Pre-Eclampsia in SARS-CoV-2 pregnant woman

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Pre-eclampsia (PE) is a hypertensive disorder of pregnancy (>140/90 mmHg), occurring after 20th week of gestation associated to proteinuria and/or other complications. PE is a multifactorial disease whose pathogenes. COVID-19 has the same pathological characteristics. Whereas PE and COVID-19 have overlapping clinical features, a role for SARS-CoV-2 as a leading cause of pre-eclampsia in COVID-19 positive pregnant women has not been clarified yet but there is the possibility to existence of such a link.

Keywords: pre-eclampsia ; SARS-CoV2 ; hypertension RAS system ; covid-19

1. Pre-Eclampsia: A COVID-19 Mimicry

PE is a complex medical disorder which affects 2–8% of the general pregnant population. After 20 weeks' gestation, pregnant individuals affected by PE present several symptoms characterized by de novo hypertension, (ISSHP), proteinuria, and signs of damage to different organ system: the liver, kidneys, the Central Nervous System (CNS) and fetal growth [1]. PE may be a serious disease if not monitored. Its rapid evolution can progress to serious complications, including death of both mother and fetus [1]. There are two types of PE definitions depending on the weeks of gestation: early-onset PE before 34 weeks of gestation and late-onset PE after 34 weeks of gestation. The difference between early and late-onset PE is associated with a different healthy status. In fact, early-onset PE present an impaired placentation in early pregnancy while late-onset PE is associated with metabolic and cardiovascular maternal risk [2][3]. For these reasons, the maternal and neonatal outcomes are different and look like two maternal hemodynamic different entities.

The impairment of placentation during early-onset PE is mostly related to fetus complications resulting in prematurity and growth restriction or in severe cases perinatal death. On the contrary, late-onset PE, derived by maternal pre-existing risks, is more associated with maternal complications. For these reasons and for the different etiologic backgrounds, early- and late-onset PE are often assessed separately in pathophysiologic studies [4]. Untreated PE can lead to serious complications, not only for the baby but even for the pregnant individual. In fact, PE is the main cause of maternal mortality worldwide [5]. Although the first paper in Medline about PE is dated 1914 [6], after more than a century of exhaustive research efforts, it is still not clear how PE may occur in pregnancies with no apparent risk factors [7]. However, one of the most accepted theories is that a poor or inadequate placentation in early pregnancy may result in PE [8]. In fact, since early 1940 placental lesions have been associated with PE [9] and the placenta remained the major focus of PE research for many years. Lately, the role of the placenta has been revised and the role of the cardiovascular system has gained more and more importance; although the placenta is necessary for the occurrence of PE, the problem resides probably in the response of the whole maternal cardiovascular system [3]. Different cardiovascular profiles may account for different forms of pre-eclampsia and other complications of pregnancy in which placental perfusion may be only a part of the problem. Early onset pre-eclampsia associated with fetal growth restriction may be associated to elevated maternal Peripheral Vascular Resistance and low cardiac output; this condition may be at the basis of placental hypoperfusion. The so-called "three stage" model tries to explain pre-eclampsia onset: in the first stage occurring early during pregnancy, an incomplete immune–maternal toleration of the fetus provides an unbalanced intrauterine environment. The second and consequential stage leads to an abnormal placental development, a disrupted spiral placental artery remodeling with different problems such as, first, decreased placental blood flow, then decreased uteroplacental perfusion with risk of ischemia reperfusion injury [10]. The third stage derives from the production of different pro-inflammatory cytokines, which characterizes the second stage [11], and antiangiogenic factors by syncytiotrophoblasts in abnormal placental conditions. The overproduction of all these pro- inflammatory factors lead to the activation of the maternal inflammatory system and endothelial dysfunctions [4]. However, while dysfunctional placenta remains a good starting point to study PE, recent clinical findings show that placental lesions are not specific to PE diagnosis [12]. Moreover, this exclusively placental vision does not appropriately account for those forms of late onset pre-eclampsia with gestational-age fetuses without evidence of placental dysfunction, usually associated to normal or low peripheral vascular resistance and elevated cardiac output. This new point of view led researchers to look for other factors which may be associated with PE. Some predisposing and

risk factors for CVD, like advanced maternal age, obesity, ethnicity, diabetes, and chronic hypertension, have been always considered to be related to poor placentation.

Some recent data have also shown that chronic hypertensive patients may be associated with altered cardiovascular parameters before and at the beginning of pregnancy, long before the placentation process is completed.

