EnM OPEN ACCESS
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2025;40:940-949
https://doi.org/10.3803/EnM.2025.2475
pISSN 2093-596X · eISSN 2093-5978

Investigating Birth and Thyroid Outcomes of Maternal-Fetal Environmental Exposures (IBM-E): A Cohort Protocol for Dietary Iodine and Endocrine Disruptors

Yun Ji Jung[1,*], Jeong Eun Shin[2,*], Ju-hee Yoon[1], Suhra Kim[1], Hayan Kwon[1], Sungbo Shim[2], Dong Yeob Shin[3], Minseo Gim[4], Younglim Kho[4], JoonHo Lee[1]

[1]Department of Obstetrics and Gynecology, Institute of Women's Medical Life Science, [2]Division of Neonatology, Department of Pediatrics, [3]Division of Endocrinology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [4]School of Human and Environmental Sciences, Eulji University, Seongnam, Korea

Background: Endocrine-disrupting chemicals (EDCs) are environmental pollutants that may impair maternal and fetal health by disrupting hormonal systems, including the thyroid. Both iodine deficiency and excess are associated with thyroid dysfunction and adverse obstetrical outcomes. However, the combined impacts of EDCs and iodine exposure on maternal-fetal thyroid homeostasis remain undetermined. We established the Investigating Birth and Thyroid Outcomes of Maternal-Fetal Environmental Exposures (IBM-E) cohort to prospectively assess the effects of maternal exposures to dietary iodine and EDCs on thyroid function, pregnancy complications, and offspring growth and development.

Methods: In this prospective observational study, we aim to enroll 556 pregnant women between 2024 and 2027 at a tertiary hospital in Korea. Maternal blood and urine samples will be collected at six time points, spanning from early pregnancy through 15 months postpartum, with infant samples collected at three time points. EDCs will be quantified using ultra-high performance liquid chromatography-tandem mass spectrometry. Thyroid function and urinary iodine concentration will be measured in both mothers and infants.

Results: As of the current interim analyses of 193 mothers and 229 neonates, 15.0% of mothers had thyroid dysfunction and 11.4% developed preeclampsia. Preterm birth occurred in 23.8% of cases, and 16.6% of neonates were small for gestational age.

Conclusion: The IBM-E cohort is designed to enable the longitudinal assessment of gestational environmental exposures and their potential impacts on maternal and fetal thyroid function, as well as pregnancy and neonatal outcomes. The findings of this study may inform preventive strategies and guide policy development in perinatal environmental health.

Keywords: Endocrine disruptors; Thyroid diseases; Iodine; Pregnancy complications; Maternal exposure; Environmental exposure; Fetal development; Longitudinal studies

Received: 26 May 2025, **Revised:** 22 June 2025, **Accepted:** 30 June 2025

Corresponding author: JoonHo Lee
Department of Obstetrics and Gynecology, Institute of Women's Medical Life Science, Yonsei University College of Medicine, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2234, **Fax:** +82-2-313-8350, **E-mail:** jleemd@yuhs.ac

*These authors contributed equally to this work.

INTRODUCTION

Environmental exposures during pregnancy, including synthetic chemicals and essential micronutrients, are increasingly recognized as critical determinants of maternal and fetal health. Among these, the World Health Organization characterizes endocrine-disrupting chemicals (EDCs) as exogenous substances capable of altering endocrine system function and causing adverse health effects in both mothers and their offspring [1]. EDCs are ubiquitous environmental pollutants that are routinely detected in agricultural chemicals, industrial materials (such as heavy metals), and everyday consumer products (including plastics, cleaning agents, and personal care items) [2]. Common EDCs such as bisphenol-A (BPA), phthalates, and perfluoroalkyl and polyfluoroalkyl substances (PFAS) are able to cross the placental barrier, disrupt hormonal signaling, and provoke systemic inflammatory responses [3-5].

Moreover, growing evidence indicates that EDCs specifically impair thyroid function, prompting their designation as thyroid-disrupting chemicals (TDCs) [6]. These compounds may interfere with multiple facets of thyroid hormone regulation, including synthesis, metabolism, transport, and receptor binding [7,8]. Given the essential role of thyroid hormones in fetal brain development, even subtle disruptions in maternal-fetal thyroid homeostasis during pregnancy may result in lasting neurodevelopmental consequences [9,10].

Similarly, iodine intake, a critical factor for thyroid hormone production, constitutes a major environmental determinant of thyroid function during pregnancy [11]. Both iodine deficiency and excess have been linked to maternal thyroid dysfunction and adverse developmental outcomes in the fetus [12-14]. Notably, excessive iodine intake, often due to unregulated supplement use in iodine-sufficient populations, may increase the risk of hypothyroidism via the Wolff–Chaikoff effect [15,16].

Prenatal exposure to EDCs and iodine may affect maternal and neonatal health through both direct and indirect mechanisms. These exposures are directly associated with obstetric complications such as preeclampsia, preterm birth, and intrauterine growth restriction, and may also disrupt maternal thyroid function [17-20], leading to indirect effects. Furthermore, *in utero* exposure may negatively influence neonatal and early childhood outcomes, including altered thyroid function, impaired growth and neurodevelopment, and heightened susceptibility to metabolic disorders [9,21-23]. Considering these interconnected biological pathways, prenatal exposure to EDCs and iodine may increase perinatal risk through both thyroid-dependent and thyroid-independent mechanisms.

