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Early-life exposure to widespread environmental toxicants and maternal-fetal health risk: A focus on metabolomic biomarkers

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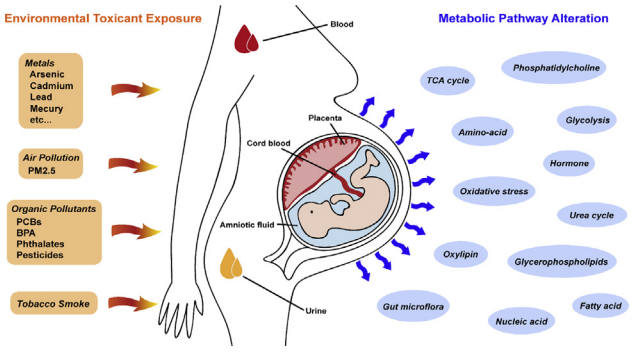
HIGHLIGHTS

- Metabolites in maternal urine and blood, cord blood, and amniotic fluid are related to environmental toxicant exposure.
- Prenatal exposure to environmental toxicants can affect the metabolic pathways of lipids, amino acids and nucleic acids.
- Changes in metabolic profiles are related to energy and hormone metabolism, oxidative stress and inflammation.
- No epidemiologic studies have focused on the relationship between environmental toxicant and placental metabolomics.

GRAPHICAL ABSTRACT



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ABSTRACT

Prenatal exposure to widespread environmental toxicants is detrimental to maternal health and fetal development. The effects of environmental toxicants on maternal and fetal metabolic profile changes have not yet been summarized. This systematic review aims to summarize the current studies exploring the association between prenatal exposure to environmental toxicants and metabolic profile alterations in mother and fetus. We searched the MEDLINE (PubMed) electronic database for relevant literature conducted up to September 18, 2019 with some key terms. From the initial 155 articles, 15 articles met the inclusion and exclusion criteria, and consist of highly heterogeneous research methods. Seven studies assessed the effects of multiple environmental pollutants (metals, organic pollutants, nicotine, air pollutants) on the maternal urine and blood metabolomic profile; five studies evaluated the effects of arsenic, polychlorinated biphenyls (PCBs), nicotine, and ambient fine particulate matter ($PM_{2.5}$) on the cord blood metabolomic profile; and one study assessed the effects of smoking exposure on the amniotic fluid metabolomic profile. The alteration of metabolic pathways in these studies mainly involve energy metabolism, hormone metabolism, oxidative stress and inflammation. No population study investigated the association between environmental toxicants and placental metabolomics. This systematic review provides evidence that prenatal exposure to a variety of environmental pollutants can

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affect maternal and fetal metabolomic characteristics. Integration of environmental toxicant exposure and metabolomics data in maternal-fetal samples is helpful to understand the interaction between toxicants and metabolites, so as to reveal the pathogenesis of fetal disease or diseases of fetal origin.

1. Introduction

Omics technologies can quickly and accurately identify comprehensive toxicological information of molecular and biological pathway changes in cells and tissues (Buesen et al., 2017). Metabolomics measures both the endogenous compounds created and assembled by our bodies and the exogenous compounds introduced by ingestion and environmental exposure, and reflects changes in the genome, proteome and response of the body to environmental influences (Board on Life Sciences, 2016). Low molecular weight metabolites (molecular weight < 1 kDa) can be sorted out by metabolomics technology as a single final product. These molecules are characteristic of various aspects of cell metabolism, including breakdown of fuels, such as carbohydrates, amino acids and fats, to generate energy and biosynthetic precursors for growth (Kaushik and DeBerardinis, 2018). Different analytical techniques might be generally adopted: non-destructive analysis such as nuclear magnetic resonance (NMR) spectroscopy, *vs.* destructive analysis such as liquid chromatography-mass spectrometry (LC–MS) and gas chromatography–mass spectrometry (GC–MS). A common application of metabolomics has been to determine the relationship between exposure and risk-predictive intermediate biomarkers through different maternal and fetal samples. Metabolic profiles of biological samples from the mother (blood, urine and amniotic fluid) and fetus (umbilical cord blood and placenta) can provide valuable information about fetal development and maternal health (Fanos et al., 2013b).

During the entire intrauterine period, the placenta, umbilical cord and amniotic fluid play a critical part in growth, development, and survival of the fetus. After the syncytiotrophoblast cells of the blastocyst invade the uterine wall, the placenta begins to grow with the formation of chorionic villi, which constitute the fetal side of this temporary organ (Luyten et al., 2018). Placental cells protect the developing embryo from rejection by suppressing the maternal immune system and providing a place for mother and fetus to carry out the exchange of metabolic waste and nutrients (Levkovitz et al., 2013; Nugent and Bale, 2015). The umbilical cord develops from and contains remnants of the allantois and yolk sac at the fifth week of embryo development. During prenatal development, the umbilical cord connects the placenta and fetus and is a physiological and genetic part of the fetus. The single umbilical vein carries oxygenated blood to the fetus, while the two umbilical arteries spiral around the umbilical vein within the cord to return de-oxygenated blood back to the placenta (Hubbard and Stanford, 2017). Amniotic fluid generated from maternal plasma in the amniotic sac can pass through fetal membranes by osmotic and hydrostatic forces, and protects the developing fetus, allowing for easier fetal movement, and promoting skeletal and muscular development (Notice, 1981; Underwood et al., 2005). In addition, maternal blood is constantly exchanged with the fetus through the placenta, providing nutrients required for growth and development, and maternal urine generally reflects the metabolism of mother and fetus (Orczyk-Pawilowicz et al., 2016; Wang et al., 2018a). Hence, metabolic profiling of mothers is a useful tool for the evaluation of effects on the fetus health (Liu et al., 2017).

Any harmful factors during pregnancy not only endanger the pregnant women's own health, but also affect the pregnancy process and outcome, and may pose a potential threat to fetal development and later life (Varshavsky et al., 2019). Prenatal exposure to widespread environmental toxicants, including tobacco smoke, ambient air pollution, persistent organic pollutants (POPs) and heavy metals, can lead to changes in metabolic pathways that may affect maternal health, fetal development, and health throughout life. The "developmental origins of health and disease" (DOHaD) hypothesis recognizes that the risk of developing chronic noncommunicable diseases in adulthood is influenced not only by genetic and adult lifestyle factors, but also by detrimental environmental factors present in early life (Barker, 2007; Gluckman and Hanson, 2004). Some environmental toxicants enter into the umbilical cord blood and amniotic fluid through the placenta *via* active or passive transport and can adversely affect fetal development and growth (Koren and Ornoy, 2018; Vrooman et al., 2016). Harmful environmental toxicants already identified in this context are polybrominated diphenyl ethers (PBDEs) (Xu et al., 2015), polychlorinated biphenyls (PCBs) (Govarts et al., 2018), polycyclic aromatic hydrocarbons (PAHs) (Yang et al., 2018), bisphenol A (BPA) (Mireia et al., 2015), perfluorooctanoic acid (PFOA) (Mora et al., 2017), heavy metals (Wai et al., 2017), ambient air pollution (Zhang et al., 2018), nicotine (Mackay et al., 2017), and pesticides (Harley et al., 2016). All have been found to be detrimental to birth outcomes and increase the risk of disease in adulthood.

Metabolomics technology has been widely used to explore the impact of environmental exposure on maternal and fetal health, better understand the pathogenesis of different diseases, and screen disease biomarkers (Cai et al., 2020; Eguchi et al., 2017; Fanos et al., 2013b; Maitre et al., 2018). Several reviews have described the relationship between prenatal environmental toxicant exposure and maternal and fetal health outcomes (Ballesteros et al., 2017; Cao et al., 2016; Huang et al., 2020; McDermott et al., 2015), but changes in maternal and fetal metabolomic characteristics related to prenatal exposure to environmental toxicants have not been summarized. The purpose of this systematic review is to summarize current metabolic studies understanding the relationships between early-life exposure to environmental toxicants and changes in maternal and fetal metabolic profiles.

