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

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\textsubscript{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...
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; Maître 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 metabolic 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 lipidomics’, 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 pregnancy.

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 1H 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, maternal plasma/serum samples, cord plasma/serum samples, and amniotic fluid. These studies were conducted in eleven different countries, including France, Portugal, China, Poland, Japan, Mexico, and Bangladesh. 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 microbiota.

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 trimester arsenic exposure samples, including 18-carboxy-dinor-LTE4, 20-COOH-LTE4, thioceysteine, glutathione, cystathionine ketamine, 1-(beta-o-rifufuranosyl)-1,4-dihydroxycinnamidine, LysoPc (14:0), p-cresol glucuronide and vanillic acid, to be strongly associated with low-dose arsenic exposure (Li et al., 2017). For the first and third trimester pregnant women, Maître 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 by-products, including negative associations with estrogen metabolites and positive associations with pregnannone-3-glucuronide in the first trimester (Maître et al., 2018). In urine samples from first and third trimester of pregnancy, Maître 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 silyno-inositol. Cord blood mercury was related to lower urinary estrogen metabolites and elevated taurine in the third trimester (Maître 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, MBBP, MBzP, and MCPP) are correlated with amino acids, N-acetylenearuric 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 sphenomycin, cholesterol and metabolites reflecting components of the biological membrane, including phosphatidylyserine (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 perfluorooalkyl substances (PFASs) and BPA, were not consistently associated with the urinary metabolome during pregnancy (Maître 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 PCaC28:1, PCaC23:2, PCaC25:1, PCaC32:2, PCaC40:1 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 prosta-glandin 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 butyrylglycerol and tartrate in maternal peripheral blood were correlated with the low levels of inorganic
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Population location and number</th>
<th>Environmental toxicant: sample source and collection time</th>
<th>Metabolomic measurement: analytical technique and sample collection time</th>
<th>Effect on maternal urine metabolites</th>
<th>Metabolic pathway affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonvallot et al. (2013)</td>
<td>France (n = 83)</td>
<td>Pesticide exposure (undetected).</td>
<td>1H NMR (11th week of pregnancy)</td>
<td>Glycine, threonine, lactate, GPC, citrate and hippurate</td>
<td>Amino-acid metabolism, oxidation/reduction pathways, mitochondrial metabolism, TCA cycle</td>
</tr>
<tr>
<td>Gil et al. (2018)</td>
<td>Portugal (n = 107)</td>
<td>Chemical industrial exposure. [Polyurethanes, thermoplastic materials, chlorine-alkali, aniline, and derivatives and industrial gases (undetected)]</td>
<td>1H NMR (7th–39th week of pregnancy)</td>
<td>Alanine, glycine, 3-hydroxyisobutyrate, cis-aconitate, furoglycine, allantoin, 2-hydroxyisobutyrate and β 4:5</td>
<td>Amino-acid metabolism, TCA cycle, oxidative stress</td>
</tr>
<tr>
<td>Li et al. (2017)</td>
<td>China (n = 246)</td>
<td>Arsenic. [Urine (1st trimester pregnancy)]</td>
<td>UPLC-QTOF-MS (11th–13th week of pregnancy)</td>
<td>LysoPC (14:0), glutathione, 18-carboxy-dinor-LTE4, 20-COOH-LTE4, cystathionine ketimine, 1-(β-o-rifuboranosyl)-1,4-dihydronicotinamide, thiocysteine, p-cresol glucuronide and vanillanic acid</td>
<td>Oxidative stress and metabolic disorders of liver and kidney</td>
</tr>
<tr>
<td>Li et al. (2019)</td>
<td>China (n = 246)</td>
<td>Cadmium. [Urine (1st trimester pregnancy)]</td>
<td>UPLC-QTOF-MS (11th–13th week of pregnancy)</td>
<td>L-cystine, L-tyrosine, dityrosine, histamine and uric acid</td>
<td>Amino acid and purine metabolism, tricarboxylic acid cycle, oxidative stress, kidney dysfunction</td>
</tr>
<tr>
<td>Wang et al. (2018a, 2018b)</td>
<td>China (n = 232)</td>
<td>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)]</td>
<td>UPLC-QTOF-MS (1st, 2nd and 3rd trimesters of pregnancy)</td>
<td>Indole, 3-indoleacetonicitrile, indole-5,6-quinoine, 2-oxoarginine, N2-succinyl-L-glutamic acid 5-SEMIA, N-methyltryptamine, N-succinyl-L-4,2,6-diaminoipimelate and creatinine</td>
<td>Triptophan metabolism, tyroside metabolism, lysine biosynthesis, and arginine and proline metabolism</td>
</tr>
<tr>
<td>Maitre et al. (2018)</td>
<td>Spain (n = 750)</td>
<td>Organochlorines: BHC, DDE, PCB congeners 138, 153 and 180; PFASs: PFHxS, PFNA, PFOA, PFOS. [Urine (1st trimester pregnancy)] Cotinine. [Urine (3rd trimester pregnancy)]</td>
<td>DDt, mercury, [Cord blood (at birth)]</td>
<td>Taurine, dimethylamine, sucinate and 3-hydroxyisovalerate</td>
<td>Citrate, furoglycine and N-methylpyridinium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 metals: arsenic, cadmium, cobalt, copper, mercury, molybdenum, nickel, lead, antimony, selenium, thallium, zinc. [Urine (1st and 3rd trimester pregnancy)]</td>
<td></td>
<td></td>
<td>Estrogen metabolites and taurine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPA. [Urine (1st and 3rd trimester pregnancy)]</td>
<td></td>
<td></td>
<td>TAMG, homarine, pregnanolone-3-glucuronide, N-acetylated metabolites, dimethylamine, carnitine, formate, acetyl, scyllo-inositol and estrogen metabolites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phthalate metabolites: MECPF, MBzP, MEHP, MEHPP, MEHPP, MEHP, MEOP, MEP, DIBP, MBP, MnBP, 7OH–nMeOp, MCMPH, MCMHP. [Urine (1st and 3rd trimester pregnancy)]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**

