicine (Seattle, WA), Reproductive Science Center (San Francisco-Bay area, CA), Reproductive Partners Medical Group (Los Angeles area, CA), and Shady Grove Fertility. Shady Grove has three locations under one network (Baltimore, MD, Rockville, MD, and Chesterbrook, PA). This study was reviewed and approved by the Human Subjects Division at the University of Washington.

Medical records were obtained for women initiating an IVF cycle between 1 January 2012 and 31 December 2013. There were 19,003 IVF cycles with intent of a fresh embryo transfer. The study population were further restricted to autologous cycles ($n = 14,640$), first cycle ($n = 8,505$), and cycles progressing to oocyte retrieval ($n = 7,861$).

Outcome and covariate data

The primary outcomes of this study were live birth and pregnancy loss. Clinics have near complete data on live birth outcomes as these are reported to the National Artificial Reproductive Technology (ART) Surveillance System (NASS). Secondary outcomes included percent oocytes fertilized (number fertilized/number inseminated), good grade embryos (any/none), positive human chorionic gonadotropin (hCG) test (yes/no), and positive ultrasound confirmed pregnancy (yes/no). Embryos were graded as poor, fair, and good according to uniform Society for Assisted Reproductive Technology (SART) guidelines.^{19,20} An hCG test occurs 2 weeks after embryo transfer; high hCG (>25 mIU/mL) indicates pregnancy. An ultrasound occurs 5–6 weeks after embryo transfer to confirm a visible gestational sac in the uterus.

Outcomes were defined using two methods. First, positive outcomes were assessed for overall likelihood within the total study population (eFigure 1a; <http://links.lww.com/EE/A30>). Second, negative outcomes were assessed using risk sets sequentially restricted by each outcome (eFigure 1b; <http://links.lww.com/EE/A30>). These included negative hCG (among those who had an embryo transfer), negative ultrasound (among those who had a positive hCG), and pregnancy loss (ultrasound confirmed pregnancy not resulting in live birth).

The medical record for an individual listed up to three infertility diagnoses. These were dichotomized as “any/none” for each diagnosis; individual could be categorized with multiple diagnoses. Categorization of diagnoses was as follows:

diminished ovarian reserve (DOR), male infertility, ovulation/polycystic ovarian (PCO) disorders, tubal factors (hydrosalpinx, tubal ligation, other), endometriosis, uterine factor, unexplained, other. Data were extracted on race (white/non-white), smoking history if available, age, and body mass index (BMI) at cycle start.

Residential addresses were recorded from the medical record at the date of data extraction (December–February 2016) and geocoded using ArcGIS 10.5.1. Of 7,681 eligible participants, 7,463 had valid geocodes for exposure estimation. Invalid addresses included: international, noncontiguous U.S., P.O. or military box, and addresses that were not resolved within 500 m. Due to the nature of how data were collected, without participant contact, we were unable to confirm the address location. Neighborhood socioeconomic status (NSES) was measured using a census tract-level index.²¹

Air pollution exposure

Exposure to fine particulate matter ≤ 2.5 μm in diameter ($\text{PM}_{2.5}$), particulate matter ≤ 10 (PM_{10}), and nitrogen dioxide (NO_2) at participant-specific addresses were estimated using prediction models.²² Our primary exposures were based on year- and pollutant-specific national spatial models. This model provides predictions for all areas of the contiguous U.S. and is based on regulatory monitoring data from the Environmental Protection Agency (EPA) Air Quality System (AQS) and Interagency Monitoring of Protected Visual Environments (IMPROVE) networks. Models used universal kriging, a geostatistical regression that combines land-use regression with spatial smoothing. Candidate geographic covariates were reduced to a few derived components determined by partial least squares (PLS). Cross-validated R^2 for $\text{PM}_{2.5}$ ranged from 0.73 to 0.91, for PM_{10} from 0.40 to 0.62, and for NO_2 from 0.79 to 0.89.^{22,23} We weighted predicted exposures to approximate the year before IVF cycle start using the number of days in year of and number of days in year before cycle start date.

