Review

Genetic Background of Fetal Growth Restriction

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Abstract: Fetal growth restriction (FGR) is one of the most formidable challenges in present-day antenatal care. Pathological fetal growth is a well-known factor of not only in utero demise in the third trimester, but also postnatal morbidity and unfavorable developmental outcomes, including long-term sequalae such as metabolic diseases, diabetic mellitus or hypertension. In this review, the authors present the current state of knowledge about the genetic disturbances responsible for FGR diagnosis, divided into fetal, placental and maternal causes (including preeclampsia), as well as their impact on prenatal diagnostics, with particular attention on chromosomal microarray (CMA) and noninvasive prenatal testing technique (NIPT).

Keywords: fetal growth restriction; genetics; single nucleotide polymorphism; chromosomal microarray

1. Introduction

Fetal growth restriction (FGR) is one of the most formidable challenges in antenatal care. While numerous formulae evaluating fetal growth have been established, the most common takes the head circumference (HC), abdominal circumference (AC) and femur length (FL) into account [1]. Although definitions of small for gestational age (SGA) and FGR are often used interchangeably, a clear distinction between those two must be made. A fetus is considered to be SGA when an estimated weight for a given gestational age falls below a preset threshold, usually the 10th centile [2]. A group of SGA fetuses does not necessarily contain unhealthy individuals; the majority of them are rather constitutionally small. On the other hand, a growth-restricted fetus is unable to reach its genetically programmed growth potential. Moreover, according to the newest criteria, an FGR fetus' weight could even lie within normal ranges, and clear definitions have been established by Delphi consensus [2,3]. Nevertheless, both SGA and FGR should not be defined with rigid criteria, but rather considered as spectrum disorders [4].

Pathological fetal growth is a well-known factor of not only in-utero demise in the third trimester, but also postnatal morbidity and unfavorable developmental outcomes, including long-term sequalae such as metabolic disturbances, diabetic mellitus or hypertension [5–7]. In clinical considerations, two main types of FGR are often distinguished—early and late, i.e., diagnosed before or after 32 gestational weeks. Both types differ substantially, mostly in management, prevalence and pathophysiology. Although early FGR is associated with a higher risk of perinatal complication, late FGR is more common in clinical practice [2].

Multiple factors playing roles in the pathophysiology of FGR have been reported. Nevertheless, impaired placentation remains as the main and most common culprit [2]. Recent development of diagnostic techniques allowed better analysis of genetic reasons for FGR, including chromosomal, submicroscopic and single gene disorders [8]. Although

it is not a universal rule, genetic anomalies are more prevalent in severe cases and early gestational ages [8]. The genetic cause of FGR can be either fetal, maternal or impaired placental function [9]. The currently available genetic diagnostics, including the noninvasive prenatal testing technique (NIPT), as well as invasive sampling procedures (chorionic villus sampling CVS and amniocentesis) allow us to determine these abnormalities [10]. The most common factors involved in the pathophysiology of FGR are presented in Figure 1.

MATERNAL FACTORS:
1. Chronic diseases (i.a. hypertension, chronic kidney disease, autimmune diseases)
2. Preeclampsia
3. **Genetic predisposition** (i.a. ET-1, FOXD1, TNFα, ESR1, MTHFR gene variants)
4. Chronic malnutrition
5. Drug use

FGR

PLACENTAL FACTORS:
1. Inadequate spiral artery remodeling
2. **Genetic** (i.a. CPM, mtDNA mutations)
3. Structural abnormralities of the placenta (bilobed placenta, low-insertion placenta)
4. Placental tumors (i.a. chorangioma)

FETAL FACTORS:
1. **Genetic abnormalities**:
   ➢ Chromosomal aberrations (i.a. T13, T17, T18, cri-du-chat syndrome)
   ➢ Monogenic disorders (i.a. Cornelia de Lange, Smith-Lemli-Opitz, Meier-Gorlin, Noonan syndromes)
   ➢ Abnormal methylation (i.a. Silver-Russell syndrome)
2. Intrauterine infections (i.a. TORCH)
3. Multiple pregnancies (selective IUGR)

Figure 1. The most common factors involved in the pathophysiology of FGR.

The primary objective of this narrative review was to explore to which extent genetic disturbances are responsible for FGR diagnosis. Since the genetic diagnosis determines the prognosis, it is of great importance to offer proper diagnostic testing. The secondary objective of this paper was to indicate the impact of possible genetic abnormalities on appropriate prenatal diagnostics and consequently on the prognosis and management strategies in women with FGR.

2. Fetal FGR Causes

The causes of fetal FGR vary [8] and include fetal chromosomal aberration, monogenic syndromes and abnormal methylation. Chromosomal anomalies were reported in up to 19% of fetuses with FGR, with aneuploidy being the most common aberrations, accounting for 5.8% [11,12]. Significant fetal growth restriction is often seen with trisomy 13 and trisomy 18, which are usually confirmed with multiple malformations by ultrasound. Similarly, FGR is the most common symptom of trisomy 17; however, the presence of this aberration is very rare [13]. The other genetic disorders with the same prenatal manifestation as FGR are Cri-du-chat syndrome (CdCS), resulting from a deletion of the short (*p*) arm of chromosome 5 [14–16], and Williams–Beuren syndrome, caused by a heterozygous deletion in the chromosome 7q11.23 region [17].

Recently, with the advancement of molecular genetic methods, the percentage of detected chromosomal aberrations has increased. The most recent non-invasive prenatal testing (NIPT), using cell-free fetal DNA in maternal blood, which is derived from the placental cytotrophoblast, was first designed for detecting fetal trisomies 21, 18 and 13.

However, using a genome-wide approach, other rare chromosome anomalies can also be detected [10]. These aberrations were often "lost" during cell culture when performing a classical karyotype from trophoblast. Therefore, their frequency and clinical significance is now being investigated. In invasive prenatal diagnostics, using chromosomal microarray analysis (CMA), Tzadikevitch et al. revealed that the overall rate of chromosomal aberrations was significantly higher in all FGR cases when compared to the control group of normal uncomplicated pregnancies. The efficiency of CMA was also significantly higher in cases with major structural defects (29.4 vs. 3.4%, $p = 0.001$) compared to isolated FGR [18]. An and coauthors evaluated the incidence of chromosomal aberrations in a group consisting of 127 FGR cases without concomitant structural anomalies. In 9.4% (12/127) of cases with isolated FGR, chromosomal abnormalities were detected. Taking into account gestational age at diagnosis, the detection rate was 9.6% (5/52) in the early-onset group and 9.3% (7/75) in the late-onset group [19]. However, de Wit recommends performing CMA testing in cases of FGR between 18 and 24 weeks of gestation [20]. Peng et al. showed an inverse relationship between the gestational age at FGR diagnosis and the detection rate of chromosomal aberrations. It was 7% in the early-onset group and 1.8% in the late-onset group. An association between the chromosomal abnormality rate and FGR severity was also demonstrated: from 7.8% in fetuses with estimated fetal weight (EFW) below the 10th centile and 10% in those with EFW below the 5th centile, to 18% for fetuses with EFW below the 3rd centile [14]. A systematic review by Sagi-Dain et al. including 14 studies revealed a chromosomal abnormality rate of 6.4% (47/874) in isolated FGR cases [21].

When early-onset fetal growth restriction results from chromosomal abnormalities or is accompanied by fetal structural malformations, it may be associated with poor pregnancy outcomes. Nevertheless, the final pregnancy outcome depends also on the level of mosaicism. Chen et al. presented a case of low-level mosaicism for trisomy 16 in pregnancies complicated by early-onset FGR with a favorable outcome [22]. Gupta et al. found, however, an elevated risk of adverse pregnancy outcomes, even in patients with early-onset fetal growth restriction without fetal or genetic anomalies [23]. In a group of 122 patients, the incidence of intrauterine fetal death (IUFD) was 5.7%. High rates of other pregnancy complications, such as preterm birth (20%), low birth weight (59.3%) and gestational hypertension (14.1%), were also demonstrated. The prognosis worsens with early-onset and increased severity of growth restriction. Additionally, the presence of echogenic bowel and abnormal umbilical artery Doppler indices were associated with poor pregnancy outcomes of 17.4 versus 2.2%, OR 9.68, 95%CI 1.65–56.73 and 35.3 versus 0%, OR 4.46, 95%CI 2.65–7.50 respectively. [23].

