A NEW HORIZON IN EPH-GESTOSIS Vs TOXAEMIA (PREECLAMPSIA): THE IMMUNOLOGIC FETO-MATERNAL DIALOGUE

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Introduction:

■The name "Toxaemia of Pregnancy" is an old name of the syndrome of EPH-Gestosis and it was discarded among 131 other names. All of these names were unsatisfactory and did not fulfill description of all aspects of the condition.

Introduction:

■It is amazing to negotiate the same terminology that was omitted all through these decades, because no toxins were isolated at that time. Inspite of the fact that I myself prefer this old term as it is in Arabic is frightening for the people, hence force them to seek strict medical antenatal checks, which is not the rule in our developing community. However, preeclampsia is the most popular name of the syndrome.

Introduction:

■EPH-Gestosis was first proposed by **Rippmann (1969)** as a descriptive name of a syndrome of collection of symptoms and signs that occurs specifically in man-kind and high apes' pregnancy (species specific). It occurs more commonly in the first pregnancies. If it occurs in the 1st pregnancy it has a tendency to recur in the 2nd & 3rd at least in 50% of ladies, i.e., the 1st pregnancy is a test of "compatibility / incompatibility of the fetal allograft".

Nomenclature:

EPH-Gestosis is referred to as:

■(E) denotes edema.
■(P) denotes proteinuria.
■(H) denotes hypertension.
■(Gest) denotes pregnancy.
■(Osis) denotes pathophysiology.

Classification: The Modified Gestosis Index ***(El-Kabarity, 2000):***

Etiological Background:

■The etiology is unknown and hence it's named the disease of theories. The end station in its etiology was its description as an vascular endothelial damage that triggers the cascade of various hormonal, biochemical, enzymatic reactions like the cascade of thrombus formation. But, what is the cause behind this triggered cascade?

The Puzzle and the Lip Stick of EPH-Gestosis

■ The genius description of this mysterious condition as to be a syndrome rather than a disease (putting the available data as the pieces of the puzzle game) was first proposed by **Rippmann (1969).** He described the lines of therapy to be like the lip sticks (cosmetic) rather than reversing the pathology and hence it is symptomatic lines of therapy, with the termination of pregnancy as the real curative line of therapy.

The Hypothesis:

■It is felt now, by arranging these pieces of the puzzle that the picture (figure) starts to appear & reforms. Professor **Irma** of Pisa University, Italy **(2002)** has suggested the immunologic basis for the vascular endotheliosis that triggers the syndrome.

■The Immunologic challenge between the fetus together with the placenta as an allograft and his hosting mother with the proved imbalance may point to the triggering factor for the vascular endothelial damage.
■So the station of vascular endothelial damage we all reached now is not the final station. More logically it is the changing point to another train: "The Immunologic Theory of the Syndrome of EPH-Gestosis".

The Immunologic Basis For Evolution Of The Disease:

■EPH-Gestosis is a species specific syndrome to pregnancy of mankind and high apes.
■As the immune response is species specific, a fact that can be seen in the syndrome of AIDS affecting the humans by the HIV from monkeys or the lethal respiratory disease in humans caused by the birds influenza virus, which is not grave to birds.

The Immunologic Basis:

■Being a disease of primigravidas and once it occurred in the 1st pregnancy it has a 50% chance to recur in the 2nd and 3rd pregnancy. A man married for consecutive ladies with repeated occurrence of EPH-Gestosis in all these wives may point to the fetus as an allograft carrying 50% foreign proteins (DNA) coming from the husband and this may point to the immunologic challenge of the allograft (fetus) to the maternal immune system.

The Immunologic Basis:

■The EPH-Gestosis syndrome is more likely to develop in the **"very pregnant"** ladies of multiple pregnancy and molar pregnancy and pregnancies of hyperplacentosis.