We conducted a sensitivity analysis using exposure estimates predicted using spatiotemporal models developed for the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA-Air) study.²⁴ These models utilized additional data from monitors at MESA-Air participant residential locations, fixed sites throughout MESA-Air regions, and near-roadway monitors, and provided predictions for $\text{PM}_{2.5}$ and NO_2 on a 2-week time scale averaged up to an annual average before IVF cycle for participants at the LA, Baltimore, and Rockville clinics. Further details on these models have been published previously.²⁵

Finally, in a post-hoc analysis, we analyzed distance to roadway (DTR) as an alternate exposure measure. Roadways are classified as A1, A2, or A3 by the U.S. Census feature class codes. A1 is “primary highway with limited access,” A2 is “primary road without limited access,” and A3 is “secondary and connecting road.” Fixed distance from residential address to A1, A2, and A3 road was calculated using the TeleAtlas road network. We classified near road residence as within 100 m of an A1 or A2 or within 50 m of an A3.²⁶

Statistical analysis

IVF outcomes as associated with exposures ($\text{PM}_{2.5}$, PM_{10} , NO_2 , DTR) were assessed via a modified Poisson regression using robust variance estimation. This method is similar to a log-binomial model without model convergence issues and can be used with binary data.²⁷ This allows effect estimates that approximate risk despite common outcomes (live birth). Percent oocytes fertilized was analyzed using a linear regression model.

Hypothesized confounders were determined a priori via the use of a directed acyclic graph (DAG) (eFigure 2; <http://links.lww.com/EE/A30>). A staged modeling approach was used to

investigate which variables had the strongest impact on the effect estimate. Model 1 adjusted for age, BMI, race (white/non-white), and NSES. Model 2 added adjustments for clinic (indicators for Seattle, SF, LA, Baltimore/Chesterbrook, and Rockville). Our primary model is model 2, which includes all a priori confounders. Air pollution measures were evaluated on a continuous scale, and effect estimates were reported based on approximate interquartile range (IQR).

We explored effect modification (EM) by infertility diagnosis of the air pollution–live birth association. EM was evaluated using model 2 adjustments and adjustments for infertility diagnoses (excluding the one under evaluation). Additive interaction was evaluated using relative excess risk due to interaction (RERI).²⁸ RERI tests for departure on an additive scale categorizing individuals according to both exposures with the double unexposed group as the referent. We defined exposed/unexposed for each pollutant as 25th versus 75th percentile. We conducted traditional multiplicative interaction test using a continuous measure for air pollution exposure.

Results

The final analytic sample included 7,463 individuals. The majority were from the Shady Grove clinic (64.5%); 52.9% from Rockville, 9.8% from Baltimore, and 1.8% from Chesterbrook. For analysis, Chesterbrook was combined with Baltimore due to the small sample size and geographic proximity to Baltimore.

Baseline descriptives of the population are shown in Table 1 (clinic-stratified in eTable 1; <http://links.lww.com/EE/A30>). Recorded infertility diagnoses included 17.5% with DOR, 14.1% with an ovulation disorder or PCO, and 12.9% with a tubal factor. Male infertility was reported in 29.7% of participants, the most common factors being oligospermia and asthenospermia. Unexplained and other infertility included nonclinical reasons, such as same-sex partner or single female, and clinical factors, such as unexplained recurrent spontaneous abortion.

The distribution of air pollution estimates by clinic is shown in the Figure. Overall, the mean (IQR) for air pollutants were: $PM_{2.5}$ 8.7 $\mu g/m^3$ (1.4), PM_{10} 14.9 $\mu g/m^3$ (3.8), and NO_2 9.0 ppb (4.7). Exposure distributions differed by location with LA having the highest exposures across all pollutants, Seattle had the lowest for $PM_{2.5}$ and PM_{10} , and Rockville had the lowest for NO_2 .