Despite these converging pathways of thyroid disruption, few studies have systematically assessed the combined effects of EDCs and dietary iodine exposure on maternal thyroid function using a prospective, longitudinal design [24,25]. To address this gap, we established the Investigating Birth and Thyroid Outcomes of Maternal-Fetal Environmental Exposures (IBM-E) cohort, a prospective study designed to evaluate the impact of combined environmental exposures—particularly EDCs and iodine—on maternal-fetal thyroid function and perinatal health. The IBM-E study is designed to assess the effects of maternal environmental exposures, including dietary iodine and EDCs, on maternal thyroid function during pregnancy. It further investigates how altered maternal-fetal thyroid status is related to pregnancy complications and perinatal outcomes and evaluates the long-term consequences of perinatal environmental exposures and thyroid dysfunction on postnatal growth and developmental trajectories in offspring.

METHODS

Study design

Participant recruitment and the inclusion criteria

The IBM-E cohort is a prospective observational study designed to investigate the association between maternal exposure to dietary iodine and/or EDCs and adverse pregnancy outcomes, including maternal thyroid dysfunction, as well as the potential effects on offspring health and development. Recruitment of pregnant women began in July 2024 and is ongoing at Severance Hospital in Seoul, Korea, through December 2027.

Pregnant women are recruited during routine prenatal visits. Eligible participants are those who are currently pregnant and willing to provide written informed consent. There is no strict gestational age limit for enrollment. However, we aim to recruit pregnant women as early as possible—preferably during the first trimester—to maximize biospecimen collection across all prenatal visits. All participants must be enrolled before delivery to ensure paired maternal and neonatal data collection and analysis. For newborn inclusion, consent is also required from their legal representative. Participants are excluded if they are pregnant with three or more fetuses, have a previous history of thyroidectomy, or are currently receiving antithyroid treatment for overt hyperthyroidism. In addition, women with a history of overt hypothyroidism who have been taking levothyroxine for more than 12 months and are still on treatment at the time of recruitment are excluded. Women with other severe comorbidities

are also not eligible to participate.

Sample size

Based on an expected incidence of maternal thyroid disorder of approximately 10% during pregnancy [26,27], we estimate that at least 50 events are required for exploratory analysis and preliminary modeling of the associations between EDC exposure and thyroid dysfunction. To ensure sufficient statistical power, a minimum of 500 participants is required. The target enrollment is set at 556 mother-child pairs to allow for a 10% loss to follow-up.

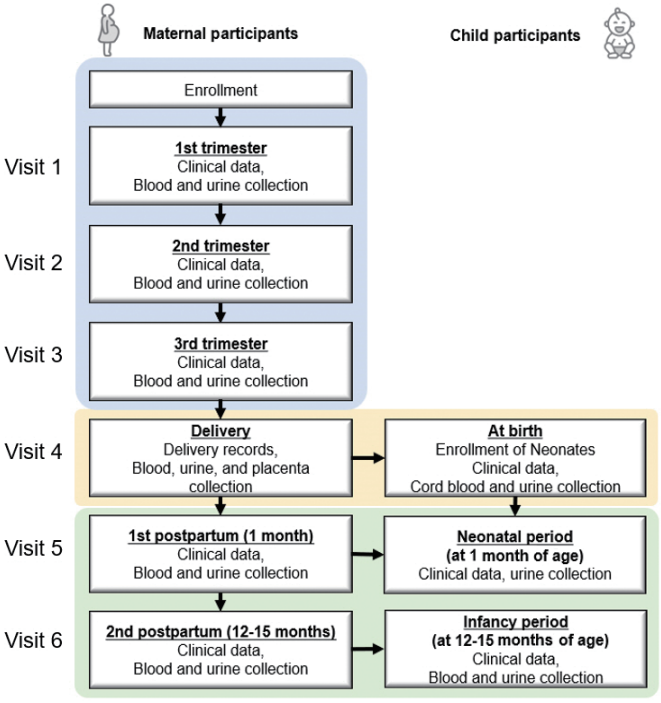

Fig. 1. Study design.

Participant follow-up

Fig. 1 illustrates the timeline and procedures for participant follow-up. Maternal participants are scheduled for six visits: during the first trimester (visit 1: 11 to 13 weeks of gestation), second trimester (visit 2: 24 to 28 weeks of gestation), third trimester (visit 3: 34 to 36 weeks of gestation), at delivery (visit 4), 1 month postpartum (visit 5), and 12 to 15 months postpartum (visit 6).

