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Ambient air pollution and *in vitro* fertilization treatment outcomes

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Abstract

STUDY QUESTION: Is air pollution associated with IVF treatment outcomes in the USA?

SUMMARY ANSWER: We did not find clear evidence of a meaningful association between reproductive outcomes and average daily concentrations of particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and ozone (O_3).

WHAT IS KNOWN ALREADY: Maternal exposure to air pollution such as $PM_{2.5}$, nitrogen oxides, carbon monoxide or O_3 may increase risks for adverse perinatal outcomes. Findings from the few studies using data from IVF populations to investigate associations between specific pollutants and treatment outcomes are inconclusive.

STUDY DESIGN, SIZE AND DURATION: Retrospective cohort study of 253 528 non-cancelled fresh, autologous IVF cycles including 230 243 fresh, autologous IVF cycles with a transfer of ≥ 1 embryo was performed between 2010 and 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We linked 2010–2012 National ART Surveillance System data for fresh, autologous IVF cycles with the ambient air pollution data generated using a Bayesian fusion model available through the Centers for Disease Control and Prevention's Environmental Public Health Tracking Network. We calculated county-level average daily $PM_{2.5}$ and O_3 concentrations for three time periods: cycle start to oocyte retrieval (T1),

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Authors' roles

Substantial contribution to conception and design: S.B., M.S. and Y.Z. Data acquisition: S.B., M.S., Y.Z., J.S. and D.K. Data analysis: S.B., M.S. and Y.Z. Data interpretation and revising the manuscript for important content: all authors. Drafting the article: S.B., M.S. and Y.Z. Final approval of the article: all authors.

Conflict of interest

The authors have nothing to declare. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

oocyte retrieval to embryo transfer (T2) and embryo transfer + 14 days (T3). Multivariable predicted marginal proportions from logistic and log-linear regression models were used to estimate adjusted risk ratios (aRR) and 95% CI for the association between reproductive outcomes (implantation rate, pregnancy and live birth) and interquartile increases in $PM_{2.5}$ and O_3. The multipollutant models were also adjusted for patients and treatment characteristics and accounted for clustering by clinic and county of residence.

MAIN RESULTS AND THE ROLE OF CHANCE: For all exposure periods, O_3 was weakly positively associated with implantation (aRR 1.01, 95% CI 1.001–1.02 for T1; aRR 1.01, 95% CI 1.001–1.02 for T2 and aRR 1.01, 95% CI 1.001–1.02 for T3) and live birth (aRR 1.01, 95% CI 1.002–1.02 for T1; aRR 1.01, 95% CI 1.004–1.02 for T2 and aRR 1.02, 95% CI 1.004–1.03 for T3). $PM_{2.5}$ was not associated with any of the reproductive outcomes assessed.

LIMITATIONS, REASONS FOR CAUTION: The main limitation of this study is the use of aggregated air pollution data as proxies for individual exposure. The weak positive associations found in this study might be related to confounding by factors that we were unable to assess and may not reflect clinically meaningful differences.

WIDER IMPLICATIONS OF THE FINDINGS: More research is needed to assess the impact of air pollution on reproductive function.

STUDY FUNDING/COMPETING INTEREST(S): None.

Keywords

IVF; air pollution; fine particulate matter ($PM_{2.5}$); ozone (O_3); air quality; pregnancy

Introduction

Since 1981, ART, defined as fertility treatments in which both eggs and embryos are handled, has been increasingly used in the USA to treat infertility (Centers for Disease Control and Prevention, 2018a). In 2016, over 260 000 ART cycles were performed at US fertility clinics, resulting in nearly 77 000 live born infants (Centers for Disease Control and Prevention, 2018b). IVF is the most common type of ART and involves the surgical removal of eggs from a woman’s ovaries and fertilization with sperm in the laboratory. After fertilization is confirmed, the resulting embryos are either returned to the uterus or frozen for future use. While many factors affect embryo development during IVF, results from some studies suggest that poor air quality in clinical embryology laboratories may be associated with decreased rates of fertilization, blastocyst conversion, implantation, pregnancy and live birth (Cohen et al., 1997; Hall et al., 1998; Heitmann et al., 2015; Morbeck, 2015; Munch et al., 2015; Esteves and Bento, 2016). Accordingly, use of air filtration equipment, especially systems that remove volatile organic compounds (VOCs), has been shown to improve the outcomes (Boone et al., 1999; Khoudja et al., 2013; Heitmann et al., 2015; Morbeck, 2015; Munch et al., 2015).