The results for the primary regression analyses are shown in Table 2. For percent oocytes fertilized, there was a negative association for $PM_{2.5}$ and PM_{10} that did not reach statistical significance and a 0.04% (95% CI = -0.08, -0.004) lower oocyte fertilization with a 5-ppb higher NO_2 . Results for embryo grade, positive hCG test, and positive ultrasound were all close to null for all pollutants. A 2- $\mu g/m^3$ higher $PM_{2.5}$ was associated with a 4% (95% CI = 0.90, 1.02) lower likelihood of live birth. Results were similar for PM_{10} and NO_2 . Results for DTR indicated a lower likelihood for having positive outcomes for those with near-roadway residence. This included a 10% lower likelihood of positive hCG test (95% CI = 0.83, 0.97); positive ultrasound (95% CI = 0.92, 0.98), and for a live birth (95% CI = 0.82, 0.99) comparing for near-roadway residence compared with not near-roadway.

Results for poor outcomes defined by sequential risk sets are shown in Table 3. Results for negative hCG test and negative ultrasound were close to null for all pollutants except for a nonsignificant 5% higher likelihood of negative ultrasound with increased NO_2 (95% CI = 0.92, 1.20). A 2- $\mu g/m^3$ higher $PM_{2.5}$ was associated with a 9% (95% CI = 0.93, 1.26), a 4- $\mu g/m^3$ higher PM_{10} with a 6% (95% CI = 0.95, 1.17), and a 5-ppb higher NO_2 with a 10% (95% CI = 0.97, 1.23) higher likelihood of pregnancy loss. Results for DTR indicated a 13% (95% CI = 1.04, 1.22) higher likelihood of having a negative hCG test, for those with residence near-roadway. There was no association

Table 1

Baseline and outcome characteristics of women undergoing IVF at select clinics, 2012–2013

Participant characteristic	N	Mean (standard deviation)
Age at cycle start (years)	7,463	34.9 (4.6)
BMI at cycle start (kg/m^2)	7,463	25.3 (5.1)
Neighborhood SES z score	7,425	0.0 (5.1)
Percent oocytes fertilized (%)	7,379	68 (24)
		N (%)
Study site		
Seattle, WA	1,171	(15.7)
San Francisco, CA	759	(10.2)
Los Angeles, CA	719	(9.6)
Baltimore, MD/Chesterbrook, PA	865	(11.6)
Rockville, MD	3,949	(52.9)
Ethnicity		
White	4,291	(57.5)
Non-white	3,172	(42.5)
Smoking history		
Yes	355	(4.8)
No	4,590	(61.5)
Unknown	2,518	(33.7)
Infertility diagnosis		
Male infertility	2,219	(29.7)
Diminished ovarian reserve	1,305	(17.5)
Ovulation disorders/PCO	1,050	(14.1)
Tubal factors	961	(12.9)
Endometriosis	431	(5.8)
Uterine factor	276	(3.7)
Unexplained	1,674	(22.4)
Other	923	(12.4)
Semen source		
Donor/mix	373	(5.0)
Partner	7,090	(95.0)
Near-roadway residence ^a	893	(11.9)
IVF outcomes		
Embryo grade: good quality	5,397	(72.3)
Positive hCG	3,811	(51.1)
Positive ultrasound	3,273	(43.9)
Live birth	2,684	(36.0)
Sequential risk set outcomes ^b		
Negative hCG	2,673	(41.2)
Negative ultrasound	578	(15.0)
Pregnancy loss	589	(18.0)

^aDTR dichotomized as near-roadway residence versus not near road residence. Near-roadway defined as within 100 m of an A1 or A2 or within 50 m of an A3 class roadway.

^bSequential risk set outcomes: hCG restricted to those who had an embryo transfer, ultrasound restricted to those who had a positive hCG, pregnancy loss defined as no live birth among those with positive ultrasound. See eFigure 1b (<http://links.lww.com/EE/A30>) for explanation of sample size.

between near-roadway residence and having a negative ultrasound, a positive hCG test, or with pregnancy loss.

