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Factors associated with partitioning behavior of persistent organic pollutants in a feto-maternal system: A multiple linear regression approach

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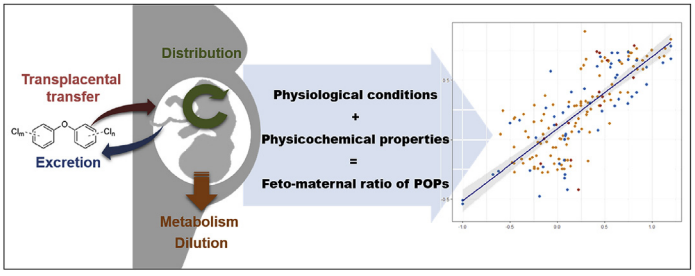
HIGHLIGHTS

- The factors affecting feto-maternal ratio (FM-ratio) of POPs are investigated.
- New approach using multiple linear regression is employed.
- The lipid content in the cord and maternal blood are associated with FM-ratio of POPs.
- The molecular size and lipophilicity are negatively associated with FM-ratio of POPs.
- The high FM-ratios of PBDEs suggest an additional transplacental transporting mechanism.

GRAPHICAL ABSTRACT



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ABSTRACT

Prenatal exposure to persistent organic pollutants (POPs) has been a matter of particular concern because such exposure can severely affect the health of the fetus. The mechanistic understanding of the partitioning behavior of POPs in the feto-maternal system and the associated factors, however, have rarely been studied. Here, we employed a new approach based on multiple linear regression (MLR) analysis to predict the feto-maternal ratio (FM-ratio) of POPs and to assess the factors associated with feto-maternal partitioning behavior. Two preliminary exploratory MLR models were built using physiological conditions of the participants, and molecular descriptors were calculated with a computational model. The FM-ratio was calculated from the concentrations of polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins and furans (PCDD/Fs), and polybrominated diphenyl ethers (PBDEs) in 20 pairs of maternal and cord blood. The models showed that the lipids and cholesterols in the maternal and cord blood and the placenta significantly influence the partitioning of POPs. The body mass index (BMI) change during pregnancy was also related to the FM-ratio. The physicochemical properties associated with lipophilicity and molecular size were also related to the FM-ratio. Even though the results should be interpreted with caution, the preliminary MLR models illustrate that feto-maternal partitioning is

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governed by transplacental transporting mechanisms, toxicokinetics, and the molecular physicochemical properties of POPs. Overall, the new approach used in this study can improve our understanding of the partitioning behavior in the feto-maternal system.

1. Introduction

A fetus in the uterus is surrounded by an amniotic sac, and the placenta is the only material exchange pathway between the maternal and fetal circulatory systems. As a protective organ, the placenta filters viruses and xenobiotics from the maternal circulatory system. Persistent organic pollutants (POPs) in fetal tissues and blood have been detected in previous studies (Kim et al., 2015; Needham et al., 2011), which have provided evidence of the transplacental transport (TPT) of POPs through the placental membrane. POPs are persistent, toxic and bioaccumulating chemicals (UNEP, 2001) and have relatively long biological half-lives (Aylward et al., 2005; Ritter et al., 2010; Thuresson et al., 2006). POPs exposed to the human body circulate in the body, partitioning among fatty compartments (Rönn et al., 2011; Yu et al., 2011), and they exert various adverse health effects, such as mutagenicity, carcinogenicity, metabolic disorders, and hormonal disruption (Mandal, 2005; Porta, 2006; Romieu et al., 2000; Uemura et al., 2009). In particular, prenatal exposure to POPs and the resulting health effects have been a matter of particular concern, as the fetus is undergoing rapid development and growth (Arbuckle, 2010; Herbstman et al., 2008; Kurzel and Cetrulo, 1981).

While prenatal exposure has been assessed in previous studies, the partitioning behavior and its associated factors are poorly understood. Few studies have assessed the TPT rate of POPs in various systems. For example, the quantitative structure-activity relationship (QSAR) evaluates the TPT rate of POPs based on the physicochemical properties of the molecule (Fujikawa et al., 2007; Giaginis et al., 2009). *Ex-vivo* and *in vitro* perfusion tests, using implanted human placental membranes and cultured placental cells, respectively, have assessed the TPT rate of POPs and other xenobiotics (Carreira et al., 2011; Frederiksen et al., 2010; Poulsen et al., 2009). The TPT rates estimated by those methods were inadequate for representing exposure doses to the fetus, as actual fetal exposure is governed by TPT as well as distribution, dilution, metabolism, and excretions in the feto-maternal system. Furthermore, *ex-vivo* and *in vitro* perfusion tests have used buffer solutions (Mathiesen et al., 2014), thus ignoring the potential TPT of POPs facilitated by transporters and carriers, such as lipoproteins and transthyretin (Kim et al., 2015).

Another approach to investigate feto-maternal partitioning behavior is to assess the feto-maternal ratio (FM-ratio) of the POPs. The FM-ratio, the ratio between concentrations of cord and maternal blood, is an indicator that can be used to evaluate the partitioning behavior of POPs as a result of toxicokinetics and physiological characteristics of the mothers and their fetuses. Furthermore, the FM-ratio enables indirect estimation of fetal POP exposure by multiplying maternal POP levels with the FM-ratio. Several studies have demonstrated the FM-ratio and its associated factors, such as demographic characteristics and physiological condition of the mothers (Apelberg et al., 2007; Patayová et al., 2013; Vizcaino et al., 2014; Zhang et al., 2018), and physicochemical properties of the POPs (Lancz et al., 2015). These studies employed simple bivariate analysis; therefore, there are too many confounding factors, so a mechanistic understanding is still lacking.

