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The Environment and Reproductive Health (EARTH) Study: A Prospective Preconception Cohort

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Abstract

Background—The Environment and Reproductive Health (EARTH) Study is an ongoing prospective preconception cohort designed to investigate the impact of environmental, nutritional, and lifestyle factors among both women and men on fertility and pregnancy outcomes.

Methods—The EARTH Study recruits women 18 to 45 years and men 18 to 55 years seeking fertility evaluation and treatment at the Massachusetts General Hospital (MGH) Fertility Center, Boston, USA. Women and men are eligible to join either independently or as a couple. Participants are followed from study entry throughout each fertility treatment cycle, once per trimester of pregnancy (for those achieving pregnancy), and up to labor and delivery, or until they discontinue treatment or withdraw from the study. The study collects biological samples, self-reported questionnaire data (including a food frequency questionnaire) and clinically abstracted information.

Results—As of June 2017, the study cohort included 799 women and 487 men (447 couples; 40 men joined without female partners). Women were on average 34.7 years old at time of enrolment and predominantly Caucasian (81%), educated (49% have a graduate degree), and nulliparous (83%). Men were on average 36.6 years at baseline and mostly Caucasian (86%) and never-smokers (67%).

Conclusions—The EARTH Study is one of the few cohorts designed to examine multiple potentially critical windows of vulnerability, including the paternal and maternal preconception windows and the periconception and prenatal windows in pregnancy. It is also one of the few human studies that has assessed potential interactions between environmental exposures and dietary factors.

Keywords

prospective; preconception; cohort; infertility; environmental exposures; diet; pregnancy; male and female reproduction

Introduction

Accumulating epidemiologic evidence over the last several decades has shown associations of environmental chemicals with adverse reproductive health outcomes, including male and female infertility, poor pregnancy outcomes, and increased risk of diseases in childhood and beyond (Bergman, et al., 2012, Woodruff, et al., 2008). Nutritional factors also impact reproductive health both directly and by modifying the potential effects of some environmental chemicals on these same endpoints (2006, Homan, et al., 2007, Sharpe and Franks, 2002). Most studies to date have been designed to examine environmental or nutritional factors during pregnancy on fetal and infant health but few studies have simultaneously assessed environmental and nutritional exposures and even fewer have included assessments during the preconception period. Experimental animal studies and limited human studies have shown that the sensitive window of exposure for fetal and infant

health includes the preconception period in both women and men (Braun, et al., 2017, Chapin, et al., 2004, Louis, et al., 2008). Investigating the maternal and paternal preconception period is challenging in most observational studies and requires a design that identifies and recruits women and men attempting pregnancy to be followed until conception and onward (Buck Louis, et al., 2011). Furthermore, early and sensitive reproductive endpoints of interest (e.g., ovarian follicle growth, fertilization, implantation, biochemical pregnancy loss) in relation to diet and environmental chemical exposures are largely unobservable in population-based designs.

In an effort to address these challenges, we established the Environment and Reproductive Health (EARTH) Study, an ongoing prospective preconception cohort of couples seeking care at the Massachusetts General Hospital (MGH) Fertility Center, to investigate environmental, nutritional, and lifestyle factors among both women and men in relation to fertility and pregnancy outcomes. The EARTH Study was designed to examine multiple potentially relevant periods of vulnerability, including the paternal and maternal preconception windows as well as the periconception and prenatal windows in pregnancy. The study has been funded by the National Institute of Environmental Health Sciences since its inception in 2004. A comprehensive assessment of diet was added in 2007. Future goals include following the children of the couples, as well as the mothers and fathers who enrolled in the EARTH Study.

Methods

Participant Eligibility and Recruitment

The EARTH Study recruits women and men seeking fertility evaluation and medically assisted reproductive treatment at the Massachusetts General Hospital (MGH) Fertility Center. Women 18 to 45 years, and men 18 to 55 years who have not had a vasectomy and who are not taking hormones at the time of enrollment, are eligible to join either independently or as a couple. The study has strong support and collaboration from physicians and other medical personnel from the MGH Fertility Center who identify potentially eligible patients in their practice and briefly inform them of the study at any point during their care, including at the start of their fertility investigation or after initiating treatment. A study staff member then approaches potential participants and further determines their eligibility and interest. The study staff provides each potential participant with complete information about the requirements and expectations of enrolling in the EARTH Study and answers questions. All participants agreeing to join in the study provide written informed consent. The study was approved by the Institutional Review Boards of MGH (Partners), Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

