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Residential proximity to major roadways and traffic in relation to outcomes of in vitro fertilization

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ABSTRACT

Background: Emerging data from animal and human studies suggest that traffic-related air pollution adversely affects early pregnancy outcomes; however evidence is limited.
Objective: We examined whether residential proximity to major roadways and traffic, as proxies for traffic-related air pollution, are associated with in vitro fertilization (IVF) outcomes.
Methods: This analysis included 423 women enrolled in the Environment and Reproductive Health (EARTH) Study, a prospective cohort study, who underwent 726 IVF cycles (2004–2017). Using geocoded residential addresses collected at study entry, we calculated the distance to nearest major roadway and the traffic density within a 100 m radius. IVF outcomes were abstracted from electronic medical records. We used multivariable generalized linear mixed models to evaluate the associations between residential proximity to major roadways and traffic density and IVF outcomes adjusting for maternal age, body mass index, race, education level, smoking status, and census tract median income.
Results: Closer residential proximity to major roadways was statistically significantly associated with lower probability of implantation and live birth following IVF. The adjusted percentage of IVF cycles resulting in live birth for women living ≥400 m from a major roadway was 46% (95% CI 36, 56%) compared to 33% (95% CI 26, 40%) for women living < 50 m (p-for-comparison, 0.04). Of the intermediate outcomes, there were suggestive associations between living closer to major roadways and slightly higher estradiol trigger concentrations (p-trend = 0.16) and lower endometrial thickness (p-trend = 0.06). Near-residence traffic density was not associated with outcomes of IVF.
Conclusion: Closer residential proximity to major roadways was related to reduced likelihood of live birth following IVF.

1. Introduction

Traffic emissions are a major source of local variability in air pollution levels (European Environment Agency (EEA), 2016; Singh et al., 2014), with the highest concentrations and risk of exposure occurring near major roadways (Karner et al., 2010). Motor vehicle emissions represent a complex mixture of air pollutants, including carbon dioxide (CO_2), carbon monoxide (CO), nitrogen oxides (NO_x), hydrocarbons, volatile organic compounds (VOCs), and particulate matter (Health Effects Institute (HEI), 2010). Each of these components, along with their secondary by-products, such as ozone and secondary aerosols, can adversely affect health (Health Effects Institute (HEI), 2010). Of the motor vehicle generated air pollutants, diesel exhaust particles (DEPs) account for a high percentage of the particles emitted in many towns and cities (United Nations Environment Program (UNEP), 1994) and are almost exclusively found in the submicrometer fraction. While DEPs represent a complex and variable mixture of components, their content of elemental and organic carbon, polycyclic aromatic hydrocarbons, and metals have received the most attention as the components responsible for DEPs negative health effects (Sydbom et al., 2001).

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Because the mixture of traffic-related air pollutants can be difficult to measure and model, many epidemiologic studies rely on measures of traffic (e.g., proximity to major roads and cumulative traffic density within a buffer) as surrogates of exposure.

Over the past decade, chronic exposure to traffic-related air pollution has become increasingly recognized as an important risk factor for adverse pregnancy outcomes (Stieb et al., 2016) including preterm birth (Yorifuji et al., 2011), gestational diabetes (Robledo et al., 2015), preeclampsia (Wu et al., 2009), restricted fetal growth (Fleisch et al., 2015), and low birth weight (Brauer et al., 2008). The proposed biological mechanisms mediating air pollution's effect on these later pregnancy and birth outcomes such as increased oxidative stress (Moller et al., 2014), systemic inflammation (Panasevich et al., 2009), endothelial dysfunction (Wauters et al., 2013), and DNA damage (Risom et al., 2005) could also affect earlier pregnancy outcomes such as fertilization, early embryo development, and implantation. However, limited research has been conducted to this regard.

The objective of this study was to utilize data from an ongoing prospective cohort of couples undergoing in vitro fertilization (IVF) to explore the relationship between proxies of traffic-related air pollution and female reproductive outcomes using a unique model of human reproduction where clinically relevant, yet otherwise unobservable outcomes, such as fertilization and implantation, can be studied.

2. Methods

2.1. Study population

Study participants were recruited into the Environment and Reproductive Health (EARTH) Study between November 2004 and July 2016 from patients presenting for infertility evaluation and treatment at the Massachusetts General Hospital (MGH) Fertility Center. All women between 18 and 46 years of age at enrollment were eligible to participate. Approximately 60% of those contacted by the research nurses participated in the study. Upon enrollment into the study, all participants provided their residential address for reimbursement purposes. Women were then followed through each of their subsequent infertility treatment cycles until discontinuation of treatment or live birth.