In this study, an approach employing multiple linear regression (MLR) was employed to investigate factors associated with the FM ratio. The MLR predicted the FM-ratio with physiological characteristics of the mothers and their fetuses and the physicochemical properties of the POPs. The FM-ratios were calculated with the concentrations of polychlorinated biphenyl (PCB), polychlorinated dibenzo-p-dioxins and furan (PCDD/F), and polybrominated diphenyl ether (PBDE) from 20 pairs of maternal and cord blood. Based on the results of two exploratory MLR models, the factors affecting the feto-maternal partitioning behavior of POPs were investigated.

2. Material and methods

2.1. Physiological conditions of the participants

Twenty pregnant women were recruited from Kyoungpook National University Hospital in Daegu, South Korea in 2010. All subjects were without a premature rupture of membrane (over 24 h) or high-risk pregnancy, and the mothers had no congenital, infectious, or genetic diseases. All blood samples were collected after explanation by a doctor and the consent of participants. This study was approved by the Institutional Review Board of Kyungpook National University Hospital (No. KNUH_10_1076). The characteristics of the mothers, such as age, parity, height, and weight before and after pregnancy, were recorded during the mothers' regular check-up at the hospital. In addition, the characteristics of the neonates, including gestational age and birth weight, were measured and recorded just after delivery. Maternal blood was obtained within 24 h prior to delivery, and cord blood was collected just after delivery. The total lipid (TL) in the samples was measured gravitationally, and the levels of triglyceride (Tg), high-density lipoproteins (HDL), and total cholesterol (TC) were measured with enzymatic methods. The lipid content of the placental tissue was determined gravitationally after Soxhlet extraction.

2.2. Persistent organic pollutants (POPs)

Fifteen PCBs, five PBDEs, and seventeen toxic PCDD/Fs were analyzed in 20 pairs of cord and maternal blood sample, the details of the analytical procedure were as described in our previous study (Kim et al., 2015). In brief, the blood samples from the mothers and umbilical cords were centrifuged, and the serum was isolated. PCBs and PCDD/Fs were extracted from each sample by liquid-liquid extraction and cleaned up with a multi-silica gel and an alumina column. PBDEs in the samples were extracted with an Oasis HLB solid-phase extraction (SPE) cartridge (540 mg) and cleaned up with a Sep-Pak silica-acid silica cartridge (0.1–1.0 g). A high resolution gas chromatograph equipped with a high resolution mass spectrometer (HRGC-HRMS) (JMS-800D, JEOL, Japan) was employed for the instrumental analysis.

The isotope dilution method was used, and the recoveries of ^{13}C-labeled compounds were 50–120%. The evaluated accuracy estimated with certified (SRM, 1958 and SRM, 1947 from NIST, USA) and in-house reference materials was within 15% of the reference value. The isotopic ratio between two selected ions was within 15%, and the linearity of the calibration curves was more than 0.99. The

resolution of the HRMS was maintained at more than 10,000 in the monitored mass range. The instrumental limit of detection (LOD) was calculated as three times the signal-to-noise ratio, and values less than the LOD were assigned as LOD/2.

2.3. Physicochemical properties of POPs

The physicochemical properties of the POPs were evaluated with e-Dragon 5.5 software (Talete srl, Italy) (Tetko et al., 2005). Among the thousands of calculated molecular descriptors, those possibly associated with the proposed TPT mechanism of POPs were used (Kim et al., 2015). Eventually, thirteen molecular descriptors were selected, which illustrate the molecular size, lipophilicity, binding capability to biomolecules, polarizability, and surface charge. The molecular descriptors include molecular weight (MW), sum of atomic Van der Waals volumes (Sv), sum of Sanderson electronegativities (Se), sum of atomic polarizabilities (Sp), number of rotatable bonds (RBN), number of halogen atoms (nX), number of aromatic rings (nCIC), radius of gyration (RGyr), span R (SPAN), molecular eccentricity (MEcc), number of hydrogen bonding acceptor atoms (nHacc), K global shape index (Ku), and Ghose-Crippen octanol-water partition coefficient (ALOGP). The molecular descriptors calculated with e-Dragon and used in this study are presented in Table S1 in the Supplementary Material.

2.4. Multiple linear regression analysis

Fig. 1 presents a procedure to build the exploratory MLR model to estimate factors affecting the FM-ratio of the POPs. The POP congeners, which were detected in more than 70% of both the maternal and cord serum samples, were selected for FM-ratio assessment. The congeners include PCB 31/28, 51, 52, 48/47/75, 70, 99, 118, 105, 153/168, 138, 156, 187/182, and 170/190, OCDD, BDE 28, 47, 99, 100, and 153. The FM-ratio was calculated by dividing the POP levels in the cord serum with those in the maternal serum. The FM-ratios that were based on the wet POP concentrations were used for the MLR analysis because lipid-adjusted concentrations can confound the influence of lipid content on the FM-ratio. The independent variable, the FM-ratio, was log-transformed, and the outliers were normalized to ± 1.2. The dependent variables were also log-transformed to correct skewness, but the BMI change, parity, RBN, nX, nCIC, and nHacc, which have negative and zero values, were converted to a standard Z-score. The molecular descriptors and physiological factors that were not correlated with one another ($r<0.7$, $p>0.05$) and could be practically calculated with ease were selectively inputted into the model. The Spearman's rank sum correlation coefficients of molecular descriptors and physiological conditions are presented in Table S3-S5 in the Supplementary Material.

The associations were analyzed with the stepwise method (entry when $F < 0.05$ and removal when $F > 0.10$) and hierarchical order; the physiological characteristics of the mothers and their fetuses were in Group 1, and the physicochemical properties of POPs were in Group 2. The physicochemical properties for the congeners that could not be separated by gas chromatography were entered as an averaged value of the molecular predictors of the unseparated congeners. In Model 1, which had a total of 104 cases, only PCB data were used in order to focus on the effect of molecular size on the control of ring size. In Model 2, the data set was expanded to include PCBs, OCDD and PBDEs, which have differences in their ring structure, oxygen bridge, and halogen atom. The optimal model was selected by the adjusted coefficient of determination (R^2*), variation of F and p-value. The variation inflation factors (VIF) of the independent variables were examined, and the residual autocorrelation was tested with the Durbin-Watson test. The MLR analysis was performed with IBM SPSS Statistics for Windows, Version 20.0 (SPSS Inc., Chicago, USA) and software R (R Core Team, 2019, Vienna, Austria).

