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Ambient $PM_{2.5}$ and clinically recognized early pregnancy loss: A case-control study with spatiotemporal exposure predictions

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ABSTRACT

Background: Experimental research suggests that ne particulate matter ($PM_{2.5}$) exposure might a ect embryonic development. However, only few population-based studies have investigated the impact of maternal exposure to $PM_{2.5}$ on the early pregnancy loss.

Objectives: To estimate associations between clinically recognized early pregnancy loss (CREPL) and exposure to ambient $PM_{2.5}$ at individual residences during peri-conception periods, with the aim to identify susceptible exposure time windows.

Methods: CREPL cases and normal early pregnancy controls (of similar age and gravidity presenting within one week, a total of 364 pairs) were recruited between July 2017 and July 2018 among women residing in Tianjin, China. Average ambient $PM_{2.5}$ concentrations of ten exposure windows (4 weeks, 2 weeks and 1 week before conception; the rst, second, third and fourth single week, the rst and second 2-week periods, and the entire 4-week period after conception) at the women's residential addresses were estimated using temporally-adjusted land use regression models. Associations between $PM_{2.5}$

physiological systems, and also is the most susceptible stage to environmental chemicals exposure (Cooke, 2014). However, there is less information on the e ects of maternal exposure to $PM_{2.5}$ on human embryonic development during early pregnancy. Relevant research is needed to investigate the exposure-response relationships and exposure-e ect mechanisms, and to provide evidence for adopting appropriate interventions to prevent adverse pregnancy outcomes and possible fetal exposure-related adulthood diseases.

Early pregnancy loss (EPL), also known as miscarriage or spontaneous abortion, is a typical indicator which re ects severe abnormalities of embryonic development. It is one common type of adverse pregnancy outcomes, with an incidence of approximately 10% of all clinically recognized pregnancies (The American College of Obstetricians and Gynecologists, ACOG, 2015). EPL is de ned as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo (prior to 8 weeks post-conception) or fetus (beyond 8 weeks post-conception) without fetal heart activity within the rst trimester (ACOG, 2015). The occurrence of EPL is mainly related to embryonic chromosomal abnormalities, endocrine factors, reproductive immune dysfunction or prethrombotic state, but the upstream factors and pathogenic mechanisms are not completely clear (Practice Committee of the American Society for Reproductive Medicine, 2012; Royal College of Obstetricians and Gynaecologists, RCOG, 2011). Recent studies have suggested that EPL was related to oxidative stress and in ammation in maternal systemic and maternal-fetal interface (Cross et al., 2015; Lyu et al., 2013; Wu et al., 2016; Zhang et al., 2016; Zhu et al., 2017).

Exposure to $PM_{2.5}$ may induce human systemic in ammation and oxidative damage (Feng et al., 2016; Hassanvand et al., 2017; Liu et al., 2015; Moller and Loft, 2010; Pope et al., 2016). Maternal exposure to ambient $PM_{2.5}$ during preconception and speci c periods of pregnancy has been associated with intrauterine in ammation indicated by placental pathology at delivery (Nachman et al., 2016). Additionally, animal experimental studies have found that $PM_{2.5}$ exposure can increase oxidative stress in peripheral blood of pregnant mice and induce placental in ammation and increased absorbed blastocysts in rats (Liu et al., 2017; Liu et al., 2016). Accordingly, we hypothesize that maternal $PM_{2.5}$ exposure during early pregnancy might be associated with EPL, likely through increasing oxidative stress and in ammation.

The epidemiological evidence for e ects of $PM_{2.5}$ on pregnancy loss is still limited (Grippo et al., 2018). Based on our latest literature retrieval until 1 August 2018, there were only three relevant population-based studies. A retrospective study identi ed associations between ambient $PM_{2.5}$ and spontaneous abortion by examining fetal deaths per calendar month based on medical records and monthly average $PM_{2.5}$ concentrations measured at administrative monitoring stations (Enkhmaa et al., 2014). Another retrospective study assessed the relationship between cases of EPL diagnosed in the emergency department and regional daily $PM_{2.5}$ at 3-day and 7-day lags (Sawyer et al., 2018). Recently, a prospective cohort study of 343 pregnancies (including 97 pregnancy losses occurred before 18 weeks of gestation) provided evidence that $PM_{2.5}$ concentrations averaged over the entire pregnancy (chronic exposure) were associated with faster time to pregnancy loss. Ambient $PM_{2.5}$ at two acute exposure windows (2 weeks before ovulation and the last 2 weeks of pregnancy) was also estimated, but was unrelated to risk of pregnancy loss (Ha et al., 2018).