Design and Follow-up

All participants enrolling in the EARTH Study are scheduled for a detailed entry visit with a study staff member. During this first visit, female and male participants complete a series of baseline questionnaires, undergo anthropometric measurements, and provide a spot urine and blood sample. They are also given a comprehensive self-reported questionnaire (take-

home or online) (Figure 1). Couples trying to conceive using medically assisted reproduction undergo different types of treatment, including in-vitro fertilization (IVF) based technologies (i.e., fresh or frozen IVF protocols, including intracytoplasmic sperm injection) and non-IVF based treatments (i.e., intrauterine insemination (IUI), ovulation induction, and ovarian stimulation). Both IVF and non-IVF based treatments require careful and detailed cycle follow-up at the clinic. During the monitoring phase of the treatment cycle (approximate follicular days 3 to 9), women provide a single spot urine sample and non-fasting blood sample, and at the same time complete a questionnaire regarding personal care product use in the past 24 hours. Following the monitoring phase, on the clinic visit day of the scheduled fertility procedure [i.e., on day of oocyte-retrieval (for fresh IVF protocols) or embryo transfer (for frozen IVF protocols) or on day of IUI procedure (for non-IVF based cycles)], women complete another product use questionnaire and provide an additional spot urine sample (Figure 1). Women undergoing oocyte retrieval also provide a follicular fluid sample. All women are followed to determine pregnancy status after each individual treatment cycle, which includes a routine human chorionic gonadotropin (β -hCG) blood test on day 12 to 17 following the IVF or IUI procedure day. Women achieving a positive pregnancy test undergo an ultrasound scan at approximately gestational week 6 for clinical confirmation of an intrauterine pregnancy and are followed throughout the prenatal period. Pregnant participants provide a spot urine and non-fasting blood sample and complete a product use questionnaire once per trimester at approximately 6 weeks, 24 weeks, and 33 weeks gestation (Figure 1).

In addition to the other baseline questionnaires, anthropometric measurements, blood and urine specimens, men provide a semen sample and complete an abstinence time questionnaire at enrollment if their study entry visit coincides with a routine semen sample collection. On the day their female partner undergoes their scheduled fertility treatment procedure, male participants provide another spot urine sample, non-fasting blood sample, and semen sample along with the abstinence time questionnaire (Figure 1). For men participating without their female partner, we obtain consent to release the birth and newborn nursery records from the delivering hospital.

Data and Biospecimen Collection

The EARTH Study prospectively collects a combination of biological samples, self-reported questionnaire data, and medical information abstracted from fertility clinic and delivery records (Table 1).

Biological Samples—The EARTH Study was designed to examine exposures across several windows: paternal and maternal preconception windows, and maternal periconception and prenatal windows. We obtain prospective repeated urine and blood samples at several times during these periods (Figure 1). There is also an optional voluntary hair sample collection. All samples were collected using methods to minimize exogenous contamination by known environmental chemicals (Calafat, et al., 2015). To date, we have collected 32,792 and 8,967 urine aliquots, and 8,156 and 3,875 blood aliquots from women and men, respectively. These have been archived and stored at the Harvard T.H. Chan School of Public Health. The CDC has quantified urinary biomarkers of >40 chemicals, including:

phthalates and diisononyl cyclohexane-1,2-dicarboxylate (DINCH) metabolites, phenols (e.g., bisphenol A, triclosan, parabens), and pesticides (metabolites of organophosphates, pyrethroids, 2,4-dichlorophenoxyacetic acid, and N,N-diethyl-m-toluamide). Organophosphate flame-retardants and polybrominated diphenyl ethers were measured at Duke University.

In whole blood, we have quantified heavy metals and metalloids (e.g., lead, cadmium, manganese) at the Mount Sinai School of Medicine in a subgroup of 150 women. We have measured serum folate, vitamin B12, fatty acids, and vitamin D concentrations among 100 women. Among 558 women, we have also analyzed serum for thyroid hormones (thyroid stimulating hormone, free thyroxine 4 (T4), T4, free T3, T3, thyroglobulin, and thyroperoxidase antibodies). To date, we have quantified mercury in more than 1,200 hair samples. We have also analyzed more than 1200 semen samples for standard semen quality parameters. From participants undergoing oocyte retrieval, we have stored 6,041 follicular fluid aliquots and we have analyzed 147 of them from 143 women for phthalate metabolites and phenols. In small pilot studies, we have measured non-coding micro RNAs in semen, and obtained and archived amniotic fluid samples.

