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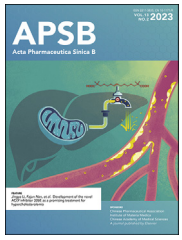

REVIEW

Developmental toxicity and programming alterations of multiple organs in offspring induced by medication during pregnancy

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Abstract Medication during pregnancy is widespread, but there are few reports on its fetal safety. Recent studies suggest that medication during pregnancy can affect fetal morphological and functional development through multiple pathways, multiple organs, and multiple targets. Its mechanisms involve direct ways such as oxidative stress, epigenetic modification, and metabolic activation, and it may also be indirectly caused by placental dysfunction. Further studies have found that medication during pregnancy may also indirectly lead to multi-organ developmental programming, functional homeostasis changes, and susceptibility to related diseases in offspring by inducing fetal intrauterine exposure to too high or too low levels of maternal-derived glucocorticoids. The organ developmental toxicity and programming alterations caused by medication during pregnancy may also have gender differences and multi-generational genetic effects mediated by abnormal epigenetic modification. Combined with the latest research results of our laboratory, this paper reviews the latest research progress on the developmental toxicity and functional programming alterations of multiple organs in offspring induced by medication during pregnancy, which can provide a theoretical and experimental basis for rational medication during pregnancy and effective prevention and treatment of drug-related multiple fetal-originated diseases.

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1. Introduction

It is well known that medication during pregnancy is prevalent. Clinical studies in many countries have shown that more than 80% of pregnant women have used drugs during pregnancy[1–3], mainly including antiemetics, antibiotics, and analgesics[4]. Since the storm in 1960s caused by the deformity of offspring due to the use of thalidomide during pregnancy, the fetal safety of medication during pregnancy has attracted more and more attention. Epidemiological investigations have shown that various drugs, such as anticoagulants, antiepileptics, and antihistamines, have fetal developmental toxicity, leading to miscarriage, birth defects, and other adverse pregnancy outcomes[5–7]. Many experimental studies have found that medication during pregnancy can result in multi-organ developmental toxicity and programming alterations in offspring, manifested as organ structure and function abnormalities and enhanced susceptibility to various adult chronic diseases in offspring. The "Developmental Origins of Health and Disease (DOHaD)" theory has been expanded in many fields since it was creatively opened up[8], and the "DOHaD" theory is the best analysis of offspring's organ developmental programming, functional homeostasis changes, and susceptibility to related adult diseases owing to medication during pregnancy. Given the "double-edged sword" effect of medication during pregnancy on the mother and fetus, clinicians must meticulously weigh the risks and benefits of prenatal drug use and formulate a reasonable medication plan for pregnant women. This paper comprehensively reviews the intrauterine mechanisms, gender differences, and multigenerational genetic effects of offspring's multi-organ developmental toxicity and functional programming alterations caused by medication during pregnancy, which has important theoretical and practical significance for deeply analyzing "DOHaD" theory, guiding appropriate drug use during pregnancy, and effectually preventing and treating drug-related diseases of fetal origin.

2. Multi-organ developmental toxicity in offspring induced by medication during pregnancy and the mechanisms

Organ developmental toxicity refers to the structural and functional impairment of offspring's organs caused by exposure to adverse environments during pregnancy. During pregnancy, the adverse environment includes environmental factors (physical, chemical and biological factors) and maternal factors (maternal diseases, malnutrition and stress). Among them, drugs are one of the environmental inducing factors fully demonstrated to cause organ development toxicity.

2.1. Characteristics of multi-organ developmental toxicity in offspring induced by medication during pregnancy

Intrauterine organ development is vulnerable to adverse environments such as prenatal drug use, and many different kinds of drugs have been shown to damage the development of the same organ (Table 1[9–56]). The liver is the crucial organ for the metabolism of many exogenous compounds, including drugs. Studies have confirmed that hepatic development is susceptible to many kinds of drugs, including antibiotics[9–14], synthetic glucocorticoids[15,16], antithyroid drugs[17], hypoglycemic agents[18], non-steroidal anti-inflammatory drugs (NSAIDs)[19], antipsychotics[20], antipyretic-analgesic drugs[21], traditional Chinese medicine (or its ingredients)[22–27] and so on. Hippocampal, bone, and gonadal development are also vulnerable to a variety of drugs. Anesthetics[28–32], antipsychotics[33–36], and synthetic glucocorticoids[37] have been shown to affect hippocampal development; synthetic glucocorticoids[38,39], antibiotics[12,40], anticancer drugs[41,42], antimalarials[43], antiviral drugs[44], NSAIDs[45], and synthetic estrogen[46] have been shown to affect bone development and chondrogenesis; NSAIDs[47–49], antipyretic-analgesic drugs[50,51], synthetic glucocorticoids[52,53], synthetic estrogens[54,55], and hypoglycemic agents[56] can affect testicular or ovarian development. It is not difficult to find that studies on drug-induced organ developmental toxicity are mainly based on animal models. However, some findings in humans have been reported. For example, the use of phenobarbital, clindamycin, and tenofovir during pregnancy has been shown to respectively cause reduced hepatic functional maturity, bone deformities and lower bone mineral content in human offspring[20,40,44]. It is worth noting that thanks to mature *in vitro* culture and xenotransplantation techniques of human testis and ovaries, studies have proved that ibuprofen, acetaminophen and metformin can affect the development of human gonadal function[48–51,56].

Studies have also found that a single drug may simultaneously impair the development of multiple organs, such as dexamethasone[20,37–39,52,53,57–59], betamethasone[16,60,61], diethylstilbestrol[54,55,62,63], metformin[18,56,64], acetaminophen[21,50,51], indomethacin[19,45,47], diclofenac[45,65], phenobarbital[20,66], Xiaoaiping[25], and psoralen[26] (Table 2[16,18–21,25,26,37–39,45,47,50–66]). Notably, the developmental toxicity of multiple organs caused by drugs used during pregnancy is often triggered through multiple targets. For example, *in utero*, dexamethasone can respectively up-regulate hepatic forkhead protein O1, inhibit hippocampal cAMP responsive element binding protein/brain-derived neurotrophic factor/tropomyosin receptor tyrosine B pathway, inhibit cartilage transforming growth factor β signaling pathway, down-regulate testicular steroidogenic acute regulatory protein, and inhibit adrenal cytochrome P450 cholesterol side chain cleavage enzyme, which affects the development of the corresponding organs[15,37,38,52,59]. Therefore, the developmental toxicity of drugs often has multi-organ and multi-target effects.

Sensitivity to drug-induced organ developmental toxicity on offspring differs in different gestational trimesters. The first trimester is the pivotal period for organogenesis[67], so medication during this period often causes severe damage to offspring's organ development, such as deformity. For example, epidemiological studies have shown that exposure to cyclophosphamide and macrolides in early pregnancy significantly increases the risk of bone and digestive malformation in offspring, respectively, while the risk of teratogenesis is low when they are used in late pregnancy[42,68]. It is worth noting that sensitivity to drug-induced organ developmental toxicity may also be different in the second and third trimesters. For instance, the use of dexamethasone in the second trimester of pregnancy can more seriously affect the development of long bone and articular cartilage in offspring mice than in the third trimester[38,39]. Conversely, aspirin use in the third trimester can cause kidney damage in offspring, while its use in the second trimester is relatively safe[69]. Therefore, it is vital to explore the "toxic time window" of drugs on the intrauterine development of different organs for choosing proper medication timing during pregnancy.

Table 1 Developmental toxicity of multiple drugs in the same organ.