At each visit, clinical data, including vital signs (blood pressure and pulse) and anthropometric measurements (height, weight, and body mass index [BMI]), are collected from electronic medical records. EDCs are assessed through blood and urine samples obtained at the defined time points. Maternal thyroid function tests (TFTs) are conducted using blood samples, and urine samples are analyzed for the urinary iodine concentration (UIC) and creatinine levels to calculate the iodine-to-creatinine ratio. Placental tissues are collected at delivery (visit 4) (Table 1). In addition, data on pregnancy complications, such as gestational diabetes mellitus (GDM), preeclampsia, and preterm birth, as well as obstetric outcomes, including mode of delivery, gestational age at birth, and neonatal birth weight, are reviewed from electronic medical records.

Child participants are enrolled at birth and followed up at ages 1 and 12–15 months, aligning with maternal visits 5 and 6. At each visit, clinical data, including weight, height, head cir-

Table 1. Measurements of Maternal and Child Participants

Measurement	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Maternal participants						
Vital signs (blood pressure, pulse rate)	○	○	○	○	○	○
Anthropometric measurements	○	○	○	○	○	○
Blood: Thyroid function test[a], EDC analysis	○	○	○	○	○	○
Urine: Iodine/creatinine, EDC analysis	○	○	○	○	○	○
Placenta: Placental pathology				○		
Child participants						
Anthropometric measurements				○	○	○
Blood: Thyroid function test[a], EDC analysis				○[b]		○
Urine: Iodine/creatinine, EDC analysis				○	○	○

EDC, endocrine-disrupting chemical.
[a]Thyroid function test include thyroid-stimulating hormone, free thyroxine, triiodothyronine, and antithyroid peroxidase antibody; [b]At visit 4 (delivery), neonatal blood is collected via cord blood sampling.

cumference, developmental milestones, and comorbidities, are collected. EDCs are measured in blood and urine samples collected at the designated time points. Blood samples are obtained at birth (cord blood) and again at 12 to 15 months of age (venous blood, corresponding to maternal visit 6). In addition to EDC analysis, both samples are subjected to TFTs. Urine samples are collected at three time points: immediately after birth (first-void urine), within the first month of life (aligned with maternal visit 5), and at ages 12 to 15 months. All urine samples are analyzed for EDCs, UIC, and creatinine levels to calculate the iodine-to-creatinine ratio (Table 1). Furthermore, neonatal and infant clinical outcomes are reviewed from electronic medical records, including neonatal intensive care unit admission, respiratory complications, neonatal jaundice, infections, anthropometric parameters (weight, height, head circumference), and neurodevelopmental evaluations during follow-up.

All collected biological specimens—including maternal serum and urine, paired cord serum, neonatal serum and urine, and placental tissue—are stored at −70°C until analysis to ensure sample stability and integrity.

Evaluation of iodine status

UICs are determined from spot urine samples using an inductively coupled plasma mass spectrometry system (ICP-MS, 7900 series, Agilent Technologies, Santa Clara, CA, USA). Urinary creatinine levels are analyzed using the kinetic alkaline picrate method with the Architect TBA-C16000 analyzer (Abbott, Abbott Park, IL, USA). To account for urine dilution, UIC values are normalized by urinary creatinine concentration.

Measurement of thyroid function

Thyroid function is assessed by measuring serum levels of free thyroxine (fT4), total triiodothyronine (T3), and thyroid-stimulating hormone (TSH) using a chemiluminescent microparticle immunoassay, performed with the Architect i2000 System (Abbott Korea, Seoul, Korea). The reference ranges are as follows: fT4, 0.70–1.48 ng/dL (9.01–19.05 pmol/L); T3, 80–200 ng/dL (1.23–3.08 nmol/L); and TSH, 0.38–4.94 μIU/mL. In accordance with the revised Korean Thyroid Association guidelines [11], we adopted a TSH upper limit of 4.0 mIU/L for the first trimester of pregnancy. A TSH level between 4.0 and 10.0 mIU/L with a normal fT4 level is defined as subclinical hypothyroidism. A TSH level greater than 10.0 mIU/L is defined as overt hypothyroidism, regardless of the fT4 level.

EDC measurement

This study aims to measure the concentrations of EDCs in maternal and child biological samples, specifically blood, urine, and cord blood. Three classes of compounds will be analyzed: phthalate esters and their metabolites (phthalates; $n=37$), environmental phenolic compounds (phenols; $n=24$), and PFASs ($n=33$) (Supplemental Table S1). The samples were prepared to measure urinary phthalate metabolites and environmental phenols using methods described in previous studies [28,29].

Phthalates and their metabolites in urine

Phthalates and alternative plasticizer metabolites are analyzed in urine samples using solid-phase extraction (SPE). Calibration standards are prepared by combining 450 μL of synthetic urine, 50 μL of standard solution, and 50 μL of internal standard. Urine samples (500 μL) are mixed with 50 μL of internal standard, followed by 10 μL β-glucuronidase and 150 μL of 1 M ammonium acetate buffer (pH 5). After vortexing, samples are incubated at 37°C for 2 hours. Hydrolyzed samples are then treated with 350 μL phosphate buffer (pH 2) and centrifuged for 5 minutes. The supernatants are loaded onto Sep-Pak cartridges (1 cc, 100 mg; Waters, Milford, MA, USA) on a Resolvex A200 system (Tecan, Männedorf, Switzerland). After washing and elution, extracts are dried under vacuum and reconstituted in 200 μL of 50% acetonitrile containing 0.1% acetic acid. Analysis is performed using ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) with a Nexera LC-40 XS system (Shimadzu, Kyoto, Japan) and TQ 5500+ mass spectrometer (SCIEX, AB Sciex, Framingham, MA, USA) (Supplemental Tables S2, S3).