FGR can also be a result of monogenic disorder. Variants in genes described in FGR cases are often associated with fetal growth, short stature or other skeletal anomalies (like skeletal dysplasia). Most of these syndromes will result in short stature, but many of them are additionally associated with intellectual disability [24]. Patients with FGR can be divided into two groups due to the clinical result of the mutation. The first group represents disorders where all fetal dimensions (such as head circumference, long bones) correspond to the same gestational age. This group includes, for example, the syndromes: Cornelia de Lange (most common mutation in the *NIPBL* gene), Smith–Lemli–Opitz (mutation in the *DHCR7* gene), Meier–Gorlin (mutation in the *ORC1*, *ORC4*, *ORC6*, *CDT1* or *CDC6* genes) or 3 M (most common mutation in the *CUL7* gene) [10,25–27]. The second group contains fetuses with extremely short long bones, but normal other dimensions and includes disorders such as Noonan Syndrome (most common mutation in the *PTP11* gene), achondroplasia or hypochondroplasia (mutation in the *FGFR3* gene) [10,28,29].

FGR is associated with an increased risk of developing metabolic diseases later in life [30]. Genetic variants in the *FTO* (fat mass and obesity-associated) and *PPARγ* (peroxisome proliferator-activated receptor-gamma) genes are known to be associated with the incidence of metabolic disease, body mass index and obesity. Barbieri et al. studied the association of selected *FTO* (rs1421085, rs55682395, rs17817449, rs8043757, rs9926289, and rs9939609) and *PPARγ* (rs10865710, rs17036263, rs35206526, rs1801282, rs28763894,

rs41516544, rs62243567, rs3856806, and rs1805151) single-nucleotide polymorphisms (SNPs) with FGR in a Brazilian birth cohort. They revealed that *PPARγ* SNP was positively correlated and *FTO* SNP negatively correlated with FGR, and these effects were gender specific [31]. Karimi-Zarchi et al. suggested that the Apa1 polymorphism of insulin growth factor 2 (IGF-2) is associated with an increased risk of FGR [32]. Additionally, epigenetic changes, including i.a. DNA methylation, seems to be crucial in the origin of metabolic diseases. Krishna and coauthors compared the change in DNA methylation in umbilical cord blood samples of growth-restricted and appropriate for gestational age (AGA) babies to explore the differentially methylated candidate genes and their biological importance. Genomic DNA methylation varied significantly between FGR and AGA newborns (FGR: 3.12 ± 1.24; AGA: 4.40 ± 2.03; *p* value: <0.01), and a global shift toward hypomethylation was seen in FGR cases, targeted to regulatory regions and, specifically, promoters. As expected, pathway analysis identified dysregulation of the pathways responsible for the development of metabolic diseases [33]. One of the well-characterized diseases associated with FGR is Silver–Russel syndrome, which has multiple etiologies, but epigenetic changes in chromosome 11p15.5 and maternal UPD7 are the main causes of the syndrome [34,35].

3. Placental FGR Causes

Possible mechanism and diagnostic implications of placenta-limited genetic anomalies refers to the situation when the chromosomal anomaly can be confined to the placenta and cause growth restriction in a chromosomally normal fetus. Mosaicism is defined as the presence of two or more different chromosomal sets in the fetoplacental unit developed from a single zygote. It is caused by a viable somatic post-mitotic error occurring in an initially normal conceptus, or a meiotic error resulting in trisomy with subsequent post-zygotic trisomic rescue [36]. Placental mosaicism is observed in approximately 2% of analyzed chorionic villi samples and can engage different types of chromosomal abnormalities (structural or numerical) [37,38]. Especially in pregnancies with the isolated FGR, the possible mechanism of growth restriction is a presence of chromosomal abnormality limited to the placenta. In 9–16% of pregnancies with isolated FGR, chromosomal mosaicism confined to placental tissue (confined placental mosaicism, CPM) has been observed [39]. CPM can be divided into three types (I–III) and its type, as well as the particular chromosomal involvement and the origin of trisomy (mitotic or meiotic) in the aneuploid clone is related to specific pregnancy outcomes. When meiotic CPM with trisomy is detected in the placenta, there is a high risk of the fetus having uniparental disomy (UPD) for the chromosomal pair that is trisomic in the placenta [40,41]. Lazier et al. described maternal uniparental disomy of chromosome 6 [upd(6)mat] as a rare disorder with the main associated phenotype being FGR [42]. An additional special mention should be made for trisomy of chromosome 16, which is a cause of complication in more than 1% pregnancies [43]. However, CMP of chromosome 16 is associated with SGA in 43–58%, congenital malformation in 20–22%, preeclampsia 16–24% and prematurity in 37–37%. The normal outcome is observed in up to 36% of newborns [43–45]. Del Gobbo et al. presented a case of a liveborn male with FGR associated with confined placental mosaicism involving eight 2.4–3.9 Mb de novo duplications. These duplications were mosaic, detected not in the whole placenta, but only in its specific regions, and re-engaged both parental chromosomes, indicating a post-zygotic origin. Among the duplicated genes, there were some (including *KISS1* and *REN*) involved in trophoblast proliferation and angiogenesis and thus important for placental function and fetal growth [46]. CPM diagnosis not only explains the pathogenesis of FGR, but also ensures significant information for postnatal follow up. Thus, it is of importance to examine placentas from pregnancies with isolated FGR for the presence of genetic anomalies. This phenomenon is particularly visible, when the NIPT technique has been introduced on a large scale [47–49]. Van Opstal et al. performed NIPT in 2527 cases, and in 41 samples, chromosomal aneuploidies other than 13, 18 and 21 were detected. Among those 41, 22 were confined to the placenta. In 6 out of 22, FGR was observed, and in an additional four pregnancies SGA (small for gestational age (<p10)) was described [47]. Amniotic fluid

sampling is regarded as the gold standard to differentiate true fetal mosaicism (TFM) from CPM, two conditions with a completely different prognosis [40,50–52]. Grati et al. reviewed 67,030 consecutive cytogenetic placental diagnoses, among which 1457 mosaic CVs were detected (2.17%). In 1100 of them amniocentesis was performed and TFM was identified in 13.5% of the cases (n = 148) [40]. In contrast to amniotic fluid, chorionic villi sampling is not relevant to CPM detection. Identifying mosaicism using this method is associated with FGR, pregnancy loss or IUFD only in some cases [37,41,53–55]. Clinical outcomes of CPM cover a wide range of results—from normal pregnancy to IUFD. The exact mechanism by which chromosomally abnormal cells in the placenta alter its function is unknown, but the effect seems to be related to specific chromosomes—especially chromosomes 2, 7–10, 13–18, 21, 22 containing genes important for fetal growth and placental function. These chromosomes have been demonstrated to be associated with adverse perinatal outcomes [39].

Alteration in gene expression in the placenta can cause abnormal fetal growth and development. More than 50 genes have been discovered to be necessary for fetal growth. One of the most important families of genes, essential for the proper functioning of the placenta, are Homeobox genes. These genes—*DLX3*, *DLX4*, *MSX2* and *GAX*, *ESX1L*, *TGIF-1* and *HLX1*—are expressed in the human placenta and play an important role in embryonic development. The downregulated expression of Homeobox genes *HLX1* and *ESX1L* (leading to proliferation, migration and invasion inhibition) and upregulated expression of homeobox genes *DLX3*, *DLX4* and *TGIF-1* (related to enhanced differentiation and apoptosis) has been found in idiopathic FGR cases [56–58]. *DLX3*, a transcription factor, interacts with the DNA-binding domain and the first transactivation domain of transcription factors glial cells missing 1 (GCM1), and this interaction inhibits GCM1-mediated placental growth factor expression [59]. Chelbi et al. measured SERPINA3 messenger RNA (mRNA) quantity in the placentas from normal and FGR pregnancies and showed that these levels were seven-fold higher in isolated FGR than in uncomplicated pregnancies [60]. Gascoin-Lachambre et al. divided the examined placentas in four groups: isolated preeclampsia (PE), PE associated with FGR, idiopathic FGR and vascular FGR. They demonstrated that the expression of *CUL1*, *CUL4A*, *CUL4B* and *CUL7* was significantly increased in pathological placentas in comparison to healthy controls, and its expression was position-dependent and necessary for early embryonic development. *CUL4B* and *CUL7* were particularly involved in placental-derived pathologies, including FGR [61]. Insulin-like growth factor 1 (IGF-1), IGF-2 and IGF-binding protein 3 (IGFBP-3) are also known to play an important role in intrauterine fetal growth. [62,63]. Börzsönyi B et al. performed a study aiming to evaluate gene expression patterns of IGF-1, IGF-2 and IGFBP-3 in human FGR placentas. They demonstrated significantly higher umbilical cord glucose and insulin levels in uncomplicated pregnancies when compared to FGR cases. There was an overexpression of IGF-2 and IGFBP-3 genes in FGR placentas (IGF-2: 1.67-fold expression, $p = 0.04$, IGFBP-3: 1.55-fold expression, $p = 0.03$). This overexpression of IGF-2 in the FGR placentas reflects its physiological role in optimizing energy distribution in a low-energy environment [64]. Additionally, Lee et al. presented significantly lower concentrations of glucose, insulin, IGF-1 and IGF-2 in the umbilical cord blood in FGR pregnancies. They also confirmed overexpression of IGF-2 and decreased IGF-1 expression in FGR placentas ($p < 0.05$) [65]. Giabacani et al. reported some new variants of IGF1R (coding type 1 insulin-like growth factor receptor) related i.a. to small for gestational age neonates [66].

