Clinical & Experimental Immunology
The Journal of Translational Immunology

doi: 10.1111/cei.13311
Clinical and Experimental Immunology REVIEW ARTICLE

REVIEW SERIES: IMMUNOLOGY OF PREGNANCY
Series Editors: Angelo A. Manfredi and Patrizia Rovere-Querini

Overview of procalcitonin in pregnancy and in pre-eclampsia

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Accepted for publication 3 May 2019
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Summary

Procalcitonin (PCT), a precursor for calcitonin, is a prohormone involved in the inflammatory processes, which has been poorly studied in the context of pregnancy. During severe inflammation, PCT derives from almost all cell types, including monocytes and parenchymal tissues, making it a good predictive and diagnostic marker of an inflammatory state with rapidly increased serum levels in inflammation or sepsis. In normal pregnancy, PCT is basally expressed at very low level by decidual cells, even if decidual macrophages, which in normal pregnancy are skewed to M2 macrophages, are resistant to lipopolysaccharide (LPS)-induced production of PCT. As PCT increase is associated with an inflammatory state, several research groups investigated whether PCT can be considered a marker of pre-eclampsia, a pregnancy disease characterized by systemic inflammation. The first aim of this review is to summarize what is already known about the tissues synthesizing PCT, about the stimuli that cause the increase of circulating PCT levels and how PCT acts as a proinflammatory stimulus by itself. Secondly, we will describe the role of this prohormone in normal pregnancy and in pregnancies complicated by pre-eclampsia, highlighting the involvement of the decidual macrophages and the proinflammatory cytokine tumor necrosis factor-α in the modulation of PCT expression in the decidual microenvironment.

Keywords: macrophages, procalcitonin, pregnancy, pre-eclampsia, TNF-α

Procalcitonin: general characteristics

Procalcitonin (PCT), the prohormone of calcitonin (CT), is a protein that consists of 116 amino acids and a molecular mass of approximately 14 kDa (Fig. 1), and was first described in the late 1970s [1,2].

PCT is produced from the (calcitonin-related polypeptide alpha-1 (CALC-1) gene located on chromosome 11 (11p15.2), containing six exons (Fig. 1). The mRNA product is known as pre-PCT, which is further cleaved to generate the PCT (116 amino acid). Finally, this protein is cleaved into three distinct molecules: active CT (32 amino acid), katacalcitonin (21 amino acid) and N-terminal PCT (57 amino acid) [3]. Normally, the CALC-1 gene in thyroid C cells is induced by elevated calcium level, glucocorticoid, calcitonin gene-related peptide (CGRP), glucagon, gastrin or β-adrenergic stimulations (Fig. 1) [3,4]; almost all the PCT formed in thyroid C cells is converted to CT, so that no PCT is released into the circulation [4]. Hence, the PCT level in healthy subjects is very low (<0·05 ng/ml) [5].

PCT as a marker of sepsi or severe inflammation

During severe inflammation or sepsis the serum levels of PCT rapidly increase (>0·5–1 ng/ml) [4]. For this reason, PCT is now generally accepted as a good predictive and diagnostic marker of the inflammatory process and as an additional tool to guide antibiotic prescribing [4,6–8]. The serum PCT levels rise more rapidly than C-reactive protein (CRP) levels and peak within a very short time. Moreover, if the patient responds appropriately to the treatment, the level of PCT returns to normal range faster than CRP, which makes it a more effective biomarker for sepsis [9]. During bacterial