2. Methods

2.1. Search strategy

We searched the MEDLINE (PubMed) electronic database for relevant literature conducted up to September 18, 2019 with the key terms 'maternal blood metabolomics', 'maternal serum metabolomics', 'maternal plasma metabolomics', 'maternal urinary metabolomics', 'maternal urine metabolomics', 'cord metabolomics', 'placenta metabolomics', 'placenta lipidomic', and 'amniotic fluid metabolomics', and their combinations, all combined with 'exposure'. Articles were included or excluded on the basis of full-text articles (Chen et al., 2018; Wang et al., 2018b). In selected studies, metabolomics platforms, such as NMR, LC–MS and GC–MS, were used to explore the association between environmental toxicant exposure and metabolic alterations in maternal urine and blood, umbilical cord blood, and amniotic fluid during maternity.

2.2. Inclusion and exclusion criteria

First, we screened the literature according to the exclusion criteria, including non-English writing, non-full text and review. Next, based on screening title, abstract and full text, studies were excluded if they met the following criteria: a) used non-metabolomics techniques, b) measured non-metabolites or non-environmental exposure, or c) were without biological samples (maternal blood and urine, cord blood and amniotic fluid) from pregnant women or fetuses. After collecting the literature that met these requirements, we manually

searched the metabolic information of different environmental chemicals.

2.3. Assessment of quality of studies

In order to ensure the quality and quantity of literature and reduce subjective bias of a single investigator, two investigators took part in the literature retrieval and screening. Then another two investigators double-checked the literature search, and all investigators read all papers and independently extracted and archived the relevant information, after which all members met to discuss and deal with the inclusion or exclusion of disputed literature.

2.4. Data synthesis and analysis

We used a pre-designed data collection form to assess each study and contained the following information: title, journal, author(s), data of publication, study population, study location, sample size, metabolomics analysis platform, type of sample, collection time of sample, number of differential metabolites, exposure outcome(s) assessed. Because of the heterogeneous nature of each study, instead of meta-analysis, we performed a qualitative summarization. The report of this review's results refers to the PRISMA statement (Moher et al., 2009).

3. Results

3.1. Study characteristics

From the initial 155 articles, 15 articles met the inclusion and exclusion criteria for this systematic review, and the selection flowchart is shown in Fig. 1. The basic information of all 15 articles is shown in Table S1. These research works were published in 2013 or later. Four studies used a ^{1}H NMR metabolomic platform to measure metabolites, eleven studies used an LC–MS platform to measure metabolites, and one study combined GC–MS and LC–MS platforms to measure metabolites. Two studies indirectly evaluated the effects of pesticides (agricultural area) and industrial chemicals on maternal urinary metabolites, respectively (Bonvallot et al., 2013; Gil et al., 2018). Two studies investigated the effects of co-exposure to multiple metals and organic pollutants on the metabolomic profile in maternal urine (Maitre et al., 2018; Wang et al., 2018a). The other studies only explored the association between a single environmental toxicant and metabolomic profile

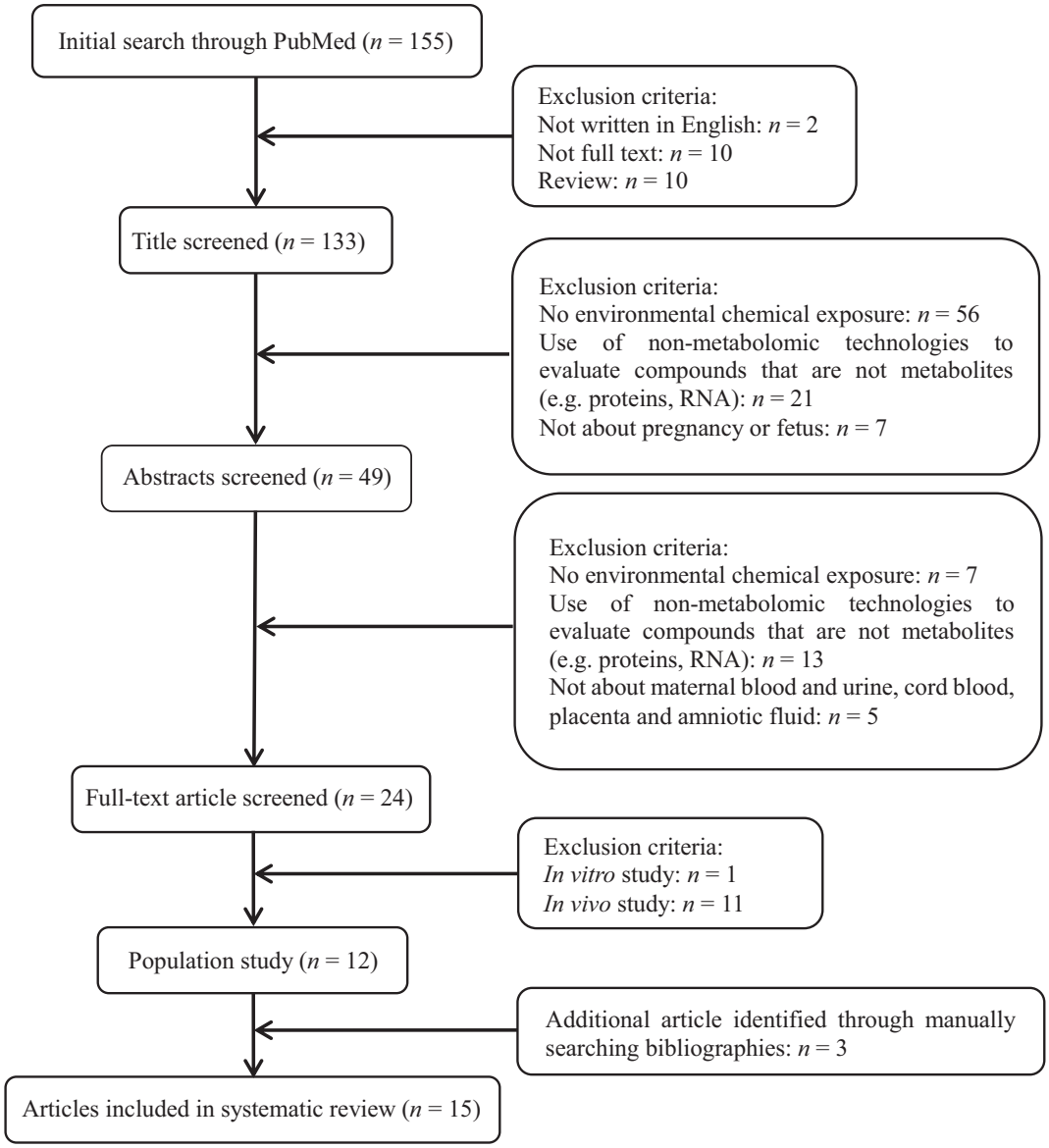

Fig. 1. Systematic review study selection flowchart. From the 155 initially screened articles, 15 were included the systematic review.

alterations. These studies measured the metabolomic profile in different biological samples, including maternal urine samples ($n = 7$), maternal plasma/serum samples ($n = 7$), cord plasma/serum samples ($n = 5$), and amniotic fluid ($n = 1$). These studies were conducted in eleven different countries, including France ($n = 1$) (Bonvallot et al., 2013), Portugal ($n = 1$) (Gil et al., 2018), Spain ($n = 1$) (Maitre et al., 2018), Poland ($n = 1$) (Zbucka-Kretowska et al., 2018), Germany ($n = 1$) (Rolle-Kampczyk et al., 2016), Belgium ($n = 1$) (Wei et al., 2017), USA ($n = 3$) (Fischer et al., 2017; Yan et al., 2019; Zhou et al., 2018), China ($n = 3$) (Li et al., 2017; Li et al., 2019; Wang et al., 2018a), Bangladesh ($n = 1$) (Wei et al., 2017), Japan ($n = 1$) (Eguchi et al., 2017), and Mexico ($n = 1$) (Laine et al., 2017). Three Chinese studies were conducted on the same population from the Wuhan Medical and Health Center for Women and Children. Urine sample collection spanned three different trimesters of pregnant women (Table 1). The collection of maternal blood samples concentrated on the second and third trimesters (Table 2). Cord blood was collected at birth (Table 3). Amniotic fluid collection was performed in the second trimester (Table 4).