There is also some evidence for the important role of placental mitochondrial DNA (mtDNA) alterations in the development of FGR. Using the whole mitochondrial genome sequencing, Naha et al. identified novel variants in both coding and non-coding regions of mtDNA in FGR placentas, performed Western blot analysis to determine the expression of mitochondrial Sirt3—a member of Sirtuin family proteins, responsible for maintaining mitochondrial homeostasis–and detected a significant increase in Sirt3 expression in FGR placentas. Additionally, a positive correlation between Sirt3 expression and birth weight in FGR cases has been demonstrated [67].

4. Maternal FGR Causes

Maternal variants, causing abnormal gene function, can also play a significant role in fetal FGR. An example can be endothelin 1 (ET-1)—the most potent vasoconstrictor. The pathogenesis of causing placental vasoconstriction is not known but enhanced contractile response of placental vessels to ET-1 has been proposed as a mechanism of FGR [68–70]. Arslan et al. in their trial enrolled 25 women with FGR pregnancy and 19 controls. The results of the study showed that the mean maternal ET-1 (FGR pregnancy 13.4 ± 6.2 vs. control 9.9 ± 2.9 pmol/L) and mean fetal ET-1 (FGR pregnancy 14.5 ± 4.2–11.7 ± 3.1 pmol/L) concentrations were significantly higher in FGR patients [71]. Quintero-Renderos et al. demonstrated Forkhead Box D1 (*FOXD1*) mutations' central role in recurrent pregnancy loss (RPL), recurrent implantation failure (RIF), FGR and PE pathogenesis via complement C3 and placental growth factor (PlGF) regulation and described a functional link between *FOXD1* and implantation and placental diseases [72]. Another study suggested that the maternal -308G > A tumor necrosis factor α (TNF-α) gene variant may play a role in the development of FGR. It is known that in the placenta, TNF-α participates in the inflammatory response, induction of apoptosis, and cell proliferation, differentiation and migration [73]. Golovchenko et al. also identified haplotype TG (polymorphisms rs2234693-rs9340799) of the estrogen receptor α (ESR1) gene as a risk factor for developing FGR [74]. ESR1 is a ligand-activated transcription factor indispensable for appropriate hormone binding. During pregnancy, estrogen stimulates i.a. the activation of IGF-1 receptor, promoting fetal growth and response to different signals, such as hypoxia, hormones and nutrients [63,75]. Although in the last few years a lot of studies have been published concerning the potential association of methylenetetrahydrofolate reductase (MTHFR) 677C > T polymorphism with the risk of FGR and placental abruption, they didn't bring enough evidence to support introducing MTHFR genetic testing into routine clinical practice [76–78]. The meta-analysis of case-control studies published in 2020 provided, however, moderate to strong evidence for the association between MTHFR 677C > T polymorphism and increased risk of developing FGR and placental abruption, especially in Caucasians and Africans [79].

The most common genetic causes of FGR are summarized in Table 1.

Table 1. Most common causes of FGR.

Origin	Type of Genetic Abnormality	Examples	Referenes
Fetal	Chromosomal aberrations	Trisomy 13, 17 and 18	[11–13]
		Cri-du-chat syndrome (5p15.2 or 5p15.3 deletion)	[14–16]
		Williams–Beuren syndrome (7q11.23 deletion)	[17]
	Monogenic syndromes	Cornelia de Lange syndrome (*NIPBL* mutation)	[10,25–27]
		Smith–Lemli–Opitz syndrome (*DHCR7* mutation)	
		Meier–Gorlin syndrome (*ORC1*, *ORC4*, *ORC6*, *CDT1* or *CDC6* mutation)	
		3 M syndrome (*CUL7* mutation)	
		Noonan syndrome (*PTP11* mutation)	
		Achondroplasia or Hypochondroplasia syndrome (*FGFR3* mutation)	[10,28,29]
	Abnormal methylation	Silver–Russel syndrome (11p15.5 epigenetic changes)	[34,35]

Table 1. *Cont.*

Origin	Type of Genetic Abnormality	Examples	Referenes
Placental	Confined placental mosaicism	Most common chromosomes: 2, 6, 7–10, 13–18, 21, 22	[36–55]
	Alterations in gene expression	Upregulation	
		DLX3 and 4	[56–58]
		TGIF-1	
		HLX1	
		CUL1	[61]
		CUL4B, 4a	
		CUL7	
		IGF-2 and IGFBP-3	[62–65]
		Downregulation	
		ESX1L	[56–58]
		HLX1	
		IGF-1	[65]
	Single nucleotide variants	*IGF1R*	[66]
	Mitochondrial increased expression	Sirtuin-3	[67]
Maternal	Gene mutations causing its abnormal function	ET-1	[68–71]
		FOXD1	[72]
		TNFα	[73]
	Single nucleotide polymorphisms	rs2234693-rs9340799 ESR1 variants	[74,75]
		MTHFR 677C > T variant	[76–79]
	Genetic causes of preeclampsia		

IGF-1—insulin growth factor 1; IGF-2—insulin growth factor 2; IGFBP-3—IGF-binding protein 3; IGF1R—insulin-like growth factor receptor type 1; ET-1—endothelin 1; TNFα—tumor necrosis factor α; ESR1—estrogen receptor α; MTHFR—methylenetetrahydrofolate reductase.

5. Fetal Growth Restriction and Preeclampsia as a Maternal Factor

PE is defined according to The International Society for the Study of Hypertension in Pregnancy (ISSHP) as the presence of a new-onset hypertension after 20 weeks of gestation accompanied by proteinuria or evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, or FGR [80]. In particular, early-onset preeclampsia is very often accompanied by FGR. In a study performed by Hung et al., FGR was diagnosed in 50.6% of women with early-onset PE and in 25.5% patients with late-onset disease [81]. Such a high incidence of FGR during PE is related to the very similar pathomechanism of these two pregnancy complications, based on the inadequate trophoblast invasion into maternal spiral arteries and maternal endothelial dysfunction [82,83]. However, it is still under consideration why among women with the same risk factors, some of them develop only FGR and some of them develop PE with or without FGR.

The role of genetic factors in PE is undeniable because of the family history of the disease. Despite this, large genome-wide association studies (GWAS) performed in recent years have not brought expected results [84]. In the largest GWAS study in PE consisting of the offspring of 4380 PE patients and 310,238 controls, the only SNP in the fetal genome associated with the PE risk was the SNP in *FLT1* gene, coding soluble fms-like tyrosine kinase 1 (sFlt-1)—a crucial antiangiogenic factor involved in PE pathophysiology [85]. The largest PE GWAS study in the maternal genome was the HAPO study (hyperglycaemia and adverse pregnancy outcome), but in its results no individual SNPs were significantly associated with PE, despite over one million SNPs being assayed [86]. However, there are some case-control observational studies indicating the possible relationship of different polymorphisms with PE and FGR. The relationship of Storkhead Box 1 (*STOX1*) gene

