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Associations of Mitochondrial Function, Stress, and Neurodevelopmental Outcomes in Early Life: A Systematic Review

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Abstract

Early life stress is commonly experienced by infants, especially preterm infants, and may impact their neurodevelopmental outcomes in their early and later lives. Mitochondrial function/dysfunction may play an important role underlying the linkage of prenatal and postnatal stress and neurodevelopmental outcomes in infants. This review aimed to provide insights on the relationship between early life stress and neurodevelopment and the mechanisms of mitochondrial function/dysfunction that contribute to the neuropathology of stress. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to develop this systematic review. PubMed, Scopus, PsycINFO, and Biosis databases were searched for primary research articles published between 2010 and 2021 that examined the relationships among mitochondrial function/dysfunction, infant stress, and neurodevelopment. Thirty studies were identified. There is evidence to support that mitochondrial function/dysfunction mediates the relationship between prenatal and postnatal stress and neurodevelopmental outcomes in infants. Maternal transgenerational transmission of mitochondrial bioenergetic patterns influenced prenatal stress induced neurodevelopmental outcomes and behavioral changes in infants. Multiple

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Author Contributions

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functionally relevant mitochondrial proteins, genes, and polymorphisms were associated with stress exposure. This is the first review of the role that mitochondrial function/dysfunction plays in the association between stress and neurodevelopmental outcomes in full-term and preterm infants. Although multiple limitations were found based on the lack of data on the influence of biological sex, and due to invasive sampling, and lack of longitudinal data, many genes and proteins associated with mitochondrial function/dysfunction were found to influence neurodevelopmental outcomes in the early life of infants.

Keywords

Stress; Mitochondrial function/dysfunction; Neurodevelopmental outcomes; Infant

Introduction

Neurodevelopmental deficits are characterized by limitations in intellectual functioning and adaptive behavior, e.g., lack of competence in social, conceptual, and practical skills [1]. Increased preterm birth rates and improved survival rates of these infants (<37 weeks' gestational age [GA]) come with increased complications and risk for neurodevelopmental deficits in these populations [2, 3]. Through the transition from the intrauterine to the extrauterine world, newborn infants are exposed to multiple prenatal stress, e.g., maternal childhood maltreatment (MCM) and intrauterine growth restriction (IUGR), as well as postnatal stress, e.g., prematurity, toxic postnatal environment, and painful/stressful experiences during neonatal intensive care hospitalization. Mitochondrial function/dysfunction has been found to be associated with multiple neurodegenerative diseases such as Parkinson [4], Alzheimer's disease [5], and neuropathic pain [6]. It may also influence infant neurodevelopmental outcomes, especially in preterm infants who experience excessive pain/stress in early life [7, 8].

Preterm infants may face multiple challenges in both the prenatal and postnatal periods. Mother of infants may experience high rate of MCM, defined as maternal childhood abuse (physical, sexual, emotional) or neglect (physical, emotional) [9, 10]. 18% of preterm infants have IUGR [11], defined as fetal growth repression and failure to reach full growth potential [12]. Both MCM and IUGR were reportedly associated with early-life adversity in infants, although the evidence is still limited and requires further investigation. Infant born preterm lose the protection of the placenta, which modulates homeostasis in the intrauterine environment and epigenetic effects on neurodevelopment in infants [13]. The very preterm infant is at high risk of neurodevelopmental deficits due to impaired myelination of the posterior limb of internal capsule (PLIC) which is normally initiated in the uterus by 23–29 weeks of GA [14–18]. In addition, during the neonatal intensive care unit (NICU) hospitalization, preterm infants are exposed to multiple stress events associated with adverse neurodevelopmental outcomes [19]. It has been reported that intermittent hypoxic stress during the first 2–3 months after birth was associated with motor impairment, cognitive, or language delay at 18 months in preterm infants [20]. Although the negative impacts of early life pain/stress on physiological and behavioral changes are known after birth [21]

and persist in childhood and later life [22, 23], less is known regarding the biological mechanisms of stress and neurodevelopmental deficits in preterm infants.

Accumulating evidence suggests that acute and chronic stressors influence mitochondrial biology and function [24]. Mitochondrial function is the organelle's ability to generate the chemical energy required to support the cell's biochemical reactions and regulate communication between cells and tissues to sustain the metabolic homeostasis [25]. Besides being the powerhouse of each cell, generating adenosine triphosphate (ATP), mitochondria play a central role in reactive oxygen species (ROS) generation, calcium buffering, ion homeostasis, biosynthetic pathways, signaling, and programmed cell death [24, 26]. Prolonged and excessive stress exposure may damage mitochondrial structure and function. Mitochondrial dysfunction is defined as the inability to generate the chemical energy required to support the cell's biochemical reaction and can occur due to mitochondrial structure fragmentation, mitochondrial DNA (mtDNA) damage, decreased ATP production, and increased ROS generation, which all pose a high risk for neuronal loss [13, 27–30]. Although mitochondrial dysfunction has been found to be related to neurological disorders such as Huntington's disease [31], multiple sclerosis [32], and amyotrophic lateral sclerosis [33], the mechanism of mitochondrial dysfunction in stress-associated neurodevelopmental deficits in preterm infants is still poorly understood.

As mitochondrial function/dysfunction has been shown to be an important mechanism underlying neurodevelopmental outcomes in preterm infants, it is of interest to incorporate this mechanism into a conceptual model for the purpose of research in the field. Therefore, we developed a conceptual model to address mitochondrial function/dysfunction related to stress which impacts the neurodevelopmental outcomes in preterm infants. The model proposes that prenatal and postnatal stress-related high energy demand request increased mitochondrial function to adapt to the external changes. However, prenatal/postnatal stress overload will damage the mitochondrial function due to its limited adaptive capacity and induce the neurodevelopmental deficits (see Fig. 1). By guiding with this conceptual model, a systematic review of the literature was undertaken to provide a synthesis of the current research. In addition, this review provided insights into advances in understanding the association between infants' early life stress and neurodevelopment and identified specific biomechanism and the significance of mitochondrial function/dysfunction in predicting neurodevelopmental outcomes in preterm infants. The research questions addressed in the review were as follows: (1) Is prenatal/postnatal stress associated with mitochondrial function/dysfunction in mothers and infants? and (2) Is mitochondrial function/dysfunction associated with neurodevelopmental outcomes in full-term and preterm infants?

Methods

Review Design

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [34] statement was used in the development of this systematic review [35] to examine the role of mitochondrial function/dysfunction in the association between prenatal and postnatal stress and neurodevelopmental deficits in full-term and preterm infants. Inclusion criteria were (a) quantitative studies using any quantitative research design and methods;

(b) human subject participants born prematurely (less than 37 weeks of gestational age [GA]) or full-term with early life stress, and/or women who experienced stress/adversities during pregnancy and/or the postpartum period; (c) studies focused on neurodevelopmental outcomes and mitochondrial function/dysfunction; and (d) studies published in English between 2010 and 2021. Exclusion criteria were (a) studies focused on topics other than stress, neurodevelopmental outcomes, and mitochondrial function/dysfunction; (b) studies with enrolled infants having congenital neurological deficits; and (c) qualitative research studies.

Literature Search and Data Synthesis Procedures

Articles were searched in PubMed, Scopus, PsycINFO, and Biosis Database. Four key terms were searched: stress, neurodevelopment, mitochondria, and infant. The categories were searched as follows, stress: MCM, oxidative stress, stress, pain, and fetal growth restriction (FGR); infant: preemie, preterm, young gestational age, neonatal, premature babies; genomic/proteomic of mitochondria; neurodevelopment: brain, white matter, brain injury, encephalopathy. Identified studies were imported to EndNote to remove the duplicates. The target outcomes were grouped in three main parts: (a) stress in infants including preterm infants; (b) the impact of stress in mitochondrial function/dysfunction; and (c) mitochondrial function and neurodevelopmental outcomes.

