PREECLAMPSIA AND MORPHOLOGICAL EVIDENCE OF ANATOMOPATHOLOGICAL LESIONS

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Abstract. Preeclampsia is an obstetric complication that is characterized through hypertension and proteinuria which appear after week 20 of pregnancy, more frequent in the last week before labour. The pregnancy can induce or worsen hypertension; the increase in systolic blood pressure with 30 mmHg and/or the diastolic blood pressure with 15 mmHg represents a risk factor in preeclampsia. The prediction of preeclampsia has a prognostic of over 75% if the data is correlated with the pulsatility index obtained by uterine artery Doppler procedure and is also correlated with the cranio-caudal length of the fetus.

INTRODUCTION

Preeclampsia represents a pathological state that is specific to the period of pregnancy (having an incidence of 3-5%) which is characterized by *de novo* high blood pressure and proteinuria. It appears after 20 weeks of pregnancy. Although it begins in the placenta and is inextricably linked to its presence, preeclampsia is a multisystem disease that implies an increased incidence of morbidity and mortality, both for the mother and for the conception product (7, 11)
This condition can appear even in the absence of the foetus (like the hydatidiform mole for example) and the symptoms usually resolve when the placenta is delivered. Pre-eclampsia is a condition that starts in the placenta and ends in the maternal endothelium, being characterized by a generalized endothelial dysfunction. It affects all susceptible vascular beds: kidneys, the central nervous system, liver, and placenta (7, 8, 9, 20).
In Romania, recent studies have shown that the annual incidence of preeclampsia cases is situated between 6-12%, with a variation of 10 to 14% for primiparous and 5.7-7.3% for multiparous women, with a significantly increased incidence of preeclampsia cases for the pregnant women with twin/multiple pregnancy, in the case of the women who had preeclampsia during their previous pregnancies, and also in the case of the primiparous women under 20 or over 35 years old (17).

MATERIAL AND METHODS

Preeclampsia is not a “simple” disease; it is a combination of maternal, placental and fetal factors. In the aetiology of preeclampsia one can distinguish genetic causes, but also endocrine/ metabolic – including and an altered production of prostaglandins, utero-placental ischemia, immunologic causes, or situations where there are no known causes identified. The theories that are currently used in the field of researching the physiopathology of preeclampsia are focused on analysing the following phenomena (7, 19):

1. the abnormal trophoblast invasion;
2. the impairment of the vascular endothelium;
3. anomalies of coagulation and eicosanoid incrimination;
4. immunological intolerance between maternal and fetal placental tissue;
5. mother’s failure to adapt to cardiovascular or inflammatory changes during pregnancy;
6. genetic factors (genetic predisposition);
7. external environmental factors (insignificant role).

RESULTS AND DISCUSSIONS

The abnormal trophoblast invasion

Placental blood flow is provided by utero-placental arteries that grow based on the spiral arteries. The trophoblast invasion causes the destruction of the muscular layer and the damages the autonomic innervation of the spiral arteries. The insufficiently perfused trophoblast releases substances that are toxic for the endothelial cells.

The utero-placental arterial bed is characterized by low resistance and intense flux. These qualities are designed to ensure embryo-fetal development.
The changes described affect the spiral arteries to the internal third of the myometrium and they occur in 2 stages: the 10-th and the 16-th week; in preeclampsia these changes are limited to the decidual segment, and the second wave of the trophoblast migration is inhibited.

The impairment of the vascular endothelium

The vascular endothelium represents a modulator of the contractile activity of underlying smooth muscles and of platelet aggregation. The impairment of the vascular endothelium increases the synthesis of PGI2 and decreases the nitric oxide (relaxing factors), and these phenomena causes vasodilation in the uterine circulation.
The impairment of the endothelium induces the production of antivascular antibodies, which are attached to the endothelial cells and cause a series of effects such as: vasoconstrictor peptide release (endothelins), an increased platelet adhesion, complement activation, an impaired secretion of PGI2, increased plasma fibronectin concentrations, the stimulation of vonWillebrand factor and of the tissue plasminogen activator.
In terms of risk of developing preeclampsia type pathology, the endothelial dysfunction is an individual phenomenon. The question arises whether this dysfunction is the cause or consequence of preeclampsia.

