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Correlations of placental histopathology, clinical signs and perinatal outcomes in preeclampsia and fetal growth restriction

Summary of the PhD thesis

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LIST OF FULL PAPERS THAT SERVED AS THE BASIS OF THE PH.D. THESIS

I. Dankó I, Tankó A, Kelemen E, Cserni G. Placental pathology of preeclampsia from a clinical point of view: Correlation between placental histopathology, clinical signs of preeclampsia and neonatal outcome. J Obstet Gynaecol Res. 2023;49(6): 1471–80.
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II. Dankó I, Kelemen E, Tankó A, Cserni G. Correlations of Placental Histopathology, Neonatal Outcome, and Cardiotocogram Baseline Variability and Acceleration Patterns in the Growth Restricted Preterm Population. Pediatric and Developmental Pathology. 2023;26(5): 447-457.
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1. INTRODUCTION

Placental histopathology has a great importance in the field of perinatology, as placental changes give us significant information about the intrauterine milieu in which the fetus was in the antepartum period. The information provided by the histopathological evaluation of placental tissue is crucial in the assessment of possible intrauterine insults and pregnancy-associated pathological entities.

Preeclampsia (PE) is a common complication of pregnancy with potential transition to eclampsia and significant morbidity and mortality affecting both the mother and the fetus. Although the exact pathogenesis of PE is not fully understood, several details have been described on molecular and histopathological levels. Numerous histopathological changes have been reported in placentae from PE and it is also known that oxydative stress, pathologic placentation and pathologic angiogenesis have an important role in the development of the disease.

Early-onset (EO) and late-onset (LO) PE are two distinct entities with different maternal and neonatal prognosis and a distinct pathology; the 34th week of gestation at the time of diagnosis is the boundary between the two subtypes. Association of fetal growth restriction (FGR) with PE is the main cause of unfavourable perinatal outcome, especially if FGR is evident at the onset of PE.

FGR is a common complication of pregnancy, with a significantly increased risk of perinatal death and is associated with several consequences of neonatal and perinatal morbidity. FGR is

defined as fetal weight below the 10th percentile for the given week of gestation; it is a severe condition, in which the fetus does not grow according to its genetically expected percentile (which is characteristic to the given population).

Cardiotocography (CTG) is a non-invasive and widely accessible tool for the assessment of fetal condition. CTG monitoring of preterm fetuses does not have reference standards and well-defined guidelines in contrast with the CTG interpretation of term fetuses.

The placenta is affected by numerous histopathological alterations in FGR. These changes lead to chronic intrauterine hypoxia and malnutrition; the result of this altered placental metabolic and transport function is FGR with all of its consequences.

Similarly to PE, EO and LO FGR have been distinguished, and their pathogenesis, histopathological background and prognosis seem different, suggesting that these two entities are different.

FGR has a notable tendency to recur, and recurring FGR in a consecutive pregnancy is also a clinically important subtype worth to be distinguished from non-recurrent cases.

Ultrasound is a helpful tool in the follow-up and management of FGR; the amniotic fluid index (AFI), biophysical profile of the fetus, fetal biometry, femoral length/abdominal circumference (FL/AC) ratio, umbilical (AUM) and middle cerebral artery (MCA) Doppler indices are highly useful methods helping the

clinician in the assessment of intrauterine fetal development and/or wellbeing.

2. AIMS

1. To analyze the placental histopathological background of EO- versus LO-PE, EO- versus LO-FGR, and to investigate the placental histological background of PE complicated with FGR, recurring FGR and recurring PE.

2. To assess the clinicopathological implications of placental histopathology in cases with PE and/or FGR on neonatal outcomes.

3. To find possible connections between rate of villous capillarization, percentage of intact terminal villi and pregnancy outcomes.

4. To analyze the possible connections between placental histopathology and CTG baseline variability and acceleration patterns in the growth restricted preterm population.