A PRISMA flow diagram was developed (see online suppl. Fig. S1; see www.karger.com/doi/10.1159/000526491 for all online suppl. material) based on inclusion and exclusion criteria for study selection [34]. The quality appraisal was conducted using the Critical Appraisal Skills Programme [36]. The 11 items on the checklist evaluated the research aim, research method, subjects' recruitment, control selection, and (exposure) measurement, etc. (see online suppl. Table S1). Due to the early level of research in the field, it was of interest to include all research studies, thus no studies were restricted based on the quality appraisal if they failed to match the requirement of one item. However, studies were excluded from the review if they did not match any requirement of 11 items. Data were extracted for study purpose, study design, sample size and characteristics, measurements (stress indicators; mitochondrial related gene, protein, function measurements, neurodevelopmental and behavioral outcomes and assessment), and main findings. The first and corresponding authors validated the literature search and extraction.

Results

A total of 317 papers were identified in the initial phase by searching the databases (see online suppl. Fig. S1). After removing duplications, reviews, mitochondrial disease and mutation publications, and preclinical studies, total 30 studies remained for the final systematic review ($N = 30$). Of these publications, studies were from 12 countries including the USA, Germany, Italy, Spain, France, the UK, Serbia, India, Belgium, Iran, the Czech Republic, and Japan (see Table 1).

The 28 prospective observational study and two experimental studies were included in the systematic review. The total of 2,812 infants (preterm infants were 980, 34.85%), 1,346

mothers and 391 adults were enrolled in these 30 studies. Sample size was varied in individual studies, ranged from 290 subjects [37] to 12 subjects [38]. All the 30 studies met first three requirements of quality appraisal check list (see online suppl. Table S1), which worth proceeding with the remaining items [36].

Infant Subjects and Biological Sampling

Of the publications identified, 11 studies focused on preterm infants. Some studies focused on identifying the indicators and consequences of mitochondrial dysfunction by assessing: (1) the association between hyperoxia and SIRT1/resveratrol signaling [39], (2) FMRP/mTOR signaling cascade and hypoxic-ischemic brain injury [40], (3) altered glutamate and glutamine and white matter injury (WMI) [41], (4) polymorphisms of antioxidant enzymes and ROS-induced complications [42], and (5) 8-OHdG and neurodevelopment outcomes [43]. Other studies explored the association between ROS and complications of antioxidant capacity, pain, low birth weight, DNA damage, placenta lesion, and preterm prelabor rupture of the membranes (PPROM) in preterm infants [44–50].

Biological samples collected in the studies included saliva [51], buccal swabs [51], cerebrospinal fluid (CSF) [52], peripheral blood mononuclear cells (PBMC) [39, 53–55], umbilical cord blood (UBMC) [44–46, 48–50, 52–57], whole blood [37, 42, 47], placenta [38, 58–66], brain [40], cytotrophoblast cells [65], urine [43], and fibroblast [66]. Placenta samples (9 studies) and umbilical cord blood (9 studies) were the most common sampling sources among the 30 studies (60%). Only four studies of preterm infants applied noninvasive tests (e.g., saliva, buccal swabs, urine, and magnetic resonance spectroscopy [MRS]) [41, 43, 51, 67].

Intervention on the Biological Samples

Two of the 30 studies tested an intervention on the biological samples collected. Thomas et al. [38] showed that hydrogen peroxide (H_2O_2) could induce ROS in placenta explants and decrease ATP and placental fatty acid oxidation (FAO). Resveratrol, a plant polyphenolic compound, was used in Yang's study as a natural agonist of silent mating-type information regulation 2 homolog 1 (SIRT1) to inhibit the hyperoxia toxicity in cultured PBMC [39].

Stress Indicators and Measurements

Stress types in these 30 studies were ROS, pain, preterm birth, placental lesion, PPROM, and meconium-stained amniotic fluid, MCM, childhood trauma, maternal stress, IUGR, hypoxic ischemic, glutamate excitotoxicity, and $PM_{2.5}$.

Hyperoxia-Associated ROS—Both in vitro and in vivo ROS were examined in Yang's study: (1) preterm infants received the oxygen supplementation during their hospitalization and (2) the extracted PBMC from preterm infants was treated with different levels of oxygen [39]. In Giusti's study, although there was no direct ROS assessment in preterm infants, the respiratory distress syndrome (RDS) diagnosis and the history of mechanical ventilation treatment indicating ROS overload [42]. Thomas et al. [38] also reported on ROS induced by H_2O_2 exposure using placenta samples. Bartha et al. [63] assessed the level of FAO in placentas, which was related to ROS-induced preeclampsia. Garrabou et al.

[56] considered carbon monoxide, the byproduct of smoking, as a stress factor that could impact the pregnancy. The questionnaire of Fagerstrom test was administered to assess the smoking dependence in smoking [56]. Self-reported tobacco consumption together with cotinine levels in the plasma of pregnant women and infants and urine samples of mothers were evaluated to assess the reliability of the questionnaire [56].

Pain and Other Stress Associated with ROS—Only one paper in our review focused on the association between procedure pain and ROS [47]. The pain scores were assessed using the Premature Infant Pain Profile (PIPP) which included seven items of GA, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow [47]. Tissue damaging procedures such as tape removal and indwelling central arterial or venous catheter were considered as pain stress which positively associated with ROS production [47].

Díaz et al. [64] focused on the small for GA-associated ROS production in infants. The association between ROS caused by preterm birth, twin birth, maternal stress, meconium-stained amniotic fluid, placenta lesion, PPROM, and infants' growth were also the focus in our reviewed studies [43–46, 48–50, 57].

Hypoxic Ischemic—Hypoxic-ischemic encephalopathy (HIE) as a stress in term and preterm infants was examined in three studies [40, 52, 67]. The perinatal HIE is diagnosed if four signs are present: prenatal distress, immediate depression, metabolic acidosis, and early neonatal encephalopathy [52]. HIE was then categorized into three stages (mild, moderate, and severe) based on the severity of the symptoms [52].

Maternal Childhood Maltreatment and Childhood Trauma—Three studies focused on MCM. The participants from these studies were mothers within 1 week after parturition [53–55]. They were all assessed retrospectively using the German short version of the Childhood Trauma Questionnaire (CTQ) during the mothers' psychodiagnostics interview. CTQ includes emotional, physical, and sexual abuse, as well as emotional and physical neglect subscales. Each subscale has 5 items and a total of 25 items with scores from 25 to 125. The CTQ score was documented as MCM load. Four groups from "none" to "severe" MCM experience were classified based on CTQ sum scores.

Maternal Stress—The pregnant mothers' lifetime stress (previous 12 months) was assessed using Life Stressor Checklist-Revised (LSC-R) [58, 59], LSC-R included 30 traumatic events (e.g., sexual assault, abortion, interpersonal violence). Mothers' prenatal negative life events (previous 6 months) were assessed using the Crisis in Family Systems-Revised survey which has 11 domains (e.g., income, job, relationships, safety, and housing). Further, the Diagnostic and Statistical Manual of Mental Disorder-posttraumatic stress disorder (PTSD) were used to assess the PTSD symptomatology.