Organ	Drug type	Drug name	Dosage regimen	Developmental toxicity manifestation	Ref.
Liver	Antibiotic	Ciprofloxacin	40 mg/kg·day, GD7−17, i.p.	Abnormal blood vessels and nuclear pyknosis in fetal rat liver	9
		Erythromycin	14.2 mg/kg·day, GD14−19, i.p.	Focal hepatic necrosis in offspring mice	10
		Azithromycin	150 mg/kg·day, GD9−18, i.p.	Vacuolation of fetal mouse hepatocytes and abnormal glucose and lipid metabolism	11
		Doxycycline	5 mg/kg·day, GD6−14, i.g.	Increased necrosis of fetal rat hepatocytes	12
		Triclosan	0.55 μmol/L, 6−120 hpf	Increased apoptosis of hepatocytes in zebrafish larvae	13
		Isoniazid	4 mmol/L, 6−72 hpf	Loose cell-to-cell contacts and large vacuoles in hepatocytes of zebrafish embryos	14
	Synthetic glucocorticoids	Dexamethasone	0.2 mg/kg·day, GD9−21, s.c.	Decreased proliferation of fetal rat hepatocytes	15
		Betamethasone	0.1 mg/day, GD14, s.c.	Liver growth retardation in mice	16
	Antithyroid drug	Methimazole	4.5 mg/kg·day, GD9−18, i.g.	Abnormal structure and glucose and lipid metabolism of fetal mouse liver	17
	Hypoglycemic agent	Metformin	250 mg/kg·day, GD0−18, *p.o.*	Abnormal differentiation and glucose metabolism of fetal mouse liver	18
	NSAID	Indomethacin	13.97 μmol/L, 24−168 hpf	Suppressed hepatogenesis of zebrafish embryo	19
	Antipsychotic	Phenobarbital	—	Reduced functional maturity of human offspring liver	20
	Antipyretic-analgesic drug	Acetaminophen	250 mg/kg·day, GD12, i.p.	Declined hematopoietic stem cell frequency in fetal mouse liver	21
	Traditional Chinese medicine	Monocrotaline	20 mg/kg·day, GD9−20, i.g.	Decreased liver weight and liver index of fetal rats	22
		Retrorsine	20 mg/kg·day, GD9−20, i.g.	Reduced hepatocyte numbers and potentiated hepatic apoptosis in fetal rats	23
		Triptolide	0.8 μmol/L, 72−120 hpf	Hepatocytes necrosis and decreased liver volume of zebrafish embryos	24
		Xiaoaiping	0.4 mg/mL, 6−120 hpf	Loose cell-to-cell contacts of zebrafish embryo hepatocytes	25
		Psoralen	3.54 μmol/L, 4−96 hpf	Reduced liver area of zebrafish embryos	26
		Aconitine	7.27 μmol/L, 4−96 hpf	Liver growth retardation in zebrafish	27
Hippocampus	Anesthetic	Isoflurane	3%, GD14, inhale	Abnormal hippocampal structure and dysfunction of memory in offspring rats	28
		Ketamine	40−60 mg/kg·h for 2 h, GD14, i.v.	Hippocampal neuron injury, memory impairment, and mental disorder in offspring rats	29
		Sevoflurane	2.5% for 2 h, GD15−17, inhale	Inhibition of fetal rat hippocampus neurogenesis and impaired memory in offspring	30
		Propofol	20 mg/kg·h for 4 h, GD18, i.v.	Impaired learning and memory in offspring rats	31

Table 1 (*continued*)

Organ	Drug type	Drug name	Dosage regimen	Developmental toxicity manifestation	Ref.
		Cocaine	40 mg/kg·day, GD8−18, s.c.	Cognitive impairment in offspring mice	32
	Antipsychotic	Quetiapine	55 mg/kg·day, GD6−21, *p.o.*	Neuronal cell deficit and enhanced apoptotic neurodegeneration in fetal rat hippocampus	33
		Haloperidol	10 mL/kg·day, GD6−16, i.p.	Abnormal hippocampal structure and impaired memory in offspring rats	34
		Risperidone	10 mL/kg·day, GD6−16, i.p.	Abnormal hippocampal structure and impaired memory in offspring rats	34
		Phenytoin	50 mg/kg·day, GD0−20, i.g.	Impaired learning in offspring rats	35
		Carbamazepine (CBZ)	3.5 g CBZ/kg in fodder, GD0−20, *p.o.*	Decrease of hippocampal neurons in newborn mice	36
	Synthetic glucocorticoids	Dexamethasone	0.2 mg/kg·day, GD9−20, s.c.	Decreased proliferation and increased apoptosis of fetal rat hippocampal cells and cognitive impairment	37
Bone/Cartilage	Synthetic glucocorticoids	Dexamethasone	0.8 mg/kg·day, GD12−14, s.c.	Bone and cartilage growth retardation in mice	38,39
	Antibiotic	Doxycycline	5 mg/kg·day, GD6−14, i.g.	Shortness in the ulna and radius bones of fetal rats	12
		Clindamycin	—	Skeletal malformations in human offspring	40
	Anticancer drug	5-Fluoro-2′-deoxyuridine	55 mg/kg·day, GD11, s.c.	Thoracic and lumbar vertebra and sternum variations of fetal rats	41
		6-Mercaptopurine-riboside	7 mg/kg·day, GD11, s.c.	Thoracic and lumbar vertebra and sternum variations of fetal rats	41
		Cyclophosphamide	—	Long bone hypoplasia of human offspring	42
	Antimalarial	Artesunate	15 mg/kg·day, GD9−11, i.g.	Fetal rat limb deformity	43
	Antiviral agent	Tenofovir	—	Lower bone mineral content in human newborn	44
	NSAID	Indomethacin	10^{-5} mol/L for 24 h	Proliferation suppression and increased cell death of fetal rat chondrocytes	45
		Ketorolac	10^{-5} mol/L for 24 h	Proliferation suppression and increased cell death of fetal rat chondrocytes	45
		Diclofenac	10^{-5} mol/L for 24 h	Proliferation suppression and increased cell death of fetal rat chondrocytes	45
		Piroxicam	10^{-5} mol/L for 24 h	Proliferation suppression and increased cell death of fetal rat chondrocytes	45
	Synthetic estrogen	Diethylstilbestrol	10 μg/kg·day, GD9−16, s.c.	Shorter femurs in female offspring mice	46
Gonad	NSAID	Indomethacin	10 μmol/L for 24 h	Decreased testosterone secretion in fetal rat testes	47
		Ibuprofen	10^{-5} mol/L for 72 h/10 μmol/L for 7 days	Decreased testosterone production in human fetal testes/Increased cell apoptosis and necrosis in human fetal ovaries	48,49
	Antipyretic-analgesic drug	Acetaminophen	60 mg/kg·day for 7 days, *p.o.*/ 10 μmol/L for 7 days	Decreased testosterone production in human fetal testis xenografts/Reduced germ cells in human fetal ovaries	50,51

(*continued on next page*)

Table 1 (*continued*)

Organ	Drug type	Drug name	Dosage regimen	Developmental toxicity manifestation	Ref.
	Synthetic glucocorticoids	Dexamethasone	0.2 mg/kg·day, GD9−20, s.c./ 0.5 mg/kg·day, GD16−18, s.c.	Abnormal morphology and decreased testosterone production of offspring rats/Decreased volume and increased germ cell apoptosis of fetal rat ovaries	52,53
	Synthetic estrogen	Diethylstilbestrol	—/100 μg/kg·day, GD9−16, s.c.	Cryptorchidism in human offspring/Ovarian malformation in offspring mice	54,55
	Hypoglycemic agent	Metformin	500 μmol/L for 72 h	Reduced testosterone secretion in human fetal testes	56

GD, gestational day; i.p., intraperitoneal injection; i.g., intragastrically; hpf, hours post-fertilization; s.c., subcutaneous injection; *p.o.*, orally; NSAID, non-steroidal anti-inflammatory drug; i.v., intravenous injection.

Table 2 Multi-organ developmental toxicities of a single drug.