3. Results

3.1. Characteristics of the subjects

Table 1 presents the characteristics of the mothers and their fetuses. The ages of the mothers ranged from 21 to 42 years, and the mean age was 32.1 years. The maternal BMIs before and after pregnancy were 15.6–33.3 kg/m^2 and 18.4–33.6 kg/m^2, respectively. Seven mothers had no children, and 8 and 5 mothers had one and two children, respectively. Five neonates were born by vaginal delivery, while fifteen neonates were delivered by Cesarean section. The gestational ages of the fetuses ranged from 234 to 286 days, and their birth weights ranged from 1990 to 3590 g. The average lipid content and Cd levels in the placenta were 6.97% and 2.12 ng/g, respectively. The lipid content in the maternal blood samples was higher than in the cord blood samples. The mean TC, HDL, and Tg levels in the maternal blood samples were 203.5, 58.3, and 220.0 mg/dL, while those in the cord blood samples were 97.5, 37.6, and 58.2 mg/dL, respectively.

3.2. The FM-ratio

The FM-ratios that were calculated based on the wet and lipid-adjusted concentrations of PCBs, OCDD, and PBDEs are presented in Fig. 2. The median values of the wet FM-ratios were higher than those in most of the compounds except some PCB congeners, which ranged from 0.46 to 1.80 for PCBs, 2.68 for OCDD, and 1.19–6.25 for PBDEs. The median values of the lipid-adjusted FM-ratio were less than one for most compounds, with the exception of some PBDE congeners. The lipid-adjusted FM-ratios were 0.23–0.83 for PCBs, 0.68 for OCDD, and 0.34–2.30 for PBDEs. In both the wet and lipid-adjusted FM-ratios, the mean values were higher than the median values because their distributions were skewed to the right. The detailed FM-ratios are presented in Table S2 in the Supplementary Material.

3.3. Model 1: PCBs

Table 2 describes the results of the MLR analysis that predicted the FM-ratio of PCBs, and Fig. 3 presents the corresponding scatterplot. In the result of Model 1, R was 0.821, and adjusted R^2 was 0.657, implying that the model explained 65.7% of the variance of the FM-ratio. The TC in the maternal blood, body mass index (BMI) change during pregnancy, and nX were significantly associated with the FM-ratio in a negative manner, whereas TC in the cord blood had the opposite association. The absolute value of the standardized coefficient (β) was the highest in TC in the cord blood, followed by TC in the maternal blood. The result of the Durbin-Watson test was 1.628, and VIFs of all variables were less than 1.5, implying that the model did not show residual autocorrelation and collinearity of the predictors. The relationship between standardized residuals and standardized predicted variables of Model 1 is presented in Figure S1 in the Supplementary Material, which showed no significant trend. The partial regression plots for the predictor variables of Model 1 are shown in Fig. 4.

3.4. Model 2: PCBs, OCDD, and PBDEs

Table 3 describes the results of the MLR analysis predicting the FM-ratios of PCBs, OCDD, and PBDEs, and Fig. 5 presents the corresponding scatterplot. In Model 2, R and adjusted R^2 were 0.777

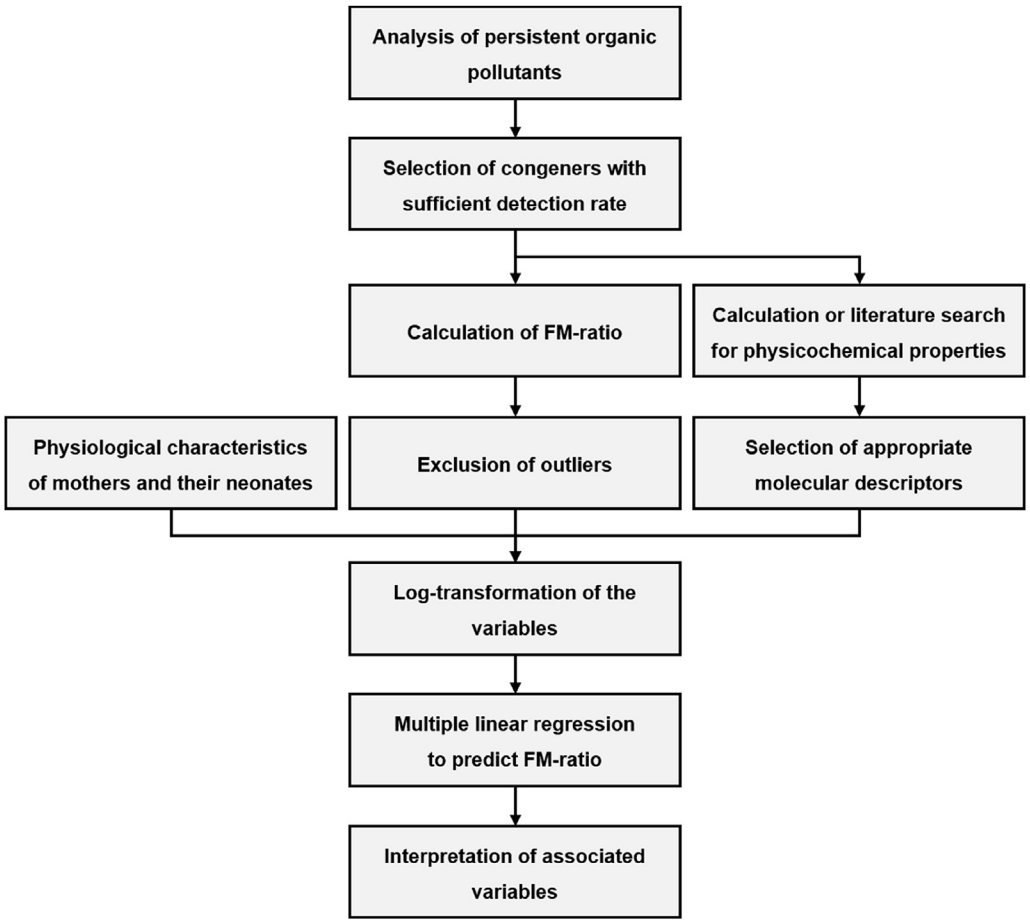

Fig. 1. Schematic diagram of the investigation of factors affecting the FM-ratio of POPs in the fetal-maternal system.