Proteomics data

The proteome represents all proteins found in biological compartment, like an organism, a cell, an organelle or a fluid (blood, amniotic fluid, urine). Urine represents one of the fluids that are accessible for investigations. The presence of abnormal proteinuria is not specific only to kidney conditions. Urinary proteomics is useful in identifying the biomarkers for pre-eclampsia more than 10 weeks before term. Two of the markers are fragments of SERPINA1 and albumin. SERPINA1 is the serine-protease inhibitor and it is synthesized in many cell types, including the trophoblasts; its levels increase in inflammatory conditions such as vasculitis or cardiovascular diseases. SERPINA-defective proteins were detected in pre-eclamptic placentas. The patients with pre-eclampsia who had to deliver the baby before the term have a unique urinary proteomic profile, which includes non-random fragments of SERPINA1 and albumin. This profile proved to be a predictive element that is even better than the sFlt-1/PlGF ratio and the proteinuria/creatininuria ratio. Chen et al. described 31 different proteins whose concentrations differ for the women with pre-eclampsia in comparison with the ones having a normal pregnancy (3, 7). These proteins play an important role in coagulation, cell adhesion and also in the immune response. The most important markers are angiotensin, SERPINA1 and albumin. The levels of albumin and SERPINA1 are higher for the women with pre-eclampsia, but they decrease for the ones with pregnancy-induced hypertension, indicating the possibility of using them in the differential diagnosis. The levels of urinary angiotensinogen are significantly reduced in pre-eclampsia or pregnancy-induced hypertension when compared with the levels in a normal pregnancy.
Another model of urinary proteome that is specific to pre-eclampsia was described by Carty et al. (7) and it includes fragments of collagen, fibrinogen and uromodulin; this model obtained better predictive results than sFlt-1 and PlGF. Yet, the model with 100% sensitivity and specificity was valid only for pregnancies at 28 weeks and for the women who had 2 risk factors. It is interesting to notice that the uromodulin gene that encodes for the Tamm-Horsfall protein (the most frequent protein that can be found in normal urine) seems to play an essential role in anti-inflammatory and anti-infective protection (3, 7, 10).

Metabolomics data

Metabolomics is a growing number of technologies that can characterize an almost complete collection of metabolites and small molecules that are present in cells, tissues or biological fluids. Odibo et al. and also Bahado et al. (10, 12) described the presence of 4 metabolites (hydroxyl hexanoic carnitine, alanine, phenyl alanine, glutamate) which show significant increases in preeclampsia. If taken individually, these markers have a prediction rate of 70-80% but also 20% false positive results. Another metabolome (citrate, glycerol, hydroxyisovalerate and methionine) was identified in the first semester of pregnancy with 75% accuracy regarding the prediction of preeclampsia and only 5% false positive results.

Complications

The disease that is triggered early in pregnancy (20-32 weeks) is accompanied by perinatal risk and even bigger maternal complications. The condition is considered serious if the mother shows signs of organic damage: cardiac decompensation, stroke, pulmonary edema, respiratory, renal, hepatic impairment, intracranial haemorrhage, coma, death, showing the mortality between 0.5-5%. The fetal risk which is directly proportional with the level of proteinuria and the diastolic blood pressure increases dramatically if the mother has an evolution towards eclampsia in pregnancy (1, 2, 4, 15, 16).

Maternal affection

PREECLAMPSIA (PE) = the symptomatic triad: high blood pressure associated with proteinuria, edema or both (9).

ECLAMPSIA = the appearance of tonic-clonic seizures, amid induced hypertension or hypertension aggravated by pregnancy, connected to a concomitant neurological condition, in the case of a woman who satisfies the criteria for preeclampsia (8).

Eclampsia is classified in ante-, intra- and post-partum. Almost without exception preeclampsia precedes onset eclamptic seizures, so they rarely show up all of a sudden, for a pregnant woman who seems to be healthy (18).

