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Review

Pregnancy Complications and Transgenerational Health Outcomes: Mechanistic Pathways and Future Research Horizons

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Abstract

Objective: Summarize evidence across six common pregnancy complications—gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), thyroid dysfunction, intrahepatic cholestasis of pregnancy (ICP), hyperemesis gravidarum (HG), and preterm birth (PTB)—and clarify short- and long-term consequences for mothers and their children. **Mechanism**: Adverse outcomes converge on shared pathways: abnormal placental development and perfusion, inflammatory and oxidative stress signaling, endocrine and metabolic dysregulation, and epigenetic remodeling at imprinted loci. These processes program fetal organ systems (brain, heart, lungs, kidneys) and shape lifelong disease risk. **Findings in Brief**: GDM increases large-for-gestational-age birth, respiratory morbidity, and later metabolic disease. HDP drive fetal growth restriction and enduring cardiovascular and neurocognitive sequelae. Thyroid dysfunction worsens obstetric outcomes and may impair offspring neurocognition. ICP raises risks of PTB and stillbirth. HG is associated with low birth weight and small for gestational age. PTB independently predicts lifelong cardio-respiratory, endocrine, and neurodevelopmental disorders. Management spans glucose control; antihypertensive therapy and magnesium sulfate; levothyroxine or antithyroid drugs; ursodeoxycholic acid; antiemetics and nutritional support; progesterone and antenatal corticosteroids. Emerging precision strategies target angiogenic balance, inflammation, and the microbiome. **Conclusions**: Pregnancy complications are sentinel events with intergenerational implications. Stage-appropriate screening, timely intervention, and longitudinal follow-up are essential, while multi-omics research and placental-targeted trials are needed to validate strategies that mitigate offspring risk across the life course.

Keywords: pregnancy complications; transgenerational health effects; neonatal outcomes; pregnancy management

1. Introduction

Pregnancy complications, as a significant issue in the field of obstetrics and gynecology, have always been a subject of widespread concern in the medical community. Pregnancy complications not only affect the health of both mother and infant but also have a profound impact on the development of perinatal medicine. Although most pregnancies are considered normal medically and can be delivered safely without causing serious health problems for the child, globally up to 15%–40% of pregnancies experience a range of pregnancy and childbirth complications [1–3]. Pregnancy complications such as pre-eclampsia, preterm birth (PTB), recurrent miscarriage, and fetal growth restriction (FGR) affect more than 12% of pregnant women worldwide. These complications not only pose a threat to the health of the pregnant woman but can also have long-term effects on the development of the fetus. For example, pre-eclampsia can lead to placental dysfunction (refers to the placenta's inability to properly perform its physiological functions during pregnancy, thereby affecting the material exchange between the mother and fetus), which in turn affects the nutritional and oxygen supply to the fetus, increasing the risk of PTB and low birth weight (LBW). Preterm infants, due to immature organ development, are more prone to respiratory distress, infections, and neurological developmental issues. Recurrent miscarriage may involve immune system abnormalities or chromosomal abnormalities, bringing significant psychological and financial burdens to families. FGR can lead to postnatal growth retardation and may even affect health in adulthood [4,5].

This article specifically addresses 6 common complications encountered during pregnancy: gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), thyroid disorders during pregnancy, intrahepatic cholestasis of pregnancy (ICP), hyperemesis gravidarum (HG) and PTB. These conditions can significantly complicate the course of pregnancy. These diseases have complex mechanisms of action, involving multiple physiological and biochemical pathways. The development of pregnancy complications involves multiple fields including genetics, epigenetics, and metabolism, and interacts with lifestyle and environmental factors. They not only pose a threat to the health of the mother but can also have profound long-term effects on the health of the fetus. The intrauterine environment (the biological and physiological conditions within the uterus during pregnancy) has a profound impact on the developing fetus, a phenomenon known as "developmental programming", which affects multiple systems [6].

Furthermore, the dual effects of intrauterine adverse exposures and environmental factors may increase the susceptibility of individuals to future diseases and elevate the risk of chronic illnesses later in life [7,8]. Exposure to pregnancy complications can affect the fetus in utero through multiple pathways, including lipid metabolism, organ development, and various aspects of developmental and endocrine diseases, which may further exacerbate the vicious cycle of metabolic disorders [9,10]. Furthermore, pregnancy complications can also indirectly affect fetal growth and development by altering placental function and maternal metabolic status. Therefore, understanding the mechanisms of these complications is crucial for developing effective prevention and treatment strategies.

Currently, there is insufficient understanding of the short-term and long-term effects of complications during pregnancy, especially those affecting the postpartum period. This article delves into the pathophysiological mechanisms of pregnancy complications, providing a deeper insight into how these diseases affect fetal health. The manuscript offers a detailed analysis of the diagnostic criteria for pregnancy complications, their impact on the fetus during pregnancy, and the long-term effects of these complications. The aim is to emphasize the importance of early diagnosis and intervention, and to provide clinicians with practical guidance to help them more effectively manage these complex health issues during pregnancy, thereby significantly improving the health outcomes for newborns.

2. Gestational Diabetes Mellitus

GDM is the most common complication during pregnancy and is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The average prevalence of gestational diabetes worldwide is approximately 14% [11]. The observed variation in prevalence estimates primarily stems from heterogeneity in case-finding methodologies, application of standardized diagnostic parameters (Table 1), and differential risk profiles across study populations [12,13]. GDM changes the maternal metabolic and uterine environment, thus increasing the risk for short- and long-term adverse outcomes for both mother and child. GDM is correlated with various adverse pregnancy outcomes, such as premature birth, cesarean delivery, and shoulder dystocia. Furthermore, offspring of GDM are more prone to obesity and face a higher likelihood of hormonal imbalances and metabolic complications [14,15].

2.1 Macrosomia

About 15–45% of babies born to diabetic mothers can have macrosomia, which is a 3-fold higher rate when compared to normoglycemic controls [16]. During pregnancy, fetuses of diabetic mothers often exhibit a specific characteristic of overgrowth. These newborns typically have larger circumferences of the shoulders and limbs, a diminished head-to-shoulder ratio, notably elevated body fat percentage, and augmented thickness of the skin folds on the upper extremities. There is no increase in fetal head size, yet the shoulder and abdominal circumference can undergo significant enlargement, increasing the risk of Erb's palsy, shoulder dystocia, and brachial plexus trauma. Infants with macrosomia face a sixfold increased risk of trauma during delivery, and the likelihood of brachial plexus injury may be as high as twenty times [17]. The hyperglycemic condition of the mother triggers a series of biological cascading reactions, characterized by the excessive production of insulin in the fetus. This condition leads to enhanced glucose metabolism, which in turn stimulates the accelerated development of fat cells, ultimately causing fetal overgrowth. When the maternal glucose regulatory function is impaired and blood glucose levels rise, this metabolic excess diffuses through the placental barrier. Nevertheless, insulin derived from the mother or administered exogenously does not permeate the placenta. Consequently, when the fetus's pancreas starts to secrete insulin independently to manage high blood sugar levels, no longer depending on glucose stimulation, this simultaneous presence of hyperinsulinemia and hyperglycemia fosters an increase in fetal fat and protein reserves, ultimately resulting in macrosomia [18]. In this population of newborns, the incidence of jaundice in macrosomia is twice that of infants born to normal mothers. Due to their higher oxygen requirements, macrosomia may increase the risk of fetal hypoxia, leading to a higher likelihood of stillbirth and asphyxia at birth [19]. Additionally, relative intrauterine hypoxia can promote the production of erythropoietin, which in turn causes polycythemia and hyperbilirubinemia [20]. When these red blood cells are broken down, an increased amount of bilirubin is produced, which raises the likelihood of neonatal jaundice [19,21].

2.2 Diabetes Susceptibility

GDM is recognized as a significant disruptor of the intrauterine environment, predisposing offspring to metabolic dysregulation [22]. The Pima Indian cohort study demonstrated significantly elevated rates of metabolic sequelae in GDM-exposed offspring compared with their non-exposed counterparts. Longitudinal analysis of the Pima Indian cohort revealed a 2.3-fold increase in metabolic sequelae among GDM-exposed progeny versus unexposed controls. Complementary case-control data from this population demonstrated birth order effects, with post-diagnosis offspring exhibiting a 68% greater diabetes susceptibility compared to pre-diagnosis siblings, persisting after adjustment for genetic confounders [23,24]. Pathophysiological mechanisms involve GDM-driven proinflammatory milieu characterized by placental upregulation of tumour necrosis factor-α (TNF-α) and interleukin (IL)-6, which synergistically impair insulin signaling pathways through c-Jun N-terminal kinase (JNK)/insulin receptor substrate-1 (IRS-1) phosphorylation [25].

Table 1. Diagnosis of gestational diabetes mellitus (GDM).

Diagnostic approaches		Glucose concentration, mg/dL			
		Fasting	1-hour	2-hour	3-hour
One-step	All women complete a 75 g oral glucose tolerance test (OGTT) after ≥8 hours of fasting		/		
Two-step	GDM is defined as having ≥1 measurement above the criteria		/		
	International association of diabetes and pregnancy study group (plasma)[a]	92	180	153	NA
	Initial screening involves a non-fasting 50 g glucose challenge test (GCT)		/		
	Women screening positive on the 50 g GCT (1-hour glucose ≥130–140 mg/dL) proceed to a fasting 100 g OGTT				
	GDM is defined as having ≥2 measurement above the criteria				
	O' Sullivan (whole blood)	90	165	145	125
	National diabetes data group (plasma)	105	190	165	145
	Carpenter and coustan (plasma)[a]	95	180	155	140

[a] Currently recommended criteria from the Korean Diabetes Association for the diagnosis of GDM. NA, not applicable.

Table 2. Diagnosis of hypertensive disorders of pregnancy (HDP).

Type of HDP	Diagnosis standards
Gestational hypertension	Blood pressure (BP) ≥140/90 mmHg; Negative quantitative proteinuria testing; Return to normal within 12 weeks postpartum
Preeclampsia	BP ≥140/90 mmHg; Proteinuria ≥0.3 g/24 h; Or proteinuria/creatinine ≥0.3; Or random proteinuria (+)
Eclampsia	With the progression of preeclampsia, tonic-clonic seizures occur
Pregnancy with chronic hypertension	History of primary or secondary hypertension; BP ≥140/90 mmHg before 20 weeks of pregnancy; No significant worsening during pregnancy or acute severe hypertension; Hypertension persists >12 weeks postpartum
Chronic hypertension with superimposed preeclampsia	Chronic hypertension in pregnancy; Negative quantitative proteinuria before 20 weeks of pregnancy; Quantitative proteinuria ≥0.3 g/24 h or random proteinuria ≥ (+) after 20 weeks of pregnancy; Or increased proteinuria significantly after 20 weeks of pregnancy in those with proteinuria before 20 weeks

+ positive.

2.3 Neonatal Respiratory Distress Syndrome

Neonatal respiratory distress syndrome (NRDS) represents a prevalent complication among neonates born to mothers with GDM. A comprehensive systematic review and meta-analysis provides strong evidence that there is a significant positive correlation between GDM and NRDS. The pathophysiological mechanisms underlying this association are multifaceted, involving complex interactions between maternal hyperglycemia and fetal pulmonary development. Central to this phenomenon is the impairment of pulmonary maturation, where maternally derived hyperglycemia has been implicated in delayed pulmonary maturation through multiple pathways [25]. Fetal hyperglycemia may disrupt normal alveolarization processes by interfering with the synthesis and secretion of pulmonary surfactant—a critical lipoprotein complex responsible for reducing alveolar surface tension, maintaining alveolar patency, and facilitating efficient gas exchange. Surfactant deficiency may precipitate alveolar collapse, culminating in NRDS pathogenesis. Notably, the hyperglycemic intrauterine environment exerts dual detrimental effects on fetal lung development. Hyperglycemia-induced oxidative stress and inflammatory responses in fetal pulmonary tissue have been shown to disrupt cellular differentiation pathways and extracellular matrix remodeling [26]. Concurrently, GDM-associated placental insufficiency may compromise fetal oxygenation and nutrient delivery, creating a synergistic effect that exacerbates pulmonary developmental abnormalities [27]. The cumulative impact of these mechanisms significantly elevates neonatal susceptibility to respiratory failure, particularly in late preterm and early term infants.

2.4 Neurodevelopmental and Reproductive Health Outcomes

Long-term consequences of GDM extend beyond metabolic dysregulation to encompass neurodevelopmental and reproductive health outcomes. Experimental and clinical evidence indicates that intrauterine hyperglycemia induces developmental programming alterations in fetal pancreatic β-cell function, establishing persistent susceptibility to glucose metabolism disorders including insulin resistance and impaired glucose tolerance. Emerging neurodevelopmental research reveals significant associations between maternal GDM and offspring cognitive profiles characterized by deficits in expressive language competence, episodic memory consolidation, and facial recognition acuity. Furthermore, epidemiological data demonstrate a dose-dependent relationship between maternal glycemic severity and subsequent risk of neuropsychiatric hospitalizations in offspring, with particular elevation in autism spectrum disorder (ASD) incidence [28–30]. Notably, recent longitudinal investigations have identified accelerated pubertal maturation patterns in female offspring exposed to maternal GDM. These individuals exhibit significantly earlier thelarche initiation and accelerated pubarche progression compared to non-exposed controls. Mechanistic studies suggest this phenotypic acceleration may derive from hyperglycemia-induced epigenetic modifications affecting hypothalamic-pituitary-gonadal axis regulation [15].

3. Hypertensive Disorders of Pregnancy

HDP, a heterogeneous group of pregnancy-specific conditions, primarily containing gestational hypertension, preeclampsia, eclampsia, pregnancy with chronic hypertension, and chronic hypertension with superimposed preeclampsia [31]. Globally, HDP affects approximately 5–10% of pregnancies, though regional disparities exist, with incidence rates ranging from 7.8% in high-income countries to 15.2% in low-resource settings [32]. Clinical diagnosis primarily relies on the presence of vasoconstriction (manifested as hypertension), increased capillary permeability (e.g., proteinuria, peripheral edema, cerebral edema, hepatic congestion, pulmonary edema), and abnormal endothelial/platelet interactions (e.g., thrombocytopenia, disseminated intravascular coagulation) among other signs and symptoms (Table 2).