3.2. Alteration of the maternal urine metabolomic profile (Table 1)

3.2.1. Effects of complex environment exposure on the urine metabolic profile

Two studies compared the difference of metabolic fingerprints in pregnant women between high and low exposure groups. In the 11th week of pregnancy, after adjusting for confounding factors, complex pesticide mixtures could change the levels of glycine, lactate, glycerophosphocholine (GPC) (upward trend), and citrate (downward trend). These metabolites are involved in the tricarboxylic acid (TCA) cycle, oxidation/reduction pathways, amino-acid metabolism and mitochondrial metabolism (Bonvallot et al., 2013). Another study observed the changes in urinary metabolic fingerprints spanning the three trimesters in pregnant women from a chemical industrial site and reference region. Compared with the reference region, Gil et al. (2018) noted that only a few metabolites [increased alanine, 2-hydroxyisobutyrate (2-HIBA), 3-hydroxyisobutyrate (3-HIBA), cis-aconitate, and allantoin] seemed to follow slightly distinct trajectories in pregnant women residing near the chemical industrial site, which may reflect small changes in amino acid metabolism, TCA cycle, oxidative stress, and gut microflora.

3.2.2. Effects of metal exposure on the urine metabolic profile

Li et al. (2017, 2019) found that low-level environmental arsenic and cadmium exposure could induce changes in urinary metabolic profiles in early pregnancy. Nine potential urinary metabolite biomarkers were identified by comparing first and third quantile arsenic exposure samples, including 18-carboxy-dinor-LTE4, 20-COOH-LTE4, thiocysteine, glutathione, cystathionine ketamine, 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide, LysoPC (14:0), *p*-cresol glucuronide and vanillactic acid, to be strongly associated with low-dose arsenic exposure (Li et al., 2017). For the first and third trimester pregnant women, Maitre et al. (2018) observed that arsenic exposure was positively associated not only with urinary trimethylamine-n-oxide (TMAO) and dimethylamine, but also with a newly identified metabolite homarine that has never been measured in humans. Li et al. (2019) identified maternal cadmium levels to be positively related to dityrosine, L-tyrosine, and L-cystine concentrations, but were negatively associated with uric acid and histamine concentrations. These metabolites are involved in amino acid metabolism and TCA cycle. Throughout pregnancy, cadmium exposure was positively related to arginine, proline and lysine metabolic intermediates but was negatively related to indole, creatinine, and *N*-methyltryptamine (Wang et al., 2018a). Besides urinary cadmium, copper, thallium and lead displayed trimester-specific associations with steroid hormone byproducts, including negative associations with estrogen metabolites and positive associations with pregnanlolone-3-glucuronide in the first trimester (Maitre et al., 2018). In urine samples from first and third trimester of pregnancy, Maitre et al. (2018) found that thallium, copper, lead and cesium are mostly associated with decreased *N*-acetylated metabolites, dimethylamine, and increased carnitine, formate, acetate and scyllo-inositol. Cord blood mercury was related to lower urinary estrogen metabolites and elevated taurine in the third trimester (Maitre et al., 2018). In addition, Wang et al. (2018a) reported that exposure to cobalt, vanadium, thallium, manganese, copper, and cesium during normal pregnancy have significant effects on maternal lysine, tyrosine, proline, arginine and tryptophan metabolism.

3.2.3. Effects of organic pollutant exposure on the urine metabolic profile

Zhou et al. (2018) found that levels of urine phthalate metabolites (MBP, MiBP, MBzP, and MCOP) are correlated with amino acids, *N*-acetylneuraminic acid (Neu5AC), thymine, adenine and nicotinic acid metabolites in the middle and later stages of pregnancy. They also found that phthalate exposure was correlated with sphingomyelin, cholesterol and metabolites reflecting components of the biological membrane, including phosphatidylserine (PS), phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidylcholine (PC), and phosphatidylethanolamine (PE). The members of an inflammatory signaling pathway, such as ceramide-1-phosphate, ceramide, sphingosine, and sphingosine-1-phosphate, also appear to be related to the phthalate exposure. Urinary phthalate level was not only related to multiple triacylglyceride (TAG) species, but also related to degradation metabolites mediated by phospholipid and TAG phospholipase. Another study reported that maternal urinary phthalate metabolites were consistently correlated with decreased urinary acetate and succinate in both trimesters, especially with stronger association in the 1st trimester. Maternal serum PCBs were consistently related to decreased 3-hydroxyisovalerate, which is a product of the L-leucine mitochondrial catabolic pathway. Maternal urinary cotinine in the third trimester was correlated with lower citrate and furoylglycine. Other pollutants, such as perfluoro-alkyl substances (PFASs) and BPA, were not consistently associated with the urinary metabolome during pregnancy (Maitre et al., 2018).

3.3. Alteration of the maternal plasma/serum metabolomic profile (Table 2)

3.3.1. Effects of smoking exposure on the maternal serum metabolomic profile

At the 34th week of gestation, maternal smoking was associated with an up-regulation of amino acids and down-regulation of PCaaC28:1, PCaaC32:3, PCaeC30:1, PCaeC32:2, PCaeC40:1 and SM C26:0, but the antioxidative capacity of water-soluble compounds did not change significantly (Rolle-Kampczyk et al., 2016). Another study showed that low-level nicotine exposure (maternal serum cotinine level < 2 ng/mL) can affect leukotriene, linoleate and eicosapentaenoic acid metabolism pathways in maternal serum (Fischer et al., 2017).

3.3.2. Effects of air pollution on the maternal serum metabolomic profile

Yan et al. (2019) identified six significantly different metabolites in second trimester pregnant women between high and low traffic air pollution exposure groups, of which creatinine and myo-inositol were positively related to traffic air pollution, while serine, L-histidine, heptadecanoic acid, and linoleic acid were negatively related to traffic air pollution. Their results showed that prenatal exposure to traffic-related air pollution could alter lipid-related pathways (phospholipid metabolism, linoleate metabolism, fatty acid metabolism, and prostaglandin and leukotriene metabolism), vitamin E metabolism, and amino acid metabolism pathways (histidine, cysteine, and methionine pathways).

3.3.3. Effects of arsenic exposure on the maternal serum metabolomic profile

A pilot study reported that inorganic arsenic levels in toenails of pregnant women in the first trimester were correlated with that in umbilical cord serum, and the levels of butylglycine and tartrate in maternal peripheral blood were correlated with the low levels of inorganic

Table 1
Studies describing the relationship between environmental toxicant exposure and changes in the maternal urine metabolomic profile.