Overall, observed effect estimates from a priori analyses were strongest for lower likelihood of live birth and increased likelihood of pregnancy loss. The ad-hoc analysis of near-roadway residence resulted in the strongest observed effect estimate for higher likelihood of negative hCG test.

Effect modification by infertility diagnosis

The results from the EM analysis are shown in Table 4. The RERI analysis suggests those with DOR have fewer live births (negative excess risk) if they also have high levels of exposure to $PM_{2.5}$ ($P = 0.003$), PM_{10} ($P = 0.01$), and NO_2 ($P < 0.001$) compared with those without DOR and who have low exposure. Similarly, there was interaction on the additive scale for those with male infertility and high exposure to $PM_{2.5}$ ($P < 0.001$), PM_{10} ($P < 0.001$), and NO_2 ($P < 0.001$) compared with those without male infertility and who have low exposure. The RERI analysis with ovulation disorders and with tubal disorders indicated no additive excess risk with high exposure. We tested

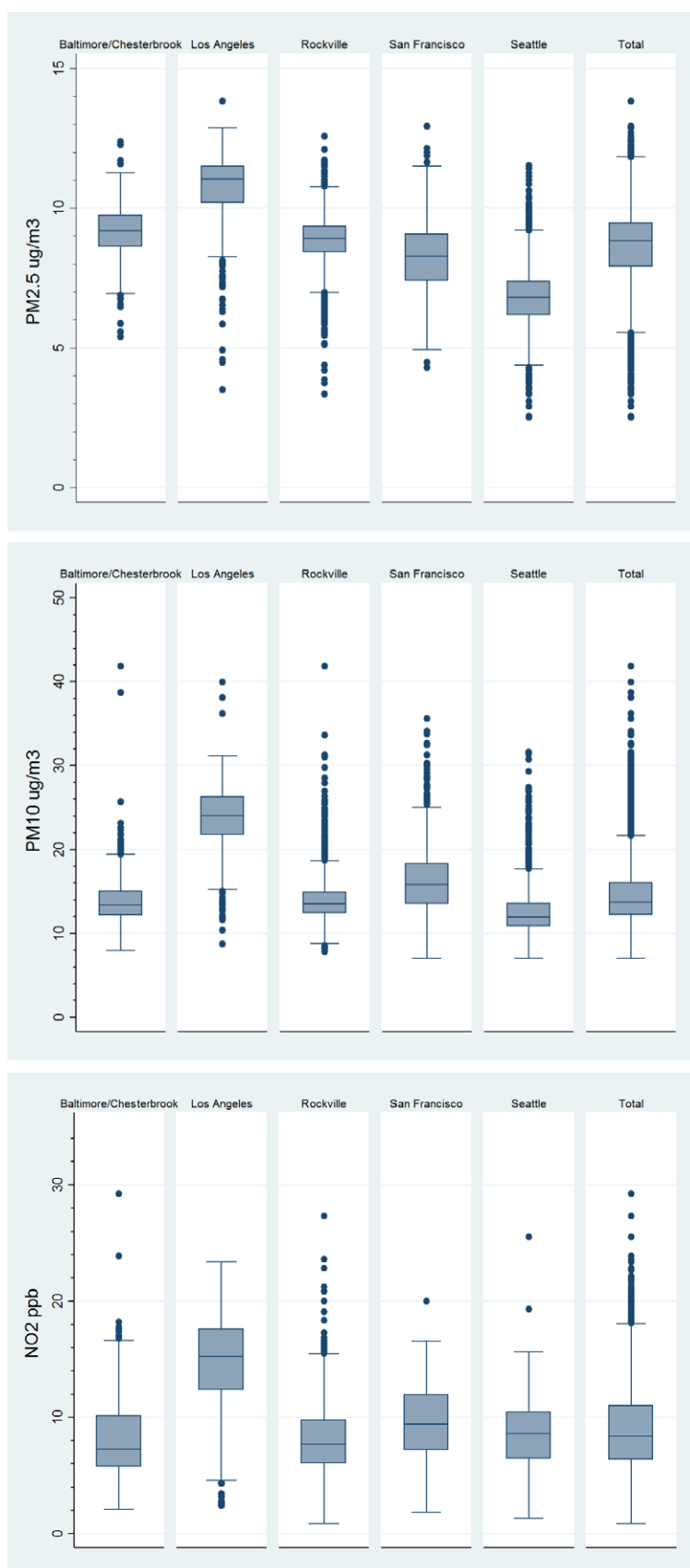


Figure. Distribution of PM_{2.5} ($\mu\text{g}/\text{m}^3$), PM₁₀ ($\mu\text{g}/\text{m}^3$), and NO₂ (ppb) by clinic location.

Table 2**Association of air pollution with successful markers of IVF^a**

	N	Change in % (95% CI)
Percent oocytes fertilized	7,379	
PM _{2.5}		-0.25 (-0.524, 0.020)
PM ₁₀		-0.13 (-0.262, 0.010)
NO ₂		-0.04 (-0.075, -0.004)
Near-roadway ^b		-0.01 (-1.66, 1.64)
Embryo grade: good	7,463	
PM _{2.5}		0.99 (0.96, 1.01)
PM ₁₀		1.00 (0.98, 1.02)
NO ₂		0.99 (0.97, 1.01)
Near-roadway ^b		0.97 (0.93, 1.02)
Positive hCG test	7,463	
PM _{2.5}		0.98 (0.94, 1.02)
PM ₁₀		0.99 (0.95, 1.01)