In another study, self-administered questionnaires were administered at the 2nd and 3rd trimesters to assess maternal psychosocial stress in pregnancy (MPSP) [60]. MPSP questionnaires included the Perceived Stress Scale (PSS-14), the Pregnancy Related

Anxieties Questionnaire (PRAQ)-Revised, the Perinatal PTSD Questionnaire (PPQ), and the State-Trait Anxiety Inventory for Adults (STAI).

Intrauterine Growth Restriction—Three studies introduced IUGR as a stress indicator. IUGR was identified if the fetal growth was under 5th percentile using longitudinal sonographic measurements [65]. IUGR was also identified once the ultrasound estimation of fetal weight was <10th percentile for its gestational age [61, 62].

$PM_{2.5}$ and Glutamate Excitotoxicity—One study reported maternal $PM_{2.5}$ exposure as a stress indicator. Brunst et al. [59] used an exposure model assessing temporally and spatially resolved $PM_{2.5}$ to estimate $PM_{2.5}$ level of the pregnant women. The daily $PM_{2.5}$ was estimated based on subjects' location and time at each address. Wisnowski's team assessed the glutamate-induced excitotoxicity in neonatal WMI, grade I or II intraventricular hemorrhage, and cerebellar hemorrhage using magnetic resonance spectroscopy [41].

Mitochondrial Function and Genetic Variations

The genetic variations assessed in the reviewed 30 studies included polymorphisms of genes *5-HTTLPR*, *NR3C1*, *FKBP5*, *SOD1*, *SOD2*, *SOD3*, and *CAT*, *MT-ND6* methylation, and mtDNA copy number (mtDNAcn); protein levels of SIRT1, mTOR, total FMRP, phosphor FMRP, NRF1, SIRT3, COX, VDAC, respiratory chain complexes (RCC); gene expression of *PGC-1* α; and all 13 protein-coding genes encoded by mitochondria, seven key nuclear glycolysis regulatory genes (*PDK1*, *PDK2*, *PDK3*, *PDK4*, *PKLR*, *PKM*, *OGT)*, *CPT-1b*, *PPAR*-α, *LCHAD*, *MCAD*, *NRF1*, *RCC*. The major findings are shown below.

ROS and Mitochondrial Function—Findings from the reviewed studies showed that ROS overexposure-induced mitochondrial dysfunction may occur via the nitric oxide mediated injury pathway by inhibiting oxidation state of cytochrome-c-oxidase (oxCCO) activity in infants with HIE injury [67]. Decreased citrate synthase activity [68], mitochondrial intracellular density and respiration [51], FAO [38], and increased 8-Hydroxy-2-deoxy guanosine (8-OH-dG) [43, 45, 46, 57], Malondialdehyde (MDA) [47], and 15-F_{2t}-isoprostane [44], were associated with ROS induced mitochondrial dysfunction. Increased Glutamine and decreased N-acetylaspartate (NAA) were found in parietal white matter in infants with WMI [41], Negative relationship between the activity of glutathione peroxidase (GPX) in CSF and the adverse neurological outcomes was found in preterm infants with severe HIE injuries [52]. Dose-response relationship increased the childhood maltreatment load with higher level of pro-inflammatory cytokines and ROS in mother's PBMC [55].

Polymorphism and Mitochondrial Function—T allele in *FKBP5* was significantly associated with higher cortisol level, while methylation levels of *MT-ND6* was positively associated with adverse childhood experiences (ACE) [51]. rs8192287 *SOD3* polymorphism is a protective factor for intraventricular hemorrhage (IVH) in preterm infants [42].

mtDNAcn and Mitochondrial Function

mtDNAcn was found to be negatively associated with the Edinburgh Postnatal Depression Scale (EPDS) and $PM_{2.5}$ exposure [58, 59]. In contrast, mtDNAcn was found positively associated with early life adversity [37]. mtDNAcn, ROS and mitochondrial gene expression were all associated with pathology of IUGR [59]. The increased mtDNAcn, decreased SIRT3 protein expression, and decreased succinate dehydrogenase (SDH) activity indicated mitochondrial dysfunction and were associated with IUGR [62]. Decreased mtDNAcn and SOD activity were associated with FGR in the placenta for the small for GA pregnancy [64].

Genetic Signal Pathway and Mitochondrial Function—Hyperoxia or ROS could activate SIRT1 expression and activity and induce SIRT1 transportation from the nuclei of PBMC to the cytoplasm [39]. The maximum respiratory capacity was only modestly increased and no change was found in *PGC-1*α expression in mothers with MCM, which may not explain the intergenerational transmission of MCM [54]. FMRP/mTOR signal pathway was associated with hypoxic-ischemic encephalopathy [40]. Increased mitochondrial content and *NRF1* gene expression level in IUGR placenta could explain fetal growth restriction caused by increased oxygen consumption in placenta and limited oxygen delivered to the fetus [65].

Biological Sex and Ethnicity Difference in Mitochondrial Function

Five studies identified differential stress levels and mitochondrial function by biological sex and ethnicity in their findings. Female infants were found to have a higher mitochondrial respiration rate than male cohorts, which was independent of MCM [53]. At 25–40 gestational weeks, $PM_{2.5}$ exposure level was positively associated with placenta mtDNAcn in boys with high maternal trauma level, while negative associations were observed in girls with the low maternal trauma level [59]. Mandò also studied gender difference although no significant findings were reported [65]. High level of prenatal stress and psychological symptom scores and lower mtDNAcn as a marker of mitochondrial dysfunction, were found in non-white mothers, which may impact infants' health outcomes [58]. Higher levels of 15-F_{2t}-isoprostane were found in male preterm infants compared with female cohorts, which dependent of maternal stress exposure [44].

Neurodevelopmental Outcomes in Infants

Among 30 studies, 10 studies discussed the neurodevelopment outcomes in infants and adults with early life adversity. Measurements of Bayley scores, stress tests, anxiety tests, neurological symptoms, psychiatric diagnosis, encephalopathy diagnosis, temperament assessment were applied in these 10 studies.

Mitra et al. [67] assessed infants' neurodevelopmental outcomes following HIE and found that the ratio of thalamic lactate/N-acetylasperate higher than 0.3 using the NICHD neonatal MRS brain injury scoring system between days 5 and 7 after birth was associated with poor neurodevelopmental outcomes. They also used the Bayley Scales of Infant Development-III to evaluate the neurodevelopmental outcomes in infants at 1 year of age [67]. Infants who scored less than 85 of Bayley were considered to have adverse outcomes [67]. Another study conducted neurodevelopmental assessment using the Mental Developmental Index (MDI) and the Psychomotor Development Index (PDI) of Bayley scale at 18 months' corrected

age in preterm infants with very low birth weight (<1,500 g) [43]. MDI lower than 80 was considered as subnormal outcomes [43].

Trier Social Stress Test was conducted in adult participants to assess the acute stress response to psychosocial stimulators [51]. Lifetime psychopathology was evaluated using the Structured Clinical Interview for DSM-IV (SCID), the Inventory for Depressive Symptoms-Self Report, the State-Trait Anxiety Inventory, and the Perceived Stress Scale [37]. Psychiatric symptom load was also measured using a HADS depression sum score and HADS anxiety sum score [55]. In one study, Infant Behavior Questionnaire Revised (IBQ-R) was given to mothers to rate infants' temperament-related behaviors at 6 months of age [60]. Six constructs of activity level, smile and laughter, fear, distress to limitations, duration of orientation, and soothability were covered by IBQ-R. Denver Developmental Screening Test was used to assess the neurodevelopmental outcomes in term infants at 1-year corrected GA [52]. The infants were categorized into three groups (normal, motor developmental delay, and severe adverse outcome) based on the Denver Developmental Screening Test score [52].