(involved in the differentiation of proliferative trophoblast into invasive type) with the family history of PE was confirmed in the Danish population [87]. In a meta-analysis performed in 2018, the only detected correlation with PE risk was 4G/5G polymorphism of plasminogen activator inhibitor 1 (PAI-1) [88,89]. Gannoun et al. investigated genetic polymorphisms in the promoter region of matrix metalloproteinases 9 and 2 (MMP-9 and -2) in a Tunisian Arab population and revealed that the MMP-9 rs3918242 (-562 C > T) variant is related to increased MMP-9 production and is a risk factor for PE [90]. In a recently published meta-analysis, Liu et al. identified transforming growth factor-beta 1(TGF-β1) rs800469 variant as a possible risk factor for PE in Asian population [91]. TGF-β1 is a cytokine produced during pregnancy by trophoblast cells, involved in the regulation of trophoblast proliferation, differentiation and invasion. Plasma TGF-β1 levels, as well as its expression in the placenta, are significantly higher in PE patients than in healthy controls [92]. In another meta-analysis, concerning genetic variations in other cytokines: intrelukin-1 and -6 (IL-1 and IL-6), it was demonstrated that two IL-β1 polymorphisms (rs1143634 and rs16944) are related to the risk of developing PE during pregnancy [93]. Additionally, Mazlum et al. showed that the IL-32 rs4786370 variant was related to elevated serum levels of IL-32 in women with PE and thus can be regarded as a risk factor for PE [94]. PE is often associated with proteinuria and renal injury, most of all affecting the number and function of podocytes, the cell population crucial in appropriate glomerular filtration [95]. Khaliq et al. investigated polymorphisms in two genes important for renal function: actin binding protein 4 (ACTN4) and nephrin (NPHS1). It is known that individuals with a mutation in the ACTN4 gene have clinical signs of nephrotic syndrome. Similarly, patients with NPHS1 mutation suffer from renal injury. This study revealed that the C allele of rs437168 NPHS1 is significantly associated with early-onset PE, whereas there was no association of ACTN4 polymorphisms with the risk of PE [96]. Ma et al. indicated the TC 96121524 variant of endoplasmic reticulum aminopeptodase-1 (ERAP-1) gene as potential risk factor for developing PE, where endoplasmic reticulum stress is one of the well-documented processes underlying PE pathophysiology [97,98]. The other very important factor in the pathophysiology of PE is the role of nitric oxide (NO)—the major vasodilator involved in the regulation of arterial blood pressure. Studies on animal models have shown the crucial role of the NO/NO synthase (NOS) system for normal spiral artery remodeling [99,100]. During uncomplicated pregnancy, vascular endothelial growth factor (VEGF) increases the expression of endothelial NOS (eNOS) and activates it. In PE and FGR pregnancies, excessive production of sFlt-1 leads to the binding of VEGF and thus to the lack of appropriate eNOS activity [101]. Jakovljevic et al. revealed that -786 T/C and VNTR 4b/a eNOS gene polymorphisms were associated with PE risk [102]. A recently published meta-analysis confirmed that the c.894 T (p.298Asp) and g.-786C alleles of eNOS gene may influence the NO bioavailability and were significantly associated with PE [103].

The impact of different polymorphisms and genotypes on the risk of developing FGR and PE is summarized in Table 2.

Table 2. The impact of different polymorphisms and genotypes on risk of developing FGR and PE.

Gene	Variant/Genotype	Effect Size	References
		FGR	
TNFα	-308GA	OR 1.65 (95% CI 0.93–2.93) $p = 0.06$ OR 2.8 $p = 0.01$ with uterine arteries flow abnormatlities	[72]
ESR1	rs2234693/rs9340799 TG genotype	OR 1.94 $p = 0.001$	[73]
MTHFR	677C > T TT + TC vs. CC overall Caucasian ethnicity African ethnicity	OR 0.14 (95% CI 0.049–0.045) $p < 0.001$ OR 0.15 (95% CI 0.04–0.561) $p = 0.005$ OR 0.162 (95% CI 0.06–0.436) $p < 0.001$	[78]

Table 2. *Cont.*

Gene	Variant/Genotype	Effect Size	References
		PE	
FLT1	rs4769613 C allele (fetal genome)	OR 1.22 (95% CI 1.14–1.31)	[84]
PAI-1	4G/5G	OR 1.36 (95% CI 1.13–1.64)	[88]
MMP-9	rs3918242 (-562C > T)	OR 1.62 (95% CI 1.03–2.56)	[89]
TGFβ1	rs1800469	OR 1.17 (95% CI 1.02–1.35) OR 1.35 (95% CI 1.06–1.72) OR 1.48 (95% CI 1.07–2.05) Allele, recessive and homozygous model respectively	[90]
IL-1β	rs1143634 T allele	OR 1.28 (95% CI 1.04–1.58)	[92]
NPHS1	rs437168 C allele C vs. T CC vs. CT/TT	OR 1.287 (95% CI 1.021–1.622) OR 1.398 (95% CI 1.005–1.945)	[95]
ERAP-1	96121524 TC genotype	OR 2.002 (95% CI 0.687–5.831) $p = 0.02$	[96]
eNOS	-86T/C (CC variant)	$p = 0.006$ PE $p = 0.01$ 9 early onset PE $p = 0.012$ late onset PE	[101]
	VNTR 4a4a homozygote	OR 7.68 (95% CI 0.89–65.98) $p = 0.04$	[101]
IL-32	rs4786370 T allele CT/GT TT/TT TT/GT	OR 2.75 (95% CI 1.34–5.642) OR 3.266 (95% CI 1.279–8.339) OR 3.438 (95% CI 1.354–8.73)	[93]

TNFα—tumor necrosis factor α; ESR1—estrogen receptor α; MTHFR—methylenotetrahydrofolate reductase; PAI-1—plasminogen activator inhibitor 1; MMP-9—matrix metalloproteinase 9; TGFβ1—transforming growth factor β1; NPHS1—nephrin; ERAP-1—endoplasmic reticulum aminopeptidase-1; eNOS—endothelial nitric oxide synthase; IL-32—interleukin 32.

6. Summary

The results showed that an invasive prenatal procedure is strongly recommended when FGR is diagnosed. CMA detects all the chromosomal aberration detected by karyotyping and has a 5.5% additional detection rate of a genetic cause of FGR, which could impact the clinical decision. CMA as the first-line test is thus effective and feasible as a joined prenatal testing for suspected FGR cases. Additionally, a recent advantage in molecular methods enables investigation of single nucleoid variants in many genes simultaneously. Few gene panels have been designed for FGR investigation, which include from 25 up to 44 genes involved in fetal growth restriction. Additionally, the introduction of exome sequencing gives the possibility of investigating all coding regions in one test; however, the diagnostic rate in FGR cases remains unknown. Recently, a promising method was successfully developed for assessing the risk of FGR at an early gestational age based on the maternal plasma cfDNA nucleosome profiling. Through the whole-genome sequencing data analysis of FGR cases and controls, genes with significantly differential DNA coverage at promoter regions were identified and the non-invasive 'FGR classifier 1', based on 14 genes with differential promoter coverage, was developed [104].

Genetic testing in FGR cases is particularly valuable not only in cases with concomitant structural malformations, but also in isolated FGR. The detection of genetic abnormalities in such cases significantly affects the prognosis and management strategy, as well as the postnatal care of the growth-restricted newborn.