The first suggested link between COVID-19 and PE is RAS dysfunction. During pregnancy, there are many functional adaptations in the hemodynamic systems. Plasma volume is increased and to keep blood pressure in normal range, body adaptation involves: decreased sensitivity to RAS [13], increased compliance of the vascular wall [14], and increased NO production by ECs [15]. Moreover, cardiac output is increased together with glomerular filtration [4]. All these phenomena lead to a complex mechanism of adaptation whose impairment leads to PE. For these reasons, pre-eclamptic pregnant woman have lower levels of components of RAS (AngII) than healthy pregnant women do. However, importantly, AngII sensitivity is increased in pre-eclamptic women compared with healthy pregnant women [13]. The importance of AngII adaptation is strictly dependent on its role. In fact, Ang II is a vasoconstrictor agent and lack of AngII adaptation during pregnancy may develop hypertension [4]. The reason why AngII is increased during PE is unknown. One hypothesis leads to the alteration of placental and/or vascular AT1R expression, or heterodimerization of AT1R with bradykinin receptors [16]. Other mechanisms, such as increased angiotensin 1–7 expression, *AT1-R autoantibodies* (AT1R-AAs), and hemopexin could also be involved [16]. That RAS dysregulation is one of the main factors leading to PE is well established [17][18]. In this regard, it has to be highlighted that all the components of renal RAS are also present at local levels at the uteroplacental unit [19][20] and very recently it has been hypothesized that renin and RAS molecules secreted by the placenta may contribute to the development of PE via the activation of intrarenal RAS (iRAS). This phenomenon could rely on exosome shedding, which not only contains RAS molecular components but also microRNAs (miRNAs) which may target mRNA encoding for RAS proteins and ATR1/AAs, agonists of AngII. Both miRNAs and ATR1/AAs lead to the suppression of circulating RAS and to the activation of iRAS [21]. Indeed, a role for mir155 in PE has already been suggested, although discordant results have been reported [22][23] as well as for mir663, upregulated in the pre-eclamptic condition, which targets renin [24].

Although recent studies suggest that SARS-CoV-2 infection does not have a severe course in pregnant women [25], an increased incidence of PE has been reported among pregnant women infected with SARS-CoV-2 compared with the general population. ACE2 upregulation confers protective effects in acute lung injury. Nevertheless, SARS-CoV-2 downregulates ACE2 expression [26]. In women of reproductive age and especially in the second and third trimester of pregnancy, high level of estrogens could be protective by increasing the expression of ACE2 counteracting SARS-CoV-2-dependent ACE2 downregulation. In vivo experimental studies have demonstrated that during pregnancy, the placenta and uterus increase ACE2 levels. ACE 2 generate the vasodilator Ang1–7 inhibiting the vasoconstrictor AngII. During the third trimester of pregnancy, there is an increase in plasma levels of Ang-1-7 [27] which are different between healthy pregnant women and pre-eclamptic pregnant women [28]. This may contribute to the systemic vasodilation and decrease in blood pressure and to other physiological adaptations that occur in normal pregnancy. ACE2 regulates blood pressure and fetal development. Previous reports record that especially maternal viral infections contribute to the development of PE inducing maternal systematic inflammatory response [29]. In fact, PE induces an exaggerated inflammatory response leading to endothelial damage [30]. In addition, severe COVID-19 is characterized by a systemic hyperinflammatory response. The same proinflammatory cytokines typical of the COVID-19 cytokine storm are overexpressed in mesenchymal stromal cells of pre-eclamptic placentas [31][32] Possibly, SARS-CoV-2 intrauterine infection may alter the expression of ACE2. This alteration raises AngII levels in the placenta, inducing PE [33]. Finally, thrombocytopenia (<100,000/mL), which characterizes pre-eclamptic conditions, is a parameter used to evaluate the severity of COVID-19 patients [34].

2. Integrating SARS-CoV-2 Infection and Pre-Eclampsia

The experience with SARS-CoV and MERS-CoV showed different pregnancy outcomes, ranging from mild consequences to high pressure, PE, acute renal failure for pregnant women; from no consequences, to *intrauterine growth restriction* (IUGR) and pre-term birth (PTB) [35][36] to death for newborns [37]. Despite the wide body of clinical and molecular evidence (see above) that underpins an interrelationship between COVID-19 and PE a causative role for SARS-CoV-2 in the development of pre-eclamptic conditions has still to be clearly demonstrated. However, it has been reported that in SARS-CoV-2-positive pregnant women, the incidence of PE was 15.7% with respect to 9.3% of non-COVID-19 pregnancies [38]. This may depend on potential intrauterine SARS-CoV-2 infection, leading to the increased expression of ACE2 and elevated AngII levels in placental villi with subsequently vasoconstriction and restricted fetal blood flow, all phenomena typical of early-onset PE [39]. Data related to SARS-CoV-2 entry molecules ACE2 and TMPRSS2 expression in the human placenta are contradictory. Indeed, ACE2 has been reported to be widely expressed in the human placenta,