Stress, Mitochondrial Function/Dysfunction, and Neurodevelopmental Outcomes

Findings from ten studies reported a significant association between prenatal and postnatal stress and neurodevelopmental outcomes, and found this relationship was mediated by mitochondrial function/dysfunction. MPSP-induced mitochondrial dysfunction was associated with infant temperament changes at 6 months of age [60]. oxCCO-MABP semblance at 48 after birth could be used to predict HIE-associated neurodevelopmental deficits at 1 year of age [67]. Neonatal hypoxic-ischemic brain damage and mitochondrial ROS overproduction were associated with neurodevelopmental outcomes at 12 months after birth [52]. Abnormal lipid peroxidation was associated with developmental deficits in preterm infants at 18 months [43]. Further, stress-induced mitochondrial genetic variations lead to WMI and encephalopathy of prematurity in preterm infants [40, 41]. In adults, mitochondrial dysfunction played a role in (1) MCM-associated stress and anxiety, (2) parental loss and childhood trauma-associated psychiatric symptoms, and (3) stress-associated adult females with ACE [37, 51, 55].

Discussion

To the best of our knowledge, this is the first systematic review to explore the relationship between prenatal/postnatal stress, mitochondrial function/dysfunction, and neurodevelopmental outcomes in infants. Findings from the review support our proposed conceptual framework which explains the association between early life stress-associated mitochondrial function/dysfunction and neurodevelopmental outcomes in term and preterm infants. The findings suggest that mitochondrial function/dysfunction and relative genetic variations might interface between the association of early life stress and neurodevelopmental outcomes in infants. This result warrants early stress intervention at birth, as this stress experience during their early life might have life-long consequences for neurodevelopmental and behavioral health.

Stress and Mitochondrial Function/Dysfunction

Accumulative evidence has shown the association between stress and mitochondrial function/structure changes. Stress at a moderate level will initiate the prosurvival process: increased energy demand, promote mitochondrial biogenesis, stabilize cellular response, and improve immune function [68]. However, stress overload will produce more ROS, damage the mitochondrial function, and decrease ATP production [69]. The imbalance between ROS and antioxidant ability caused by stress overload are more common in preterm infants due to their developmental vulnerability and unmature antioxidant system compared with term infants [70].

In this review, evidence was found to support the notion that both prenatal and postnatal stress influence infants' mitochondrial function/dysfunction. Prenatal stress such as MCM as a stress indicator is associated with increased ROS production, and decreased mitochondrial function in mothers [55], and was intergenerationally transmitted to their infants [53, 60, 71]. These intergenerational transmission effects of MCM were also found to play a role in infants' physical and mental health [72, 73]. Although mitochondrial bioenergetic cross-generational transmission mechanisms are still underdeveloped, MCM-related epigenetic alternations have been documented during the embryo period through genetic maternally inherit (DNA, RNA, and protein regulation) [71]. IUGR is another example of prenatal stress which induces maternal phenotype and genotype intergenerational transmission [74]. IUGR is associated with increased ROS production, mtDNA abundance, and antioxidants consumption in the placenta, which leads to the decreased oxygen and antioxidants deliver to the fetus [61], resulting in infants' low birth weight, complications of metabolic syndrome, and pulmonary arterial hypertension.

During the postnatal period, the preterm infant is exposed to pain stimulation, hypoxic ischemic, and hyperoxia, which all lead to ROS overproduction and mitochondrial dysfunction because of an immature antioxidant system [43]. Although procedure pain is very common in preterm infants during their NICU stay, only one study reported the association between procedure pain and mitochondrial function. Mitochondrial function such as ATP production, ROS production, mitochondrial permeability transition pore (MPTP), apoptotic pathways, and intracellular calcium mobilization play a role in the pathology of procedure pain [47, 75, 76]. Normal mitochondria produce a small but stable amount of ROS leak along the electron transport chain sustaining the redox state [77]. Alan and Isha stated that the mismatch of oxygen supply and demand will damage cellular function and mitochondrial function [78]. Long episode of hypoxic ischemia increases electron leakage, increases mitochondrial ROS production, and impairs efficacy of the antioxidant system causing the mitochondrial dysfunction [79]. Hyperoxia exposure such as oxygen therapy is standard procedure in preterm infants to sustain normal heart rate and blood oxygen level [80]. However, an excess supply of oxygen to infants will cause excessive ROS and lead to multiple organs (lung, central nervous system, and retina) injury [81].

Mitochondrial Function/Dysfunction and Neurodevelopmental Outcomes

High energy demand of brain (20% of the body energy demand) requests high concentration of mitochondria [82]. In response to stress, mitochondria adjust their activity to meet the energetic demand. In our review, mitochondrial dysfunction and associated ROS have been increasingly recognized as the causes of WMI and hypoxic ischemic brain injury or abnormality although the pathological mechanisms are still unknown [41, 67]. Preclinical study showed that hypoxic ischemia induced mitochondrial fission, fragmentation, and loss of motility in myelinated axons [83]. This was consistent with our findings that mTOR signal pathway was inhibited in infants with encephalopathy which attenuate the normal mitochondrial energy production [40, 84]. Additional, mitochondrial respiration and density were increased in neonates and their mothers with MCM [53]. Mitochondrial function mediated impact of MCM in pregnancy on infant temperament development [60].

Our study found many genes, proteins, and metabolites were associated with mitochondrial function/dysfunction and could be used as biomarkers to predict neurodevelopmental outcomes in infants' later life. However, there is a lack of longitudinal data to support these findings. Further, the signal pathways related to mitochondrial dysfunction, such as p38 MAPK, AKT/mTOR, SIRT1/Nrf2, SIRT1/p53, SIRT1/PGC-1a, AKT/SIRT3/SOD2 signaling, were not found in our reviews but were reported in the preclinical studies, which needs to be addressed in the future study design. No study in our review examined the posttranslational protein modification, such as phosphorylation, acetylation, and O-GlcNAcylation of proteins related to mitochondrial function/dysfunction in different stress levels in term and preterm infants.

Most studies in our review conducted invasive sampling using placenta, PBMC, UBMC, brain, CSF, etc. However, a few publications applied noninvasive sampling of saliva, buccal swabs, urine, and the MRS to assess the infants' and adults' mitochondrial function and brain development. It is urgent to verify the highly sensitive and accurate noninvasive sampling to assess mitochondrial function and predict neurodevelopmental outcomes in infants' early and later life, avoiding any additional stress [85–87]. These findings point out the new directions for future clinical study focused on the association between stress-induced mitochondrial dysfunction and neurodevelopmental deficits in infants.

The lack of standardized infant developmental scales makes it more difficult to identify and compare neurodevelopmental deficits and behavioral changes in different age groups [88]. The time to initiate Bayley scale is another concern. In our review, two studies conducted the Bayley test; however, they applied this scale at different time points: one was at 1 year and another was at 18 months' corrected age [43, 67]. Although the two time points described above are both within the scale range, the author should assess the infants' stability, not just the age. Low correlation between Bayley scores and other scores were reported [89]. To confirm the validity and reliability, future study should consider choosing one standard scale at specified time range or using more than one scale to measure the neurodevelopmental outcomes [88].

CTQ was commonly used to measure childhood trauma and satisfactory validity [90]. The validity of IBQ-R was still the concern when it was applied in diverse samples [91].

For questionnaires, bias may exist in maternal recall behavior (e.g., childhood trauma) or parents-reported child temperament (e.g., IBQ-R) because of maternal psychopathology [92].