5. To investigate the connections of placental histopathological changes and different Doppler indices measured by prenatal ultrasound, and to assess the possible correlations of placental microscopic changes and ultrasound biometry parameters.

3. MATERIALS AND METHODS

3.1

All placentae from preeclamptic pregnancies submitted for histological evaluation between 2007 and 2022 were retrieved from the archives of the Pathology Department, and were evaluated by the same observer according to a uniform scheme. The retrospective review of placental signs was blinded to clinical details and neonatal outcomes, the only information that was given for the examiner was the gestational age at the time of delivery. Exclusion criteria included twin pregnancies, placental abruption, fetal genetic or structural disorders, pregnancies complicated with intrauterine infection, and presence of gestational diabetes.

All placentae were fixed in buffered formalin after delivery, and tissue blocks were taken from at least three different places. All slides represented basal plate, villous tree and chorionic plate in each instance. Formalin fixed and paraffin embedded material was used and 3-4 micrometer thick sections were stained with hematoxylin and eosin (HE).

Histological signs of maternal vascular malperfusion (MVM; the studied MVM-associated placental changes were: chorionic villous infarction, accelerated villous maturation (AVM), distal villous hypoplasia (DVH)), decidual arteriopathies, fetal vascular malperfusion (FVM; the studied FVM-associated placental chages were chorionic plate and/or stem vessel thrombosis, fibrinoid necrosis of large fetal vessels, avascular villi), delayed villous maturation (DVM), villitis of unknown etiology (VUE) and chorangiosis were studied. All of the above mentioned lesions were

diagnosed according to the histological definitions of the Amsterdam Placental Workshop Group Consensus Statement; chorangiosis was studied by using the criteria of Altshuler.

As far as decidual arteriopathies are concerned, acute atherosis, fibrinoid necrosis of vessel wall, medial hypertrophy of decidual vessels, perivasculitis and arterial thrombosis were separately recorded as components of this entity; in all cases, maternal decidual vessels were extensively studied.

Avascular villi were categorized into three groups (small, intermediate and large foci). Diagnosis and grading of VUE were also made following explicit criteria. In case of the other histopathological changes, focal and diffuse manifestations of the lesions were distinguished: a lesion was considered focal if present in only one full-thickness placental slide, and diffuse if it appeared on two or more slides.

DVM was only studied after the 36th week of pregnancy. Diagnosis of AVM was only made before the 36th week of gestation.

The percentage of intact terminal villi (PITV) was determined according to our own methodology: ten non-overlapping areas of placenta were evaluated under high power magnification, and 100 adjacent villi were counted in each area to determine the percentage of intact villi.

The number of intact capillaries in 100 adjacent villi in five different, randomly selected areas of the placental slides were also determined: the capillary-villus ratio (CVR; also our own method for

the purpose of quantification) was calculated using the number of capillaries (identified on HE stain) in these villi (CVR = capillary number in 500 villi/500).

The corresponding clinical data, obstetrical and neonatal history were retrieved from the digital charts. EO-PE and LO-PE were compared for histological features, then we studied the distinct character of PE complicated with FGR.

Ultrasound scans and Doppler measurements were done to assign the resistance index (RI) of umbilical artery and to diagnose the persistence of diastolic notch of uterine artery.

24-hour-proteinuria in PE is a useful prognostic marker of severity; we classified proteinuria values of patients in three groups. The severity of hypertension in PE was characterized by the number of medicines needed to control hypertension.

Comparative statistical analysis was made by using the Pearson's Chi-square test and when the numbers were low (<10 in any subgroup) the Fisher exact test was used instead. The Mann-Whitney U test was used for the comparison of PITV and CVR in different subgroups. Statistical significance was defined as $p<0.05$.

3.2

In this retrospective study, we examined FGR cases delivered before the 37th week of gestation. In each case, placental histopathological examination was performed after delivery, and continuous, uninterrupted CTG monitoring of the baby was done before vaginal delivery.