in particular in syncytiotrophoblasts, cytotrophoblasts, vascular cells of villi (ECs and smooth muscle cells (SMCs)) in the decidua and even in ECs and SMCs of umbilical cord [40][41]. Furthermore, a cytokine proinflammatory profile (IL-2, IL6, IL-7, and TNF-α) is found both in SARS-CoV2-infected and pre-eclamptic pregnant women, as well as ferritin plasma and low platelet count [31][42]. In particular, a low platelet count (<100,000/mL) is an independent risk factor used to determine the severity in PE [43], but it is also a useful parameter to determine COVID-19 severity [31]. Mendoza et al. report that six out of eight COVID-19 pregnant women with severe pneumonia revealed laboratory test results and biophysical and biochemical parameters typically occurring in late-onset pre-eclamptic women [44]. Moreover, a case report related to the analysis of the placenta of a COVID-19-affected pregnant woman with hypertension, coagulopathy, and PE, who underwent pregnancy termination of pre-viable pregnancy, by dilation and evacuation, at 22 weeks of gestation, demonstrated SARS-CoV-2 infection of the placenta—especially in syncytiotrophoblasts, overlapping ACE2 expression [41]—and the umbilical cord, both by real-time PCR and electron microscopy. Fetal tissues were, however, negative for SARS-CoV-2 at the molecular testing [45], confirming those reports assessing no vertical transmission of the infection. Other studies on the morphological characteristics of placentas derived from COVID-19-affected pregnant women testify a gross malfunctioning of the local vasculature, with diffuse fetal thrombi, arteriopathy of the decidua, and villitis of unknown etiology with respect to normal pregnancies [46]. These findings, together with the demonstration of the direct placenta infection by SARS-CoV-2, may suggest an involvement of ACE2/Ang1-7/Mas axis in determining the vascular pathology of COVID-19 placentas and in the SARS-CoV-2-dependent onset of early onset PE, which, as stated above, is characterized by decreased levels of Ang1-7 [28]. An interesting analysis of the expression of ACE2 and TMPRSS2 in placental tissues derived from non-COVID-19 affected women at different time of gestation and with different pathological features demonstrated an increase in ACE2 and TMPRSS2 in placentas from the first pregnancy trimester, to decline at later stages, suggesting a major susceptibility to SARS-CoV-2 infection early during pregnancy. No changes in the expression of these two SARS-CoV-2 entry molecules—which were barely detectable—have been found at the decidual interface in PTB and pre-eclamptic pregnancies, compared to uncomplicated pregnancies [47]. However, a decrease in ACE2 mRNA was detected in the uterus of a rat model of pregnancy-induced hypertension, when compared to control pregnant rats [48]. Studies on the human placenta performed at the single cell level gave opposite results. In fact, Li et al. observed 32 cell types within a population of 65,000 cells, 4 of which expressed ACE2 at considerable levels, including decidual stromal and perivascular cells, cytotrophoblasts in villi, and syncytiotrophoblasts in placenta. Co-expression of ACE2 and TMPRSS2 was also observed in villous cytotrophoblasts and syncytiotrophoblasts, although TMPRSS2 was found at low levels in these latter [49]. Conversely, another publication reported negligible co-expression of these two molecules both at the single cell level and at single nuclear level in placental cells [50]. However, recently, another work confirmed the expression of both ACE and TMPRSS2 in human placenta at the single cell level, but most importantly, also at the protein level, by immunohistochemical analyses of placental tissues, with different degrees of expression according to the trimester of pregnancy and the cell type evaluated [51]. This last report suggests that, although limited, a vertical transmission of SARS-CoV-2 infection is possible, as recently described [52].

A computational comparison between differentially expressed genes by SARS-CoV-2 infection and PE associated genes [53][54][55] reported that SARS-CoV-2 modulates the expression of several genes typical of pre-eclamptic conditions. Intriguingly, *Gene Set Enrichment Analyses* (GSEA) showed that one of the most affected pathways is related to defective vascular response. Indeed, many angiogenic/antiangiogenic and vasoactive molecules have been found to be deregulated by SARS-CoV-2 [53]. Of note, among them sFlt-1 and *endoglin* (ENG), two antiangiogenic molecules contributing to PE development, are upregulated by SARS-CoV-2. As stated above, sFlt-1 act as a decoy for PlGF, preventing its binding to membrane-bound Flt-1 [56] and impairing its angiogenic function. ENG impairs *Vascular Endothelial Growth Factor* (VEGF) and PlGF activity, cooperating with sFlt-1 [57][58]. Moreover, vasoconstrictive (Urotensin-2, Angioteninogen, Endothelin-1) and pro-thrombotic peptides (e.g., Thrombomodulin, Plasminogen Activator Inhibitor-1, *Sigma-1 ligand 4-phenyl-1-(4-phenylbutyl) piperidine* (PPBP)) are also deregulated [59], possibly suggesting at least one of the molecular mechanism–besides RAS dysfunction-for the vascular malformations detected in COVID-19 pregnant patients.

Another issue to take into account is the presence of genetic polymorphisms predisposing one either to PE or SARS-CoV-2 infection. To date, the one linked to the risk both to develop PE and COVID-19 is the *ACE I/D* (insertion/deletion) polymorphism. This polymorphism consists in the insertion or deletion of a 287 bp sequence in the intron 16 of *ACE* gene. The DD genotype results in higher ACE levels and risk to develop hypertension [60] due to an increase in AngII levels, whereas the II genotype is characterized by low ACE. Despite controversial results, some reports established a relationship between the DD ACE genotype and PE [61]. Intriguingly, the II ACE genotype is inversely correlated both to COVID-19 incidence and mortality [62], suggesting the DD genotype as a predisposing factor to develop the disease and confirming hypertension as an underlying clinical condition contributing to the pathogenesis of both COVID-19 and PE.

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