Findings from a growing body of research also suggest that maternal exposure to air pollution such as particular matter (PM), nitrogen dioxide (NO_2), carbon monoxide (CO), VOCs or ozone (O_3) may increase risks for adverse perinatal outcomes including

hypertensive disorders of pregnancy (Hu et al., 2014), pregnancy loss (Ha et al., 2017a), preterm birth (Lamichhane et al., 2015; Li et al., 2017), low birth weight (Berry and Bove, 1997; Lamichhane et al., 2015) and low infantile growth (Chang et al., 2017). However, results are inconsistent, possibly due to differences in study design, populations and exposures. Some studies failed to detect an association (Savitz et al., 2015; Johnson et al., 2016), and others suggested that factors such as temperature (Giorgis-Allemand et al., 2017; Ha et al., 2017b) or atmospheric pressure (Giorgis-Allemand et al., 2017) play a more important role than air pollution in predicting poor birth outcomes. The mechanism by which air pollution influences pregnancy outcomes is not known; however, it has been hypothesized that pollution-associated increases in oxidative stress and inflammation may lead to perturbations in fetal growth and development (Ferguson and Chin, 2017).

IVF treatment cycles present a unique opportunity to study air pollution because timing of conception is known with certainty, and reproductive outcomes such as embryo implantation can be assessed. To date, findings from the few studies that have investigated associations between specific pollutants and treatment outcomes have been variable. For example, findings from two Brazilian studies indicated an association between exposure to fourth quartile particulate matter with aerodynamic diameter <10 μm (PM_{10}) concentrations and increased rates of miscarriage, but with no difference in rates of implantation and pregnancy (Perin et al., 2010a,b). An US study found that the odds of pregnancy and live birth decreased with increasing concentrations of NO_2 both at the patient's address and the fertility clinic during all phases of treatment from cycle start to pregnancy testing (Legro et al., 2010). However, while fine particulate matter at embryology laboratories was associated with decreased odds of pregnancy, no effect was noted for other outcomes or exposure periods (Legro et al., 2010). Among Korean women undergoing IVF, exposure to high levels of PM_{10}, NO_2 and CO during controlled ovarian stimulation and after embryo transfer was associated with reduced probability of pregnancy (Choe et al., 2018). Lastly, a retrospective study at a French university hospital found that acute exposure to high levels of NO_2 and PM_{10} was associated with lower ovarian response and fewer high-quality embryos (Carre et al., 2017a). Although these studies provide some evidence of an association between air pollution and IVF outcomes, the results are contradictory and inconclusive. In addition, some of the studies are old and limited by small sample size. The aim of the current study was to use recent data from a large, national surveillance system to further investigate the association between county-level particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$) and O_3 exposure and treatment outcomes among women undergoing IVF treatment.

Materials and Methods

Study population

We used data from the Centers for Disease Control and Prevention's (CDC) National ART Surveillance System (NASS), a national reporting system for the collection of information on ART cycles performed in the US fertility clinics, as required by the Fertility Clinic Success Rates and Certification Act (US GPO, 1992). NASS includes information on nearly all (98%) cycles performed in the USA and contains data on patient demographics, obstetrical and medical history, ART treatment procedures, and resultant pregnancies and

births. To verify accuracy of reporting, a random sample of fertility clinics that submit data to NASS is selected annually for data validation and trained abstractors visit the clinics and compare reported data with medical records. In 2016, discrepancy rates were <6% for all fields examined (Centers for Disease Control and Prevention, 2018a).