E ects on the pregnant women, the placenta and embryo/fetus from toxic exposures depend on the exposure time window. EPL is a gradual process, and symptoms do not always appear immediately after embryonic or fetal death. It is therefore di cult to determine the speci c time that EPL occurred. Estimating $PM_{2.5}$ exposure during the entire pregnancy or for periods in the latter part of pregnancy, seemed not to be sensible. To some extent, a number of chemical components of $PM_{2.5}$ are also teratogen or at least have some toxicological e ects. According to the U.S. Food and Drug Administration (FDA), teratogen exposures during the rst 2 weeks after conception are not known to cause congenital anomalies; however, such exposures may interfere with implantation of the blastocyst or cause spontaneous abortion. Further, the embryo is most easily disrupted by teratogen exposures during organogenesis (3 to 8 weeks post-conception) (U.S. FDA, 2005).

Although prospective cohort is considered the most perfect design in environmental epidemiological studies, it is unsuitable for subjects' recruitment and exposure assessment of specic disease as EPL. Firstly, portions of EPL do not end up in medical institutions. Sometimes women may not even notice the EPL, and may interpret the EPL as the next menstrual period. Secondly, women usually do not realize that they are pregnant until a menstrual period is missed, by which time the ability to monitor exposure in the peri-conception period would have passed. Thus, to identify speci c periods of heightened vulnerability, we conducted this case-control study to estimate spatiotemporal $PM_{2.5}$ exposures using temporally-adjusted land use regression models, focusing on the short-term exposure windows before and after conception. To the best of our knowledge, this is the rst environmental epidemiological study to estimate associations between clinically recognized early pregnancy loss (CREPL) and acute exposures to $PM_{2.5}$ during several peri-conception (especially post-conception) exposure time windows.

2. Methods

2.1. Study participants

This study used a matched case-control design with pre-designed interviewer-administered questionnaire. CREPL cases and normal early pregnancy controls were recruited from The Second Hospital of Tianjin Medical University and Tianjin Central Hospital of Gynecology and Obstetrics, between July 2017 and July 2018, among women residing in six central districts or four adjacent suburban districts (total area 2084 km^2) of Tianjin who had not changed residences during the previous year. Tianjin is a megacity in northern China that experiences high levels of air pollution. In 2017, the annual average concentration of $PM_{2.5}$ was 62 g/m^3 (Ministry of Ecology and Environment of the People's Republic of China, 2018). The two hospitals have the two largest family planning departments in Tianjin. A total of about 10,000 induced abortions are performed each year in the two departments, including unintended pregnancies and CREPL cases requiring surgical evacuation to terminate the pregnancy.

Case and control volunteer study participants provided written informed consent and completed an interviewer-administered questionnaire. The questionnaire provided information on participant residential address, the pregnancy and demographic characteristics. Where information was unclear, telephone follow-up was conducted shortly after recruitment. Fasting peripheral blood of pregnant women and early pregnancy chorionic villus (the same as chorionic villi) tissues were collected on the day of surgical evacuation. The study was approved by the Medical Ethics Committee of the Second Hospital of Tianjin Medical University (No.KY2017K003).

2.2. Definition of cases and controls

The diagnostic criteria of CREPL were based on a thorough medical history, physical examination, ultrasonography and serum -human chorionic gonadotropin (-hCG) testing, in line with the Society of Radiologists in Ultrasound guidelines for transvaginal ultrasonographic diagnosis of EPL (ACOG, 2015; Doubilet et al., 2013). The inclusion criteria of CREPL cases were: pregnancy < 13 weeks gestation; with regular menstrual cycle (the range of variation was ± 1 day during the previous year); clinical diagnosis of EPL with transvaginal ultrasonography demonstrating crown–rump length of 7 mm and no heartbeat, mean sac diameter of 25 mm and no embryo, or absence of embryo with heartbeat 11 days after a scan that showed a gestational sac with a yolk sac (Doubilet et al., 2013; Morin et al., 2016). The

inclusion criteria of controls were: pregnancy < 13 weeks gestation; with regular menstrual cycle; ultrasonography showing an intrauterine pregnancy with an embryo or fetus with heartbeat; no vaginal bleeding during the present pregnancy; no history of pregnancy loss, fetal malformation, preterm birth or delivered a newborn with low birth weight.