3.1 Fetal Growth Restriction

Approximately 30% to 50% of patients with early-onset HDP also experience FGR growth restriction, primarily due to impaired placental development and insufficient uteroplacental blood flow [33]. In placental ischemia, an imbalance between reactive oxygen species, including superoxide anion (O^{2-}) and hydrogen peroxide (H_2O_2), and antioxidants results in oxidative stress, endothelial dysfunction, and fetal malnutrition [34]. Pregnant women with HDP and FGR exhibit maladaptive cardiovascular changes, including reduced heart rate and cardiac output [35], while hypertension and placental dysfunction contribute to iatrogenic PTB (43.7% of cases), increasing neonatal mortality, morbidity, and long-term neurodevelopmental risks such as cognitive deficits, cerebral palsy (CP), and sensory impairments [36]. DNA methylation analysis of placental samples revealed placenta-specific hypomethylation at *H19* imprinted maternally expressed transcript (*H19*)-differentially methylated region (DMR) and insulin-like growth factor 2 (*IGF2*)-DMR in FGR and HDP cases (incidence: 1.5%, 3/202 cases), leading to biallelic *H19* expression and a significantly elevated *H19*/*IGF2* expression ratio. This suggests that epigenetic dysregulation may contribute to the intergenerational effects of pregnancy-related complications [37]. These findings underscore that HDP-induced FGR not only compromises immediate neonatal outcomes but also predisposes offspring to chronic diseases through placental insufficiency and epigenetic dysregulation.

Additionally, depending on the presence or absence of concurrent maternal hypertensive disorders (such as preeclampsia, gestational hypertension, or chronic hypertension with superimposed preeclampsia), there are significant differences in the pathophysiological mechanisms and clinical management priorities. When early-onset FGR is accompanied by maternal hypertensive disorders, the core pathology is typically placental in origin, stemming from severe placental ischemia due to shallow implantation and inadequate spiral artery remodeling [38]. Systemic maternal vascular endothelial dysfunction and inflammatory responses further exacerbate poor placental perfusion, creating a vicious cycle. This type often progresses rapidly, with early and severe Doppler flow abnormalities (such as elevated uterine artery pulsatility index or absent/reversed end-diastolic flow in the umbilical artery), frequently accompanied by prominent maternal symptoms (e.g., hypertension, proteinuria). It is prone to iatrogenic preterm delivery and carries an extremely high risk of neonatal complications. In contrast, early-onset FGR without hypertensive disorders is also primarily caused by placental insufficiency, but the contributing factors may be more diverse, including but not limited to placental structural abnormalities (e.g., small placenta, infarctions), genetic or chromosomal anomalies, infections, antiphospholipid syndrome, severe maternal malnutrition, or chronic hypoxia. Although the degree of placental dysfunction in such cases may be milder than in those with concurrent hypertension and maternal risks are lower, the harm to the fetus remains significant and can still lead to adverse pregnancy outcomes, necessitating close monitoring and timely intervention [39].

3.2 Neurocognitive Impairments

HDP is associated with a spectrum of neurocognitive impairments across developmental stages [40]. Meta-analytic evidence indicates that offspring exposed to HDP, particularly preeclampsia, face significantly elevated risks

of neurodevelopmental sequelae. Term infants (≥37 weeks) born to preeclamptic mothers exhibit a threefold increased risk of CP compared to normotensive pregnancies [41]. Preschoolers with combined exposure to preeclampsia and being small-for-gestational-age (SGA) demonstrate reductions in verbal intelligence quotient (IQ) and full-scale IQ relative to controls [40]. Longitudinal studies reveal persistent deficits: preeclampsia-exposed children exhibit impaired motor function at ages 10–17 years, characterized by reduced coordination and balance, potentially linked to placental insufficiency-driven cerebellar dysmaturation [42,43]. Cognitive limitations extend into adolescence, with population-based cohorts showing HDP-exposed 11-year-olds have a 2.5-fold higher likelihood of mild cognitive impairment (IQ 50–85) [44]. Mechanistically, third-trimester placental dysfunction in HDP may induce fetal brain vulnerability through hypoxia-ischemia and oxidative stress. The cerebellum—a critical hub for motor learning undergoing rapid development during late gestation—is disproportionately affected by nutrient-glucose deprivation, correlating with observed motor deficits [45]. Furthermore, prenatal HDP exposure elevates ASD risk by 32%, likely mediated by oxidative damage to neuroprogenitor cells and trace element deficiencies (e.g., zinc, selenium) essential for synaptic pruning [46]. These findings collectively implicate HDP-induced placental pathology and resultant neuroinflammation as key pathways driving multigenerational neurocognitive morbidity.

3.3 Neonatal Respiratory Distress Syndrome and Bronchopulmonary Dysplasia

HDP significantly impairs offspring respiratory health through placental dysfunction and systemic vascular dysregulation. HDP induces atherosclerotic changes in uterine spiral arteries, reducing placental perfusion and causing chronic fetal hypoxia, which predisposes NRDS and asphyxia [47]. Concurrently, HDP-triggered maternal inflammation and endothelial dysfunction disrupt trophoblast microvillous exchange, limiting fetal oxygen/nutrient uptake and increasing risks of LBW—a key contributor to respiratory morbidity [48,49]. Furthermore, HDP-exposed infants exhibit elevated bronchopulmonary dysplasia (BPD) incidence due to combined prenatal and postnatal insults. Prenatally, impaired pulmonary angiogenesis and alveolarization result from FGR, oxidative stress, and inflammatory cascades [50]. Postnatally, prematurity-related interventions (mechanical ventilation, oxygen toxicity) exacerbate lung injury, particularly in early-gestation infants requiring intensive respiratory support [50,51]. These multifactorial disruptions in lung development underscore the persistent cardiopulmonary sequelae observed in HDP offspring.

3.4 Cardiovascular Dysfunction

HDP, particularly preeclampsia, is closely linked to the remodeling and dysfunction of the cardiovascular system in offspring. Preeclampsia directly impairs fetal cardiac function by increasing afterload and placental vascular resistance (elevated by 1.8-fold), leading to the redistribution of left ventricular output. This condition clinically presents as cardiomegaly, ventricular hypertrophy, and dysfunction in both diastolic and systolic function [52]. Clinical observations highlight early functional abnormalities in preeclampsia-exposed offspring: preterm infants (29–35 weeks gestation) exhibit significantly higher systolic/diastolic blood pressure (BP) within the first 3 postnatal days compared to controls [53], with BP differences persisting from age 7 to 18 [54]. Maternal preeclampsia demonstrates a significant association with congenital heart disease (CHD) in offspring, exhibiting a 30% higher prevalence of severe CHD (35.0 vs. 26.9 per 10,000 births) and a 15-fold elevated risk of atrioventricular septal defects compared to normotensive pregnancies, suggesting potential shared pathogenic pathways [55]. Offspring exposed to early-onset preeclampsia had significantly higher peripheral and central systolic BP. Notably, these children also included preterm and SGA infants, which are also associated with higher BP in childhood [56]. Mechanistically, placental oxidative stress and angiogenic imbalance [soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio] drive fetal cardiovascular maladaptation through hypoxia-inducible factor-1α (HIF-1α)-mediated myocardial remodeling and endothelial progenitor cell depletion, directly linking hypoxic-ischemic injury to persistent hypertension and cardiac structural anomalies observed clinically [57].

The placenta plays a central mechanistic role in mediating these adverse developmental programming effects. Pathological changes in HDP/preeclampsia, including chronic uteroplacental insufficiency, reduced perfusion, and oxidative stress, trigger a cascade of placental dysfunction. This involves aberrant inflammation (elevated pro-inflammatory cytokines like TNF-α, IL-6), excessive production of anti-angiogenic factors (sFlt-1), diminished pro-angiogenic factors [(PlGF, vascular endothelial growth factor (VEGF)], and endothelial damage [58]. These placental alterations compromise nutrient/oxygen transfer, expose the developing fetus to a hostile biochemical milieu, and induce epigenetic modifications (e.g., DNA methylation) in key genes regulating cardiovascular development and function [e.g., those involved in the renin-angiotensin-aldosterone system (RAAS), nitric oxide signaling, and glucocorticoid response]. Consequently, fetal adaptive responses lead to permanent structural and functional changes in the heart and vasculature, predisposing the offspring to early-onset cardiovascular disease. Moreover, prolonged hypoxia and insufficient nutrient supply, compounded by the dual impact of inadequate placental perfusion during uterine contractions, can lead to intrapartum fetal distress. Its manifestations include pathological cardiotocography (CTG) patterns, fetal acidosis (umbilical artery pH $<$7.20,

elevated lactate levels), and meconium-stained amniotic fluid (MSAF) [59].

3.5 Renal Dysplasia and Dysfunction

Numerous studies indicate that children born to mothers with preeclampsia may face risks of fetal kidney underdevelopment and abnormal function. Adverse factors within the intrauterine environment can impair the growth and development of the kidneys, resulting in renal dysfunction and hypertension in adulthood. Khalsa *et al*. [60] confirmed that adolescents with a history of PTB, particularly those with LBW, more frequently exhibit elevated BP and a reduced estimated glomerular filtration rate. Their study focused on evaluating the kidney function of children with extremely LBW compared to a control group at the ages of 7 and 11 years. The results indicated that children with extremely LBW had significantly smaller kidney volumes and elevated levels of cystatin C, providing evidence of early signs of kidney dysfunction that has manifested during childhood [61]. Alterations in the renin-angiotensin system have been confirmed to play a key role in cardiovascular diseases and in the programming of hypertension in offspring experiencing HDP or fetal programming due to prenatal environmental insults [62].

4. Thyroid Disease in Pregnancy

Thyroid disorders constitute prevalent endocrine disturbances during gestation, with epidemiological studies indicating a 4% prevalence of hypothyroidism and 2.4% incidence of hyperthyroidism in pregnant populations. The diagnosis of gestational thyroid diseases mainly relies on serum thyroid function tests. This includes, but is not limited to, the measurement of indicators such as thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). When TSH levels are abnormal, combined with changes in FT4, the state of thyroid function can be preliminarily determined (Table 3) [63]. Mounting evidence highlights the dual clinical ramifications of maternal thyroid dysregulation: immediate obstetric risks (e.g., preterm delivery, preeclampsia) and enduring developmental sequelae in offspring. Mechanistically, fetal exposure to altered maternal thyroid hormone concentrations during critical periods of organogenesis (weeks 8–20 gestation) disrupts neurogenesis, cortical layering, and hypothalamic-pituitary-thyroid axis programming [51,64]. Longitudinal cohort studies demonstrate that untreated maternal hypothyroidism correlates with a 7–10-point reduction in offspring IQ scores, while uncontrolled hyperthyroidism increases risks of intrauterine growth restriction by 3.2-fold [65,66].

4.1 Perinatal Outcomes

Maternal thyroid dysfunction during pregnancy exerts profound effects on perinatal outcomes, with distinct pathophysiological mechanisms and clinical risks depending on the type of thyroid disorder. Regarding PTB and LBW, uncontrolled maternal hyperthyroidism amplifies uterine contraction frequency through β-adrenergic receptor overactivation, elevating preterm delivery risk by 2-fold compared to euthyroid pregnancies [67]. Conversely, hypothyroidism characterized by insufficient FT4 levels reduces placental blood perfusion, strongly correlating with FGR and LBW [68]. For miscarriage and stillbirth, overt hypothyroidism demonstrates a 60% increased miscarriage risk and 4-fold higher stillbirth incidence, attributable to thyroid hormone deficiency-induced embryonic implantation defects and placental insufficiency. Although the clinical significance of subclinical hypothyroidism remains debated, studies confirm a statistically significant rise in miscarriage risk when maternal TSH exceeds 4.0 mIU/L [50].

4.2 Abnormal Thyroid Function in Offspring

Maternal thyroid disorders during gestation exert profound effects on offspring thyroid homeostasis through distinct mechanisms involving antibody transfer, pharmacologic interference, and hormonal dysregulation. Neonatal thyrotoxicosis predominantly originates from maternal Graves' disease, where placental transfer of TSH receptor antibodies stimulates fetal thyroid receptors, affecting 1–5% of neonates with manifestations including tachycardia, heart failure, and even craniosynostosis [69]. Furthermore, excessive use of antithyroid drugs during late pregnancy may suppress fetal thyroid function, with subsequent withdrawal leading to rebound thyrotoxicosis due to compensatory hormone hypersecretion. Conversely, neonatal hypothyroidism demonstrates strong associations with maternal thyroid status and therapeutic interventions. Untreated maternal hypothyroidism increases the risk of congenital hypothyroidism in offspring, which is attributed to insufficient placental thyroxine (T4) transport [70]. Notably, transplacental passage of maternal thyroid autoantibodies, particularly thyroid peroxidase antibodies (TPOAb), may induce immune tolerance dysregulation in offspring, predisposing them to lifelong risks of autoimmune thyroid disorders such as Hashimoto's thyroiditis [71].

4.3 Neurodevelopment and Cognitive Function

Maternal thyroid dysfunction during pregnancy exerts profound and stage-specific impacts on offspring neurodevelopment and cognitive function. During the first trimester, a critical window for fetal brain development, insufficient maternal T4 levels—particularly FT4 deficiency—are associated with a 7–10 point reduction in offspring IQ, with pronounced deficits in language acquisition and executive function [72]. Mechanistically, early gestational T4 inadequacy disrupts neuronal migration and impairs synaptic formation in the hippocampus and cerebral cortex, compromising structural brain maturation [73,74]. In later pregnancy, maternal hyperthyroidism may perturb fetal neurodevelopment via suppression of cere-

Table 3. Classification and diagnosis of thyroid disease in pregnancy.