Our study included all fresh embryo, autologous oocyte IVF cycles that were started between 2010 and 2012 and were not cancelled prior to oocyte retrieval (n = 270 898). We excluded cycles that used a gestational carrier (n = 2556), cycles for patients that were non-US residents (n = 10 309), cycles with missing information on patient residential ZIP code (n = 755) and cycles for patients residing in or clinics located in Alaska, Guam, Hawaii, Puerto Rico, American Samoa and the US Virgin Islands (n = 2589) because air quality data were not available for those locations. Using the US Department of Housing and Urban Development (HUD) (2018) ZIP code crosswalk file, we allocated the US Postal Service ZIP codes collected in NASS to counties. For ZIP codes that spanned more than one county, we employed the fixed allocation approach and assigned the ZIP code to the county with the highest weight. This method has been found to yield the greatest accuracy at an individual level (Hibbert et al., 2009).

Assessment of exposure

The air pollution data used for this study were provided by the US Environmental Protection Agency (EPA) for CDC's Environmental Public Health Tracking Network. These data include predictive $PM_{2.5}$ (daily average) and O_3 concentrations (daily 8 hours maximum) generated using Bayesian downscaler models that incorporate air-quality-monitoring data from the National Air Monitoring Stations/State and Local Air Monitoring Stations and numerical output from the Models-3/Community Multiscale Air Quality. These models provide complete information for the entire contiguous United States and perform better than numerical models alone (Berrocal et al., 2010). After excluding daily $PM_{2.5}$ and O_3 concentrations beyond three standard deviations (outliers) from the mean for each census tract (1.5%), we linked the air pollution data with the NASS data by county. Of the 254 689 IVF cycles eligible for linkage with the air pollution data, 1161 (0.45%) were excluded because the ZIP codes could not be linked with the HUD ZIP code crosswalk file. After excluding those 1161 cycles, a total of 253 528 fresh, autologous oocyte retrieval cycles were linked with the air pollution exposure data and included in the analysis.

We calculated average daily $PM_{2.5}$ ($\mu g/m^3$) and O_3 exposures (ppb) for three exposure periods: interval between date of cycle start and date of oocyte retrieval, interval between date of oocyte retrieval and date of embryo transfer, and interval between date of transfer +14 days (which included the implantation window and few days postimplantation). For the period between oocyte retrieval and embryo transfer when the embryo is cultured in the laboratory, air pollution measurements from the clinic location were used; all other periods used the information on exposure at the patient's residence.

Statistical analyses

We examined the distributions of patient and treatment characteristics for all cycles. We also calculated mean and median $PM_{2.5}$ and O_3 concentrations during the three exposure periods.

For each exposure period, we classified $PM_{2.5}$ and O_3 concentrations into quartiles and used multivariable predicted marginal proportions from logistic and log-linear regression models to estimate adjusted risk ratios (aRR) and 95% CI for the association between select reproductive outcomes and an interquartile increase in average air pollutant concentration. The outcomes of interest were rates of implantation, pregnancy (clinical intrauterine gestation) and live birth (the live birth of at least one infant >20 weeks of gestational age). For the exposure period between cycle start and oocyte retrieval, all non-cancelled cycles were included in the analysis. For the periods between oocyte retrieval and embryo transfer and embryo transfer +14 days, embryo transfers were analyzed (among cycles with the transfer of one or more embryos). Implantation rates were calculated as the number of embryos implanted (assessed by fetal heartbeats) divided by the total number of embryos transferred. When the number of embryos' fetal heartbeats was missing, we used the number of live and stillborn infants. If number of fetal heartbeats and number of live and stillborn infants were missing, the implantation rate was considered missing. There is currently no national database of the concentrations of NO_2, CO and VOCs by county in the USA. Because traffic is a significant source for these pollutants, we used CDC's urban/rural classification for each county as a proxy for traffic emission (Ingram and Franco, 2014). The urban category includes large central and fringe metropolitan areas, medium metropolitan areas and small metropolitan areas. The rural category includes micropolitan and non-metropolitan areas. We used multipollutant models that included $PM_{2.5}$, O_3 and urban/rural classification as well as covariates selected *a priori* (patient age, parity, infertility diagnosis, number of prior ART cycles, number oocytes retrieved, and season and year of cycle start). We included confounders that have been shown to be associated with the outcome and a risk factor for the outcome and that are not known to be affected by the exposure or disease (Rothman et al., 2008). The models also accounted for clustering by county and fertility clinic. We used SAS 9.4 (SAS Institute, Cary, North Carolina, USA) and SUDAAN 11.0 (RTI International, Research Triangle Park, North Carolina, USA) for all analyses.