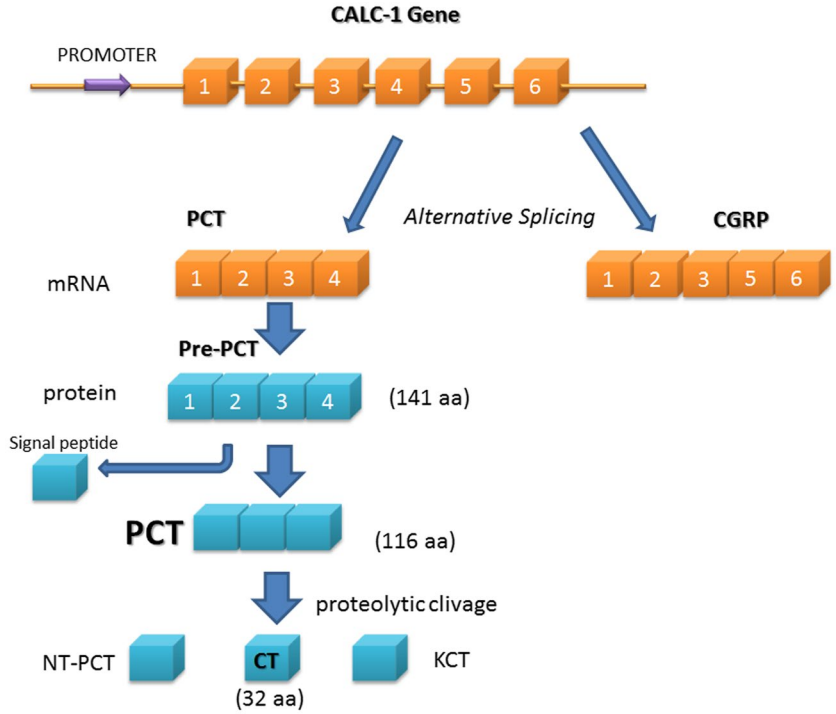

Fig. 1. Schematic representation of the gene calcitonin-related polypeptide alpha-1 (CALC-1) and procalcitonin (PCT) synthesis. CT = calcitonin; NT-PCT = N-terminal PCT; KCT = katacalcitonin. PCT mRNA is produced by alternative splicing of the same gene of calcitonin gene-related peptide (CGRP). mRNA translation leads to the synthesis of a protein of 141 amino acids, named pre-PCT, that is cleaved in PCT.

infection and sepsis, almost all the peripheral tissues have some involvement in PCT production (Fig. 2), including monocytes and parenchymal tissues, making its up-regulation less dependent on one type of cell, tissue or organ [4,10]. Several studies have shown that the induction of PCT during infection is still abundant in the serum of infected patients with total thyroidectomy [5,11,12].

During inflammatory status, PCT is released as an acute-phase reactant in response to inflammatory stimuli, especially those of bacterial origin. In these cases, PCT is produced mainly by two alternative mechanisms: the direct pathway, induced by bacterial endotoxins or other toxic metabolite from microbes (such as DNA, fimbriae or peptidoglycans) and the indirect pathway, induced by various proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-8 [5,13,14]. For example, on one hand, bacteria may induce the expression of a specific transcription factor enhancer or, alternatively, displace a constitutive negative regulator of PCT expression leading to the transcription of PCT [5]. On the other hand, an indirect induction of PCT by proinflammatory cytokines has also been suggested by different studies. In fact, perfusion of patients with TNF-α or IL-6 results in increased blood concentration of PCT [15]. Similarly, intravenous administration of TNF-α and IL-2 leads to rapid and substantial release of PCT in cancer patients [16]. Kettelhack *et al.* showed that isolated limb perfusion with TNF-α leads to an induction of systemic serum PCT [17]. Whang *et al.* confirmed the results in another experimental setting, where the injection of hamsters with TNF-α resulted in robust PCT induction in the serum, similar to PCT elevation seen in experimental sepsis [18]. Balog *et al.* reported that bacteria-induced stimulation of PCT by human leukocytes (monocytes and granulocytes) was inhibited by incubation of these cells with anti-TNF-α monoclonal antibodies [19]. In this experiment, the intracellular PCT expression was up-regulated by an 18-h *in-vitro* stimulation with *Staphylococcus aureus*, known to be able to induce TNF-α synthesis [20]. Incubation of cells with *S. aureus* resulted in TNF-α production by mononuclear and granulocytic cells [19,20]. Incubation of cells with *S. aureus* in the presence of monoclonal antibody against TNF-α resulted in neutralization of the TNF-α in the cell culture supernatant and failed to stimulate intracellular PCT synthesis [19]. These findings demonstrate that TNF-α is the main mediator in the *S. aureus*-induced stimulation of PCT production in monocytes and granulocytes, as the effect could be almost totally abrogated when the cytokine was neutralized by anti-TNF-α [19].