Environmental phenols in urine

A total of 24 environmental phenols (11 bisphenols [BPs] and 13 parabens) are selected as target analytes to assess urinary exposure, and liquid-liquid extraction is employed for their analysis. Calibration samples are prepared using 450 μL of synthetic urine, 50 μL of standard solution, and 50 μL of internal standard. For each sample, 500 μL of urine is combined with 50 μL of internal standard, 10 μL of β-glucuronidase/arylsulfatase, and 150 μL of 1 M ammonium acetate buffer (pH 5). After a 4-hour incubation at 37°C, 5 mL of ethyl acetate is added. Samples are rotated for 30 minutes and centrifuged at 5,000 rpm for 10 minutes. The supernatant is collected and combined with a second extract prepared using the same procedure. The combined organic phase is evaporated under vacuum until 100 μL remains, followed by reconstitution in 100 μL of 50% methanol, filtra-

tion, and injection. Analysis is performed using an ultra-performance liquid chromatography (UPLC) system coupled with an API 4000 triple quadrupole mass spectrometer (SCIEX) (Supplemental Tables S4, S5).

PFASs in serum

Maternal and cord serum samples are analyzed for PFASs. A total of 31 compounds, including 11 perfluorocarboxylic acids (PFCAs), seven perfluorosulfonic acids (PFSAs), nine precursors, and four alternative compounds, are selected as target analytes.

For each 200 μL serum sample, 20 μL of an internal standard mixture and 500 μL of 0.1% formic acid are added. Samples are processed using automated SPE with Strata-X-AW Tab-Less SPE cartridges (30 mg, 1 mL; Phenomenex, Torrance, CA, USA) on a Resolvex A200 system. After sample loading, cartridges are washed with water and 30% methanol, and eluted sequentially with 4 mL of methanol and 4 mL of methanol containing 0.1% ammonium hydroxide. The eluates are evaporated to dryness using a vacuum concentrator (Speed-Vac CVE-3000, EYELA, Tokyo, Japan) and reconstituted in 200 μL of acetonitrile. Quantitative analysis is conducted using a UPLC system (Agilent Infinity 1290 series, Agilent Technologies) coupled with a tandem mass spectrometer (API 4000) (Supplemental Tables S6, S7).

Quality control of EDC measurements

All analyses are conducted following validated protocols, with rigorous quality control procedures to ensure analytical reliability and accuracy. Calibration curves are established by spiking artificial urine or bovine serum with standard solutions at various concentrations, and all target compounds demonstrate excellent linearity, with coefficients of determination (r^2) exceeding 0.99. Method detection limits (MDLs) are calculated based on regression analysis in accordance with National Institute for Occupational Safety and Health (NIOSH) guidelines, reflecting the lowest concentration of each compound that can be reliably detected with 99% confidence. MDLs generally range from 0.01 to 0.3 ng/mL across compounds (Supplemental Tables S8-S10). Accuracy is assessed by evaluating recovery rates at low, medium, and high concentrations, with most compounds showing recoveries within the acceptable range of 80% to 120%. Precision is determined by calculating the coefficient of variation across repeated measurements, with most results within the 15% threshold, indicating stable reproducibility. Isotopically labeled internal standards are added to all samples to enhance quantification accuracy, and quality control samples are included in each batch to continuously monitor consistency and analytical performance (Supplemental Tables S11-S13).

Statistical analysis

Statistical analyses will be performed to examine associations between urinary concentrations of 37 phthalates and 24 phenols, and serum concentrations of 33 PFASs and perinatal outcomes. Only individual compounds detected in ≥70% of all urine samples will be included in the analysis. For compounds with concentrations below the limit of quantification (LOQ), values are imputed as LOQ divided by the square root of 2 (LOQ/√2). Total concentrations are calculated by summing 18 phthalate metabolites (ΣPhthalates), eight ΣBPs, and selected PFASs, with values below the LOQ treated as zero.

Urinary concentrations of target analytes will be adjusted for specific gravity (SG) using the formula: SG-adjusted concentration=concentration×[(SG_mean−1)/(SG_ind−1)], where SG_mean and SG_ind represent the mean and individual SG values, respectively. Depending on the distribution of the exposure and outcome variables, appropriate normalization methods, such as natural log transformation, will be applied prior to statistical modeling.

To assess associations of continuous EDC exposure and UIC with thyroid function and perinatal outcomes, Pearson or Spearman correlation tests will be used based on variable distribution. These correlation analyses serve as an exploratory step. Generalized additive models with smoothing functions will be used to explore potential nonlinear relationships among EDC exposure, iodine status, and perinatal outcomes, including thyroid function. Interaction terms between EDCs and iodine status will be incorporated to assess potential combined effects. Model fit will be evaluated using the Akaike information criterion, where lower values indicate better fit.

