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An essay of reflection: Why does preeclampsia exist in humans, and why are there such huge geographical differences in epidemiology?

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ABSTRACT

This workshop had four main objectives: (A) Trying to look at the preeclampsia (PE) problem "from the Space Shuttle": why preeclampsia has emerged in humans (a specific human reproductive feature among 4300 mammal species)? (B) *Epidemiology*: there are major geographical differences concerning early onset PE and late onset PE throughout the world. (C) *Vascular*: The very promising use of pravastatin in the treatment of the vascular maternal syndrome (based on the metabolism of carbon monoxide (CO), the role of inositol phosphate glycans P-type (IPG-P), a major role in comprehending the insulin resistance phenotype in preeclampsia. (D) *Immunology*: the specialty of these workshops since their start in 1998; our understanding of the role of the immune system and the regulation of the deep implantation of the human trophoblast (and the obligatory compromises between the fetal/placental unit and the mother) have reached a kind of "maturity," following the pivotal studies exploring the biology of repetitive sperm exposure in the female genital tract. The meeting of people who never meet each other in the course of their normal professional lives (obstetricians, evolutionists, geneticists, immunologists, fundamentalist vascular biologists, epidemiologists, anthropologists, neonatologists, etc.) permitted some fruitful reflections to be made again this year.

1. Introduction

This paper tries to recall the four main objectives of the 2014 workshop on Reunion Island:

(A) *Reflection on preeclampsia (PE) in the light ofevolution*: why has preeclampsia emerged in humans (and not in other mammals)?
(B) *Epidemiology*: emerging at the end of the 1990s and reaching a large consensus around 2005–2006, there are two different kinds of PE, roughly before and after the 34th week of gestation, i.e., early onset and late onset PE. Our reflections will show that there are indeed major geographical differences concerning early onset PE and late onset PE in the world.
(C) The obligatory discussion on the vascular aspects of PE leading to global endothelial cell disease in mothers.
(D) The state of the art concerning reproductive immunology and PE.

1.1. Preeclampsia and evolution

Since humans have been able to trace their cultures with the invention of writing 5000 years ago, throughout the world, in Asia (Middle and Far East), Europe (Greece), and Africa (Egypt), there have been reports of terrifying events at the time of giving birth of convulsions (often resulting in the death of the young parturient, and therefore the newborns), i.e., eclampsia (Lindheimer et al., 1999). The invention of writing is by definition the beginning of written history, and if human history is seen on a 24-hour time scale, written history started at 22:34 of the accepted (minimum) existence of *Homo Sapiens* of 100,000 years (agriculture occurred at 21:36, Jesus Christ–the present international calendar – at 23:31). Humans have lived for 22:34 min in "pre"-history. Of course, there are no formal medical reports of epileptic seizures, in the "medical literature," since physicians did not exist as such. But convulsions are such a spectacular event that you do not need to be a physician to make the diagnosis, and these convulsions have been interpreted in all cultures as a sign of being possessed by bad spirits or, later, by evil. To illustrate the terror that convulsions at birth provoked in our ancestors, we have as an example a semantic relic in modern French slang: one of the words for "to die" is: "*clamser*" or

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"*clampser*" (to "clamps"). By logic and analogy, there is absolutely no reason to think that eclampsia appeared in the human species at 22:34, but clearly the condition has existed at least since the beginning of *Sapiens* speciation. Serious demographic evaluations have calculated that, since the beginning of *Homo sapiens*, 100–108 billion humans have existed on earth (40 billion during the last 2000 years) (Haub, 2002). Consequently, it is easy to calculate that, since the beginning, the human species has had to deal with approximately one billion (1000 million) cases of eclampsia (the natural human rate of eclampsia on a global scale, without medical interventions, is known to have been around 1% of human births until the 1950s in developed countries), 3–5 billion cases of "pre"-eclampsia, and around 10 billion cases of "simple" gestational hypertension. Nowadays, according to WHO evaluation 500,000–700,000 cases of eclampsia occur every year (95–98% in developing countries), the burden of preeclampsia and eclampsia being some 4 million births inducing approximately 50,000 maternal deaths (Ghulmiyyah and Sibai, 2012).

Eclampsia/preeclampsia is a specific feature of the human species. There have been some case reports of pregnant gorillas with seizures, but no substantive support for a formal diagnosis of gorilla eclampsia. Placentation in humans and the great hominoid apes is characterized by a very deep endovascular cytotrophoblast invasion of the spiral arteries. This deep cytotrophoblast invasion extends remodeling of the spiral arteries as far as the inner myometrium (Carter et al., 2015).

We have previously hypothesized (and it has not been formally challenged to our knowledge) that the only possible explanation for the "necessity" of this deep, endovascular cytotrophoblast invasion is the huge extended nutritional needs of the human fetus (Robillard et al., 2003). The ratio brain/body weight of the human neonate (fetus) needing 60% of nutritional exchanges between the mother and the fetus in the last trimester of pregnancy is exceptionally high when compared with the typical 20% in other mammals (Martin, 1996). The only major contest is probably the brain size of the dolphin fetus. However, it should be noted that dolphins have an epitheliochorial placenta. Indeed, in placental mammals, we have three kinds of placenta. Epitheliochorial (pigs, horses, dolphins, etc.) and endotheliochorial (cats, dogs) placentae represent a physical barrier between the mother and the fetus (epithelium or endothelium). This feature is very different from hemochorial placentae (rodents, primates, humans), where the two worlds, mother and fetus, are physically integrated, with trophoblast cells (half paternal) being directly in contact with maternal tissues.