Author (year)	Population location and number	Environmental toxicant: sample source and collection time	Metabolomic measurement: analytical technique and sample collection time	Effect on maternal urine metabolites	Metabolic pathway affected
Bonvallot et al. (2013)	France ($n = 83$)	Pesticide exposure (undetected).	^{1}H NMR (11th week of pregnancy)	Glycine, threonine, lactate, GPC, citrate and hippurate	Amino-acid metabolism, oxidation/reduction pathways, mitochondrial metabolism, TCA cycle
Gil et al. (2018)	Portugal ($n = 107$)	Chemical industrial exposure. [Polyurethanes, thermoplastic materials, chlorine-alkali, aniline, and derivatives and industrial gases (undetected)]	^{1}H NMR (7th–39th week of pregnancy)	Alanine, glycine, 3-hydroxyisobutyrate, cis-aconitate, furoylglycine, allantoin, 2-hydroxyisobutyrate and δ 8.45	Amino-acid metabolism, TCA cycle, oxidative stress
Li et al. (2017)	China ($n = 246$)	Arsenic. [Urine (1st trimester pregnancy)]	UPLC-QTOF-MS (11th–13th week of pregnancy)	LysoPC (14:0), glutathione, 18-carboxy-dinor-LTE4, 20-COOH-LTE4, cystathionine ketimin, 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide, thiocysteine, *p*-cresol glucuronide and vanillactic acid	Oxidative stress and metabolic disorders of liver and kidney
Li et al. (2019)	China ($n = 246$)	Cadmium. [Urine (1st trimester pregnancy)]	UPLC-QTOF-MS (11th–13th week of pregnancy)	L-cystine, L-tyrosine, dityrosine, histamine and uric acid	Amino acid and purine metabolism, tricarboxylic acid cycle, oxidative stress, kidney dysfunction
Wang et al. (2018a, 2018b)	China ($n = 232$)	16 metals: aluminum, vanadium, manganese, iron, cobalt, copper, zinc, arsenic, selenium, rubidium, strontium, cadmium, cesium, barium, thallium and lead. [Urine (1st, 2nd and 3rd trimester pregnancy)]	UPLC-QTOF-MS (1st, 2nd and 3rd trimesters of pregnancy)	Indole, 3-indoleacetonitrile, indole-5,6-quinone, 2-oxoarginine, *N2*-succinyl-$_L$-glutamic acid 5--semialdehyde, *N*-methyltryptamine, *N*-succinyl-$_{L,L}$-2,6-diaminopimelate and creatinine	Tryptophan metabolism, tyrosine metabolism, lysine biosynthesis, and arginine and proline metabolism
Zhou et al. (2018)	America ($n = 115$)	Phthalate metabolites: MEP, MBP, MiBP, MEHP, MEHHP, MEOHP, MECPP, MBzP, MCPP, MCOP, MCNP. [Urine (20–36 weeks pregnancy)]	QQQ LC–MS/MS (20th–36th week of pregnancy)	Amino acid metabolites, Neu5AC, thymine, adenine and nicotinic acid metabolites, PC, PS, PE, PI, cholesterol, sphingomyelin, ceramide-1-phosphate, ceramide, sphingosine, sphingosine-1-phosphate, TAGs, LPC, LPE, LPA, LPS, DAGs, MAGs, and FFA	Antioxidation, posttranslational modification, biosynthesis of proteins, urea cycle, nucleic acid degradation, lipid biosynthesis and degradation, components of the biological membrane
Maitre et al. (2018)	Spain ($n = 750$)	Organochlorines: bHCH, DDE, HCB, PCB congeners 138, 153 and 180; PFASs: PFHxS, PFNA, PFOA, PFOS. [Serum (1st trimester pregnancy)]	^{1}H NMR (1st and 3rd trimesters of pregnancy)	Taurine, dimethylamine, succinate and 3-hydroxyisovalerate	Pyruvate metabolism, TCA cycle, acetyl-coA metabolism, L-leucine mitochondrial catabolic pathway
		Cotinine. [Urine (3rd trimester pregnancy)]		Citrate, furoylglycine and *N*-methypyridinium	Citrate metabolism, mitochondrial perturbation, oxidative stress
		Mercury. [Cord blood (at birth)]		Estrogen metabolites and taurine	Estrogen metabolism
		12 metals: arsenic, cadmium, cobalt, cesium, copper, molybdenum, nickel, lead, antimony, selenium, thallium, zinc. [Urine (1st and 3rd trimester pregnancy)]		TMAO, homarine, pregnanlolone-3-glucuronide, *N*-acetylated metabolites, dimethylamine, carnitine, formate, acetate, scyllo-inositol and estrogen metabolites	Gut microflora metabolism, oxidative stress, estrogen metabolism
		BPA. [Urine (1st and 3rd trimester pregnancy)]		/	/
		Phthalate metabolites: MECPP, MBzP, MEHHP, MEHP, MEOHP, MEP, DiBP, MiBP, MnBP, 7OH-mMeOP, MCMHP. [Urine (1st and 3rd trimester pregnancy)]		/	/

GPC: glycerophosphocholine; TCA: tricarboxylic acid; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MiBP: mono-isobutyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: mono(2-ethyl-5-oxohexyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: monobenzyl phthalate; MCPP: mono(3-carboxypropyl) phthalate; MCOP: monocarboxyoctyl phthalate; MCNP: monocarboxynonyl phthalate; Neu5AC: *N*-acetylneuraminic acid; PC: phosphatidylcholine; PS: phosphatidylserine; PE: phosphatidylethanolamine; PI: phosphatidylinositol; TAG: triacylglyceride; LPC: lysophosphatidylcholine; LPE: lysophosphatidylethanolamine; LPA: lysophosphatidate; LPS: lysophosphatidylserine; DAGs: diacylglycerides; MAGs: monoacylglycerides; FFA: free fatty acid; bHCH: b-hexachlorocyclohexane; DDE: dichlorodiphenyldichloroethylene; HCB: hexachlorobenzene; PCB: polychlorinated biphenyl; PFASs: perfluoroalkyl substances; PFHxS: perfluorohexanesulfonate; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonate; BPA: bisphenol A; DiBP: di-isobutylphthalate; MnBP: mono-N- butylphthalate; 7OH-mMeOP: mono-(4-methyl-7- hydroxy-octyl) phthalate; MCMHP: mono[2-(carboxymethyl)hexyl] phthalate; TMAO: trimethylamine oxide.

arsenic in umbilical cord serum, but not with the levels of inorganic arsenic in prenatal toenails (Wei et al., 2017).

3.3.4. Effects of organic pollutant exposure on the maternal plasma/serum metabolomic profile

Low molecular weight phthalate in second trimester urine was positively associated with dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), steroid hormones (estradiol, cortisol, and testosterone), free fatty acids, lysolipids, ceramide and triacylglycerol metabolites in maternal plasma (Zhou et al., 2018). Exposure to PCBs during mid-pregnancy led to differences in 14 metabolites in maternal serum between the lowest and highest exposed groups, and changes in these compounds were linked to the metabolic pathways for purines, glutathione, pyrimidines, cysteine and methionine (Eguchi et al., 2017). Zbucka-Kretowska et al. (2018) identified six metabolites associated with maternal BPA concentrations, including palmitoleoyl ethanolamide, palmitoleamide, oleamide, palmitamide, stearamide, and LPE 18:0.

Table 2
Studies describing the relationship between environmental toxicant exposure and changes in the maternal serum/plasma metabolomic profile.