Additionally, multivariate logistic regression models will be used to estimate adjusted odds ratios for perinatal outcomes and thyroid outcomes across categories of EDC exposure or iodine status. Covariates such as maternal age, pre-pregnancy BMI, parity, and *in vitro* fertilization status will be considered potential confounders. Covariate inclusion is based on statistical significance or impact on effect estimates during model selection. In cases of limited outcome events, the number of covariates will be restricted according to the events-per-variable principle. All statistical analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 18.0 (IBM, Chicago, IL, USA), with statistical significance defined as a two-tailed $P<0.05$.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Severance Hospital (IRB No. 4-2017-0348), and all mother-child pair participants provided written informed consent.

RESULTS

As of April 2025, 193 pregnant women have been enrolled in this ongoing prospective study, which began in 2024. The median maternal age was 35 years (range, 24 to 48), and 53.4% were nulliparous. Multiple pregnancies accounted for 17.6% of cases. Chronic hypertension was present in 3.1% of participants. Pre-GDM was identified in 1.0% (n=2) of the participants, and both cases were managed with insulin therapy. Pregnancy-related complications included preeclampsia, which occurred in 11.4% of participants, and GDM, which was diagnosed in 8.3% (n=16); among those with GDM, six required insulin treatment (Table 2).

Thyroid dysfunction—defined as hyperthyroidism, hypothyroidism, or subclinical hypothyroidism (excluding thyroid nodules or thyroiditis)—was observed in 15.0% (n=29) of participants. One participant with hyperthyroidism was treated with antithyroid medication, and all five participants with overt hypothyroidism received levothyroxine. Among the 16 participants with subclinical hypothyroidism, six received short-term levothyroxine therapy during early pregnancy, nine were treated throughout pregnancy, and one did not receive any medication.

The median gestational age at delivery was 38.2 weeks (range, 18.4 to 40.6), and 23.8% of the participants experienced preterm birth. Cesarean section was performed in 86.0% of the cases. Placental pathology was observed in 42.0% of cases, with maternal vascular underperfusion identified in 24.7%. Among 229 neonates, the median birthweight was 2,880 g (range, 196 to 4,180), and 53.7% were male. Small for gestational age was observed in 16.6% of neonates, and 24.0% were admitted to the neonatal intensive care unit. Among the neonates, 14.0% experienced at least one complication, including respiratory distress syndrome, sepsis, or neonatal death (Table 3).

Table 2. Maternal Characteristics in the Preliminary Data (n=193)

Variable	Value
Age, yr	35 (24–48)
Nulliparity	103 (53.4)
Previous abortion history	32 (16.6)
Multiple pregnancy	34 (17.6)
Pre-existing conditions	
Pregestational diabetes	2 (1.0)
Chronic hypertension	6 (3.1)
Cerebrovascular disease	7 (3.6)
Thyroid dysfunction	29 (15.0)
Hyperthyroidism	8 (27.6)
Hypothyroidism	5 (17.2)
Subclinical hypothyroidism	16 (55.2)
Other thyroid diseases[a]	7 (3.6)
Pregnancy-related complications	
Gestational diabetes mellitus	16 (8.3)
Preeclampsia	22 (11.4)

Values are expressed as median (range) or number (%).
[a]Others included thyroiditis or thyroid nodules.

DISCUSSION

Exposure to EDCs during pregnancy has become a significant

Table 3. Delivery and Neonatal Outcomes

Variable	Value
Delivery outcomes	n=193
Gestational age at delivery, wk	38.2 (18.4–40.6)
Preterm birth (<37 weeks)	46 (23.8)
Cesarean section	166 (86.0)
Placenta pathology	81 (42.0)
Acute chorioamnionitis	9 (11.1)
Chronic chorioamnionitis	6 (7.4)
Funisitis	3 (3.7)
Maternal vascular underperfusion	20 (24.7)
Neonatal outcomes	n=229
Birth weight	2,880 (196–4,180)
Fetal sex	
Male	123 (53.7)
Female	106 (46.3)
Small for gestational age	38 (16.6)
Large for gestational age	10 (4.4)
Respiratory distress syndrome	22 (9.6)
Bronchopulmonary dysplasia	3 (1.3)
Intraventricular hemorrhage	3 (1.3)
Necrotizing enterocolitis	3 (1.3)
Sepsis	7 (3.1)
NICU admission	55 (24.0)
Neonatal death	3 (1.3)

Values are expressed as median (range) or number (%).
NICU, neonatal intensive care unit.

public health concern owing to their potential to disrupt maternal metabolic regulation, placental function, and fetal development. Common EDCs, such as phthalates, BPA, and PFAS, have been linked to adverse pregnancy outcomes, including GDM, preeclampsia, and preterm birth [18,30,31]. These effects are mediated through endocrine dysregulation, systemic inflammation, and placental insufficiency [5,18,32]. Mechanistic studies suggest that EDCs affect trophoblast proliferation, angiogenesis, and immune signaling via oxidative stress, DNA methylation, and peroxisome proliferator-activated receptor-γ modulation, thereby impairing placental development [33-35]. Consequently, maternal and fetal health may be compromised.

