Journal of Reproductive Immunology 133 (2019) 30–36

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

Review article

High incidence of early onset preeclampsia is probably the rule and not the exception worldwide. 20th anniversary of the reunion workshop. A summary

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ARTICLE INFO

Keywords:
Preeclampsia
Epidemiology
Immunology

ABSTRACT

The 11th workshop on Immunology of preeclampsia in Reunion 2018 celebrated its 20th candle In this paper we try to summarize the main tracks of reflections during these two decades. First, of course, the advances in immunology of reproduction in the field of preeclampsia, which was poorly developed 2 decades ago when we first started in 1998. But, this workshop has not been dedicated only to immunology. Second, one of the main reflections has always been, workshop after workshop: "why does preeclampsia exists in humans?" in an evolutionary view, as we have no established natural animal models in the other some 4500 other mammal species. Third, besides the reflections on the biological plausibility of preeclampsia-disease-of-first-pregnancies-at-a-level-of-a-couple (primipaternity rather than primigravidity), i.e. immunology, paternal-maternal conflict, we had to face an apparent conundrum: the human species should have disappeared (almost 40–50% incidence of hypertensive disorders of pregnancy in couples conceiving within the first 4 months of sexual cohabitation). We report then the dialogues we were obliged to have with zoologists who themselves had no clues on our apparent "extravagant sexuality" and strange reproduction (ridiculous low fertility rate of the human female: 25%). Fourth, debates on the main difference between early onset ("rather immunological") and late onset PE ("rather maternal vascular predispositions"). Further, the debate of why high income countries report 90% of their PE being LOP, while other countries describe epidemiologically very high incidences of EOP. Finally, and always present at all workshops, the physiopathology of the reversible systemic maternal vascular inflammation.

1. Introduction

We have chosen the title emphasizing a fact which will be discussed in the paragraph 4 below. The title is important to us as it might explain the relative gap, when we work in tropical areas, between what we read in the literature on preeclampsia (PE) and what we observe. In international literature (from high income countries), late onset preeclampsia, LOP, represents 90% of all PE cases. LOP (after 34 weeks of gestation), even if it is a maternal risk (HELLP syndrome, eclampsia) including future maternal cardiovascular diseases, is not a major public health concern for neonatal outcomes even in middle- and low-income Countries. The frame is totally different in areas where we are overwhelmed by early onset PE (EOP), with dramatic consequences for the mother and the fetus.

This workshop celebrated in 2018 its 20th candle (the first one being held in 1998 in Moorea, Tahiti). It was then time to make a point of what has been discussed in this group during these 2 decades. Since the first event, after some hesitations, we had coined its name as the "INTERNATIONAL WORKSHOP of REPRODUCTIVE IMMUNOLOGY, IMMUNOLOGICAL TOLERANCE and IMMUNOLOGY of PREECLAMPSIA". We have kept it by tradition (and provocation?), but, these workshops tackled also other aspects than immunology only. As a matter of fact, immunologists and immunologists of reproduction never represented more than 30% of the participants at any workshop (see

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https://doi.org/10.1016/j.jri.2019.05.003
Received 29 March 2019; Received in revised form 6 May 2019; Accepted 31 May 2019

Appendix A). Particularly, in each workshop, we also dedicated many discussions on the harmful global maternal endothelial disease (Roberts and Redman, 1993), very strange as it is only cured by the end of pregnancy (and removal of the placenta).