NO ₂		0.99 (0.95, 1.02)
Near-roadway ^b		0.90 (0.83, 0.97)
Positive ultrasound	7,463	
PM _{2.5}		0.98 (0.93, 1.03)
PM ₁₀		0.99 (0.95, 1.02)
NO ₂		0.98 (0.93, 1.02)
Near-roadway ^b		0.90 (0.82, 0.98)
Live birth	7,463	
PM _{2.5}		0.96 (0.90, 1.02)
PM ₁₀		0.98 (0.94, 1.02)
NO ₂		0.96 (0.91, 1.00)
Near-roadway ^b		0.90 (0.82, 0.99)

^aAir pollution levels reported per unit IQR (PM_{2.5} per 2-μg/m³, PM₁₀ per 4-μg/m³, NO₂ per 5-ppb change). Model adjustments: age, BMI, race, NSES, clinic location.

^bDTR dichotomized as near-roadway residence versus not near road residence. Near-roadway defined as within 100 m of an A1 or A2 or within 50 m of an A3 class roadway.

Table 3**Association of air pollution with poor IVF outcomes^a**

	N	RR (95% CI)
Negative hCG ^b	6,484	
PM _{2.5}		1.01 (0.95, 1.07)
PM ₁₀		1.03 (0.98, 1.07)
NO ₂		1.01 (0.96, 1.06)
Near-roadway ^c		1.13 (1.04, 1.22)
Negative ultrasound ^d	3,851	
PM _{2.5}		1.01 (0.87, 1.17)
PM ₁₀		0.98 (0.88, 1.09)
NO ₂		1.05 (0.92, 1.20)
Near-roadway ^c		1.01 (0.79, 1.29)
Pregnancy loss ^e	3,273	
PM _{2.5}		1.09 (0.93, 1.26)
PM ₁₀		1.06 (0.95, 1.17)
NO ₂		1.10 (0.97, 1.23)
Near-roadway ^c		0.98 (0.78, 1.23)

^aAir pollution levels reported per unit IQR (PM_{2.5} per 2-μg/m³, PM₁₀ per 4-μg/m³, NO₂ per 5-ppb change). Model adjustments: age, BMI, race, NSES, clinic location.

^bNegative hCG compared with positive hCG among those who had a preceding embryo transfer.

^cDTR dichotomized as near-roadway residence versus not near road residence. Near-roadway defined as within 100 m of an A1 or A2 or within 50 m of an A3 class roadway.

^dNegative ultrasound compared with positive ultrasound among those who had a preceding positive hCG test.