Author (year)	Population location and number	Environmental toxicant: sample source and collection time	Metabolomic measurement: analytical technique and sample collection time	Effect on maternal blood metabolites	Metabolic pathway affected
Yan et al. (2019)	America ($n = 160$)	Traffic related air pollutant (CO, NOx, and PM2.5). [Air samples (1st trimester pregnancy)]	LC-HRMS (16th week of pregnancy)	Serine, creatinine, L-histidine, myo-inositol, heptadecanoic acid and linoleic acid	Urea cycle/amino group, glycosphingolipid, histidine, glycerophospholipid, linoleate, glycine, serine, alanine, threonine, and pyrimidine metabolism, fatty acid activation, *de novo* fatty acid biosynthesis, glycosphingolipid metabolism, keratan sulfate degradation, fatty acid metabolism, TCA cycle, prostaglandin formation from arachidonate, lysine, glycerophospholipid, and xenobiotics metabolism, glycolysis and gluconeogenesis, methionine, cysteine, fructose, mannose, vitamin E, butanoate, linoleate, phosphatidylinositol phosphate, purine, leukotriene and sialic acid metabolism
Rolle-Kampczyk et al. (2016)	Germany ($n = 35$)	Tobacco smoke metabolites: S-Phenyl mercapturic acid, S-Benzyl mercapturic acid, cotinine. [Maternal urine (34th week of gestation)]	LC–MS/MS (34th week of pregnancy)	Arginine, glutamine, glycine, histidine, methionine, threonine, tryptophan and tyrosine; PCaaC28:1, PCaaC32:3, PCaeC30:1, PCaeC32:2, PCaeC40:1 and SM C 26:0	Amino acid and phosphatidylcholine metabolism
Fischer et al. (2017)	America ($n = 81$)	Cotinine. [Maternal serum (2nd trimester of pregnancy)]	HILIC-MS/MS (2nd trimester of pregnancy)	Leukotriene, linoleates and eicosapentaenoic acid	Polyunsaturated fatty acids metabolism
Eguchi et al. (2017)	Japan ($n = 93$)	PCBs. [Maternal serum (32nd week of gestation)]	HILIC-MS/MS (32nd week of pregnancy)	Phosphorylcholine, hypoxanthine, cytosine, putrescine, carbamoyl phosphate, N6-Acetyl-L-lysine, glutathione, uracil, norepinephrine, citraconic acid, xanthosine, kynurenic acid, serine and *N*-acetyl-glucosamine-1-phosphate	Purine, glutathione, pyrimidine, and cysteine and methionine metabolism pathways
Zhou et al. (2018)	America ($n = 115$)	Phthalate metabolites: MEP, MBP, MiBP, MEHP, MEHHP, MEOHP, MECPP, MBzP, MCPP, MCCP, MCNP. [Maternal urine (20th–36th week of gestation)]	QQQ LC–MS/MS (20th–36th week of pregnancy)	DHT, DHEA, estradiol, cortisol, testosterone, pregnenolone and sulfate	Hormone metabolism
Zbucka-Kretowska et al. (2018)	Poland ($n = 40$)	BPA. [Maternal plasma (15th–18th week of gestation)]	LC-QTOF-MS (15th–18th week of pregnancy)	Palmitoleoyl ethanolamide, palmitoleamide and oleamidn	Distortion of endocannabinoid system
Wei et al. (2017)	Bangladesh ($n = 20$)	Arsenic. [Maternal toenail (≤16th week of gestation)]	UPLC-MS/MS, GC–MS (28th week of pregnancy)	Butyrylglycine and tartrate	NA.

CO: carbon monoxide; NO: nitrogen oxides; PM: particulate matter; TCA: tricarboxylic acid; PC: Phosphatidylcholines (a, a-diacyl form; a, e acylether form); PCBs: polychlorinated biphenyls; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MiBP: mono-isobutyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: mono(2-ethyl-5-oxohexyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: monobenzyl phthalate; MCPP: mono(3-carboxypropyl) phthalate; MCOP: monocarboxyoctyl phthalate; MCNP: monocarboxynonyl phthalate; DHT: dihydrotestosterone; DHEA: dehydroepiandrosterone; BPA: bisphenol A; LPE: lysophosphatidylethanolamine.

3.4. Alteration of the cord serum/plasma metabolomic profile (Table 3)

3.4.1. Effects of smoking exposure on the cord blood serum metabolomic profile

Rolle-Kampczyk et al. (2016) conducted a targeted metabolomics analysis of 163 lipid metabolites in 40 cord sera, and observed that smoking exposure can cause increases in PCaa, PCae, SM, and down-regulation of acylcarnitines.

3.4.2. Effects of $PM_{2.5}$ exposure on the cord plasma metabolomic profile

Martens et al. (2017) found that three 5-LOX metabolites [5-HETE, 5-oxoETE and 9(*S*)-HODE] were positively associated with fine particulate matter ($PM_{2.5}$) exposure *in utero* during the 2nd trimester, and four 5-LOX metabolites (5-HETE, 5-oxoETE, 9,10,13-TriHOME and 9,12,13-TriHOME) were positively related to $PM_{2.5}$ exposure during the entire pregnancy. Other arachidonic acid-derived metabolites (8-HETE, 11-HETE, 12-HETE, 12-oxoETE, and 15-HETE), linoleic (13-HODE), eicosapentaenoic acid [12(*S*)-HEPE], and dihomo-γ-linolenic [15(*S*)-HETE] from the 12/15-LOX pathway were positively related to $PM_{2.5}$ exposure during the 2nd trimester pregnancy.

3.4.3. Effects of arsenic exposure on the cord serum metabolomic profile

Wei et al. (2017) found that the disruption of fatty acid pathways characterized by elevated laurate (12:0), 4-vinylphenolsulfate and 17-methylstearate levels was associated with inorganic arsenic in cord blood, and that these elevated metabolites were associated with low

Table 3
Studies describing the relationship between environmental toxicant exposure and changes in the cord serum/plasma metabolomic profile.

Author (year)	Population location and number	Environmental toxicant: sample source and collection time	Metabolomic measurement: analytical technique and sample collection time	Effect on cord blood metabolites	Metabolic pathway effect
Wei et al. (2017)	Bangladesh ($n = 35$)	Arsenic. [Cord serum (at birth)]	UPLC-MS/MS, GC–MS (At birth)	Laurate (12:0), 4-vinylphenolsulfate and 17-methylstearate	Fatty acid pathways
Laine et al. (2017)	Mexico ($n = 50$)	Arsenic. [Maternal urine (prior to the time of delivery) and cord serum]	^{1}H NMR (At birth)	Methionine, taurine and ethionine, glutamate, *O*-acetylcholine, isoleucine, valine, glycine; betaine, acetoacetate, lactate, glycine, glycerol, mannose, serine, taurine, pyruvate tyrosine and acetone	Carbohydrate, lipid, amino acid, cofactor, vitamins, energy and glutamine/D-glutamate metabolism
Eguchi et al. (2017)	Japan ($n = 93$)	PCBs. [Cord serum (at birth)]	HILIC-MS/MS (At birth)	Dihydroorotate, *p*-hydroxybenzoate, purine, ethanolamine, guanidoacetic acid, hydroxyproline, sedoheptulose 1,7-bisphosphate, betaine, tyrosine and glucosamine	Synthesis of lipid, mitochondrial electron transport
Rolle-Kampczyk et al. (2016)	Germany ($n = 40$)	Tobacco smoke metabolites: S-Phenyl mercapturic acid, S-Benzyl mercapturic acid, cotinine. [Maternal urine (34th week of gestation)]	LC–MS/MS (At birth)	Glutamine, methionine, C18:2, PCaaC28:1, PCaaC32:3, PCaeC30:1, PCaeC32:2, PCaeC40:1 and SM C 26:0	Phosphatidylcholine metabolism
Martens et al. (2017)	Belgium ($n = 197$)	$PM_{2.5}$. (Total $PM_{2.5}$ exposure for entire pregnancy duration was calculated as the mean $PM_{2.5}$ concentration of all pregnancy days)	UPLC-ESI-MS/MS (At birth)	5-HETE, 5-oxoETE, 9(*S*)-HODE, 5-HETE, 5-oxoETE, 9,10,13-TriHOME, 9,12,13-TriHOME, 8-HETE, 11-HETE, 12-HETE, 12-oxoETE, 15-HETE, 13-HODE, 12(*S*)-HEPE and 15(*S*)-HETE	Oxylipin metabolism

PCBs: polychlorinated biphenyls; PC: phosphatidylcholines (a, a-diacyl form; a, e acylether form); PM: particulate matter.

birth weight and jointly mediate 64.5% of the side effects of inorganic arsenic exposure. Other findings showed a total of 17 metabolites were related to inorganic arsenic and/or inorganic arsenic metabolites, and were involved in changes of important metabolic pathways, including the TCA cycle, vitamins, amino acids, cofactors, and glutamine/D-glutamate metabolism (Laine et al., 2017).