CHAUSSIER prodromal triad: ***helmet headache •visual disorders •epigrastric pain in the front part.***

The eclamptic crisis (eclamptic seizure) consists of 4 phases (20):

1. The period of invasion (the aura is exceptional) – small contractions of facial muscles (eyelids, nose, oral commissure), a fixed gaze upwards, the protrusion of the tongue, small movements of pronation, head leaned on the side and dilated pupils.

2. The period of tonic seizures moves very fast and takes about 20-30 seconds.

All the muscles in the body are involved: opistotonus, trismus, tight closed fists; forearms in pronation, the tongue which is projected out of the mouth can be bitten. The involvement of respiratory muscles and myocardium can sometimes result in death in case the period of time is extended. Blood pressure values reach the climax at 20-27 mmHg and in case the vascular bed has an increased frailty there can be haemorrhages, the cerebral ones being the most serious ones.

3. Clonic seizures period lasts between 1-2 minutes, but it can extend to 15-20 minutes – after a long deep breath in and a loud breath out, the muscles relax and contract in a clonic manner through convulsive, irregular, rapid moves. The upper limbs have “drummer” moves, the lower ones “swim-like” moves, the whole body can fall out of bed and there can appear severe trauma, the tongue can be bitten. Breathing is irregular, the pulse small and tough.

4. The coma period lasts for an indefinite time – it starts with the contractions giving away, muscle resolution, with loss of consciousness and senses, drowsiness or even coma. When the

patient is in the coma, the muscle resolution is complete, without sensitivity, with a congested face, eyes wide open, mydriasis, abolished corneal reflex, regular stertorous breathing, more rarely Cheyne-Stockes (periodic), urinary incontinency. The blood pressure is constantly increased, oliguria is constant, with intense albuminuria in the urine, which can be dark brown-reddish, and that means a meningeal hemorrhage or an inflammatory complication. The coma comes after one or more seizures. The crises can be repeated, thus becoming subintrance; there can always be some new seizures that aggravate the coma, in a progressive way to the death, as a consequence of meningo-cerebral hemorrhage, hepatic or kidney failure. During the coma the patient may develop a posteclamptic psychosis; sometimes with permanent sequel (permanent blindness), but in general they can see again after some time.

UTERO-PLACENTAL APOPLEXY – retro-placental hematoma - risk a complication of preeclampsia. It is characterized by minimal metrorrhagia, abdominal pain, uterus with an increased tonus to the point of "woody uterus", gradually increasing in volume.

HELLP SYNDROME

- microangiopathic haemolytic anaemia (H= haemolysis)
- an Increase in liver transaminases (EL= elevated liver enzymes)
- thrombocytopenia (LP= low platelet count).

Preeclampsia is usually severe with blood pressure>160/110 mmHg.

Symptoms: nausea, vomiting, headache.

The most important and alarming symptom is severe epigastric pain or pain felt in the right upper quadrant, caused by the distended hepatic sinusoids, after the obstruction of the small movement through deposits of fibrin.

Haemolytic anaemia is characterized by schizocytosis, the fragile erythrocytes being lysed by fibrin deposits.

Thrombocytopenia (generally below 100.000/mm^3) is characteristic for CID.

The maternal and fetal prognostic is severe.

THE OCULAR-RETINAL ACCIDENTS may result in retina discoloration and blindness (the exploration of FO, the avoiding of difficult expulsion).

CEREBRAL HEMORRAGE can appear mainly during expulsion in the case of the patients with high levels of the blood pressure (it is recommended to avoid difficult expulsions, and eventually the use of the forceps).

ACCUTE RENAL FAILURE caused by renal cortical necrosis. It is characterized by oliguria, the rapid growth of azotemia and disturbances in the water and electrolyte metabolism (supportive care and dialysis).

Fetal distress

MALNUTRITION AND FETAL HYPOTROPHY lead to hypoxia and consecutive acidosis and even to the intrauterine death of the fetus in the severe forms. The close monitoring of the fetus state (maternal estrioluria, utero-placental and umbilical artery velocimetry, Manning fetal biophysical score). Ultrasonographic assessment of fetal maturity level.