Type of thyroid dysfunction	Definition of thyroid dysfunction	Diagnosis standards
Hhyperthyroidism	Group of clinical syndromes resulting from insufficient synthesis, secretion, or biological action of thyroid hormones for various reasons.	Thyroid-stimulating hormone (TSH) > upper reference range (or 4.0 mU/L in early pregnancy), and free thyroxine (FT4) < lower reference range.
Subclinical hyperthyroidism	Mild hypothyroidism. Elevated TSH but FT4 in the normal range.	TSH > upper reference range (or 4.0 mU/L in early pregnancy), and FT4 in the normal range.
Hypothyroidism	Thyroid gland synthesizes and secretes too much thyroid hormone for various reasons, resulting in a series of hypermetabolic syndromes and sympathetic excitations.	TSH < lower limit of reference range (or <0.1 mU/L in early pregnancy), FT4 or free triiodothyronine (FT3) > upper limit of reference range.
Subclinical hypothyroidism	Reduced serum TSH from various causes with normal FT3 and FT4 levels.	TSH < lower limit of reference range (or <0.1 mU/L in early pregnancy), and normal FT4 and FT3.

bral deiodinase type 3, reducing local triiodothyronine (T3) bioavailability and impairing myelination processes critical for neural circuit integrity [75]. Conversely, persistent maternal hypothyroidism during mid-to-late gestation correlates with elevated risks of neurodevelopmental disorders in offspring, including a 1.4-fold increase in attention-deficit/hyperactivity disorder and ASD incidence, likely mediated by chronic cerebral hypothyroidism [76].

5. Intrahepatic Cholestasis of Pregnancy

ICP, an obstetric-specific condition, is characterized by pruritus (usually localized to the palms and soles without a rash) (Table 4) during the mid-to-late gestational period and elevated serum total bile acid (TBA) levels ($\geq$10 µmol/L). Its pathogenesis involves abnormal estrogen metabolism, dysfunctional hepatocyte bile transport proteins [e.g., ATP-binding cassette subfamily B member 4 (*ABCB4*) gene mutations], and genetic susceptibility. Globally, ICP affects 0.3–5% of pregnancies, demonstrating significant geographic variation influenced by genetic and environmental factors [77,78]. Emerging evidence indicates that ICP not only increases the risk of adverse perinatal outcomes but may also exert long-term metabolic and neurodevelopmental sequelae in offspring.

5.1 Preterm Birth

ICP is strongly associated with an elevated risk of PTB, with reported rates ranging from 11.7% to 60%, predominantly occurring between 32 and 36 weeks of gestation. While a substantial proportion of preterm deliveries result from iatrogenic interventions due to deteriorating maternal or fetal conditions, emerging evidence highlights the role of spontaneous preterm labor in ICP pathophysiology. A dose-response meta-analysis further revealed that maternal serum TBA levels $\geq$20 µmol/L significantly elevate spontaneous PTB risk [79]. Mechanistically, bile acids (BAs) exhibit a dose-dependent pro-contractile effect on the myometrium, as evidenced by rodent models and human tissue studies. Bas upregulate oxytocin receptor expression in uterine smooth muscle cells and enhance myometrial sensitivity to oxytocin. *In vitro* experiments using myometrial cells from ICP patients demonstrate a 2.3-fold increase in oxytocin-induced contractility compared to controls, suggesting that BAs-driven hyperresponsiveness promotes unregulated uterine activity, thereby predisposing to spontaneous preterm labor. This pathway is further potentiated by BAs-induced placental oxidative stress and inflammatory cytokine release (e.g., IL-8 and TNF-α), which may synergistically disrupt uterine quiescence [80].

5.2 Stillbirth

ICP is associated with an elevated risk of stillbirth, with reported rates of 0.1–0.3% beyond 37 weeks of gestation—a 3–5 fold increase compared to the general obstetric population. While the precise pathophysiological mechanisms remain incompletely elucidated, postmortem examinations of affected fetuses demonstrate acute anoxic insults without characteristic features of chronic uteroplacental insufficiency [81]. Histopathological analysis of ICP placentas reveals abrupt vascular changes, suggesting rapid-onset catastrophic events rather than progressive placental dysfunction [82]. Emerging evidence implicates BAs-induced cardiac toxicity as a critical pathway. Clinical observations document fetal arrhythmias in ICP pregnancies [83], corroborated by *in vitro* experiments demonstrating BAs' dose-dependent arrhythmogenic effects on neonatal rat cardiomyocytes, including reduced contractility and disrupted electrophysiological stability [84].

The proposed dual-pathway model encompasses two distinct mechanisms: BAs-mediated vasoconstriction of placental chorionic vessels inducing acute anoxia [85], synergistically interacting with direct cardiotoxic effects that

Table 4. Diagnosis and severity classification of intrahepatic cholestasis of pregnancy (ICP).

Diagnostic methods	Grade based on severity
Be alert to ICP if there is itching of the skin that cannot be explained by other causes during pregnancy (Highly recommended with strong evidence support).	Mild ICP diagnostic criteria: (1) Fasting serum total bile acid (TBA) level 10–39 μmol/L or postprandial serum TBA level 19–39 μmol/L; (2) Clinical symptoms are mainly skin itching, without obvious other symptoms. (strongly recommended, high evidence level)
Fasting TBA ≥10 μmol/L or postprandial TBA ≥19 μmol/L in pregnant women can be diagnosed as ICP (Strong recommendation supported by strong evidence).	Severe ICP diagnostic criteria: (1) Pregnant women serum TBA level 4–99 μmol/L; (2) Serum bilirubin level higher than normal; (3) Accompanied by other conditions, such as multiple pregnancy, preeclampsia, recurrent ICP, has caused perinatal death due to ICP; (4) Early-onset ICP. (strongly recommended, evidence level medium)
Serum transaminase can be utilized as a biochemical reference index for the diagnosis of ICP, but it is not an essential criterion for ICP diagnosis (Weak recommendation, low level of evidence).	Extremely severe ICP diagnostic criteria: Pregnant women serum TBA level ≥100 μmol/L. (strongly recommended, evidence level medium)
To establish a diagnosis of ICP, abnormalities in laboratory indicators such as skin itching or elevated serum TBA levels caused by other causes must be ruled out. It is recommended to perform routine ultrasound to rule out hepatobiliary diseases in pregnant women (Highly recommended with strong evidence support).	/

trigger lethal ventricular arrhythmias through myocardial potassium channel inhibition [86]. Notably, fetal myocardial dysfunction severity correlates strongly with maternal serum TBA concentrations, with significant myocardial deformation observed exclusively in severe ICP cases (TBA ≥40 μmol/L) [87].

5.3 Meconium-Stained Amniotic Fluid

MSAF complicates 10–44% of ICP cases, representing a 2–3 fold increased risk compared to non-ICP pregnancies [88]. While the pathophysiology remains partially defined, 2 predominant hypotheses emerge: (1) traditional fetal hypoxic stress triggering defecation reflex, and (2) direct BAs-mediated stimulation of fetal colonic motility. Experimental models provide compelling evidence for BAs-specific mechanisms. In *ex vivo* rabbit colonic strips, cholic acid exposure (50–200 μmol/L) induced dose-dependent increases in smooth muscle contraction amplitude [89]. These findings challenge the conventional hypoxia paradigm and suggest BAs toxicity alone may suffice to induce meconium passage.

5.4 Neonatal Respiratory Distress Syndrome

A prospective multicenter cohort study (N = 504) of gestational age-matched pregnancies (ICP = 77, controls = 427) demonstrated that ICP confers significant neonatal respiratory morbidity, with adjusted analyses revealing a 2.1-fold increased risk of NRDS and a 0.2% incremental NRDS probability per 1 μmol/L rise in maternal serum BAs after controlling for prematurity and delivery mode [90].

6. Hyperemesis Gravidarum

HG, a severe pregnancy complication characterized by intractable nausea, vomiting (>3 episodes/day), and metabolic disturbances (e.g., ≥5% prepregnancy weight loss, ketonuria, or electrolyte imbalances), affects 0.3–3.6% of pregnancies globally, with variability attributed to heterogeneous diagnostic criteria and ethnic disparities (Table 5) [91]. Although maternal deaths due to HG remain extremely rare (<0.1%) in high-income countries, research evidence indicates that this condition can have transgenerational persistent effects through mechanisms such as placental-endocrine disruption and epigenetic reprogramming [92].

6.1 Impact of Offspring Birth Outcomes

The impact of HG on offspring birth outcomes has been substantiated by multiple prospective studies and mechanistic investigations. A recent meta-analysis demonstrated that HG significantly elevates the risk of LBW and SGA incidence, primarily attributed to placental dysfunction caused by chronic maternal nutritional deficiencies and

Table 5. Diagnosis of hyperemesis gravidarum (HG).

Type of diagnostic methods	Diagnostic criterion
Fairweather criteria (1968)	More than 3 episodes of vomiting a day
	Weight loss
	Ketonemia
	Electrolyte imbalance
	Volume depletion
	Onset usually at 4–8 weeks of pregnancy
Windsor definition (2021)	Compulsory features
	At least one of nausea and vomiting is severe
	Incapability of normal drinking or eating substantially impacts on daily living activities Initiation of symptoms in early pregnancy (Early pregnancy was defined as before a gestational age of 16 weeks)
	Contributory features
	Symptoms of dehydration

metabolic disturbances [93]. Pathological studies of placental tissue have revealed that under hyperglycemic conditions during pregnancy, common variations in genes encoding placental proteins [namely growth differentiation factor 15 (*GDF15*) and insulin-like growth factor binding protein 7 (*IGFBP7*)] and hormone receptors [namely GDNF family receptor alpha like (*GFRAL*) and progesterone receptor (*PGR*)] are involved, along with decreased levels of placental angiogenic factors such as PlGF. These changes directly restrict the fetus's access to nutrients and oxygen [94].

6.2 Neurodevelopmental and Behavioral Abnormalities in Offspring

The association between HG and neurodevelopmental/behavioral abnormalities in offspring has emerged as a critical focus of research, with recent evidence uncovering a multifactorial pathogenic network. A Dutch birth cohort study demonstrated that prenatal HG exposure elevates the risk of ASD in offspring by 1.6-fold, exhibiting a dose-dependent relationship with the duration of ketosis during early gestation [95]. Mechanistically, maternal thiamine (vitamin B1) deficiency induced by HG disrupts mitochondrial function in the fetal hippocampus and prefrontal cortex, impairing neuronal synaptic plasticity via suppression of alpha-ketoglutarate dehydrogenase activity and subsequent reduction in acetyl-CoA production [96]. Furthermore, elevated human chorionic gonadotropin (hCG) levels associated with HG may dysregulate fetal cortical T4 homeostasis by hyperactivating maternal thyroid hormone receptor-beta, triggering microglial activation and neuroinflammation [97–99]. Researchers from the United States and Denmark have noted that children exposed to HG in utero show signs of reduced cortical area and volume in the brain. Additionally, they found an association between abnormal neurodevelopment and a decrease in brain size. Furthermore, fetal head growth in HG patients is positively correlated with maternal weight gain in the second trimester, indicating that malnutrition related to HG in the first half of pregnancy may affect the growth and development of the fetal brain, explaining the increased risk of neurodevelopmental delays in childhood [100,101].

6.3 Respiratory Diseases

Additional research has revealed a possible connection between HG experienced by mothers during pregnancy and an increased risk of respiratory diseases in their children during early childhood [102]. The study revealed a dual risk of HG: on one hand, it may cause intrauterine damage, affecting the normal development of the fetus's lungs; on the other hand, HG may lead to malnutrition in pregnant women, which hinders the normal growth of the fetus and consequently restricts the growth and development of the fetal lungs. This includes reduced lung capacity, fewer branching airways, fewer alveoli, and reduced blood vessel formation [103]. In addition, malnutrition during pregnancy may indirectly affect the development of the fetal lungs due to deficiencies in key micronutrients such as vitamin A, vitamin C, and vitamin D. Hormones involved in metabolic regulation play a crucial role in the development of the lungs during pregnancy, and impaired function of these hormones can also lead to incomplete lung development. Mechanistically, HG-induced maternal micronutrient deficiencies—particularly vitamins A and D—disrupt fetal lung branching morphogenesis and alveolarization.

7. Preterm Birth

PTB, clinically defined as delivery occurring between 24^{+0} and 36^{+6} weeks of gestation [World Health Organization (WHO) criteria], imposes a significant global health burden with profound interregional disparities. However, defining PTB solely by gestational age fails to reflect the highly heterogeneous pathophysiological mechanisms un-

Table 6. Etiology-based classification and diagnosis of preterm birth (PTB) phenotypes.

Type of phenotype	Pathophysiological mechanisms	Diagnostic markers
Infectious/Inflammatory	1. Microbial invasion (chorioamnionitis, deciduitis or systemic infection) 2. Sterile inflammation (e.g., alarmin-mediated)	1. Maternal C-reactive protein (CRP)/interleukin (IL)-6 ↑ 2. Positive amniotic fluid culture 3. Placental histopathology: chorioamnionitis
Vascular/Ischemic	1. Placental insufficiency 2. Maternal vascular disorders (e.g., preeclampsia) 3. Thrombophilia 4. Placental abruption	1. Uterine artery Doppler abnormalities 2. Increased soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio 3. Placental infarction pathology
Endocrine/Stress	1. Premature activation of hypothalamic-pituitary-adrenal (HPA) axis 2. Maternal physiological/psychological stress	1. Elevated maternal salivary cortisol 2. Dynamic cervical shortening (without contractions)
Cervical insufficiency	1. Structural/functional cervical defects	1. Transvaginal ultrasound: cervical length <25 mm (second trimester) 2. History of second-trimester miscarriage
Iatrogenic/Indicated	1. Medically indicated delivery for maternal/fetal compromise	1. Maternal indications: severe preeclampsia/heart failure 2. Fetal indications: Fetal growth restriction (FGR)/abnormal fetal heart rate

↑ indicates that the indicator level is in an "elevated" state.

derlying this condition. Modern clinical practice emphasizes etiology-based classification, which is critical for understanding risks and guiding tailored prevention and treatment strategies (Table 6). Global estimates indicate an incidence of 10.6% of live births, translating to approximately 15 million cases annually, of which over 80% occur in low- and middle-income countries (LMICs) where limited healthcare access exacerbates outcomes [104,105]. It is a common and serious complication during pregnancy, posing a major threat to the newborn's quality of survival and long-term health, and is the leading cause of perinatal death.