2. Immunology

The necessity of such discussions when we began the first workshop in 1998 seemed evident as in 1996 when we tried by Medline search (PubMed now) the association "preeclampsia, immunology", the answer was: "these two items do not match". But it arose also from 3 facts we had to try to decipher: a) preeclampsia was well known since the 1970's to be associated with a defect of the trophoblastic implantation. Brosens described that in humans the trophoblastic invasion was very deep, invading not only the decidua but also 1/3 of the uterine muscle (myometrium), with a complete remodeling of the spiral arteries (Brosens et al., 1972). Brosens and Pijnenborg described also that in preeclampsia, there was a defect of the "second wave" (lasting until the end of the 1st trimester, 14–16 weeks) 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" (Pijnenborg et al., 1980). b) preeclampsia being supposed to be a disease of primigravidae with no special recurrence in successive pregnancies was challenged by the Guadeloupean studies (Robillard et al., 1994). Preeclampsia remained a disease of first pregnancies but at the level of a specific couple, and not only on the maternal side (Robillard et al., 1999); c) What were then the biological plausibility of these findings? To date, two major hypotheses (which may be complementary): David Haig's paternal-maternal conflict in every pregnancy (Haig, 1993; Varas Enriquez et al., 2018), and the immunological one mainly based on the concept of a necessary long sperm exposure (paternal tissues) allowing a safe commensality between the mother and the fetus. Table 1 summarizes the important steps in immunology of reproduction over the last two decades. Gérard Chaouat in this issue will present his 20-year reflections on the subject. Indeed, workshop after workshop, the proposal of immunological models made significant leaps forward (Chaouat et al., 2005).

3. Evolutionary reflections on the fact that eclampsia/preeclampsia is the plague of human reproduction

This reflection begins with a statement: preeclampsia/eclampsia is one of the rare diseases which has no large-scale natural animal model (we would have then for long found the solution by in vivo experiments, especially for a treatment of the maternal vascular inflammation syndrome). For 3 decades there have been few papers reporting pregnancy convulsions in related or lowland gorillas or even chimpanzees (Stout and Lemmon, 1969; Baird, 1981; Thornton and Onwude, 1992). That convulsions exist in female mammals when they deliver is undoubtable: they can have in very rare occasions epileptic seizures in case of hypoglycemia (after a very long and exhausting labor), or by hypovolemia (in case of a severe per or post-partum hemorrhage), and, at a very large scale in humans: eclampsia (if we let nature do, eclampsia has always represented some one percent of all human births). If we combine the epileptic problem with the "pre-eclamptic" state and their 70,000 maternal deaths every year in our species (WHO, 2015), such a public health problem seems to be spared in other mammal species. This is why, until proof of otherwise, we will reason on eclampsia/preeclampsia being mainly a human disease. Then, what can be the differences between the human placenta (trophoblastic implantation) and those of some other 4500 other mammal species?

One of the major gestational differences between humans and other mammals are the different placentae. Placentae are variously classified: First, the "Grosser classification" (1909, 1927) according to the intimacy of fetal-maternal contact (histological classification), there are placentae with a maternal physical barrier between the mother's and the fetal sides: epithelium (epitheliochorial, pig, horse, dolphin, whales …); endothelium (endotheliochorial, cat, dog, elephant), syndesmochorial (sheep, cow). Our species belongs with rodents, rabbits, primates to the haemochorial placentae where there are no physical barriers between the mother and the fetus. In contrary, the two kinds of tissues are intermixed, and, on the maternal side there are no separating histological layer between the conceptus (half foreign tissue) and her own cells. In evolution haemochorial placentae have been in eutherian mammals the original ones, the "placental common ancestor". Endotheliochorial and epitheliochorial placentae arose later, and especially the epitheliochorial placentae belong to the smallest branch (Elliot and Crespi, 2008) of the some 4500 mammal's species.

Second, another taxonomy: placental classification by their macroscopic appearance (Bernischke, 2012; Chuong et al., 2013). a) Discoid placentae (ape, primate, human and rodents): a single disk shaped placenta. b) Zonary placentae: complete or incomplete band of tissues that wraps around the fetus (cat, dog, elephants, carnivores). c) Cotyledonary placentae (ruminants, sheep, goat): the placenta consists of multiple, discrete areas of attachment between the mother and the conceptus. And, finally d) diffuse placentae (horse, pig, whale, dolphin) where the placenta spreads widely across the entire uterine surface. This allows to these last species to have relatively heavy conceptuses (large nutritional exchanges between the mother and the fetus) while having a very shallow trophoblastic invasion, compensated by a dramatic increase of the surface area of its placental interface.

