



## Historical evolution of ideas on eclampsia/preeclampsia: A proposed optimistic view of preeclampsia



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### ABSTRACT

Eclampsia (together with epilepsy) being the first disease ever written down since the beginning of writings in mankind 5000 years ago, we will make a brief presentation of the different major steps in comprehension of Preeclampsia. 1) 1840. Rayer, description of proteinuria in eclampsia, 2) 1897 Vaquez, discovery of gestational hypertension in eclamptic women, 3) In the 1970's, description of the "double" trophoblastic invasion existing only in humans (Brosens & Pijnenborg.), 4) between the 1970's and the 1990's, description of preeclampsia being a couple disease. The "paternity problem" (and therefore irruption of immunology), 5) at the end of the 1980's, a major step forward: Preeclampsia being a global endothelial cell disease (glomeruloendotheliosis, hepatic or cerebral endotheliosis, HELLP, eclampsia), inflammation (J.Roberts. C Redman, R Taylor), 6) End of the 1990's: Consensus for a distinction between early onset preeclampsia EOP and late onset LOP (34 weeks gestation), EOP being rather a problem of implantation of the trophoblast (and the placenta), LOP being rather a pre-existing maternal problem (obesity, diabetes, coagulopathies etc...). LOP is predominant everywhere on this planet, but enormously predominant in developed countries: 90% of cases. This feature is very different in countries where women have their first child very young (88% of world births), where the fatal EOP (early onset) occurs in more than 30% of cases. 7) What could be the common factor which could explain the maternal global endotheliosis in EOP and LOP? Discussion about the inositol phospho glycans P type.

Preeclampsia is characterized by the new onset of hypertension and proteinuria, or any other organ manifestation (including fetal growth restriction), after 20 weeks of gestation in a previously normotensive woman. Eclampsia is the occurrence of grand mal seizures in a woman with gestational hypertension or preeclampsia (Ghulmiyyah and Sibai, 2012).

It has been exactly one century (Zweifel, 1916) that preeclampsia has been first described as "a disease of theories", a statement confirmed by Williams et al. (2007) and Higgins and Brennecke (1998) at the end of the 20th century. Where are we now? This paper wishes to historically describe the major steps in its description, definition, discoveries and comprehension of this strange human-specific reproductive disease and –hopefully, make a convincing case- that indeed giant leaps have been achieved to date to reach the 'top of the mountain'. We think that we are probably closer than ever to reach a

full comprehension of this disease, and that any reader can envisage to see the solution of the preeclamptic syndrome during his/her life time.

At first, preeclampsia (in contrast to eclampsia, curse of human reproduction) is a very young disease: a 20th-century's description. Also, we have to constantly keep in mind the central tenet of this disease: all its acute harmful maternal consequences are completely reversible with the termination of pregnancy. To date, it is well known that the only definitive cure of preeclampsia is yet to deliver the baby and more specifically in fact the placenta (Roberts and Bell, 2013).

We propose in this analysis nine major steps:

1) Eclampsia the "eternal" disease

As far as writings had existed (5000 years ago, 3000 B.C.), we have reports coming from all continents (Lindheimer, 1999): Atharta Veda/Sushruta (India), Wang Dui Me (China), Egyptian Papyrus (Africa), Hippocrates- Celsus-Galen (Europe). Epilepsy is such a spectacular

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event that it has been reported since the beginning of writings (the witness-writer being not a physician of course). Since then, birth-associated convulsions in mothers have constantly followed mankind as a possible eventuality in every pregnancy. Epilepsy-seizures-convulsions have highly frightened our ancestors, and, logically so (muscle contractions, visual disturbances, unusual head or eye movements, mouth alteration, loss of consciousness, and moreover a complete amnesia after the event), have been interpreted in all civilizations as a possession by a bad spirit and/or evil or that somebody had casted a spell on that pregnant woman. Eclampsia has terrorized our ancestors, namely because it happened during the fundamental event of human pregnancy, and also in very young, not to say adolescent, women (almost always during first pregnancies), with also a risk of maternal death in about 1/3 of cases. Mauriceau, at the end of the 17th century (1694) noticed that “primiparous women are at far most risk to develop convulsions than multiparous ones”. He did not use the term of “eclampsia” since the term has apparently been proposed by Bossier de Sauvage only in the mid-18th century (1739) distinguishing this maternal event from epilepsy (Bell, 2010; Chesley, 1984). We have recently proposed (Robillard et al., 2017a) that a grave dated of 28,000 years B.P. (“the human most ancient mother” ever found by paleoanthropologists, a 20 years old woman buried with her baby in her womb estimated at 8 months gestation) might well have died of eclampsia (23,000 years before the historic period, i.e. the invention of writings).

2) Tremendous leap: discovery of proteinuria. The emergence of the concepts: “toxemia” AND “pre”-eclampsia, 1840-43

In the era that midwives and physicians had a quite fatalistic approach concerning the inevitable, unpredictable (and incomprehensible) risk of developing eclampsia, the mid-19th century did see the fundamental discovery of proteinuria. We will refer also in this paragraph to the Mandy Bell’s (2010) and Leon Chesley’s papers (1984).