7.1 Neurodevelopmental Outcomes

PTB, particularly occurring before 32 weeks of gestation, poses significant risks of lifelong neurological deficits by disrupting normal brain development through multiple pathways. Cohort studies demonstrate stronger correlations between smaller gestational ages and adverse outcomes: Infants born before 28 weeks have a 30%–40% probability of developing severe disabilities (compared to 5%–8% in full-term controls), including CP, intellectual disability, and ASDs [106–108]. This dramatically increases the risk of neurodevelopmental impairments, with negative effects persisting throughout childhood and into adulthood, forming the characteristic "premature neurodevelopmental phenotypic spectrum". The core mechanisms underlying these long-term impacts involve forced interruptions during critical brain development phases (mid-to-late gestation) and exposure to adverse uterine conditions (such as inflammation, hypoxia-ischemia, nutritional stress, and abnormal sensory stimulation). These factors lead to white matter damage [particularly periventricular leukomalacia (PVL)], gray matter developmental abnormalities, and impaired construction of complex neural networks [109,110]. The manifestations are multidimensional functional impairments: In motor domains, CP risk increases dramatically (extremely preterm infants face 20–40 times higher risks than full-term infants), with developmental coordination disorder becoming more prevalent [111]. Cognitive domains exhibit an age-of-birth gradient effect, marked by declining average IQ levels, particularly pronounced executive dysfunction, attention deficits, slowed processing speed, and learning difficulties, significantly increasing special education needs [112]. Behavioral and mental health aspects show that PTB is one of the strongest environmental risk factors for attention deficit/hyperactivity disorder (ADHD) (with 2–5 times increased risk, predominantly in attention deficit variants), substantially elevating ASD prevalence (extremely preterm infants face 4–10 times higher risks than full-term infants), while also raising risks for anxiety, depression, social-emotional difficulties, and behavioral regulation disorders [113]. Sensory function domains demonstrate markedly elevated incidence rates of sensorineural hearing loss, retinopathy of prematurity (ROP), refractive errors, strabismus, cortical visual impairment (CVI), and sensory processing disorder (SPD, characterized by abnormal sensory regulation) [114,115].

7.2 Cardiovascular Conditions

PTB, particularly very preterm (<32 weeks) and extremely preterm (<28 weeks) delivery, is increasingly recognized as a significant risk factor for lifelong cardiovascular morbidity. Cohort studies with extended follow-up demonstrate a gestational age-dependent gradient in cardiovascular risk, persisting into adulthood. Adults born preterm exhibit a 1.5- to 2.5-fold increased incidence of essential hypertension compared to term-born controls, with alterations in 24-hour BP profiles (e.g., reduced nocturnal dipping) detectable as early as adolescence [116]. This predisposition is mechanistically linked to developmental programming perturbations: Premature extrauterine transition during critical windows of cardiovascular development (mid-to-late gestation) induces permanent structural and functional adaptations, including impaired vascular endothelial function, accelerated arterial stiffening, and aberrant left ventricular remodeling [117,118]. Concurrently, dysregulation of neurohormonal axes—specifically hyperactivity of the RAAS and sympathetic nervous system—further amplifies cardiovascular risk [119]. Epidemiological data further associate PTB with a 1.6-fold elevated risk of ischemic heart disease, a 2.1-fold risk of heart failure (predominantly preserved ejection fraction phenotype), and early-onset metabolic syndrome (insulin resistance, dyslipidemia), which synergistically accelerate atherogenesis [120]. Importantly, these effects persist after adjustment for conventional risk factors and intrauterine growth restriction, establishing PTB as an independent determinant of cardiovascular health.

7.3 Respiratory Conditions

PTB imposes profound and persistent burdens on respiratory health by disrupting critical developmental processes. Infants born before 37 weeks of gestation exhibit structural lung immaturity, characterized by impaired alveolar septation, deficient pulmonary surfactant synthesis, and dysregulated angiogenesis due to aberrant VEGF signaling. These defects can acutely manifest as respiratory distress syndrome, and more than 60% of newborns born before 28 weeks of gestation are affected by atelectasis due to insufficient surfactant [121]. Iatrogenic interventions—including mechanical ventilation-induced volutrauma and oxygen toxicity—further drive nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated cytokine release (IL-6, IL-8), culminating in BPD, defined as oxygen dependency at 36 weeks postmenstrual age [122].

7.4 Endocrine Conditions

PTB confers enduring endocrine dysfunction through disruption of hypothalamic-pituitary axis maturation and metabolic programming [123]. Epidemiological studies consistently demonstrate that individuals born preterm exhibit an elevated risk of developing endocrine disorders across the life course. Notably, systematic reviews and meta-analyses reveal a 1.5- to 3-fold increased incidence of insulin resistance, type 2 diabetes mellitus (T2DM), and metabolic syndrome in adulthood compared to term-born counterparts [124,125]. This predisposition is mechanistically linked to developmental programming alterations in hypothalamic-pituitary-adrenal (HPA) axis function and pancreatic β-cell maturation.

8. Discussion

Pregnancy complications—including GDM, HDP, ICP, HG, PTB and thyroid dysfunction—are pivotal determinants of global maternal morbidity (affecting 15–20% of pregnancies) and offspring health trajectories, with intergenerational consequences spanning cardiometabolic, neurodevelopmental, and epigenetic domains [103,126]. Robust evidence from the developmental origins of health and disease (DOHaD) consortium demonstrates that unmanaged GDM increases offspring obesity risk by 3-fold, while HDP elevates childhood hypertension incidence by 40% (Table 7) [127,128]. Thus, optimizing antenatal care transcends clinical obligation, emerging as a public health imperative to disrupt cycles of transgenerational disease transmission.

8.1 Predisposing Factors

GDM is strongly associated with maternal metabolic dysfunction, including obesity [body mass index (BMI) $\geq$25 kg/m^2], advanced maternal age ($\geq$35 years), family history of diabetes, and ethnic predisposition (e.g., South Asian, Hispanic, or African ancestry). Genetic polymorphisms in transcription factor 7 like 2 (*TCF7L2*), melatonin receptor 1B (*MTNR1B*), and glucose transporter type 4 (*GLUT4*) genes impair insulin secretion or sensitivity. Additional risks include polycystic ovary syndrome (PCOS), prior macrosomia, and sedentary lifestyle, which exacerbate insulin resistance through inflammatory pathways [129,130].

HDP arise from a combination of maternal vascular susceptibility (pre-existing hypertension, diabetes, or autoimmune diseases), placental dysfunction (defective spiral artery remodeling, elevated anti-angiogenic factors like sFlt-1) [131], and genetic predisposition [angiotensinogen (*AGT*), Fms-related tyrosine kinase 1 (*FLT1*) polymorphisms] [132]. Demographic factors, multifetal gestation, and lifestyle factors (high-sodium diet, vitamin D deficiency) further amplify risks. A history of prior HDP or placental insufficiency (e.g., FGR) significantly increases recurrence likelihood.

Gestational Thyroid Dysfunction (hypothyroidism or hyperthyroidism) is influenced by autoimmune disorders (e.g., Hashimoto's thyroiditis, Graves' disease), iodine imbalance (deficiency or excess), and genetic susceptibility [TSH receptor (*TSHR*), thyroglobulin (*TG*) gene variants] [69]. Advanced maternal age, obesity, and prior thyroid disease are significant risks.

Table 7. Key clinical management points for high-prevalence diseases during pregnancy.

Type of disease	Management strategies	Pharmacotherapy key	Critical considerations
GDM	1. **Lifestyle modification**: Medical nutrition therapy + 30 min/day moderate exercise.	1. **Insulin**: Aspart/Detemir (dose adjusted to glucose levels).	1. Avoid hypoglycemia/ketoacidosis.
	2. **Glycemic control**: Insulin (1st-line) or metformin (2nd-line).	2. **Oral agents**: Metformin (limited safety data in pregnancy).	2. Postpartum OGTT at 6–12 weeks.
	3. **Fetal surveillance**: Growth ultrasound + amniotic fluid assessment.		3. Long-term type 2 diabetes mellitus (T2DM) risk counseling.
HDP	1. **BP control**: Target <140/90 mmHg (severe: <160/110 mmHg).	1. **Antihypertensives**: Labetalol (1st-line), nifedipine, hydralazine.	1. Monitor for hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome [platelets <100 k, lactate dehydrogenase (LDH) ↑].
	2. **Eclampsia prophylaxis**: Magnesium sulfate (for severe hypertension).	2. **$MgSO_4$**: 4–6 g IV loading dose, then 1–2 g/h (monitor reflexes/urine output).	2. Postpartum BP monitoring for 6 weeks.
	3. **Delivery timing**: Based on gestational age and severity.		
Thyroid disease in pregnancy	1. **Hypothyroidism**: Levothyroxine (LT4) adjusted to trimester-specific TSH targets [Trimester 1 (T1): <2.5 mIU/L; Trimester 2 (T2)/Trimester 3 (T3): <3.0 mIU/L].	1. **Hypothyroidism**: LT4 dose ↑ by 25–30% at conception.	1. Monitor for fetal thyroid dysfunction (hyperthyroidism overtreatment).
	2. **Hyperthyroidism**: Propylthiouracil (PTU) (1st-line in T1) or methimazole (T2 onward), aiming for FT4 at upper-normal range.	2. **Hyperthyroidism**: PTU (50–150 mg/day) or methimazole (5–15 mg/day); avoid overtreatment.	2. Postpartum thyroiditis screening [if particularly thyroid peroxidase antibodies (TPOAb)+].
ICP	1. **Symptom relief**: Ursodeoxycholic acid (UDCA, 10–15 mg/kg/day).	1. **UDCA**: First-line.	1. BAs >40 μmol/L ↑ stillbirth risk.
	2. **Fetal surveillance**: Daily fetal movement + cardiotocography (CTG).	2. **S-Adenosyl methionine (SAMe)**: Adjunctive therapy.	2. Avoid estrogen-containing medications.
	3. **Delivery**: Recommended at 34–36 weeks if bile acids (BAs) ≥40 μmol/L.	3. **Vitamin K**: Prophylaxis if coagulopathy.	
HG	1. **Rehydration**: IV fluids with thiamine + electrolyte correction.	1. **First-line**: Pyridoxine + doxylamine.	1. Exclude thyroid dysfunction/gastrointestinal (GI) disorders.
	2. **Antiemetics**: Pyridoxine (10–25 mg q8h) + doxylamine (12.5 mg q8h); ondansetron (refractory cases).	2. **Second-line**: Ondansetron.	2. Psychological support (high anxiety/depression risk).
	3. **Nutrition**: Enteral/parenteral support if severe.	3. **Refractory cases**: Methylprednisolone (short-term).	
PTB	1. **Prevention**: Vaginal progesterone if corpus luteum (CL) ≤25 mm.	1. **Tocolytics**: Nifedipine (1st-line); indomethacin (<32 weeks).	1. Avoid >48 h tocolysis.
	2. **Promote fetal lung maturation**: Antenatal corticosteroids (ACS)	2. **ACS**: Betamethasone 12 mg intramuscular (IM) × 2.	2. Complete ACS >24 h pre-delivery.
	3. **Neuroprotection and infection prophylaxis**	3. **Neuroprot**: $MgSO_4$ (<32 weeks).	3. Delayed cord clamping ≥60 s.

↑ indicates that the indicator level is in an "elevated" state.

ICP is linked to hormonal dysregulation (elevated estrogen/progesterone), genetic mutations [*ABCB4*, ATP-binding cassette subfamily B member 11 (*ABCB11*) bile transporter genes], and environmental triggers (low selenium levels) [133]. Multiparity, advanced maternal age, and geographic factors are notable risks. A history of ICP in prior pregnancies or gallbladder disease also elevates susceptibility.

HG is driven by hormonal hyperstimulation, particularly elevated hCG and TSH, often exacerbated by thyroid dysfunction. Genetic variants (*GDF15*, *IGFBP7*) affecting nausea pathways, young maternal age, primigravidity, obesity, and psychosocial stress are key contributors [94]. A history of motion sickness or prior HG further predisposes to severe symptoms.

PTB is strongly associated with maternal biological vulnerability, including cervical insufficiency (e.g., short cervical length $<$25 mm), infection/inflammation (genitourinary tract infections, subclinical chorioamnionitis), and environmental stressors (low socioeconomic status, chronic psychological distress) [134,135]. Demographic factors (extremes of maternal age $<$18 or $>$35 years), multifetal gestation, and behavioral risks (smoking, short interpregnancy interval $<$6 months) further amplify risks [136,137]. Critically, PTB rarely results from a single insult but represents a final common pathway wherein infectious, mechanical, vascular, endocrine, and immune perturbations synergistically precipitate premature activation of the parturition cascade.

8.2 Latest Treatment Advances

Recent advances in GDM management focus on precision therapeutics and technological integration to optimize maternal-fetal outcomes. Emerging microbiome-targeted interventions, exemplified by Lactobacillus and Bifidobacterium probiotic supplementation combined with dietary modulation, demonstrate enhanced insulin sensitivity [138,139]. Pharmacological innovation includes ultra-long-acting insulin analogs such as degludec, which, when paired with rapid-acting aspart, reduce hypoglycemia risk through stabilized glycemic profiles and minimized peak-trough fluctuations [140]. Additionally, anti-inflammatory strategies targeting IL-6 signaling and omega-3 fatty acid supplementation show promise in trials, addressing subclinical inflammation implicated in placental insulin resistance [141,142]. These multimodal approaches underscore a paradigm shift toward individualized, pathophysiology-driven therapies, though long-term efficacy and safety warrant further validation in diverse cohorts.

