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REVIEW

Developmental origin and sex-specific risk for infections and immune diseases later in life

Dimitra E. Zazara[1] · Petra Clara Arck[1,2]

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Abstract

The intrauterine environment is an important determinant of immunity later in life of the offspring. An altered prenatal immune development can result in a high postnatal risk for infections, chronic immune diseases, and autoimmunity. Many of these immune diseases show a strong sex bias, such as a high incidence of autoimmune diseases and allergies in adult females or a high risk for infections in males. Here, we comprehensively review established pathways and propose novel concepts modulating the risk for such poor immunity during childhood and throughout life. Moreover, we highlight how an adverse fetal environment may affect or aggravate the risk for poor immunity in a sex-specific manner. An improved understanding of a sex-specific susceptibility to poor immunity along with insights on how such risk can be modulated before or around birth will allow the development of tailored prevention strategies.

Keywords Sex-specificity · Children's health · Pregnancy · Infections · Chronic immune diseases

Fetal programming of the immune system and its modulation by prenatal challenges

The concept of fetal programming, often also referred to as "the developmental origins of health and disease," subsumes that the intrauterine environment determines postnatal health [1]. The concept encompasses that the intrauterine environment is altered upon maternal exposure to environmental factors during pregnancy, which subsequently affect the developing fetus and alter the risk for diseases later in life [2–4]. These insights emerged from a wealth of epidemiological studies linking specific intrauterine insults to certain diseases of the offspring during child- and adulthood. Many of these studies focused on maternal nutritional insults during pregnancy, such as under- and overnutrition, which have been associated with obesity, metabolic dysfunction, and hypertension in the offspring [5, 6]. Furthermore, prenatal exposure to air pollution as well as prenatal maternal smoking was shown to increase the risk for childhood respiratory diseases, such as asthma [7–10]. Similarly, a link between maternal stress perception or the experience of adverse life events during pregnancy and immune disorders in the children has been identified. Here, immune disorders include again allergic diseases in the offspring, i.e., asthma and allergic dermatitis [11], but also an increased risk for infections [12, 13]. However, insights into the mechanisms underlying the pathogenesis of immune diseases later in life still remain largely unknown.

A potential target of prenatal modulators is the developing immune system. Immune system development commences prenatally and continues to mature postnatally in all mammals, including humans [14]. At birth, the neonatal immune system is still immature, and hence, immune responses to pathogens coincide with the ongoing postnatal maturation process. Fetal innate and adaptive immune cells have weak effector functions before birth, and the tolerogenic immune phenotype protects the fetus from potential intrauterine inflammatory responses [15, 16]. Fetal $CD4^+$ T cells preferentially give rise to regulatory T (Treg) cells upon stimulation, which in turn support not only fetal tolerance, but also tolerance of the maternal immune response toward the haploidentical fetus [17, 18]. Additionally, the inflammatory type 1 T helper (Th1) cell response of the fetus and neonate is

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✉ Petra Clara Arck
p.arck@uke.de

[1] Department of Obstetrics and Fetal Medicine, Laboratory for Experimental Feto-Maternal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2] Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg, Martinistraße 52, Campus Research (N27) / Rm. 04.039, 20246 Hamburg, Germany

weak and slowly mounted [16]. Furthermore, a recently identified unique immunosuppressive population of physiologically enriched $CD71^+$ erythroid cells in human and mouse neonates also contributes to the neonatal tolerance toward aberrant immune cell activation while at the same time increasing the risk for infections [19]. On the other hand, in human newborn infants, defense against infections seems to be mediated by interleukin-8 (IL8 or chemokine (C-X-C motif) ligand 8, CXCL8) production, a major neonatal T cell effector function that leads to neutrophil and γδ T cell activation [20]. These distinct features of fetal and neonatal immunity sustain homeostasis by dampening an overshooting reaction to the physiological microbial colonization while allowing a certain degree of defense against infections.

Intrauterine challenges can alter the function of immune cells, organ cellular morphology, and homeostatic balance and program postnatal immunity. For instance, maternal dietary components such as retinoids promote fetal thymus development as well as hematopoiesis and act as regulators of B lymphocyte growth and apoptosis [21–24]. Furthermore, maternal retinoid intake affects the size of secondary lymphoid organs (SLO) in the fetus by controlling fetal type 3 innate lymphoid cells (ILC3). Since SLO are critical for resistance to infections and ILCs have been implicated in the pathogenesis of autoimmune and chronic inflammatory diseases, maternal retinoids may serve as key mediators of immune efficiency in the offspring [25, 26]. On the other hand, mineral deficiencies during pregnancy have been associated with reduced fetal thymus size and thus impaired T cell development in the offspring. In turn, a limited T cell repertoire increases the offspring's susceptibility to infections [27]. Surprisingly, despite these intriguing insights, the evaluation of sex-specific effects has often been neglected in these studies.