Stress, Mitochondrial Function/Dysfunction, and Neurodevelopmental Outcomes

Mitochondria play a central role at the interface between prenatal and postnatal stress and the neurodevelopmental deficits in infants' early and later life. In our review, the stress indicators varied from prenatal stress, such as maternal stress, childhood maltreatment, IUGR to postnatal stress, to infant exposure to pain, hypo-, or hyperoxia stressors. Besides prenatal mitochondrial energetic transgenerational transmission we discussed above, during the postnatal period, impaired maternal caregiving capacity [93], poor bonding, and MCM associated depression [94] may be the major causes of developmental deficit in infants. Animal experiments showed that maternal separation in early life caused cognitive dysfunction that could persist in adolescence [95]. IUGR associated blood flow and nutrients delivery shortages further damaged fetal growth. In human IUGR and animal models, WMI is the most common neurodevelopmental deficit caused by placental insufficiency [96–98]. IUGR induced fetal hypoxia is another common clinical issue that increases the risk of neurodevelopmental deficit in the infant. Animal models pointed out that early chronic intermittent hypoxia exposure plays a role in infant WMI [99]. Although preterm infants have immature lung and antioxidant systems, they often require high oxygen concentrations (90–100%) during their NICU stay [99]. Both human and animal studies showed that hyperoxia exposure at the 2nd to 14th postnatal days put premature infants at high risk of neurodevelopmental deficit and other comorbidities such as retinopathy of prematurity and bronchopulmonary dysplasia [100–102].

Although the physiological or psychosociological difference exists between prenatal and postnatal stress factors, the mechanisms and genetic variations associated with mitochondrial function were all connected with shaping the brain structure and function. Gluckman and Hanson called this process "developmental programming" [103]. Although the mechanisms of association among stress, mitochondrial function/dysfunction, and neurodevelopmental outcomes were still unclear. The younger the GA and the smaller the birth weight are, the more sensitive the infants' brain response to environmental changes is [87], and the more adverse consequence of neurodevelopment it is throughout the entire lifespan.

The present review included studies suggesting that mitochondrial function/dysfunction mediates the impact of prenatal and postnatal stress on neurodevelopmental outcomes in infants. Evidence from animal studies strongly demonstrates that stress impaired neurodevelopment through mitochondrial dysfunction and changed gene expression [92]. However, it remains challenging to identify the association among stress, mitochondrial dysfunction, and neurodevelopmental deficits in clinical studies due to translational failure from preclinical results to the current clinical settings [92].

Limitation of Current State of Scientific Knowledge

There has been a growing interest in studying the role played by sex difference in brain programming through regulating mitochondrial function. However, sex disparity in stress load, mitochondrial function/dysfunction, and neurodevelopmental outcomes in early life has received limited attention (5 out of 30 studies). The ethical and practical difficulties hinder the researchers from conducting the clinical trial in preterm infants. A limited number of studies were conducted on preterm infants (11 of the 30 studies). It is urgent to be aware of the challenges and the clinical needs of infants. The lack of standardized developmental scales of infants and longitudinal studies need to be addressed in future studies. Future studies are needed to identify the longitudinal impact of stress-induced mitochondrial dysfunction on neurodevelopmental outcomes in infants. Another major concern was that only five out of 30 studies conducted noninvasive sampling, which avoids extra stress. Limited early stress intervention during NICU stay and noninvasive sampling warrants more attention to prevent stress-influenced brain impairment.

Conclusions

Mitochondrial function/dysfunction was at the interface between stress and neurodevelopmental deficits in infants and understanding this association might provide alternative strategies to manage the stress-induced neurodevelopmental deficit. Prenatal intrauterine and postnatal NICU hospitalizations are critical periods for the brain development of preterm infants. Early GA and low birth weight increase the risk of neonatal neurodevelopmental deficits upon exposure to prenatal and postnatal stress. To prevent mitochondrial bioenergetic intergenerational transmission in infants, psychological assessment and social support should be provided to mothers with MCM and further research on effective interventions is warranted. Additionally, individualized care should be applied to diminish biological sex disparities in infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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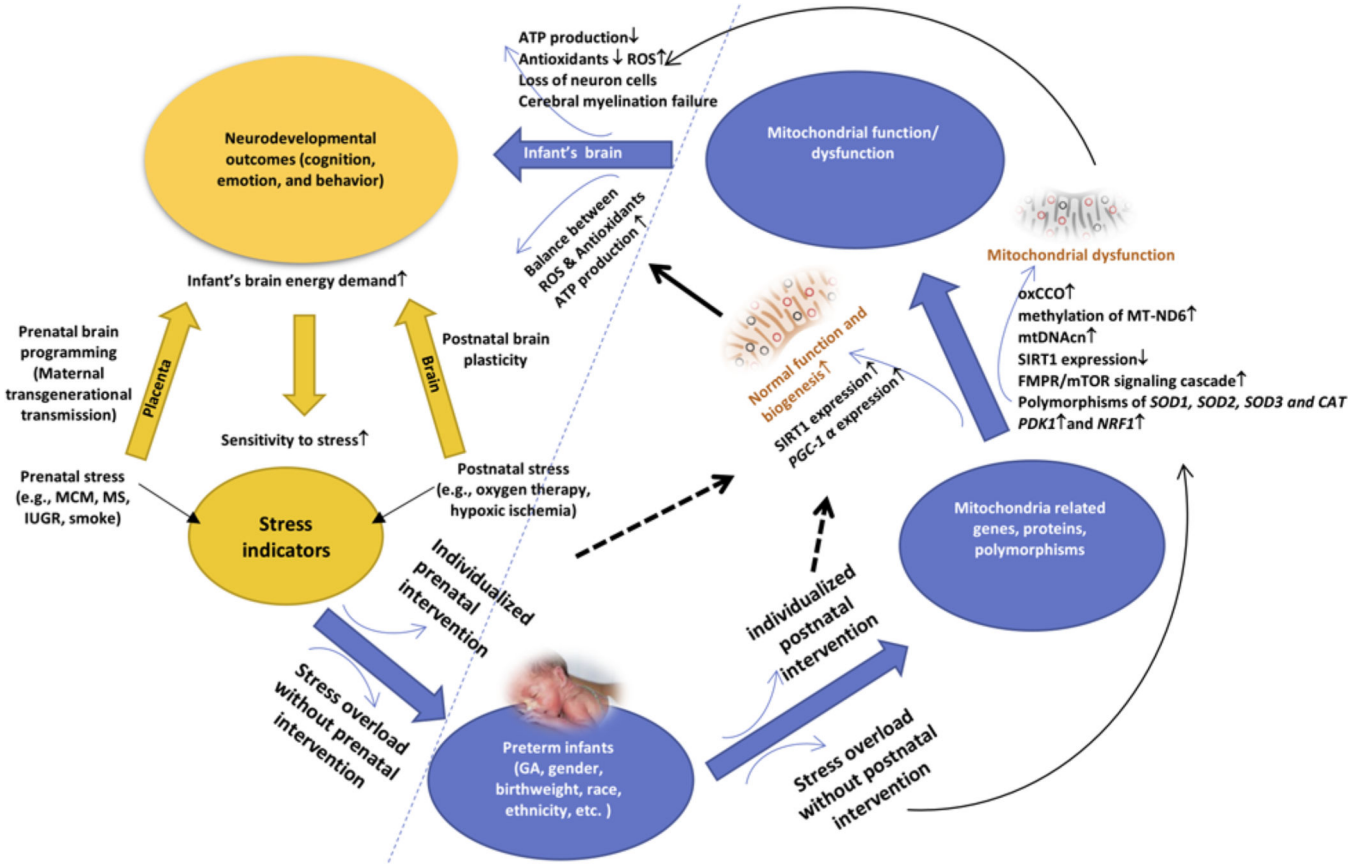

Fig. 1.