Self-Reported Questionnaires—Both female and male participants complete the Baseline Questionnaire (BQ), which includes demographic, medical history, and lifestyle questions (Table 1). They also complete the self-reported Full Questionnaire (FQ) with information on family, medical, and reproductive history, occupational history, and lifestyle (e.g., physical-activity, frequency of tobacco, alcohol and illicit substance use) and the Food Frequency Questionnaire (FFQ). Overall, 95% of women (n=759/799) and 99% of men (n=484/487) completed the BQ; 91% of women (n=729/799) and 77% of men (n=376/487) completed the FQ. The Product Use Questionnaire is administered at baseline and once per treatment cycle to identify recent exposure to and time since last use of common products including lotions, soaps, cleaning products, plastics, pesticides, smoking and secondhand tobacco smoke exposure, specific foods, weight loss/weight gain products, and over-the-counter and prescription pharmaceuticals.

Diet Assessment—Diet is assessed using a previously validated self-administered FFQ (Rimm, et al., 1992, Yuan, et al., 2017). Participants are asked to report how often, on average, they consume specified amounts of the 131 foods, beverages, and supplements listed in the questionnaire over the past year with 9 possible response categories ranging from never/almost never to 6 times per day. Open-ended questions are used for usual brand and type of margarine, cooking oil, cold breakfast cereal, and multivitamins. Intakes for over 100 nutrients and non-nutritive food constituents are estimated by linking participant responses to a custom nutrient composition database maintained and updated by the Department of Nutrition, Harvard T H. Chan School of Public Health.

Other Environmental and Biological Samples—We have collected 240 home dust samples and 120 primary teeth from children of EARTH Study participants. For a small subset of volunteers (118 women and 52 men) we also measured electromagnetic fields using a portable magnetic field monitor. Recently, using couples' self-reported residential addresses at study entry, we collected and estimated distance to major roadway, near-

residence traffic density, and PM2.5, BC, NO2, CO, and SO2 concentrations during each fertility treatment cycle.

Electronic Medical Record Abstraction – Cycle, Pregnancy, and Delivery Data

—We have an extensive clinical abstraction process to obtain prospective data during each individual fertility treatment cycle and throughout follow-up (up to the birth of an infant for those achieving pregnancy). Trained study staff abstract pertinent clinical information from the electronic medical records at the MGH to ascertain the outcome of each cycle, including mode of conception, cycle cancellation, oocyte parameters, early embryo development, implantation, biochemical pregnancy (with β -hCG measurements), clinical pregnancy (with ultrasound assessment), physician-assigned infertility diagnosis, polycystic ovarian syndrome, terminations, pregnancy complications and pathology, glucose tolerance tests during pregnancy, and delivery outcomes (e.g., livebirths, stillbirths, birth weight, gestational age, infant sex, complications and pathologies).

Anthropometry—At study entry, trained study staff measure and record each participant's height, weight, and waist circumference. Additional weight measurements taken during routine prenatal visits are abstracted from electronic medical records.

Child Follow-Up—Two pilot studies have been conducted on small subsets of children born to EARTH Study participants. In one, we measured anogenital distance in male and female infants at 3 to 18 months of age. In the second, we assessed behavior in 166 children via parent-completed mailed questionnaires adapted from the Behavior Assessment System for Children (BASC, 2nd edition), Social Responsiveness Scale, and Preschool Activity Inventory (Constantino and Gruber, 2012, Golombok and Rust, 1993, Reynolds and Kamphaus, 1998).

Results

Study Population

Among patients initially approached by the EARTH Study staff as of June 2017, approximately 65% (N=806) of women and 45% of men (n=492) were eligible and agreed to enroll (Figure 2). Participants are followed from study entry throughout their fertility care, pregnancy, and birth (for those achieving pregnancy), or until they discontinue treatment or withdraw from the study. During the course of follow-up, 7 women and 5 men discontinued treatment or withdrew. As of June 2017, the cohort included 799 women and 487 men (447 couples; 40 men joined without female partners) (Figure 2). Women in the EARTH Study were on average 34.7 years old with a Body Mass Index (BMI) of 24.6 kg/m² at time of enrollment (Table 2). They are predominately Caucasian (81%), highly educated (49% have a graduate degree), never-smokers (73%), and nulliparous (83%). Approximately one third of women (35%) have a female factor of infertility as their primary diagnosis. Men were on average 36.6 years old with a BMI of 27.5 kg/m² at time of enrollment. Most men are Caucasian (86%), highly educated (41% with graduate degree), and never-smokers (67%), and 30% have a male factor as their primary infertility diagnosis (Table 2).