This may suggest that if the human species in phylogeny had "chosen" to have an epitheliochorial placenta (and it might have been possible, see Eliott's paper in this issue), the preeclampsia problem would not have existed.

In the light of this, we started the workshop with the presentations of Gérard Chaouat, Michael Eliott, and Sonia Chelbi. Sonia brought us the genetic – epigenetic generation view of the problem in populations in the long term ("Why preeclampsia still exists") (Chelbi et al., 2013). Gérard reminded us that placentation is not only a mammalian specificity, but has existed for eons, including in invertebrates, and in some fishes and reptiles(!), and discussed the evolution of NK and Treg cells in phylogeny (Chaouat, 2013). Michael Eliott taught us (amongst other features) that, in phylogeny, the hemochorial placenta (ours) is the rule and endothelial or the epitheliochorial placentae are the exceptions. Moreover, for evolutionists, comparative data in mammals suggest that placental invasiveness is associated with variation in fetal brain growth rates and newborn/adult brain–body allometry.

1.2. Epidemiology

Recently Rasmussen et al. (2014) reported that in Norway, 76% of PE cases occur there at term (>36 weeks gestation), and 90.3% after 34 weeks! These data were based on the exhaustive national data of the birth registry of Norway during the period 2007–2010. These results were identical during the 12-year period 1999–2010 (679,000 pregnancies). We also have similar patterns in other settings, such as in Japan (Shiozaki et al., 2013). Silvia Iacobelli in this issue presents data that attempt to synthesize international literature.

The first author has been working on preeclampsia for 25 years, and more or less naively thought that everybody was speaking of the same thing when meeting colleagues on different occasions. Being an epidemiologist, but also a clinician and neonatologist, and having spent his whole career working in tropical countries (Guadeloupe, French West Indies, Tahiti, French Polynesia, and Reunion, Indian Ocean), he had been teaching younger physicians for decades: "there are two plagues in neonatology: multiple births and preeclampsia" (see Table 1). The perinatologists (obstetricians and neonatologists) have to deal with a tremendous rate of prematurity in PE (e.g., looking at Table 1, 24% of cases of PE involve very low birthweight <1500 g, 10% below 1000 g). A young Norwegian neonatal intern would probably not dare to contradict the preceding statement, but would rather think that with 90% of babies born after 34 weeks, PE is obviously (at least nowadays) not a major neonatal public health problem.

The explanation could be the now well-accepted heterogeneity of preeclampsia. It was the work of Chris Redman and Ian Sargent in

Table 1
Morbidity and mortality of the "two plagues in neonatology" (preeclampsia and multiple pregnancies) compared with singleton new-borns. Fourteen-year experience of the entire community of the Southern part of Reunion Island, 2001–2014. In a community where early onset preeclampsia is epidemiologically predominant, preeclampsia is the major morbidity risk in new-borns. All comparisons in this table have a p value <0.0001.

	Preeclampsia singletons $N = 1307$	Controls singleton newborns $N = 55,580$	Oddsratios [95% CI] (PE vs. singletons)	Twin new-borns PE excluded $N = 2300$	Odds ratios [95% CI] (twin vs. singleton controls)
Prematurity rate < 37 weeks	794 (60.7)	5522 (9.9)	14.0 [12.5–15.8]	1444 (62.8)	13.5 [12.3–14.8]
Grand prematurity < 33 weeks	351 (26.9)	1511 (2.7)	13.1 [11.5–15.2]	426 (18.5)	6.7 [5.9–6.7]
Birthweight < 1000 g	134 (10.2)	697 (1.25)	9.0 [7.4–11.0]	173 (7.5)	6.4 [5.4–7.6]
Birthweight < 1500 g VLBW	314 (24.0)	1212 (2.2)	14.2 [12.3–16.4]	360 (15.6)	6.7 [5.9–7.6]
Birthweight < 2500 g LBW	828 (63.4)	6118 (11.0)	14.0 [12.4–15.7]	155 (67.4)	14.9 [13.5–16.3]
Small for gestational age SGA	378 (28.9)	5757 (10.4)	3.5 [3.1–4.0]	503 (21.9)	2.3 [2.1–2.6]
Transfers in neonatal department	598 (45.8)	3751 (6.7)	11.6 [10.4–13.1]	885 (38.5)	7.5 [6.9–8.3]
In utero fetal deaths	39 (3.0)	418 (0.8)	4.0 [2.9–5.7]	44 (1.9)	2.4 [1.7–3.3]
Perinatal mortality	72 (5.5)	952 (1.7)	3.35 [2.6–4.3]	128 (5.6)	3.2 [2.6–3.9]
Cesareans sections	770 (58.9)	8388 (15.1)	8.1 [7.2–9.0]	1171[a] (50.9)	5.4 [4.9–5.9]
Medically induced deliveries – induced del + C-sections	1201 (91.9)	17,705 (31.9)	24.2 [19.7–29.8]	1458 (63.4)	3.5 [3.2–3.8]

[a] In some cases, twin 1 delivers vaginally, while twin 2 has to be delivered by C-section.