^ePregnancy loss defined as no live birth compared with live birth among those who had a preceding positive ultrasound.

the robustness of these results by replicating this analysis with a different exposure cut point (10th vs. 90th percentile) and the RERI results did not meaningfully change.

The multiplicative interaction analysis with DOR diagnosis suggested an interaction with PM_{2.5}, PM₁₀, and NO₂ ($P = 0.002$, 0.005 , <0.001 , respectively) on the likelihood of live birth. The multiplicative interaction for the other infertility diagnoses and air pollution were not statistically significant.

Discussion

Our results suggest that there may be an association between annual average ambient air pollution exposure before IVF cycle and outcomes including decrease in percent of oocytes fertilized, lower likelihood of live birth, and increased likelihood of pregnancy loss although a fair amount of uncertainty remains on the size of these effects. This is consistent with previous studies that found that both long- and short-term exposure to PM_{2.5} and NO₂ were associated with a decrease in fecundability and pregnancy rates in the general population and studies in IVF populations that found decreases in pregnancy and live birth with exposure to PM_{2.5} and PM₁₀.^{15,17,18,29} We found synergistic effects of having one of two specific infertility diagnoses, DOR and male infertility, in addition to having high levels of air pollution exposure on the likelihood of live birth.

Some observed effects for a decreased likelihood of good grade embryo, positive hCG, and increased likelihood of negative ultrasound with higher exposure were attenuated after adjustment by clinic (model 1, eTables 2a, 2b; <http://links.lww.com/EE/A30>). Adjustment for clinic removes between-region variability in the exposure but is necessary to control for differences in clinic-specific practices such as laboratory set-ups. Most of the observed high exposure values were in LA; therefore, limited variability in exposure within regions may have hindered our ability to detect a true effect. In our original design, we planned to include a second known high exposure location, but the clinic did not opt to participate.

Results from sensitivity analyses stratified by clinic indicated some differences by location. There was a significantly lower likelihood of live birth and other outcomes with exposure to higher levels of NO₂ in the San Francisco area (eTable 3; <http://links.lww.com/EE/A30>) and an increased likelihood of live birth and positive hCG in Seattle. This is indicative of unmeasured confounders that differ by region.

To investigate potential bias based on who were included in our study, we conducted two sensitivity analyses. First, excluding those who were listed as “single female” ($n = 100$) or “same-sex partner” ($n = 49$) who did not have a specific infertility diagnosis listed; second, excluding those with male infertility, but not a listed female factor ($n = 1,378$). With these exclusions, the majority of the results were unchanged (eTables 4, 5; <http://links.lww.com/EE/A30>).

We conducted a post-hoc analysis evaluating the association between DTR and IVF outcomes given recent evidence from a study in a US-based IVF population.³⁰ The results from this analysis indicate that DTR is related to a lower likelihood of positive hCG, positive ultrasound, live birth, and higher likelihood of having a negative hCG test among those who had an embryo transfer. We observe more robust findings for near-roadway residence relative to pollutant-specific findings. There are several potential reasons we may see these results. First, the DTR analysis may be picking up effects of other pollutants, such as ozone or volatile organic compounds (VOCs), or effects of a mixture of pollutants not captured in the single pollutant analysis. That is, DTR may be capturing traffic-related air pollution not captured by the pollutant estimation prediction models. Second, the DTR findings may reflect other environmental exposures, such as noise or other aspects of the social environment beyond what our NSES index captures. Both noise and the social environment may be relevant exposures if they impact general maternal stress levels.