Concerning eclampsia/preeclampsia-human -disease, we shall then focus only on haemochorial placenta, and the human placenta is the most invasive of the eutherian placentae, penetrating deeply into maternal tissues, even in the myometrium. In humans, trophoblastic implantation is rather a "Panzer division invasion". This is not the case in other primates, where the trophoblast remains located in the decidua. In their fundamental paper Elliot and Crespi (2008) state that fetal brain growth is a key strait in the evolution of mammalian life history, and that more invasive forms of placentation are associated with steeper brain-body allometry. Concerning primates, Cole (2015) showed that considering brain-body size ratio expressed in percentages (1st percentage) and implantation depth in percent of uterine thickness (2nd percentage), for the lower simian primate it is respectively 0.17% and 0.3%, for advanced simian primates 0.74% and 10%, for early hominids brain body size ratio of 1.2% and no data on uterine invasion. In human however the percentages are respectively 2.4% (brain) and 30% of invasion of the uterine wall (and this feature was probably

Table 1
Summary of major advances in immunology of reproduction these last 2 decades.

Major advances in Immunology of Reproduction	Redman & Sargent 2010
• 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) BA.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	
• Pivotal role of T Reg cells (≈ 2010's)	

similar or close in *Homo neanderthalensis* and *Homo erectus*). We had proposed (Robillard et al., 2003a; Chaline, 2003) that the only major difference between humans and other primates was the size of the fetal brain, explaining the extraordinary nutritional needs for the human fetus (in the last trimester of pregnancy, 60% of nutritional supply-exchanges by the mother in only for the fetal brain vs 20% in other species, Martin, 1996). This may explain the very aggressive human trophoblastic invasion. Here, we may have the objection (Elliot, 2016) that there is no need to have a deep trophoblastic invasion to have a big brain per body-size ratio (dolphin, whales). The creature having the largest brain-to-body- mass ratio is *Homo sapiens* (0.024 or 2.4%). Dolphin come next (0.016, which is also the value for *H. habilis*), followed by the apes, especially the chimpanzee (0.006), Chaisson, 2013. However, it is fascinating to notice that dolphins and whales have combined two advantages: epitheliochorial placentae (poor maternal-fetal immunological contacts) and diffuse placentae (enormous surface of exchanges). Humans, having non-extensible discoid placentae, had "no other choice" for very high maternal-fetal nutritional exchanges that to deepen the invasiveness of their trophoblasts. But, having "kept" the original haemochorial placenta, our females have to face serious immunological issues with the non-hidden fetal interface. The human (deep invasive) placenta might not then be the best developed placenta in evolution, because this solution it has huge risk of maternal mortality by eclampsia and postpartum hemorrhage.

4. Complementary reflections on the « Guadeloupean cohort » (Lancet 1994, Fig. 1)

Besides the biological plausibility (Immunology, sperm exposure, paternal-maternal conflict), already discussed we had also to face another immediate problem. In the Guadeloupean findings, logically, the human species should have disappeared: new couples conceiving within the 4 first cycles of sexual cohabitation present for women a very high risk of gestational hypertension (40–50% incidence, see Fig. 1), and during 99% of existence of our species, there was no reliable contraception (Léridon, 1993). Therefore, women should become pregnant since the beginning of sexual relationship (the basic feature in all mammals). The answer came from the zoologists (working at the scale of the 4500 species of mammals) as they were themselves facing a conundrum with absolutely no explanation until the end of the 20th century (Léridon, 1993; Diamond, 1997a; Miller, 2000): why are human sexuality and reproduction so weird when compared with other animals? This is coined as "extravagant sexuality" (Diamond, 1997a; Miller, 2000). In terms of reproductive success, in humans, sexual intercourse occurs at the wrong time in the extreme majority of cases (more than 99% of cases, Diamond, 1997b). This is apparently a monumental inefficiency from a biological point of view and an anthropological and biological puzzle (Léridon, 1993; Diamond, 1997a; Miller, 2000). Left column of Table 2 summarizes the synthesis of the zoologists' puzzles. We must emphasize what is apparently the major mystery: the human female presents a ridiculous fecundity rate (Léridon, 1993): 25% at the peak of maximum fecundity in women in their twenties (15% after 30 years). Two other complementary puzzles: loss of oestrus and concealed ovulation (Table 2, Diamond, 1997a; Miller, 2000). For the Guadeloupean cohort, this was in fact a relief: that in average the most fertile human couples at a level of a population take 7 months to conceive may be linked to the avoidance of the hypertensive disorders of pregnancy (adaptation of our species? see Fig. 1). The right column of Table 2 displays the proposed explanation: this relatively low fecundity rate is protective for becoming pregnant directly after starting intercourse. And thereby (together with concealed ovulation and loss of oestrus) lowering the incidence of PE in first pregnancies. "Extravagant sexuality" is then the biological solution for immunological tolerance induction and might be a smart adaptation allowing a safe and very aggressive trophoblastic invasion (Robillard et al., 2003b).