Table 1
The characteristics of the participants.

	Mean	min	Q 1	Median	Q 3	Max
Age of mother (year)	32.1	21.0	30.0	31.5	35.8	42.0
BMI before pregnancy (kg/m^2)	23.3	15.6	19.3	21.9	27.5	33.3
BMI after pregnancy (kg/m^2)	25.3	18.4	22.0	25.1	29.1	33.6
BMI change (%)	10.7	−29.1	6.7	15.7	21.9	32.3
Gestational age (day)	264	234	259	265	273	286
Birth weight (g)	2915	1990	2555	2945	3412	3590
Parity (n)	**0**	7	**1**	8	**2**	5
Delivery mode	**Vaginal Delivery**	5	**Cesarean Section**	15		
The placenta						
Total lipid (%)	6.97	3.59	5.58	6.07	7.08	16.4
Lipid contents in the maternal blood						
Total cholesterol (mg/dL)	204	89.0	183	201	237	271
HDL cholesterol (mg/dL)	58.3	40.0	50.3	56.0	66.3	83.0
Triglyceride (mg/dL)	220	15.0	161	224	262	371
Total lipid (%)	0.488	0.150	0.387	0.527	0.587	0.680
Lipid contents in the cord blood						
Total cholesterol (mg/dL)	97.5	45.0	70.0	89.0	123	172
HDL cholesterol (mg/dL)	37.6	20.0	32.3	35.0	40.0	66.0
Triglyceride (mg/dL)	58.2	8.0	14.5	50.5	82.0	245
Total lipid (%)	0.214	0.069	0.124	0.194	0.302	0.476

and 0.595, respectively. TL in the maternal blood and TL in the cord blood were significantly associated with the FM-ratio. In addition, TL in the placenta and SPAN of the POP molecules were significantly negatively associated with the FM-ratio. The absolute value of β was the highest in TL in the cord blood, followed by TL in the maternal blood. The result of the Durbin-Watson test was 1.472, and VIFs of all variables were less than 1.2. The relationship between standardized residuals and standardized predicted variables of Model 2 is presented in Figure S2 in the Supplementary Material, which had no significant trend. The partial regression plots for the predictor variables of Model 2 are presented in Fig. 6.

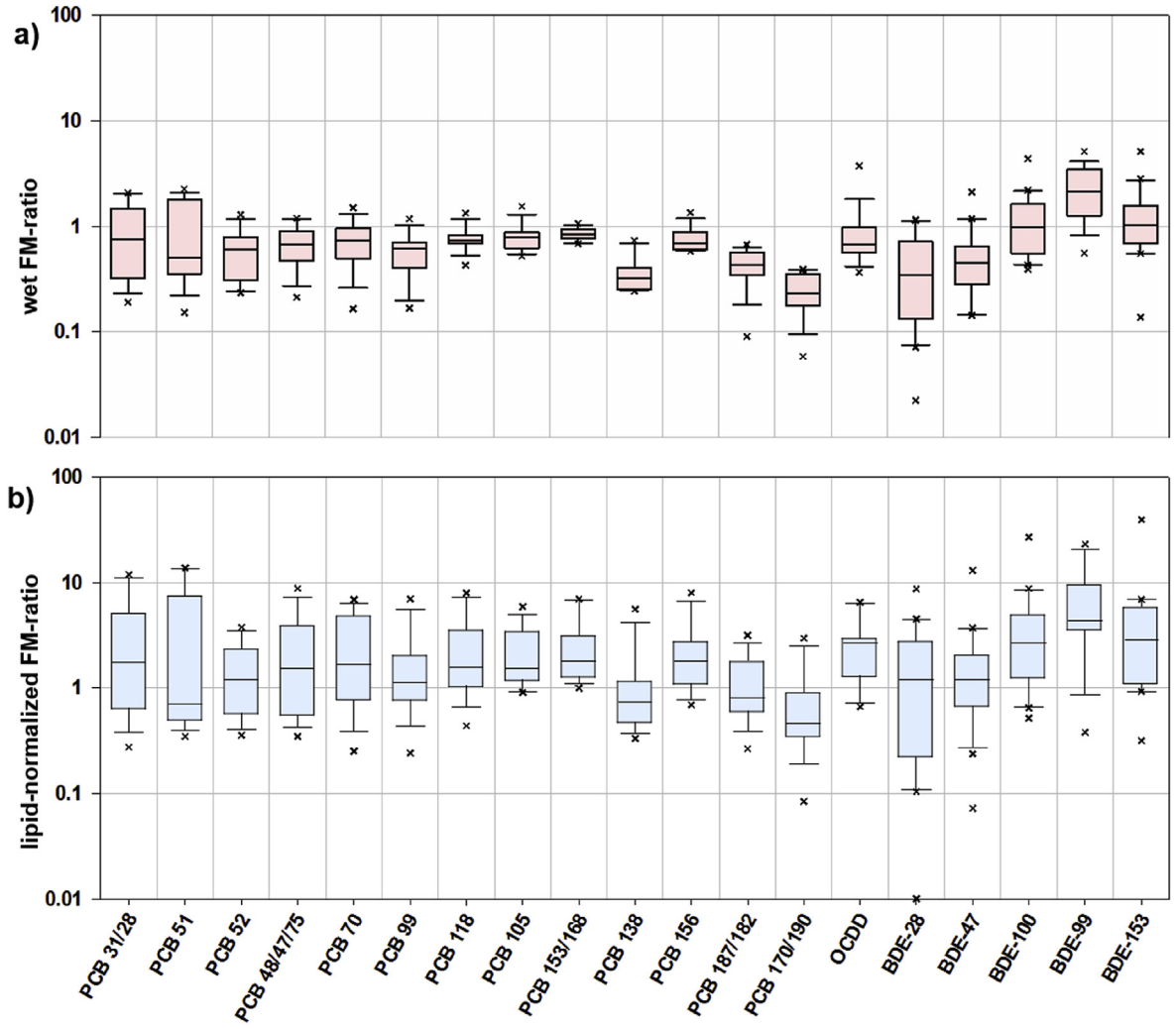

Fig. 2. The FM-ratio of POPs based on their a) wet and b) lipid-normalized concentrations.

