Preeclampsia as modulator of offspring health

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Abstract

A balanced intrauterine homeostasis during pregnancy is crucial for optimal growth and development of the fetus. The intrauterine environment is extremely vulnerable to multisystem pregnancy disorders such as preeclampsia, which can be triggered by various pathophysiological factors, such as angiogenic imbalance, immune responses and inflammation. The fetus adapts to these conditions by a mechanism known as developmental programming which can lead to increased risk of chronic non-communicable diseases (NCDs) in later life. This is shown in a substantial number of epidemiological studies which associates preeclampsia with an increased onset of cardiovascular and metabolic diseases in later life of the offspring. Furthermore, animal models based predominantly on one of the pathophysiological mechanism of preeclampsia e.g. angiogenic imbalance, immune response or inflammation do address the susceptibility of the preeclamptic offspring to increased maternal blood pressure and disrupted metabolic homeostasis. Accordingly, we extensively reviewed the latest research on the role of preeclampsia on offspring’s metabolism and cardiovascular phenotype. We conclude that future research on the pathophysiological changes during preeclampsia and methods to intervene the harsh intrauterine environment will be essential for effective therapies.
Introduction

The global prevalence of chronic non-communicable (NCDs) cardiometabolic diseases such as hypertension, cardiovascular disease (CVD), diabetes mellitus type 2 and metabolic syndrome has markedly increased during the past decades [1]. A number of genes and behavioral changes have been identified as initiators and mediators of these complex cardio-metabolic diseases [2–4]. However, the increasing prevalence of NCDs cannot be accounted only to these determinants. Biological factors already present during early development can lead to immediate cardiometabolic fetal responses that might have long-term effects.

The Developmental Origins of Health and Disease (DOHaD) or the ‘Barker’ hypothesis attempts to explain the high incidence of chronic non-communicable diseases (NCD's) by unfavorable in utero conditions. Depending on the severity of the insult during specific critical windows of fetal development, permanent tissue adjustments can occur, leading to long-term changes in organ function [5]. During pregnancy, the key regulatory organ of the intrauterine environment is the placenta, which serves as a metabolic, immune and endocrine organ. It enables and regulates the transport of gases, nutrients, hormones, immunoglobulins and waste products between the mother and the fetus in order to maintain a favorable developmental homeostasis [6]. Hostile environmental factors present during early life, when rapid growth and differentiation is expected, can have a powerful impact on physiological health for a lifetime.

Preeclampsia is a pregnancy-associated syndrome, characterized by hypertension and proteinuria, affecting 2-8% of the population worldwide [7]. It remains a major obstetric problem due to the high prevalence of maternal and fetal mortality and morbidity. Although the etiology is puzzling, several pathophysiological mechanisms combined were proven to be involved at least in the clinical course of preeclampsia. Antiangiogenic imbalance, excessive inflammation, hypoxia and/or autoantibodies targeting the renin-angiotensin system comprise the harsh intrauterine environment during preeclampsia [8,9]. All these factors may interact with the genome of the mother and the fetus in terms of gene expression modulation, ultimately affecting expressed phenotype.

In this review, firstly we address epidemiological and human studies that show a contribution of preeclampsia to cardiometabolic alterations in the offspring. Further, we focus on animal studies in this research area, approaching three different mechanistic scenarios of preeclampsia. Finally, we discuss possible mechanisms that may explain the relevance of preeclampsia in developmental programming of metabolic and cardiovascular diseases in the offspring.
Evidence from human studies: offspring status after preeclampsia

Birth weight screening is still an important assessment of optimal in utero nutrition and development. During preeclampsia, 13-60% of the pregnancies are complicated by decreased birth weight depending on the region, maternal age and the severity of the disease [10,11]. Therefore, preeclampsia is one of the leading factors of fetal growth restriction (FGR) [12,13]. Low birth weight per se is already an established risk factor for cardiovascular and metabolic diseases in later life, although the causal mechanisms are still speculative [14,15].