Cycle Endpoints

Participants have been followed for a total of 813 IVF-based treatment cycles, 941 non-IVF based treatment cycles, and 151 non-medically assisted/naturally conceived cycles during follow-up in the EARTH Study. These 1905 initiated cycles resulted in 713 pregnancies of which 11% (n=76/713) were only chemically detected by a β -hCG blood test and not clinically visualized on ultrasound (biochemical losses). Among the remaining 637 ultrasound-confirmed pregnancies, 19% ended in a spontaneous loss before 20 weeks gestation, 1% ended in a therapeutic abortion, 2% in ectopic loss, 1% ended in stillbirth (loss on or after 20 weeks), or were lost to follow-up during pregnancy (2%) (Figure 2). There have been 474 successful pregnancies resulting in 563 live births: 387 singletons and 176 multiples (85 pairs of twins, 2 sets of triplets). Among these births, 47 females and 17 males were recurrent participants who returned for further treatment and delivered (or their female partner delivered) 1 singleton and 46 twins. The overall live birth rate per initiated cycle is 26% (n=487/1905) and the live birth rate among cycles achieving pregnancy is 68% (n=487/713). Among IVF only cycles, the live birth rate per initiated cycle is 37% (n=299/813) and the live birth rate among cycles achieving pregnancy is 80% (n=299/375).

Key Findings

A summary of key environmental chemical, dietary, and lifestyle factor findings can be found in Table 3.

Environmental Chemicals—Among women in the EARTH Study undergoing assisted reproductive technology (ART), higher urinary concentrations of metabolites of di-(2-ethylhexyl) phthalate (DEHP) were associated with reduced oocyte yields, lower likelihood of clinical pregnancy, increased risk of pregnancy loss, and lower likelihood of live birth following infertility treatment (Hauser, et al., 2016, Messerlian, et al., 2016). Exposure to certain phthalates among men was also associated with decreased odds of implantation and live birth (Dodge, et al., 2015). Maternal soy and folate intake significantly modified the association between BPA and IVF outcomes in women (Chavarro, et al., 2016, Minguez-Alarcon, et al., 2016). We also examined whether urinary biomarkers of environmental chemicals were associated with antral follicle count (AFC) measured by ultrasound on day 3 of the follicular phase of a woman's unstimulated menstrual cycle (Messerlian, et al., 2016, Souter, et al., 2013), or with second trimester glucose levels (Chiu, et al., 2017). Among men, higher monobutyl phthalate concentrations were associated with decreased semen quality in a dose-dependent manner (Hauser, et al., 2006).

Nutrition and Lifestyle Factors—Among women undergoing ART, we found that pre-treatment intake of folate and vitamin B12 (Gaskins, et al., 2014, Gaskins, et al., 2015), whole grains (Gaskins, et al., 2016), and soy products (Vanegas, et al., 2015) were each independently and positively related to the probability of live birth. Maternal serum vitamin D levels were also positively associated with fertilization rates; however, this did not lead to higher probability of pregnancy or live birth (Abadia, et al., 2016). Paternal habitual caffeine intake was negatively associated with live birth, while maternal caffeine intake was not (Abadia, et al., 2017). Maternal vigorous activity prior to ART treatment was positively associated with probability of live birth among women of normal BMI but not among

overweight or obese women (Gaskins, et al., 2016). Within occupational factors, women who reported lifting/moving heavy objects at work had fewer total and mature oocytes, as well as a small reduction in mean AFC, compared with women who reported never lifting/moving heavy objects (Minguez-Alarcon, et al., 2017).

In the EARTH Study, men's soy food intake was negatively associated with sperm concentration (Chavarro, et al., 2008). Saturated (Attaman, et al., 2012) and trans fatty acid intake was also inversely associated with sperm concentration (Chavarro, et al., 2011). Fish intake and omega 3 fatty acids (Attaman, Toth, Furtado, Campos, Hauser and Chavarro, 2012) were associated with an increase in percent of morphologically normal sperm (Afeiche, et al., 2014), while processed meat was associated with the opposite effect ((Afeiche, Gaskins, Williams, Toth, Wright, Tanrikut, Hauser and Chavarro, 2014). High pesticide residue fruit and vegetable intake was associated with lower total sperm count and lower morphologically normal sperm (Chiu, et al., 2015). Among the lifestyle factors examined, physical activity had a positive effect on sperm concentration, while a BMI 35 kg/m^2 was associated with lower total sperm count (Chavarro, et al., 2010). We found no association between mobile phone use and semen parameters in this cohort (Lewis, et al., 2017).

Personal Care Product Use and Exposure—The EARTH Study has also identified determinants of environmental exposures, particularly due to personal care product use. We evaluated whether questionnaire-based self-reported use of personal care products predicted urinary biomarkers of phthalates and parabens in men (Supplementary Data, Figure S1)⁵⁰ and women (Supplementary Data, Figure S2) (Braun, et al., 2014, Nassan, et al., 2017).