Moreover, EDCs are increasingly recognized as TDCs because they interfere with thyroid hormone synthesis, metabolism, and action [6-8]. Given the critical role of thyroid hormones in fetal brain development, particularly during early gestation when the fetus relies on maternal thyroid hormones, disrupted maternal-fetal thyroid homeostasis may result in enduring and long-lasting neurodevelopmental consequences [9,10]. Similarly, excessive or deficient intake of iodine—a critical nutrient for thyroid hormone biosynthesis—may independently or synergistically exacerbate thyroid dysfunction during pregnancy [36,37]. Iodine excess induces transient hypothyroidism through the Wolff–Chaikoff effect, particularly in populations with preexisting thyroid autoimmunity or immature fetal thyroid systems [15,16]. Conversely, iodine deficiency remains a global concern and has been associated with neurocognitive impairment and cretinism in severe cases [38,39]. The dual risk posed by insufficient and excessive iodine intake highlights the importance of precise evaluation of iodine status during gestation.

Despite these concerns, previous studies have predominantly relied on cross-sectional or trimester-specific designs, which limit the ability to assess temporal dynamics and causality [40,41]. To overcome these limitations, the IBM-E cohort was established as a prospective, longitudinal study designed to evaluate the impacts of maternal exposure to nutritional (e.g., iodine) and non-nutritional (e.g., EDCs) environmental factors on maternal-fetal thyroid function and perinatal outcomes.

The IBM-E study builds upon findings from the prior Ideal Breast Milk (IBM) cohort, which included high-risk pregnancies at a tertiary hospital and evaluated dietary iodine intake and its association with thyroid function and obstetrical outcomes [42,43]. The IBM cohort was a prospective birth cohort of 442 pregnant women recruited at Seoul National University Hospital between June 2016 and December 2019. In that study, despite widespread excessive iodine intake due to traditional dietary practices such as postpartum seaweed soup consumption, maternal iodine status showed no significant association with maternal or neonatal thyroid dysfunction or with adverse birth outcomes [44]. These findings were inconsistent with earlier studies in iodine-replete populations, highlighting the need for validation in broader and more diverse cohorts [45-47]. Furthermore, a secondary analysis in the IBM cohort focused on twin pregnancies found that maternal PFAS levels were linked to vascular malperfusion and placental asymmetry, emphasizing the need to further assess EDC effects in vulnerable subpopulations [29].

The IBM-E cohort addresses these needs by incorporating serial biospecimen collection at multiple predefined time points during pregnancy and postpartum, allowing for time-resolved exposure profiling and identification of critical windows of susceptibility. Integration of maternal, placental, and neonatal biospecimens with electronic medical records supports comprehensive evaluation of endocrine and metabolic phenotypes. By concurrently evaluating UICs and EDC metabolites, the IBM-E study enables the characterization of combined nutritional-toxicant exposure profiles and their associations with thyroid hormone levels.

An additional strength of the IBM-E cohort is its potential for integrative analysis with the original IBM cohort [42]. By pooling data from both cohorts, we anticipate increased statistical power and the ability to validate key exposure—outcome associations, particularly regarding iodine and EDC interactions with thyroid function. This approach also facilitates exploration of gene–environment interactions and epigenetic mechanisms underlying the observed clinical phenotypes.

Although the IBM-E cohort is based at a single tertiary center, it employs standardized protocols and state-of-the-art analytical platforms, such as UHPLC–MS/MS, enabling precise quantification of trace-level environmental toxicants [48]. While generalizability may be limited, the high fidelity of clinical and biochemical data collection enhances internal validity. Future directions include extending follow-up into childhood to assess long-term developmental outcomes and incorporating multiomics analyses to elucidate biological pathways linking environmental exposure with health trajectories.

The IBM-E cohort represents a methodologically rigorous platform to investigate the complex interplay between environmental exposures, thyroid homeostasis, and perinatal health. These findings may inform clinical guidelines, public health policies, and individualized strategies for risk mitigation in vulnerable pregnant populations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2025-02272995).

AUTHOR CONTRIBUTIONS

Conception or design: Y.J.J., J.E.S, J.Y., S.S., D.Y.S., M.G., Y.K., J.H.L. Acquisition, analysis, or interpretation of data: Y. J.J., J.E.S., J.Y., S.K., H.K., S.S., D.Y.S., M.G., Y.K., J.H.L. Drafting the work or revising: Y.J.J., J.E.S., J.Y., M.G., Y.K., J.H.L. Final approval of the manuscript: Y.J.J., J.E.S., D.Y.S., Y.K., J.H.L.