The exclusion criteria for cases and controls were pregnancy complications including reproductive tract infections, uterine malformations or uterine myoma or systemic diseases (e.g., hypertension, diabetes, or thyroid disease) or change of residential address in the previous year. Because maternal exposure to $PM_{2.5}$ might be associated with fetal DNA damage or placental DNA hypomethylation and altered gene expression (Janssen et al., 2013; Qin et al., 2017; Teng et al., 2016; Winckelmans et al., 2017) which could mediate the effects of $PM_{2.5}$ on EPL, we did not routinely screen for chromosomal abnormalities in the participants or include chromosomal abnormalities as exclusion criteria.

After enrollment of each CREPL case, a corresponding control was recruited consisting of a woman with a normal early pregnancy of similar age (±5 years) and gravidity (±1 number of pregnancies) presenting within one week of the corresponding case. The matching criteria were determined due to maternal age is the most common risk factor of EPL, and gravidity is an important indicator of female fertility (ACOG, 2015; RCOG, 2011). Controls were also pregnant woman requesting an induced abortion to allow collection of biological samples, especially chorionic villus, for subsequent biomarker measurements. Parity was not considered as one of the matching variable, because in China, a couple can have two children at most, and the induced abortion is legal. Therefore, parity was more closely related to social factors, rather than physiological factors.

2.3. Exposure estimation

Our spatiotemporal exposure predictions were based on a land use regression (LUR) model with high spatial resolution (1 km) as described previously (Chen et al., 2017), combined with temporal adjustment. In brief, the same procedures as used in European Study of Cohorts for Air Pollution Effects (ESCAPE) were followed for model development and validation (Eeftens et al., 2012; ESCAPE, 2009). $PM_{2.5}$ concentration data were collected from 28 routine monitoring sites operated by the Tianjin Environmental Monitoring Center in 2014. The geographic predictor variables included in the final $PM_{2.5}$ LUR model were population density, road length within a 1 km buffer, industrial land area within a 2 km buffer and distance to the coast. Model predictive accuracy was very good with a leave-one-out cross-validation (LOOCV) R^2 of 0.73 (Chen et al., 2017).

To estimate spatial exposure, all subjects' residential addresses were geocoded and spatially linked to the gridded outputs from the LUR models. Google Maps was used to obtain longitude and latitude of all residential addresses (available on http://www.gpsspg.com/maps.htm). ArcGIS 10.2 software (ESRI Inc., CA, USA) was used to integrate the layers of longitude and latitude, administrative districts map of Tianjin and the raster map of the LUR model. In order to effectively avoid the exposure misclassification due to maternal residential mobility, we recruited the subjects who had not changed residences during the previous year.

To temporally-adjust the $PM_{2.5}$ exposure during different exposure time windows, date of ovulation of each subject was estimated by obstetricians based on the last menstrual period (LMP) and menstrual cycle, and combined with transvaginal ultrasonography if necessary. Because fertilization usually occurs within 24 h after ovulation, we assumed the ovulation date to be the date of conception. To be specific, we used the following equation to estimate the date of ovulation, based on the fact that the interval from ovulation to the next menstruation (luteal phase length) is relatively fixed at 14 days (Crawford et al., 2017; Lam et al., 2011; Practice Committee of the American Society for Reproductive Medicine, 2015):

$$\text{Date of ovulation} = \text{LMP} + \text{menstrual cycle} - 14\ \text{days}$$

We collected reports of transvaginal ultrasonography of all subjects. For each of the controls, the crown–rump length (CRL) of the embryo was generally in line with the corresponding gestational age. We used the above-mentioned methods to estimate the timing of conception of all controls. In the vast majority of cases, due to EPL, the CRL of the embryo or mean sac diameter was less than gestational age. We also used the above-mentioned methods to estimate the timing of conception. But for 13 cases, the CRL of the embryo or mean sac diameter was significantly larger than its normal size at the gestational age. After further inquiries, the cases recognized that the last menstrual volume was obviously less than usual. Actually, it was just the vaginal bleeding after pregnancy (threatened abortion). Therefore, we plugged the previous menstrual period, i.e., the real LMP, into the above-mentioned equation, to estimate the timing of conception.

CI: 1.03, 1.23; p = 0.010) and for the entire four-week period after conception (OR = 1.22; 95% CI: 1.02, 1.46; p = 0.027). Di erences between the unadjusted and adjusted models were not notable.

Unadjusted and adjusted ORs (95% CIs) for associations between CREPL and $PM_{2.5}$ estimates (for a 10 g/m^3 increase in PM

other pollutants as well as sources of $PM_{2.5}$. Such studies would help point the way to focus e orts in preventing exposure-related e ects on embryonic development.

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