EO-FGR and LO-FGR cases were studied separately; corresponding clinical data were coupled with each case (Apgar scores at 5 and 10 minutes; umbilical artery pH after birth (UA pH), umbilical artery blood lactate level after birth (UA lactate), birth weight percentile); UA pH and UA lactate results were studied from the first 15 minutes after birth of the newborn.

Each cardiotocogram was assessed by the same person (to exclude inter-observer variability) according to a uniform scheme using the definitions of the FIGO CTG guidelines. Evaluation of the cardiotocogram reads was performed retrospectively, the study was done by a licensed obstetrician; in each case, the examiner was blinded to clinical details, gestational age, neonatal outcomes and placental findings, respectively.

Baseline fetal heart rate was between 120 and 160 beats per minute (bpm) in each case, and none of the studied cardiotocograms had any form of decelerations or bradycardia. The presence of accelerations was evaluated in each cardiotocogram – if acceleration was not registered in the last 60 minutes (but at least one acceleration was present in every 30 minutes in the previous segments of cardiotocograms), 'lack of accelerations' was diagnosed.

Histopathological study of placental slides were accomplished the same way as in the previously described study of preeclampsia.

Exclusion criteria included stillbirth, twin pregnancies, indeterminate gestational age, genetic or structural abnormalities of

the fetus, intrauterine infection diagnosed before or after delivery, gestational diabetes or disorders of placental implantation; cases where any medications or general anaesthetics (except for intravenous antibiotics, intramuscularly administered dexamethasone, saline infusion, and anaesthetics used for intradural analgesia) were administered in the last 48 hours of pregnancy (to avoid potential overlapping effects of medications on CTG patterns). The use of intravenous oxytocin was also excluded. We did not study cases with umbilical cord complications in order to eliminate the possible effect of cord compression on CTG patterns.

We looked for any associations between neonatological parameters with CTG in the EO-FGR and LO-FGR groups separately and together. Possible connections of the studied placental changes and CTG baseline variability and acceleration patterns were evaluated. The PITV was evaluated in different subgroups. The CVR of different groups were also statistically analyzed.

3.3

In this retrospective study, we examined placentae from FGR pregnancies from the interval between 2007 and 2022. The clarification of gestational age was done in all cases using the crown-rump length (CRL) of the embryo from the ultrasound scan conducted in early pregnancy.

We studied only singleton pregnancies with a gestational age over the 24th week at the time of birth. Exclusion criteria included: twin pregnancies, genetic or structural disorder(s) of the fetus,

stillbirth, pregnancies complicated with gestational diabetes; maternal thrombophilia; uncertain age of gestation; placental abruption; pregnancies with signs of intrauterine infection.

We analyzed the differences between histopathological alterations in EO-FGR versus LO-FGR, FGR with PE versus FGR without PE, and recurring versus non-recurring FGR.

We also studied the connections between placental histological changes and clinical features or neonatal outcome, notably AFI, AUM and MCA Doppler indices; fetal birth weight; FL/AC ratio diagnosed with ultrasound at the time of diagnosis of FGR; and maternal body mass index (BMI) at the time of birth. The AUM Doppler indices were considered pathologic in case of absent end diastolic flow (AEDF), reverse end diastolic flow (REDF) or when the resistance index (RI) was beyond the 95th percentile of the reference values for gestational age. MCA Doppler indices were considered pathologic when RI were below the 5th percentile for gestational age.

The presented studies were approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungary (ETT-TUKEB, IV/2992-3/2022/EKU).

4. RESULTS

4.1

Diffuse DVH ($p=0.01$), diffuse AVM ($p<0.01$), diffuse medial hypertrophy of maternal decidual arteries ($p<0.01$), diffuse

perivasculitis ($p<0.01$), and large foci of avascular villi ($p<0.01$) were significantly more common in EO-PE, whereas LO-PE had significantly more frequent villous infarction ($p=0.04$) and chorionic plate or stem vessel thrombosis ($p=0.02$).