Table 2
Multiple linear regression model to predict the FM-ratios of PCBs. (Model 1).

R	0.821	F	40.514		Durbin-Watson	1.628
Adjusted R^2	0.657	**p-value**	<0.001		**Case (n)**	104
	B (CI 95%)		*β*	**t**	**p-value**	**VIF**
(intercept)	−2.167 (−4.333 - −0.001)			−1.985	0.050	
TC in the cord blood	−1.802 (−2.088−−1.515)		−0.762	−12.484	0.000	1.121
TC in the maternal blood	2.377 (1.497−3.256)		0.370	5.362	0.000	1.434
BMI change	−0.115 (−0.183−−0.046)		−0.218	−3.330	0.001	1.288
TL in placenta	−0.373 (−0.692−−0.054)		−0.146	−2.319	0.022	1.183
nX	−0.121 (−0.175−−0.067)		−0.255	−4.413	0.000	1.000

4. Discussion

4.1. The FM-ratio of POPs

In this study, both the wet and lipid-adjusted FM-ratios of PCBs, OCDD, and PBDEs were calculated. The patterns of individual congeners of the wet and lipid-adjusted FM-ratios were similar to each other. The FM-ratios based on the wet concentrations were higher than those based on lipid-adjusted concentrations because of the lower lipid content in cord blood relative to maternal blood. There was a significant trend in the FM-ratios of PCBs, which were relatively high in tri-to hexa-CBs and decreased in hepta-CBs. OCDD and PBDEs showed higher FM-ratios compared to PCBs with the identical number of halogen atoms. In particular, PBDEs showed the highest median FM-ratios, which were larger than 1. It should be noted that the FM-ratio >1 means higher exposure levels in the fetus than in the mother.

Several previous studies on the FM-ratio of POPs and most studies have reported lipid-adjusted FM-ratios. The lipid-adjusted FM-ratios of PCBs, PCDD/Fs, and organochlorine pesticides (OCPs)

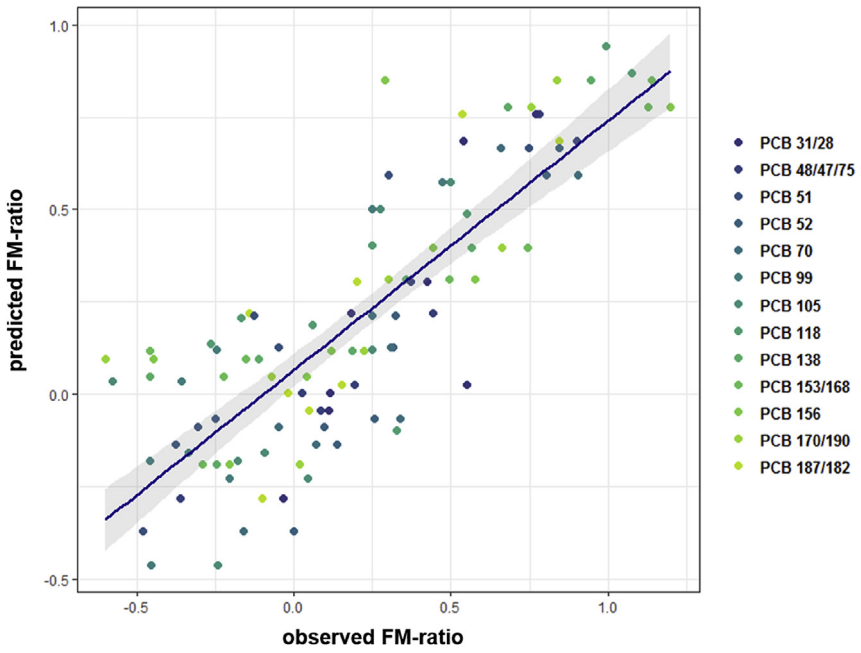

Fig. 3. Scatter plot for the observed versus predicted FM-ratio based on the wet concentrations of PCBs (Model 1).

were generally close to or less than 1 (Bergonzi et al., 2009; Kim et al., 2011; Nakano et al., 2005; Needham et al., 2011; Patayová et al., 2013; Vizcaino et al., 2014). Only some POP compounds, such as DDT and PBDE congeners, exhibited a lipid-adjusted FM-ratio that was higher than one (Chen et al., 2014; Kim et al., 2015; Vizcaino et al., 2014).

When the FM-ratio was measured with *in vitro* approaches using cultivated placental cells and *ex-vivo* approaches with implanted human placenta membranes, the resulting FM-ratio was much lower than the FM-ratios measured with *in vivo* monitoring studies (Carreira et al., 2011; Frederiksen et al., 2010). That can be ascribed to two reasons. First, the *in vitro* and *ex vivo* approaches only reflect the metabolic and TPT rates of POPs over a short time, and they do not reflect the accumulation or partitioning of POPs that occurs in fetal tissues and fluids over long-term pregnancy. In addition, as these experiments used an aqueous buffer solution with albumin to simulate maternal blood (Carreira et al., 2011; Frederiksen et al., 2010; Myllynen et al., 2010), they could not accurately capture the effect of carriers in the blood that aid in the TPT of POPs.