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

GPC: glycerophosphocholine; TCA: tricarboxylic acid; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MBzP: mono-n-octyl phthalate; MEHP: mono-(2-ethyl-5oxyhexyl) phthalate; MEHPP: mono-(2-ethyl-5-octoxyethyl) phthalate; MCPP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHPP: 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; Pt: phosphatidylinositol; TAC: triacylglyceride; LPC: lysophosphatidylcholine; LPE: lysophosphatidylethanolamine; LPA: lysophosphatidic acid; LPS: lysophosphatidylserine; DAGs: diacylglycerides; MAGs: monoacylglycerides; FFA: free fatty acid; BHC: b-hexachlorocylohexane; DDE: dichlorodiphenyl dichloroethylene; HCB: hexachlorobenzene; PCB: polychlorinated biphenyl; PFASs: perfluoralkyl substances; PFHxS: perfluorohexanesulfonate; PFNA: perfluorononanoic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonate; BPA: bisphenol A; DIBP: di(isobutyl)phthalate; MnBP: mono-n-butylphthalate; 7OH–nMeOp: mono-(4-methyl-7-hydroxy-octyl) phthalate; MCMHP: mono-[2-(carboxymethyl)hexyl] phthalate; TAMG: 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.
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 PCa, PCAe, SM, and down-regulation of acylcarnitines.

3.4.2. Effects of PM2.5 exposure on the cord plasma metabolomic profile

Martens et al. (2017) found that three 5-LOX metabolites [5-HETE, 5-oxoETE and 5(S)-HETE] were positively associated with fine particulate matter (PM2.5) exposure in utero during the 2nd trimester, and four 5-LOX metabolites [5-HETE, 5-oxoETE, 9,10,13-Trim HOME and 9,12,15-Trim HOME] were positively related to PM2.5 exposure during the entire pregnancy. Other arachidonic acid–derived metabolites (8-HETE, 11-HETE, 12-HETE, 12-oxoETE, and 15-HETE), linoleic (13- HODE), eicosapentanoic acid [12(S)-HEPE], and dihomo–γ-linolenic [15(S)-HETE] from the 12/15-LOX pathway were positively related to PM2.5 exposure during the entire 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-vinylphenosulfate and 17-methyltearate levels was associated with inorganic arsenic in cord blood, and that these elevated metabolites were associated with low