The Immunologic Basis:

■Some previous publications caught from the literature documenting the disturbed immune balance in EPH-Gestosis. The involvement of abnormal adaptive immune system in the pathogenesis of EPH Gestosis is well documented by: * Saito et al., 1999 c.
* Rein et al., 2002. * Satai et al., 2002.
* Wilczynski et al., 2002.

The Immunologic Basis:

■Cytokine has a cross talk between the mother and the embryo-placenta unit **(Saito, 2001).** Cytokines are regulatory glycoproteins that can affect virtually every cell type in the body and have pleiotrophic regulatory effects on hematopoietic, endocrine, nervous and immune systems. Chemokines, a member of the cytokine family, mediate leukocyte migration through specific protein coupled receptors in various tissues.

The Immunologic Basis:

■To explain why fetuses are not rejected by the maternal system, **Wegmann et al., (1993)** proposed that the cytokines produced by Th2 predominate during pregnancy and suppress Th1 immune reaction by cytotoxic T-cells that might attack the fetus and trophoblasts.

The Immunologic Basis:

■Interleukin-12 secretion by peripheral blood mononuclear cells is decreased in normal pregnant, subjects and increased in preeclamptic patients (Masatoshi et al., 2002). Moreover, the ratio of interleukin IL-18 to IL-12 secreted by peripheral blood mononuclear cells is increased in normal pregnant subjects and decreased in preeclamptic patients **(Masatoshi et al., 2004).**

The Immunologic Basis:

■**El-Kabarity et al., (2004)** stated that vascular endothelial growth factor (VEGF), interleukin-6 (IL-6) and homocysteine (HCY) all were significantly increased in EPH-Gestotic patients. Moreover these parameters significantly correlate to the severity of the gestosis according to "The Modified Gestosis Index".

The Immunologic Basis:

■**Borzova et al., (2004)** in his presentation of "Differentiation of T-helpers and interleukin-12 production in gestosis" reached to conclusion that there was significant decrease of Th2 and an increase of Th1 in comparison to women of normal pregnancy. These shifts are different from that occur in normal pregnancy in its early stages.

The Immunologic Basis:

■**Trophoblast deportation in human pregnancy: Johansen et al., (1999)** investigated the hypothesis that trophoplast deportation may be the process by which a factor derived from the deported villi, entering the maternal circulation, causing endothelial cell damage. Trophoblasts were found in the uterine vein blood of normal pregnant women with higher levels in preeclampsia. **Saito (2004)** reported a daily deportation of 30 mcg in cases of preeclampsia.

The Immunologic Basis:

■**Trophoblastic injury:** New etiological and pathological concept of preeclampsia. **Kanayama, (2004)** concluded that trophoblastic injury is attributable to the uteroplacental circulation failure.

The Immunologic Basis:

■**Holzgreve et al. (2004) stated that:** "In 1994our group reported the novel finding that preeclampsia may be associated with an increased influx of fetal cells into the maternal circulation.

■They proved in double controlled study that the underlying placental dysfunction leading to increased fetal cell traffic to the mother resulting in development of preeclampsia.

The Immunologic Basis:

■**Recent finding:** the cell free fetal DNA is present in maternal plasma in higher amounts in sera of gestotic women than in normal pregnancy and this increase is positively correlated to the severity of the disease and may offer the possibility of new screening tool to detect women at risk of preeclampsia.

In Summary:

■From the above pieces of knowledge we can suggest that EPH-Gestosis is a description of a **Maternal Immunologic Reaction Imbalance** to the fetus as an **allograft**; carrying 23 foreign paternal chromosomes with foreign fetal DNA and RNA.

In Summary:

■Its compatibility and incompatibility to the maternal tissues can describe the pathophysiologic reaction of acute vascular endotheliosis which triggers the cascade of reactions either **hormonal or biochemical.** Hence, the vasopressor effects with its grave sequels would occur in various maternal and feto-placental tissues in cases of EPH-Gestosis.

Thank You