4.2. Physiological characteristics of the mothers and their fetuses

In Model 1 and Model 2, the TC and TL levels were significantly associated with the FM-ratio, respectively. Both TC and TL in the maternal blood were significantly associated with the FM-ratio in a positive manner, while those in the cord blood were associated in a negative manner. Notably, the absolute value of β of this the lipid in the maternal blood was the highest among independent variables, indicating that maternal lipid content is the primary factor influencing the FM-ratio of the POPs. It should not be ignored that TC and TL levels in each circulatory system are significantly correlated with each other. This result was in contrast to the expectation that the FM-ratio would decrease with higher lipid content in the maternal blood and increase with elevated lipid content in the cord blood because of the lipophilicity of POPs. The result of this study suggests that the POP distribution in the feto-maternal system is not a two-way partitioning equilibrium; rather, it shows one-way transport kinetics. Because the TPT of both POPs and lipids is facilitated by lipoprotein-related transporters on the placental membrane (Baardman et al., 2013; Desoye et al., 2011; Kim et al., 2015), higher maternal cholesterol level can stimulate the TPT of POP and increase the FM-ratio. The negative association of fetal TC and TL levels can also be attributed to the TPT mechanism of lipoproteins because the placental membrane receptors that facilitate the TPT of lipoproteins act via a concentration gradient.

The BMI change during pregnancy was negatively associated with the FM-ratio in Model 1. As higher maternal BMI and can be regarded as a larger POP reservoir, maternal BMI increases during pregnancy can inhibit the TPT of POPs by preserving POPs in the maternal body. In Model 1, the TL in the placenta was negatively associated with the FM-ratio, and TL in the placenta was significantly correlated with birth weight. When TL in the placenta was replaced with birth weight, the model was significant ($p < 0.001$) with a high R^2 ($R = 0.828$, adjusted $R^2 = 0.669$). As birth weight is a reservoir of POPs in the fetal circulatory system, it may dilute POP levels in the fetal circulatory system, as suggested by Patayová et al. (2013). On the other hand, it should be noted that POP exposure may hamper fetal growth (Dewan et al., 2013; Ouidir et al., 2019; Tan et al., 2009), while Verner et al. (2013) suggested that the negative association between POP exposure and fetal body weight might be confounded by maternal weight gain during pregnancy. Here, we also suggest that the negative association of fetal growth and fetal serum POP levels might partly be the result of a decreased FM ratio. Furthermore, maternal age, parity, and delivery mode were not significantly associated with the FM-ratio of the POPs, although they were suggested to be related with POP levels in cord blood (Apelberg et al., 2007; Barr et al., 2010; Nakamura et al., 2008).

4.3. Influence of the placental membrane

The association of placental TL content with the FM-ratio seemed to be related to the accumulation of POPs in the placental membrane. Due to the lipophilicity of POPs, lipids in the placenta can inhibit transportation from the placental cell membrane to the

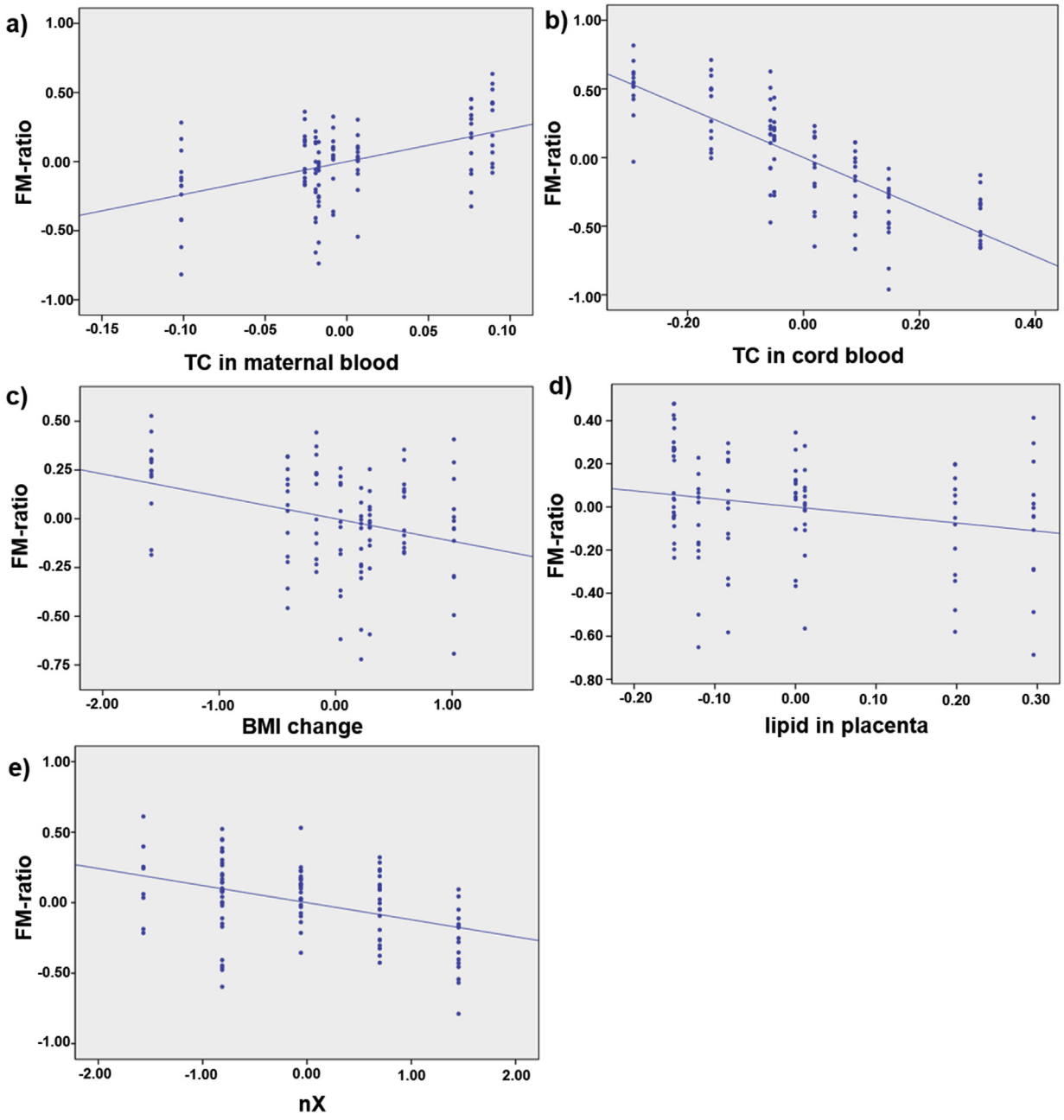

Fig. 4. Partial regression plots for the independent variables of Model 1. a) TC in the maternal blood, b) TC in the cord blood, c) BMI change, d) lipid in the placenta, and e) nX versus the FM-ratio.