Preeclampsia is characterized by new-onset hypertension during pregnancy (≥140/90 mmHg), along with proteinuria. However, little is known about neonatal blood pressure after this complication of pregnancy. An early report indicated that term neonates from preeclamptic mothers have transient hypertension [16]. A more recent study showed that premature neonates from preeclamptic mothers, compared to controls, have an early neonatal hypotension [17]. As indicated, blood pressure levels are also altered in these children, which appears to be associated with the gestational age. Furthermore, observation of blood pressure in school-age children previously exposed to preeclampsia showed higher systolic and diastolic blood pressure already at age of 8 years [18–23]. Additionally, it was reported that these children have smaller hearts, increased heart rate and features of cardiac diastolic dysfunction [24], and an increased risk of congenital heart defects namely septal defects [25,26]. However, in a cohort study, 65 years follow up of preeclamptic offspring did not show an increased risk of coronary heart disease, but they reported increased stroke incidence [27].

Evaluation of endothelial functionality with non-invasive assessment can provide considerable insight into blood pressure risk stratification. School-age children, previously exposed to preeclampsia showed increased vascular stiffness in the pulmonary and peripheral vascular system [24,28]. Moreover, intact endothelial morphology is a potent vascular tone regulator. Analysis of endothelial cord cells showed a decreased number of endothelial colony forming cells in contrast to increased senescent progenitor cells [29,30]. This is indicative for at least advanced endothelial cord cell aging in the preeclamptic neonates.

The body mass index (BMI), plasma glucose, and lipid concentrations serve as strong indicators of optimal metabolic functioning and, when increased, are risk factors for cardiovascular and metabolic diseases. Preeclampsia shares many features with the metabolic syndrome including increased maternal concentrations of pro-inflammatory cytokines, insulin, leptin, triglycerides, free fatty acid and low-density cholesterol, usually in the absence of diabetes [31]. Children from preeclamptic mothers show an increased risk of hospitalizations for endocrine and metabolic diseases in the first five years of life [32]. In adolescence, premature born preeclamptic males have an increased BMI in comparison to premature males born from normotensive pregnancies [33]. Cord blood samples from preeclamptic children show altered lipid profiles and increased tumor
necrosis factor alpha (TNFa) when studied for metabolic and inflammatory parameters [31,34,35], but in adolescence, these changes in glucose and lipid profiles are not prominent anymore [19,21]. These effects may be influenced to some extent by maternal metabolic blood parameters and placental insufficiency. However, in school-age children previously exposed to preeclampsia, the metabolic phenotype shows changes only after subclustering of this group. The Quantitative Insulin Sensitivity Check Index (QUICKI) serves as a predictive marker for diabetes onset based on fasting plasma glucose and insulin levels, and low values correspond to increased insulin resistance. Subdivision of groups based on QUICKI did show increased leptin and triglycerides levels in preeclampsia exposed children that had independently low QUICKI values [36]. This suggests that insulin resistance independently, superimposed on earlier preeclampsia exposure can serve as a strong predictor of the metabolic syndrome. These clinical observations reflect a transiently affected neonatal metabolism, which is not continuous through adolescence but possibly can lead to increased susceptibility to the metabolic syndrome after a second environmental stressor, such as a metabolic stress.

Intrauterine adverse environment during preeclampsia and offspring outcome: animal studies

Animal models of preeclampsia can provide a unique possibility to understand the causal relationship and the molecular networks of preeclampsia-induced offspring pathology. Unfortunately, there is currently no perfect animal model of preeclampsia due to the complex and poorly understood pathophysiology of this disease (see Table 1 for overview). Most of the presented models are based only on one pathophysiological feature, failing to reproduce the whole spectrum of preeclampsia characteristics. It is important to unravel whether all these experimental pathophysiological changes, which appear during preeclampsia, contribute to a partial or full range of cardiovascular and metabolic changes in the offspring. The use of several animal models of preeclampsia could help to distinguish the independent and/or dependent contribution of each of these factors to the developmental programming of offspring health. Below, we will discuss the animal studies that involve offspring follow up after induction of major pathophysiological conditions of preeclampsia, excluding the genetic or surgically induced animal models of preeclampsia.