References

1. Hammami, A.; Mazer Zumaeta, A.; Syngelaki, A.; Akolekar, R.; Nicolaides, K.H. Ultrasonographic Estimation of Fetal Weight: Development of New Model and Assessment of Performance of Previous Models. *Ultrasound Obstet. Gynecol.* **2018**, *52*, 35–43. [CrossRef]
2. Lees, C.C.; Stampalija, T.; Baschat, A.; da Silva Costa, F.; Ferrazzi, E.; Figueras, F.; Hecher, K.; Poon, L.C.; Salomon, L.J.; Unterscheider, J. ISUOG Practice Guidelines: Diagnosis and Management of Small-for-Gestational-Age Fetus and Fetal Growth Restriction. *Ultrasound Obstet. Gynecol.* **2020**, *56*, 298–312. [CrossRef] [PubMed]
3. Gordijn, S.J.; Beune, I.M.; Thilaganathan, B.; Papageorghiou, A.; Baschat, A.A.; Baker, P.N.; Silver, R.M.; Wynia, K.; Ganzevoort, W. Consensus Definition of Fetal Growth Restriction: A Delphi Procedure. *Ultrasound Obstet. Gynecol.* **2016**, *48*, 333–339. [CrossRef] [PubMed]
4. Nowacka, U.; Papastefanou, I.; Bouariu, A.; Syngelaki, A.; Akolekar, R.; Nicolaides, K.H. Second Trimester Contingent Screening for Small for Gestational Age Neonates. *Ultrasound Obstet. Gynecol.* **2021**. [CrossRef]
5. Nowacka, U.; Kosińska-Kaczyńska, K.; Krajewski, P.; Saletra-Bielińska, A.; Walasik, I.; Szymusik, I. Predictive Accuracy of Singleton Versus Customized Twin Growth Chart for Adverse Perinatal Outcome: A Cohort Study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 2016. [CrossRef] [PubMed]
6. Nohuz, E.; Rivière, O.; Coste, K.; Vendittelli, F. Prenatal Identification of Small-for-Gestational Age and Risk of Neonatal Morbidity and Stillbirth. *Ultrasound Obstet. Gynecol.* **2020**, *55*, 621–628. [CrossRef]
7. Barker, D.J.P.; Osmond, C.; Forsén, T.J.; Kajantie, E.; Eriksson, J.G. Trajectories of Growth among Children Who Have Coronary Events as Adults. *N. Engl. J. Med.* **2005**, *353*, 1802–1809. [CrossRef]
8. Meler, E.; Sisterna, S.; Borrell, A. Genetic Syndromes Associated with Isolated Fetal Growth Restriction. *Prenat. Diagn.* **2020**, *40*, 432–446. [CrossRef]
9. Nardozza, L.M.M.; Caetano, A.C.R.; Zamarian, A.C.P.; Mazzola, J.B.; Silva, C.P.; Marçal, V.M.G.; Lobo, T.F.; Peixoto, A.B.; Araujo Júnior, E. Fetal Growth Restriction: Current Knowledge. *Arch. Gynecol. Obstet.* **2017**, *295*, 1061–1077. [CrossRef]
10. Merriel, A.; Alberry, M.; Abdel-Fattah, S. Implications of Non-Invasive Prenatal Testing for Identifying and Managing High-Risk Pregnancies. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2021**, *256*, 32–39. [CrossRef] [PubMed]
11. Snijders, R.J.; Sherrod, C.; Gosden, C.M.; Nicolaides, K.H. Fetal Growth Retardation: Associated Malformations and Chromosomal Abnormalities. *Am. J. Obstet. Gynecol.* **1993**, *168*, 547–555. [CrossRef]
12. Anandakumar, C.; Chew, S.; Wong, Y.C.; Malarvishy, G.; Po, L.U.; Ratnam, S.S. Early Asymmetric IUGR and Aneuploidy. *J. Obstet. Gynaecol. Res.* **1996**, *22*, 365–370. [CrossRef]
13. Li, L.; Zhang, X.; Shi, Q.; Li, L.; Jiang, Y.; Liu, R.; Zhang, H. Ultrasonographic Findings and Prenatal Diagnosis of Complete Trisomy 17p Syndrome: A Case Report and Review of the Literature. *J. Clin. Lab. Anal.* **2021**, *35*, e23582. [CrossRef]
14. Peng, Y.; Pang, J.; Hu, J.; Jia, Z.; Xi, H.; Ma, N.; Yang, S.; Liu, J.; Huang, X.; Tang, C.; et al. Clinical and Molecular Characterization of 12 Prenatal Cases of Cri-Du-Chat Syndrome. *Mol. Genet. Genom. Med.* **2020**, *8*, e1312. [CrossRef] [PubMed]
15. Honjo, R.S.; Mello, C.B.; Pimenta, L.S.E.; Nuñes-Vaca, E.C.; Benedetto, L.M.; Khoury, R.B.F.; Befi-Lopes, D.M.; Kim, C.A. Cri Du Chat Syndrome: Characteristics of 73 Brazilian Patients. *J. Intellect. Disabil. Res.* **2018**, *62*, 467–473. [CrossRef] [PubMed]
16. Espirito Santo, L.D.; Moreira, L.M.A.; Riegel, M. Cri-Du-Chat Syndrome: Clinical Profile and Chromosomal Microarray Analysis in Six Patients. *BioMed Res. Int.* **2016**, *2016*, 5467083. [CrossRef]
17. Yuan, M.; Deng, L.; Yang, Y.; Sun, L. Intrauterine Phenotype Features of Fetuses with Williams-Beuren Syndrome and Literature Review. *Ann. Hum. Genet.* **2020**, *84*, 169–176. [CrossRef] [PubMed]
18. Tzadikevitch Geffen, K.; Singer, A.; Maya, I.; Ben-Shachar, S.; Sagi-Dain, L.; Daum, H.; Michaelson-Cohen, R.; Greenbaum, L.; Feingold-Zadok, M.; Sukenik Halevy, R. The Yield of Chromosomal Microarray in Pregnancies Complicated with Fetal Growth Restriction Can Be Predicted According to Clinical Parameters. *Fetal Diagn. Ther.* **2021**, *48*, 140–148. [CrossRef] [PubMed]
19. An, G.; Lin, Y.; Xu, L.P.; Huang, H.L.; Liu, S.P.; Yu, Y.H.; Yang, F. Application of Chromosomal Microarray to Investigate Genetic Causes of Isolated Fetal Growth Restriction. *Mol. Cytogenet.* **2018**, *11*, 33. [CrossRef]

20. de Wit, M.C.; Srebniak, M.I.; Joosten, M.; Govaerts, L.C.P.; Kornelisse, R.F.; Papatsonis, D.N.M.; de Graaff, K.; Knapen, M.F.C.M.; Bruggenwirth, H.T.; de Vries, F.a.T.; et al. Prenatal and Postnatal Findings in Small-for-Gestational-Age Fetuses without Structural Ultrasound Anomalies at 18-24 Weeks. *Ultrasound Obstet. Gynecol.* **2017**, *49*, 342–348. [CrossRef]

21. Sagi-Dain, L.; Peleg, A.; Sagi, S. Risk for Chromosomal Aberrations in Apparently Isolated Intrauterine Growth Restriction: A Systematic Review. *Prenat. Diagn.* **2017**, *37*, 1061–1066. [CrossRef] [PubMed]

22. Chen, C.-P.; Chen, M.; Wang, L.-K.; Chern, S.-R.; Wu, P.-S.; Ma, G.-C.; Chang, S.-P.; Chen, S.-W.; Wu, F.-T.; Lee, C.-C.; et al. Low-Level Mosaicism for Trisomy 16 at Amniocentesis in a Pregnancy Associated with Intrauterine Growth Restriction and a Favorable Outcome. *Taiwan J. Obstet. Gynecol.* **2021**, *60*, 345–349. [CrossRef] [PubMed]

23. Gupta, S.; Naert, M.; Lam-Rachlin, J.; Monteagudo, A.; Rebarber, A.; Saltzman, D.; Fox, N.S. Outcomes in Patients with Early-Onset Fetal Growth Restriction without Fetal or Genetic Anomalies. *J. Matern. Fetal Neonatal Med.* **2019**, *32*, 2662–2666. [CrossRef] [PubMed]

24. Hall, J.G. Review and Hypothesis: Syndromes with Severe Intrauterine Growth Restriction and Very Short Stature—Are They Related to the Epigenetic Mechanism(s) of Fetal Survival Involved in the Developmental Origins of Adult Health and Disease? *Am. J. Med. Genet. Part A* **2010**, *152*, 512–527. [CrossRef] [PubMed]

25. Shaikh, S.; Shettigar, S.K.G.; Kumar, S.; Kantharia, S.; Kurva, J.; Cherian, S. Novel Mutation in Cul7 Gene in a Family Diagnosed with 3M Syndrome. *J. Genet.* **2019**, *98*, 21. [CrossRef] [PubMed]

26. de Munnik, S.A.; Hoefsloot, E.H.; Roukema, J.; Schoots, J.; Knoers, N.V.A.M.; Brunner, H.G.; Jackson, A.P.; Bongers, E.M.H.F. Meier-Gorlin Syndrome. *Orphanet J. Rare Dis.* **2015**, *10*, 114. [CrossRef] [PubMed]

27. Boyle, M.I.; Jespersgaard, C.; Brøndum-Nielsen, K.; Bisgaard, A.-M.; Tümer, Z. Cornelia de Lange Syndrome. *Clin. Genet.* **2015**, *88*, 1–12. [CrossRef]

28. Ornitz, D.M.; Legeai-Mallet, L. Achondroplasia: Development, Pathogenesis, and Therapy. *Dev. Dyn.* **2017**, *246*, 291–309. [CrossRef]

29. Roberts, A.E.; Allanson, J.E.; Tartaglia, M.; Gelb, B.D. Noonan Syndrome. *Lancet* **2013**, *381*, 333–342. [CrossRef]

30. Simeoni, U.; Armengaud, J.-B.; Siddeek, B.; Tolsa, J.-F. Perinatal Origins of Adult Disease. *Neonatology* **2018**, *113*, 393–399. [CrossRef]

31. Barbieri, M.R.; Fontes, A.M.; Barbieri, M.A.; Saraiva, M.C.P.; Simões, V.M.F.; da Silva, A.A.M.; Abraham, K.J.; Bettiol, H. Effects of FTO and PPARγ Variants on Intrauterine Growth Restriction in a Brazilian Birth Cohort. *Braz. J. Med. Biol. Res.* **2021**, *54*, e10465. [CrossRef]

32. Karimi-Zarchi, M.; Zanbagh, L.; Javaheri, A.; Tabatabaei, R.S.; Abbasi, H.; Meibodi, B.; Hadadan, A.; Bahrami, R.; Mirjalili, S.R.; Neamatzadeh, H. Association of Insulin-like Growth Factor-II Apa1 and MspI Polymorphisms with Intrauterine Growth Restriction Risk. *Fetal Pediatr. Pathol.* **2020**, *40*, 605–611. [CrossRef]

33. Krishna, R.G.; Vishnu Bhat, B.; Bobby, Z.; Papa, D.; Badhe, B.; Kalidoss, V.K.; Karli, S. Identification of Differentially Methylated Candidate Genes and Their Biological Significance in IUGR Neonates by Methylation EPIC Array. *J. Matern.-Fetal Neonatal Med.* **2020**, *24*, 1–9. [CrossRef]

34. Cammarata-Scalisi, F.; Callea, M.; Stock, F.; Zambito, V.; Sparago, Á.; Riccio, A. Silver-Russell Syndrome. Clinical and Etiopathological Aspects of a Model Genomic Imprinting Entity. *Arch. Argent. Pediatr.* **2020**, *118*, e258–e264. [CrossRef] [PubMed]

35. Spiteri, B.S.; Stafrace, Y.; Calleja-Agius, J. Silver-Russell Syndrome: A Review. *Neonatal Netw.* **2017**, *36*, 206–212. [CrossRef]

36. Gardner, R.; McKinlay, J.; Amor, D.J. *Chromosome Abnormalities and Genetic Counseling*, 5th ed.; Gardner and Sutherland's: London, UK, 2018.