Sensitivity analysis

To account for heterogeneity of the population of women using IVF, we conducted a sensitivity analysis of the associations between reproductive outcomes and $PM_{2.5}$ and O_3 restricted to first-time IVF patients (women with no prior IVF cycles) and women <35 years of age.

To assess confounding by pollutants for which national monitoring data are not available, we acquired average daily summary data on NO_2, sulfur dioxide (SO_2) and CO for a subset of counties during 2010–2012 (US Environmental Protection Agency, 2019) and merged this information with $PM_{2.5}$ and O_3 data. We used Pearson correlation coefficients to evaluate linear relationships between the five pollutants and found a moderate positive correlation between NO_2 and CO ($r_p = 0.41$), both of which are traffic-related pollutants. Given potential problems with model stability when correlated pollutants are included (Dominici et al., 2010) and recent data suggesting that nitrogen oxides are the best proxy measure for complex urban air pollution mixtures (Levy et al., 2014), we opted to exclude CO from the sensitivity analysis. As in the main analysis, we linked the air pollution data with the

NASS data by county and used multivariable predicted marginal proportions from logistic and log-linear regression models to estimate aRRs and 95% CIs for associations between reproductive outcomes and concentrations for the four pollutants. To examine the individual and combined effects of adding NO_2 and SO_2 to the model, we constructed three separate multipollutant models: (i) including $PM_{2.5}$, O_3 and NO_2; (ii) including $PM_{2.5}$, O_3, and SO_2 and (iii) including $PM_{2.5}$, O_3, NO_2 and SO_2. The models included the same covariates as the models for the entire study population, with the exception of the urban/rural classification variable.

Ethical approval

This study was approved by CDC's Institutional Review Board.

Results

Characteristics of study population

Of the 253 528 fresh, autologous cycles included in the analysis, 230 243 involved the transfer of one or more embryos. Approximately, one-third of all fresh, autologous cycles were performed among women 35–39 years of age, and most (>71%) were nulliparous (Table I). Male factor infertility (37.6%) and diminished ovarian reserve (24.0%) were the most commonly reported infertility diagnoses. A vast majority of women (95.4%) lived in an urban area. Rates of implantation, pregnancy and live birth per transferred cycle were 25.9, 40.5 and 33.2%, respectively.

Air pollution concentrations

The mean concentrations of $PM_{2.5}$ ranged from 9.2 to 9.5 μg/m^3 by exposure period (Table II). Median $PM_{2.5}$ concentrations were also similar (9.1–9.2 μg/m^3). Mean and median O_3 concentrations were approximately 38 ppb regardless of exposure period.

Air pollution and IVF outcomes

Results from the unadjusted models are presented in Supplementary Table SI. In the adjusted models, O_3 was weakly positively associated with implantation for all exposure periods (cycle start to oocyte retrieval, aRR 1.01, 95% CI 1.001–1.02; oocyte retrieval to embryo transfer, aRR 1.01, 95% CI 1.001–1.02 and embryo transfer +14 days, aRR 1.01, 95% CI 1.001–1.02) and with live birth for all exposure periods (cycle start to oocyte retrieval, aRR 1.01, 95% CI 1.002–1.02; oocyte retrieval to embryo transfer, aRR 1.01, 95% CI 1.004–1.02 and embryo transfer +14 days (aRR 1.02, 95% CI 1.004–1.03) (Table III). $PM_{2.5}$ was not associated with any of the reproductive outcomes or exposure periods assessed.

Sensitivity analyses

Results were similar when the study population was restricted to first-time patients and women <35 years (Supplementary Tables SII and SIII).