Prenatal challenges, such as maternal under- or overnutrition can serve as a maternal stressor, leading to hypothalamic–pituitary–adrenal (HPA) axis activation and increased glucocorticoid levels in both mother and fetus [28–30]. Similarly, high maternal stress perception, induced i.e. by adverse life events during pregnancy, also plays a key role in programming immunity of the offspring [31]. It can affect fetal thymus development, lymphopoiesis, and Th1/Th2 balance as well as normal macrophage and neutrophil function [32, 33]. Additionally, maternal stress mediators can indirectly alter offspring's immunity by affecting the developing fetal HPA axis [34]. An impaired early-life HPA axis activation has been associated with altered cytokine expression, antibody production, natural killer cell function, and febrile responses in the offspring, features that collectively increase the risk for infectious and allergic diseases [35–40]. Moreover, prenatal maternal stress reduces placental blood flow, which in turn results in insufficient fetal oxygen and nutrition intake, increased reactive oxygen species (ROS) production, and fetal oxidative stress [41, 42]. Oxidative stress favors the development of atopic diseases in the offspring as it affects T cell signaling pathways and gene expression while promoting Th2 immune skewing [42, 43].

Besides nutritional aspects and adverse life events during pregnancy, maternal microbiota and exposure to infections during pregnancy may affect immune development [44–47]. Maternal microbiota have been shown to induce an intestinal transcriptional reprogramming in the offspring that can result, among others, in an upregulation of genes coding for antibacterial peptides thereby preparing the ground for intestinal microbial colonization after birth [48]. Human studies focusing on the impact of prenatal microbial exposures in farming environments on offspring's immunity revealed that such an environment during pregnancy boosts the number and suppressive function of Treg cells in the offspring, while reducing Th2 immune responses, allergen-specific IgE antibodies [49–51], thereby decreasing the risk for asthma and atopic dermatitis during childhood [52–54]. On the other hand, maternal viral infections, including HIV-1 infection, during pregnancy have been shown to directly interfere with fetal immune development thereby causing abrupt immune activation and shifting fetal immunity towards a proinflammatory state. An altered fetal inflammatory environment can subsequently result in an increased susceptibility to infections, altered response to vaccinations, and potentially a higher risk for autoimmunity and allergies later in life [55–58].

Several studies suggest that these effects are epigenetically driven [59–61]. Epigenetic modifications are heritable alterations in gene activity and expression that do not involve changes in DNA sequence. The main mechanisms inducing such alterations are DNA methylation, histone modifications, and abnormal microRNA (miRNA) expression [59]. Moreover, physiological immune development is also controlled through epigenetic mechanisms, including Th1 and Th2 cell differentiation as well as forkhead/winged-helix family transcriptional repressor p3 (FoxP3) expression, which is a commonly used marker for Treg cells [62–64]. Interestingly, the allergy-preventing effect of prenatal exposure to farming conditions was associated with a hypomethylation of *FOXP3* in the protected offspring [51]. This epigenetic alteration led to increased Treg number and function and thus a reduced risk for allergic diseases in the offspring. On the other hand, excessive maternal folic acid intake has been associated with increased *FOXP3* methylation that results in decreased FOXP3 expression and Treg production in the offspring [65]. Again, the evaluation of sex-specific effects has often been neglected in these studies.

As previously mentioned, poor immunity during childhood often shows strong sex-specific differences (Fig. 1). For example, during infancy and childhood, boys exhibit a higher susceptibility and severity of infectious diseases compared to girls [66–68]. This male bias can be mainly attributed to physiological sex-specific differences, including the interplay between sex hormones and immunity, while behavioral factors

