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Is apoptosis cause of pre-eclampsia?

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Abstract. – **Pre-eclampsia is the main cause of fetal and maternal morbidity and death associated with hypertension during complicating pregnancy.**

During physiological pregnancy, the immunological system undergoes secondary modifications, with an "exchange" between mother and fetus.

Cytokines play an important role in the complex condition of partial fetal "rejection". It has suggested that the condition depend on immunological factors. In line with this hypothesis, apoptosis appear to play a key role in the pathophysiology of placental ischemia and the mechanism underlying this condition may be influenced by substances such as Bcl-2 which inhibits apoptosis.

Neither aspirin nor calcium appear to improve maternal hypertension and proteinuria, although late ongoing trials may alter this view. At present, the condition can be resolved only by the end of pregnancy.

Further studies are required in order to improve our understanding of these immunological mechanisms underlying hypertension during pregnancy, as the key to effective therapy may be their ability to "manipulate" them in an appropriate way.

Key Words:

Hypertension, Pregnancy, Apoptosis.

Introduction

Hypertension, one of the most frequent conditions in pregnant women without previous disease is, according to the World Health Organization, the most frequent cause of perinatal morbidity and mortality[1]. It affects 10 to 15% of pregnant women, but a number of these women already have hypertension before pregnancy, or would anyway have developed the condition at a later age.

Pre-eclampsia has three main symptoms: hypertension, proteinuria and edema. There is also a variant of pre-eclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), in which moderate intravascular hemolysis is associated with an increase in transaminases and thrombocytopenia[2]. While no significant preponderance of hypertension during pregnancy has been found for a particular ethnical group or immigrant population, the condition tends to affect subjects with a family history of hypertension or heart disease, and is more frequent in subjects who are obese, have intolerance to carbohydrates and/or hypercholesterolemia. Women who have been on oral estroprogesterone contraception are also more susceptible[3].

Pathophysiology

Placental insufficiency (Second trimester of pregnancy)

Experimental protocols conducted on animals through immunization against placental extracts demonstrated that acute or chronic placental ischemia can induce hypertension and proteinuria[4]. Brosens et al[5] have reported that pregnant women with placental lesions present hypertension toward the sixteenth week of pregnancy, while pre-eclampsia tends to appear in the third trimester. The condition therefore depends on a defect occurring in the second trophoblastic invasion of the spiral arteries in the myometrium. During the course of this colonization, suppression of the endothelium and of the elastic and muscular tissue occur, with a loss of hormonal receptors, accompanied by passive

vascular – dilatation, which allows the increased blood flow required. If throphoblastic invasion is incomplete or absent, the flow is insufficient leadying to placental ischemia.

Of course, the ischemia of placenta is not simply caused by a mechanical compression of the aorta and/or arteries by the uterus, as occurs in for example twin pregnancies and hydramnics.

The genetic hypothesis appears more likely. Eclampsia, for which there is a familial predisposition, is correlated with a variant in the angiotensinogen gene, and a high number of patients with hypertension during pregnancy have biochemical alteration[6]. Among these are an increase in permeability and cellular Ca^{++} concentrations, already found in red blood cell and platelets, which could activate cellular function processes, thus explaining the increased resistance and hypertension in the periarterial myocells[7,8].

Moreover, the increased cholesterol/triglycerides ratio found in the erythrocytic membranes of pregnant women with hypertension, may condition the greater flow of calcium ion, thus being a biochemical genetic marker, involved in the pathophysiologic mechanism of hypertension in pregnancy[9].

But the immunological hypothesis is the most convincing. During normal pregnancy the immunological system undergoes modifications secondary to an "exchange" between mother and fetus. In the uterus , in the maternal immunocompetent structures reached by the trophoblastic cells as well as in the fetal immunocompetent structures that reach the maternal cells via the blood. The B and T lymphocyte ratio inversion in early pregnancy in favor of B lymphocytes involves the depletion of T suppressor cells, with a consequent increase in B cells, the function of which is to increase the production of antibodies, such as blocking factors. This mechanism would prevent the rejection of fetal structures, that otherwise simulate a heterologous transplant.

Scott and More[11] suggest that in hypertension during pregnancy, on the other hand, there is an altered immuno-tolerance, with an increase in bollo peripheria of T helper lymphocytes and of CD4 cells, with a greater expression of the anti-Tac antigen (CD25), indicating that there is a sustained lymphocytary activation. Also at the level of decidua, an increase of CD4 and CD25 lymphocytes has been found indicating an anomolous local reaction[12]. In this complex condition of partial "rejection" of the fetus an important role is played by the cytokines network[13] and the adhesion molecules[14], which bind the cellular structures, and whose functional expression is alternately stimulated or inhibited. In fine with this hypothesis, apoptosis may also play a key role in the pathophysiology of placental ischemia. During programmed cellular death, in fact, the cell partecipates in its own destruction with the mediation of cytokines and inducer cells[15]. This activity is markedly reduced during preeclampsia and this may explain why during the second trophoblastic invasion the spiral arteries of the myometrium do not undergo the structural modifications that enable an adequate placental flow to be maintanied. The pathophysiological mechanism may be influenced by substances, such as BCL-2, that inhibit apoptosis or substances, such as APO-1 or Fas, that induce apoptosis[16].