Information on $PM_{2.5}$, O_3, NO_2 and SO_2 concentrations was available for 4.4% (119/2695) of counties included in the full analysis and accounted for approximately 37% (n = 88 494) of the total number of cycles. The median concentrations and interquartile ranges for

$PM_{2.5}$, O_3, NO_2 and SO_2 during the period from cycle start to oocyte retrieval were 8.6 (4.1) μg/m^3, 38.7 (15.6) ppb, 11.7 (6.1) ppb and 0.9 (1.1) ppb, respectively. In models with $PM_{2.5}$, O_3 and NO_2, we found that NO2 was negatively associated with implantation for all exposure periods (Supplementary Tables SIV-SVI). In models with $PM_{2.5}$, O_3 and SO_2, SO_2 was negatively associated with all reproductive outcomes in all exposure periods. In models with all four pollutants, patterns were similar although aRRs for NO_2 were attenuated in pregnancy and birth models (Supplementary Tables SV and SVI). Inclusion of NO_2 or SO_2 in the models resulted in weak positive associations between $PM_{2.5}$ and outcomes for some exposure periods. Ozone was not associated with any of the outcomes in any of the exposure periods when $PM_{2.5}$ and NO_2, SO_2 or both were included in the models.

Discussion

Using national data on fresh, autologous IVF cycles performed in the USA between 2010 and 2012, we did not find clear evidence of a meaningful association between reproductive outcomes and average daily concentrations of $PM_{2.5}$ and O_3. Overall, our findings of weak associations between O_3 and implantation and live birth are consistent with other studies that found exposure to high levels of O_3 during the follicular phase was associated with moderately increased odds of live birth (Legro et al., 2010) and improvements in ovarian response and embryo quality (Carre et al., 2017a). However, the results of our sensitivity analysis indicate that other pollutants such as NO_2 and SO_2 may influence relationships between O_3 and IVF outcomes. Similar to studies conducted by Legro et al. (2010) and Carre et al. (2017a), we found that associations between O_3 and rates of implantation and live birth were attenuated when other pollutants were included in the model. Ozone and some $PM_{2.5}$ are secondary air pollutants, which are not directly emitted but form when primary pollutants react in the atmosphere. Ozone forms when hydrocarbons and nitrogen oxides combine in the presence of sunlight, and there could be substantial non-linearities in this process (Sillman, 1999; Zhou et al., 2014). For example, reductions in nitrogen oxide emissions can lead to either increases or decreases in O_3 concentration, depending on the atmospheric conditions. In our sensitivity analysis, we found that NO_2 and O_3 were weakly negatively correlated ($r_p = -0.22$). It should also be noted that multipollutant models can produce biased risk estimates when two pollutants are correlated, but only one is an independent risk factor for the outcome of interest (Tolbert et al., 2007).

Overall, we did not find an association between $PM_{2.5}$ and rates of implantation, pregnancy or live birth among this population of women undergoing IVF. Although particulate matter has been shown to be associated with increased risk for infertility (Carre et al., 2017b), spontaneous abortion (Grippo et al., 2018) and stillbirth (Siddika et al., 2016; Grippo et al., 2018) in the general population, there is little information specific to women undergoing IVF. Results of one study suggested that increased $PM_{2.5}$ concentration at the embryology laboratory was associated with decreased rates of pregnancy; however, no effects were found during other periods of exposure (Legro et al., 2010). Another study found that PM_{10} levels during the interval between embryo transfer and pregnancy testing were inversely associated with pregnancy (Choe et al., 2018). When we included O_3, NO_2 and SO_2 in the models, $PM_{2.5}$ was weakly positively associated with pregnancy and live birth, suggesting potential synergistic or antagonistic effects among this combination of pollutants.