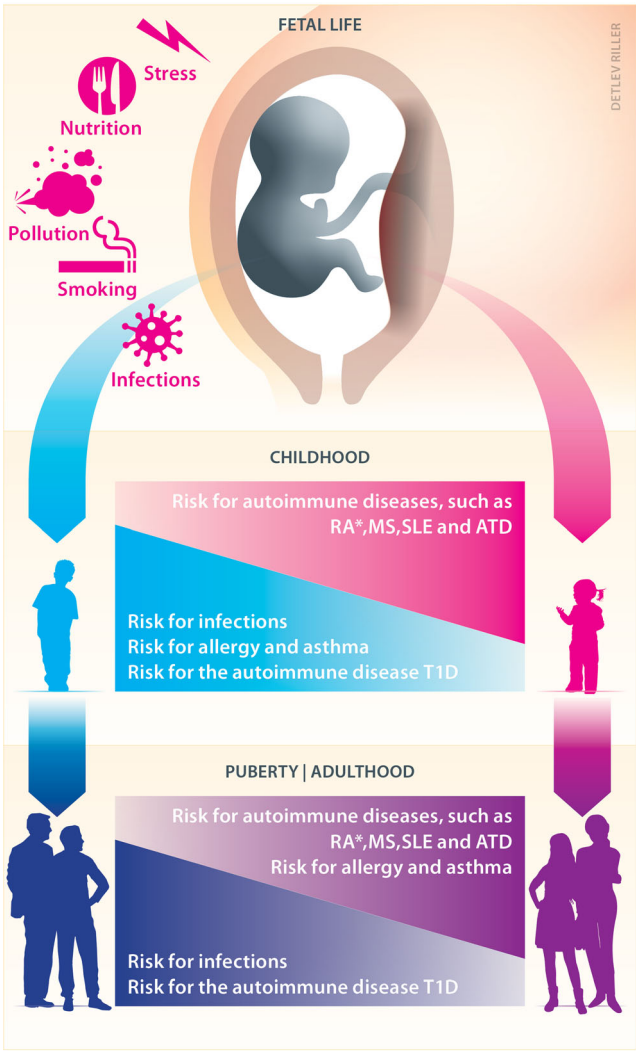

Fig. 1 Sex differences in immune diseases vary dynamically across the lifespan. The intrauterine exposure to adverse conditions can be a pivotal determinant of postnatal sex-specific risks for immune diseases. During childhood, girls are more susceptible to autoimmunity while the prevalence and severity of infections as well as the risk for asthma, allergies, and some autoimmune diseases (type 1 diabetes) are higher in boys. Interestingly, during puberty and adulthood, most of these trends reverse and poor immunity burdens mainly women, who are more likely to suffer from asthma, allergies, and autoimmune diseases. Abbreviations used in the figure: RA*, juvenile idiopathic arthritis and rheumatoid arthritis; MS, multiple sclerosis; SLE, systematic lupus erythematosus; T1D, type 1 diabetes; ATD, autoimmune thyroid disease

modulating pathogen exposure seem to drive the sex-specific risk for infection only in a few cases [66]. Similarly, the incidence of asthma is increased among preadolescent boys [69]. This sex-specific bias reverses during adolescence and adulthood, when the incidence in females increases [70–73]. On the other hand, girls are more susceptible to autoimmune diseases like juvenile idiopathic arthritis [74, 75], juvenile dermatomyositis [76, 77], multiple sclerosis [78], autoimmune thyroid disease [79, 80], and systemic lupus erythematosus [81], which have low but gradually increasing incidences during childhood [82]. Only few autoimmune diseases, type 1 diabetes and Crohn's disease (where an autoimmune pathogenesis is still debated), show male predominance [83–89]. Interestingly, the high susceptibility of females to autoimmune diseases persists during adulthood [90–95] (Table 1). To date, the understanding if and how intrauterine insults further aggravate the risk for poor postnatal immunity in a sex-specific manner is still limited.

Modulators of sex-specific programming of immune diseases: insights from observational studies in humans

The fact that the risk for chronic immune diseases in the offspring shows distinct sex-specific incidences underpins that poor immunity may be aggravated in a sex-specific manner. This implies that male and female fetuses may be differently affected by intrauterine insults [96]. Some of the prenatal challenges implicated in sex-specific programming of immune diseases in humans are environmental pollution, tobacco exposure, maternal stress, and diet [11, 97–99]. Two recent human studies identified a link among prenatal exposure to ambient air pollution, maternal stress, fetal sex, and development of asthma during childhood [97, 100]. Specifically, maternal pollution exposure during pregnancy was associated with an increased risk for asthma, especially in boys that were also exposed to increased prenatal maternal stress. Notably, maternal exposure to toxins as well as stress during pregnancy may affect fetal lung development and thus can be implicated in the pathogenesis of respiratory diseases in the offspring [101, 102]. Hence, since both prenatal challenges may act on developing tissues via common immune and oxidative pathways, a simultaneous exposure can exert a synergistic detrimental effect on the male immature lung, thereby increasing the risk for asthma after birth [97, 100]. Although a coexistence of both insults seems to synergistically affect male offspring's immunity, prenatal environmental pollution exposure at mid-gestation alone may also be sufficient to increase the risk for asthma development in boys [103]. A possible explanation for this sex-specific association encompasses the role of androgens, which are known to delay lung development in male fetuses [104]. Lower or delayed surfactant production in males may justify the higher incidence of respiratory distress syndrome (RDS) in both preterm and term newborn boys compared to girls [105, 106]. Similarly, sex-specific differences in fetal lung development may account for the higher prevalence of bronchopulmonary dysplasia in male premature infants [107]. The reported high vulnerability of the male developing lungs upon environmental pollution exposure may also justify the higher prevalence of asthma and respiratory infections in boys [108] during childhood.