Mechanism underlying hypertension (Third trimester of pregnancy)

In the third trimester of pregnancy placental ischemia secondary to defective vascular arborization is followed by a series of anomalies that are testimony to the involvement of the vascular endothelium in hypertensive disease.

A condition of sympathetic vasoconstrictive activity[17] is associated with a greater vasoactive response of the vessels of resistance to pressor hormones such as angiotensin II, with an increase in: the number of receptors[18], the endothelin present on the umbelical cord[19], the reduced release of vasodilatatory substances, such as nitric oxide[20] and prostacyclin, while thromboxan levels are either normal or increased[21]. The activation of hemostasis with thrombocytopenia is also associated with a higher incidence of materno-fetal complications during pre-eclampsia[22]. Biochemical endothelial markers like fibronectin, factor VIII and VCAM-I adhesion molecules are selectively raised in the serum of patients with pre-eclampsia[14].

The main factors may underlie eclampsic vascular disease are placental ischemia and hypertension (Figure 1). The cytokines that modulate the decidual structural variations in the early stages of pregnancy could play an

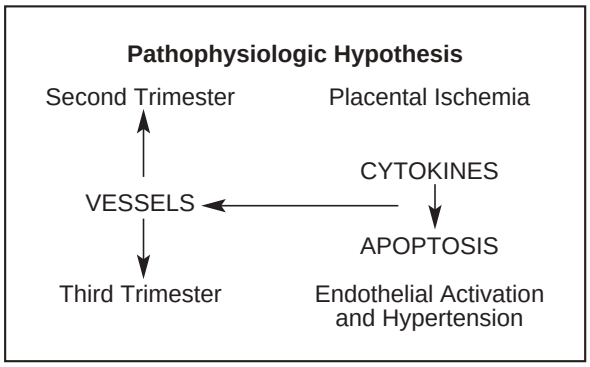

Figure 1.

active role in the endothelial site, thus modifying cellular apoptosis.

In normal conditions, there is a vascular perfect balance between cellular proliferation and death. A selective increase in cell growth with respect to apoptosis, could lead to hyperplasia and, viceversa, an increase in apoptosis could lead to atrophy. In arterial hypertension, on the other hand, there an increase in both proliferation and in apoptosis, with a new balance "at a higher level" and a remodelling of the wall, with a reduced vessel lumen[23].

From pathogenesis to therapy

The disappointing results with therapy confirm that new routes are required to explain the pathophysiology of hypertension in pregnancy. At least fifteen controlled studies have failed to show that anti-hypertensive drugs are beneficial, and confirm that the fetal prognosis is not affected by a reduction in the maternal blood pressure, and that no one drug is better than another. Present findings therefore suggest that anti-hypertensive therapy should be prescribed only if the mother is at a high risk of developing vascular complications (hypertensive crisis, cerebral hemorrhage, left ventricular insufficiency, myocardial infarction). In such cases, treatment with atoxic drugs should be prompt and pressure gradually reduces so as to avoid further compromising utero-placental perfusion.

Several approches have been proposed for the prevention of pre-eclampsia but large controlled multicentre trials are required to ascertain any benefit these preventive strategies may provide.

Calcium supplementation is based on the rationale that epidemiological studies have described an inverse relationship between calcium intake and pre-eclampsia[24].

A meta-analysis of randomized controlled trials has confirmed that calcium supplementation during pregnancy leads to an important reduction in systolic and diastolic blood pressure and preeclampsia[25]. A large, randomized, double-blind, placebo-controlled trial has recently been completed by the US National Institute of Child Health and Development.

In USA, moreover, parenteral magnesium sulfate is the treatment of choice for the prevention and treatment of eclampsia.

European physicians use a variety of narcotics, barbiturates and benzodiazepine derivates. Phenytoin it has been the agent of choice in the UK; it has no sedative side effects. The recent Collaborative Eclampsia Trial comparing magnesium sulfate, diazepam and phenytoin in the treatment of eclampsia has concluded that magnesium sulfate should be administrated to the patients with eclampsia[26].

In several clinical studies on hypertension during pregnancy attempts have been made to prevent placental ischemia, with early aspirin therapy in order to restore the balance between prostaglandins and thromboxan and to induce an antithrombotic action[27]. However, recent metanalyses have failed to demonstrate that anti-platelet therapy has a preventive or therapeutic effect in pregnant women at risk of developing pre-eclampsia[28]. Women at a high risk of pre-eclampsia might be the most likely to benefit but they cannot be identified in advance[29]. Maternal hypertension and proteinuria can be stopped only by termination of pregnancy.

In conclusion, hypertension, a frequent complication in pregnancy, is still the main cause of maternal and fetal morbidity and death. Its pathophysiology, which is not yet clearly understood, involves immunological modulators that could initially induce an apoptocic deficit at the decidual towards the 16th week and, in the third trimester of pregnancy, and modify the balance between hyperplasia and apoptosis in the endothelial site in the vessels of resistance, thus activating hypertensive vasoconstriction.

Further studies are required in order to improve our understanding of these immunological mechanisms: the key to effective therapy may lie in our ability to "interfere" with them in an appropriate way.

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