37. Kalousek, D.K.; Dill, F.J.; Pantzar, T.; McGillivray, B.C.; Yong, S.L.; Wilson, R.D. Confined Chorionic Mosaicism in Prenatal Diagnosis. *Hum. Genet.* **1987**, *77*, 163–167. [CrossRef] [PubMed]

38. Toutain, J.; Goutte-Gattat, D.; Horovitz, J.; Saura, R. Confined Placental Mosaicism Revisited: Impact on Pregnancy Characteristics and Outcome. *PLoS ONE* **2018**, *13*, e0195905. [CrossRef] [PubMed]

39. Miura, K.; Yoshiura, K.-I.; Miura, S.; Kondoh, T.; Harada, N.; Yamasaki, K.; Fujimoto, Y.; Yamasaki, Y.; Tanigawa, T.; Kitajima, Y.; et al. Clinical Outcome of Infants with Confined Placental Mosaicism and Intrauterine Growth Restriction of Unknown Cause. *Am. J. Med. Genet. Part A* **2006**, *140*, 1827–1833. [CrossRef] [PubMed]

40. Grati, F.R.; Malvestiti, F.; Branca, L.; Agrati, C.; Maggi, F.; Simoni, G. Chromosomal Mosaicism in the Fetoplacental Unit. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2017**, *42*, 39–52. [CrossRef]

41. Johnson, A.; Wapner, R.J.; Davis, G.H.; Jackson, L.G. Mosaicism in Chorionic Villus Sampling: An Association with Poor Perinatal Outcome. *Obstet. Gynecol.* **1990**, *75*, 573–577.

42. Lazier, J.; Martin, N.; Stavropoulos, J.D.; Chitayat, D. Maternal Uniparental Disomy for Chromosome 6 in a Patient with IUGR, Ambiguous Genitalia, and Persistent Mullerian Structures. *Am. J. Med. Genet. Part A* **2016**, *170*, 3227–3230. [CrossRef] [PubMed]

43. Grau Madsen, S.; Uldbjerg, N.; Sunde, L.; Becher, N. Danish Fetal Medicine Study Group; Danish Clinical Genetics Study Group Prognosis for Pregnancies with Trisomy 16 Confined to the Placenta: A Danish Cohort Study. *Prenat. Diagn.* **2018**, *38*, 1103–1110. [CrossRef]

44. Neiswanger, K.; Hohler, P.M.; Hively-Thomas, L.B.; McPherson, E.W.; Hogge, W.A.; Surti, U. Variable Outcomes in Mosaic Trisomy 16: Five Case Reports and Literature Analysis. *Prenat. Diagn.* **2006**, *26*, 454–461. [CrossRef]

45. Post, J.G.; Nijhuis, J.G. Trisomy 16 Confined to the Placenta. *Prenat. Diagn.* **1992**, *12*, 1001–1007. [CrossRef]

46. Del Gobbo, G.F.; Yuan, V.; Robinson, W.P. Confined Placental Mosaicism Involving Multiple de Novo Copy Number Variants Associated with Fetal Growth Restriction: A Case Report. *Am. J. Med. Genet. Part A* **2021**, *185*, 1908–1912. [CrossRef] [PubMed]

47. Van Opstal, D.; van Maarle, M.C.; Lichtenbelt, K.; Weiss, M.M.; Schuring-Blom, H.; Bhola, S.L.; Hoffer, M.J.V.; Huijsdens-van Amsterdam, K.; Macville, M.V.; Kooper, A.J.A.; et al. Origin and Clinical Relevance of Chromosomal Aberrations Other than the Common Trisomies Detected by Genome-Wide NIPS: Results of the TRIDENT Study. *Genet. Med.* **2018**, *20*, 480–485. [CrossRef]

48. Grati, F.R.; Ferreira, J.; Benn, P.; Izzi, C.; Verdi, F.; Vercellotti, E.; Dalpiaz, C.; D'Ajello, P.; Filippi, E.; Volpe, N.; et al. Outcomes in Pregnancies with a Confined Placental Mosaicism and Implications for Prenatal Screening Using Cell-Free DNA. *Genet. Med.* **2020**, *22*, 309–316. [CrossRef] [PubMed]

49. Shaw, J.; Scotchman, E.; Chandler, N.; Chitty, L.S. PREIMPLANTATION GENETIC TESTING: Non-Invasive Prenatal Testing for Aneuploidy, Copy-Number Variants and Single-Gene Disorders. *Reproduction* **2020**, *160*, A1–A11. [CrossRef] [PubMed]

50. Cremer, M.; Treiss, I.; Cremer, T.; Hager, D.; Franke, W.W. Characterization of Cells of Amniotic Fluids by Immunological Identification of Intermediate-Sized Filaments: Presence of Cells of Different Tissue Origin. *Hum. Genet.* **1981**, *59*, 373–379. [CrossRef] [PubMed]

51. Grati, F.R.; Bajaj, K.; Zanatta, V.; Malvestiti, F.; Malvestiti, B.; Marcato, L.; Grimi, B.; Maggi, F.; Simoni, G.; Gross, S.J.; et al. Implications of Fetoplacental Mosaicism on Cell-Free DNA Testing for Sex Chromosome Aneuploidies. *Prenat. Diagn.* **2017**, *37*, 1017–1027. [CrossRef]

52. Hayata, K.; Hiramatsu, Y.; Masuyama, H.; Eto, E.; Mitsui, T.; Tamada, S. Discrepancy between Non-Invasive Prenatal Genetic Testing (NIPT) and Amniotic Chromosomal Test Due to Placental Mosaicism: A Case Report and Literature Review. *Acta Med. Okayama* **2017**, *71*, 181–185. [CrossRef] [PubMed]

53. Wapner, R.J.; Simpson, J.L.; Golbus, M.S.; Zachary, J.M.; Ledbetter, D.H.; Desnick, R.J.; Fowler, S.E.; Jackson, L.G.; Lubs, H.; Mahony, R.J. Chorionic Mosaicism: Association with Fetal Loss but Not with Adverse Perinatal Outcome. *Prenat. Diagn.* **1992**, *12*, 347–355. [CrossRef] [PubMed]

54. Wolstenholme, J. Confined Placental Mosaicism for Trisomies 2, 3, 7, 8, 9, 16, and 22: Their Incidence, Likely Origins, and Mechanisms for Cell Lineage Compartmentalization. *Prenat. Diagn.* **1996**, *16*, 511–524. [CrossRef]

55. Wilkins-Haug, L.; Quade, B.; Morton, C.C. Confined Placental Mosaicism as a Risk Factor among Newborns with Fetal Growth Restriction. *Prenat. Diagn.* **2006**, *26*, 428–432. [CrossRef] [PubMed]

56. Sharma, D.; Sharma, P.; Shastri, S. Genetic, Metabolic and Endocrine Aspect of Intrauterine Growth Restriction: An Update. *J. Matern. Fetal Neonatal Med.* **2017**, *30*, 2263–2275. [CrossRef] [PubMed]

57. Majewska, M.; Lipka, A.; Paukszto, L.; Jastrzebski, J.P.; Szeszko, K.; Gowkielewicz, M.; Lepiarczyk, E.; Jozwik, M.; Majewski, M.K. Placenta Transcriptome Profiling in Intrauterine Growth Restriction (IUGR). *Int. J. Mol. Sci.* **2019**, *20*, 1510. [CrossRef]

58. Murthi, P. Review: Placental Homeobox Genes and Their Role in Regulating Human Fetal Growth. *Placenta* **2014**, *35*, S46–S50. [CrossRef]