Interestingly, prenatal maternal stress and excessive glucocorticoid exposure may also program postnatal health and

Table 1 Sex bias in immune disease incidence in children and adults. *M*, male; *F*, female; *N/A*, not applicable

Disease	Sex bias in children	Sex bias in adults	References
Asthma	M > F (< 12 years) M < F (> 12 years)	M < F	[71–73]
Allergic rhinitis	M > F (< 11 years) M < F (> 11 years)	M < F	[69, 70, 72]
Atopic dermatitis	M = F (< 11 years) M < F (> 11 years)	M < F (< 65 years) M > F (> 65 years)	[69, 70, 72]
Infections	M > F	M > F	[66–68]
Multiple sclerosis	M > F (< 6 years) M < F (> 6 years)	M < F	[78, 90, 92]
Type 1 diabetes	M ≈ F (< 11 years) M > F (> 11 years)	M > F	[83, 88, 89]
Crohn's disease	M > F	M < F	[84–87]
Ulcerative colitis	M ≈ F	M ≈ F	[87, 92]
Celiac disease	M = F	M < F	[82, 93]
Autoimmune thyroid disease	M < F	M < F	[79, 80, 94]
Systemic lupus erythematosus	M < F	M < F	[81, 91, 92]
Juvenile idiopathic arthritis	M < F	N/A	[74, 75]
Rheumatoid arthritis	N/A	M < F	[92, 95]
Juvenile dermatomyositis	M < F	M < F	[76, 77]

disease in a sex-dependent manner. The enhanced glucocorticoid-related susceptibility to diabetes [109, 110], cardiovascular diseases [111], hypertension [112, 113], and neuropsychiatric disorders such as depression and anxiety [114] affects primarily the male offspring [115–119]. Furthermore, prenatal maternal stress alone is also known to increase susceptibility to wheezing phenotypes during childhood sex-specifically. A longitudinal prospective study in Canada, the "Project Ice Storm," revealed that disaster-induced maternal stress during pregnancy increases the risk for wheezing and asthma only in girls [120]. Since prenatal stress is known to decrease maternal progesterone during pregnancy, low progesterone may account for a higher risk for asthma in girls. Indeed, low maternal progesterone levels during early pregnancy increase the risk for atopic dermatitis, asthma, and allergic rhinitis in girls during childhood [121, 122]. Accordingly, high maternal progesterone levels during the first trimester of pregnancy were associated with a lower risk for asthma or allergic diseases only in the female offspring [121]. A pregnancy cohort performed in Mexico revealed that pre- and postnatal maternal stress challenges were associated with an increased risk for wheezing phenotypes in both boys and girls [123]. Another cohort study demonstrated that prenatal stress affected mostly boys, while postnatal stress and cumulative stress across both prenatal and postnatal periods affected mainly the girls and increased their susceptibility to childhood asthma [124]. Maternal stress during pregnancy has also been associated with an increased risk for type 1 diabetes in girls during childhood [125]. Despite a certain degree of ambiguity between these studies, a majority of these studies highlight that female children are more susceptible to a developmental or early life origin of asthma and type 1 diabetes in response to maternal stress. To date, the underlying mechanisms for this sex-specific risk modulation remain unknown.

Observational studies in humans have further identified that nutritional insults during pregnancy, such as a decreased prenatal maternal consumption of vitamin E, vitamin D, and zinc, increase the risk for asthma and wheezing in children [126, 127]. On the other hand, children whose mothers followed a Mediterranean diet during pregnancy seem to be protected from atopy and wheezing [128]; and therefore, implementation of such a diet scheme during pregnancy might be beneficial for the primary prevention of childhood allergy [129].

Sex-specific differences in fetal programming of immune diseases: insights from animal studies

Several animal models have been used to mimic adverse prenatal conditions in order to identify the mechanisms causally involved in poor fetal development and the increased risk for diseases later in life. Some of the most commonly used models include the exposure of pregnant animals to sound stress [121, 130], prenatal glucocorticoid treatment [131, 132], distinct dietary challenges [133, 134], infections [135], and nicotine [136, 137].

Interestingly, the outcomes of the prenatal challenges in animal models largely mirror the outcome of human studies and often reveal sex-specific immune responses to prenatal challenges. For instance, an impact of prenatal smoke exposure on lung developmental pathways has been predominantly

observed in female offspring. Smoking-induced epigenetic alterations of promoter methylation and expression of insulin-like growth factor 1 and its receptor (*Igf1* and *Igf1r*), two key mediators of pre- and postnatal mouse development, may account for these sex-specific effects [137, 138] and the reduction of *Igf1* and *Igf1r* expression may indicate impaired postnatal lung development, especially in female offspring [137]. Besides lung development, prenatal smoking exposure may have a detrimental effect on the developing immune system, such as an impaired fetal thymus development [136], but insights into sex-specific effects are still sparse.