ORCID

Yun Ji Jung *https://orcid.org/0000-0001-6615-6401*
Jeong Eun Shin *https://orcid.org/0000-0002-4376-8541*
Ju-hee Yoon *https://orcid.org/0009-0004-4078-3852*
Suhra Kim *https://orcid.org/0009-0008-5305-6856*
Hayan Kwon *https://orcid.org/0000-0002-5195-7270*
Sungbo Shim *https://orcid.org/0000-0001-9703-7050*
Dong Yeob Shin *https://orcid.org/0000-0003-1048-7978*
Minseo Gim *https://orcid.org/0009-0000-3771-4566*
Younglim Kho *https://orcid.org/0000-0002-2590-4722*
JoonHo Lee *https://orcid.org/0000-0001-5911-7690*

REFERENCES

1. Chen Y, Yang J, Yao B, Zhi D, Luo L, Zhou Y, et al. Endocrine disrupting chemicals in the environment: environmental sources, biological effects, remediation techniques, and perspective. Environ Pollut 2022;310:119918.
2. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30:293-342.
3. Puche-Juarez M, Toledano JM, Moreno-Fernandez J, Galvez-Ontiveros Y, Rivas A, Diaz-Castro J, et al. The role of endocrine disrupting chemicals in gestation and pregnancy outcomes. Nutrients 2023;15:4657.
4. Shekhar S, Sood S, Showkat S, Lite C, Chandrasekhar A, Vairamani M, et al. Detection of phenolic endocrine disrupting chemicals (EDCs) from maternal blood plasma and amniotic fluid in Indian population. Gen Comp Endocrinol 2017;241:100-7.
5. Gingrich J, Ticiani E, Veiga-Lopez A. Placenta disrupted: endocrine disrupting chemicals and pregnancy. Trends Endocrinol Metab 2020;31:508-24.
6. Boas M, Feldt-Rasmussen U, Main KM. Thyroid effects of endocrine disrupting chemicals. Mol Cell Endocrinol 2012;355:240-8.
7. Zoeller TR. Environmental chemicals targeting thyroid. Hormones (Athens) 2010;9:28-40.
8. Pearce EN. Endocrine disruptors and thyroid health. Endocr Pract 2024;30:172-6.
9. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C, et al. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience 2017;342:68-100.
10. Gilbert ME, Rovet J, Chen Z, Koibuchi N. Developmental thyroid hormone disruption: prevalence, environmental contaminants and neurodevelopmental consequences. Neurotoxicology 2012;33:842-52.
11. Ahn HY, Yi KH. Diagnosis and management of thyroid disease during pregnancy and postpartum: 2023 revised Korean Thyroid Association Guidelines. Endocrinol Metab (Seoul) 2023;38:289-94.
12. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015;3:286-95.
13. Leung AM, Pearce EN, Braverman LE. Iodine nutrition in pregnancy and lactation. Endocrinol Metab Clin North Am 2011;40:765-77.
14. Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 2016;4:35-43.
15. Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol 2014;10:136-42.
16. Sohn SY, Inoue K, Rhee CM, Leung AM. Risks of iodine excess. Endocr Rev 2024;45:858-79.
17. Abel MH, Caspersen IH, Sengpiel V, Jacobsson B, Meltzer HM, Magnus P, et al. Insufficient maternal iodine intake is