59. Chiu, Y.-H.; Yang, M.-R.; Wang, L.-J.; Chen, M.-H.; Chang, G.-D.; Chen, H. New Insights into the Regulation of Placental Growth Factor Gene Expression by the Transcription Factors GCM1 and DLX3 in Human Placenta. *J. Biol. Chem.* **2018**, *293*, 9801–9811. [CrossRef] [PubMed]

60. Chelbi, S.T.; Wilson, M.L.; Veillard, A.-C.; Ingles, S.A.; Zhang, J.; Mondon, F.; Gascoin-Lachambre, G.; Doridot, L.; Mignot, T.-M.; Rebourcet, R.; et al. Genetic and Epigenetic Mechanisms Collaborate to Control SERPINA3 Expression and Its Association with Placental Diseases. *Hum. Mol. Genet.* **2012**, *21*, 1968–1978. [CrossRef]

61. Gascoin-Lachambre, G.; Buffat, C.; Rebourcet, R.; Chelbi, S.T.; Rigourd, V.; Mondon, F.; Mignot, T.-M.; Legras, E.; Simeoni, U.; Vaiman, D.; et al. Cullins in Human Intra-Uterine Growth Restriction: Expressional and Epigenetic Alterations. *Placenta* **2010**, *31*, 151–157. [CrossRef]

62. Mamsen, L.S.; Zafeiri, A.; Bøtkjær, J.A.; Hardlei, J.R.; Ernst, E.; Oxvig, C.; Fowler, P.A.; Andersen, C.Y. Expression of the Insulin-like Growth Factor System in First- and Second-Trimester Human Embryonic and Fetal Gonads. *J. Clin. Endocrinol. Metab.* **2020**, *105*, dgaa470. [CrossRef]

63. Hellström, A.; Ley, D.; Hansen-Pupp, I.; Hallberg, B.; Löfqvist, C.; van Marter, L.; van Weissenbruch, M.; Ramenghi, L.A.; Beardsall, K.; Dunger, D.; et al. Insulin-like Growth Factor 1 Has Multisystem Effects on Foetal and Preterm Infant Development. *Acta Paediatr.* **2016**, *105*, 576–586. [CrossRef] [PubMed]

64. Börzsönyi, B.; Demendi, C.; Nagy, Z.; Tóth, K.; Csanád, M.; Pajor, A.; Rig, J.; Joó, J.G. Gene Expression Patterns of Insulin-like Growth Factor 1, Insulin-like Growth Factor 2 and Insulin-like Growth Factor Binding Protein 3 in Human Placenta from Pregnancies with Intrauterine Growth Restriction. *J. Perinat. Med.* **2011**, *39*, 701–707. [CrossRef] [PubMed]

65. Lee, M.H.; Jeon, Y.J.; Lee, S.M.; Park, M.H.; Jung, S.-C.; Kim, Y.J. Placental Gene Expression Is Related to Glucose Metabolism and Fetal Cord Blood Levels of Insulin and Insulin-like Growth Factors in Intrauterine Growth Restriction. *Early Hum Dev.* **2010**, *86*, 45–50. [CrossRef] [PubMed]

66. Giabicani, E.; Willems, M.; Steunou, V.; Chantot-Bastaraud, S.; Thibaud, N.; Abi Habib, W.; Azzi, S.; Lam, B.; Bérard, L.; Bony-Trifunovic, H.; et al. Increasing Knowledge in IGF1R Defects: Lessons from 35 New Patients. *J. Med. Genet.* **2020**, *57*, 160–168. [CrossRef] [PubMed]

67. Naha, R.; Anees, A.; Chakrabarty, S.; Naik, P.S.; Pandove, M.; Pandey, D.; Satyamoorthy, K. Placental Mitochondrial DNA Mutations and Copy Numbers in Intrauterine Growth Restricted (IUGR) Pregnancy. *Mitochondrion* **2020**, *55*, 85–94. [CrossRef]

68. Margarit, L.; Griffiths, A.N.; Tsapanos, V.; Tsakas, S.; Gumenos, D.; Decavalas, G. Second Trimester Amniotic Fluid Endothelin-1 Concentrations and Subsequent Development of Intrauterine Growth Restriction. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2007**, *134*, 192–195. [CrossRef]

69. Thaete, L.G.; Dewey, E.R.; Neerhof, M.G. Endothelin and the Regulation of Uterine and Placental Perfusion in Hypoxia-Induced Fetal Growth Restriction. *J. Soc. Gynecol. Investig.* **2004**, *11*, 16–21. [CrossRef]

70. Aydin, H.I.; Eser, A.; Kaygusuz, I.; Yildirim, S.; Celik, T.; Gunduz, S.; Kalman, S. Adipokine, Adropin and Endothelin-1 Levels in Intrauterine Growth Restricted Neonates and Their Mothers. *J. Perinat. Med.* **2016**, *44*, 669–676. [CrossRef]

71. Arslan, M.; Yazici, G.; Erdem, A.; Erdem, M.; Arslan, E.O.; Himmetoglu, O. Endothelin 1 and Leptin in the Pathophysiology of Intrauterine Growth Restriction. *Int. J. Gynaecol.* **2004**, *84*, 120–126. [CrossRef]

72. Quintero-Ronderos, P.; Jiménez, K.M.; Esteban-Pérez, C.; Ojeda, D.A.; Bello, S.; Fonseca, D.J.; Coronel, M.A.; Moreno-Ortiz, H.; Sierra-Díaz, D.C.; Lucena, E.; et al. FOXD1 Mutations Are Related to Repeated Implantation Failure, Intra-Uterine Growth Restriction and Preeclampsia. *Mol. Med.* **2019**, *25*, 37. [CrossRef] [PubMed]

73. Kaluba-Skotarczak, A.; Magiełda, J.; Romała, A.; Kurzawińska, G.; Barlik, M.; Drews, K.; Ożarowski, M.; Łoziński, T.; Seremak-Mrozikiewicz, A. Importance of Polymorphic Variants of Tumour Necrosis Factor-α Gene in the Etiology of Intrauterine Growth Restriction. *Ginekol. Pol.* **2018**, *89*, 160–168. [CrossRef] [PubMed]

74. Golovchenko, O.; Abramova, M.; Ponomarenko, I.; Reshetnikov, E.; Aristova, I.; Polonikov, A.; Dvornyk, V.; Churnosov, M. Functionally Significant Polymorphisms of ESR1and PGR and Risk of Intrauterine Growth Restriction in Population of Central Russia. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2020**, *253*, 52–57. [CrossRef] [PubMed]

75. Banjac, L.; Kotur-Stevuljević, J.; Gojković, T.; Bokan-Mirković, V.; Banjac, G.; Banjac, G. Relationship between Insulin-Like Growth Factor Type 1 and Intrauterine Growth. *Acta Clin. Croat.* **2020**, *59*, 91–96. [CrossRef] [PubMed]

76. Chen, J.; Chen, L.; Zhu, L.-H.; Zhang, S.-T.; Wu, Y.-L. Association of Methylenetetrahydrofolate Reductase (MTHFR) C677T Polymorphism with Preterm Delivery and Placental Abruption: A Systematic Review and Meta-Analysis. *Acta Obstet. Gynecol. Scand.* **2016**, *95*, 157–165. [CrossRef] [PubMed]

77. Zhang, Y.; He, X.; Xiong, X.; Chuan, J.; Zhong, L.; Chen, G.; Yu, D. The Association between Maternal Methylenetetrahydrofolate Reductase C677T and A1298C Polymorphism and Birth Defects and Adverse Pregnancy Outcomes. *Prenat. Diagn.* **2019**, *39*, 3–9. [CrossRef] [PubMed]

78. Hogeveen, M.; Blom, H.J.; den Heijer, M. Maternal Homocysteine and Small-for-Gestational-Age Offspring: Systematic Review and Meta-Analysis. *Am. J. Clin. Nutr.* **2012**, *95*, 130–136. [CrossRef]

79. Bahrami, R.; Schwartz, D.A.; Asadian, F.; Karimi-Zarchi, M.; Dastgheib, S.A.; Tabatabaie, R.S.; Meibodi, B.; Neamatzadeh, H. Association of MTHFR 677C>T Polymorphism with IUGR and Placental Abruption Risk: A Systematic Review and Meta-Analysis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2021**, *256*, 130–139. [CrossRef]

80. Brown, M.A.; Magee, L.A.; Kenny, L.C.; Karumanchi, S.A.; McCarthy, F.P.; Saito, S.; Hall, D.R.; Warren, C.E.; Adoyi, G.; Ishaku, S.; et al. The Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis & Management Recommendations for International Practice. *Pregnancy Hypertens.* **2018**, *13*, 291–310. [CrossRef] [PubMed]