A conceptual framework for the association of stress, mitochondrial function/dysfunction, and neurodevelopmental outcomes.

Table 1.

Included studies that examine association of stress, mitochondrial function/dysfunction, and neurodevelopmental outcomes

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
Gumpp et al. [53] 2020, Germany	To explore the intergenerational transmission of maternal MCM exposure induced mt bioenergetic alternation from mother to child	Observational study	*N* = 209 (mothers, *n* = 105; newborns, *n* = 104); maternal PBMC and neonatal umbilical cord blood	N/A	MCM	Mitochondrial respiration and density	CTQ was used to assess MCM	1. Maternal and neonatal citrate synthase activity was positively correlated. 2. Female infants had higher mt respiration than male cohorts which was independent of maternal CM exposure. 3. Maternal CM load is only associated with mt respiration and density in mothers, but not in infants	L: no neurodevelopmental outcomes were evaluated R: Need to be confirmed in larger sample size
Mitra et al. [67] 2019, UK	To explore the role of oxCCO and MABP in HIE associated brain metabolic activity	Observational study	*N* = 23, stable term infants	N/A	Therapeutic hypothermia following hypoxic ischemic encephalopathy	oxCCO-MA BP semblance at 48 h after birth, and Lac/NAA (day 5–7) to predict the neurodevelopment outcomes	Bayley III at 1 year	oxCCO-MABP semblance at 48 h can be used as a biomarker to (1) predict early and 1 year of age neurodevelopmental outcome after HIE; (2) differentiate between the infants with good or poor neurodevelopmental outcomes after HIE	L: no data within 24 h; no gender difference; small sample size; did not measure mitochondrial function R: Enlarge sample size
Lapp et al. [51] 2019, USA	To explore the association between adverse childhood experience (ACE) and mitochondrial genetic variation	Observational study	*N* = 90,48.4% female, age = 32.12±15.1; buccal swabs; two groups (ACE = 0, ACE ≥4)	N/A	Adverse childhood experience, lifetime discrimination, daily discrimination, perceived stress, and city stress	Polymorphisms of gene *5-HTTLPR, NR3C1, FKBP5;* MT-ND6 methylation and mtDNAcn	Current stress test	(1) mitochondrially encoded NADH dehydrogenase 6 (MT-ND6) methylation level was higher in ACE ≥4 group compared with ACE = 0 group; (2) No mtDNAcn difference between these two groups	L: No gender difference was assessed; small sample size R: Future study should explore the biological mechanisms between early life stress and mitochondrial DNA methylation

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
Brunst et al. [59] 2018, USA	To assess the combined effect of utero $PM_{2.5}$ and maternal stress exposure on mtDNAcn	Observational study	*N* = 167, first time pregnant women, placenta samples, infants' cord blood samples	N/A	Maternal stress and $PM_{2.5}$ exposure	mtDNAcn	N/A	Increased $PM_{2.5}$ and maternal trauma were associated with decreased mtDNAcn; 2. $PM_{2.5}$ exposure level between 25 and 40 GW was positively associated with placental mtDNAcn in boys with high maternal trauma level, while negatively associated with mtDNAcn in girls with low maternal trauma level	L: No neurodevelopmental outcomes assessed in infants R: Longitudinal study should be conducted to explore the association between mt involved genetic variations and neurobehavioral changes
Yang et al. [39] 2018, USA	To explore the variation of SIRT1 in preterm infants exposed to hyperoxia and the protective effect of resveratrol	1st experimental design (*n* = 10: ctrl no O_2; *n* = 30 O_2) 2nd experimental design (*n* = 40, no O_2, divided in 4 groups)	Total *N* = 80 (40 control, 40 neonatal respiratory distress syndrome [NRDS]), premature infants, gestational age <32 weeks; PBMC	Resveratrol	Oxidative stress	Protein levels of SIRT1; ROS level; MDA level	N/A	Hyperoxia or ROS injury induced SIRT1 transportation from nuclei of PBMC to cytoplasm and decreased SIRT1 expression and activity can be protected by Resveratrol	L: No neurodevelopmental outcomes assessed; no gender difference analyzed; no mitochondrial function detected R: Future study will focus on SIRTI's pharmacological regulation
Boecket al. [54] 2017, Germany	To explore the association between MCM and cortisol, oxytocin, and mitochondrial oxygen consumption	Cohort (baseline, 3 months postpartum follow up)	*N* = 49 (mothers, 22–44 years old); PBMC blood sample	N/A	MCM: maltreatment load using CTQ	Mitochondrial oxygen consumption; Gene expression of *PGC-1*α (qPCR)	N/A	(1) Mother with higher CTQ had higher level of anxiety; (2) The maximum respiratory capacity was only modestly increased, and no change was found in *PGC-1*α expression in mothers with MCM	L: small sample size and no gender difference was assessed R: Future study should focus on larger sample size
Brunst et al. [58] 2017, USA	To examine the associations among maternal stress, psychological	Prospective cohort study	*N* = 147, first time pregnant women,	N/A	Maternal stress (prenatal stress, postnatal depression,	Mitochondrial DNA copy number (mtDNAcn)	N/A	Higher level of prenatal stress and psychological symptom scores	L: no gender difference; no infants' neurodevelopmental

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
	functioning, and placental mt function		placenta samples		PTSD, and cumulative lifetime stress)			and lower mtDNAcn were found in non-white compared with white women; prenatal stress was negatively associated with mtDNAcn (marker of mt dysfunction)	outcomes R: Future study should focus on the stress intervention in pregnant women which will benefit maternal-infant health
Tyrka et al. [37] 2016, USA	To explore the association between the variation of mtDNAcn and the early life adversity and psychiatric disorder	Observational study	*N* = 290 adults, blood sample; 4 groups by combining adverse (+/−) and diagnose (+/−)	N/A	Parental loss (death and separation) and childhood trauma	mtDNAcn	Psychiatric diagnosis using SCID, IDS-SR, STAI, PSS, CD-RISC, CTQ scales and/or inventory	The early life adversity was associated with mtDNAcn while (−/−) group had lower mtDNAcn compared with other three groups; participants who had anxiety and past substance, lifetime depressive disorder had higher mtDNAcn	L: Not preterm infants; no gender difference was assessed R: Future study should further analyze larger sample size and mitochondrial genetic variations
Lechpammer et al. [40] 2016, USA	To explore the role of FMRP/mTOR signaling cascade in the pathology of encephalopathy in premature infants	Pilot study	*N* = 30 (newborns' normal brain, *n* = 15; premature hypoxic-ischemic injured brain, *n* = 11; adult normal control brain, *n* = 4)	N/A	Hypoxic-ischemic brain injury	Proteins of mTOR, total FMRP, phospho-FMRP(Ser^{499})	Encephalopathy of prematurity	(1) During 36–39 GW, overexpression of FMRP was confirmed in the cortical of normal brain, although down regulated total FMRP, phospho-FMRP, and overexpressed mTOR was found in cortical in preterm infants with encephalopathy; (2) During 23–37 GW, FMRP level was predominantly increased in premature white matter compared with normal brain; (3) Co-expression of mGluR5 with FMRP has been observed	L: Did not consider gender; did not measure mitochondrial function; no history of neurodevelopmental outcomes R: Future study needs to focus on gender difference, and larger sample size