Table 2

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

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Population location and number</th>
<th>Environmental toxicant: sample source and collection time</th>
<th>Metabolomic measurement: analytical technique and sample collection time</th>
<th>Effect on maternal blood metabolites</th>
<th>Metabolic pathway affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yan et al. (2019)</td>
<td>America (n = 160)</td>
<td>Traffic related air pollutant (CO, NOx, and PM2.5); [Air samples (1st trimester pregnancy)]</td>
<td>LC-HRMS (16th week of pregnancy)</td>
<td>Serine, creatinine, L-histidine, myo-inositol, heptadecanoic acid and linoleic acid</td>
<td>Urea cycle/amino group, glycosphingolipid, histidine, glycerophospholipid, linoleate, glycerine, 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 arachidonic acid, lymna, glycerophospholipid, and xenobiotics metabolism, glycolysis and gluconeogenesis, methionine, cysteine, fructose, mannose, vitamin E, butanoate, linoleate, phosphatidylinoisitol, phosphatase, purine, leukotriene and sialic acid metabolism</td>
</tr>
<tr>
<td>Rolle-Kampczyk et al. (2016)</td>
<td>Germany (n = 35)</td>
<td>Tobacco smoke metabolites: 5-Phenyl mercapturic acid, 5-Benzyl mercapturic acid, cotinine. [Maternal urine (14th week of gestation)]</td>
<td>LC-MS/MS (14th week of pregnancy)</td>
<td>Arginine, glutamine, glycine, histidine, methionine, threonine, tryptophan and tyrosine; PCaaC28:1, PCaaC29:3, PCaeC30:1, PCaeC32:2, PCaeC40:1 and SM C 26:0</td>
<td>Amino acid and phosphatidylcholine metabolism</td>
</tr>
<tr>
<td>Fischer et al. (2017)</td>
<td>America (n = 81)</td>
<td>Cotinine. [Maternal serum (2nd trimester of pregnancy)]</td>
<td>HILIC-MS/MS (2nd trimester of pregnancy)</td>
<td>Phosphorylcholine, hypoxanthine, cysteine, putrescine, carnabomyl phosphate, N6-Acetyl-c-lysine, glutathione, uracil, norepinephrine, citraconic acid, xanthosine, kynurenine acid, serine and N-acetyl-glucosamine-1-phosphate</td>
<td>Polyunsaturated fatty acids metabolism</td>
</tr>
<tr>
<td>Eguchi et al. (2017)</td>
<td>Japan (n = 93)</td>
<td>PCBs. [Maternal serum (32nd week of gestation)]</td>
<td>HILIC-MS/MS (32nd week of pregnancy)</td>
<td>DHT, DHEA, estradiol, cortisol, testosterone, pregnenolone and sulfate</td>
<td>Purine, glutathione, pyrimidine, and cysteine and methionine metabolism pathways</td>
</tr>
<tr>
<td>Zbucka-Kretowska et al. (2018)</td>
<td>Poland (n = 40)</td>
<td>BPA. [Maternal plasma (15th–18th week of gestation)]</td>
<td>LC-QTOF-MS (15th–18th week of pregnancy)</td>
<td>Butyrylglycine and tartrate</td>
<td>Distortion of endocannabinoid system</td>
</tr>
<tr>
<td>Wei et al. (2017)</td>
<td>Bangladesh (n = 20)</td>
<td>Arsenic. [Maternal toenail (≤10th week of gestation)]</td>
<td>UPLC-MS/MS, GC–MS (28th week of pregnancy)</td>
<td>NA.</td>
<td></td>
</tr>
</tbody>
</table>