Drug name	Organ	Dosage regimen	Developmental toxicity manifestation	Ref.
Dexamethasone	Liver	—	Reduced functional maturity of human offspring liver	20
	Hippocampus	0.2 mg/kg·day, GD9−20, s.c.	Decreased proliferation and increased apoptosis of fetal rat hippocampal cells and cognitive impairment	37
	Bone/Cartilage	0.8 mg/kg·day, GD12−14, s.c.	Bone and cartilage growth retardation in mice	38,39
	Testis	0.2 mg/kg·day, GD9−20, s.c.	Abnormal morphology and decreased testosterone production of male offspring rats	52
	Ovary	0.5 mg/kg·day, GD16−18, s.c.	Decreased volume and increased germ cell apoptosis of fetal rat ovaries	53
	Kidney	125 μg/kg·day, GD20−23, s.c.	Reduced nephron number in fetal spiny mice	57
	Heart	0.1 mg/kg·day, GD12−15, s.c.	Impaired cardiac diastolic function in fetal rats	58
	Adrenal gland	8 mg/kg·day, GD12−18, s.c.	Decreased synthesis of cortisol in fetal mouse adrenal	59
Betamethasone	Liver	0.1 mg/day, GD14, s.c.	Liver growth retardation in mice	16
	Kidney	0.17 mg/kg·day, GD80−81, i.m.	Decrease of nephrons and glomerular filtration rate of sheep offspring	60
	Adrenal gland	—	Decreased adrenal volume in human infants	61
Diethylstilbestrol	Bone	10 μg/kg·day, GD11−14, s.c.	Reduced bone mineral content in male offspring mice	62
	Testis	—	Cryptorchidism and epididymal cyst in human male offspring	54
	Ovary	100 μg/kg·day, GD9−16, s.c.	Ovarian malformation in female offspring mice	55
	Prostate	0.02 μg/kg·day, GD13−18, s.c.	Prostate enlargement in offspring mice	63
Metformin	Liver	250 mg/kg·day, GD0−18, *p.o.*	Abnormal differentiation and glucose metabolism of fetal mouse liver	18
	Testis	500 μmol/L for 72 h	Reduced testosterone secretion in human fetal testes	56
	Pancreas	100 μmol/L for 35 days	Abnormal pancreatic differentiation from human embryonic stem cells	64
Acetaminophen	Liver	250 mg/kg·day, GD12, i.p.	Declined hematopoietic stem cell frequency in fetal mouse liver	21
	Testis	60 mg/kg·day for 7 days, *p.o.*	Decreased testosterone production in human fetal testes	50
	Ovary	10 μmol/L for 7 days	Reduced germ cells in human fetal ovaries	51
	Airway	250 mg/kg·day, GD12, i.p.	Airway inflammation in mouse offspring	21

Table 2 (*continued*)

Drug name	Organ	Dosage regimen	Developmental toxicity manifestation	Ref.
Indomethacin	Liver	13.97 μmol/L, 24−168 hpf	Decreased proliferation of zebrafish embryo hepatocytes	19
	Cartilage	10^{-5} mol/L for 24 h	Proliferation suppression and increased cell death of fetal rat chondrocytes	45
	Testis	10 μmol/L for 24 h	Decreased testosterone secretion in fetal rat testes	47
Diclofenac	Cartilage	10^{-5} mol/L for 24 h	Proliferation suppression and increased cell death of fetal rat chondrocytes	45
	Artery	10 mg/kg, once, i.v.	Ductus arteriosus constriction and pulmonary hypertension in fetal rats	65
Phenobarbital	Liver	—	Reduced functional maturity of human offspring liver	20
	Adrenal gland	250 μmol/L for 24 h	Decreased synthesis of cortisol, aldosterone, and progesterone in human fetal adrenal cortical cells	66
Xiaoaiping	Liver	0.4 mg/mL, 6−120 hpf	Loose cell-to-cell contacts of zebrafish embryo hepatocytes	25
	Heart	0.8 mg/mL, 6−120 hpf	Thinner heart walls and pericardial edema in zebrafish embryos	25
Psoralen	Liver	3.54 μmol/L, 4−96 hpf	Reduced liver area of zebrafish embryos	26
	Heart	3.54 μmol/L, 4−72 hpf	Increased pericardial area of zebrafish embryos	26

GD, gestational day; s.c., subcutaneous injection; i.m., intramuscular injection; *p.o.*, orally; i.p., intraperitoneal injection; hpf, hours post-fertilization; i.v., intravenous injection.

2.2. *Direct mechanisms of multi-organ developmental toxicity in offspring induced by medication during pregnancy*

Drug molecules in maternal blood can be transferred across the placenta through passive diffusion, carrier-mediated transport, and endocytosis pathways. To some extent, almost all drugs can enter the fetal circulation across the placenta in one of these ways[70] and then directly act on various fetal organs and affect their development. There are diverse direct mechanisms of organ development toxicity of drugs, mainly including oxidative stress injury, abnormal epigenetic modification, and metabolic activation.

2.2.1. *Oxidative stress injury*

There are both oxidation and antioxidant systems in the body. The oxidation system principally includes reactive oxygen species (ROS) and other active substances, while the antioxidant system includes superoxide dismutase (SOD), glutathione peroxidase, catalase, and reduced glutathione[71]. Oxidative stress refers to the pathological process where ROS production and the antioxidant defense in the body are out of balance under adverse conditions, which results in oxidative damage to tissues and cells. Exogenous substances can increase ROS production in the fetus and interfere with the key signals of organogenesis, thereby affecting the development of fetal organs[72]. The organ development toxicity of some drugs is closely related to oxidative stress. For example, the use of erythromycin during pregnancy can significantly increase the level of malondialdehyde (MDA) and decrease the level of reduced glutathione in offspring mouse liver, which suggests the occurrence of oxidative stress injury[10]; the use of ketamine during pregnancy can increase the autophagy rate and apoptosis rate of the fetal mouse hippocampus, which may be associated with the inhibition of antioxidant defense and excessive accumulation of ROS[73]. Zebrafish is a popular alternative animal model for drug toxicology research, and the organ development toxicity of many drugs mediated by oxidative stress has been proved in this model. The pathological lesion of zebrafish embryonic hepatic tissue caused by exposure to triclosan, Xiaoaiping, psoralen, and isoniazid is accompanied by increased production of ROS and MDA and decreased SOD activity[13,14,25,26]. In zebrafish embryos exposed to aconitine, the level of ROS increases in a dose-dependent manner, while the activity of SOD decreases, which leads to malformations and abnormal cardiac and hepatic structures of zebrafish offspring[27]. Exposure to acetyl-11-keto-beta-boswellic acid, a Chinese herbal medicine component, increases MDA levels in a dose-dependent manner and reduces catalase and glutathione peroxidase activities in zebrafish larvae, leading to their decreased heart rate and cardiac structural abnormalities such as pericardial edema[74]. In summary, oxidative stress injury is an important mechanism for the organ development toxicity of many drugs, mainly including Chinese herbal medicines such as Xiaoaiping, psoralen, aconitine, and acetyl-11-keto-beta-boswellic acid.

2.2.2. *Abnormal epigenetic modification*

Epigenetics refers to changes in phenotype without a change in DNA sequence. During intrauterine physiological development, epigenetic modification is vital for cell differentiation and organ development[75]. However, medication during pregnancy may lead to abnormal epigenetic modification in the fetus and thus damage fetal organ development.