5. Early onset (EOP) and late onset (LOP) preeclampsia (PE). The « voice of the south »

"Why are there such huge geographical differences in epidemiology?" of EOP and LOP on this planet was in the title of a preceding paper (Robillard et al., 2016). This workshop being held in a tropical area, has always been sensitized by the situation we encounter in developing countries, where we find the vast majority of some 70,000 cases of annual maternal deaths by eclampsia/preeclampsia. This is a major issue. Most of the international literature on preeclampsia (and therefore conclusions) are from high income countries (12% of world births) and they report 90% of preeclamptic cases being LOP (therefore only 10% EOP). On the neonatal side, dealing with LOP (34 weeks onward) is not a major problem, even in poor countries, neonatologists can cope with 2000 g newborns quite everywhere in the world. The

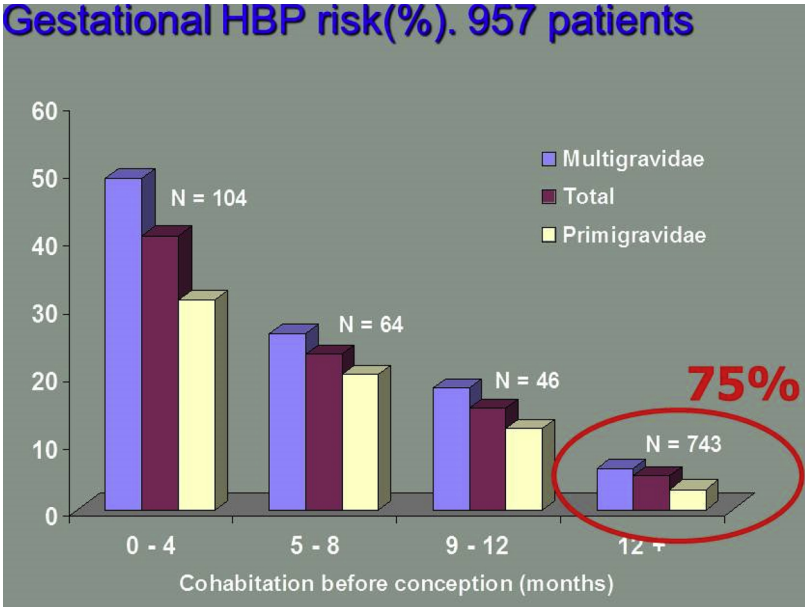

Fig. 1. sexual cohabitation before conception and risk of hypertensive disorders of pregnancy, the "Guadeloupean cohort", Lancet 1994.

Table 2
Biological puzzle of human reproduction for mammalian-zoologists (left column). Proposal of explanation (right column). The human "extravagant sexuality" might be an adaptation allowing a safe trophoblastic (very aggressive) implantation.