MORPHOLOGICAL EVIDENCE OF ANATOMOPATOLOGICAL LESIONS

The impairment of gestational trophoblastic in the ***placenta*** develops placental chorioangioma. It is a benign tumour, with a specific incidence of about 1% (7).

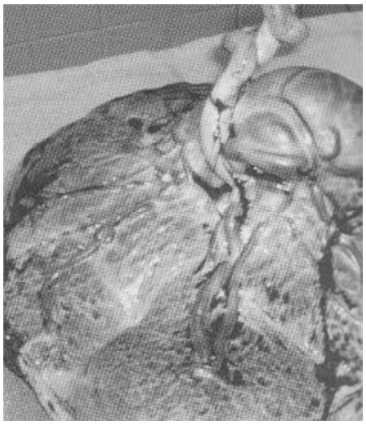

Fig. 1. Choriangioma, fetal protrusion in the circumcised mass
(in Williams Obstetrics, Cunningham FG et al)

Rarely, preeclampsia causes acute tubular necrosis ***in the kidney*** or even renal cortical necrosis. The renal failure of moderate severity was met in the neglected cases and it was, invariably induced by the presence of posthaemorrhagic hypotension (20).

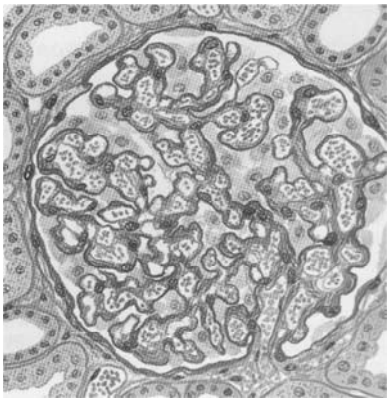

Fig. 2. Fibrin depositing and glomerular epithelial cells filling
(in Netter’s Obstetrics & Gynecology, Smith RP)

When speaking about ***the liver***, the most frequent lesion that was identified in the case of the women with eclampsia and an unfavourable prognosis, was periportal necrosis, at the edge of the liver (7, 19).

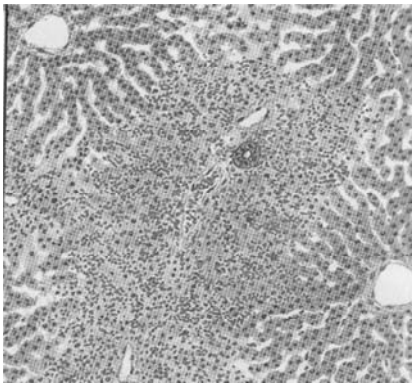

Fig. 3. Periportal necrosis in the liver section
(in Netter's Obstetrics & Gynecology, Smith RP)

The most frequent cause of death for the women with eclampsia was pulmonary edema, but the brain lesions were an important cofactor of lethality. Moreover, the literature mentions that ***brain injuries*** are the third leading cause of death (7).
The main lesions proven morphologically were the massive intracerebral haemorrhages (over 60% of the causes of death for women with eclampsia), cortical and subcortical petechial haemorrhages, subcortical edema (7, 19).

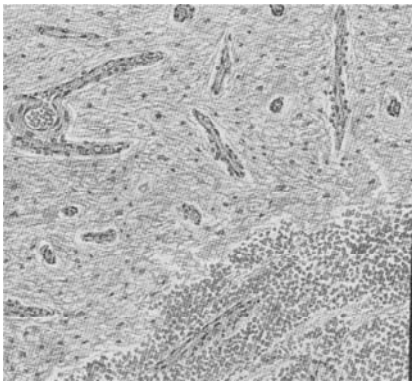

Fig. 4. Cerebral haemorrhage and necrosis
(in Netter's Obstetrics & Gynecology, Smith RP)

CONCLUSIONS

The point mutations in the uromodulin gene are associated with hypertension and chronic renal infections.
The prediction of preeclampsia has a prognostic of over 75% if the data is correlated with the pulsatility index obtained by uterine artery Doppler procedure and is also correlated with the craniocaudal length of the fetus.
The fetal risk was directly proportional with the level of proteinuria and the diastolic blood pressure if the mother has eclampsia in pregnancy.

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