When comparing neonatal outcomes of EO-PE versus LO-PE, the former had worse prognosis.

Analyzing PE with FGR versus PE without FGR, their histology showed several differences. We found a significant increase of diffuse DVH ($p<0.01$), diffuse AVM ($p<0.01$), diffuse perivasculitis ($p=0.02$), diffuse arterial thrombosis of maternal decidual vessels ($p<0.01$), diffuse chorionic plate or stem vessel thrombosis ($p<0.01$), large foci of avascular villi ($p<0.01$) and multifocal high grade VUE ($p=0.01$) in PE with FGR.

Medial hypertrophy of maternal decidual arteries and perivasculitis were significantly more prevalent in EO-PE. Perivasculitis was remarkably more common among recurring PE cases (7/8 in recurring cases of PE, 6/41 in non-recurring cases; $p<0.01$), but there were no differences in other vascular lesions.

Comparing the rate of the studied vascular lesions in mothers with an increased RI of umbilical artery and those with physiologic RI of umbilical artery, we found a significant association between both medial hypertrophy of maternal decidual vessels ($p=0.02$) and acute atherosis ($p=0.02$) and an increased RI. We could also demonstrate that the presence of medial hypertrophy of maternal decidual vessels is significantly associated with the persistence of

diastolic notch of the uterine artery compared to cases without it ($p=0.01$).

Of the VUE-associated avascular villi cases, all were described in EO-PE, 8/10 were PE cases with FGR, and 7/10 were recurring PE cases, respectively. Therefore, the presence of VUE-associated avascular villi has a strong connection with EO-PE ($p<0.01$), PE with FGR ($p=0.01$) and recurring PE ($p<0.01$).

Of the histopathological phenomena investigated, only the presence of large foci of avascular villi was correlated with the degree of proteinuria ($p<0.01$).

CVR was significantly lower in case of hypertension requiring a three-drug combination of antihypertensive medications ($p=0.01$), PE with FGR ($p=0.03$), and stillbirth versus live birth ($p=0.02$).

4.2

A total of 50 cases were studied from the period between 2010 and 2020; 24 cases were EO-FGR, and 26 cases were LO-FGR.

As far as the CTG baseline variability patterns and neonatal parameters are concerned, we found that reduced baseline variability on CTG in the whole study population was significantly associated with 10-minute Apgar score <7 ($p=0.03$), UA pH 7.01-7.2 ($p=0.02$), UA pH <7.01 ($p<0.01$), UA lactate ≥10 mmol/L ($p<0.01$), and birth weight below the 2nd percentile ($p<0.01$).

According to our findings, absence of accelerations was associated with 5-minute Apgar <7 (<0.01), UA pH <7.01 ($p=0.04$)

and UA lactate level 3.75-4.99 mmol/L ($p=0.04$) in the EO-FGR subgroup; it was associated with 5-minute Apgar <7 ($p<0.01$) and birth weight below 2nd percentile ($p=0.02$) in the LO-FGR subgroup; in the whole study population it was significantly associated with 5-minute Apgar score below 7 ($p<0.01$), 10-minute Apgar score below 7 ($p=0.04$), UA pH <7.01 ($p<0.01$), UA lactate level between 3.75 and 4.99 mmol/L ($p<0.01$), and birth weight below the 2nd percentile ($p<0.01$), respectively.

As far as the associations of the studied placental histopathological changes and CTG baseline variability is concerned, villous infarction, DVH, AVM, decidual arterial thrombosis, chorionic plate thrombosis, avascular villi, and VUE were significantly more common in the whole study population when baseline variability was reduced.

Absence of accelerations was significantly associated with arterial thrombosis, avascular villi and chorangiosis in the EO-FGR subgroup; it was associated with DVH, avascular villi and chorangiosis in the LO-FGR subgroup; in the whole study population absence of accelerations was significantly associated with DVH, VUE and chorangiosis.