ANTHROPOLOGICAL MYSTERIES ON HUMAN "EXTRAVAGANT" SEXUALITY DISCONNECTED WITH REPRODUCTION (Diamond 1997)	EVOLUTIONARY ADAPTATION OF HUMAN REPRODUCTION (and therefore « extravagant » sexuality)
• **Incredible Low fertility rate (20-25% at youngest ages)** • **Loss of oestrus** • **Concealed ovulation** • **No sperm competition at conception** • **Society, nuclear families, universality of marriage** • **Common parental care (birds and not mammals)** • **Testes size of human males (too big as compared with other primates without sperm competition)** • **(Menopause)**	• **« Necessity» in humans of a fœtal big brain** • **Therefore a deeper trophoblastic implantation (nutritional exchanges X 2/per body size)** • **BUT hominids have HAEMOCHORIAL placentae: intimate cohabitation between maternal and paternal (trophoblast) tissues. No physical barrier on the maternal side. Therefore major immunological issues of « compatibility-tolerance ».** • **Maternal habituation to specific paternal tissues through a significant sperm exposure = > a) big testes (impregnation b) low fertility rate** • **Therefore, loss of estrus (impossible with a 25% fertility rate)** • **Concealed ovulation: To remain constantly attractive**

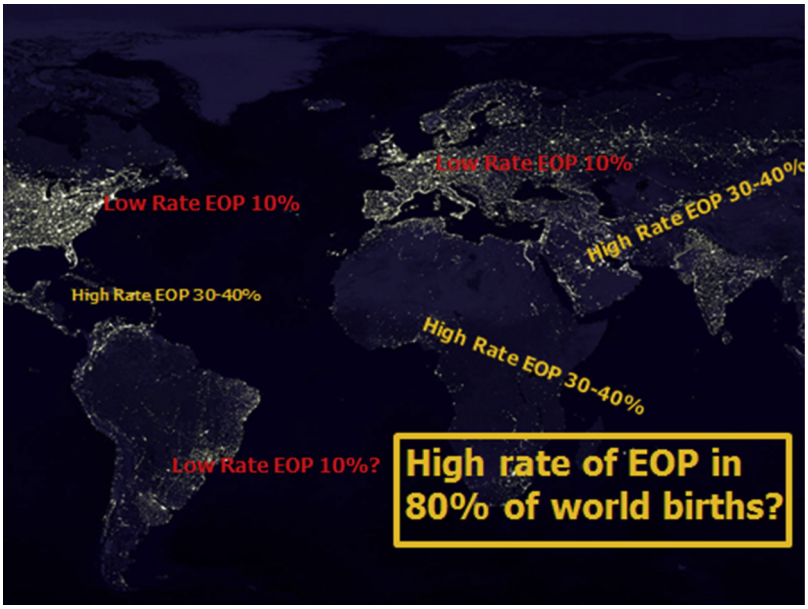

Fig. 2. Our planet as seen by the space shuttle at night: countries which have electricity are also those who do the international scientific research. Those which are in the darkness are also those who publish scarcely in science, while they represent 95% of the 50,000 maternal deaths annually because of preeclampsia.

situation is dramatically different in areas where EOP represents over 30% of PE cases. We have recently published a 8-month survey in the university maternity of Antananarivo, Capital of Madagascar, (Ratsiatosika et al., 2018): 38% of preeclamptic AND eclamptic cases are EOP (60% of perinatal deaths, 5% of maternal deaths in the eclamptic group). In this study, we could find 10 international locations with a similar high rate of EOP: Zimbabwe (58%), Madagascar (38%), China (38%), Cameroon (37%), Mauritius (34%), Thailand (34%), Guadeloupe, Réunion (31%), Turkey (29%), India (26%). After one more year of research, we can add now Indonesia (48%), Taiwan (30%) and Philippines (30.3%). Fig. 2 represent countries with electricity as seen by the space shuttle at night (similar slide than medical research and publications). We have put these high EOP rate countries on the map: aren't then the developed countries with their 10% of EOP the exception and not the rule? Are statements on preeclampsia in the international literature universal? Late onset PE (LOP), i.e. primarily maternal preeclampsia might not be linked with a defective trophoblastic invasion in the first weeks of gestation but rather to a maternal predisposition for inflammation (notably, obesity, food inflammation, chronic hypertension) and/or vascular problems (thrombophilia, obesity, diabetes, antiphospholipid syndrome, dyslipidemia, insulin resistance etc…).