Comment

The EARTH Study is one of the few cohorts to have repeated exposure measurements - including biospecimen data from men and women from the period before conception, throughout attempted pregnancy cycles, and from each trimester among pregnant participants (see Figure 1). There are several advantages to multiple biospecimens collected from men and women over an extended time. First, we can identify distinct periods of sensitivity and account for the correlation between exposure windows and within couples. Second, having more than one urine or blood sample for each exposure window reduces the potential for exposure misclassification, particularly for chemicals with short half-lives such as phthalates and phenols. We are also able to study the largely unexplored pre- and peri-conception periods as we have at least one urine sample collected from men and women from this window. The EARTH Study has measured more than forty different biomarkers of environmental chemical exposures, thus enabling us to investigate the relationships between mixtures of chemicals and endpoints of interest. The study is designed to assess very early pregnancy stages and outcomes for each attempted cycle, allowing for the evaluation of endpoints that are unobservable in most pregnancy cohorts. Documentation of outcomes is also highly accurate as it relies on clinical abstraction of cycle endpoints by trained study staff. We also have comprehensive covariate data collected through self-reported measures as well as from electronic medical records. Finally, due to the intensive collection of dietary data, the EARTH Study is also one of the few human studies able to assess potential

interactions between environmental chemicals and dietary factors, which are an important and emerging area of research.

While the fertility clinic setting provides the opportunity to measure environmental exposures across different windows of vulnerability and evaluate their potential effects on critical early fertility, pregnancy, and delivery outcomes, findings may be less generalizable to naturally conceived pregnancies (Messerlian, 2017). Pregnancies conceived to subfertile couples may also be more vulnerable to exposures and results may be specific to the population under study. However, this potential concern is outweighed by the study strengths – a research design that is internally valid and sufficiently powered to explore previously unstudied paternal and maternal exposures in relation to relevant and measurable endpoints. We further believe that this vulnerable population represents an important public health subpopulation given the growing number of babies born using IVF-based treatment, estimated to be 1.6% of all births or >68,000 births annually in the USA, with even higher proportions in certain European nations. The fraction of births using non-IVF based ART treatment in the USA is even higher at ~4.6% (~191,000 births), totaling >250,000 births per year in the USA (Dyer, et al., 2016, Schieve, et al., 2009, Sunderam, et al., 2017, Zegers-Hochschild, et al., 2014).

One particular challenge, however, in studying an infertile subpopulation involves the complexity of disentangling the effects of underlying infertility or its treatment from the exposure – outcome association of interest. The study is limited by the absence of fertile couples as a comparison group that is unconfounded by infertility or its treatment. Nevertheless, we attempt to control for causes of infertility and treatment either through adjustment or stratification (Messerlian, et al., 2017). Analytical plans, have also relied on the use of directed acyclic graphs to identify potential confounders that are not causal intermediates between exposure and outcomes (Messerlian, 2017). Furthermore, while we can control for many potential confounders, we cannot adjust for some co-exposures to unmeasured environmental chemicals or other unknown determinants of both exposure and health outcomes. Lastly, while the EARTH Study has tested many *a priori* hypotheses, we have undertaken multiple comparisons and cannot rule out the possibility that some of our findings may be spurious or due to chance.

Where can I find out more?

The EARTH Study has collaborated with students, post-doctoral and clinical fellows and visiting scientists, and welcomes the opportunity for new and continued collaborations. All inquiries should be made to Dr. Russ Hauser, Principal Investigator, Harvard T.H. Chan School of Public Health (rhauser@hsph.harvard.edu). More information about the study and a complete list of our publications can be found at: <https://www.hsph.harvard.edu/earth/>