In the pharmacological management of HDP, labetalol and nifedipine sustained-release tablets remain the first-line antihypertensive agents. However, methyldopa is newly recommended as a safer alternative for pregnant women with coexisting FGR. For patients with moderate-to-severe preeclampsia, magnesium sulfate must be administered during the antenatal period and within 24 hours postpartum to prevent eclamptic seizures, regardless of the presence of neurological symptoms. Concurrently, the guidelines have clarified adjustments to contraindicated medications: angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) are strictly prohibited (due to their teratogenic risk), and diuretics are restricted to cases complicated by pulmonary edema or heart failure. However, the current management model for HDP is gradually shifting from traditional therapies to novel treatment approaches targeting placental dysfunction and inflammatory pathways. Leading advancements include anti-angiogenic therapies and sFlt-1 apheresis (e.g., Apharesis), which reduces circulating sFlt-1 and prolongs gestation by 7–10 days in trials [143]. Immunomodulatory strategies show promise: complement inhibitors (e.g., eculizumab) mitigate refractory cases associated with complement overactivation [144], and pravastatin reduces the risk of early-onset preeclampsia by upregulating PlGF and suppressing sFlt-1 [145]. While these innovations highlight a shift toward precision medicine, rigorous evaluation of fetal safety and long-term efficacy remains essential. Future directions emphasize multi-omics integration and placental-targeted drug delivery to optimize outcomes.

The management of thyroid dysfunction during pregnancy has advanced beyond conventional approaches, such as levothyroxine (LT4) for hypothyroidism and propylthiouracil (PTU) for hyperthyroidism. Recent innovative studies have focused on optimizing hormone delivery systems, modulating autoantibody activity, and developing personalized nutritional regimens. Evidence confirms that thyroid hormone analogs, including nanoformulated LT4 [(e.g., Tirosint-solution (SOL)], enhance bioavailability while reducing interpatient dosage variability compared to conventional formulations [146]. TSH receptor monoclonal antibodies (such as K1-70) are currently in Phase I clinical trials and may potentially block maternal TSH receptor autoantibodies to protect thyroid function in fetuses with Graves' disease [147].

Current management of ICP primarily involves ursodeoxycholic acid (UDCA) to reduce BAs toxicity, often combined with cholestyramine for pruritus relief. Recent advances aim to address BAs dysregulation and genetic underpinnings: novel BAs modulators, such as the Farnesoid X receptor (FXR) agonist obeticholic acid, can inhibit BAs synthesis. Research findings indicate that oral BAs preparations can improve fetal BAs metabolism [148]. Gut microbiota-targeted therapies, including fecal microbiota transplantation, reshape BAs-metabolizing bacteria (e.g., Bacteroides), lowering serum BAs in preclinical models [149].

Current management of HG relies on conventional approaches, including antiemetics (e.g., ondansetron), corticosteroids, intravenous hydration, and nutritional support. Recent advances have introduced targeted therapies ad-

dressing underlying molecular and neuroendocrine mechanisms. Neurokinin-1 receptor antagonists such as aprepitant suppress central vomiting reflexes, showing efficacy in refractory HG cases. Additionally, gut microbiota modulation via probiotic formulations may attenuate vomiting frequency through gut-brain axis regulation, though requiring validation in large-scale trials [150].

Recent advances in PTB prevention and management emphasize targeted molecular interventions and precision risk stratification to mitigate neonatal morbidity. In monitoring technology, the innovative application of electrophysiological sensing platforms tracks real-time electrophysiological activities and intracellular calcium transients, enabling dynamic monitoring of uterine cellular behavior during inflammation-associated PTB [151]. This facilitates investigation into mechanisms of inflammation-driven PTB and further development of targeted therapies. Emerging anti-inflammatory strategies—such as the use of a small peptide, HSJ633, which antagonizes the IL-6 receptor to block IL-6 signaling—inhibit the inflammation cascade associated with PTB and mitigate adverse neonatal outcomes [152]. Novel microbiome-based interventions include vaginal microbiota transplantation from Lactobacillus-dominant donors, reducing PTB recurrence in bacterial vaginosis [153,154]. Despite these advances, clinical translation confronts persistent barriers: real-time electrophysiological monitoring techniques are prohibitively costly for routine screening, and novel anti-inflammatory agents lack robust human safety data.

8.3 Crosstalk of Pregnancy Complications

Gestational metabolic and endocrine disorders, including GDM, HDP, ICP, HG, and thyroid dysfunction, exhibit intricate pathophysiological crosstalk mediated by shared mechanisms such as inflammatory activation, oxidative stress, placental dysfunction, and hormonal dysregulation. Insulin resistance in GDM activates NF-κB signaling, exacerbating systemic inflammation and endothelial dysfunction, which synergize with anti-angiogenic factors (e.g., sFlt-1) from HDP placentas to impair β-cell function and glucose metabolism [155]. Elevated BAs in ICP trigger Toll-like receptor 4-mediated placental oxidative stress and pro-inflammatory cytokine release (e.g., IL-6, TNF-α), aggravating vascular endothelial damage in HDP [156]. Thyroid dysfunction further modulates this network: hypothyroidism reduces antioxidant enzyme activity [e.g., superoxide dismutase (SOD), glutathione peroxidase (GPx)], worsening metabolic disturbances in GDM and HDP [157,158].

Placental dysfunction serves as a central hub for crosstalk. HIF-1α activation in HDP suppresses insulin receptor substrate signaling, intensifying insulin resistance, while hyperglycemia in GDM dysregulates placental VEGF, exacerbating defective vascular remodeling [159,160]. BAs accumulation in ICP damages syncytiotrophoblasts, impairing placental barrier integrity and promoting transplacental transfer of inflammatory mediators, thereby elevating long-term risks of GDM and cardiovascular diseases [161]. Maternal hypothyroidism, via reduced placental VEGF expression, worsens HDP and FGR [162].

Hormonal interplay further links these disorders: HG-associated hyperemesis elevates hCG, which cross-reacts with TSH receptors to induce transient gestational thyrotoxicosis, while malnutrition from severe vomiting disrupts thyroid hormone synthesis [163]. GDM-driven hyperinsulinemia suppresses thyroid peroxidase activity via phosphoinositide 3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog (Akt) signaling, increasing subclinical hypothyroidism risk [164]. Adipokine imbalances (e.g., elevated leptin/adiponectin ratios) in GDM and HDP perturb TSH secretion through hypothalamic-pituitary-thyroid axis dysregulation [165].

9. Conclusion

In conclusion, our review discussed that pregnancy complications function not only indicate perinatal risks but may also exert transgenerational impacts on offspring lifespan health through mechanisms including epigenetic regulation, placental dysfunction, and maternal-fetal metabolic interactions. However, these mechanisms remain incompletely elucidated, such as the interactive mechanisms underlying comorbid pregnancy complications. Meanwhile, tracking of offspring long-term outcomes predominantly terminates at adolescence, lacking life-course multi-omics longitudinal data. Future research is expected to provide further insights into both the independent pathogenesis of pregnancy complications and their cross-talking interaction mechanisms. This mechanistic clarity will catalyze the development of precision screening modalities and targeted therapeutic strategies. However, while current clinical guidelines provide frameworks for complication management, interventions capable of reducing or blocking offspring impacts remain unvalidated—to improve the long-term health effects on offspring of pregnancy complications globally, these areas still require in-depth research.

In the future, by focusing on genetic and epigenetic regulatory networks, we will systematically investigate the genetic susceptibility genes and the critical roles of epigenetic modifications (e.g., DNA methylation and non-coding RNAs) in pregnancy complications, aiming to elucidate their biological basis in mediating transgenerational health effects on maternal and offspring outcomes. Building on this foundation, we will delve into metabolic interaction mechanisms, employing multidimensional approaches to unravel the molecular linkages between gestational metabolic dysregulation (such as bile acid imbalance and insulin resistance) and these complications, with a particular emphasis on the dynamic metabolic crosstalk at the placental-maternal-fetal interface, thereby establishing a robust theoretical foundation for targeted interventions. Furthermore, through the integration of multi-omics tech-

nologies (metabolomics, proteomics, and microbiome analysis), we will identify early-stage specific biomarkers reflecting pathological progression, develop high-sensitivity and high-specificity screening models for pregnancy complications, and drive the transformation of clinical diagnostic paradigms from a "symptom-driven" to a "prevention-oriented" framework.

Abbreviations

GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; ICP, intrahepatic cholestasis of pregnancy; HG, hyperemesis gravidarum; PTB, preterm birth; FGR, fetal growth restriction; LBW, low birth weight; OGTT, oral glucose tolerance test; GCT, glucose challenge test; TNF-α, tumour necrosis factor-α; IL, interleukin; NRDS, neonatal respiratory distress syndrome; ASD, autism spectrum disorder; BP, blood pressure; SGA, small-for-gestational-age; CHD, congenital heart disease; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; HIF-1α, hypoxia-inducible factor-1α; RAAS, renin-angiotensin-aldosterone system; CTG, cardiotocography; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; T4, thyroxine; TPOAb, thyroid peroxidase antibodies; T3, triiodothyronine; TBA, total bile acid; BAs, bile acids; MSAF, meconium-stained amniotic fluid; hCG, human chorionic gonadotropin; WHO, World Health Organization; LMICs, low- and middle-income countries; CRP, C-reactive protein; PVL, periventricular leukomalacia; CP, cerebral palsy; ADHD, attention deficit/hyperactivity disorder; ROP, retinopathy of prematurity; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; CVI, cortical visual impairment; SPD, sensory processing disorder; BPD, bronchopulmonary dysplasia; T2DM, type 2 diabetes mellitus; HPA, hypothalamic-pituitary-adrenal; DOHaD, developmental origins of health and disease; LDH; lactate dehydrogenase; LT4, levothyroxine; ACS, antenatal corticosteroids; PTU, propylthiouracil; UDCA, ursodeoxycholic acid; CL, corpus luteum; SAMe, S-Adenosyl methionine; GI, gastrointestinal; PCOS, polycystic ovary syndrome; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; FXR, Farnesoid X receptor; SOD, superoxide dismutase; GPx, glutathione peroxidase; VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; Akt, v-akt murine thymoma viral oncogene homolog; JNK, c-Jun N-terminal kinase; IRS-1, insulin receptor substrate-1; *H19*, *H19* imprinted maternally expressed transcript; DMR, differentially methylated region; *IGF2*, insulin-like growth factor 2; *GDF15*, growth differentiation factor 15; *IGFBP7*, insulin-like growth factor binding protein 7; *GFRAL*, GDNF family receptor alpha like; *PGR*, progesterone receptor; *TCF7L2*, transcription factor 7 like 2; *MTNR1B*, melatonin receptor 1B; *GLUT4*, glucose transporter type 4; *AGT*, angiotensinogen; *FLT1*, Fms-related tyrosine kinase 1; *TSHR*, TSH receptor; *TG*, thyroglobulin; *ABCB4*, ATP-binding cassette subfamily B member 4; *ABCB11*, ATP-binding cassette subfamily B member 11; HELLP, hemolysis, elevated liver enzymes, and low platelets; T1, Trimester 1; T2, Trimester 2; T3, Trimester 3; BMI, body mass index; SOL, solution; IQ, intelligence quotient; NA, not applicable; IM, intramuscular.

Author Contributions

JL, SC and YY drafted and revised the manuscript. JL, SC and YY made substantial contributions to data acquisition and analysis and critically reviewed the important intellectual content. The table was conducted by JL. YY contributed to preparing draft and editorial revisions. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Couture C, Girard S. Diagnostic or Therapeutic Strategies for Pregnancy Complications. Journal of Clinical Medicine. 2022; 11: 3144. https://doi.org/10.3390/jcm11113144.

[2] Bodunde EO, Buckley D, O'Neill E, Al Khalaf S, Maher GM, O'Connor K, *et al*. Pregnancy and birth complications and long-term maternal mental health outcomes: A systematic review and meta-analysis. BJOG: an International Journal of Obstetrics and Gynaecology. 2025; 132: 131–142. https://doi.org/10.1111/1471-0528.17889.

[3] Downing J, Sjeklocha L. Trauma in Pregnancy. Emergency Medicine Clinics of North America. 2023; 41: 223–245. https://doi.org/10.1016/j.emc.2022.12.001.

[4] Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ (Clinical Research Ed.). 2002; 325: 157–160. https://doi.org/10.1136/bmj.325.7356.157.

[5] Panaitescu AM, Popescu MR, Ciobanu AM, Gica N, Cimpoca-Raptis BA. Pregnancy Complications Can Foreshadow Future Disease-Long-Term Outcomes of a Complicated Pregnancy. Medicina (Kaunas, Lithuania). 2021; 57: 1320. https://doi.org/10.3390/medicina57121320.

[6] Taylor HS. Role of the uterus in fertility, pregnancy, and developmental programming. Fertility and Sterility. 2018; 110: 849–850. https://doi.org/10.1016/j.fertnstert.2018.08.032.

[7] Oulerich Z, Sferruzzi-Perri AN. Early-life exposures and long-term health: adverse gestational environments and the programming of offspring renal and vascular disease. American Journal of Physiology. Renal Physiology. 2024; 327: F21–F36. https://doi.org/10.1152/ajprenal.00383.2023.

[8] Gómez-Roig MD, Pascal R, Cahuana MJ, García-Algar O, Sebastiani G, Andreu-Fernández V, *et al*. Environmental Exposure during Pregnancy: Influence on Prenatal Development and Early Life: A Comprehensive Review. Fetal Diagnosis and Therapy. 2021; 48: 245–257. https://doi.org/10.1159/000514884.

[9] Mulder JWCM, Kusters DM, Roeters van Lennep JE, Hutten BA. Lipid metabolism during pregnancy: consequences for mother and child. Current Opinion in Lipidology. 2024; 35: 133–140. https://doi.org/10.1097/MOL.0000000000000927.

[10] Hintze G. Endocrinology and pregnancy. Deutsche Medizinische Wochenschrift (1946). 2023; 148: 1. https://doi.org/10.1055/a-1485-9124. (In German)

[11] Gao C, Sun X, Lu L, Liu F, Yuan J. Prevalence of gestational diabetes mellitus in mainland China: A systematic review and meta-analysis. Journal of Diabetes Investigation. 2019; 10: 154–162. https://doi.org/10.1111/jdi.12854.

[12] Moon JH, Jang HC. Gestational Diabetes Mellitus: Diagnostic Approaches and Maternal-Offspring Complications. Diabetes & Metabolism Journal. 2022; 46: 3–14. https://doi.org/10.4093/dmj.2021.0335.