Table 3
Multiple linear regression model to predict the FM-ratios of PCBs, OCDD, and PBDEs. (Model 2).

R	0.777	F	62.995		Durbin-Watson	1.472
Adjusted R^2	0.595	**p-value**	<0.001		**Case (n)**	170
	B (CI 95%)		*β*	**t**	**p-value**	**VIF**
(intercept)	0.321 (−1.358–2.001)			0.378	0.706	
TL in the cord blood	−1.165 (−1.347–−0.983)		−0.654	−12.648	<0.001	1.115
TL in the maternal blood	0.713 (0.359–1.068)		0.200	3.977	<0.001	1.054
TL in the placenta	−0.359 (−0.621–−0.096)		−0.137	−2.700	0.008	1.075
SPAN	−2.792 (−4.703–−0.881)		−0.142	−2.884	0.004	1.010

fetal circulatory system. Although the preliminary models used in this study only included TL content in the placental membrane as

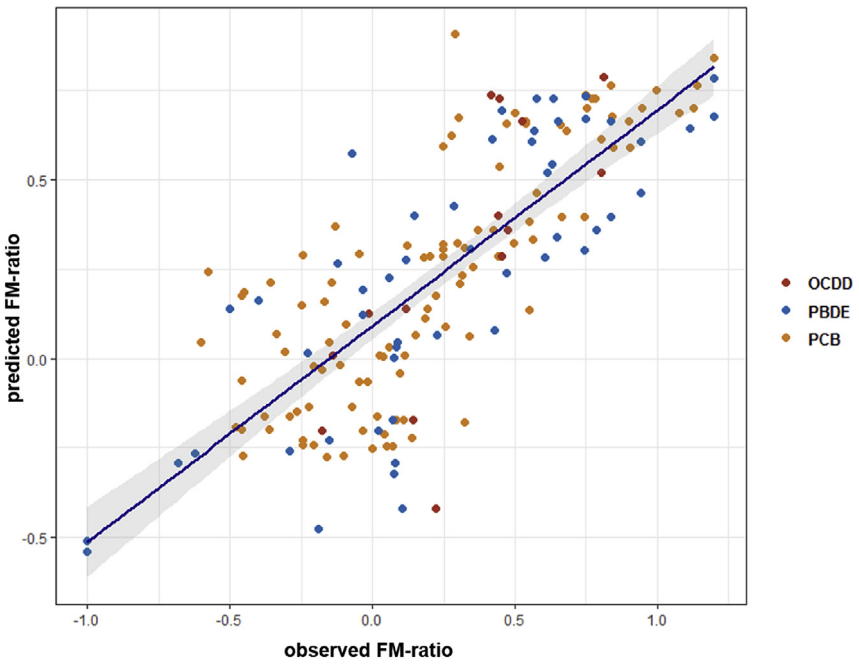

Fig. 5. Scatter plot for the observed versus predicted FM-ratio based on the wet concentrations of PCBs, OCDD, and PBDEs. (Model 2).