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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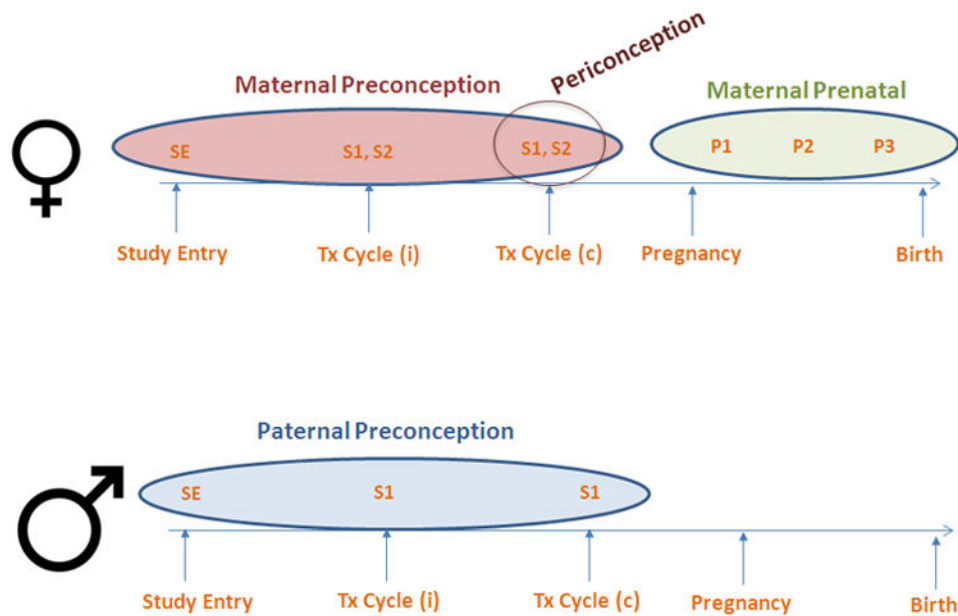


Figure 1. Maternal and Paternal Assessment in the Environment and Reproductive Health (EARTH) Study

Female participants: Study Entry (SE) Assessment includes: baseline urine and blood samples, and completion of the Baseline and Full Questionnaires (includes the Food Frequency Questionnaire).

Treatment (Tx) Cycle (i), connotes any number of followed cycles including those treated with in-vitro fertilization (IVF) based technologies or non-IVF based procedures.

Assessment at two points in time during each Treatment (Tx) Cycle: S1 - includes the first spot urine sample and blood sample collected during the follicular phase of the cycle (days 3 to 9) and the completion of the Product Use Questionnaire (PQ) at the same point in time.

S2 - includes the second spot urine sample collected at the time of scheduled treatment procedure (oocyte retrieval, embryo transfer or intrauterine insemination) and a follicular fluid sample collected during oocyte retrievals. *All SE, S1, and S2 samples represent exposure in the maternal preconception period.*

Treatment (Tx) Cycle (c) connotes the index cycle of conception. Clinical information about the mode of conception (IVF-based, non-IVF based, or non-medically assisted) is abstracted from electronic medical records by trained study staff. *S1 and S2 samples collected in the index conception represent exposure in the maternal periconception period.*

P1/P2/P3 - includes a single urine sample and blood sample and Produce Use Questionnaires collected in the 1st, 2nd, and 3rd trimester of pregnancy, respectively. *P1, P2, and P3 samples collected following the index conception represent the maternal prenatal exposure period.*

Male participants: Study Entry (SE) Assessment includes: baseline urine and blood samples, and completion of the Baseline and Full Questionnaires (includes the Food Frequency Questionnaire). Men also provide a semen sample and an abstinence time questionnaire at baseline if their study entry visit coincides with a routine semen sample collection.

assessment at Treatment (**Tx**) cycle: **S1** includes a spot urine sample, blood sample, and semen sample along with the abstinence time questionnaire on the day their female partner undergoes their scheduled fertility treatment procedure. ***SE and S1 samples collected up to the index conception represent the paternal preconception exposure period.***

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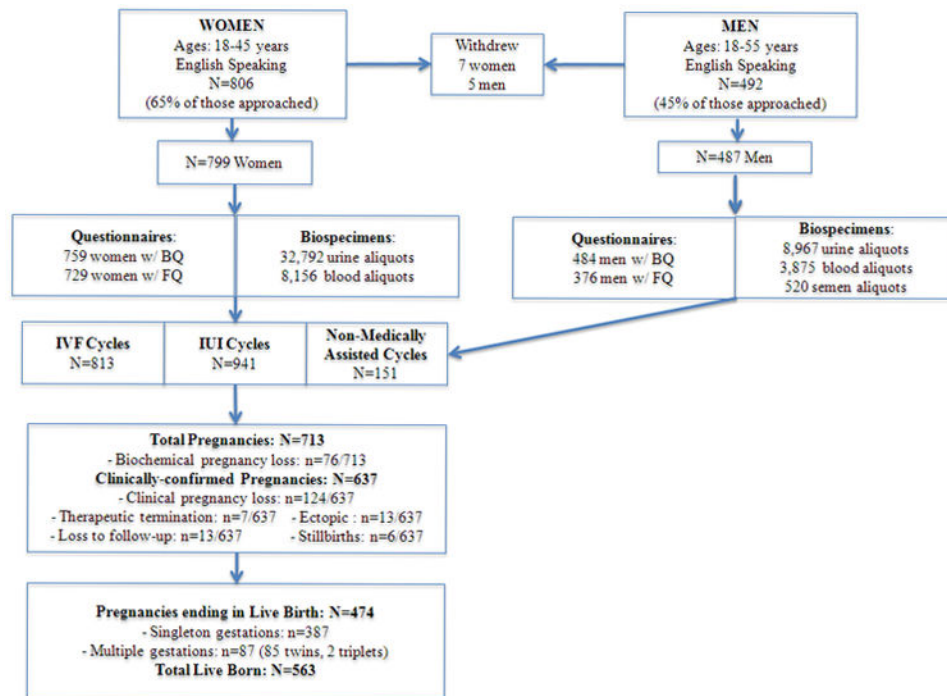