6. Some other aspects of the 2018 workhop : - immunology

Further progress was made on the involvement of T regs in preeclampsia. Shigeru Saito,for his own, demonstrated that clonal Ag specific populations of Tregs are increased in case of pregnancy in human, this expansion being much more important in the decidua than in peripheral blood (where it seems almost non existent in the first pregnancy). However, such a decidual T regs expansion is deficient in preeclamptic women. Interestingly also, reflecting that (1st) allo pregnancy in human (as in mice) is during pregnancy itself a localized "tolerance", the clone types of T regs differs between peripheral blood and decidua. Interestingly enough also, there is a sharing of T cell receptors (TCR) repertoires of decidual effector Treg cells between previous and subsequent pregnancies. Very similar data were obtained in case of miscarriages. In the same vein, Sarah Robertson,after recalling her (and others's) data in mice on the role of seminal plasma, demonstrated the existence of variations amongst fertile men in strength and nature of female tract response induced by their seminal plasma, linked to variations in the balance of inductive factors (eg. TGFβ (Transforming Growth Factor Beta) and inhibitory factors (eg IFN-γ -gamma Interferon). This inhibitory effect is due to the fact that too high INFγ suppresses female CSF-2 induced by TGFβ, a factor predictive

of unexplained infertility in men. These data, for the older attendant, are in line with the"immuno dystrophism" theory of Hill and Choy. Interestingly levels of gamma interferon are linked to CXCL8 (IL8) and LPS, implying a role for microbiome / inflammation. Debra Wohl presented data of importance as far as decidual NK cells are concerned. Her group has been pioneer in showing that decidual NK cells rather than Killers become Builders in the uterus during pregnancy (Gamliel et al., 2018). Now they demonstrate that decidual NK cells "remember" a first pregnancy, with a key role for NKG2 C, which is overexpressed in multiparous women (a key molecule in HLA-E recognition).This over expression is decidual NK cell specific, and independent of age, pregnancy week (and does not require that pregnancy goes to term). This activation leads to a higher expression of pregnancy supporting factors, with a key role for VEGF alpha. Furthermore, these cells appear to be recruited in the uterus itself from local precursors, which are "activated" by pregnancy

Besides immunology, we had also the pleasure to have Erry Gumilar from Indonesia (4th country in the world in terms of population, with 20 maternal deaths per day because of preeclampsia/eclampsia), and Lalita Dawonauth from Mauritius island. We could also confront ideas with Basky Thilaganathan. What he showed us is of paramount importance: a normal pregnant woman has to deal with pregnancy with a similar training than a competition sportsman. During pregnancy the cardio-vascular system manages a BMR (basal metabolic rate) multiplied by two (cyclists of the "Tour de France" deal with X 2.5 BMR), especially in the last trimester of pregnancy. As consequence, at the end of every pregnancy, women have a physiological myocardial hypertrophy similar with endurance sportsmen after 4 or 5 years of regular training. Try then to imagine what occurs when additionally they have to face the important vascular inflammation encountered in preeclampsia. We had however a disagreement that "an alternative explanation for preeclampsia is that placental dysfunction is secondary to maternal cardiovascular maladaptation" (Perry et al., 2018). We challenged then Basky to build a complete model on this perspective taking into account all the known aspects on preeclampsia filling all the lines of the grid proposed by Christopher Redman in 1991 and completed by Robillard et al in 1999 (Robillard et al., 1999). Basky and Ralf Dechend sensitized also the audience that a serious cardiologic follow-up should be necessary in women having experienced preeclampsia during their pregnancies in the following years and decades after delivery.