We pursued an EM analysis based on sufficient component cause theory that indicates that there may be synergistic effects of exposures without evidence of individual effects.³¹ We hypothesized causal pies including both high air pollution and the presence of a biologically plausible infertility diagnosis. DOR and male infertility were hypothesized as component causes, as both factors are known to be affected by exogenous factors. There is strong existing evidence that male fertility and sperm quality

Table 4**Additive (RERI) and multiplicative effect modification of air pollution exposure and infertility diagnosis on the likelihood of live birth^{a,b}**

Infertility diagnosis	PM _{2.5}			PM ₁₀			NO ₂			Near-roadway ^c		
	RERI	RERI P value	Multiplicative P interaction ^d	RERI	RERI P value	Multiplicative P interaction ^d	RERI	RERI P value	Multiplicative P interaction ^d	RERI	RERI P value	Multiplicative P interaction ^d
Diminished ovarian reserve	-0.13	0.003	0.002	-0.12	0.01	0.005	-0.22	<0.001	<0.001	-0.01	0.93	0.80
Male infertility	-0.06	<0.001	0.20	-0.08	<0.001	0.19	-0.16	<0.001	0.12	-0.04	0.80	0.01
Ovulation disorders	-0.01	0.91	0.95	0.02	0.52	0.50	0.04	0.45	0.42	-0.06	0.61	0.66
Tubal disorder	0.07	0.21	0.20	0.03	0.55	0.54	0.09	0.13	0.12	-0.22	0.10	0.13

^aAir pollution exposure defined as high at 75th percentile versus low at 25th percentile of exposure.^bModel adjustment: age, race, BMI, clinic location, other infertility factors (diminished ovarian reserve, male factor, ovulation disorder, tubal disorder).^cDTR dichotomized as near-roadway residence versus not near road residence. Near-roadway defined as within 100 m of an A1 or A2 or within 50 m of an A3 class roadway.^dP interaction using continuous exposure measures.

and growing evidence that oocyte quality and ovarian function are impacted by environmental factors.^{8,9,32,33} We evaluated EM of tubal factor diagnosis expecting a null result given that these are primarily the result of physiological complications unrelated to environmental factors. Evaluation of EM for ovulation disorder was done in an exploratory manner.

The EM results should be interpreted cautiously. The main analysis represents an averaging of effect over the subpopulations defined by infertility diagnosis, the additive negative effects seen for DOR and male infertility imply additive positive effects for the other subgroups (those without DOR or without male infertility), which is contrary to biologic plausibility.³⁴ After further investigation of participants with tubal factors in our study population, we found that most of these individuals had undergone treatment for their tubal infertility factor, which is known to increase IVF success.^{35,36} Having a tubal factor may act as a proxy for treatment and may bias the main results toward the null.³⁴

These EM results do not have direct clinical implications, instead the type of infertility may be relevant to the overall biologic mechanisms that connect air pollution to IVF and pregnancy outcomes. This is supported by recent evidence from the Nurses' Health Study that found an increased risk of overall infertility with increased long-term exposure to PM and proximity to roadway.¹⁶

To date, there are few epidemiologic studies evaluating air pollution exposure within the IVF setting.^{17,30,37} Most evidence supporting this association comes from animal models. Evidence from mouse models indicates that exposure to PM_{2.5} is associated with embryo development, exposure to NO₂ and PM₁₀ are associated with increased implantation failure, and NO₂, PM_{2.5}, and PM₁₀ are associated decreases in live birth.^{38,39} An epidemiological study in the IVF setting found that higher average NO₂ exposure from medication start to hCG test was associated with reduced pregnancy and birth, and that higher PM_{2.5} both at patient address and at IVF lab address were associated with lower pregnancy.¹⁷ A study of women undergoing IVF in Brazil, which has higher overall levels of air pollution exposure, found that women with high PM₁₀ exposure during early pregnancy (first 14 days), had a higher risk of miscarriage compared with women with lower exposure.³⁷ Our study provided weak evidence of an association between higher PM_{2.5} and NO₂ exposure and decreased likelihood of live birth and evidence of near-roadway residence on the likelihood of a positive pregnancy test in women undergoing IVF.

