CONCERNING A NEW PATHOGENETIC HYPOTHESIS OF THE E.P.H. GESTOSIS (Note I)

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SUMMARY

The Authors, after having evaluated the literature data, report, on the basis of their clinical experience, a new pathogenetic hypothesis of the E.P.H. gestosis, which would be:

" Disease due to missed materno-foetal adaptation ", correlated to the activation of the maternal immunocompetent system against the " not self " antigens, carried by the trophoblast and codified by the genoma of the father's origin.

It is also due to missed destruction of the tunica media of the placental bed arteries and to the thromboplastinic activity of the trophoblastic cells damaged by the immunologic reaction.

This disease, clinically represents, the appearance of a " temporaneous " (pre-eclampsia) or " definitive " (eclampsia) defeat of the fibrinolytic control mechanisms against a disseminated intravascular coagulopathy.

It is known that the foetus does not cause any reaction of the maternal organism, in spite of the antigenic expression codified by the genoma of the father's origin.

Several studies conducted during the last few years, nowadays allow to sustain with relative security that pregnancy, considered as foetal allograft, is protected by rejection from an enhancing physiologically induced by HCG, and that is mediated by the lymphocitary modulation controlled by the hormone, also for the probable mediation of the SP_3 ([1, 2, 8, 10, 12, 13, 17]).

It finds in the mother a guest who opposes with at least, two mechanisms:

— the first, local, less improved, founded on a barrier effect of the endometrium transformed into decidua;

— the second, sistemic, more improved, founded on the control of the homeostasis, of the maternal organism performed by the immunocompetent system.

Nevertheless, the presence of circulating HCG, modules, in advantage to the foetus, the maternal response, since the decidua and the maternal vessels are respectively transformed into niches and nutritional pathways for the embryo, while the activity of the B-lymphocites, is to prevent the damages which can be caused by the activity of the T-lymphocites ([7, 15, 17]).

In fact, HCG controls directly the possibility of implantation, while the trophoblast, in the first weeks of gestation, penetrates into the myometrium, invading and replacing the maternal vascular endothelium ([15]).

This activates the maternal immunologic surveillance and after the parietovasal immunologic reaction, the media muscularis and the internal lamina elastica are replaced by fibrinoid material.

These modifications involve the decidual spiral arteries, the myometrial ones and, for a long tract, even the radial ones, allowing the reduction of vascular resistances, and the block of the capacity of modulating the vascular caliber.

Anyhow, in the gestosis, these modifications, which are characteristic of the physiological pregnancy, are interrupted at the decidual region of the spiral arteries, without involving the endometrial arterial portions, probably due to a reduced trophoblastic penetration into the maternal vessels, due to activation of the immunologic surveillance.

In fact, the entity of penetration must be considered as inverse function of the maternal immunologic activation: the more the immunocompetent system is activated, the less it will allow the trophoblastic penetration.

Considered our actual knowledge, few doubts are left on the fact that, the trophoblast invades the maternal vascular endothelium, damaging it and causing a platelet aggregation which determines the liberation of tissular factors which create a situation predisposing to disseminated intravascular coagulopathy, tendency which would be exasperated by the piastrinic factor 3 (PF_3) ([3, 11, 18]).

The increased presence of trophoblastic tissue in the uterine veins of patients affected by gestosis, acquires particular importance, since the trophoblast has a thromboplastic activity per gram of tissue, higher than that of any other tissue.

So, it has been possible to describe, in patients affected by gestosis, the rise of cryofibrinogen and fibrin degradation products with a platelet reduction, besides an increase in the disponibility of phospholipids precursors of the haemocoagulation ([3, 4, 11, 18]).

Generally, the immunologic damage to the tissues, mediated by the complement (C′), with damage to the basal membrane of the vessels, activates factor XII followed by the activation of factor XI with beginning of the haemocoagulative cascade ([9, 14, 16]).

On the basis of the above described, it is today possible to propose a new pathogenetic pattern of EPH-gestosis, which has to be considered " disease due to missed materno-foetal adaptation, for the activation of the immunocompetent system against the extraneous antigens brought by the trophoblast and due to the missed destruction of the tunica media of the placental bed' vessels and due to the thromboplastic activity of the trophoblastic cells damaged by the immunologic reaction, antigen-antibody-complement ".

Therefore it would represent the clinical and morphologic appearance of a temporaneous (pre-eclampsia) or definitive (eclampsia) defeat of the fibrinolytic control mechanisms against a disseminated intravascular coagulopathy.

It must be explained that the clinic damage and the degrees of DIC, depend not much on the entity of cellular damage, but on the dinamic relation between liberation of factors with thromboplastinic activity and activity of the control fibrinolytic system.