As in all the past workshops, also the reflection on the possible cause (s) of the global endothelial cell disease (Roberts and Redman, 1993; Redman et al., 1999) in preeclamptic/eclamptic mothers, i.e. the second stage of the two-stage model (Redman and Sargent, 2005). Ananth Karumanchi discussed on what became now the "gold standard" for a detection of preeclampsia before the clinical onset of the disease (few weeks before), Soluble Flt-1/PIGF ratio (Redman and Staff, 2015; Karumanchi, 2016; Cerdeira et al., 2018). However, this test can only be a blood test by vascular or capillary puncture. The discussion went then on a complementary alternative with the same early detection/prediction: IPG-P or inositol phosphate glycans type P (Paine et al., 2006; Williams et al., 2007). The interest of this complementary possible test is that it is a urine test, very simply accessible, cheap (it has been tested on a large scale in Mauritius island also, an emerging country, Dawonauth et al., 2014; L'Omelette et al., 2018) showing an excellent specificity and good predictivity for preeclampsia. This is based on the observation that urinary IPG-P are increased in healthy pregnancy (Scioscia et al., 2012, 2014) but they can treble during clinically acknowledged preeclampsia (Paine et al., 2006) and in most cases weeks before the onset of the disease (Williams et al., 2007; L'Omelette et al., 2018). As a very simple technique (antibody-based ELISA test), it can be developed as a urine strip. There was a consensus with all the participants that it was urgent that such a urinary dipstick should be elaborated as soon as possible to be tested globally in the world.. Gus Dekker presented the SCOPE data (Kho et al., 2009), clearly demonstrating that short sexual relationships are primarily related to lack of spiral artery remodeling, and therefore IUGR, plus or minus maternal features. Dekker also discussed the controversial issues of how to define SGA. Population centiles are clearly not adequate, since preterm babies mostly have a degree of growth restriction. The recently promoted INTERGROWTH centiles are based on the concept of the 'ideally healthy, not poor, not smoking, non-obese, not short, not stressed pregnant woman'. In the SCOPE cohort – consisting of 'healthy nulliparous women – 75% of the women did not fit the INTERGROWTH criteria. The SCOPE data also clearly showed that when using 'INTERGROWTH" centiles, the rate of SGA dropped to 5%. Customized centiles are probably the best centiles, and having birthweight $< 5^{th}$ or 10^{th} centile do correlate better with acute perinatal mortality and morbidity compared with population centiles or INTERGROWTH centiles. The potential risk of using customized centiles is that it introduces the potential of customizing for inequity and social disparity, e.g. as is clear in Australian aboriginal population. Douglas Kell in this issue will also present very convincing data linking microbial connections with preclampsia. This is an interesting aspect of possible association between the preeclamptic maternal global inflammation and the bacterial world (microbiome also?) through lipopolysaccharides (LPS). This may be also a complementary link with the overload of IPG-P in the maternal circulation which may also have a LPS effect (Caro et al., 1996).

In conclusion as stated by the Oxford team in a recent paper (Cerdeira 2017) "there are exciting times in the field of pre-eclampsia", and our group tries to do its best to advance those discussions.

Appendix A. Participations Workhops, Speakers 1998-2018.

	Nb	Years
- Pierre-Yves Robillard, CHU Sud-Réunion	11	1998-2018
- Gérard Chaouat, INSERM Paris		
- Gustaaf Dekker, Adelaide,Australia	10	Except 2000
- Thomas Rademacher, University London, UK		Except 1998
- Christopher Redman, Oxford, UK	8	1998 & 2004-2018 (except 2010)
- Marco Scioscia, Abano Terme, Padua, Italy		2004-2018
- LalitaDawonauth, university Mauritius		2002,2004,2008-2018
- Shigeru Saito,University Toyama, Japan	7	2002-2006,2010-2018
- James Walker, Leeds, UK		1998,2000,2006,2008, 2012-2016
- SiccoScherjon, Groningen, the Netherlands	6	2004,2008-2012,2016,2018
- Debra Wohl, university Hadassah, Jerusalem Israel		2000,2006-2008,2012,2016, 2018
		2002,2006,2010-2014
- Phillippe Le Bouteiller, INSERM, Toulouse	5	2002 to 2008, 2012
- GuillerminaGirardi, King's college, London, UK		2008 to 2016
- Ian Sargent, Oxford, UK		2002,2006,2010-2014
- Fiona Lyall, Glasgow, UK	4	2008-2014