Mouse models of prenatal stress challenge have revealed insights into the observed sex-specific programming of asthma, as an impaired fetal lung development, along with the fact that a reduction of tolerogenic Treg cells and an increased severity of asthma-like symptoms during adulthood were predominately observed in female offspring [102]. These observed sex-dependent effects of prenatal stress challenge may be attributed to a stress-induced reduction of maternal progesterone during pregnancy [139]. Progesterone, as well as androgens and estrogens, plays a central role in lung development. In contrast to the inhibitory effects of androgens on lung maturation, estrogens and progesterone stimulate alveolarization and surfactant production, respectively [140, 141]. Interestingly, prenatal supplementation with the progesterone derivative dihydrodydrogesterone (DHD) in stress-challenged pregnant mice attenuates the prenatal stress-related asthma-like phenotype exclusively in female offspring [121]. Sex-dependent differences in progesterone receptor (PR) expression in the lung could explain the sex-specific stress-induced fetal programming of asthma. Indeed, a recent study in rats demonstrated a higher mRNA PR expression in female fetal distal lung epithelial cells compared to male ones [106]. Such PR abundance may render the female fetal lung more susceptible to stress-induced variations in progesterone levels compared to males. Under normal conditions and balanced hormonal levels, the female lung is more mature at birth, but smaller, with less respiratory bronchioles, due to—among others—low androgen levels that are known to promote branching morphogenesis [140, 141]. Therefore, any alteration in the levels of progesterone, estrogens, and androgens and the respective receptors may disturb the finely tuned maturation process and aggravate the already existing sex differences. These early-life structural differences between male and female lungs persist throughout life and could account for the higher prevalence of asthma among females after puberty [140].

As described earlier, maternal diet during pregnancy can be another determinant of offspring's immunity. A recent mouse study reported that a high-fiber diet during pregnancy alters maternal gut microbiota, thereby suppressing the development of allergic airway disease in murine offspring. This protective effect of the high-fiber diet could be attributed to an enhancement of Treg cell numbers and function as well as to suppression of the expression of genes associated with asthma in the mouse fetal lung [134].

Despite the availability of mouse models mirroring a number of chronic immune and autoimmune diseases, such as inflammatory bowel diseases [142], systemic lupus erythematosus [143], rheumatoid arthritis [144], diabetes [145–147], or multiple sclerosis-like symptoms [148], to our knowledge, no insights are available into fetal programming of postnatally observed sex-specific differences in their prevalence and phenotype.

Sex-specific fetal programming of infectious diseases

Infectious diseases are a significant health burden throughout life. Susceptibility to infections as well as the severity of infections highly depends on the ability of the immune system to clear the infectious stimuli, while simultaneously maintaining tissue homeostasis and avoiding autoimmune reactions. Interestingly, the mechanisms underlying this balance between immunoreactivity and immunotolerance are different in males and females. Hence, it is not surprising that the incidence as well as the course of infections vary between sexes. During infancy and childhood, boys are at higher risk for viral, bacterial, parasitic, and fungal infections compared to girls [68]. In addition, the course of the infection tends to be more severe in boys. For instance, respiratory tract infections, except sinusitis and otitis externa, are more frequent and often associated with higher mortality in boys [108]. In this case, the sex bias may be partially due to sex-specific anatomic differences of the respiratory tract. Specifically, girls have smaller sinus ostia compared to boys and thus are more likely affected by sinusitis [149]. On the contrary, boys have narrow distal airways and are more susceptible to lower respiratory tract infections, such as bronchiolitis [140]. Apart from anatomic differences, the lower susceptibility of females to infections can also be attributed to their ability to mount more powerful humoral and cellular immune responses to antigens compared to males. Although beneficial when it comes to infections, this increased immunoreactivity might account for the higher risk for autoimmunity in females. This sexual dimorphism in immune responses is largely based on endocrine-immune interactions that are mostly mediated by sex hormones. Notably, estrogens and progesterone enhance immunity by influencing immune cell development, function, and recruitment as well as cytokine production. On the other hand, androgens decrease immune cell proliferation and antibody and cytokine production, among others, thereby suppressing immune responsiveness [150]. Although the role and concentration of sex hormones become more prominent in puberty and adulthood, the physiological sex steroid surge during the first months of life, the so-called mini puberty, might account for the early-life sexual dimorphism in infectious diseases [151,

152]. Hence, differential levels of sex hormones may—at least partially—explain the observed differences in the prevalence and severity of infectious diseases between males and females throughout life. Interestingly, epidemiological studies show that behavioral factors affect the exposure to a contagion. However, such behavior plays a secondary role in driving the male bias to infections, but has been shown to account for the sex-specific risk for infections in the context of cutaneous leishmaniasis, tuberculosis, and leptospirosis [66]. Strikingly, for most infectious diseases, a male bias is also present in infancy, when sex-specific behavioral patterns have not yet evolved, but sex steroids begin to rise [66]. Hence, physiological factors, including the interaction between sex hormones and immune mediators, appear to be key determinants of sex-specific differences in infectious diseases.