3.4.4. Effects of PCB exposure on the cord serum metabolomic profile

A study showed that ten cord serum metabolites (p-hydroxybenzoate, dihydroorotate, purine, ethanolamine, guanidoacetic acid, hydroxyproline, sedoheptulose 1,7-bisphosphate, betaine, tyrosine and glucosamine) displayed differences between the lowest and highest PCB-exposed groups (Eguchi et al., 2017).

3.5. Alteration of the amniotic fluid metabolic profile (Table 4)

3.5.1. Effects of smoking exposure on the amniotic fluid metabolic profile

Fischer et al. (2017) found a relationship between low maternal levels of nicotine exposure and disruption of amniotic fluid metabolism in the second trimester. They found that disruptions in asparagine and asparagine metabolism (decreased N1-acetylspermine, N1, N12-diacetylspermine and acetylspermidine, increased adenosine monophosphate), nucleic acid metabolism (decreased cytosine and thymidine, increased cytidine triphosphate), and amino acid metabolism (decreased proline, increased arginine) were associated with low levels of nicotine exposure.

4. Discussion

Maternal metabolism during pregnancy is the main determinant of the intrauterine environment and fetal outcome. Since maternal urine best reflects the overall metabolite profile and involves non-invasive sample collection, it is the most commonly used fluid for metabolomics (Fanos et al., 2013a). A birth cohort study found that metabolic characteristics associated with fetal birth outcomes in the maternal urine are linked to clinical and environmental factors. Physical activity and other modifiable lifestyle/clinical factors are the potential sources of metabolic variation during pregnancy (Fanos et al., 2013a; Maitre et al., 2016). Living in a complex toxic environment, pregnant women's metabolic processes are susceptible to chemical contaminants. Changes in these metabolic pathways, such as TCA cycle, oxidation/reduction pathway, mitochondrial metabolism, amino acid metabolism, and gut microflora, can elevate oxidative stress, disturb energy metabolism, and lead to disruption of transplacental exchange (Bonvallot et al., 2013; Gil et al., 2018). Bonvallot et al. (2018a) established an animal model to simulate physiological environmental exposure to pesticides. Their results suggest that the disordered metabolites are involved in glucose and energy metabolism in the livers of offspring, as well as oxidative stress in the brains of male offspring. These results differ from a population study (Bonvallot et al., 2013), but they can supplement the previous observations. The aforesaid studies lack objective indicators of environmental pollution and have relatively few participants, so it is doubtful whether these data truly reflect the relationship between

Table 4
Studies describing the relationship between environmental toxicant exposure and changes in the amniotic fluid metabolomic profile.

Author (year)	Population location and number	Environmental toxicant: sample source and collection time	Metabolomic measurement: analytical technique and sample collection time	Effect on amniotic fluid metabolites	Metabolic pathway effect
Fischer et al. (2017)	America ($n = 81$)	Cotinine. [Maternal serum (2nd trimester of pregnancy)]	HILIC-MS/MS (2nd trimester of pregnancy)	N1-acetylspermine, N1,N12-diacetylspermine, acetylspermidine, adenosine monophosphate, cytosine, thymidine, cytidine triphosphate, proline and arginine	Asparagine, asparagine, nucleic acid and amino acid metabolism

environmental pollutants and maternal urine metabolomics. In addition, other sources of exposure, such as local lifestyle and diet during study, are thought to play a greater role in determining the general metabolism of pregnant women. These confounding factors should be fully considered when collecting and analyzing data. Bonvallot et al. (2013) and Maitre et al. (2018) considered these confounding factors in their studies, but this point has not been done enough in other studies. Zhou et al. (2018) found that maternal pre-pregnancy BMI was negative related to over 20 of metabolic compounds in plasma. Therefore, when recruiting pregnant women as the study population, the current physical conditions and living habits of them should be considered, as well as their pre-pregnancy status.

Cross-sectional epidemiological study design does not guarantee the abilities of biomarkers to predict future health effects (Bonvallot et al., 2018b). Nutrition and metabolism in different gestation stages are closely related to fetal growth and development. Continuous longitudinal investigation of metabolic changes in pregnant women is particularly important. A British longitudinal cohort study found that maternal serum metabolite ratios can predict fetal growth restriction at term (Sovio et al., 2020). However, specific metabolic biomarkers are lacking in these population studies, since metabolomics is currently not available to propose biomarkers associated with early effects of environmental exposure (Bonvallot et al., 2018b). Few studies have explored the mediating role of metabolites between pollutant exposure and birth outcomes. Metabolomics techniques can serve as a bridge between environmental science and medicine, combining epidemiology, toxicology and analytical chemistry to explain the potential health effects of pollutant exposure. In the future, we can also integrate the multi-omics data including exposome, metabolome, transcriptome and proteome to comprehensively explore the impact of external pollutants on human health. Exposure to environmental arsenic during pregnancy is associated with increased risks of diabetes and hypertension in pregnant women, as well as poor delivery outcomes (Farzan et al., 2015; McDermott et al., 2014; Peng et al., 2015; Wu et al., 2011). Even exposure to low levels of arsenic and cadmium during pregnancy can cause metabolic changes associated with oxidative stress and kidney and liver diseases (Li et al., 2017; Li et al., 2019). Urinary arsenic levels during pregnancy are linked to TMAO and dimethylamine that are involved in gut microflora metabolism (Maitre et al., 2018). Wei et al. (2017) found that maternal peripheral blood metabolites mediate the toxic effects of inorganic arsenic exposure on low birth weight. Since the sample size ($n = 20$) is insufficient to guarantee statistical power, the mechanisms that emphasize the mediating effect of metabolites needs to be corroborated in a large sample population. Prenatal inorganic arsenic exposure also affects the fatty acid pathway, TCA cycle, and amino acid and vitamin metabolism in cord serum, and the biological transformation of arsenic may have different effects on the neonatal metabolome (Laine et al., 2017; Wei et al., 2017). Some of these metals, such as copper, lead, arsenic, cadmium, mercury, or thallium, not only possess essential metabolic functionalities, but also can be regarded as endocrine disruptors (Maitre et al., 2018). Pregnancy exposure to other metals (cobalt, cadmium, vanadium, thallium, manganese, copper, and cesium) could affect multiple amino acid metabolic pathways, including tyrosine metabolism, tryptophan metabolism, lysine biosynthesis, and proline and arginine metabolism. These critical pathways are involved in regulating neurotransmitter production and neurodevelopment in normal pregnancy (Wang et al., 2018a).

In addition to metal exposure, some organic pollutants have been found to be related to several adverse health outcomes reported in human and animal models. Exposure to phthalates during pregnancy has been associated with a variety of metabolic disorders, including increased inflammatory response, defective mitochondrial metabolism (Krebs cycle, acetyl-coA metabolism, pyruvate), changes in lipid biosynthesis and degradation, and hormone and nucleic acid metabolism (Maitre et al., 2018; Zhou et al., 2018). Phthalates may disrupt the close hormonal communication between the developing placenta and fetus (Zhou et al., 2018). Maternal exposure to PCBs mainly affects the metabolic pathways of amino acid (L-leucine, cysteine, methionine and glutathione), purine, and pyrimidine (Eguchi et al., 2017; Maitre et al., 2018). Eguchi et al. (2017) observed that the changes in the metabolic profile of cord blood after exposure to PCBs are linked to lipid synthesis and mitochondrial electron transport, which are associated with fetal survival, growth, and health. Their results show no changes in metabolic biomarkers or pathways directly related to fetal birth weight. Maitre et al. (2018) found no potential association between PFAS/BPA exposure and urinary metabolic profile during pregnancy. However, Zbucka-Kretowska et al. (2018) found that levels of BPA in maternal plasma are positively associated with levels of several fatty acid amides (FAA) known as endocannabinoids. The resulting potential distortion of the endocannabinoid system and BPA exposure are risk factors for miscarriage. Therefore, they speculated that BPA exposure may contribute to adverse pregnancy outcomes by acting on the endocannabinoid system. BPA and bisphenol S exposure also can affect the placental-brain axis of the developing mouse fetus through disrupt docosahexaenoic acid and estradiol metabolism in trophoblast giant cells (Mao et al., 2020). In addition, the results of *in vitro* study demonstrated that PFOA exposure interfered with the metabolism of lipids, amino acids, and carbohydrates in human peripheral blood lymphocytes, which may induce the disruption of immune system (Li et al., 2020).