Coming back to the mid-19th century, eclampsia, with proteinuria, was therefore also linked to renal diseases (globally called “Bright disease”). Even while Demanet noted a connection between edematous women and eclampsia in 1797 (Chesley, 1978), it was Pierre Rayer, a Frenchman, in 1840 who described the presence of proteinuria in eclamptic women (Rayer, 1840). Because of the reversibility of the syndrome after delivery, in 1843 John Lever, an Englishman, and, one month later, JY Simpson, a Scotchman, specified that it was indeed a disease different from the Bright syndrome (Lever, 1843, Simpson, 1843). Nonetheless, this discovery widened the vision of eclampsia, as 2/3 of proteinuric women did not end in convulsions, but it also proposed an association with something else (“toxemia”, and, therefore appeared the concept of “pre-eclampsia”). It must be finally brought to the credit of an Irishman, also in 1843, R Johns that he described the premonitory symptoms of eclampsia in women presenting proteinuria (Johns, 1843). These were exactly the same signs which we teach our students or midwives nowadays: headache, temporary loss of vision, severe pain in the stomach etc.... (Bell, 2010). It has been already well known since Mauriceau (1694) and De la Motte (1722) that delivery has a beneficial effect on convulsions (Chesley, 1984; Bell, 2010). You may imagine the reflections and apprehension of our masters at this time, when they had to manage a term pregnant woman with term proteinuria.

3) Giant leap: the discovery of hypertension, 1897–1903

It was only after Riva Rocci’s discovery, a young 31 year old Italian physician, of the inflatable arm-band in 1896 that blood pressure measurements entered in clinical practice. Vaquez in France in 1897 is credited with the discovery of eclamptic hypertension (Vaquez, 1897), followed few years later in 1903 by Cook and Briggs in the USA (Lindheimer, 1999). At that stage we realized that the “eternal eclampsia” was indeed only the tip of an iceberg: approximately 10% of human pregnancies present with gestational hypertension (therefore reversible), of which 3% evolve to preeclampsia (proteinuria), and, without medical intervention, around 1% suffer of eclampsia. The 20th

century followed with a comprehensive exploration of the epidemiology of hypertensive disorders of pregnancy achieved by tremendous major textbooks all along the century (Robillard et al., 2017b), with the essential motto: preeclampsia, “disease of primigravidae”. Many examples have been analyzed in a preceding paper (Robillard et al., 1999).

4) Another giant leap: the discovery of the human-specific deep trophoblastic (haemochorial) implantation and its failure in preeclampsia, 1970’s.

In the early 1970’s, Brosens described that in humans, contrarily to other mammals (some 4300 different known species), the trophoblastic invasion was very deep, invading not only the decidua but also 1/3 of the uterine muscle (myometrium), but also that this deep trophoblast invasion was associated with a complete remodeling of the spiral arteries (Brosens et al., 1972). This very invasive process indeed lasts several weeks until the end of the first trimester (14th-16th week gestation), and in contrast with most other mammals (except perhaps the hominoid great apes, our cousins) where invasion occurs only in the first one or two weeks after implantation. Brosens and Pijnenborg proposed the concept of “double wave” implantation (Pijnenborg et al., 1980). They described that in preeclampsia, there was a defect of the second wave of this deep invasion in humans and that, for the rest of the gestation the trophoblast thus remained in a state they defined as “shallow implantation”. This first allowed to understand two facts: the explanation why this strange disease is essentially human (isolated reports of suspicion of eclampsia have been made for gorillas, but there was never a description of an epidemiological phenomenon as it is in humans, there is absolutely no teaching on eclampsia in veterinary schools). It also lead to the comprehension of why preeclamptic women presented hypertension: rising the maternal blood pressure could be a compensatory mechanism to try to bring enough nutrients to the human fetus across the placenta despite the shallow implantation (and even though, in many cases the fetus is in a state of growth restriction).

But the presence of this deep cytotrophoblast invasion in normal pregnancy raised also some fundamental questions. The haemochorial placenta in primates, and in particular this deep invasion in human represents a scenario where the human mother is facing a major immune challenge by what we may very roughly call the “fetal hemi-allograft paradox”. Moreover, besides the deep implantation, the deep trophoblastic implantation also results in a tremendous vascular remodeling with the maternal endothelial cells being replaced by trophoblastic cells inside the myometrium and being directly in contact with the maternal bloodstream, and hence the immune leucocytes. All these processes require direct cell to cell communication between maternal and placental (fetal) cell lineages. This intimate imbrication is less involved in epithelio or endotheliochorial placentae, where the maternal and fetal circulations are separated by at least four or five layers.

This raises two questions: first why the “need” of such an aggressive trophoblastic invasion in humans? A “non-hemochorial mammal like” decidual implantation might have avoided the major risk of preeclampsia/eclampsia in human reproduction. Logically, in an evolutionary view, the answer seems to be: the human fetus needs higher nutritional exchanges with his mother compared with other hemochorial mammals.

One may pose the question: what are the nutritional differences between human fetuses and other hemochorial mammals (per body weight). Obviously, the main difference is the fetal brain development: in humans, in the last trimester of pregnancy 60% of nutritional supplies are only for the fetus brain (as compared with approximately 20% in most other mammals, Martin, 1996). Laurence Cole had already shown in the last decade that, especially in Primates, the different structures of the sugar side chains in hyperglycosylated chorionic gonadotrophin (H-HCG) where the degree of glycosylation correlates with the deepness of hemochorial placentation. Let us quote the paramount recent paper by Cole in Primatology, 2015 (open source) where

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