1. Angiogenic disparity

Angiogenic dysbalance is a well-known feature of preeclampsia. The antiangiogenic factors soluble fms like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) are increased in preeclamptic patients, after the 30th week of pregnancy [37]. sFlt-1 and sEng promote vascular dysfunction and capillary permeability, liver dysfunction and neurological abnormalities via antagonization of proangiogenic factors such as VEGF and PIGF or TGFb signaling respectively [38–40].
### Table 1. Spectrum of cardiometabolic alterations in offspring from preeclamptic mothers (animal models).

<table>
<thead>
<tr>
<th>Model</th>
<th>Species/ strain</th>
<th>Offspring outcome</th>
<th>Offspring age</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>sFlt-1 overexpression</td>
<td>CD-1 mice</td>
<td>Catch up growth, iPGTT variations</td>
<td>24 weeks</td>
<td>[42]</td>
</tr>
<tr>
<td>sFlt-1 overexpression</td>
<td>CD-1 mice</td>
<td>Hypertension in males, low BW in comparison to controls</td>
<td>9 weeks</td>
<td>[41]</td>
</tr>
<tr>
<td>sFlt-1 overexpression 2nd impact: prepregnancy obesity</td>
<td>CD-1 mice</td>
<td>Hypertension in male offspring</td>
<td>24 weeks</td>
<td>[45]</td>
</tr>
<tr>
<td>Prepregnancy obesity and sFlt-1 overexpression</td>
<td>CD-1 mice</td>
<td>Fasting glucose increased in males</td>
<td>12 weeks</td>
<td>[43]</td>
</tr>
<tr>
<td>AT1-AA immunization 2nd impact: high sugar diet 20% sucrose</td>
<td>Wistar rats</td>
<td>Insulin resistance</td>
<td>40 weeks</td>
<td>[54]</td>
</tr>
<tr>
<td>AT1-AA passive immunization</td>
<td>Wistar rats</td>
<td>Myocardial remodeling</td>
<td>3 weeks</td>
<td>[143]</td>
</tr>
<tr>
<td>AT1-AA passive immunization</td>
<td>C67Bl/6J mice</td>
<td>Abnormal kidney and liver development</td>
<td>GD 18</td>
<td>[53]</td>
</tr>
<tr>
<td>LPS injections</td>
<td>Sprague Dawely rats</td>
<td>Increased BW and fat deposits, hyperleptinemia, hypertension (no major sex-specific effects)</td>
<td>24 weeks</td>
<td>[60]</td>
</tr>
<tr>
<td>LPS injections</td>
<td>Sprague Dawely rats</td>
<td>Hypertension, proteinuria, decreased glomeruli</td>
<td>25 weeks</td>
<td>[61]</td>
</tr>
<tr>
<td>LPS injections</td>
<td>Sprague Dawely rats</td>
<td>Hypertension, left ventricle hypertrophy</td>
<td>32 weeks</td>
<td>[62]</td>
</tr>
<tr>
<td>LPS injections</td>
<td>CD-1 mice</td>
<td>Decreased body weight, impaired spermatogenesis</td>
<td>35 weeks</td>
<td>[64]</td>
</tr>
</tbody>
</table>
Adenoviral overexpression of sFlt-1 mimics the clinical course of preeclampsia in rodents [38]. Fetuses in this model show restricted growth that can be maintained until adulthood or can show catch up growth until the age of 6 months (Table 1) [41,42]. Solely, sFlt-1 exposure during pregnancy imposes sex-specific glucose and/or insulin responses (to a glucose bolus) in the offspring, suggesting sex-specific differences in developmental programming of glucose metabolism. In addition, hypertension was observed only in male offspring [41–43]. Sex-specific offspring outcomes are poorly understood, but one of the possible reasons can be sexually dimorphic adaptations of the placenta [44].