Although the crosstalk between the endocrine and immune system dynamically shapes immunity throughout life, the programming of sexually dimorphic immune responses to infectious stimuli begins in utero. As already discussed, maternal nutrition during pregnancy may exert differential effects on the developing immune system in a sex-dependent manner. In a Gambian study, maternal micronutrient supplementation during pregnancy altered the CpG methylation pattern of genes associated with immunity and response to infections, especially in the female offspring [153]. Similarly, maternal vitamin B, C, and E supplementation during pregnancy and lactation reduced the mortality risk in girls but not boys born to HIV-infected mothers [154]. The vitamins B, C, and E interfere with the Th1/Th2 balance thereby favoring Th1 immune responses, enhancing innate immunity and defense against infections [155]. Hence, vitamin supplementation might be beneficial mostly for girls because they tend to have a strong Th2 cell bias [156]. Interestingly, breastfeeding may also program infant immunity in a sex-specific manner, as it has been associated with a lower risk for respiratory infections in girls, but not boys [157], although insights into distinct nutritional breast milk components accounting for this effect are still unknown.

Prenatal stress and excessive maternal glucocorticoids may also sex-specifically program offspring's risk for infections. Here, the interactions with the developing fetal HPA axis may be key, as HPA axis activation is crucial for the regulation of inflammatory responses to infectious challenges. Upon infection or injury, proinflammatory cytokines are secreted by immune cells, hereby orchestrating the local and systemic responses to clear the pathogen. Proinflammatory cytokines also activate the HPA axis, and subsequently, glucocorticoids rise and act as a negative feedback regulation that suppresses further cytokine release. Hence, glucocorticoids exert a crucial regulatory effect that controls inflammation and sustains tissue homeostasis. Prenatal glucocorticoid surges may disturb the negative feedback regulation of the HPA axis [158]. Impaired negative inhibitory loops result in chronic HPA axis activation and increased resistance to the anti-inflammatory and immunosuppressive effects of glucocorticoids at peripheral tissues. In a mouse study, perinatal stress exposure attenuated HPA axis reactivity to influenza virus infection resulting in a sex-dependent immune response pattern in the offspring. Specifically, only neonatally stress-challenged female mice exhibited increased mRNA expression of cytokines including IL-1α, IL-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ in response to influenza virus infection compared to the respective control mice [159].

The role of the placenta in mediating sex-specific fetal programming of immunity

The placenta is the key mediator of fetal growth and development. Through the placenta, the fetus acquires essential nutrients and oxygen from the mother while discarding waste products to maternal circulation. The placenta also produces cytokines and hormones that influence maternal physiology and fetal development [160]. Placental function can be affected by environmental insults, which may alter the placental epigenome and gene expression. An altered placental development or inappropriate function can affect the developing fetus and increase the risk for diseases later in life.

Under physiological conditions, placental gene and protein expression as well as placental function are determined by the sex of the fetus [161, 162]. In normally progressing human pregnancies, a higher number of genes involved in critical functions such as cellular growth and proliferation, placental development, and angiogenesis are upregulated in the female placenta, compared to the male one [161, 163], which may be related to the reduced risk of placenta in pregnancies with a female fetus to develop intrauterine inflammation or bacterial infections [164, 165]. Conversely, an upregulation of immune-related signaling pathways has been detected in male placentae, likely in an effort to adjust to intrauterine adversities and improve the survival of the male fetus [162, 166, 167].

A recent study identified a sex-specific Th1/Th2 imbalance favoring Th2 immunity in placentae and peripheral blood of children who subsequently suffered from allergic diseases. For instance, a placental downregulation of Toll-like receptor 7 (TLR7), a known promoter of Th1 immunity, in females, resulted in reduced Th1 cytokine activation, altered T cell differentiation, including $CD8^+$ T cells and Treg cells, and a subsequent higher risk for eczema development. On the other hand, in males, altered placental expression of matrix metallopeptidase 9 (MMP9) was shown to affect immune cell recruitment and promote Th2 immunity, thereby increasing susceptibility to eczema. Similarly, rhinitis in boys could be associated with a placental upregulation of *KITL1* whereas female asthma was correlated with a placental downregulation of *ORMDL3* [168]. Moreover, a link between placenta-mediated programming of fetal immune development and an

increased susceptibility to allergies in the offspring could recently be observed. For instance, reduced placental FOXP3 expression has been observed in infants that eventually developed an allergic disease [169]. Clearly, it will now be the next pivotal step to provide insights on how placental functions and the expression of placental genes can be modulated to favor offspring's immunity, while considering the physiological sex-specific placental differences. The sensitivity of placental gene expression to external stimuli and challenges has already been proven, as outlined below.