Strengths of our study include the use of a large, national dataset that represents at least 98% of all ART cycles in the USA. Ours is the largest study to date to examine associations between air pollution and IVF outcomes. In addition, these data were derived from a national surveillance system that uses yearly audits, site visits and data validation processes to ensure the accuracy of the data. Reported discrepancy rates for these data were at or below 6% for all fields validated in 2015 (Centers for Disease Control and Prevention, 2018a). We were also able to control for important confounders such as infertility diagnosis and number of oocytes retrieved. The $PM_{2.5}$ and O_3 predictions generated by the Bayesian downscaler model used in our study provide complete spatial and temporal coverage for the entire contiguous United States, and our estimates were consistent with national data on air quality (US Environmental Protection Agency, 2012). Furthermore, compared with Bayesian melding and ordinary kriging, predictions from this Bayesian downscaler model have been shown to perform better, as evidenced by better calibration and generation of predictive intervals with empirical coverage closer to the nominal values (Berrocal et al., 2010).

Our findings are also subject to several limitations. The main limitation of this study is the use of aggregated air pollution data as proxies for individual exposure. Second, we did not have access to national data on other pollutants such as nitrogen oxides, SO_2, CO and VOCs. Although we were unable to fully account for other pollutants in our models, we included a variable indicating urban versus rural residence as a surrogate for these exposures. We also conducted a sensitivity analysis that accounted for concurrent SO_2 and NO_2 exposures in a subset of the study population. Third, we did not have personal exposure information for women undergoing IVF treatment. For example, we lacked data on potentially important confounders such as maternal occupation and place of employment, which could impact personal exposure (Izawa et al., 2007; Guven et al., 2008). Because exposure before oocyte retrieval and after embryo transfer was assigned by residence at cycle start, we could not account for exposures at other locations and the degree to which women spent time at locations other than their residence. In addition, if a woman relocated after the cycle was started, her residential exposure may have been misclassified. The patient-level identifiers in the NASS database are clinic specific. Therefore, we were unable to account for correlations between cycles for women who contributed multiple cycles as women may change clinics during the course of treatment. However, the results of the sensitivity analysis restricted to patients with no previous cycles are consistent with the full sample. Also, most people spend the majority of their time indoors, and we did not have data on the indoor residential or workplace air quality. While indoor and outdoor air qualities may differ, we assume that they were at least correlated and that indoor air quality is reflective of outdoor air quality. We were not able to assess the types of air filtration systems used at individual clinics. As such, our use of outdoor air quality only could lead to exposure misclassification. Finally, the effect estimates for this observational study were small and may be explained by residual confounding.

Our analysis only took into consideration women undergoing IVF, and it is unknown whether these women are more or less vulnerable than the general population to air pollutants. For outcomes such as atherosclerosis, associations with fine particles in some studies appear to be gender specific, with postmenopausal women being the most susceptible (Kunzli, 2013). Likewise, results from one study indicated that the association

between $PM_{2.5}$ and preterm birth among certain subgroups of women (e.g. women over 30 years of age, women with low educational attainment, women working as farmers and women with previous pregnancies) was stronger, suggesting an increased sensitivity to air pollution for women with certain characteristics. While the findings of our study were consistent when restricted to first-time patients and women younger than 35, there may be other characteristics of women undergoing IVF that affect their susceptibility. Notably, acute exposure to air pollution may be associated with reduced fecundity (Nobles et al., 2018).

Although there is evidence that exposure to air pollution can reduce both the quantity and quality of gametes (Carre et al., 2017b) and may contribute to adverse birth outcomes (Lamichhane et al., 2015; Grippo et al., 2018), we did not find convincing evidence of an association between air pollutants and reproductive outcomes in the present study. However, given the array of pollutants to which women may be exposed and the complex temporal and spatial interactions between pollutants, it is difficult to assess the role of individual exposures. Our analysis was limited to women undergoing IVF, whose exposure patterns and risk factors may be different from general population of reproductive aged women in the USA. Future national studies are needed to examine reproductive outcomes in the context of additional pollutants and taking into account variations in individual-level exposures as well as the potential confounding effects of indoor air quality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Patient and treatment characteristics of fresh, autologous ART cycles, 2010—2012.