When another environmental stressor, such as maternal obesity, is introduced during sFlt-1 induced preeclampsia the offspring’s birth weight is not compromised. On the contrary, several biochemical parameters such as blood glucose, cholesterol, triglycerides and leptin are increased, in combination with increased fat tissue depositions and aberrant carotid vascular reactivity in both sexes [43,45]. This may indicate that a single antiangiogenic intrauterine insult can influence sexual dimorphic changes in placenta, by priming the males towards hypertensive phenotype, but this is not sufficient for profound metabolic alterations without additional trigger factors.

Unfortunately, the effects of increased soluble endoglin (sEng) on the offspring health are still largely unknown. In vivo studies in mice have shown that direct administration of sEng increases the vascular resistance and subsequently the blood pressure [46]. In patients with diabetes and hypertension, sEng is positively correlated with the basal glucose levels suggesting a potential role in the glucose metabolism [47]. In accordance with previous findings and the known synergistic effect of sEng and sFlt-1 on preeclampsia outcome, we can speculate on the effects on offspring health in a similar or superimposed manner.
2. Angiotensin II type I receptor antibodies

The prevalence of angiotensin II type I receptor autoantibodies (AT1 AA) has a range of 70 to 95% in women diagnosed with preeclampsia, compared to 30% of healthy controls. A higher antibody titer is proportionally correlated to the severity of the disease [48,49]. In addition, AT1 AA display an agonistic effect on the AT1 receptor, promoting vasoconstriction and aldosterone secretion, similarly to angiotensin II [50–52].

Passive immunization with AT1 AA in rodents is associated with the development of proteinuria and hypertension at the end of pregnancy [53,54]. The fetuses show growth restriction and remodeling in several organs, such as the liver, the heart, and the kidney. At the histopathological level, glomerular loss, myocardial apoptosis and immature cell liver infiltration are observed in the offspring, suggesting an adaptive decline in fetal growth and organogenesis possible due to maternal-fetal transfer of AT1 AA. Irani et al. reported unaffected functionality of these transported antibodies [53], and successful activation of fetal AT1 receptors may contribute to systemic vasoconstriction and hypoxia, that can predispose the offspring to organ maladaptation.

Zhang et al. did long-term follow up on offspring derived from dams actively immunized against AT1 receptor antigen [54]. A middle-age checkup at 10 months of age showed elevated fasting insulin levels and increased homeostasis model assessment (HOMA) index, suggesting the development of insulin resistance (Table 1). This was expected especially because AT1 receptors are involved in insulin signaling of beta cells [55]. An additional, two months feeding with high sugar diet of these adult offspring leads to even more pronounced metabolic alterations such as increased triglycerides, decreased high-density cholesterol, impaired glucose tolerance and enlarged visceral fat depositions [54]. All these alterations are contributors to the progression of the metabolic syndrome. Surprisingly, blood pressure was normal in these animals, although they had been exposed to the AT1 antibodies in utero and in the weaning period via the maternal milk. One possible interpretation is that intrarenal angiotensin II, contrary to plasma angiotensin II, may be positively involved in blood pressure regulation. Another important comment is that vascular endothelium has relatively large regeneration capacities, and if there is no constant provocation with AT1 antibodies, no endothelial-related rise of the blood pressure will occur.

In sum, AT1 antibody exposure does not affect the fetal blood pressure, but can have detrimental effects on organ formation and insulin resistance, which can be
potentiated with an unhealthy diet. Nevertheless, more studies are needed in order to elucidate the underlying mechanisms of AT1 AA induced fetal metabolic programming.