[13] Sweeting A, Hannah W, Backman H, Catalano P, Feghali M, Herman WH, *et al*. Epidemiology and management of gestational diabetes. Lancet (London, England). 2024; 404: 175–192. https://doi.org/10.1016/S0140-6736(24)00825-0.

[14] Fall CHD. Evidence for the intra-uterine programming of adiposity in later life. Annals of Human Biology. 2011; 38: 410–428. https://doi.org/10.3109/03014460.2011.592513.

[15] Kowalcze K, Burgio S, Gullo G, Kula-Gradzik J, Ott J, Krysiak R. The Impact of Gestational Diabetes Mellitus on Minipuberty in Girls. International Journal of Molecular Sciences. 2024; 25: 11766. https://doi.org/10.3390/ijms252111766.

[16] Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Annals of Nutrition & Metabolism. 2015; 66 Suppl 2: 14–20. https://doi.org/10.1159/000371628.

[17] McFarland MB, Trylovich CG, Langer O. Anthropometric differences in macrosomic infants of diabetic and nondiabetic mothers. The Journal of Maternal-fetal Medicine. 1998; 7: 292–295. https://doi.org/10.1002/(SICI)1520-6661(199811/12)7:6<292::AID-MFM7>3.0.CO;2-A.

[18] Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. Diabetes. 1980; 29: 1023–1035. https://doi.org/10.2337/diab.29.12.1023.

[19] Dudley DJ. Diabetic-associated stillbirth: incidence, pathophysiology, and prevention. Obstetrics and Gynecology Clinics of North America. 2007; 34: 293–307, ix. https://doi.org/10.1016/j.ogc.2007.03.001.

[20] Salvesen DR, Brudenell JM, Snijders RJ, Ireland RM, Nicolaides KH. Fetal plasma erythropoietin in pregnancies complicated by maternal diabetes mellitus. American Journal of Obstetrics and Gynecology. 1993; 168: 88–94. https://doi.org/10.1016/s0002-9378(12)90891-1.

[21] Hunter DJ, Burrows RF, Mohide PT, Whyte RK. Influence of maternal insulin-dependent diabetes mellitus on neonatal morbidity. CMAJ: Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne. 1993; 149: 47–52.

[22] Alejandro EU, Mamerto TP, Chung G, Villavieja A, Gaus NL, Morgan E, *et al*. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes. International Journal of Molecular Sciences. 2020; 21: 5003. https://doi.org/10.3390/ijms21145003.

[23] Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. The New England Journal of Medicine. 1983; 308: 242–245. https://doi.org/10.1056/NEJM198302033080502.

[24] Franks PW, Looker HC, Kobes S, Touger L, Tataranni PA, Hanson RL, *et al*. Gestational glucose tolerance and risk of type 2 diabetes in young Pima Indian offspring. Diabetes. 2006; 55: 460–465. https://doi.org/10.2337/diabetes.55.02.06.db05-0823.

[25] Ylinen K. High maternal levels of hemoglobin A1c associated with delayed fetal lung maturation in insulin-dependent diabetic pregnancies. Acta Obstetricia et Gynecologica Scandinavica. 1987; 66: 263–266. https://doi.org/10.3109/00016348709020759.

[26] Saucedo R, Ortega-Camarillo C, Ferreira-Hermosillo A, Díaz-Velázquez MF, Meixueiro-Calderón C, Valencia-Ortega J. Role of Oxidative Stress and Inflammation in Gestational Diabetes Mellitus. Antioxidants (Basel, Switzerland). 2023; 12: 1812. https://doi.org/10.3390/antiox12101812.

[27] Fasoulakis Z, Koutras A, Antsaklis P, Theodora M, Valsamaki A, Daskalakis G, *et al*. Intrauterine Growth Restriction Due to Gestational Diabetes: From Pathophysiology to Diagnosis and Management. Medicina (Kaunas, Lithuania). 2023; 59: 1139. https://doi.org/10.3390/medicina59061139.

[28] Fraser A, Nelson SM, Macdonald-Wallis C, Lawlor DA. Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the Avon Longitudinal Study of Parents and Children. Experimental Diabetes Research. 2012; 2012: 963735. https://doi.org/10.1155/2012/963735.

[29] Dionne G, Boivin M, Séguin JR, Pérusse D, Tremblay RE. Gestational diabetes hinders language development in offspring. Pediatrics. 2008; 122: e1073–9. https://doi.org/10.1542/peds.2007-3028.

[30] Sappler M, Volleritsch N, Hammerl M, Pellkofer Y, Griesmaier E, Gizewski ER, *et al*. Microstructural Brain Development and Neurodevelopmental Outcome of Very Preterm Infants of Mothers with Gestational Diabetes Mellitus. Neonatology. 2023; 120: 768–775. https://doi.org/10.1159/000533335.

[31] Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, *et al*. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2022; 27: 148–169. https://doi.org/10.1016/j.preghy.2021.09.008.

[32] Jiang L, Tang K, Magee LA, von Dadelszen P, Ekeroma A, Li X, *et al*. A global view of hypertensive disorders and diabetes mellitus during pregnancy. Nature Reviews. Endocrinology. 2022; 18: 760–775. https://doi.org/10.1038/s41574-022-00734-y.

[33] Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Preeclampsia: pathogenesis, novel diagnostics and therapies. Nature Reviews. Nephrology. 2019; 15: 275–289. https://doi.org/10.1038/s41581-019-0119-6.

[34] Di Martino DD, Avagliano L, Ferrazzi E, Fusè F, Sterpi V, Parasiliti M, *et al*. Hypertensive Disorders of Pregnancy and Fetal Growth Restriction: Clinical Characteristics and Placental Lesions and Possible Preventive Nutritional Targets. Nutrients. 2022; 14: 3276. https://doi.org/10.3390/nu14163276.

[35] Di Martino DD, Stampalija T, Zullino S, Fusè F, Garbin M, Parasiliti M, *et al*. Maternal hemodynamic profile during pregnancy and in the post-partum in hypertensive disorders of pregnancy and fetal growth restriction. American Journal of Obstetrics & Gynecology MFM. 2023; 5: 100841. https://doi.org/10.1016/j.ajogmf.2022.100841.

[36] Ratnasiri AWG, Parry SS, Arief VN, DeLacy IH, Lakshmin-

rusimha S, Halliday LA, *et al*. Temporal trends, patterns, and predictors of preterm birth in California from 2007 to 2016, based on the obstetric estimate of gestational age. Maternal Health, Neonatology and Perinatology. 2018; 4: 25. https://doi.org/10.1186/s40748-018-0094-0.

[37] Yamaguchi Y, Tayama C, Tomikawa J, Akaishi R, Kamura H, Matsuoka K, *et al*. Placenta-specific epimutation at H19-DMR among common pregnancy complications: its frequency and effect on the expression patterns of H19 and IGF2. Clinical Epigenetics. 2019; 11: 113. https://doi.org/10.1186/s13148-019-0712-3.

[38] Zur RL, Kingdom JC, Parks WT, Hobson SR. The Placental Basis of Fetal Growth Restriction. Obstetrics and Gynecology Clinics of North America. 2020; 47: 81–98. https://doi.org/10.1016/j.ogc.2019.10.008.

[39] Mecacci F, Romani E, Clemenza S, Zullino S, Avagliano L, Petraglia F. Early Fetal Growth Restriction with or Without Hypertensive Disorders: a Clinical Overview. Reproductive Sciences (Thousand Oaks, Calif.). 2024; 31: 591–602. https://doi.org/10.1007/s43032-023-01330-9.

[40] Whitehouse AJO, Robinson M, Newnham JP, Pennell CE. Do hypertensive diseases of pregnancy disrupt neurocognitive development in offspring? Paediatric and Perinatal Epidemiology. 2012; 26: 101–108. https://doi.org/10.1111/j.1365-3016.2011.01257.x.

[41] Mann JR, McDermott S, Griffith MI, Hardin J, Gregg A. Uncovering the complex relationship between pre-eclampsia, preterm birth and cerebral palsy. Paediatric and Perinatal Epidemiology. 2011; 25: 100–110. https://doi.org/10.1111/j.1365-3016.2010.01157.x.

[42] Grace T, Bulsara M, Pennell C, Hands B. Maternal hypertensive diseases negatively affect offspring motor development. Pregnancy Hypertension. 2014; 4: 209–214. https://doi.org/10.1016/j.preghy.2014.04.003.

[43] Ivry RB. Cerebellar involvement in clumsiness and other developmental disorders. Neural Plasticity. 2003; 10: 141–153. https://doi.org/10.1155/NP.2003.141.

[44] Heikura U, Hartikainen AL, Nordström T, Pouta A, Taanila A, Järvelin MR. Maternal hypertensive disorders during pregnancy and mild cognitive limitations in the offspring. Paediatric and Perinatal Epidemiology. 2013; 27: 188–198. https://doi.org/10.1111/ppe.12028.

[45] Bharadwaj SK, Vishnu Bhat B, Vickneswaran V, Adhisivam B, Bobby Z, Habeebullah S. Oxidative Stress, Antioxidant Status and Neurodevelopmental Outcome in Neonates Born to Pre-eclamptic Mothers. Indian Journal of Pediatrics. 2018; 85: 351–357. https://doi.org/10.1007/s12098-017-2560-5.

[46] Dachew BA, Mamun A, Maravilla JC, Alati R. Pre-eclampsia and the risk of autism-spectrum disorder in offspring: meta-analysis. The British Journal of Psychiatry: the Journal of Mental Science. 2018; 212: 142–147. https://doi.org/10.1192/bjp.2017.27.

[47] Liu A, Carlsson E, Nilsson S, Oei J, Bajuk B, Peek M, *et al*. Hypertensive disease of pregnancy is associated with decreased risk for respiratory distress syndrome in moderate preterm neonates. Hypertension in Pregnancy. 2013; 32: 169–177. https://doi.org/10.3109/10641955.2013.784786.

[48] Wang Y, Li B, Tong F. Global trends in research of immune cells associated with hypertensive disorders of pregnancy: A 20-year bibliometric analyses (from 2001 to 2021). Frontiers in Immunology. 2023; 13: 1036461. https://doi.org/10.3389/fimmu.2022.1036461.

[49] Ushida T, Nakamura N, Nakatochi M, Kobayashi Y, Sato Y, Iitani Y, *et al*. Impact of hypertensive disorders of pregnancy on respiratory outcomes in extremely and very preterm infants: A population-based study in Japan. Pregnancy Hypertension. 2022; 29: 54–60. https://doi.org/10.1016/j.preghy.2022.06.003.

[50] Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nature Reviews. Endocrinology. 2017; 13: 610–622. https://doi.org/10.1038/nrendo.2017.93.

[51] Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. European Journal of Endocrinology. 2004; 151 Suppl 3: U25–37. https://doi.org/10.1530/eje.0.151u025.

[52] Balli S, Kibar AE, Ece I, Oflaz MB, Yilmaz O. Assessment of fetal cardiac function in mild preeclampsia. Pediatric Cardiology. 2013; 34: 1674–1679. https://doi.org/10.1007/s00246-013-0702-8.

[53] Reveret M, Boivin A, Guigonnis V, Audibert F, Nuyt AM. Preeclampsia: effect on newborn blood pressure in the 3 days following preterm birth: a cohort study. Journal of Human Hypertension. 2015; 29: 115–121. https://doi.org/10.1038/jhh.2014.50.

[54] Staley JR, Bradley J, Silverwood RJ, Howe LD, Tilling K, Lawlor DA, *et al*. Associations of blood pressure in pregnancy with offspring blood pressure trajectories during childhood and adolescence: findings from a prospective study. Journal of the American Heart Association. 2015; 4: e001422. https://doi.org/10.1161/JAHA.114.001422.

[55] Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association Between Preeclampsia and Congenital Heart Defects. JAMA. 2015; 314: 1588–1598. https://doi.org/10.1001/jama.2015.12505.

[56] Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, *et al*. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. Hypertension (Dallas, Tex.: 1979). 2012; 60: 1338–1345. https://doi.org/10.1161/HYPERTENSIONAHA.112.198366.

[57] Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, *et al*. Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? Hypertension (Dallas, Tex.: 1979). 2010; 56: 159–165. https://doi.org/10.1161/HYPERTENSIONAHA.110.150235.

[58] Naderi S, Tsai SA, Khandelwal A. Hypertensive Disorders of Pregnancy. Current Atherosclerosis Reports. 2017; 19: 15. https://doi.org/10.1007/s11883-017-0648-z.

[59] Yang JM, Wang KG. Relationship between acute fetal distress and maternal-placental-fetal circulations in severe preeclampsia. Acta Obstetricia et Gynecologica Scandinavica. 1995; 74: 419–424. https://doi.org/10.3109/00016349509024402.

[60] Khalsa DDK, Beydoun HA, Carmody JB. Prevalence of chronic kidney disease risk factors among low birth weight adolescents. Pediatric Nephrology (Berlin, Germany). 2016; 31: 1509–1516. https://doi.org/10.1007/s00467-016-3384-7.

[61] Starzec K, Klimek M, Grudzień A, Jagła M, Kwinta P. Longitudinal assessment of renal size and function in extremely low birth weight children at 7 and 11 years of age. Pediatric Nephrology (Berlin, Germany). 2016; 31: 2119–2126. https://doi.org/10.1007/s00467-016-3413-6.

[62] Tain YL, Hsu CN. The Renin-Angiotensin System and Cardiovascular-Kidney-Metabolic Syndrome: Focus on Early-Life Programming. International Journal of Molecular Sciences. 2024; 25: 3298. https://doi.org/10.3390/ijms25063298.

[63] Dong AC, Stagnaro-Green A. Differences in Diagnostic Criteria Mask the True Prevalence of Thyroid Disease in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid: Official Journal of the American Thyroid Association. 2019; 29: 278–289. https://doi.org/10.1089/thy.2018.0475.

[64] Préau L, Fini JB, Morvan-Dubois G, Demeneix B. Thyroid hormone signaling during early neurogenesis and its significance

as a vulnerable window for endocrine disruption. Biochimica et Biophysica Acta. 2015; 1849: 112–121. https://doi.org/10.1016/j.bbagrm.2014.06.015.