Figure 2. Environment and Reproductive Health (EARTH) Study Participant Flow Chart
Abbreviations: BQ: Baseline Questionnaire; FQ: Full Questionnaire (includes the Food Frequency Questionnaire).

Definitions: Biochemical pregnancy loss is defined as the demise of a β -hCG-confirmed pregnancy that was never visualized on ultrasound.

Clinical pregnancy loss is defined as the demise of an ultrasound confirmed intrauterine pregnancy up to 20 weeks gestation. IVF Cycles include fresh and frozen in-vitro fertilization-based protocols. IUI Cycles include all non-IVF based procedures such as intrauterine insemination, ovulation induction, and ovarian stimulation. Non-Medically Assisted Cycles are those that were conceived naturally without treatment.

Summary of measurements collected in women (X) and men (Y) in the Environment and Reproductive Health (EARTH) Study.

Table 1

Measurement Category	Measurement or Sample	Study Visits					
		Entry	Per Cycle		Per Pregnancy		
			Visit 1	Visit 2	Visit 1	Visit 2	Visit 3
Biological Samples	Urine	X, Y	X	X, Y	X	X	X
	Blood	X, Y		X, Y	X	X	X
		<i>Serum</i>	X, Y		X, Y	X	X
		<i>Blood clot</i>	X, Y		X, Y	X	X
		<i>Whole blood</i>	X, Y		X, Y	X	X
		Follicular Fluid			X		
		<i>Supernatant</i>					
		<i>Cell pellet</i>			Y		
		Semen	Y				
		Hair	X				
Questionnaires	Children's Teeth						
	Demographics	X, Y					
	Medical history	X, Y					
	Reproductive history	X, Y					
	Occupation history	X, Y					
	Lifestyle	X, Y					
	Diet/Food Frequency	X, Y					
	Personal Care Product Use	X, Y	X	X			
	Male Abstinence	Y			Y		
	Data Abstraction	Fertility Clinic Records (Infertility Diagnosis)	X, Y				
Fertility Records (ART Medications)			X				
Fertility Clinic (ART/IUI Outcomes)							X

Measurement Category	Measurement or Sample	Study Visits					
		Entry	Per Cycle	Per Pregnancy	Visit 1	Visit 2	Visit 3
	Pregnancy Records (prenatal follow-up data)				X	X	X
	Labor/Delivery Records (maternal and infant delivery outcomes)						X
Anthropometry	Weight	X, Y			X		
	Height	X, Y					
Environmental Samples	Dust	X, Y					

Table 2

Characteristics from 799 women and 487 men (447 couples) participating in the Environment and Reproductive Health (EARTH) Study from 2004 – 2017.

Characteristic	Women N=799	Men N=487
Age (years)		
Mean (SD)	34.7 (4.5)	36.6 (5.4)
Age>35, n (%)	345 (43)	273 (56)
Race, n (%)		
White	651 (81)	419 (86)
Black	39 (5)	15 (3)
Asian	71 (9)	34 (7)
Other	38 (5)	19 (4)
Body Mass Index (BMI, Kg/m ²)		
Mean (SD)	24.6 (4.9)	27.5 (4.5)
BMI >25, n (%)	283 (35)	346 (71)
Education, n (%)		
< College	60 (8)	55 (11)
College Graduate	231 (29)	136 (28)
Graduate Degree	392 (49)	198 (41)
Missing	116 (14)	98 (20)
Smoking Status, n (%)		
Never	583 (73)	327 (67)
Former	192 (24)	131 (27)
Current	24 (3)	29 (6)
Primary Infertility Diagnosis, n (%)		
Male Factor	196 (24)	146 (30)
Female Factor	285 (36)	166 (34)
<i>Diminished ovarian reserve</i>	90/285	
<i>Ovulation disorders</i>	106/285	
<i>Endometriosis</i>	36/285	
<i>Uterine disorders</i>	11/285	
<i>Tubal factor</i>	42/285	
Unexplained	318 (40)	175 (36)
Nulliparous at study entry, n (%)	698 (87)	-
Live Births, n (%)		
Singletons, n (%)	387/563 (69)	
Multiples, n (%)	176/563 (31)	

Table 3

Key Findings in the Environment and Reproductive Health (EARTH) Study.