The average PITV was 65.8% in the study population; the average CVR was 3.65. We found no significant differences in PITV and CVR between EO-FGR and LO-FGR. Quantitative analysis of the studied placentae revealed that in case of lower UA pH, higher UA lactate levels, birth weight below vs. beyond 2nd percentile, and

reduced vs. normal baseline variability on CTG, the PITV was significantly lower.

Capillarization of villi reflected by CVR also showed significant differences, being reduced with UA pH <7.01, UA lactate ≥10 mmol/L, birth weight below 2nd percentile, absence of accelerations and decreased baseline variability. Absence of accelerations was associated with a significantly lower CVR (but not with a lower PITV). We found no differences in this quantitative analysis between normal vs. increased baseline variability on CTG.

4.3

A total of 61 placentae from pregnancies complicated with FGR were studied.

Comparative histopathological analysis of EO-FGR versus LO-FGR revealed that diffuse DVH, AVM, fibrinoid necrosis and medial hypertrophy of decidual vessel walls, large foci of avascular villi and multifocal high grade VUE were significantly more frequent in EO-FGR. None of the pathological alterations studied occurred more frequently in the LO-FGR group.

Recurring FGR (p=0.03) and complication of FGR with PE (p=0.02) were more common in case of EO-FGR than in LO-FGR. There was no association between maternal smoking and onset of FGR in this population.

There were 18 recurring FGR cases. Diffuse high grade VUE was significantly more common among recurring FGR cases than non-recurring ones (p=0.01).

Cases with AFI below 2 cm were more commonly associated with decidual arterial thrombosis (p=0.03), chorionic villous infarction (p=0.03), AVM (p<0.01), DVH (p=0.01) and avascular villi (p=0.01) than cases with AFI beyond 2 cm. When birth weight was below the 2nd percentile for gestational age, AVM (p<0.01), chorionic villous infarction (p<0.01), chorangiosis (p<0.01) and avascular villi (p=0.02) were significantly more common.

Medial hypertrophy of decidual vessels (p=0.02), AVM (p<0.01) and DVH (p<0.01) were more common in the background of increased AUM RI compared to the normal AUM RI group. The same histological alterations plus avascular villi (p=0.03) were found more commonly in cases of AEDF or REDF on AUM, of which the prognosis is much worse. Pathological MCA Doppler indices were associated with the same alterations.

Clinocopathological study of the possible connections of FL/AC ratio and perinatal outcomes was also performed; we divided the study population by FL/AC <0.25 and ≥0.25 (we considered FL/AC ratio high above 0.25, and very high above 0.26). In the background of the highest FL/AC ratio group among EO-FGR cases, infarction, DVH, and decidual arterial thrombosis were significantly more common than for lower FL/AC values, while in LO-FGR the highest FL/AC cases were associated with chorionic villous infarction and avascular villi.

CVR was significantly lower in case of EO-FGR (p=0.01), PE with FGR (p=0.02), birth weight below the 2nd percentile

(p=0.01), and pregnancies with pathologic AUM Doppler flowmetry versus normal flowmetry (p=0.04).

5. DISCUSSION

5.1

Involvement of the placental vasculature, terminal villi, intervillous and perivillous space in PE is obvious; many previous studies have described that reduced placental perfusion precedes clinical signs of PE in keeping with the two-stage model of this condition.

In EO-PE, incomplete trophoblast invasion and inadequate remodelling of maternal spiral arteries are the main pathogenetic elements, whereas LO-PE is considered to be induced by placental maturation. In other words, in EO-PE, placentation and placental vasculogenesis is *ab ovo* altered, while in LO-PE placentation itself is physiologic.

In our study population, numerous histopathologic alterations were identified in PE placentae, but the two entities of EO-PE and LO-PE were different in some respects. DVH and avascular villi – accurately differentiated from infarcted areas – could be an evidence of pathological placentation in EO-PE, while stem vessel thrombosis in the background of LO-PE could be considered as consequence of different forms of umbilical cord pathology, and as a placental change associated with fetal cardiac failure, anaemia, or fetal hypercoaguability.