Maternal smoking is associated with adverse birth outcomes such as intrauterine growth retardation (IUGR) (Abraham et al., 2017). When nicotine enters the bloodstream, it is quickly metabolized into cotinine, which has a longer half-life and is a biomarker of tobacco exposure (Benowitz et al., 2009). Elevated levels of urinary cotinine are associated with changes in citrate metabolism, possibly reflecting oxidative stress and mitochondrial perturbation (Ellis et al., 2012; Maitre et al., 2018). Maternal exposure to nicotine disturbs maternal serum polyunsaturated fatty acid and phosphatidylcholine metabolism, which is related to increased inflammation and fetal malnutrition (Fischer et al., 2017; Rolle-Kampczyk et al., 2016). Nicotine also can be rapidly assimilated into the smoker's bloodstream through the oral cavity and lungs, and quickly crosses the placental barrier to accumulate in fetal blood and amniotic fluid (Pastrakuljic et al., 1998). Exposure to nicotine during pregnancy destroys lipid molecules that make up the cell membrane, which may directly damage the fetal cell membrane (Rolle-Kampczyk et al., 2016). Only two studies have so far investigated the effect of nicotine exposure on amniotic fluid metabolomics in human and rat models. In a population study, Fischer et al. (2017) observed in amniotic fluid that low levels of nicotine exposure in pregnant women can disrupt the metabolism of nucleic acids and amino acids, particularly asparagine and aspartate. This marks an important step in revealing the importance of light maternal smoking or second-hand smoke to fetal development and birth outcomes. In a nicotine-induced IUGR rat model, Feng et al. (2014) found that the TCA cycle and glycolysis metabolism in amniotic fluid are disturbed. Therefore, abnormal transportation of the placenta may be another mechanism by which the metabolomics of biofluids are altered by prenatal nicotine exposure-induced rat IUGR.

The effects of air pollution on maternal-fetal health also cannot be neglected. Exposure to traffic air pollution in early pregnancy can perturb fatty acid, phospholipid, vitamin E and amino acid metabolism in mid-pregnancy serum. These pathways are primarily involved in inflammatory responses and oxidative stress, which may contribute to adverse birth outcomes, such as intrauterine growth restriction, preterm birth, preeclampsia, low birth weight, and neurodevelopmental disorders (Patterson, 2009; Sultana et al., 2017; Yan et al., 2019). Particles smaller than 500 nm in diameter can pass through the placental barrier, and particles smaller than 240 nm in diameter can reach the fetal blood stream. Therefore, particulate matter has a great impact on maternal-fetal health (Luyten et al., 2018; Wick et al., 2010). Du et al. (2020) observed that significant changes in glucose, amino acid and lipid

metabolism occurred in mice exposed $PM_{2.5}$. The metabolomics approach might be an effective tool to estimate the potential mechanism of $PM_{2.5}$ in inducing adverse health outcomes. The effects of $PM_{2.5}$ exposure on oxylipin pathways are different in different pregnancies. One study reported that the 5-LOX and 12/15-LOX oxylipin pathways are positively associated with intrauterine $PM_{2.5}$ exposure in the 2nd trimester, and that the 5-LOX pathway is positively associated with $PM_{2.5}$ exposure throughout pregnancy. Air pollution in early life affects levels of oxylipins, which may induce immunological alterations and may affect the occurrence and development of air pollution-associated diseases in the future (Martens et al., 2017). Liu et al. (2020) found that decreased PM can improve child cardiac autonomic function by increasing anti-inflammation capacity and energy generation.

Metabolomic methods can be used to reveal metabolic changes, in urine, blood, cord blood, amniotic fluid and placenta samples, caused by exposure to contaminants during pregnancy, to better understand the internal processes that can be disrupted, and to help link exposure to specific health outcomes. Urine samples contain a large number of endogenous metabolites that can effectively reflect the metabolic state of the human body under pathophysiological conditions. Collection of urine samples is non-invasive and is highly feasible throughout pregnancy, allowing continuous follow-up of dynamic changes in the exposome and metabolome. However, the levels of metabolites and toxicants are susceptible to urinary concentration and kidney function. Metabolic profiles of maternal blood have potential application in the diagnosis of pregnancy and the prediction of fetal development (Orczyk-Pawilowicz et al., 2016). Amniotic fluid is composed of fetal urine and lung secretions from fetal swallowing and/or resorption through fetal membranes, and these dynamic interactions can change the composition and volume of amniotic fluid and reflect the health of the mother and fetus (Brace and Cheung, 2014; Graca et al., 2009). Some studies have identified biomarkers for maternal-fetal diseases, such as preterm birth (Menon et al., 2014), gestational diabetes (Graca et al., 2012) and fetal malformations (Graca et al., 2010), through amniotic fluid metabolomics. Although the amniotic fluid metabolic profile has great value, its research application is limited due to its invasive collection process. Umbilical cord blood and placenta samples are collected only at birth, and their metabolic profiles reflect the material exchange between mother and fetus. As a very active metabolic temporary organ, placental tissue can be used to assess the biological outcomes of both maternal and fetal environmental exposure, as well as to study the link between prenatal exposure and child development (Jansson and Powell, 2013; Luyten et al., 2018). The studies of placental metabolomics focus on the pathogenesis of preeclampsia, obesity and fetal dysplasia (Austdal et al., 2015; Chi et al., 2014; Fattuoni et al., 2018). To date, no population studies have assessed the relationship between environmental toxicant exposure and placental metabolomics to predict maternal-fetal health risks. *In vitro* studies, tributyltin, perfluorinated chemicals, and mono-(2-ethylhexyl)phthalate (MEHP) exposure mainly disrupt the synthesis of diacylglycerols and triacylglycerols. However, an *in vivo* study shows Firemaster 550 exposure can affect the citric acid cycle, glycolysis and amino acid metabolism, which are associated with fetal growth and development (Gorrochategui et al., 2015; Petit et al., 2018; Rock et al., 2018). In fact, neither cell lines nor animal models can truly reflect the effects of environmental pollutants on the human placenta. Population studies are urgently needed to fill this gap.