DNA methylation and histone acetylation are important forms of epigenetic modification, and their level changes can mediate the impairment of organ function in offspring induced by medication during pregnancy. For example, prenatal cocaine exposure can promote the expression of DNA methyltransferase, increase the methylation levels of insulin-like growth factor 2 promoter region,

and inhibit its expression in the offspring mouse hippocampus, which results in cognitive defects in offspring mice[32]. The organ development toxicity of dexamethasone is related to abnormal histone modification. Prenatal dexamethasone exposure (PDE) can enhance the expression of histone deacetylase (HDAC) 2 and reduce the histone H3 lysine 14 acetylation (H3K14ac) level of brain-derived neurotrophic factor and its expression in the fetal rat hippocampus, which weakens the memory ability of offspring rats[76]. PDE can also increase the expression of HDAC7 and then reduce the histone H3 lysine 9 acetylation (H3K9ac) level of the promoter region of steroidogenic acute regulatory protein and its expression in fetal rat testes, which impairs testosterone production in offspring rats[52]. In addition, prenatal betamethasone exposure can lead to abnormal DNA methylation and H3K9ac in the promoter region of specific genes in the hippocampus of fetal guinea pigs and affect the expression of these genes[77], which may damage the hippocampal function of offspring guinea pigs.

Non-coding RNA is widely involved in embryonic development, and medication during pregnancy can also affect fetal post-transcriptional gene expression and organ function by targeting specific non-coding RNA. For example, exposure to metformin during pregnancy can promote the expression of H19 long-chain non-coding RNA and cause the hypomethylation and high expression of hepatocyte nuclear factor 4 α in fetal mice, leading to the activation of the gluconeogenetic program and abnormal glucose metabolism function of fetal mouse liver[78]. PDE can promote the expression of miRNA-134-5p and inhibit the expression of sex determining region Y-box 2 in the fetal rat hippocampus, which contributes to depressive behavior in offspring rats[79]. Furthermore, the hepatotoxic effect of triptolide on zebrafish larvae is accompanied by a decrease in the expression of miRNA-122[24].

In brief, medication during pregnancy can lead to changes in DNA methylation and histone acetylation levels of particular gene promoter regions and changes in specific non-coding RNA in offspring organs, which affect the development of the corresponding organs.

2.2.3. *Metabolic activation*

Metabolic activation refers to the biotransformation process of transforming drugs or other foreign substances from non-toxic or low toxic substances to highly toxic metabolites. The metabolic activation of drugs requires specific enzymes, and cytochrome P450 (CYP) plays a significant role in fetal drug metabolism. For instance, CYP3A7 is the primary enzyme for glyburide and oxycodone metabolism in the fetal liver[80,81]. Drugs are transformed into corresponding active metabolites by CYP in the fetus, which can act on organ tissues and cause organ toxicity. Cyclophosphamide is metabolized into 4-hydroxycyclophosphamide, phosphoramide mustard, and acrolein by CYP, and these metabolites have been proven toxic to bone development, which can cause hypoplasia of radius, ulna, and tibia[42]. Both monocrotaline and retrorsine are pyrrolizidine alkaloids found in Chinese herbal medicine, and the dihydropyrrole transformed from pyrrolizidine alkaloids by CYP can result in hepatocyte injury in mice[82]. Further studies have found that exposure to monocrotaline and retrorsine during pregnancy can promote the expression of hepatic CYP3A in female fetal rats by activating the pregnane X receptor, which increases the production of toxic metabolites and causes hepatotoxicity[22,23]. Moreover, the expression of CYP and other metabolism-related genes is abnormal in zebrafish larvae exposed to indomethacin, and their weight, tail length, deformity rate and edema rate are noticeably correlated with these gene expressions, which suggests that metabolic activation plays an essential role in the developmental toxicity of indomethacin[19]. However, the relationship between the developmental toxicity of indomethacin to specific organs and metabolic activation remains to be further explored.

Additionally, single nucleotide variation and copy number variation of CYP genes are the main factors leading to the inter-individual differences in drug toxicity[83]. Genetic variations in CYP can alter fetal drug exposure levels[84], which may be the inducement of interindividual variability in drug-induced developmental toxicity. For example, a clinical study has found that the risk of intrauterine growth retardation (IUGR) due to prenatal alcohol exposure is associated with CYP genetic polymorphisms[85]. There is also interindividual variability in the organ development toxicity of offspring caused by medication during pregnancy[86]. Therefore, CYP genetic polymorphisms are potentially a critical factor of interindividual variability in drug-induced organ developmental toxicity.

In conclusion, the drug metabolic activation in the fetus primarily mediated by CYP can affect the fetus's particular organ development, and interindividual differences in drug-induced organ developmental toxicity may be related to CYP genetic polymorphisms.

2.3. *Placental mechanism of multi-organ developmental toxicity in offspring induced by medication during pregnancy (the indirect mechanism)*

As a special organ for the communication between the fetus and the mother, the placenta has the functions of material transport, endocrine, and barrier, which are essential for fetal survival and development[87]. The impaired placental function can lead to IUGR[88], and IUGR individuals exhibit multiple organ dysplasia[89]. It has been shown that some drugs may indirectly induce multi-organ developmental toxicity by affecting the functional development of the placenta.

The placenta participates in exchanging hormones, nutrients, and metabolic wastes between the mother and the fetus. Studies have found that various drugs with organ development toxicity can affect placental transport function. For instance, dexamethasone can inhibit the expression of placental cholesterol transporters by down-regulating liver X receptor α in the rat placenta[90]; acetaminophen can inhibit the expression of thyroxine transporter and transferrin in the rat placenta, and can also affect the placental permeability of sucrose[91]; metformin can inhibit the uptake of folate and glucose in human placental cells[92]. Additionally, phenytoin and carbamazepine can also affect the folate uptake in human placental cells[93], and they can simultaneously affect the hippocampal development that requires folate[35,36,94].

The placenta is a highly active endocrine organ that secretes various hormones regulating fetal development. Using drugs during pregnancy may affect the endocrine function of the placenta. For example, estradiol is crucial for the development of fetal reproductive organs, and acetaminophen can inhibit estradiol secretion in human placental cells, which suggests that prenatal acetaminophen exposure may affect gonad development by inhibiting placental estradiol secretion[95].

The barrier function of the placenta creates an independent developmental environment for the fetus, and efflux is an integral part of this function. Breast cancer resistance protein and multi-drug resistance protein (MDR) are efflux transporters highly

expressed in the placenta[96], and their expression can be affected by drugs. For example, acetaminophen can inhibit the expression of breast cancer resistance protein in rat placenta[97]; valproic acid can reduce the expression of MDR1b in rat placenta but can increase that of MDR1a[98].

In summary, some drugs can affect placental material transport, endocrine, and barrier functions, and abnormal placental function may be an important factor for these drugs to affect fetal organ development.

3. Maternal-derived glucocorticoids and multi-organ developmental programming of offspring induced by medication during pregnancy

The permanent changes of fetal structure and function to adapt to the changes of the uterine environment are called early life programming. The change of intrauterine maternal-derived glucocorticoid level is an essential factor to induce this programming[99,100]. Appropriate glucocorticoid level *in utero* is of paramount importance for fetal development[101]. However, the adverse environment during pregnancy can cause the fetus to be exposed to abnormal levels of maternal-derived glucocorticoids, leading to abnormal fetal development[102]. As a kind of prenatal adverse environment, medication during pregnancy may indirectly change the multi-organ developmental programming of offspring through intrauterine maternal-derived glucocorticoids.

3.1. Abnormal maternal-derived glucocorticoid exposure induced by medication during pregnancy and the mechanisms

It is known that glucocorticoids in fetal circulation are mainly derived from the mother. The maternal glucocorticoid level during pregnancy is much higher than that of the fetus, which suggests that there must be a glucocorticoid barrier between the mother and the fetus[103]. The change in the maternal glucocorticoid level or the destruction of the placental glucocorticoid barrier can lead to abnormal maternal-derived glucocorticoid levels in the fetus. A clinical study has found that cord blood cortisol concentrations in newborns of appropriate gestational age range from 4.7 to 15.4 μg/dL. When the fetal blood cortisol level is significantly higher and lower than this range, it respectively represents "overexposure" and "low exposure" to maternal-derived glucocorticoids. Fetal physiological glucocorticoid levels are different in different species[104]. Some drugs used during pregnancy have been shown to expose the fetus to too high or too low concentrations of maternal-derived glucocorticoids *in utero*.