CD: 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-n-butyl phthalate; MEHP: mono-(2-ethylhexyl) phthalate; MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEP: monoethyl phthalate; MBP: mono-n-butyl phthalate; MiBP: mono-isobutyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEOHP: mono(2-ethyl-5-oxoethyl) phthalate; MECHP: mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: monobenzyl phthalate; MCCP: mono(3-carboxypropyl) phthalate; MCNP: moncarboxoethyl phthalate; MCPP: monocarboxynonyl phthalate; DHT: dihydrotestosterone; DHEA: dehydroepiandrosterone; BPA: bisphenol A; LPE: lysophosphatidylethanolamine.
PCBs: polychlorinated biphenyls; PC: phosphatidylcholines (α, α-diacyl form; α, ε acylether form); PM: particulate matter.

Studies describing the relationship between environmental toxicant exposure and changes in the amniotic fluid metabolic profile (Table 3)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Population location and number</th>
<th>Environmental toxicant: sample source and collection time</th>
<th>Metabolomic measurement: analytical technique and sample collection time</th>
<th>Effect on cord blood metabolites</th>
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<td>Arsenic. [Cord serum (at birth)]</td>
<td>UPLC-MS/MS, GC–MS (At birth) 1H NMR (At birth)</td>
<td>Laurate (12:0), 4-vinylphenolsulfate and 17-methylsterate</td>
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<td>Laine et al. (2017)</td>
<td>Mexico (n = 50)</td>
<td>Arsenic. [Maternal urine (prior to the time of delivery) and cord serum]</td>
<td>IC–MS/MS (At birth)</td>
<td>Methionine, tauroine and ethionine, glutamate, O-acetylcysteine, isoleucine, valine, glycine; betaine, acetoacetate, lactate, glycine, glycerol, mannose, serine, taurine, pyruvate, tyrosine and aceto, glutathione, cysteine</td>
<td>Carbohydrate, lipid, amino acid, cofactor, vitamins, energy and glutamate/D-glutamate metabolism</td>
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<td>Eguchi et al. (2017)</td>
<td>Japan (n = 93)</td>
<td>PCBs. [Cord serum (at birth)]</td>
<td>HILIC-MS/MS (At birth)</td>
<td>Methionine, homocysteine, glutathione, cysteine, glycine, threonine, alanine, tyrosine, proline, valine, and ornithine</td>
<td>Synthesis of lipid, mitochondrial electron transport</td>
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<td>Rolle-Kampczyk et al. (2016)</td>
<td>Germany (n = 40)</td>
<td>Tobacco smoke metabolites: 5-Phenyl mercapturic acid, 5-Benzyl mercapturic acid, cotinine, [Maternal urine (34th week of gestation)]</td>
<td>UPLC-ESI-MS/MS (At birth)</td>
<td>Glutathione, methionine, C18:2, PCaC28:1, PCaC32:3, PCaC30:1, PCaC32:2, PCaC40:1 and SM C 26:0</td>
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PCBs: polychlorinated biphenyls; PC: phosphatidylcholines (α, α-diacyl form; α, ε acylether form); PM: particulate matter.

4. Discussion

Maternal metabolism during pregnancy is the main determinant of the intrauterine environment and fetal outcome. Since maternal urine best reflects the overall metabolic 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; Maître 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 placental 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

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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 exposure, 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 microbiota 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 (Kreb 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 phosphatydylcholine 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 (Lytk 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 PM2.5. The metabolomics approach might be an effective tool to estimate the potential mechanism of PM2.5 in inducing adverse health outcomes. The effects of PM2.5 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 intraternal PM2.5 exposure in the 2nd trimester, and that the 5-LOX pathway is positively associated with PM2.5 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 pollutants and metabolites (Laine et al., 2017; Martens et al., 2017; Rolle-Kampczyk et al., 2016; Wei et al., 2017). Metabolomics has only investigated the effects of nicotine exposure, pollutants on placental metabolism. Second, the study of amniotic fluid remains to be explored. Third, the two population studies did not directly measure 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.
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.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.139626.

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.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21876065). We thank Dr. Stanley Lin for his English language editing.

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