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Preeclampsia and the 20th century: "Le siècle des Lumières"

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SUMMARY

The authors delineate seven quantum leap forward and, or revolutions having occurred during the 20th century in the understanding of the physiopathology of preeclampsia. First the discovery of the inflatable arm band permitting to measure blood pressure in 1896. Second, the discovery that eclamptic (convulsions), and later "pre"eclamptic (proteinuria) women presented hypertension in 1897 and confirmed in 1903, discovery of the hypertensive disorders of pregnancy. Third, the eight major textbooks published all along the 20th century by delineating risk factors of preeclampsia with the concept of "preeclampsia, disease of primigravidae". Fourth, the discovery in the 1970's that human trophoblast implantation was far deeper than in other mammalian species. Fifth, and a major step forward, description at the end of the 1980's that the maternal syndrome in preeclampsia (glomeruloendotheliosis, HELLP syndrome, eclampsia) could be unified in a global endothelial cell inflammation. Sixth, the epidemiological descriptions in the 1970–1990's that indeed preeclampsia was a disease of first pregnancies at the level of a couple ("primipaternity concept"), leading to an explosion in immunological research in the last decade, beginning in 1998. Seventh and finally, in the search for the "factor X" explaining the vascular inflammation in preeclamptic women (inositol phospho glycans P-type were described in 2000, while soluble Flt-1 and S-endoglins have been clearly predicted since 1997). The majority of the seeds or findings have been grounded or realized in the 20th century. Indeed, for preeclampsia, the 20th century has been le "Siècle des Lumières" (the Enlightments).

In a prestigious end-of-20th century (1997) statement of the art on preeclampsia [1], one could read: "Early scholars, having made some very accurate descriptions of pre-eclampsia/

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eclampsia…raised the notion that this disorder is due to a toxin, and realized that delivery was the only cure, would be disappointed to watch us approach the end of this century with few further advances." [1]. This pessimistic comment may deserve today a response according to the current comprehension of this strange disease, a plague apparently specific of human reproduction, since we are probably closer than ever before to come to a full comprehension of its mechanisms. Indeed, we wish to propose that the 20th century has been the one to understand many clues and when very important quantum leap forwards and major steps occurred in such a process.

The first 20th century's revolution was invention in 1896 of the inflatable arm-band, with immeasurable consequences, by a 33 year old Italian physician, Riva-Rocci, permitting to measure blood pressure on a daily clinical practice in all patients [2]. Second and consequently, very quickly, after Vaquez in 1897, in 1903, two American obstetricians, Cooks and Briggs described that eclamptic patients presented abnormal high systolic pressure at delivery (the measurement of diastolic pressure has been accomplished only in 1906 by Korotkoff). Very soon after, it has been verified that hypertension existed also in "pre"-eclamptic patients. Existence of a proteinuria in pregnant patients, often associated with edemas had been known since the 1840's, and it had been well noticed that these patients were the ones at risk of eclampsia in approximately 1/3 of cases) [2]. Moreover, there was also the discovery that pregnant women could present a pregnancy-transient-hypertension without necessarily evolving towards preeclampsia. The well-known eclampsia (convulsion, with a specific interest on women giving birth, likely the first human disease ever described in writings of all cultures, and in all continents, since their beginning 5000 years ago) [2] has been understood by then to be literally the tip of an iceberg (1/10): the hypertensive disorders of pregnancy (HDP). In this light, by its discovery, pregnancy associated hypertension, and pre eclampsia although having always existed in humans may be considered as a "20th century disease".

A third 20th century's paramount step was when the obstetricians confronted with the "gestational hypertension" problem had no other resources than to compellingly and patiently accumulate clinical evidences and delineate epidemiological risk factors differentiating preeclampsia from essential hypertension. And, indeed, our masters did a "pharaonic" work, regularly summarized in the major textbooks all along the century (Kosmak, 1931; Dieckmann, 1952; Davies, 1971; Chesley, 1978; MacGillivray, 1983; Lindheimer & Chesley, 1999) [2–8]. This led to the 20th century's dogma: Preeclampsia (and HDP) is a "disease of primigravidae". This is also summarized by Leon Chesley's testament in 2000 when he stated in a paper published a few weeks after his death [9]: "I would suggest that Editors reject any study of preeclampsia that includes multiparous unless they are analyzed separately", emphasized by the Editor's comment: « Eclampsia and 'true' preeclampsia are chiefly diseases of primiparous women, whereas in multiparous women eclampsia is more likely associated with underlying chronic hypertension ». This statement finalized the loop initiated in the 17th century concerning eclampsia by Mauriceau ("Traité des femmes grosses", 1694): "primiparae are by far at more risk of convulsions than do multiparae" [2].

The fourth 20th century's revolution: the discovery in the 1970's initiated by Brosens & Renaer [10] and established by Pijnenborg & Brosens [11,12] that humans among the 4300 different mammalian species were likely the ones who presented the deepest trophoblastic invasion in a far longer process than most of other haemochorial placentae (until the end of first trimester of pregnancy, at 14–16th week gestation, i.e. 1/3 of gestation!). Moreover, this happens with an haemochorial placenta and thus establishes intimate cellular relationships between the mother's tissues and the –physiologically– half foreign trophoblast ("semi-allograft"). A key point was that in preeclampsia (in particular when associated with intra uterine growth retardation) this deep implantation was deficient ("shallow invasion" concept). This allowed to understand two major issues: a) hypertension in women was then seen as a compensatory mechanism to try to overlap the shallow implanted placenta and deliver the maximum of nutrients to the foetus and b) this quasi-human specificity explained why there was so far no fully satisfactory natural animal model for eclampsia/preeclampsia in other mammals, as the status of the great apes in that respect remains nowadays poorly explored.