3. **Inflammatory milieu**

Mild inflammation is generally considered a normal feature of pregnancy, whereas more exaggerated systemic inflammatory responses are characteristic of preeclampsia [9]. In accordance, proinflammatory cytokine concentrations are increased (TNFα, IL-6, IL-1β) in preeclamptic patients [56–58]. The association between inflammation and preeclampsia served as the basis for an experimental animal model of preeclampsia by low-dose intravenous infusion of bacterial endotoxin [59]. Nowadays, most of the developmental studies that involve exposure to lipopolysaccharide (LPS) during pregnancy are focused on the immunological consequences without concentrating on the possible preeclamptic symptoms in the dam.

Mid-gestational LPS exposure is characterized by large range of cardiovascular events such as increased blood pressure, aortal vascular impairment, left ventricular hypertrophy, diastolic dysfunction, and myocardial apoptosis in adult offspring, without specific sex differences [60–64]. This implies striking endothelial and cardiac sensitivity of the fetus for inflammation that is maintained until adulthood, which programs health towards cardiovascular functional decline. This, in part, can be explained by upregulation of the NF-κB signaling pathway, and increase of reactive oxygen species and downregulation of the renal dopaminergic system leading to hypertension and vascular instability [64].

Combined effects of LPS and high-fat diet exposure during pregnancy have differential effects on offspring’s glucose and lipid metabolism (Table 1). It was shown that exposure to LPS in mid-gestation and high-fat feeding until 3 months of age can lead to impaired liver function and insulin resistance [65]. On the contrary, exposure to LPS in late gestation with additional high-fat diet stress after the lactation period did not result in an impaired metabolic phenotype in the offspring [66]. This suggests that timing of LPS exposure is crucial for fetal metabolic programming and in part can be explained by changes in maturational properties of the placenta, which in the last term of pregnancy are fully developed, possibly resulting in placental impermeability for the intermediate metabolic effectors of LPS [67]. Another important observation is that LPS and high-fat diet combined have a beneficial effect on blood pressure and the inflammatory response in the offspring, but not on the insulin resistance progression and liver dysfunction. Mid-
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gestation exposure to LPS seems to attenuate the offspring sensitivity to high-fat diet induced inflammation, which in association with normotension and normalized IL-6, TNFα, and leptin concentrations [65]. On the contrary, an aberrant inflammatory response on its own is not sufficient for a systemic breakdown in the regulation of insulin resistance.

Altogether, the data indicate that the developmental programming of offspring health via preeclampsia is caused by a “two-hit” combination of, first, systemic immunomodulatory and antiangiogenic signals during mid to late gestation and, second, a later host susceptibility marked by unhealthy lifestyle (e.g. Western diet). These animal data have important translational consequences, as the first hit is needed to affect the offspring’s development, and the presence of the second hit explains why only a minority of human fetuses exposed to preeclampsia develop detrimental cardiovascular and metabolic diseases later.

Underlying mechanisms of developmental programming

In order to interpret the developmental programming of cardiometabolic health via preeclampsia, we underline below the conserved mechanisms of chronic disease development, their interaction with the preeclamptic environment and their effects on embryonic growth and epigenetic status (Figure 1). Understanding the specific mechanisms by which preeclampsia impacts offspring welfare is crucial for developing appropriate strategies to improve the negative effects of the harsh intrauterine environment.

Placental permeability: the initiator

The placental blood barrier serves as a protector and nutrient sensor between the mother and the child. In preeclampsia, placental morphology is perturbed showing superficial trophoblast invasion and insufficient remodeling of spiral arteries in the myometrium [68,69]. Thus, with this defective placentation, two separate factors can influence its permeability: the placental composition and the exchange surface area. Several factors influence placental composition, including an intact syncytiotrophoblast layer and cellular junctions assembly. The syncytiotrophoblast, a continuous membrane layer of the placenta, serves as a checkpoint for placental transport [70–72]. During
preeclampsia this layer is highly apoptotic [73], suggesting a dysfunctional adaptation of the placenta to increased fetal nutrient demand or an effect of the increased proinflammatory cytokines during preeclampsia.