Therefore, it results that, for the activation of the maternal immunologic surveillance, the radial arterial vessels assigned to furnish the placental bed, in the gestosis do not undergo the structural physiologic modification. That causes, on one side, a missed adaptation to the always increasing foetal metabolic requirement and, on the other side, through the maintenance of the vascular effector (the media muscularis elastica), the achievement of arteriolar spasms subsequent to the activation of the CNS, and the frequent achievement of an acute atherosis or atherosclerosis.

Such a lack of balance, acts as if the patient destined to develop a gestosis, carries the pathophysiologic condition since the beginning of pregnancy.

Around the 28th week of gestation, the form passes the clinic horizon, that is when the placenta, for the increased foetal metabolic requirements, has to reveal its already poor functional compensation.

In fact, the placental response to the always increasing foetal metabolic requirements, is an increase in the perfusional pressure in the utero-placental district,

which damages the placental structures with consequent start of the trophoblast proliferative activity.

The latter, expresses itself by the rise of new chorial epithelial sprouts, functionally inert ([6]), and by an increase in the trophoblastic penetration, which finally activates the D.I.C., resulting in an immunologic reaction against the trophoblast.

From all this derives a trophoblastic cellular destruction, followed by a maternal antigenic inundation.

The in that way composed immunologic compounds, soluble for the excess of antigen, will deposit themselves on the subendothelial layer of Bowmann's capsule.

Finally the trophoblastic lysis will increase the thromboplastic activity, with increased platelet aggregation, which will activate the compensatory fibrinolytic mechanism.

Anyhow, the immunologic reaction is not limited to the vascular district, but it also involves the kidney, where the complement activity initiated by the immunologic compounds damages the basal membrane, altering its filtrating process with consequent *proteinuria.*

Meanwhile, in the placenta, the obstructive vasal lesion determines stasis and blood coagulation in the intervillous space with vasodilation of the foetal vessels and flacking of the epithelium and lysis of the red cells. Subsequently the infarcted zone will undergo a connectival transformation with formation of a pseudo-scar ([6]).

The electronic microscope confirms the data obtained by the optical microscopy, revealing a damage of the chorial epithelium with adhesion of fibrin and red cells, while the spiral arteries are interested by a parietal sclerosis with hyperplasia of the intima and, more or less marked luminal stenosis ([6]). As a consequence of such a phenomenon there is a decrease in the district haematic perfusion, with consequent liberation by the uterus of factors determining a *sistemic hypertension*, which seems to be maintained by the substantial increase in the haematic viscosity.

Meanwhile, the proteinuria has determined a dyscrasic oncotic pressure diminution which prevents the recovery of the interstitial plasma with *oedemas* and reduction of the blood volume.

The reduced blood volume activates ADH and Aldostero newith consequent recovery by the kidney of both water and solutes which will be displaced again in the interstitium.

The excessive weight gain, characteristic of the gestosis, can be explained by the existance of such a vicious circle.

In that way the four symptoms of the classic gestosis come into achievement. Anyhow, even with a severe perturbation of the most important physiologic parameters, it expresses the realization of an uncertain and sometimes transitory new omeostasis. This happens because, eventhough with extreme difficulty, the compensatory fibrinolytic system has been able to prevent the total functional collapse and the beginning of the D.I.C.

It is anyhow possible that a new thromboplastic phenomenon, makes the form worse, unsettling the already risked counterbalance with passage to the eclamptic gestosis.

Briefly we will explain that the pathophysiology of such a disease is represented by a situation of severe vascular and tissular distress of the encephalon, due to a decrease in the vascular perfusion induced by the perineuronal oedema and by the diffuse thrombosis of the small arterial capillaries of the encephalon.

The cerebral irritation due to the anoxia, causes an irregular activation of the neuronal pool (control gamma motoneurons?), with consequent hypertonia of all the striate muscles which is interrupted by a clonic motor activation.

The metabolic increase, correlated to such a massive muscular activity, disturbs the vital functions of an organism already severely tried.

On the other hand, the myocardium, already damaged by the irritative process, " the gestosic myocardosis ", is able to sustain the new requirements of the encephalon only by a compensatory tachicardia which is useless for, the reduced refilling time and diastolic pause, induce a fall in the volume per minute (the haematic viscosity is the highest during this phase), and in the coronary perfusion.

The compensatory haematic shunt reduces ulteriorly the renal perfusion, while the microthrombi obstruct the few renal capillaries still open; the periportal vessels of the liver are obstructed by thrombi.

Meanwhile, the enormous muscular work activates the metabolism, the body temperature rises, while the blood pressure is maintained by a generalized vasospasm.

This sequence of phenomenons explains the premonitory symptoms of the eclamptic attack, represented by *scotoma, auricolar buzzings, epigastric bar, restlessness, motor excitement*, and also the symptoms of the eclampsia: *anuria, hypertension, coma, hyperthermia.*

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