- Annetine Staff, Oslo, Norway		2012,2014-2018
- Ralf Dechend, Charite, Berlin, Germany		2012,2014-2018
- Elizabeth Bonney, University of Vermont, USA	3	199,820,062,016
- Audrey Saftlas, University Iowa, USA		2008-2012
- Sarah Robertson, Adelaide, Australia		200,220,142,018
- Silvia Iacobelli, CHU Sud-Réunion	2	2014-2016
- Mickael Elliott, Cambridge, UK		2014-2016
- Asif Ahmed, Aston, UK		2012-2014
- Francesco Tedesco, Trieste, Italy		2008-2014
- Vicky Clifton, AdealaideAustralia		2010-2012
- Thierry Fournier, INSERM Paris, France		2006-2008
- Leonardo Fainboim, Buenos Aires, Argentina		2008-2010
- Peter Johnson, Univesity Liverpool, UK		2004-2006
- David Hall, Stelenbosch, Capetown, South Africa		2002-2004
- Colin Anderson, Bethesda, USA		1998-2000
- Sandy Davidge, Alberta, Canada		1998-2000
- Franceso Colucci, Cambridge, UK	1	
- Douglas Kell, Manchester, UK		
- Erry Gulimar, Indonesia		2018
- Basky Thilaganathan, St George, London, UK		
- Manu Vatish, Oxford, UK		
- AkiNakaschima, University Toyama, Japan		
- Michaela Golic, Charite, Berlin, Germany		2016
- Paul Moss, University Birmingham, UK		
- EytanBarnea, Chery Hill, NJ, USA		
- Steve Charnok-Jones, Cambridge, UK		
- Sonia Chelbi, University Lausanne, Switzerland	1	2014
- Ronit Gilad, Hadassah University, Jerusalem, Israel		
- Jen Southcombe, Oxford, UK		
- Berthold Huppertz, University Graz, Austria		
- Sandra Blois, Berlin, Germany		
- Elizabeth Triche, Providence, Rhode Island, USA		2012
- Denise Furness, Australia		
- Annemary Hennessy, Australia		
- Ronald Wangl, Australia		2010
- Claire Roberts, New-Zealand		
- Daniel Vaiman, INSERM, Paris		
- Graham Burton		
- JM Foidart, University Liège, Belgium		
- Stefan Gebhardt, Stellenbosch, Capetown, South Africa		2008
- Laurence Cole, University New Mexico, USA		
- Kotaro Kitaya, University Kyoto, Japan		
- AnanthKarumanchi, Harvard, USA		2006
- Karen Rosenberg, Newark, USA		
- Wolfgang Holzgreve, Switzerland		
- Chandana Das, New-Delhi, India		
- Sue Hiby, Cambridge, UK		2004
- John IvarEinarsson, Houston, Texas, USA		
- Malcom Paine, Oxford, UK		
- Ann Croy, University Guelf, Canada		
- De Luca Brunori, University Pisa, Italy		
- Dorota Darmochwal-Kolarz, University Lublin, Poland		2002
- Jean Chaline, University Dijon, France		
- Robert Martin, Field Museum, Chicago, USA		
- Satish Gupta, New-Delhi, India		
- Satoshi Hayakama, University Nihon, Japan		
- KeltonTremellen, Adelaide, Australia		2000
- Michael McMaster, San-Francisco, USA		
- Kathrin Wood, Oxford, UK		
- Phil Baker, UK		
- Des Cooper, Melbourne, Australia		
- Graeme Smith, Canada		
- Scott Walsh, USA		1998
- Rick Schepert, Amsterdam, the Netherlands		
- James Roberts, University Pittsburg, USA		
- Hans Nijman, Amsterdam, the Netherlands		
- Paul Terasaki, San-Francisco, USA		

Conflict interest

Declare no conflict of interest

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