From the metabolomics detection platform to data analysis, these studies have significant heterogeneity. To date, metabolomic detection mainly include NMR, GC–MS and LC–MS. Compared with mass spectrometry, NMR can perform non-destructive and non-selective analysis of samples, but its sensitivity is relatively low, and it is not suitable for analysis of metabolites at low concentrations. GC–MS platform is unable to analyze thermally-unstable and high-molecular-weight substances. LC–MS platform is suitable for the detection of thermally-unstable, non-volatile, non-derivative and high-molecular-weight substances, which has lower requirements on concentration and purity of test samples. Therefore, LC–MS platform is more popular than other techniques in metabolomics detection, and eleven studies selected LC–MS platform among the included studies. Metabolomics data have high variability (Bonvallot et al., 2018b; Dunn and Ellis, 2005; González-Riano et al., 2020). First, the physical and chemical properties of different metabolites vary greatly, and the dynamic range of their concentrations ranges from 7 to 9 orders of magnitude. Next, many individual factors, such as age and gender, may influence the changes in metabolites. Metabolomics platforms are affected by many factors, and is prone to random measurement errors and systematic errors, making it extremely difficult to identify important biomarkers. Eleven of the selected studies performed presumptive identification of compounds by matching spectral data from reference compounds in public databases (Bonvallot et al., 2013; Eguchi et al., 2017; Fischer et al., 2017; Gil et al., 2018; Li et al., 2017; Li et al., 2019; Maitre et al., 2018; Wang et al., 2018a, 2018b; Yan et al., 2019; Zbucka-Kretowska et al., 2018; Zhou et al., 2018). The most commonly used public database is the Human Metabolome Database (HMDB, http://www.hmdb.ca/), followed by METLIN (http://metlin.scripps.edu) and Kyoto Encyclopedia for Genes and Genomes (KEGG, http://www.genome.jp/kegg/). Only four studies used self-built or software-supported databases (Laine et al., 2017; Martens et al., 2017; Rolle-Kampczyk et al., 2016; Wei et al., 2017). Metabolomics produces high-dimensional data, so we need to use multivariate statistical analysis to reveal the complex interactions between variables. Principal component analysis (PCA), as a pre-analysis and quality control step of metabolomics data, is usually used to observe whether there are classification trends and outliers between groups. Partial least squares discriminant analysis (PLS-DA) combines regression model with dimensionality reduction, and uses a certain discriminant threshold to perform discriminant analysis on the regression results. Zbucka-Kretowska et al. (2018), Fischer et al. (2017) and Gil et al. (2018) checked the location of QC samples on PCA plots to evaluate data quality, and performed PLS-DA plots to observe samples classification. Multiple linear regression models are also used to study the relationship between environmental pollutants and metabolites (Laine et al., 2017; Li et al., 2019; Wei et al., 2017). However, metabolomics data are usually not simply linear, so fitting the data with PLS-DA and linear regression models may not be good enough. In the future, we can try to apply some new high-dimensional data analysis methods and ideas by Lin et al. (2011) and Correa and Goodacre (2011) to metabolomics data analysis. Li et al. (2017) and Eguchi et al. (2017) also tried to use receiver operator characteristic (ROC) analysis to assess the diagnostic ability of identified metabolites, and divided the population into low and high exposure groups. Although metabolomics studies are easily influenced by research design, ethnicity, metabolomics analysis platforms and biological samples, and the comparability and predictability of the results are biased, the aforementioned data analysis methods can also provide certain norms for metabolomics data analysis.

Current studies have some limitations. First, the studies of placental metabolomics only include *in vivo* or *in vitro* experiments, but there is no population study to explore the actual toxic effects of environmental pollutants on placental metabolism. Second, the study of amniotic fluid metabolomics has only investigated the effects of nicotine exposure, and there has been a lack of research on exposure to other environmental toxicants. Amniotic fluid contains substances derived from fetal skin, gastric fluid, lungs, urine, and placenta, which can provide information on fetal organogenesis and metabolism during pregnancy (Bardanzellu and Fanos, 2019). Hence, the research value of amniotic fluid remains to be explored. Third, the two population studies did not directly measure the actual levels of toxic chemicals, but instead selected study participants from high toxicant exposure areas, which is not conducive to estimating the practical effects of environmental toxicants on metabolism. Finally, current population studies lack data on neonatal birth outcomes and are unable to explore specific relationships between environmental pollutants, metabolic pathways, and adverse birth outcomes.

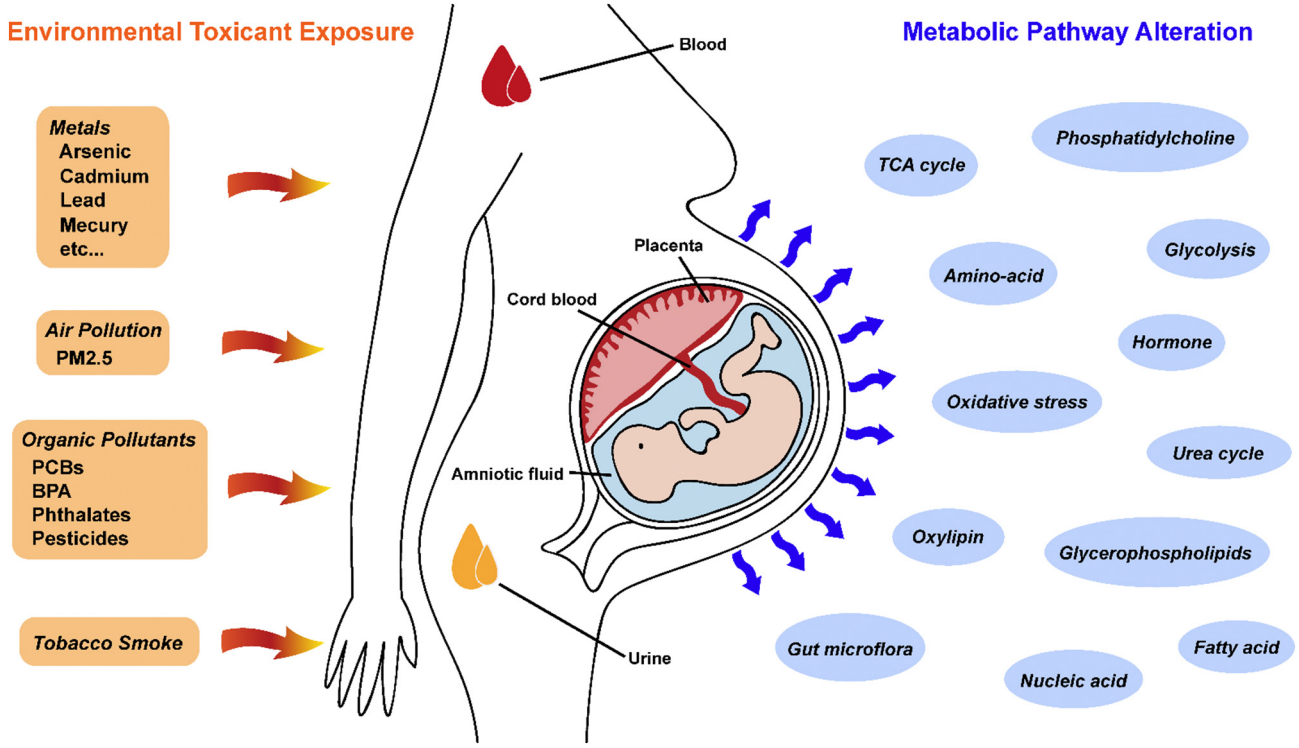

Fig. 2. Effects of environmental toxicant exposure on the alteration of metabolic pathways in maternal blood and urine, cord blood, placenta and amniotic fluid.

5. Conclusions

This review highlights the evidence linking maternal exposure to metals, organic pollutants, smoking, and air pollution to metabolic disorders in both mothers and fetuses (Fig. 2). Changes in metabolic pathways involve lipids, amino acids, and nucleic acids, which are mainly related to energy metabolism, hormone metabolism, oxidative stress and inflammation. Future studies should pay more attention to comprehensive impact of different environmental pollutants on maternal-fetal metabolic pathways during the whole gestation period, screen metabolic biomarkers reflecting adverse environmental exposure, and provide strong clues for the pathogenesis of DOHaD.

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CRediT authorship contribution statement

Yifeng Dai: Conceptualization, Methodology, Data curation, Writing - original draft.**Xia Huo:**Data curation, Validation, Writing - review & editing.**Zhiheng Cheng:**Data curation, Validation, Visualization, Writing - review & editing.**Marijke M. Faas:**Supervision, Project administration.**Xijin Xu:**Validation, Funding acquisition, Supervision, Project administration.

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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