Figure 1. The impact of preeclampsia on offspring/adult health. Schematic diagram of how possible preeclamptic scenarios are shaping the intrauterine environment, influencing the placental structure (initiator) and imposing unfavorable signaling network (mediators) in the offspring. This can program several aspects of the metabolic and cardiovascular system, mainly via organ remodeling and epigenetic modulation of gene expression (effectors).
Consistent with this idea, tight junctions integral membrane proteins, important for paracellular transport of water and nutrients, are extremely susceptible to TGFβ and IL-1β destruction which can be reversed in vitro by specific cytokine inhibitors [74,75]. Given that discontinuous placental membranes are accompanied with increased porosity, it is probable that loss of syncytiotrophoblast integrity underlines the defective nutrient transport of preeclamptic placenta.

An altered placental surface area in preeclampsia has been reported along with decreased placental weight, changes in the shape and increased thickness, probably due to compensatory mechanisms [76]. The growth of the placenta was reported to be compromised only on the minor axis, and corresponded to the severity of preeclampsia. This axis is speculated to coincide with mediolateral development of the fetus, suggesting that this area is not spared during preeclampsia. In accordance, fetal length is less compromised in offspring in comparison with severely affected abdominal circumference [34,77].

A central question is whether these structural changes in the preeclamptic placenta are transport determinants for pathological signaling molecules to the fetus. It is known that inflammatory cytokines and AT1 AA can cross the placenta, but no data on the transfer of antiangiogenic molecules to the fetus is available [53,78]. They can act as potent signaling modifiers of glucose and lipid metabolism, but a definitive description of their mechanisms of action is lacking. Currently, we rely solely on animal data: for example, challenging with an inflammatory cytokine such as TNFα induces insulin receptor downregulation in the liver that promotes the development of liver insulin resistance [79,80]. An IL-6 challenge in rodents showed increased mobilization of acyl-CoA, a metabolic active form of fatty acid, in the skeletal muscles that has been strongly associated with lipid accumulation in muscles and peripheral insulin resistance [79–81]. AT1 AA exposure has detrimental effects on function of the liver, by NF-κB and NADPH oxidase dependent release of reactive oxygen species [82,83]. Ubiquitous exposure to sFlt-1 leads to hypovascularization in several organs including pancreas and adipose tissue, which in turn can affect the beta cell mass and energy expenditure of the adipose tissue [84,85]. In addition, prolonged exposure to sFlt-1 is involved in the development of diastolic dysfunction and heart failure [86]. Taken together, increased exposure of the fetal organism to these molecules may have a detrimental effect on a proper metabolic and cardiovascular functioning.
Reactive oxygen species: the mediators

Multiple lines of evidence suggest that oxidative damage is one of the underlying mechanisms of many chronic diseases such as type 2 diabetes, obesity, hypertension, atherosclerosis and metabolic syndrome [87,88]. Oxidative stress occurs as soon as the production and consumption of reactive oxygen species (ROS) are imbalanced.

During preeclampsia, inflammatory cytokines and AT1 AA promote increased ROS production by up to 40% when compared to control placentas [89–92]. Whether oxidative distress is a cause or consequence of placental dysfunction and/or fetal nutrient demand is a matter of ongoing debate and most studies simply describe an association of ROS overflow with metabolic consequences rather than mechanistic connections.