Drugs can cause fetal overexposure to maternal-derived glucocorticoids by destroying the placental glucocorticoid barrier. 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) is one of the critical factors that constitute the placental glucocorticoid barrier. 11β-HSD2 is expressed in the syncytial layer of the placental villi, which is capable of converting biologically active cortisol into inactive cortisone so as to protect the fetus from the influence of the high maternal-derived glucocorticoid level. Adverse conditions during pregnancy such as hypoxia and nutritional restriction can affect the expression of placental 11β-HSD2[105], and the inhibitory effect of many drugs on the expression of 11β-HSD2 has also been proved. Studies have found that carbenoxolone, nicotine, caffeine, triclosan, and diethylstilbestrol can inhibit the activity of 11β-HSD2 in the placenta, which destroys the placental glucocorticoid barrier and causes fetal overexposure to maternal-derived glucocorticoids *in utero*[106–110]. Moreover, bortezomib, licorice, itraconazole, and posaconazole are all inhibitors of 11β-HSD2[111,112], which may also damage the placental glucocorticoid barrier. P-glycoprotein is also a critical component of the placental glucocorticoid barrier. As an efflux transporter highly expressed in the placenta, P-glycoprotein can reverse the concentration gradient to expel glucocorticoids from the fetus back to the mother, thereby reducing the level of maternal-derived glucocorticoids in the fetus[113]. Cannabidiol, ethanol, and opioid drugs methadone and buprenorphine can inhibit the efflux function of P-glycoprotein in the placenta, thus destroying the placental glucocorticoid barrier[114–116]. Additionally, mefloquine, primaquine, and antidepressants fluoxetine, clomipramine, paroxetine, and venlafaxine can also inhibit P-glycoprotein[117–119], which may induce fetal overexposure to maternal-derived glucocorticoids.

In addition, drugs can also lead to fetal low exposure to maternal-derived glucocorticoids by reducing the level of glucocorticoids in the mother. A study has found that the use of dexamethasone during pregnancy can significantly reduce the level of cortisol in neonatal cord blood; the animal experiment has confirmed that PDE can inhibit maternal adrenal steroid synthesis, which decreases the glucocorticoid level in the mother and the level of maternal-derived glucocorticoids in the fetus[120]. In addition, prenatal metyrapone exposure can also inhibit maternal steroid synthesis and thus reduce fetal maternal-derived glucocorticoid level with decreased placental glucocorticoid receptor (GR) expression[121].

3.2. Overexposure to maternal-derived glucocorticoids and multi-organ developmental programming alterations in offspring

Prenatal exposure to drugs such as caffeine and nicotine and the drug solvent ethanol can indirectly change the developmental programming of offspring's multiple organs (such as adrenal glands, liver, hippocampus, and bones) through high maternal-derived glucocorticoids.

3.2.1. Adrenal developmental programming alterations

As an organ for synthesizing and secreting steroids, the functional development of the adrenal gland is of significant importance for individual health. Prenatal exposure to excessively high levels of glucocorticoids can disrupt the homeostasis of offspring's adrenal function after birth, leading to offspring getting prone to diseases in adolescence and adulthood[122]. Medication during pregnancy is an important inducement of fetal adrenal overexposure to maternal-derived glucocorticoids. For example, prenatal nicotine exposure (PNE) can induce fetal intrauterine overexposure to maternal-derived glucocorticoids, which can inhibit the expression of adrenal steroid synthase in fetal rats[107]. The abnormal adrenal function of offspring rats caused by prenatal caffeine exposure (PCE) and prenatal ethanol exposure (PEE) involves "two programming". On the one hand, intrauterine overexposure to maternal-derived glucocorticoids induced by PCE and PEE can inhibit the expression of adrenal steroid synthase in fetal rats, and this effect can continue after birth; on the other hand, maternal-derived glucocorticoids with a high concentration *in utero* can down-regulate insulin-like growth factor 1 (IGF1) and inhibit steroidogenesis in fetal rat adrenal glands, while the level of IGF1 increases in offspring rats separated from intrauterine high glucocorticoid environment after birth, which can induce their catch-up growth and adrenal steroidogenesis to tend to be normal[108,123]. A further study has shown that the adrenal steroid

secretion in the PCE offspring rats is enhanced under chronic stress after birth, and thus the level of glucocorticoids in blood increases, which weakens the adrenal steroidogenic function by inhibiting the IGF1 signaling pathway in a negative-feedback way[124]. In summary, intrauterine overexposure to maternal-derived glucocorticoids caused by medication during pregnancy can affect the developmental programming of offspring's adrenal steroidogenesis function.

3.2.2. *Hepatic developmental programming alterations*

The development of hepatic lipid metabolism function is vital to maintain lipid homeostasis. Abnormal hepatic triglyceride and cholesterol metabolism can respectively lead to non-alcoholic fatty liver disease (NAFLD) and hypercholesterolemia. Intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy can result in alterations in hepatic lipid metabolic function programming in offspring and susceptibilities to related metabolic diseases. PCE and PEE can cause offspring rats to be susceptible to NAFLD, closely related to the "two-programming" mechanism. Intrauterine overexposure to maternal-derived glucocorticoids induced by PCE can up-regulate GR/CCAAT enhancer binding protein α signal and thus down-regulate the expression of silent information regulator 1 in the fetal rat liver, which enhances the triglyceride synthesis; intrauterine overexposure to maternal-derived glucocorticoids induced by PEE can increase hepatic lipid synthesis and reduce lipid output in fetal rats. The changes mentioned above in hepatic triglyceride metabolism can continue after birth, which is the "first programming"[125,126]. PCE and PEE can also affect the development of the "glucocorticoid−insulin-like growth factor 1 (GC−IGF1) axis" in the offspring rat liver. After offspring rats are separated from the intrauterine high glucocorticoid environment after birth, the up-regulation of IGF1 can aggravate the lipid metabolic disorder under the condition of high-fat diet, which is the "second programming"[126,127]. PNE can promote the expression of phosphatidylinositol 3-kinase in offspring mouse liver, resulting in lipid metabolic disorder, insulin resistance, and NAFLD[128], while glucocorticoids can induce phosphatidylinositol 3-kinase-related insulin resistance through GR[129], which suggests that NAFLD in the offspring mice may be related to intrauterine overexposure to maternal-derived glucocorticoids induced by PNE. Furthermore, PNE can also induce susceptibility to hypercholesterolemia in postnatal offspring rats through "two programming". On the one hand, intrauterine overexposure to maternal-derived glucocorticoids induced by PNE inhibits reverse cholesterol transport in the fetal rat liver, and this effect can continue after birth. On the other hand, PNE can induce the "GC−IGF1 axis" developmental programming, and the up-regulation of IGF1 in postnatal offspring rats with low serum glucocorticoid levels can promote cholesterol synthesis[130]. In conclusion, intrauterine overexposure to maternal-derived glucocorticoids caused by medication during pregnancy can affect the developmental programming of hepatic lipid metabolism in offspring and make the offspring susceptible to NAFLD and hypercholesterolemia after birth.