81. Hung, T.-H.; Hsieh, T.-T.; Chen, S.-F. Risk of Abnormal Fetal Growth in Women with Early- and Late-Onset Preeclampsia. *Pregnancy Hypertens.* **2018**, *12*, 201–206. [CrossRef] [PubMed]

82. Pankiewicz, K.; Fijałkowska, A.; Issat, T.; Maciejewski, T.M. Insight into the Key Points of Preeclampsia Pathophysiology: Uterine Artery Remodeling and the Role of MicroRNAs. *Int. J. Mol. Sci.* **2021**, *22*, 3132. [CrossRef] [PubMed]

83. Kwiatkowski, S.; Dołegowska, B.; Kwiatkowska, E.; Rzepka, R.; Marczuk, N.; Loj, B.; Torbè, A. Maternal Endothelial Damage as a Disorder Shared by Early Preeclampsia, Late Preeclampsia and Intrauterine Growth Restriction. *J. Perinat. Med.* **2017**, *45*, 793–802. [CrossRef] [PubMed]

84. Benny, P.A.; Alakwaa, F.M.; Schlueter, R.J.; Lassiter, C.B.; Garmire, L.X. A Review of Omics Approaches to Study Preeclampsia. *Placenta* **2020**, *92*, 17–27. [CrossRef]

85. McGinnis, R.; Steinthorsdottir, V.; Williams, N.O.; Thorleifsson, G.; Shooter, S.; Hjartardottir, S.; Bumpstead, S.; Stefansdottir, L.; Hildyard, L.; Sigurdsson, J.K.; et al. Variants in the Fetal Genome near FLT1 Are Associated with Risk of Preeclampsia. *Nat. Genet.* **2017**, *49*, 1255–1260. [CrossRef] [PubMed]

86. Zhao, L.; Bracken, M.B.; DeWan, A.T. Genome-Wide Association Study of Pre-Eclampsia Detects Novel Maternal Single Nucleotide Polymorphisms and Copy-Number Variants in Subsets of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cohort. *Ann. Hum. Genet.* **2013**, *77*, 277–287. [CrossRef]

87. van Dijk, M.; van Bezu, J.; van Abel, D.; Dunk, C.; Blankenstein, M.A.; Oudejans, C.B.M.; Lye, S.J. The STOX1 Genotype Associated with Pre-Eclampsia Leads to a Reduction of Trophoblast Invasion by Alpha-T-Catenin Upregulation. *Hum. Mol. Genet.* **2010**, *19*, 2658–2667. [CrossRef] [PubMed]

88. Giannakou, K.; Evangelou, E.; Papatheodorou, S.I. Genetic and Non-Genetic Risk Factors for Pre-Eclampsia: Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies. *Ultrasound Obstet. Gynecol.* **2018**, *51*, 720–730. [CrossRef]

89. Zhao, L.; Bracken, M.B.; Dewan, A.T.; Chen, S. Association between the SERPINE1 (PAI-1) 4G/5G Insertion/Deletion Promoter Polymorphism (Rs1799889) and Pre-Eclampsia: A Systematic Review and Meta-Analysis. *Mol. Hum. Reprod.* **2013**, *19*, 136–143. [CrossRef]

90. Gannoun, M.B.A.; Raguema, N.; Zitouni, H.; Mehdi, M.; Seda, O.; Mahjoub, T.; Lavoie, J.L. MMP-2 and MMP-9 Polymorphisms and Preeclampsia Risk in Tunisian Arabs: A Case-Control Study. *J. Clin. Med.* **2021**, *10*, 2647. [CrossRef] [PubMed]

91. Liu, J.; Song, G.; Zhao, G.; Meng, T. Gene Polymorphism Associated with TGF-B1 and Susceptibility to Preeclampsia: A Meta-Analysis and Trial Sequential Analysis. *J. Obstet. Gynaecol. Res.* **2021**, *47*, 2031–2041. [CrossRef] [PubMed]

92. Benian, A.; Madazli, R.; Aksu, F.; Uzun, H.; Aydin, S. Plasma and Placental Levels of Interleukin-10, Transforming Growth Factor-Beta1, and Epithelial-Cadherin in Preeclampsia. *Obstet. Gynecol.* **2002**, *100*, 327–331. [CrossRef] [PubMed]

93. Nasri, F.; Zare, M.; Hesampour, F.; Ahmadi, M.; Ali-Hassanzadeh, M.; Mostafaei, S.; Gharesi-Fard, B. Are Genetic Variations in IL-1β and IL-6 Cytokines Associated with the Risk of Pre-Eclampsia? Evidence from a Systematic Review and Meta-Analysis. *J. Matern. Neonatal Med.* **2021**, *18*, 1–10. [CrossRef] [PubMed]

94. Mazlum, F.; Gharesi-Fard, B.; Hadinedoushan, H.; Bakhshizadeh Ghashti, Y. Association between Interleukin-32 Gene Polymorphism and Susceptibility to Preeclampsia. *Hypertens. Pregnancy* **2021**, *40*, 218–225. [CrossRef] [PubMed]

95. Pankiewicz, K.; Szczerba, E.; Maciejewski, T.; Fijałkowska, A. Non-Obstetric Complications in Preeclampsia. *Menopause Rev.* **2019**, *18*, 99–109. [CrossRef] [PubMed]

96. Khaliq, O.P.; Konoshita, T.; Moodley, J.; Naicker, T. The Association of NPHS1 and ACNT4 Gene Polymorphisms with Pre-Eclampsia. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2021**, *266*, 9–14. [CrossRef]

97. Ma, C.; Zheng, Y.; Liu, X.; Zhang, W. Association Study of Polymorphisms of Endoplasmic Reticulum Aminopeptidase 1 Gene with Preeclampsia in Chinese Populations. *Clin. Exp. Hypertens.* **2021**, *43*, 550–554. [CrossRef]

98. Burton, G.J.; Yung, H.-W.; Cindrova-Davies, T.; Charnock-Jones, D.S. Placental Endoplasmic Reticulum Stress and Oxidative Stress in the Pathophysiology of Unexplained Intrauterine Growth Restriction and Early Onset Preeclampsia. *Placenta* **2009**, *30* (Suppl. A), S43–S48. [CrossRef]

99. Vatish, M.; Randeva, H.S.; Grammatopoulos, D.K. Hormonal Regulation of Placental Nitric Oxide and Pathogenesis of Pre-Eclampsia. *Trends Mol. Med.* **2006**, *12*, 223–233. [CrossRef]

100. Kulandavelu, S.; Whiteley, K.J.; Qu, D.; Mu, J.; Bainbridge, S.A.; Adamson, S.L. Endothelial Nitric Oxide Synthase Deficiency Reduces Uterine Blood Flow, Spiral Artery Elongation, and Placental Oxygenation in Pregnant Mice. *Hypertension* **2012**, *60*, 231–238. [CrossRef] [PubMed]

101. Oe, Y.; Ko, M.; Fushima, T.; Sato, E.; Karumanchi, S.A.; Sato, H.; Sugawara, J.; Ito, S.; Takahashi, N. Hepatic Dysfunction and Thrombocytopenia Induced by Excess SFlt1 in Mice Lacking Endothelial Nitric Oxide Synthase. *Sci. Rep.* **2018**, *8*, 102. [CrossRef]

102. Sljivancanin Jakovljevic, T.; Kontic-Vucinic, O.; Nikolic, N.; Carkic, J.; Stamenkovic, J.; Soldatovic, I.; Milasin, J. Association Between Endothelial Nitric Oxide Synthase (ENOS)-786 T/C and 27-Bp VNTR 4b/a Polymorphisms and Preeclampsia Development. *Reprod. Sci.* **2021**, 1–11. [CrossRef] [PubMed]

103. Shaheen, G.; Jahan, S.; Bibi, N.; Ullah, A.; Faryal, R.; Almajwal, A.; Afsar, T.; Al-Disi, D.; Abulmeaty, M.; Al Khuraif, A.A.; et al. Association of Endothelial Nitric Oxide Synthase Gene Variants with Preeclampsia. *Reprod. Health* **2021**, *18*, 163. [CrossRef] [PubMed]

104. Xu, C.; Guo, Z.; Zhang, J.; Lu, Q.; Tian, Q.; Liu, S.; Li, K.; Wang, K.; Tao, Z.; Li, C.; et al. Non-Invasive Prediction of Fetal Growth Restriction by Whole-Genome Promoter Profiling of Maternal Plasma DNA: A Nested Case–Control Study. *BJOG Int. J. Obstet. Gynaecol.* **2021**, *128*, 458–466. [CrossRef] [PubMed]