A fifth 20th century's paramount advance was the discovery by Roberts, Taylor and Redman [13,14] that almost all, if not all maternal manifestations in preeclampsia are due to a global endothelial cell disease, in particular affecting specialised endothelial cells: glomerulus (glomeruloendotheliosis), hepatic Kupfer cells (HELLP syndrome) and cerebral choroid plexus cells (eclampsia). It was then the Oxford group demonstrating that this endothelial cell dysfunction was part of a more systemic maternal inflammatory syndrome [15].

The sixth 20th century's revolution occurred in the late 1970's, and the data were confirmed in the mid-1990's: a protective effect of a first pregnancy against subsequent reoccurrence was described. Moreover, HDP were much less prominent in primigravid women who conceived after a period of long sexual cohabitation by Marti & Herrman in 1977 [16]. In the same vein (Lancet, October 8th, 1994) [17], these complications have been described in women with a short period of sexual cohabitation such as multi-gravid women who have changed their male partner, these women displaying the same disease patterns those of primigravidae [17,18]. These facts suggested that HDP/preeclampsia were in fact also a "couple disease" [19]. It is therefore a disease of first pregnancy in new couples, e.g. if a multiparous woman changes her male partner, she has the same risk as a primigravid woman. This led to the primipaternity concept [20]. The Sixth 20th century's major step forwards were key discoveries in immunology of reproduction (see Table 1). The evidences that uterus is immunologically prepared to implantation by the paramount and unexpected immunological properties of the seminal fluid by Sarah Roberston's team in Adelaide, Australia, dates from 1998 [21]. Furthermore, the discovery occurring "like a thunderstorm in a quiet sky" that Natural Killer cells were key regulators of an adequate implantation/ invasion of the trophoblast and transformation of uterine vessels into spiral arteries by Ann Croy and al dates from 2000 (and the year 2000 still belongs to the 20th century) [22], later confirmed in humans [23].

Seventh, and finally was the search of the possible cause(s) leading to the global endothelial cell disease in mothers and thus explaining all cases of preeclampsia. As a matter of fact, to date a consensus has raised amongst researchers in PE: if there are immunological

implications in the etiology of PE “placental preeclampsia”, all PE features cases cannot be explained solely by immunology (paternity). Many women present this syndrome because they have vascular predispositions (“maternal syndrome” concept). In this domain again, many seeds have been grounded before the turn of the 20th century. For example, important molecules which are still explored in 2018 have been already described such as the inositol phopshoglycan P- type described at first by Kunjara et al in 2000 [24–27], or soluble endoglins and soluble Flt-1 also well-known to be present in maternal bloodstream in preeclampia (2004) [28], have well been predicted at the end of the 20th century as major candidates [29].

To date, in the 21st century, one may feel that we are seriously approaching the answer to the preeclampsia puzzle, ninety per cent of the seeds or findings having been grounded or realized in the 20th century. Indeed, for preeclampsia, the 20th century has been le “Siècle des Lumières” (the Enlightments).

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Table 1

Summary of several historical advances in comprehension of preeclampsia.

Discovery of gestational hypertension in eclamptic women, confirmed afterwards in preeclamptic women	Cooks & Briggs 1903 (discovery of the inflatable arm band in 1896, by Riva Rocci) [2]
Numerous Epidemiological descriptions of risk factors of preeclampsia (major textbooks). “preeclampsia, disease of primigravidae)	Kosmak, 1931; Dieckmann, 1952; Davies, 1971; Chesley, 1978; MacGillivray, 1983; Lindheimer & Chesley, 1999 [2–8]
Discovery of the unique human feature of invasivness of the trophoblast (the so-called 2nd trophoblastic invasion at the end of the 1st trimester of pregnancy)	Pijnenborg & Brosens [10–12]
Preeclampsia as a global endothelial cell disease	Roberts, Taylor, Redman 1989 [13–15]
Epidemiological challenge of “preeclampsia, disease of primiparae”. Description of preeclampsia being a disease of first pregnancies at a level of a couple (“primipaternity model”)	Summarized in Robillard et al 2011 [30]
Major advances in Immunology of Reproduction • Lack of HLA-G in PE (1990’s) • Role of cytokines (Th1/Th2 paradigm) (1990’s) • Immunological role of seminal fluid (TGF β) Tremelen & Sarah Robertson (1998) • Pivotal role of NK cells (implantation and angiogenesis) • B.A. Croy, A. Moffett, S. Hiby (2000–2004) • Dysregulation of angiogenic factors by complement activation Girardi et al JEM 2006 203(9):2165–75. • Role of hyperglycosylated HCG (deepness of implantation) (≈2007), Laurence Cole. • Immunological animal model for PE (Girardi, 2008) • Pivotal role of T Reg cells (≈2010’s)	Redman & Sargent 2010 [31]
In the search of the “Factor X” (cause of the global endothelial cell disease)	IPG-P Kunjara (2000) [24,25], Soluble Flt-1 Ahmed 1997, Levine & Karumantchi 2004 [28,29]