The mechanisms by which air pollution may affect fecundity are unknown. Hypothesized pathways include increases in maternal and intrauterine oxidative stress and inflammation.⁴⁰ Increased levels of systemic oxidative stress resulting from PM

exposure may influence growth of the embryo and fetus during early development potentially through DNA damage; increased systemic inflammation may also influence transplacental nutrient exchange limiting the ability of the fetus to obtain adequate nutrients for proper growth and development.⁴¹ Other proposed mechanisms include effects of exposure on the ability of the early embryo to implant.⁴²

Our study has a few limitations. Women seeking fertility treatment are likely higher SES and therefore exposed to lower air pollution levels compared with the general population. This limits the generalizability of our study and reduced variability in exposure may limit our ability to observe effects.

This study was limited to women who are eligible for treatment via IVF and were treated at private clinics. Those who have low likelihood to have success via IVF often are not offered or do not pursue treatment due to clinical, personal, and financial reasons. This study is limited to those with the means and opportunity to pursue treatment at a private clinic, thus may be biased compared with the overall population undergoing IVF as private clinics may be differentially selective in who they accept as patients. Our study population was restricted to women who responded well to early cycle factors, particularly hormonal stimulation, so our study population potentially excluded those who have the most vulnerability due to clinical factors. Given these factors, the generalizability of our study may be limited.

Initial analysis plans included a sensitivity model adjusting for prior gravidity and parity. Whether prior gravidity and parity should be considered confounders in fertility and pregnancy research is unclear as they may be on the causal pathway potentially results in over-adjustment.^{43,44} Time at which gravidity and parity were recorded on the medical record was unclear, thus we decided not to report this given the inability to confirm if values were recorded at the start of cycle or a future time point. We opted not to include smoking as a covariate in our regression analysis due to the amount of missing data and the poor quality of this variable as smoking status was not consistently recorded on the medical record. A sensitivity analysis indicated that inclusion of smoking for those who had nonmissing data did not influence results. These limitations are a result of the use of clinical data from medical record systems without additional confirmation. Other potential unmeasured confounders may include individual-level socioeconomic and neighborhood characteristics.

Misclassification of exposure due to incorrect residential addresses could bias our findings. A study on air pollution exposure during pregnancy in a cohort based on an HMO population estimated that 18.6% of their study population moved during pregnancy and estimated a bias of 2%–10% toward the null when using residence at birth as compared with an address

history; another birth cohort estimated that 24% of their study population moved during pregnancy.^{45,46} The residential address available for exposure prediction was the residential address on file with the clinic at the time of data extraction. There was no way to confirm if address at time of IVF cycle matched the address on record at the time of data extraction. Also, there is no information on address history, so there is no way to know whether this was the correct address for the year before start of IVF cycle. This misclassification is likely nondifferential, and would attenuate observed results toward the null.

Finally, a sensitivity analysis was conducted for a subset of locations and participants using exposure estimates predicted using a spatiotemporal model developed for the MESA-Air study (eTable 6; <http://links.lww.com/EE/A30>). The results for PM_{2.5} and for NO₂ had similar effect estimates but resulted in narrower confidence intervals despite the smaller sample size. This suggests that the wide confidence intervals in the main analysis may be partially attributable to exposure misclassification by space or time, because the spatiotemporal models provide superior temporal resolution and within-region variability.

This study took advantage of a well-characterized exposure prediction model known to produce high-quality air pollution estimates. It also included locations known to have high and low air pollution levels within the United States to ensure variability in the exposure. To our knowledge, this study is the first to examine long-term exposure to air pollution in the IVF setting. Those undergoing IVF are likely the most vulnerable to additional assaults on their reproductive capability thus investigating how environmental exposures may influence the likelihood of success among this population is worthwhile. The use of a single clinical network enhanced uniformity across reporting of all clinical data.

Given that this overall study population had generally low exposure levels, for the most part well below federal guidelines, suggests that a stronger effect may be seen in areas with higher levels of exposure. In addition to the inclusion of participants in areas known to have higher levels of exposure, future research in this area would benefit from the use of prospective studies and the collection of address history from participants which would allow a more accurate measure of exposure to air pollution before pregnancy. Also, future research should consider and potentially focus on diminished ovarian reserve and male infertility in relation to ambient exposure to air pollution.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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