Placental response to external stimuli and challenges

The placental responses to challenges can vary in a sex-dependent manner [166, 170, 171]. Emerging evidence supports that female placentae are more sensitive to nutritional stimuli but more resilient to adverse effects [133]. For instance, in mice, maternal high-fat diet during pregnancy was associated with global DNA hypomethylation and deregulation of genes involved in cellular, metabolic, and physiological functions only in female placentae, whereas a control diet resulted in lower DNA methylation in male placentae [172]. Due to these epigenetic modifications, biological functions involved in leukocyte activation, cell death, metabolism, and development were enhanced in female placentae, whereas processes associated with fatty acids and glucose metabolism, neurodevelopment, and cardiovascular function were promoted in male placentae [172]. Similarly, maternal high fat and/or salt intake in rats led to sex-specifically altered morphology and gene expression, especially in the male placentae, which were significantly smaller compared to female placentae and highly expressed proinflammatory and metabolic mediators [173]. Interestingly, in the context of maternal under- or overnutrition, male fetuses seem to be unable to adjust and continue to grow, with a risk for poor development and future health, while in females, fetal growth slows down and adapts to intrauterine environment [160, 166, 174, 175].

Besides nutritional challenges, maternal glucocorticoids, either released in cases of stress or illness or administered as a treatment, determine placental development, fetal development, and postnatal health. Under physiological conditions, the fetus is protected against excessive maternal glucocorticoids by placental 11 β-hydroxysteroid dehydrogenase (11β-HSD2), an enzyme that converts active cortisol to inactive cortisone [160]. Saturation of the placental barrier with subsequent increased cortisol influx in the fetus can be observed in cases of elevated maternal glucocorticoid levels. Maternal malnutrition as well as maternal stress has been associated with a reduced placental 11β-HSD2 activity, subsequently resulting in an increased maternal cortisol transfer across the placental barrier [160, 176]. Fetal exposure to excessive glucocorticoid levels has been associated with poor fetal development, resulting not only in intrauterine growth retardation, but also in increased risk for diseases later in life [177]. The placenta itself responds to circulating glucocorticoids via the glucocorticoid and mineralocorticoid receptor [178]. During unchallenged pregnancies with physiological maternal glucocorticoid levels, term female placentae exhibit higher GR expression and 11β-HSD2 activity compared to male ones [179, 180]. This sex-specific GR upregulation may indicate that the term female placenta and female fetus are more sensitive to glucocorticoid levels compared to the male and can respond more rapidly when facing adversities in order to sustain homeostasis. This notion is supported by the recognition of sex-specific differences in molecular pathways facilitating cell survival upon stress, such as O-linked glycosylation. Importantly, the main enzyme involved in this process, O-linked-*N*-acetylglucosamine transferase (OGT), is considered to be an indicator of maternal stress and a cellular nutrient sensor [181]. Under physiological conditions, female placentae exhibit higher OGT levels compared to male placentae, which suggest enhanced cellular capacity to respond to stress and therefore stronger protection and increased sensitivity to adversities [181, 182].

The placental expression of different GR isoforms may be attributable for the observed sex-specific differences in fetal sensitivity to glucocorticoids. Specifically, the resistance of the male placenta to high glucocorticoid levels may be due to the increased expression and nuclear localization of GRβ, an isoform that inhibits cortisol binding and blocks the activity of other GR isoforms. On the other hand, the higher sensitivity to glucocorticoids observed in female placentae can be attributed to a weakened GRβ negative activity and an enhanced GRα-mediated positive signaling [183].

Maternal asthma can also sex-specifically affect placental function. A study by Scott et al. reported that maternal asthma during pregnancy led to the upregulation of cytokines such as TNF and IL-1β in female placentae, while no alterations in cytokine expression were observed in male placentae [184]. These placental differences may account for the reduced fetal growth and lower nutritional and oxygen demand in the female fetus in pregnancies with severe maternal asthma, along with a better fetal survival upon prenatal challenges, as opposed to male fetuses, which continue to grow normally in cases of maternal asthma but are unable to adjust to intrauterine insults [166, 185].

Taken together, published evidence supports that placental function can be influenced by intrauterine insults and responds in a sex-specific manner (Fig. 2). Female placentae are more sensitive to alterations of the maternal environment and capable of responding more efficiently by adjusting fetal growth. Male fetuses follow a predetermined growth pattern without taking into account maternal conditions and intrauterine insults, leading to an inability to adjust. This may explain why males are at higher risk for early-life morbidity and