	Cycles with oocyte retrieval (*n* = 253 528)
Characteristic	***N* (%)**
Female patient age	
<30	31 711 (12.5)
30–34	79 170 (31.2)
35–39	87 936 (34.7)
≥40	54 711 (21.6)
Parity	
0	180 077 (71.4)
≥1	72 145 (28.6)
Infertility diagnosis[a]	
Tubal factor	38 950 (15.4)
Endometriosis	26 120 (10.3)
Uterine factor	12 438 (4.9)
Ovulatory dysfunction	37 204 (14.7)
Diminished ovarian reserve	60 895 (24.0)
Male factor	95 383 (37.6)
Unexplained	35 312 (13.9)
Prior IVF cycles	
0	144 952 (57.2)
1	50 204 (19.8)
>1	58 272 (23.0)
Number of oocytes retrieved	
0–4	36 528 (14.4)
5–9	73 323 (28.5)
10–20	110 530 (43.6)
>20	34 147 (13.5)
Year cycle started	
2010	84 368 (33.3)
2011	85 586 (33.8)
2012	83 574 (33.0)
Season cycle started	
Winter	66 546 (26.2)
Spring	64 641 (25.5)
Summer	64 898 (25.6)
Fall	57 443 (22.7)
Urban/rural classification	
Urban	241 913 (95.4)
Rural	11 615 (4.6)

[a]Infertility diagnoses are not mutually exclusive. Patients can have more than one diagnosis unless unexplained infertility is reported.

Table II

Distribution of average air pollution concentrations for each exposure period.

	Mean (SD)	Median (IQR)
$PM_{2.5}$ μg/m^3)		
Cycle start to oocyte retrieval (patient residence)	9.3 (2.4)	9.1 (3.3)
Oocyte retrieval to embryo transfer (clinic location)	9.5 (3.1)	9.2 (4.2)
Embryo transfer +14 days (patient residence)	9.2 (2.3)	9.1 (3.2)
O_3 (ppb)		
Cycle start to oocyte retrieval (patient residence)	38.4 (10.1)	38.5 (15.9)
Oocyte retrieval to embryo transfer (clinic location)	38.1 (11.2)	37.6 (16.9)
Embryo transfer +14 days (patient residence)	38.5 (9.9)	38.7 (15.6)

Abbreviations: IQR, interquartile range; $PM_{2.5}$, particulate matter with diameter of 2.5 μm or less; ppb, parts per billion.

Table III

Associations between interquartile range increases in particulate matter with diameter of 2.5 μm or less ($PM_{2.5}$) and O_3 and implantation, pregnancy, and live birth, by time of exposure.

	$PM_{2.5}$			O_3		
	Implantation*	**Pregnancy**	**Live birth**	**Implantation***	**Pregnancy**	**Live birth**
Exposure period	**aRR‡ (95% CI)**	**aRR‡ (95% CI)**	**aRR‡ (95% CI)**	**aRR‡ (95% CI)**	**aRR‡ (95% CI)**	**aRR‡ (95% CI)**
Cycle start to oocyte retrieval	1.00 (0.99–1.004)	1.00 (0.99–1.01)	1.00 (0.99–1.02)	1.01 (1.001–1.02)	1.01 (0.997–1.02)	1.01 (1.002–1.02)
Oocyte retrieval to embryo transfer§	1.00 (0.99–1.004)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.01 (1.001–1.02)	1.01 (1.000–1.02)	1.01 (1.004–1.02)
Embryo transfer +14 days§	1.00 (0.98–1.004)	1.00 (0.99–1.01)	0.99 (0.97–1.01)	1.01 (1.001–1.02)	1.01 (1.000–1.02)	1.02 (1.004–1.03)

Abbreviations: aRR, adjusted risk ratio.

*Calculated as the number of embryos implanted divided by the total number of embryos transferred; if number of fetal heartbeats and number of live and stillborn infants was missing, then implantation rate was considered missing.

‡Models included $PM_{2.5}$, O_3, patient age, parity, infertility diagnosis, number prior IVF cycles, number of oocytes retrieved, season, urban versus rural county designation, and year and accounted for clustering by county and clinic.

§Restricted to cycles with transfer of 1 or more embryos.