[65] Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, *et al*. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. The New England Journal of Medicine. 1999; 341: 549–555. https://doi.org/10.1056/NEJM199908193410801.

[66] Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. Obstetrics and Gynecology. 2006; 107: 337–341. https://doi.org/10.1097/01.AOG.0000197991.64246.9a.

[67] Zhang C, Yang X, Zhang Y, Guo F, Yang S, Peeters RP, *et al*. Association Between Maternal Thyroid Hormones and Birth Weight at Early and Late Pregnancy. The Journal of Clinical Endocrinology and Metabolism. 2019; 104: 5853–5863. https://doi.org/10.1210/jc.2019-00390.

[68] Kent NL, Atluri SC, Moritz KM, Cuffe JSM. Maternal hypothyroidism in rats impairs placental nutrient transporter expression, increases labyrinth zone size, and impairs fetal growth. Placenta. 2023; 139: 148–158. https://doi.org/10.1016/j.placenta.2023.06.010.

[69] Bucci I, Giuliani C, Napolitano G. Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance. Frontiers in Endocrinology. 2017; 8: 137. https://doi.org/10.3389/fendo.2017.00137.

[70] Lazarus JH. Thyroid disease in pregnancy and childhood. Minerva Endocrinologica. 2005; 30: 71–87.

[71] Svensson J, Oderup C, Akesson C, Uvebrant K, Hallengren B, Ericsson UB, *et al*. Maternal autoimmune thyroid disease and the fetal immune system. Experimental and Clinical Endocrinology & Diabetes: Official Journal, German Society of Endocrinology [and] German Diabetes Association. 2011; 119: 445–450. https://doi.org/10.1055/s-0031-1279741.

[72] Korevaar TIM, Muetzel R, Medici M, Chaker L, Jaddoe VWV, de Rijke YB, *et al*. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. The Lancet. Diabetes & Endocrinology. 2016; 4: 35–43. https://doi.org/10.1016/S2213-8587(15)00327-7.

[73] Strobl MTJ, Freeman D, Patel J, Poulsen R, Wendler CC, Rivkees SA, *et al*. Opposing Effects of Maternal Hypo- and Hyperthyroidism on the Stability of Thalamocortical Synapses in the Visual Cortex of Adult Offspring. Cerebral Cortex (New York, N.Y.: 1991). 2017; 27: 3015–3027. https://doi.org/10.1093/cercor/bhw096.

[74] Salazar P, Cisternas P, Martinez M, Inestrosa NC. Hypothyroidism and Cognitive Disorders during Development and Adulthood: Implications in the Central Nervous System. Molecular Neurobiology. 2019; 56: 2952–2963. https://doi.org/10.1007/s12035-018-1270-y.

[75] Martinez ME, Pinz I, Preda M, Norton CR, Gridley T, Hernandez A. DIO3 protects against thyrotoxicosis-derived craniencephalic and cardiac congenital abnormalities. JCI Insight. 2022; 7: e161214. https://doi.org/10.1172/jci.insight.161214.

[76] Ge GM, Leung MTY, Man KKC, Leung WC, Ip P, Li GHY, *et al*. Maternal Thyroid Dysfunction During Pregnancy and the Risk of Adverse Outcomes in the Offspring: A Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology and Metabolism. 2020; 105: dgaa555. https://doi.org/10.1210/clinem/dgaa555.

[77] Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Lee RH, Mara Greenberg, Metz TD, Pettker CM. Society for Maternal-Fetal Medicine Consult Series #53: Intrahepatic cholestasis of pregnancy: Replaces Consult #13, April 2011. American Journal of Obstetrics and Gynecology. 2021; 224: B2–B9. https://doi.org/10.1016/j.ajog.2020.11.002.

[78] Falcão D, Pedroto I, Moreira T. The wide phenotypic and genetic spectrum of ABCB4 gene deficiency: A case series. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2022; 54: 221–227. https://doi.org/10.1016/j.dld.2021.07.003.

[79] Zhou Q, Yuan Y, Wang Y, He Z, Liang Y, Qiu S, *et al*. The severity of intrahepatic cholestasis during pregnancy increases risks of adverse outcomes beyond stillbirth: evidence from 15,826 patients. BMC Pregnancy and Childbirth. 2024; 24: 476. https://doi.org/10.1186/s12884-024-06645-2.

[80] Campos GA, Castillo RJ, Toro FG. Effect of bile acids on the myometral contractility of the isolated pregnant uterus. Revista Chilena De Obstetricia Y Ginecologia. 1988; 53: 229–233. (In Spanish)

[81] Reid R, Ivey KJ, Rencoret RH, Storey B. Fetal complications of obstetric cholestasis. British Medical Journal. 1976; 1: 870–872. https://doi.org/10.1136/bmj.1.6014.870.

[82] Geenes VL, Lim YH, Bowman N, Tailor H, Dixon PH, Chambers J, *et al*. A placental phenotype for intrahepatic cholestasis of pregnancy. Placenta. 2011; 32: 1026–1032. https://doi.org/10.1016/j.placenta.2011.09.006.

[83] Al Inizi S, Gupta R, Gale A. Fetal tachyarrhythmia with atrial flutter in obstetric cholestasis. International Journal of Gynaecology and Obstetrics: the Official Organ of the International Federation of Gynaecology and Obstetrics. 2006; 93: 53–54. https://doi.org/10.1016/j.ijgo.2005.12.030.

[84] Williamson C, Gorelik J, Eaton BM, Lab M, de Swiet M, Korchev Y. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death in obstetric cholestasis. Clinical Science (London, England: 1979). 2001; 100: 363–369.

[85] Sepúlveda WH, González C, Cruz MA, Rudolph MI. Vasoconstrictive effect of bile acids on isolated human placental chorionic veins. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 1991; 42: 211–215. https://doi.org/10.1016/0028-2243(91)90222-7.

[86] Vasavan T, Deepak S, Jayawardane IA, Lucchini M, Martin C, Geenes V, *et al*. Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. Journal of Hepatology. 2021; 74: 1087–1096. https://doi.org/10.1016/j.jhep.2020.11.038.

[87] Fan X, Zhou Q, Zeng S, Zhou J, Peng Q, Zhang M, *et al*. Impaired fetal myocardial deformation in intrahepatic cholestasis of pregnancy. Journal of Ultrasound in Medicine: Official Journal of the American Institute of Ultrasound in Medicine. 2014; 33: 1171–1177. https://doi.org/10.7863/ultra.33.7.1171.

[88] Lee RH, Goodwin TM, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. Journal of Perinatology: Official Journal of the California Perinatal Association. 2006; 26: 527–532. https://doi.org/10.1038/sj.jp.7211545.

[89] Falconer JD, Smith AN, Eastwood MA. The effects of bile acids on colonic motility in the rabbit. Quarterly Journal of Experimental Physiology and Cognate Medical Sciences. 1980; 65: 135–144. https://doi.org/10.1113/expphysiol.1980.sp002497.

[90] Zecca E, De Luca D, Marras M, Caruso A, Bernardini T, Romagnoli C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. Pediatrics. 2006; 117: 1669–1672. https://doi.org/10.1542/peds.2005-1801.

[91] Abramowitz A, Miller ES, Wisner KL. Treatment options for hyperemesis gravidarum. Archives of Women's Mental Health. 2017; 20: 363–372. https://doi.org/10.1007/s00737-016-0707-4.

[92] Koudijs HM, Savitri AI, Browne JL, Amelia D, Baharuddin M, Grobbee DE, *et al*. Hyperemesis gravidarum and placental dysfunction disorders. BMC Pregnancy and Childbirth. 2016; 16: 374. https://doi.org/10.1186/s12884-016-1174-7.

[93] Jansen LAW, Nijsten K, Limpens J, van Eekelen R, Koot MH, Grooten IJ, *et al*. Perinatal outcomes of infants born to mothers with hyperemesis gravidarum: A systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2023; 284: 30–51. https://doi.org/10.1016/j.ejogrb.2023.03.004.

[94] Fejzo MS, Trovik J, Grooten IJ, Sridharan K, Roseboom TJ, Vikanes Å, *et al*. Nausea and vomiting of pregnancy and hyperemesis gravidarum. Nature Reviews. Disease Primers. 2019; 5: 62. https://doi.org/10.1038/s41572-019-0110-3.

[95] Getahun D, Fassett MJ, Jacobsen SJ, Xiang AH, Takhar HS, Wing DA, *et al*. Autism Spectrum Disorders in Children Exposed in Utero to Hyperemesis Gravidarum. American Journal of Perinatology. 2021; 38: 265–272. https://doi.org/10.1055/s-0039-1696670.

[96] Fiorentini M, Nedu B, Dapoto F, Brunelli E, Pilu G, Youssef A. When time is brain: a systematic review about Wernicke encephalopathy as a dramatic consequence of thiamin deficiency in hyperemesis gravidarum. The Journal of Maternal-fetal & Neonatal Medicine: the Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2023; 36: 2223678. https://doi.org/10.1080/14767058.2023.2223678.

[97] Farshbaf-Khalili A, Salehi-Pourmehr H, Najafipour F, Alamdari NM, Pourzeinali S, Ainehchi N. Is hyperemesis gravidarum associated with transient hyperthyroidism? A systematic review and meta-analysis. Taiwanese Journal of Obstetrics & Gynecology. 2023; 62: 205–225. https://doi.org/10.1016/j.tjog.2022.11.008.

[98] Zimmerman CF, Ilstad-Minnihan AB, Bruggeman BS, Bruggeman BJ, Dayton KJ, Joseph N, *et al*. Thyroid Storm Caused by Hyperemesis Gravidarum. AACE Clinical Case Reports. 2022; 8: 124–127. https://doi.org/10.1016/j.aace.2021.12.005.

[99] Zheng H, Wang Q, Chen F. Correlation between serum beta-human chorionic gonadotropin levels and thyroid metabolic function in pregnant women with hyperemesis gravidarum. The Chinese Journal of Physiology. 2023; 66: 359–364. https://doi.org/10.4103/cjop.CJOP-D-23-00045.

[100] Koren G, Ornoy A, Berkovitch M. Hyperemesis gravidarum-Is it a cause of abnormal fetal brain development? Reproductive Toxicology (Elmsford, N.Y.). 2018; 79: 84–88. https://doi.org/10.1016/j.reprotox.2018.06.008.

[101] Muraoka M, Takagi K, Ueno M, Morita Y, Nagano H. Fetal Head Growth during Early to Mid-Gestation Associated with Weight Gain in Mothers with Hyperemesis Gravidarum: A Retrospective Cohort Study. Nutrients. 2020; 12: 1664. https://doi.org/10.3390/nu12061664.

[102] Hazan G, Sheiner E, Golan-Tripto I, Goldbart A, Sergienko R, Wainstock T. The impact of maternal hyperemesis gravidarum on early childhood respiratory morbidity. Pediatric Pulmonology. 2024; 59: 707–714. https://doi.org/10.1002/ppul.26817.

[103] Pike K, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. Seminars in Fetal & Neonatal Medicine. 2012; 17: 92–98. https://doi.org/10.1016/j.siny.2012.01.003.

[104] Torchin H, Ancel PY, Jarreau PH, Goffinet F. Epidemiology of preterm birth: Prevalence, recent trends, short- and long-term outcomes. Journal De Gynecologie, Obstetrique et Biologie De La Reproduction. 2015; 44: 723–731. https://doi.org/10.1016/j.jgyn.2015.06.010. (In French)

[105] Swarray-Deen A, Sepenu P, Mensah TE, Osei-Agyapong J, Sefogah PE, Appiah-Sakyi K, *et al*. Preterm birth in low-middle income Countries. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2024; 95: 102518. https://doi.org/10.1016/j.bpobgyn.2024.102518.

[106] Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. Seminars in Perinatology. 2016; 40: 497–509. https://doi.org/10.1053/j.semperi.2016.09.002.

[107] Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Developmental Medicine and Child Neurology. 2018; 60: 342–355. https://doi.org/10.1111/dmcn.13675.

[108] Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. Pediatric Neurology. 2015; 52: 143–152. https://doi.org/10.1016/j.pediatrneurol.2014.10.027.

[109] Schneider J, Miller SP. Preterm brain Injury: White matter injury. Handbook of Clinical Neurology. 2019; 162: 155–172. https://doi.org/10.1016/B978-0-444-64029-1.00007-2.

[110] Back SA. White matter injury in the preterm infant: pathology and mechanisms. Acta Neuropathologica. 2017; 134: 331–349. https://doi.org/10.1007/s00401-017-1718-6.

[111] Himpens E, Van den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Developmental Medicine and Child Neurology. 2008; 50: 334–340. https://doi.org/10.1111/j.1469-8749.2008.02047.x.

[112] Synnes A, Hicks M. Neurodevelopmental Outcomes of Preterm Children at School Age and Beyond. Clinics in Perinatology. 2018; 45: 393–408. https://doi.org/10.1016/j.clp.2018.05.002.

[113] Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011; 128: 344–355. https://doi.org/10.1542/peds.2010-1036.

[114] Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, *et al*. Visual and Hearing Impairments After Preterm Birth. Pediatrics. 2018; 142: e20173888. https://doi.org/10.1542/peds.2017-3888.

[115] Leung MP, Thompson B, Black J, Dai S, Alsweiler JM. The effects of preterm birth on visual development. Clinical & Experimental Optometry. 2018; 101: 4–12. https://doi.org/10.1111/cxo.12578.

[116] Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, *et al*. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension (Dallas, Tex.: 1979). 2014; 63: 1116–1135. https://doi.org/10.1161/HYP.0000000000000007.

[117] Bensley JG, De Matteo R, Harding R, Black MJ. The effects of preterm birth and its antecedents on the cardiovascular system. Acta Obstetricia et Gynecologica Scandinavica. 2016; 95: 652–663. https://doi.org/10.1111/aogs.12880.

[118] Tauzin L, Rossi P, Giusano B, Gaudart J, Boussuges A, Fraisse A, *et al*. Characteristics of arterial stiffness in very low birth weight premature infants. Pediatric Research. 2006; 60: 592–596. https://doi.org/10.1203/01.pdr.0000242264.68586.28.