associated with subfecundity, reduced foetal growth, and adverse pregnancy outcomes in the Norwegian Mother, Father and Child Cohort Study. BMC Med 2020;18:211.
18. Kolan AS, Hall JM. Association of preterm birth and exposure to endocrine disrupting chemicals. Int J Mol Sci 2023; 24:1952.
19. Charoenratana C, Leelapat P, Traisrisilp K, Tongsong T. Maternal iodine insufficiency and adverse pregnancy outcomes. Matern Child Nutr 2016;12:680-7.
20. Shin HM, Oh J, Schmidt RJ, Pearce EN. Prenatal exposure to per- and polyfluoroalkyl substances, maternal thyroid dysfunction, and child autism spectrum disorder. Endocrinol Metab (Seoul) 2022;37:819-29.
21. Yesildemir O, Celik MN. Association between pre- and postnatal exposure to endocrine-disrupting chemicals and birth and neurodevelopmental outcomes: an extensive review. Clin Exp Pediatr 2024;67:328-46.
22. Sun M, Cao X, Wu Y, Shen L, Wei G. Prenatal exposure to endocrine-disrupting chemicals and thyroid function in neonates: a systematic review and meta-analysis. Ecotoxicol Environ Saf 2022;231:113215.
23. Svensson K, Tanner E, Gennings C, Lindh C, Kiviranta H, Wikstrom S, et al. Prenatal exposures to mixtures of endocrine disrupting chemicals and children's weight trajectory up to age 5.5 in the SELMA study. Sci Rep 2021;11:11036.
24. Lu W, Sun Z, Wang Z, Qu M, Shi Z, Song Q, et al. The joint effects of bisphenols and iodine exposure on thyroid during pregnancy. Nutrients 2023;15:3422.
25. Sonavane M, Gassman NR. Bisphenol A co-exposure effects: a key factor in understanding BPA's complex mechanism and health outcomes. Crit Rev Toxicol 2019;49:371-86.
26. Kim WG, Kim WB, Woo G, Kim H, Cho Y, Kim TY, et al. Thyroid stimulating hormone reference range and prevalence of thyroid dysfunction in the Korean population: Korea National Health and Nutrition Examination Survey 2013 to 2015. Endocrinol Metab (Seoul) 2017;32:106-14.
27. Moreno-Reyes R, Glinoer D, Van Oyen H, Vandevijvere S. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. J Clin Endocrinol Metab 2013;98:3694-701.
28. Jeong Y, Mok S, Kim S, Lee I, Lee G, Kho Y, et al. Comparison of urinary exposure profiles to phthalates and bisphenol analogues in kindergartens in Korea: impact of environmental choices on children's health. Ecotoxicol Environ Saf 2024; 288:117391.
29. Park NY, Cho SW, Seo YE, Chae H, Lee I, Lee YA, et al. Exposure to and transplacental transfer of per- and polyfluoroalkyl substances in a twin pregnancy cohort in Korea. Environ Sci Technol 2024;58:21120-30.
30. Gao H, Chen D, Zang M. Association between phthalate exposure and insulin resistance: a systematic review and meta-analysis update. Environ Sci Pollut Res Int 2021;28:55967-80.
31. Mitra T, Gulati R, Ramachandran K, Rajiv R, Enninga EAL, Pierret CK, et al. Endocrine disrupting chemicals: gestational diabetes and beyond. Diabetol Metab Syndr 2024;16:95.
32. Papalou O, Kandaraki EA, Papadakis G, Diamanti-Kandarakis E. Endocrine disrupting chemicals: an occult mediator of metabolic disease. Front Endocrinol (Lausanne) 2019;10: 112.
33. Ye Y, Tang Y, Xiong Y, Feng L, Li X. Bisphenol A exposure alters placentation and causes preeclampsia-like features in pregnant mice involved in reprogramming of DNA methylation of WNT2. FASEB J 2019;33:2732-42.
34. Shoaito H, Petit J, Chissey A, Auzeil N, Guibourdenche J, Gil S, et al. The role of peroxisome proliferator–activated receptor gamma (PPARγ) in mono(2-ethylhexyl) phthalate (MEHP)-mediated cytotrophoblast differentiation. Environ Health Perspect 2019;127:27003.
35. Siwakoti RC, Harris SM, Ferguson KK, Hao W, Cantonwine DE, Mukherjee B, et al. Prenatal exposure to per- and polyfluoroalkyl substances (PFAS) and their influence on inflammatory biomarkers in pregnancy: findings from the LIFECODES cohort. Environ Int 2024;194:109145.
36. Lee SY. Editorial: consequences of iodine deficiency in pregnancy. Front Endocrinol (Lausanne) 2021;12:740239.
37. Pearce EN, Lazarus JH, Moreno-Reyes R, Zimmermann MB. Consequences of iodine deficiency and excess in pregnant women: an overview of current knowns and unknowns. Am J Clin Nutr 2016;104 Suppl 3(Suppl 3):918S-23S.
38. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 2013;382:331-7.
39. Toloza FJK, Motahari H, Maraka S. Consequences of severe iodine deficiency in pregnancy: evidence in humans. Front Endocrinol (Lausanne) 2020;11:409.
40. Liu B, Lu X, Jiang A, Lv Y, Zhang H, Xu B, et al. Influence of maternal endocrine disrupting chemicals exposure on adverse pregnancy outcomes: a systematic review and meta-

analysis. Ecotoxicol Environ Saf 2024;270:115851.
41. Chen Y, Xiao H, Namat A, Liu J, Ruan F, Xu S, et al. Association between trimester-specific exposure to thirteen endocrine disrupting chemicals and preterm birth: comparison of three statistical models. Sci Total Environ 2022;851(Pt 2): 158236.
42. Lee YA, Cho SW, Sung HK, Kim K, Song YS, Moon SJ, et al. Effects of maternal iodine status during pregnancy and lactation on maternal thyroid function and offspring growth and development: a prospective study protocol for the Ideal Breast Milk cohort. Endocrinol Metab (Seoul) 2018;33:395-402.
43. Chung CW, Kim K, Park SK, Ju DL, Park YJ, Shin CH, et al. Selenium levels and their association with thyroid autoimmunity and severe preeclampsia in pregnancy: insights from a prospective Ideal Breast Milk cohort study. Eur Thyroid J 2024;13:e240007.
44. Ju DL, Cho SW, Chung CW, Lee YA, Cheon GJ, Park YJ, et al. High intakes of iodine among women during pregnancy and the postpartum period has no adverse effect on thyroid function. Eur J Nutr 2023;62:239-49.
45. Shi X, Han C, Li C, Mao J, Wang W, Xie X, et al. Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. J Clin Endocrinol Metab 2015; 100:1630-8.
46. Li S, Zha H, Cui Y, Sun L, Yu L, Yuan Q, et al. The relationship between excessive iodine during pregnancy and adverse pregnancy complications. Endocrine 2025;88:203-10.
47. Chen R, Li Q, Cui W, Wang X, Gao Q, Zhong C, et al. Maternal iodine insufficiency and excess are associated with adverse effects on fetal growth: a prospective cohort study in Wuhan, China. J Nutr 2018;148:1814-20.
48. Metcalfe CD, Bayen S, Desrosiers M, Munoz G, Sauve S, Yargeau V, et al. Methods for the analysis of endocrine disrupting chemicals in selected environmental matrixes. Environ Res 2022;206:112616.