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
								in infants with encephalopathy at 36–39 GW.	
Boeck et al. [55] 2016, Germany	To explore whether mitochondrial activity and ROS are involved in the CM-induced inflammation	Cross-sectional design of the exploratory study	*N* = 67, women 6 days following parturition (>18 years); PBMC blood sample	N/A	CM; maltreatment load using chCTQ	Mitochondrial oxygen consumption (cellular oxygen consumption [ATP]; maximal capacity of the respiratory chain; residual oxygen consumption; flux control ratios)	Stress, anxiety and depressive symptoms	Dose-response relationship of increasing CM load with higher level of pro-inflammatory cytokines and ROS in PBMC	L: small sample size; no gender difference; no neurodevelopmental assessment; no infants assessment; not longitudinal design; no genetic evaluation R: Should have a lifespan study from childhood until adulthood to explore the association between the mitochondrial function and CM induced inflammation
Lambertini et al. [60] 2015, USA	To explore whether there is an association between the MT gene expression, MPSP and fetal temperament development	Cohort	Placenta samples, *N* = 108, mot her-infant dyads (274.26±17.16 days of gestational age)	N/A	MPSP	All 13 protein-coding mitochondrial-encoded genes were analyzed, gene MT-ND2	Infant temperament at 6 months of age is assessed by the Infant Behavior Questionnaire Revised (IBQ-R) administered to mothers	Mitochondrial function mediated negatively impact of MPSP on infants' tempera ment development	L: No gender difference assessed; no mitochondrial function detected R: Increased sample size of the cohort in the future
Wisnowski et al. [41] 2013, USA	To explore whether the altered glutamate and glutamine are associated with WMI	Observational study	*N* = 218, born <37 GA, not older than 60 weeks post concept ion a 1 age at the time of MRI, WMI diagnosed	N/A	Glutamate induced excitotoxicity	Glutamate and N-acetyl aspartate (NAA) (both released from MT of neurons)	WMI	(1) MRI/MRS can be used to as biomarker to identify WMI in preterm infants; (2) Increased Glutamine and decreased NAA were found in parietal WM in infants with WMI	L: No demographic data were presented; no neurobehavioral outcomes reported R: Future study should focus on mitochondrial function and gender difference
Giusti et al. [42] 2012, Italy	To identify the association between SNPs of SOD 1,SOD2, SOD3, and CAT and the severity of	Retrospective study	*N* = 152, preterm infants, ≤28 GW, blood DNA, polymorphisms	N/A	ROS of preterm birth	SNPs of *SOD 1,SOD2, SOD3,* and *CAT*	N/A	(1) rs8192287 SOD3 was found associated with decreased risk of developing IVH; (2) The	L: No gender difference was evaluated; 2. No neurodevelopment assessed; 3. No longitudinal genetic

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Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
	RDS (MV, BPD, IVH, and ROP) in preterm infants							association between homozygous infants for rs4880, rs5746136 for SOD2 polymorphism and lower gestational age; (3) haplotypes of *SOD1, SOD3* and *CAT* genes were risk predictors of RDS complications	variation was evaluated R: Larger sample size need to be assessed in the future
Vasiljevic et al. [52] 2011, Serbia	To examine the role of neuroinflammation, ROS, and deficient or overproduced growth factors in hypoxic-ischemic brain damage	Prospective study	*N* = 90; neonates gestational age >32 weeks with hypoxic-ischemic encephalopathy	N/A	Hypoxic-ischemic brain damage	IL-6, GPX, NSF, VEGF	Cerebrospinal fluid (CSF) and Denver Developmental Screening Test at 12 months	(1) NSE in CSF could be used as a biomarker of severity of HIE; (2) Remarkably increased GPX activity in CSF (indicate overproduced ROS) was associated with the severity of HIE; (3) Decreased VEGF and increased IL-6 in CSF were associated with the severity of H IE and brain damage	L: Did not clarify the number of preterm and term infants; no gender difference was discussed; no mitochondrial function was measured R: Future study focus on the diagnostic and prognostic value of these markers
Thomas et al. [38] 2019, USA	To testify whether the placenta mitochondria dysfunction mediates the impact of acute ROS on decreased FAO and increased esterification	Experimental study	*N* = 12, women age 21–41 years, term maternal face of the placenta were extracted	H_2O_2 incubation for 4 h (200, 400, and 800 μm); incubated for 18 h with [^{3}H]-pa Imitate	H_20_2	Genes and protein expression: CPT-1b and PPAR-α ATP production; FAO	N/A	ROS decreased placental FAO and ATP production can explain damaged placenta effectiveness which cause fetal growth restriction (FGR); However, acute ROS did not change the gene and protein expression	L: no gender difference, small sample size, no neurodevelopmental outcomes were assessed R: Future study focus on the larger sample size, mitochondrial function, and neurodevelopmental outcomes
Jones et al. [61] 2020, USA	To determine the association between the placental expression of all 13	Case-control study	50 IUGR and 100 control pregnancies, placenta samples	N/A	IUGR	13 protein-coding mitochondrial-encoded genes and seven key nuclear glycolysis-regulatory genes, PDK1,	N/A	MT-ND5, MT-ND6, and MT-ATP6 were negatively associated with IUGR, while	L: no direct mt function assessed; no gender difference R: Future study should

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
	protein-coding mitochondrial-encoded genes and seven key nuclear glycolysis-regulatory genes with IUGR					2, 3, 4, PKLR, PKM, OGT		one glycolysis-regulatory gene, PDK1 was positively associated with IUGR. mtDNA abundance and OS were positively associated with IUGR.	focus on the gender difference and mitochondrial function assessment
Naha et al. [62] 2020, India	To examine the association between the placental mtDNA and IUGR condition	Case-control study	*N* = 67 pregnant women, *n* = 29 control, *n* = 18 IUGR, *n* = 20 SGA, Placenta samples	N/A	IUGR	mtDNAcn, Whole mt genome sequencing, proteins of NRF1 and SIRT3. Succinate dehydrogenase (SDH) staining	N/A	The increased mtDNAcn, decreased SIRT3 expression, decreased SDH activity were found in IUGR placenta tissue, which indicate the association between mt dysfunction and the fetal growth restriction	L: No gender, no neurodevelopmental outcomes were assessed R: Future study will focus on the intervention strategy based on the findings
Bart ha et al. [63] 2012, Spain	To investigate the role of fatty acid oxidation (FAO) in women with preeclampsia	Observational study	*N* = 28 (ctrl = 14 and preeclapsia = 14), pregnant women, placenta samples	N/A	FAO	Gene expression of LCHAD and MC AD; mt fatty acid oxidation rate; mitochondrial citrate synthase activity	N/A	Decreased LCHAD expression but not mitochondrial content related to the FAO deficits in women with preeclampsia, which support the role of FAO in the pathology of preeclampsia	L: No gender, small sample size, no neurodevelopmental outcomes measures R: Large sample size should be considered in the future
Garrabou et al. [56] 2016, Spain	To explore the role of CO-induced mt dysfunction in reduced birth weight in newborns tobacco exposure	Observational study	*N* = 51, mother-infant dyads (non-smoking Ctrl = 21, smoking subjects = 30), pregnant women, PBMCs and CBMCs	N/A	Carbon monoxide (CO)	Protein expression of COX; citrate synthase activity (mt content); VDAC protein expression (mt apoptotic analysis); TUN EL (apoptosis in placenta)	N/A	The correlation was found between the decreased birth weight, COX activity, increased mtDNA, ROS, apoptosis and the hx of smoking in pregnant women. Which suggests mitochondrial dysfunction and apoptosis may be the key in	L: small sample size, no gender difference, no neurodevelopment outcomes was assessed R: Explore the relationship between mt mass and citrate synthase activity; enlarge the sample size to confirm the findings