[119] Bertagnolli M. Preterm Birth and Renin-Angiotensin-Aldosterone System: Evidences of Activation and Impact on Chronic Cardiovascular Disease Risks. Protein and Peptide Letters. 2017; 24: 793–798. https://doi.org/10.2174/0929866524666170728160243.

[120] Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. Preterm Birth and Risk of Heart Failure Up to Early Adulthood. Journal of the American College of Cardiology. 2017; 69: 2634–2642. https://doi.org/10.1016/j.jacc.2017.03.572.

[121] Moss TJM. Respiratory consequences of preterm birth. Clinical and Experimental Pharmacology & Physiology. 2006; 33: 280–284. https://doi.org/10.1111/j.1440-1681.2006.04359.x.
[122] Keszler M, Sant'Anna G. Mechanical Ventilation and Bronchopulmonary Dysplasia. Clinics in Perinatology. 2015; 42: 781–796. https://doi.org/10.1016/j.clp.2015.08.006.
[123] Eng L, Lam L. Thyroid Function During the Fetal and Neonatal Periods. NeoReviews. 2020; 21: e30–e36. https://doi.org/10.1542/neo.21-1-e30.
[124] Finken MJJ, Keijzer-Veen MG, Dekker FW, Frölich M, Hille ETM, Romijn JA, *et al*. Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life. Diabetologia. 2006; 49: 478–485. https://doi.org/10.1007/s00125-005-0118-y.
[125] Crump C, Sundquist J, Sundquist K. Preterm birth and risk of type 1 and type 2 diabetes: a national cohort study. Diabetologia. 2020; 63: 508–518. https://doi.org/10.1007/s00125-019-05044-z.
[126] McNestry C, Killeen SL, Crowley RK, McAuliffe FM. Pregnancy complications and later life women's health. Acta Obstetricia et Gynecologica Scandinavica. 2023; 102: 523–531. https://doi.org/10.1111/aogs.14523.
[127] Lapehn S, Paquette AG. The Placental Epigenome as a Molecular Link Between Prenatal Exposures and Fetal Health Outcomes Through the DOHaD Hypothesis. Current Environmental Health Reports. 2022; 9: 490–501. https://doi.org/10.1007/s40572-022-00354-8.
[128] Al Bekai E, Beaini CE, Kalout K, Safieddine O, Semaan S, Sahyoun F, *et al*. The Hidden Impact of Gestational Diabetes: Unveiling Offspring Complications and Long-Term Effects. Life (Basel, Switzerland). 2025; 15: 440. https://doi.org/10.3390/life15030440.
[129] Jia G, Gao Y, Li C, Zhang Y. Effects of MTNR1B Genetic Variants on Individual Susceptibility to Gestational Diabetes Mellitus: A Meta-Analysis. American Journal of Perinatology. 2020; 37: 607–612. https://doi.org/10.1055/s-0039-1685446.
[130] Li W, Yuan X, He X, Yang L, Wu Y, Deng X, *et al*. The down-regulation of miR-22 and miR-372 may contribute to gestational diabetes mellitus through regulating glucose metabolism via the PI3K/AKT/GLUT4 pathway. Journal of Clinical Laboratory Analysis. 2022; 36: e24557. https://doi.org/10.1002/jcla.24557.
[131] Hernandez-Pacheco JA, Torres-Torres J, Martinez-Portilla RJ, Solis-Paredes JM, Estrada-Gutierrez G, Mateu-Rogell P, *et al*. sFlt-1 Is an Independent Predictor of Adverse Maternal Outcomes in Women With SARS-CoV-2 Infection and Hypertensive Disorders of Pregnancy. Frontiers in Medicine. 2022; 9: 894633. https://doi.org/10.3389/fmed.2022.894633.
[132] He D, Peng X, Xie H, Peng R, Li Q, Guo Y, *et al*. Genetic Variations in *Angiotensinogen* Gene and Risk of Preeclampsia: A Pilot Study. Journal of Clinical Medicine. 2023; 12: 1509. https://doi.org/10.3390/jcm12041509.
[133] Dixon PH, Sambrotta M, Chambers J, Taylor-Harris P, Syngelaki A, Nicolaides K, *et al*. An expanded role for heterozygous mutations of ABCB4, ABCB11, ATP8B1, ABCC2 and TJP2 in intrahepatic cholestasis of pregnancy. Scientific Reports. 2017; 7: 11823. https://doi.org/10.1038/s41598-017-11626-x.
[134] Khandre V, Potdar J, Keerti A. Preterm Birth: An Overview. Cureus. 2022; 14: e33006. https://doi.org/10.7759/cureus.33006.
[135] Humberg A, Fortmann I, Siller B, Kopp MV, Herting E, Göpel W, *et al*. Preterm birth and sustained inflammation: consequences for the neonate. Seminars in Immunopathology. 2020; 42: 451–468. https://doi.org/10.1007/s00281-020-00803-2.
[136] Chun RPC, Chan HG, Lim GYS, Kanagalingam D, Partana P, Tan KH, *et al*. Preterm birth trends and risk factors in a multiethnic Asian population: A retrospective study from 2017 to 2023, can we screen and predict this? Annals of the Academy of Medicine, Singapore. 2025; 54: 296–304. https://doi.org/10.47102/annals-acadmedsg.202518.
[137] Dom AM, Mather A, Seligman NS. Prevention of preterm birth in multiples. Current Opinion in Obstetrics & Gynecology. 2021; 33: 72–77. https://doi.org/10.1097/GCO.0000000000000686.
[138] Li X, Ning X, Rui B, Wang Y, Lei Z, Yu D, *et al*. Alterations of milk oligosaccharides in mothers with gestational diabetes mellitus impede colonization of beneficial bacteria and development of RORγt^{+} Treg cell-mediated immune tolerance in neonates. Gut Microbes. 2023; 15: 2256749. https://doi.org/10.1080/19490976.2023.2256749.
[139] Kamińska K, Stenclik D, Błażejewska W, Bogdański P, Moszak M. Probiotics in the Prevention and Treatment of Gestational Diabetes Mellitus (GDM): A Review. Nutrients. 2022; 14: 4303. https://doi.org/10.3390/nu14204303.
[140] Kalra S, Atkin S, Cervera A, Das AK, Demir O, Demir T, *et al*. Multinational Consensus: Insulin Initiation with Insulin Degludec/Aspart (IDegAsp). Advances in Therapy. 2018; 35: 928–936. https://doi.org/10.1007/s12325-018-0712-2.
[141] Rehman K, Akash MSH, Liaqat A, Kamal S, Qadir MI, Rasul A. Role of Interleukin-6 in Development of Insulin Resistance and Type 2 Diabetes Mellitus. Critical Reviews in Eukaryotic Gene Expression. 2017; 27: 229–236. https://doi.org/10.1615/CritRevEukaryotGeneExpr.2017019712.
[142] Delpino FM, Figueiredo LM, da Silva BGC, da Silva TG, Mintem GC, Bielemann RM, *et al*. Omega-3 supplementation and diabetes: A systematic review and meta-analysis. Critical Reviews in Food Science and Nutrition. 2022; 62: 4435–4448. https://doi.org/10.1080/10408398.2021.1875977.
[143] Haddad B, Lefèvre G, Rousseau A, Robert T, Saheb S, Rafat C, *et al*. LDL-apheresis to decrease sFlt-1 during early severe preeclampsia: Report of two cases from a discontinued phase II trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2018; 231: 70–74. https://doi.org/10.1016/j.ejogrb.2018.09.009.
[144] Chua J, Paizis K, He SZ, Mount P. Suspected atypical haemolytic uraemic syndrome in two post-partum patients with foetal-death in utero responding to eculizumab. Nephrology (Carlton, Vic.). 2017; 22 Suppl 1: 18–22. https://doi.org/10.1111/nep.12935.
[145] Ahmed A, Williams DJ, Cheed V, Middleton LJ, Ahmad S, Wang K, *et al*. Pravastatin for early-onset pre-eclampsia: a randomised, blinded, placebo-controlled trial. BJOG: an International Journal of Obstetrics and Gynaecology. 2020; 127: 478–488. https://doi.org/10.1111/1471-0528.16013.
[146] Khoshaba L, Patarkatsi L. Switching from Natural Desiccated Thyroid to a Liquid Formulation of Levothyroxine for Hypothyroidism. Case Reports in Endocrinology. 2023; 2023: 4252894. https://doi.org/10.1155/2023/4252894.
[147] Furmaniak J, Sanders J, Sanders P, Li Y, Rees Smith B. TSH receptor specific monoclonal autoantibody K1-70^{TM} targeting of the TSH receptor in subjects with Graves' disease and Graves' orbitopathy-Results from a phase I clinical trial. Clinical Endocrinology. 2022; 96: 878–887. https://doi.org/10.1111/cen.14681.
[148] Pataia V, McIlvride S, Papacleovoulou G, Ovadia C, McDonald JAK, Wahlström A, *et al*. Obeticholic acid improves fetal bile acid profile in a mouse model of gestational hypercholanemia. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2020; 319: G197–G211. https://doi.org/10.1152/ajpgi.00126.2020.
[149] Wu L, Zhou J, Zhou A, Lei Y, Tang L, Hu S, *et al*. *Lactobacillus acidophilus* ameliorates cholestatic liver injury through inhibiting bile acid synthesis and promoting bile acid excre-

tion. Gut Microbes. 2024; 16: 2390176. https://doi.org/10.1080/19490976.2024.2390176.

[150] Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterology Clinics of North America. 2017; 46: 77–89. https://doi.org/10.1016/j.gtc.2016.09.007.

[151] Han H, Ying X, Chen Q, Fang J, Xu D, Lyu X, *et al*. Monitoring of inflammatory preterm responses via myometrial cell based multimodal electrophysiological and optical biosensing platform. Biosensors & Bioelectronics. 2025; 274: 117197. https://doi.org/10.1016/j.bios.2025.117197.

[152] Côté F, Prairie E, Sierra EM, Quiniou C, Habelrih T, Xu W, *et al*. A novel modulator of IL-6R prevents inflammation-induced preterm birth and improves newborn outcome. EMBO Molecular Medicine. 2025. https://doi.org/10.1038/s44321-025-00257-9. (online ahead of print)

[153] Meng Y, Sun J, Zhang G. Vaginal microbiota transplantation is a truly opulent and promising edge: fully grasp its potential. Frontiers in Cellular and Infection Microbiology. 2024; 14: 1280636. https://doi.org/10.3389/fcimb.2024.1280636.

[154] Jiang X, Bao Y, Li X, Qu X, Mao X, Dong J, *et al*. Characteristics of the vaginal microbiota associated with recurrent spontaneous preterm birth: a prospective cohort study. Journal of Translational Medicine. 2025; 23: 541. https://doi.org/10.1186/s12967-025-06460-z.

[155] Hart PMB, Stephenson NL, Scime NV, Tough SC, Slater DM, Chaput KH. Second trimester cytokine profiles associated with gestational diabetes and hypertensive disorders of pregnancy. PloS One. 2022; 17: e0279072. https://doi.org/10.1371/journal.pone.0279072.

[156] Xiao J, Li Z, Song Y, Sun Y, Shi H, Chen D, *et al*. Molecular Pathogenesis of Intrahepatic Cholestasis of Pregnancy. Canadian Journal of Gastroenterology & Hepatology. 2021; 2021: 6679322. https://doi.org/10.1155/2021/6679322.

[157] Pinto S, Croce L, Carlier L, Cosson E, Rotondi M. Thyroid dysfunction during gestation and gestational diabetes mellitus: a complex relationship. Journal of Endocrinological Investigation. 2023; 46: 1737–1759. https://doi.org/10.1007/s40618-023-02079-3.

[158] Wang J, Gong XH, Peng T, Wu JN. Association of Thyroid Function During Pregnancy With the Risk of Pre-eclampsia and Gestational Diabetes Mellitus. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2021; 27: 819–825. https://doi.org/10.1016/j.eprac.2021.03.014.

[159] Albers RE, Kaufman MR, Natale BV, Keoni C, Kulkarni-Datar K, Min S, *et al*. Trophoblast-Specific Expression of Hif-1α Results in Preeclampsia-Like Symptoms and Fetal Growth Restriction. Scientific Reports. 2019; 9: 2742. https://doi.org/10.1038/s41598-019-39426-5.

[160] Makker K, Afolayan AJ, Teng RJ, Konduri GG. Altered hypoxia-inducible factor-1α (HIF-1α) signaling contributes to impaired angiogenesis in fetal lambs with persistent pulmonary hypertension of the newborn (PPHN). Physiological Reports. 2019; 7: e13986. https://doi.org/10.14814/phy2.13986.

[161] Zhang Y, Pan Y, Lin C, Zheng Y, Sun H, Zhang H, *et al*. Bile acids evoke placental inflammation by activating Gpbar1/NF-κB pathway in intrahepatic cholestasis of pregnancy. Journal of Molecular Cell Biology. 2016; 8: 530–541. https://doi.org/10.1093/jmcb/mjw025.

[162] Santos BR, Dos Anjos Cordeiro JM, Santos LC, Barbosa EM, Mendonça LD, Santos EO, *et al*. Kisspeptin treatment improves fetal-placental development and blocks placental oxidative damage caused by maternal hypothyroidism in an experimental rat model. Frontiers in Endocrinology. 2022; 13: 908240. https://doi.org/10.3389/fendo.2022.908240.

[163] Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. The Journal of Clinical Endocrinology and Metabolism. 1992; 75: 1333–1337. https://doi.org/10.1210/jcem.75.5.1430095.

[164] Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. International Journal of Biological Sciences. 2018; 14: 1483–1496. https://doi.org/10.7150/ijbs.27173.

[165] Toloza FJK, Derakhshan A, Männistö T, Bliddal S, Popova PV, Carty DM, *et al*. Association between maternal thyroid function and risk of gestational hypertension and pre-eclampsia: a systematic review and individual-participant data meta-analysis. The Lancet. Diabetes & Endocrinology. 2022; 10: 243–252. https://doi.org/10.1016/S2213-8587(22)00007-9.