Out of the total number of women enrolled in EARTH ($n = 867$) only women who had completed at least 1 IVF cycle by March 2017 and were not undergoing controlled ovarian stimulation with the sole purpose of oocyte banking or egg donation were eligible ($n = 443$). From the initial 443 eligible EARTH women we excluded 20 women whose primary residence was outside of Massachusetts leaving a final sample size of 423 women and 726 IVF cycles (see Fig. S1). Twenty-two of the 423 women re-enrolled in the EARTH study after having a live birth. Of these, only 4 women had moved since their original enrollment. In these instances, the women's new addresses were applied to all cycles initiated after re-enrollment. The EARTH study was approved by the Human Studies Institutional Review Boards of the MGH and the Harvard T.H. Chan School of Public Health. All study participants signed an informed consent after the study procedures were explained by a research nurse.

2.2. Traffic-related air pollution exposures

The residential address of each woman was geocoded using ArcGIS and linked to an official state-maintained street transportation dataset which was downloaded from the Massachusetts Department of Transportation through the Office of Geographic Information (Massachusetts Office of Geographic Information (MassGIS), 2014). This dataset represents all the public and the majority of the private roadways in Massachusetts as of December 2013, including designations for interstates and highways and traffic count information. MassGIS classifies the following as major roadways: limited access highways, multi-lane highways (not limited access), other numbered routes, and major roads that are arterials and collectors. Using ArcGIS, we measured the Euclidian distance in meters from each geocoded residence to nearest major roadway. In the MassGIS data, annual average daily traffic (AADT) count information is reported by segment of road. Near-residence traffic density was defined as the length in kilometers of all roads within 100 m of a residence, multiplied by the annual average daily traffic counts for those roads (vehicles/day). Since not all segments of all roads in Massachusetts have traffic count information, it was possible for a woman to have no road segments within 100 m of her residence with traffic count information.

2.3. Outcome assessment

For fresh IVF cycles, patients underwent one of three stimulation protocols as clinically indicated: 1) luteal-phase GnRH agonist protocol; 2) follicular-phase GnRH-agonist/Flare protocol; or 3) GnRH-antagonist protocol. Patients were monitored during gonadotropin stimulation for serum estradiol, follicle size measurements and counts, and endometrial thickness. Human chorionic gonadotropin (hCG) was administered approximately 36 h before the scheduled oocyte-retrieval procedure to induce oocyte maturation. Couples underwent IVF with conventional insemination or intra-cytoplasmic sperm injection (ICSI) as clinically indicated. The nuclear maturity of oocytes was determined before ICSI but not before conventional insemination/IVF. Embryologists classified oocytes as germinal vesicle, metaphase I, metaphase II (MII) or degenerated. Embryologists determined fertilization 17–20 h after insemination as the number of oocytes with two pronuclei (2PN). The procedures regarding the timing and grading of embryo quality have varied during the follow-up of EARTH patients and thus are not included as an outcome for analysis.

For cryo-thaw cycles or donor egg recipient cycles, patients underwent either the standard endometrial preparation protocol or the resistant endometrium protocol that involves a longer low-dose estradiol period. In cryo-thaw cycles, on day 18 of the standard protocol, patients underwent an ultrasound to determine sufficient endometrial development. If the lining was ≥6 mm then intramuscular progesterone injections (or in very rare instances progesterone vaginal suppositories) began and embryo transfer was scheduled for day 24. In donor egg recipient cycles, patients were assessed for sufficient endometrial development around day 18, progesterone began on the day of donor egg retrieval, and embryo transfer occurred 6 days later (on day 5 of embryonic life).

Following embryo transfer, all clinical outcomes were assessed identically across fresh, cryo-thaw, and donor-egg recipient cycles. Specifically, successful implantation was defined as a serum β-hCG level > 6 mIU/mL typically measured 17 days (range 15–20 days) after egg retrieval, clinical pregnancy as the presence of an intrauterine pregnancy confirmed by ultrasound at 6 weeks gestation, and live birth as the birth of a neonate on or after 24 weeks gestation.

2.4. Covariate assessment

At enrollment, height and weight were measured by a trained research nurse to calculate body mass index (BMI) (kg/m^2) and data on demographics, medical history, and lifestyle characteristics was collected on a brief, nurse-administered questionnaire. Participants also completed a detailed take-home questionnaire with additional questions on lifestyle factors, reproductive health, and medical history. Census tract level median family income in the past 12 months (in 2011 inflation-adjusted dollars) from the American Community Survey 2007–2010 was used as a proxy for socioeconomic status. Clinical information including infertility diagnosis and protocol type was abstracted from electronic medical records.