As far as CVR (our indicator of capillarization of villi) is concerned, we consider it a suitable quantitative measure derived from placental histological examination at the time of delivery. At the same time, CVR gives us information only after the time of delivery, and it does not reflect timing and dynamics of placental damage.

Examining decidual arteriopathies, medial hypertrophy and perivasculitis of maternal decidual vessels seemed to be more characteristic to EO-PE. Medial hypertrophy of maternal decidual vessels also had connection with increased RI of umbilical artery and persistence of uterine artery diastolic notch, reflecting its impact on placental hemodynamics. These associations of MVM lesions with abnormal fetoplacental Doppler findings are congruent with the observations of earlier studies.

The combined PE and FGR cases had significant differences in the prevalence of histopathological alterations when compared to PE cases without FGR; these alterations were peculiar histological characteristics of EO-PE, especially the diffuse distribution of DVH and AVM.

Multifocal high grade VUE – diagnosed after exclusion of infectious etiology – was also associated with the concurrence of PE with FGR: chronic destructive inflammation of the placenta could be the additional mechanism leading to fetal malnutrition in such cases.

The connection of avascular villi with proteinuria is an interesting aspect of PE: as avascular villi were found to be

characteristic of EO-PE and could be an evidence of pathologic placentation or – at least in a proportion of cases – an accompanying entity of VUE; and besides, avascular villi could be associated with prolonged MVM as Genest et al. described.

In case of antihypertensive treatment with three medicines, CVR was significantly lower than in case of one or two medicines used for blood pressure control. The results, therefore, suggest that in case of preeclamptic placentae, not only the quality of histolopathologic changes, but also the reduced capillarization of villi has a role in pregnancy outcome and clinical signs.

5.2

Absence of accelerations and reduced baseline variability proved to be good markers of poor perinatal outcome. Reduced baseline variability in combination with lack of accelerations for 60 minutes was associated with UA pH $\leq$7.2 and UA blood lactate level $\geq$3.75 mmol/L in each case, strenghtening the linkage of these patterns with bad prognosis. Our findings suggest that absence of accelerations could have relevance in predicting fetal acidemia. As far as CTG evaluation is considered in preterm cases, baseline variability and lack of accelerations could be useful markers of altered intrauterine fetal wellbeing and these parameters could help the assessment of fetal state.

The common finding of infarction, DVH, AVM, chorionic plate thrombosis and avascular villi in placental histopathology accent an altered placental milieu in the background of pathologic

CTG findings (and FGR itself) and poor neonatal outcome. This is reasonable, as the placenta is the metabolic interface between mother and fetus. The role of VUE in the background of pathological CTG signs and poor outcome could be in the immune-mediated destruction of placental tissue, while chorangiosis seems to be a placental change with a compensational character as a response to chronic, low-grade hypoxia.

The significantly decreased PITV and significantly lower CVR in the background of cases with neonatal acidemia (reflected by pH ≤7.2 and UA lactate level ≥3.75 mmol/L) strongly point to the possibility that the described histopathological alterations could influence neonatal outcome as a measure of undercapillarization of placental villi; whereas other histological changes affecting the perivillous- and intervillous space (e.g. AVM by fibrin deposition) and the decidual vasculature (e.g. decidual arterial thrombosis) further aggravate this placental damage cummulatively leading to FGR and placental impairment.

5.3

EO-FGR and LO-FGR seem to be two different entities from the aspect of histopathology. The relatively frequent finding of VUE in the background of EO-FGR suggests immunological mechanisms in its pathogenesis, and this could explain its recurring character.

In the background of the most severe clinical symptoms of FGR (severe oligohydramnios, birth weight below the 2nd percentile, pathological Doppler indices), we found that chorionic villous

infarction, DVH, AVM and avascular villi were significantly more common. According to these findings, it seems that these histopathological changes collectively reflect or are collectively responsible for generating the placental milieu leading to chronic malperfusion and malnutrition of the fetus, causing chronic hypoxia. Therefore, these histological characteristics determine the chronic placental insufficiency at the microscopic level.