3.2.3. *Hippocampal developmental programming alterations*

Hippocampus is a central organ that regulates cognition, emotions, and other high-level neurological and spiritual activities, whose dysfunction can lead to memory and emotional disorders. Intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy can lead to hippocampal developmental programming alterations and induce related neuropsychiatric diseases in offspring after birth. An epidemiological study has shown that after pregnant women consume a large amount of licorice, a kind of 11β-HSD2 inhibitors, their offspring may be exposed to more glucocorticoids *in utero* and show a decline in cognitive abilities such as memory after birth[131], which suggests that prenatal licorice exposure may impair hippocampal functional development by inducing intrauterine overexposure to maternal-derived glucocorticoids. In addition, high maternal-derived glucocorticoids can attenuate the negative regulation of offspring's hippocampus on the hypothalamus−pituitary−adrenal (HPA) axis. Nerve fibers from the hippocampus participate in the input of glutamate signals in the hypothalamic paraventricular nucleus-projecting area and form a glutamate-γ-aminobutyric acid synaptic connection in this area, which negatively regulates the neuronal activity of the hypothalamic paraventricular nucleus[132]. Intrauterine overexposure to maternal-derived glucocorticoids induced by PEE can up-regulate hippocampal glutamate decarboxylase 67 in offspring rats and promote the transformation of glutamate to glutamate-γ-aminobutyric acid, which weakens the hippocampal negative regulation on the HPA axis and increases the potential hypothalamic excitability. This change can continue after birth and lead to the hypersensitivity of offspring rats' HPA axis[133]. A further study has found that the susceptibility to depression in offspring rats caused by PEE is related to the hypersensitivity of the HPA axis mediated by intrauterine maternal-derived glucocorticoids[134]. Moreover, prenatal opiate L-α-acetylmethadol exposure can enhance the HPA axis reactivity to stressors and increase the anxiety behavior of adult offspring rats[135]. Meanwhile, some opiates have been shown to inhibit the efflux function of placental P-glycoprotein[116], which suggests that high maternal-derived glucocorticoids may be involved in offspring's hypersensitivity of the HPA axis induced by prenatal opiate exposure. In brief, intrauterine overexposure to maternal-derived glucocorticoids caused by medication during pregnancy can affect the developmental programming of offspring's hippocampal cognitive function and induce offspring to suffer from mental illnesses related to hypersensitivity of the HPA axis.

3.2.4. *Bone and cartilage developmental programming alterations*

Bone and cartilage are the peripheral organs that support and protect the body. Intrauterine overexposure to maternal-derived glucocorticoids caused by medication during pregnancy can affect bone and cartilage development. For instance, high maternal-derived glucocorticoids *in utero* induced by PCE can activate the local renin angiotensin system in fetal rat bones, resulting in bone growth retardation and adult bone loss in offspring rats[136]; intrauterine overexposure to maternal-derived glucocorticoids caused by PNE can inhibit endochondral ossification in long bones of fetal rats[137]. Further studies have found that bone and cartilage diseases have fetal developmental origin related to maternal-derived glucocorticoids. *In utero,* overexposure to maternal-derived glucocorticoids induced by PCE can inhibit IGF1/glucose transporter 1 signal and hinder the cartilage matrix synthesis in articular cartilages of fetal rats; after birth, the up-regulation of IGF1/glucose transporter 1 separated from the high glucocorticoid environment can enhance the cartilage matrix degradation. The intrauterine and postnatal effects make adult offspring rats susceptible to osteoarthritis[138]. Meanwhile, osteoarthritis is associated with cholesterol accumulation in the cartilage[139], and the susceptibility to osteoarthritis in offspring rats induced by PNE involves cholesterol-related "two programming". On the one hand, intrauterine overexposure to

maternal-derived glucocorticoids down-regulates the expression of fetal cartilage IGF1 and leads to the obstruction of cholesterol outflow from articular cartilages, which can continue after birth; on the other hand, hypercholesterolemia mediated by the hepatic "GC−IGF1 axis" programming increases the source of cholesterol in articular cartilages[140]. In addition, intrauterine overexposure to maternal-derived glucocorticoids caused by PCE can decrease the expression of IGF1 in fetal rat osteoblasts, thereby inhibiting osteoblast differentiation. However, the up-regulation of IGF1 in offspring rats after birth is not enough to completely recover the osteogenic differentiation disorder, which contributes to their susceptibility to osteoporosis[141]. In conclusion, intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy can inhibit the development of bone and cartilage in offspring and cause them to be susceptible to osteoarthritis and osteoporosis.

3.2.5. *Developmental programming alterations of other organs*

Intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy can also affect the development of offspring's gonads, kidneys, and pancreas.

The intrauterine period is critical for gonadal development. High maternal-derived glucocorticoids *in utero* induced by medication during pregnancy can lead to testicular and ovarian developmental programming alterations, mainly manifested as testosterone and estradiol production inhibition. Intrauterine overexposure to maternal-derived glucocorticoids induced by PEE can inhibit the expression of steroidogenic factor 1 in offspring rat testis by activating GR and promote the expression of HDAC2, thereby reducing the H3K14ac level of 3β-hydroxysteroid dehydrogenase and its expression. The low expression of 3β-hydroxysteroid dehydrogenase can continue after birth, contributing to decreased testosterone production in offspring rats[142]. The developmental programming alterations of testicular and ovarian functions in offspring rats induced by PCE are related to the "GC−IGF1 axis". *In utero*, intrauterine overexposure to maternal-derived glucocorticoids induced by PCE can down-regulate IGF1 in the testis/ovary of offspring rats, resulting in the inhibition of the testosterone/estradiol production; after birth, the production of testosterone/estradiol increases in offspring rats with enhanced expression of IGF1 in testis/ovary; in adulthood, the blood glucocorticoid level of offspring rats rises under chronic stress, and the production of testosterone/estradiol is suppressed again[143,144].

Renal and pancreatic developmental programming is also susceptible to the high level of maternal-derived glucocorticoids. Intrauterine overexposure to maternal-derived glucocorticoids induced by PCE can result in low expression programming of angiotensin type two receptor and alterations in the "GC−IGF1 axis" programming in offspring rat kidneys, which respectively lead to the susceptibility of male and female offspring to glomerulosclerosis[145]. Alterations in the "GC−IGF1 axis" programming caused by PEE can lead to pancreas dysplasia and impaired insulin biosynthesis in offspring rats before and after birth, and offspring rats show age-characteristic changes in insulin sensitivity after birth, namely, insulin hypersensitivity in early life and insulin resistance in late life[146].

3.3. *Multi-organ "two-programming" mechanism mediated by overexposure to maternal-derived glucocorticoids*

The destruction of the placental glucocorticoid barrier and intrauterine high maternal-derived glucocorticoids induced by medication during pregnancy can affect the development of multiple fetal organs *in utero*, and multi-organ functional abnormalities of offspring before and after birth are often related to the "two-programming" mechanism mediated by high maternal-derived glucocorticoids.

The "first programming" is "thrifty phenotype" programming. That is, intrauterine overexposure to maternal-derived glucocorticoids caused by medication during pregnancy can enhance the function of key organs and weaken that of secondary organs in fetuses, and this differential change can last until after birth. Studies have confirmed that intrauterine high maternal-derived glucocorticoids can inhibit adrenal steroidogenesis, osteoblast differentiation, pancreatic insulin production, and gonadal testosterone/estradiol production in offspring before and after birth[108,141,142,144,146], while can promote hepatic triglyceride synthesis[125]. These differential and persistent changes attest to the hypothesis of "thrifty phenotype" development. Based on this hypothesis, to maintain survival and development in an adverse intrauterine environment, the fetus will change its metabolic process, redistribute limited energy, and limit the energy consumption of secondary organs, which ensures the development of key organs. The impact of this adaptive change on organ function will last for a long time or even be permanent[147]. Therefore, medication during pregnancy creates an adverse environment of intrauterine high maternal-derived glucocorticoids, in which the development of multiple organs shows plasticity.

The "second programming" is "GC−IGF1 axis" programming. That is, intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy can cause glucocorticoid-dependent changes in IGF1 expression and multi-organ function of offspring before and after birth. IGF1 is known to play an essential role in the development of multiple organs[148−150], and it is also a critical factor in inducing catch-up growth of IUGR offspring after birth[151]. After intrauterine overexposure to maternal-derived glucocorticoids, the glucocorticoid and IGF1 levels in offspring show reverse changes. *In utero,* the overexposure to maternal-derived glucocorticoids caused by medication during pregnancy can down-regulate IGF1 in fetal organs, thereby inhibiting the function of corresponding organs. However, after birth, the expression of IGF1 increases in offspring organs separated from the intrauterine high glucocorticoid environment, which enhances the function of corresponding organs[108,123]. Under the "GC−IGF1 axis" developmental programming, the offspring's organ functions show compensatory developmental changes before and after birth.