Normal fetal development is dependent on tightly controlled oxidative stress exposure for optimal cellular signaling, differentiation and proliferation [93]. However, during preeclampsia, the functionality of the placenta is reduced and the antioxidant capacity is diminished, suggesting increased oxidative stress transfer to the fetus. Cord blood analyzed from preeclamptic mothers showed either decreased antioxidant activity [94] or increased oxidative stress markers [95–98], but not for all [99], suggesting a possibility of lipid peroxidation and protein inactivation in the fetus [100]. Several tissues are extremely susceptible to oxidative damage, including beta cells and vascular endothelium mainly due to low cytoprotective mechanisms [101,102]. Furthermore, treatment of hypoxic dams with antioxidants during gestation ameliorates the vascular dysfunction in the offspring, indicating that antioxidant treatment may indeed be an interventional treatment [103]. On the contrary, clinical trials that involved routine antioxidant supplementation during pregnancy contradict the idea of preventive effect towards preeclampsia [104,105]. Another trial that included only high-risk preeclampsia patients reported protective effect of antioxidant vitamins in combination with L-arginine [106], suggesting that exclusive antioxidant treatment is not sufficient to combat preeclampsia.

Leptin signaling as mediator

Leptin is a satiety hormone and via Jak2/Stat3 and PI3K-Akt signaling pathways has a major impact on the energy homeostasis, body composition and appetite in early fetal and later adult life [107]. Moreover, leptin expression is responsive to the intrauterine and fetal environment, showing overexpression in monochorionic twin placenta only on the side of the growth restricted fetus [108]. The extent to which leptin
signaling is implicated in overall fetal metabolism is unknown, but there is evidence that it stimulates fatty acid oxidation in muscles, increases the glucose turnover in brain, heart, and brown adipose tissue and inhibits the global lipid accumulation [109]. By contrast, reduction of leptin concentrations and the state of leptin resistance share similar effects on the metabolism, promoting hyperinsulinemia and hyperglycemia. During preeclampsia, maternal leptin concentrations show a 2-fold increase in comparison to control subjects, irrespective of body mass index [110–114], which is usually combined with hyperinsulinemia, altered lipid profile and decreased 2-methoxyestradiol, which serves as an important vasoprotector and vasodilator [115,116]. There is a dichotomy, therefore, between the protective metabolic effects of leptin and apparently deleterious effects of hyperleptinemia on maternal health. In part, this can be explained by a development of leptin resistance, mainly due to inactivation of STAT3 intracellular activity which is also decreased in preeclamptic pregnancies [117].

Fetal cord leptin concentrations are increased [110,118] in preeclamptic pregnancies, possibly due to increased nutrient demand of the fetus and/or increased placental permeability and consecutive leptin flow to the fetus. Hyperleptinemia in utero can alter the adrenal responsiveness [56,119] in the fetus and together with increased inflammatory markers can develop a defense mechanism of leptin resistance, which ultimately can lead to deleterious effects on cardiovascular and metabolic health.

**Cellular adaptations as effectors**

Optimal organ functioning is dependent on the quantity, morphology and functionality of relevant cell types due to appropriate differentiation of pluripotent embryonic stem cells. Although the mechanisms of embryonic cell fate decisions are obscure, presence of low energy levels and prominent signaling networks are strongly correlated with disturbed metabolic stem cell fate [120–122]. Importantly, all these adverse conditions are also present in utero during preeclampsia.

Moreover, several reports showed changes in the number of nephrons, beta cells and/or cardiomyocytes in offspring exposed to a harsh intrauterine environment [123–126]. A decreased number of nephrons contributes to low rates of renal ultrafiltration that affects blood circulating volume which ultimately can lead to increased blood pressure [126]. Decreased beta-cell mass adaptation due to early life stressors, such as undernutrition and placental insufficiency, possibly can have an influence on later
disease development, e.g. diabetes mellitus [127]. Initial heart size has an influence on the end diastolic volume and serves as a predictive index for myocardial disease [24].