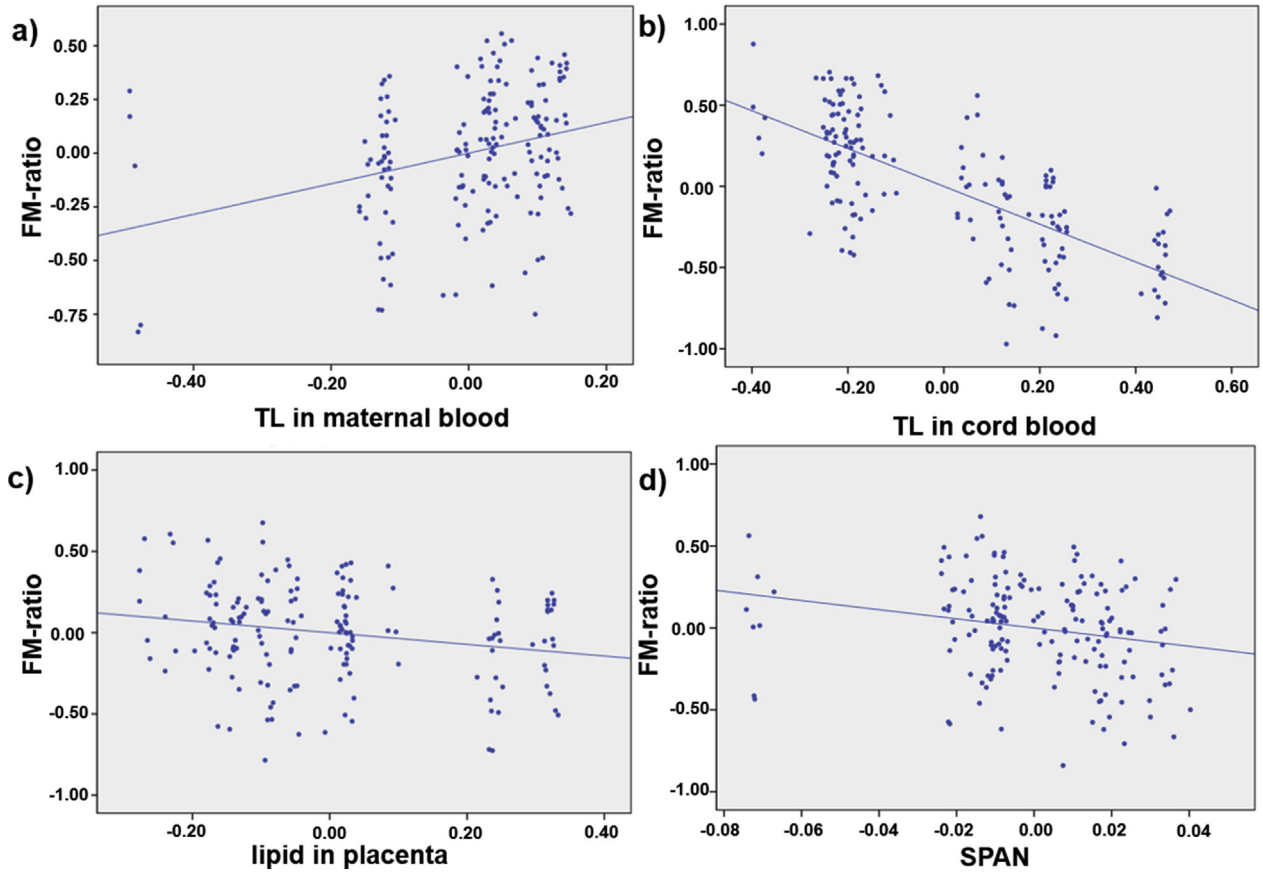

Fig. 6. Partial regression plots for the independent variables of Model 2. a) TL in the maternal blood, b) TL in the cord blood, c) lipid in the placenta, and d) SPAN versus the FM-ratio.

an independent variable, the characteristics of the placental membrane have a high potential to influence the transport, metabolism, and excretion of POPs and other xenobiotics.

There have been some reports regarding the expression of transporters, enzymes, and efflux pumps, such as lipoprotein receptors and ATP-binding cassette (ABC) transporters, LDL

receptor–related proteins (LRPs), organic anion transporter (OATP), cytochrome P450 (CYPs), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP) (Desoye et al., 2011; Myllynen et al., 2005; Prouillac and Lecoeur, 2010), which change throughout pregnancy and in response to chemical exposure (Gregoraszczuk et al., 2014; Myllynen et al., 2005). A recent study by Yin et al. (2020) suggested that the ABC transporter may play a role in the TPT of some organochlorines. Despite its importance, the role of the placental membrane in prenatal POP exposure has not been thoroughly investigated and will require further investigations.

4.4. Physicochemical properties of POPs

A negative association of nX with the FM-ratio was found in Model 1. The nX among PCB congeners is related to the molecular size and K_{OW}. It was suggested in previous studies that lipophilic and non-ionized compounds with small molecular size can easily pass through the placental membrane by means of passive diffusion (Mathiesen et al., 2014; Patayová et al., 2013). The FM-ratio of PCBs in this study corresponded with the previous suggestions, exhibiting relatively high FM-ratios in tri-to hexa-CBs and then decreased FM-ratios in hepta-CBs. The decreased FM-ratios of highly chlorinated molecules can also be ascribed to the interaction between POPs and the placental membrane because molecules with higher K_{OW} tend to accumulate in the placental membrane. Of note, lipophilic molecules are more likely to be partitioned into fetal tissues rather than circulate with fetal blood.

In Model 2, SPAN, the smallest sphere centered from the center of mass (Brown and Martin, 1996), was the only physicochemical property significantly associated with the FM-ratio, which was related to the effective molecular size of the molecule with rotational bonds. Although associations with other physicochemical properties were not found in Model 2, OCDD and PBDEs showed much higher FM-ratios than PCBs in general (Fig. 2). The higher FM-ratios of OCDD and PBDEs than PCBs might be attributed to hydrogen bonding acceptors and similar structures to the substrates of specific receptors, such as aryl hydrocarbon receptors and TH-receptors, and the high binding affinity with proteins, carriers, or transporters. Chen et al. (2014) and Kim et al. (2015) found that the lipid-adjusted FM-ratio of some PBDE congeners was higher than 1, unlike the other POPs, and suggested that TH-related transporters and carriers might facilitate the TPT of PBDEs. In addition, the FM-ratios of more hydrophilic compounds, such as perfluorinated carboxylic acid and OH-PCBs, are higher than 1, suggesting that hydrogen bonding acceptors play a significant role in the TPT of POPs (Aylward et al., 2014; Kim et al., 2011).

5. Conclusions

In this study, a method based on exploratory MLR analysis was conducted to investigate the factors affecting the FM-ratio of POPs. Two preliminary MLR models successfully found that the levels of cholesterols and lipid content in the maternal and cord blood were significantly associated with the FM-ratio. The association of BMI changes during pregnancy and lipid in the placenta with the FM-ratio could be ascribed to toxicokinetics. The physicochemical properties related to molecular size and lipophilicity, such as nX and SPAN, were also associated with the FM-ratio. The preliminary MLR models have enough explanatory power and their predictor variables were associated with the TPT mechanisms and toxicokinetics of the POPs.

The results in this study must be interpreted with caution. Many unknowns still remain, such as the expression of fetal and placental enzymes, the role of receptors and transporters in the placental membrane, and their distribution among fetal blood and tissues. In addition, the data in this study were from small size of samples. Nevertheless, the new approach used in this study based on MLR analysis could improve our understanding of the partitioning patterns in the feto-maternal system and prenatal exposures to POPs. The model can be improved in future studies by utilizing a larger sample size and more advanced independent variables.

Author's contributions (CrediT roles)

Jun-Tae Kim: Conceptualization, Formal analysis, Investigation, Visualization, Writing - original draft Dasom Oh: Data curation, Formal analysis, Investigation, Writing - original draft Sung-Deuk Choi: Methodology, Validation, Writing - review & editing Yoon-Seok Chang: Funding acquisition, Project administration; Resources, Supervision, Writing - review & editing

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2020.128247.

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