In summary, "thrifty phenotype" and "GC−IGF1 axis" jointly shape the multi-organ developmental programming mediated by intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy (Fig. 1). The "thrifty phenotype" programming has organ characteristics, which is persistent and can last for a lifetime, while the "GC−IGF1 axis" programming is multi-organ commonality and shows compensatory changes.

3.4. *Low exposure to maternal-derived glucocorticoids and multi-organ developmental programming alterations in offspring*

There are few studies on the alterations in multi-organ developmental programming mediated by intrauterine low exposure to maternal-derived glucocorticoids induced by medication during pregnancy. At present, only synthetic glucocorticoid drugs have related research reports. A clinical study has found that PDE can

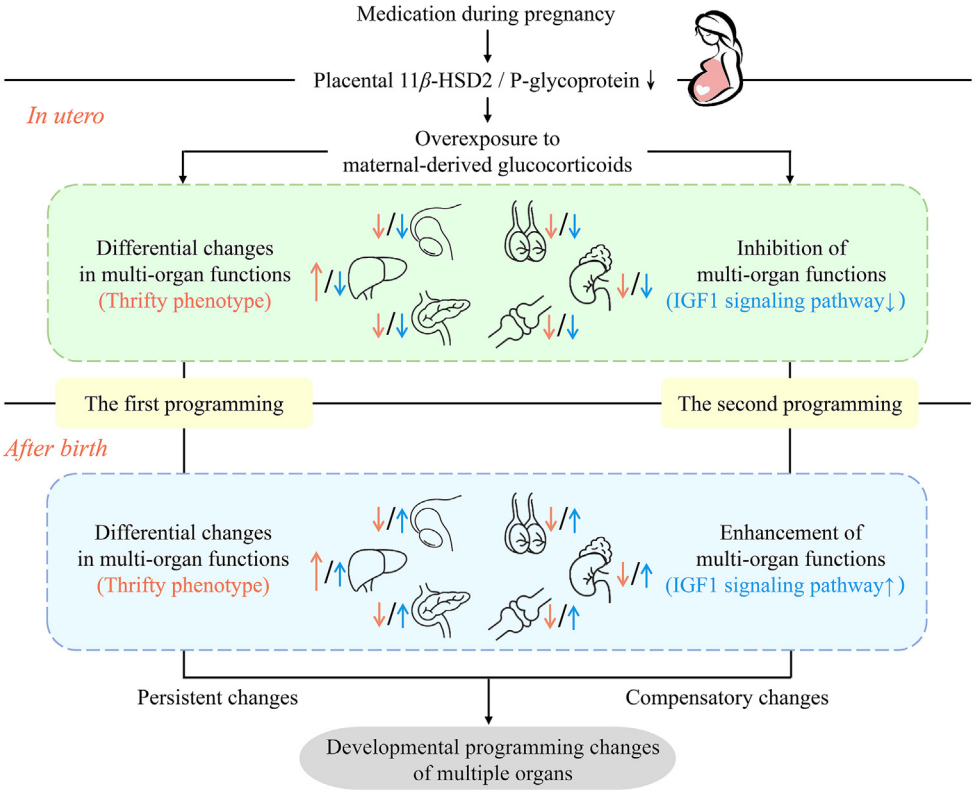

Figure 1 "Two-programming" mechanism mediated by overexposure to maternal-derived glucocorticoids. Drugs can cause fetal overexposure to maternal-derived glucocorticoids by inhibiting the placental 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) or P-glycoprotein. "Thrifty phenotype" and "glucocorticoid−insulin-like growth factor 1 (GC−IGF1) axis" jointly shape the multi-organ developmental programming mediated by intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy. The "thrifty phenotype" programming has organ characteristics, which is persistent and can last for a lifetime, while the "GC−IGF1 axis" programming is multi-organ commonality and shows compensatory changes.

lead to neonatal subclinical adrenal insufficiency[152]. The latest study reveals the relationship between fetal adrenal dysfunction and intrauterine low exposure to maternal-derived glucocorticoids induced by PDE. Low maternal-derived glucocorticoid level *in utero* caused by PDE can increase the adrenal expression of silent information regulator 3 by down-regulating miRNA-370-3p, which leads to the histone H3 lysine 27 acetylation level and expression of IGF1 decrease, thus weakening the function of adrenal steroidogenesis in offspring rats[120]. According to another clinical study, long-term use of methylprednisolone (a synthetic glucocorticoid drug) during pregnancy can also inhibit the adrenal steroidogenesis of neonates[153], and it is worth exploring whether its mechanism is also related to low exposure to maternal-derived glucocorticoids. Additionally, PDE can result in abnormal testicular function in offspring by inducing intrauterine low exposure to maternal-derived glucocorticoids. It has been found that the low glucocorticoid environment induced by PDE inhibits the miRNA-124-3p expression and thus up-regulates HDAC5, which reduces the H3K14ac level of IGF1 in fetal rat testis and its expression. The above effect can continue after birth and reduce testosterone synthesis in offspring rats. Under chronic stress after birth, the level of blood glucocorticoid in PDE offspring rats increases, so the expression of IGF1 and testosterone synthesis are also enhanced[154]. The above-mentioned studies suggest that after intrauterine low exposure to maternal-derived glucocorticoids, glucocorticoids and IGF1 in offspring change in the same direction ("positive" programming of GC−IGF1 axis), which is different from the context of intrauterine overexposure to maternal-derived glucocorticoids where glucocorticoids and IGF1 in offspring change in reverse direction ("negative" programming of GC−IGF1 axis) (Fig. 2).

4. Gender differences in organ development toxicity and programming alterations caused by medication during pregnancy

Gender is an important variable in the field of "DOHaD." Studies have found gender differences in the incidence of adverse pregnancy outcomes and the severity of chronic diseases in offspring after adverse prenatal exposure[155,156]. Medication during pregnancy may also sex-specifically affect the development and functional homeostasis of multiple organs in offspring. For example, the fetal hepatic toxicity induced by prenatal monocrotaline exposure is more significant in female offspring rats[22]. Prenatal betamethasone exposure can sex-specifically enhance the susceptibility of male offspring sheep kidneys to angiotensin II-induced oxidative stress, which is manifested by increased urinary excretion of 8-isoprostane and protein in male offspring[157]. The use of psychostimulant drugs during pregnancy impairs cognitive function more obviously in male offspring. For example, prenatal cocaine exposure can more significantly affect the memory ability of male offspring[158]. The