These (mal)adaptive changes are observed mainly in organs constructed from long-lived postmitotic cells [123,128]. As these cells are not- or rarely dividing cells, their development during intrauterine life is extremely important in order to prepare them for long-term functionality. Tightly controlled processes regulate cell number while their functioning is dependent on specific signaling molecules and energy sources. During preeclampsia, the increased concentration of inflammatory markers and improper vascular signaling molecules might perturb these regulatory processes essential in organ formation [129]. Combined with poor nutrient supply via the placenta this can lead to detrimental effects in offspring health.

**Epigenetic changes as effectors**

Exposure to different environmental stimuli, especially during critical windows of development, results in formation of adaptive epigenetic marks as part of the adaptive stress response [5]. Epigenetic marking system includes changes in DNA methylation, histone modifications and non-coding RNA (ncRNA) expression. Usually, they are established early in development and act as regulators of developmental, tissue and sex-specific gene expression [130–133].

DNA methylation is a unique form of gene regulation because it involves direct covalent interaction within the genome and can provide long-term stability in a heritable transgenerational way [134]. Methylation of important regulatory sites, e.g. gene promoters or enhancers, is mostly connected to gene repression, resulting in gene expression downregulation [135].

DNA methylation analysis of cord blood cells is a valuable target to study the early epigenetic consequences of preeclampsia to the fetus. Several studies analyzed DNA methylation of genes involved in fetal growth and development that are also highly sensitive to environmental perturbations. Hypomethylation has been observed in the promoter region of the 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) in cord blood samples from neonates exposed to preeclampsia [136]. Decreased methylation was also reported for insulin-like growth factor 2 (IGF2) in the Differentially Methylated Regions (DMR), important for gene regulation of imprinted genes [137]. By contrast, in
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Preeclamptic placentas, HSD11B2 and IGF2 gene expression levels are decreased [138,139]. Therefore, there is a discrepancy between the reported hypomethylated status and the observed downregulated activity of these genes in other studies. It is tempting to speculate that this is a compensatory change in methylation to ensure favorable offspring functioning, but on the other side, it can be an atypical decrease in gene expression which can lead to metabolic maladaptation.

A recent study used a genome-wide methylation analysis in which neonatal cord blood DNA from mothers diagnosed with early onset preeclampsia showed promoter hypomethylation or hypermethylation for different subsets of genes. Prominent DNA modifications were primarily discovered in genes involved in lipid metabolism and inflammation, pointing out that early epigenetic disruptions can be seen in preeclamptic children [140]. Altogether, these findings support an effect of preeclampsia on the methylation status of the neonates cord blood, but it is unclear whether this is a protective or maladaptive effect. Although this does not prove any causal relationship with long-term health effects, it can be used as an initial proof of principle for conduction of new cohort studies.

To our knowledge, there are no data concerning histone modifications and/or ncRNAs in offspring from preeclamptic mothers. Communication between DNA methylation and chromatin modifiers or promoter regions of ncRNAs has been established [141,142], and abnormal methylation either solely or via other epigenetic marks can be an important mediator of fetal metabolism. It is becoming clear that these molecules are implicated in several diseases and successful discovering of their implication in developmental programming can lead to possible biological biomarkers or targets for therapy.

Concluding remarks

Taking into consideration the great amount of evidence, it is reasonable to suggest that preeclampsia constrains the cardiometabolic health of the offspring. Still, it remains difficult to estimate the degree of involvement of preeclampsia into the cardiovascular and metabolic health programming of the offspring. The major obstacle is the multiple pathophysiological pathways implicated in the development and the clinical course of preeclampsia that may influence each other or act independently all at once or in series. Depending on which mechanism is dominantly involved, and which secondary
environmental stressors are present, different aspects of the metabolism and the cardiovascular system can be affected. The role of the placenta as a central initiator of long-term preeclamptic consequences in the offspring is just the beginning to be explored (Figure 1). However, understanding of all mechanisms by which preeclampsia alters fetal growth and development and later on programs it towards chronic disorders is crucial for identification of individuals at risk and for development of future clinical interventions or prevention strategies.
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