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
								the reduced birth weight in smoking pregnant women	
Díaz et al. [64] 2014, Belgium	To assess the association between fetal growth restriction (FGR) and mt dysfunction	Observational study	*N* = 48 (*n* = 24 AGA and *n* = 24 SGA); mother-infant dyads, placenta samples	N/A	ROS	mtDNA content, SOD activity, citrate synthase activity	N/A	Decreased mtDNAcn and increased SOD activity were associated with FGR in placenta in SGA pregnancy	L: No genetic analysis, small sample size, no gender difference, no neurodevelopment outcomes assessment R: Larger sample size should be considered in the future
Mandò et al. [65] 2014, Italy	To compare the different mt content, function and respiration between IUGR and preeclampsia pregnancy	Observational study	*N* = 22 (8 IUGR, 6 preeclampsia, 8 Ctrl); pregnant women; placenta; cytotrop ho blast cells	N/A	ROS	mtDNA content; *NRF1* and respiratory chain complexes (RCC) gene expression; RCC protein expression; RCC efficiency; O_2 consump-tion	N/A	Mt content and *NRF1* gene expression level were higher in placenta but reversed in the isolated cytotrophoblast cells in IUGR group compared with control group. Which suggested the placental cell linage dependent mt features. Increased placental O_2 consumption may explain the limitation of O_2 delivery to fetus. No gender difference was found in the findings	L: No gender difference, small sample size, no neurodevelopmental outcomes R: Larger sample size should be considered in the future
Minghetti, et al. [44] 2013, Italy	To evaluate ROS, antioxidant capacity in newborn twins	Observational study	80 twin preterm infant (38 F, 42 M), >28 GW, umbilical cord blood sample	N/A	Premature and twins birth caused ROS	ROS bio marker 15-F_{2t}-isoprostane and antioxidant capacity (tAOC)	N/A	Males was higher than female cohorts in 15-F_{2t}-isoprostane but not in tAOC. Gender difference in vulnerability of ROS injury	No neurodevelopmental outcomes, which should be considered in the future study

Author, year, country	Study aim	Study design	Sample (size, gender)	Intervention	Measurement			Main findings	Limitation (L) and recommendation for future study (R)
					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
								will explain the developmental gender disparity in later life	
Negi et al. [45] 2012, India	To analyze the association between ROS and low birth weight (LBW) and prematurity	Observational study	55 preterm infants (<37 GW, birth-weight <2,500g) and 24 full term controls (≥37 GW, birth-weight >2,500g), umbilical cord blood	N/A	ROS caused during pregnancy stress exposure	Oxidative DNA damage marker: 8-Hyd roxy-2-deoxy guanosine (8-OHdG) and antioxidant status marker: Malondialdehyde (MDA)	N/A	Increased level of 8-OHdG, MDA, and negative association between 8-OHdG, birthweight and GA were found in preterm infants	No neurodevelopmental outcomes, which should be considered in the future study
Bandyopadhyay et al. [57] 2017, India	To analyze the relationship between MSAF and ROS, birth weight (BW), gestational age and prematurity	Observational study	*N* = 109 [59 meconium-stained amniotic fluid (MSAF) and 50 without MSAF]	N/A	MSAF induced ROS	8-OHdG, MDA	N/A	Infants with MSAF had higher level of ROS (increased 8-OHdG, MDA), which was significantly correlated with birth weight	No neurodevelopmental outcomes, gender difference, which should be considered in the future study
Negi et al. [45] 2012, India	To investigate the association between ROS	Observational study	*N* = 240 124 preterm infants (<37 weeks, birth weight <2,500 g), 116 full term infants, umbilical cord blood	N/A	Premature caused ROS	MDA, carbonyl proteins, total antioxidant capacity and vit A, E, and C	N/A	Increased ROS and decreased antioxidant capacity were observed in the low birth weight preterm infants	No neurodevelopmental outcomes, gender difference, which should be considered in the future study
Shoji et al. [43] 2014, Japan	To assess the association between ROS and neurodevelopment in preterm infants	Observational study	*N* = 35 preterm infants (F 19, M 16), birth weight <1,500 g, urine	N/A	Premature caused ROS	8-OHdG, and 8-isoprostaglandin F2a (8-isoPGF) marker of lipid peroxidation (ELISA)	At 18 months' corrected age, (1) Mental and psychomotor: Bayley Scale of Infant Development (BSID)-II; (2) Mental Developmental Index (MDI); (3) Psychomotor Development Index (PDI)	Significant association had been observed between urinary 8-OHdG and mental development rather than psycho motor development at 18 months' corrected age in preterm infants	Larger sample size and gender difference should be considered in the future study

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					stress indicators	MT related gene, protein, function measures	neurodevelopmental and behavioral (outcomes and assessment)		
Slater et al. [47] 2012, USA	To examine the relationship between pain score and behavioral and ROS changes	Observational study	N = 80 preterm infants (<37 GW) (42 with tissue damage procedures [TDP], 38 without TDP), 0.8 mL blood from central catheter 30 min before and after TDP	N/A	Pain score measured using premature infant pain profile (PIPP)	ROS marker of MDA and uric acid (UA)	N/A	Positive association between pain scores and MDA, which indicate the relationship between pain and ROS in preterm infants	Gender difference should be considered in the future study
Norishadkam et al. [48] 2017, Iran	To test the level of ROS and DNA damage between preterm infants and term infants	Observational study	N = 50,25 preterm infant (Ml 3, FI 2) (<34 GW, birth weight <2,000 g), 25 term infant (>37 GW, birth weight >2,500 g), umbilical cord blood	N/A	ROS	Comet assay to measure tailed DNA percent, MDA, antioxidant capacity using 1,1-diphenyl-2picrylhydrazyl (DPPH), SOD activity, plasma catalase activity	N/A	Significantly increased primary DNA damage, plasma ROS, tail DNA percent and tail moment were found in preterm infants	Gender difference and neurodevelopmental outcomes should be considered in the future study
Perrone et al. [49] 2016, Italy	To test the association between placental lesion (chorioamnionitis [CA] or vascular underperfusion [VU]) and ROS	Observational study (prospective cohort study)	*N* = 120, mother infant dyads, preterm infants (<29 GW), placenta (HCA, VU, Ctrl) and umbilical cord blood	N/A	Placental lesion caused ROS	Isoprostanes (IsoPs), non-protein bound iron (NPBI), and advanced oxidative protein products (AOPP)	N/A	IsoPs, NPBI and AOPP were increased in CA and VU groups compared with Ctrl group. Which indicated that inflammation or impaired perfusion are associated with increased ROS.	Gender difference and neurodevelopmental outcomes should be considered in the future study
Musilova et al. [50] 2016, Czech Republic	To evaluate the association between ROS and preterm prelabor rupture of membranes (PPROM)	Observational study (prospective cohort study)	*N* = 165, singleton pregnancy women with PPROM, umbilical cord vein blood	N/A	PPROM with microbial invasion of the amniotic cavity (MIAC) and/or histological chorioamnionitis (HCA) caused ROS	Total antioxidant capacity (TAC), ferric reducing antioxidant power (FRAP), thiobarbituric acidreacting substances (TBARS), advanced glycation end products (AGEs) were measured	N/A	TAC, FRAP, TBARS, and AGEs were all found in PPROM sample (MIAC and HCA); The association between ROS markers and short-term neonatal morbidity, e.g., intra ventricular hemorrhage (TBARS)	Gender difference and neurodevelopmental outcomes should be considered in the future study