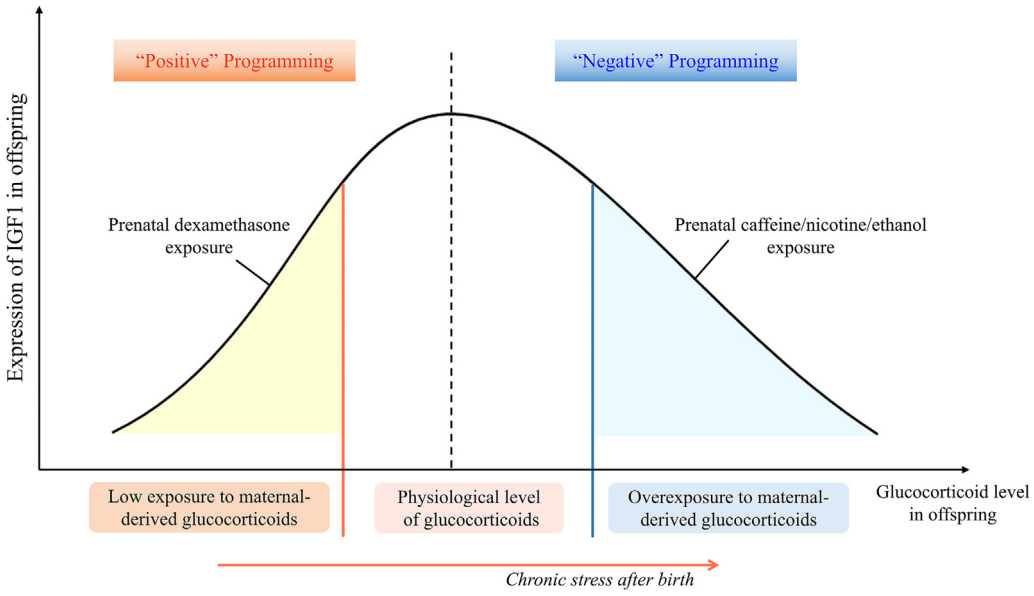

Figure 2 The "positive" and "negative" programming of glucocorticoid-insulin-like growth factor 1 (GC−IGF1) axis in offspring induced by intrauterine abnormal exposure to maternal-derived glucocorticoids: After intrauterine low exposure to maternal-derived glucocorticoids, glucocorticoids and IGF1 in offspring change in the same direction ("positive" programming of GC−IGF1 axis), which is different from the context of intrauterine overexposure to maternal-derived glucocorticoids where glucocorticoids and IGF1 in offspring change in reverse direction ("negative" programming of GC−IGF1 axis).

hippocampus is the key organ for memory function, suggesting that cocaine use during pregnancy may gender-specifically affect the development of hippocampal function in offspring. Interestingly, PDE can induce hypercholesterolemia in both male and female adult offspring rats, but their hepatic metabolic programming mechanisms are different. In the male offspring, the mechanism is associated with the sustained decrease in hepatic low-density lipoprotein receptor expression[159], and in the females, with the sustained high expression of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (to be published).

In addition, intrauterine overexposure to maternal-derived glucocorticoids induced by medication during pregnancy may also sex-specifically affect the offspring's multi-organ developmental programming. Female offspring rats of PCE show a significant increase in hepatic IGF1 expression and obviously aggravated NAFLD when fed a high-fat diet postnatally, compared to male offspring[127]. Intrauterine overexposure to maternal-derived glucocorticoids induced by PNE can sex-specifically cause cartilage dysplasia in female offspring rats, manifested as a more significant susceptibility to osteoarthritis in adult female offspring rats[140].

The idea that the gender differences in fetal development are related to the sex dimorphism of placental development is long-standing[160]. The adverse environment during pregnancy can damage the structure and function of the placenta with gender differences and thus has different effects on female and male offspring[161,162]. Sex chromosomes, sex hormones, and GR subtypes are crucial in forming this placental sex dimorphism[163]. It has been found that PDE can affect the branching morphogenesis and glycogen metabolism of the placenta with gender differences[164,165]. Additionally, female and male guinea pigs exposed to betamethasone during pregnancy have different expression patterns of GR subtypes[166]. Hence, the gender differences in organ development toxicity and programming alterations caused by medication during pregnancy may be related to placental sex dimorphism.

5. Multi-generational genetic effects of organ development toxicity and programming alterations caused by medication during pregnancy

The multi-generational genetic effect means that after an individual is exposed to the adverse environment in the sensitive developmental period, its offspring of different generations show a consistent abnormal phenotype. The intrauterine period is the sensitive period of individual development. The effect of medication during pregnancy on organ development and functional homeostasis may have multi-generational genetic effects. The effect of PDE on the phenotype of offspring of multiple generations has been reported. A study has found that PDE can program the expression of corticotropin-releasing hormone (CRH) and CRH receptor type 1 in rat hippocampus across two generations and induce depression-like behavior in two generations, which is related to the hypomethylation of CRH receptor type 1 promoter[167]. Another study has found that PDE can also change the DNA methylation pattern of the guinea pig hippocampus across three generations through paternal lineage[168]. PDE can up-regulate the histone H3 lysine 27 acetylation level of angiotensin converting enzyme in F1 and F2 generation rats, resulting in low peak bone mass in the F1 and F2 generations[169]. Moreover, the combined use of acetaminophen and ibuprofen during pregnancy can inhibit the follicular activation in offspring rats after birth and cause low ovarian function and accelerated ovarian aging of the F2 generation[170].

In addition, intrauterine overexposure to maternal-derived glucocorticoids caused by medication during pregnancy may also have multi-generational genetic effects on the offspring's organ development and functional homeostasis. Intrauterine high maternal-derived glucocorticoids induced by PEE can change the histone acetylation level of IGF1 and the "GC−IGF1 axis" programming in the offspring rat liver, which leads to heritable

changes in hepatic lipid metabolism[171]. It can also change the H3K9ac level of cytochrome P450 cholesterol side chain cleavage enzyme and its expression, thereby triggering the intergenerational effect of abnormal steroidogenesis function in offspring rat adrenal glands[172]. Intrauterine high maternal-derived glucocorticoids induced by PNE can down-regulate the histone acetylation levels of transforming growth factor β receptor 1 and type II collagen a1 chain and their expression, causing heritable changes in articular cartilage morphology of offspring rats[173]. Interestingly, PCE can reduce adrenal steroidogenesis of F1 and F3 offspring rats but increase that of F2 offspring rats, which is associated with the "contemporary" epigenetic programming of H19/let-7 axis caused by intrauterine different maternal-derived glucocorticoid levels[174].

In summary, the multi-generational genetic effects of organ development toxicity and programming alterations caused by medication during pregnancy are closely related to epigenetic modifications such as DNA methylation and histone acetylation. These abnormal epigenetic modifications can be passed to offspring through gametes and affect offspring's gene regulation and phenotype[175].

6. Conclusions and prospects

In recent years, the "DOHaD" theory has become a hot research field, and the research on the safety of medication during pregnancy has been continuously deepened in this field. In conclusion, medication during pregnancy can affect fetal morphological and functional development through multiple pathways, multiple organs, and multiple targets. Furthermore, medication during pregnancy may also indirectly cause multi-organ developmental programming, functional homeostasis changes, and susceptibility to related diseases in offspring by inducing fetal intrauterine abnormal exposure to maternal-derived glucocorticoids. Meanwhile, the alterations of multi-organ developmental programming and functional homeostasis caused by medication during pregnancy may also have gender differences and multi-generational genetic effects. This paper systematically expounds on the research progress of offspring's multi-organ developmental toxicity and programming alterations caused by medication during pregnancy, which has guiding significance for rational prenatal drug use.

Although many drugs have been proved to have organ development toxicity, their long-term effects on offspring after birth have not been fully explored. Meanwhile, studies on the relationship between maternal-derived glucocorticoid levels *in utero* and the multi-organ developmental programming alterations are still limited. On the one hand, some drugs have been shown to affect the placental glucocorticoid barrier, but their effects on offspring's multi-organ development remain to be explored; on the other hand, the intrauterine low glucocorticoid effects of certain drugs used during pregnancy and the multi-organ developmental abnormalities mediated by them are still a research direction to be extensively explored. More importantly, in the context of drug abuse during pregnancy, it is urgent to facilitate the transformation of basic research results about multi-organ dysplasia caused by medication during pregnancy into the clinical application, so as to find effective methods for prevention and treatment of drug-related multiple fetal-originated diseases.

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Author contributions

Hui Wang and Liaobin Chen conceived and supervised the project. Zhengjie Lu summed up the literature and wrote the whole passage. Yu Guo, Dan Xu and Hao Xiao were in charge of checking and revision. Yongguo Dai and Kexin Liu were involved in drawing the figures.

Conflicts of interest

The authors declare no conflicts of interest.

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