Our results further support the finding that pathologic AUM Doppler indices in FGR could have a connection with diffuse MVM-associated placental changes - in our cohort the high prevalence of DVH, AVM and diffuse infarction among the EO-FGR cases unequivocally demonstrates this histopathological background. We found that DVH had a strong association with pathologic Doppler indices of AUM; this finding further strengthens the previously described associations of villous maldevelopment and non-branching placental angiogenesis with FGR.

It seems that a FL/AC ratio ≥0.25 in FGR, besides the estimated fetal weight under the 2nd percentile, is a useful predictor of worse perinatal prognosis. In the EO-FGR group, we identified infarction, DVH, and decidual arterial thrombosis more commonly in the background of high FL/AC ratio.

The quantitative analysis of PITV pointed to the fact that the reduction of terminal villi has a direct connection with pathologic AUM flowmetry. We found no significant differences in PITV

between different FGR subtypes (by onset or recurrency) and in relation to the presence of other signs and symptoms of FGR.

Villous capillarization reflected by CVR, however, had a significant association with EO-FGR, FGR with PE, and birth weight below the 2nd percentile; this leads us to the conclusion, that CVR could be a better quantitative marker of placental pathology in FGR compared to PITV, especially in EO-FGR.

6. CONCLUSIONS

6.1 EO-PE and LO-PE are two distinct entities from the viewpoint of placental histopathology: in EO-PE placentation and placental vasculogenesis is *ab ovo* altered, and poor villous development has a key role in its pathogenesis, while in LO-PE placentation in itself is physiologic. DVH and avascular villi reflect pathological placentation in EO-PE, while in LO-PE placental changes altering placental blood flow in term or near-term are the characteristic entities.

6.2 Decidual arteriopathies, medial hypertrophy and perivasculitis of maternal decidual vessels are more characteristic to EO-PE. Medial hypertrophy of maternal decidual vessels also has a connection with increased RI of umbilical artery and persistence of uterine artery diastolic notch, reflecting its impact on placental hemodynamics.

6.3 In EO-PE with FGR, the concurrence of VUE and avascular villi is a remarkable issue, and a characteristic predisposition for recurrency.

6.4 In PE and FGR, CVR (our indicator of capillarization of villi) is a proper index of quantitative placental histological examination at the time of delivery; the absence of significant differences of CVR in different subgroups of placental weight percentiles, or in different groups of placental weight to birth weight ratios makes it an ideal, weight-independent marker of placental villous capillarization.

6.5 In the growth restricted preterm population, the significantly decreased PITV and significantly lower CVR in the background of cases with absence of accelerations, decreased baseline variability on CTG and neonatal acidemia strongly point to the fact that undercapillarization of placental villi has a key role in fetal distress; other histological changes affecting the perivillous- and intervillous space (e.g. AVM by fibrin deposition) and the decidual vasculature (e.g. decidual arterial thrombosis) further aggravate this placental damage cummulatively leading to FGR and placental impairment.

6.6 In the background of the most severe clinical symptoms of FGR (severe oligohydramnios, birth weight below the 2nd percentile, pathological CTG and pathological Doppler indices), chorionic villous infarction, DVH, AVM and avascular villi are significantly more common.

6.7 DVH has a strong association with pathologic Doppler indices of AUM; this finding further strengthens the previously described associations of villous maldevelopment and non-branching placental angiogenesis with FGR.

6.8 In FGR, FL/AC ratio ≥0.25 and estimated fetal weight under the 2nd percentile are useful predictors of bad perinatal prognosis. In the background of high FL/AC ratio in the EO-FGR group, villous infarction, DVH, and decidual arterial thrombosis were described more commonly; villous infarction and avascular villi were found more commonly in the LO-FGR group when FL/AC ratio was high.

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