Studies on Endocrine Disrupting Chemicals			
Study Participant	EDC	Key Finding	Reference
Women undergoing ART	DEHP	Decreased oocyte yield	Hauser et al., 2016 (16)
Women undergoing ART	DEHP	Decreased probability of clinical pregnancy	Hauser et al., 2016 (16)
Women undergoing ART	DEHP	Decreased probability of live birth	Hauser et al., 2016 (16)
Women conceiving with ART or non-ART	DEHP	Increased pregnancy loss	Messerlian et al., 2016 (17)
Men with female partner undergoing ART	DOP and DiNP	Decreased odds of implantation	Dodge et al., 2015 (18)
Men with female partner undergoing ART	DOP and DiNP	Decreased odds of live birth	Dodge et al., 2015 (18)
Women undergoing ART	BPA (modification by soy)	Among women not consuming soy, BPA associated with decreased probability of implantation, clinical pregnancy, and live birth	Minguez-Alarcon et al., 2016 (19)
Women undergoing ART	BPA (modification by folate)	Among women consuming <400µg food folate/day, BPA associated with decreased probability of implantation, clinical pregnancy, and live birth	Chavarro et al., 2016 (20)
Female EARTH Study participants	DEHP	Decreased number of antral follicles measured on day 3 of an unstimulated cycle.	Messerlian et al., 2016 (21)
Female EARTH Study participants	BPA	Decreased number of antral follicles measured on day 3 of an unstimulated cycle.	Souter et al., 2013 (22)
Female EARTH Study participants	BPA	Increased maternal blood glucose levels	Chiu et al., 2017 (23)
Male EARTH Study participants	DnBP	Decreased sperm concentration	Hauser et al., 2006 (24)
Studies on Nutrition			
Study Participant	Dietary Factor	Key Finding	Reference
Women undergoing ART	Folate	Increased live birth rate	Gaskins et al., 2014 (25)
Women undergoing ART	Vitamin B12	Increased live birth rate	Gaskins et al., 2015 (26)
Women undergoing ART	Whole Grains	Increased live birth rate	Gaskins et al. 2016 (27)
Women undergoing ART	Soy product	Increased live birth rate	Vanegas et al., 2015 (28)
Women undergoing ART	Vitamin D	Increased fertilization rate	Abadia et al., 2016 (29)
Male EARTH Study participants	Caffeine	Decreased live birth rate	Abadia et al., 2017 (30)
Male EARTH Study participants	Soy	Decreased sperm concentration	Chavarro et al., 2008 (33)
Male EARTH Study participants	Saturated fats	Decreased sperm concentration	Attaman et al., 2012 (34)
Male EARTH Study participants	Trans fatty acids	Decreased sperm concentration	Chavarro et al., 2011 (35)
Male EARTH Study participants	Fish and omega fatty acids	Increased percent of morphologically normal sperm	Attaman et al., 2012 (34)
Male EARTH Study participants	Processed meat	Decreased percent of morphologically normal sperm	Afeiche et al., 2014 (36)
Male EARTH Study participants	High pesticide residue fruit and vegetables	Decreased total sperm count and decreased percent morphologically normal sperm	Chiu et al., 2015 (37)
Studies on Lifestyle Factors			
Study Participant	Lifestyle Factor	Key Finding	Reference

Studies on Endocrine Disrupting Chemicals			
Study Participant	EDC	Key Finding	Reference
Women undergoing ART	Vigorous exercise	Increased live birth rate among women with normal BMI	Gaskins et al., 2016 (31)
Female EARTH Study participants	Heavy lifting/moving heavy objects at work	Fewer total and mature oocytes and decreased number of antral follicles	Minguez-Alarcon et al., 2017 (32)
Male EARTH Study Participants	Physical activity	Higher sperm concentration	Chavarro et al., 2010 (38)
Male EARTH Study Participants	BMI	Men with BMI $\geq 35\text{kg/m}^2$: decreased total sperm count	Chavarro et al., 2010 (38)

Abbreviations: Assisted Reproductive Technology (ART); Endocrine Disrupting Chemical (EDC); di-(2-ethylhexyl) phthalate (DEHP); Di-n-octyl phthalate (DOP) Di-isononyl phthalate (DiNP); Di-n-butyl phthalate (DBP); Bisphenol A (BPA); Body Mass Index (BMI).