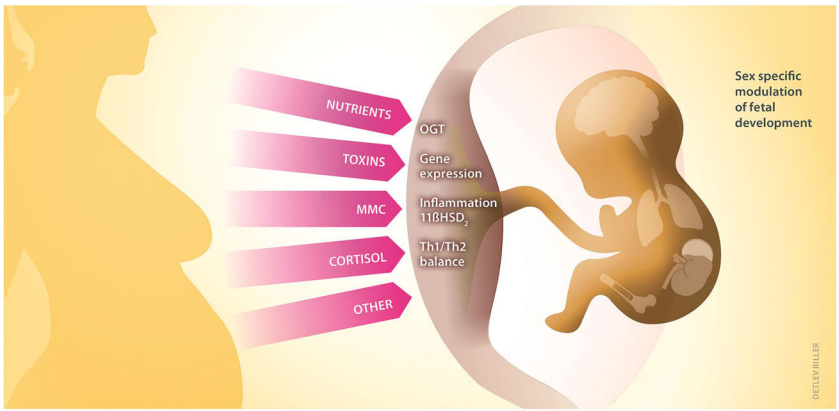

Fig. 2 The placenta plays a key role in the sex-specific programming of fetal development. Maternal cells and molecules, either exogenous or released in response to environmental insults, induce sex-specific changes in placental development and function. Sex-specific placental adaptations to challenges entail epigenetic modifications, alterations in gene expression, and immune environment as well as changes of the placental glucocorticoid barrier. These placental modifications—along with the direct transfer of maternal markers (e.g., glucocorticoids, maternal microchimeric cells, nutrients, toxins) from mother to fetus—affect fetal immune development and growth of fetal organs (brain, lung, adrenals) in a sex-specific manner. Abbreviations used in the figure: MMc, maternal microchimerism; OGT, O-linked-*N*-acetylglucosamine transferase; 11β-HSD2, 11 β-hydroxysteroid dehydrogenase; Th1/Th2, type 1 T helper/type 2 T helper

mortality, while female neonates can sufficiently overcome adversities and have better chances of survival.

Maternal microchimerism in mediating sex-specific fetal programming of immunity

During pregnancy and lactation, maternal cells pass across the placenta into the fetus, colonize into fetal immune and organ systems, and may influence their development [186]. This phenomenon, which is referred to as maternal microchimerism (MMc), persists throughout the offspring's life. Interestingly, the MMc cell compartment is not homogenous, as the phenotype of MMc cells varies among fetal organs, including MMc cells of hematopoietic origin and lineage, as well as somatic cells expressing tissue-specific antigens [187]. Of note, MMc has been associated with immunity in the offspring [17, 187]. Recent evidence suggests that MMc protects against asthma development during childhood [188]. Furthermore, the acquisition of MMc can increase the offspring's risk for malaria infection but protects from manifestation of the disease [189]. Enhanced immune defense against infection due to increased levels of MMc has been also observed in infants with severe combined immunodeficiency [190]. On the other hand, MMc has been implicated in the pathogenesis of chronic autoimmune diseases, as increased numbers of maternal microchimeric cells have been found in patients with type 1 diabetes, juvenile dermatomyositis, scleroderma, and myopathies [191]. Hence, MMc can exert both protective and potentially harmful effects on offspring's immunity.

MMc may be influenced by environmental factors like maternal inflammation [192]. Since MMc can affect the developing immune system, a direct effect of prenatal challenges such as nutrition, infection, and stress on MMc cell trafficking and phenotype might explain their role in fetal programming of postnatal immune diseases. To our knowledge, evidence is not yet available to support that MMc modulates fetal immune development in a sex-specific matter. However, based on the abovementioned findings indicating that MMc protects against childhood asthma and neonatal infections while increasing the risk for autoimmunity, one can assume that increased MMc might explain the lower incidence of asthma and infections and the high susceptibility to autoimmune diseases in girls and women respectively.

Conclusion

To date, animal models and human studies have convincingly identified an association between the impact of environmental challenges during pregnancy, offspring's sex, and disease risk during childhood. Prenatal adversities affect the intrauterine environment via endocrine- and immune-dependent pathways. Sex-specific responses have been identified that affect the developing fetus and increase the risk for childhood immune diseases and infections. Although evidence available to date may—at least in part—be limited, circumstantial, or even ambiguous, it can be summarized that male fetuses lack adaptive flexibility and are therefore unable to adjust their growth pattern when encountering hostile intrauterine conditions. This trait makes males more susceptible to the early-life consequences of prenatal insults and favors the survival of the fittest and strongest individuals. On the other hand, female placentae and fetuses seem to respond more efficiently to changes of the intrauterine environment and are capable of adjusting their developmental pattern accordingly. Due to this

adaptive agility, females face lower risk for morbidity and mortality in early life. However, this early-life female advantage comes at a price, as females are more likely affected by immune disorders, such as asthma and autoimmune diseases, later in life. Future studies addressing both sexes in their design are urgently needed to identify or confirm pathways causally involved in modulating the sex-specific risk for infections and immune diseases. This will then open avenues to develop therapeutic targets, tailored to the sex of the unborn child.

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