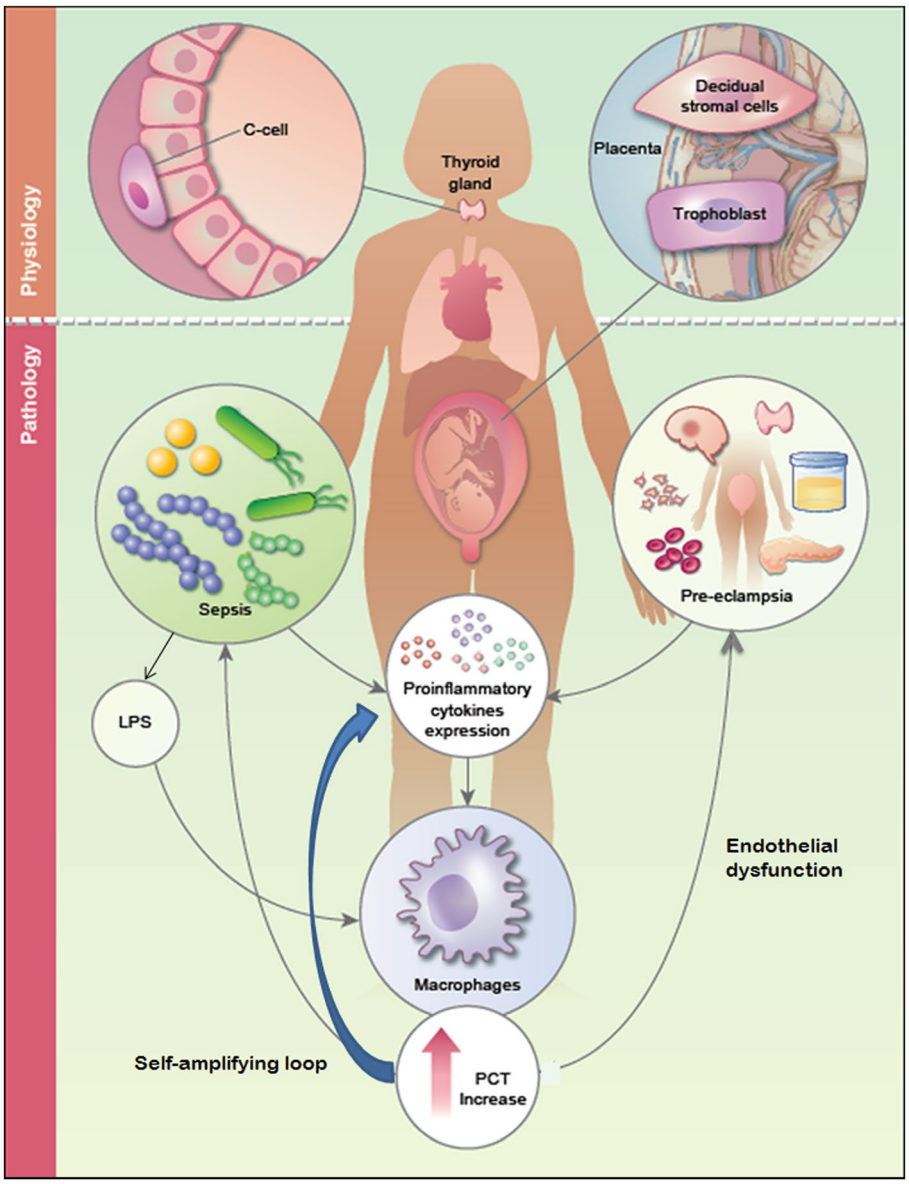

Fig. 2. Secretion and biological function of procalcitonin (PCT) in physiological and pathological pregnancy. In healthy conditions PCT is produced mainly in thyroid C cells from the calcitonin-related polypeptide alpha-1 (CALC-1) gene, but almost all the PCT formed in these cells are converted to calcitonin (CT) so that no PCT is released into the circulation. During normal pregnancy, extravillous trophoblast and decidual stromal cells start to synthesize PCT under physiological conditions, but the presence of this prohormone is destined to remain confined in the microenvironment; probably only a very little amount of this decidual PCT is able to reach the circulation contributing to the small increase of PCT serum level in pregnancy. During sepsis PCT is produced mainly by two alternative mechanisms; direct pathway induced by bacterial endotoxins [lipopolysaccharide (LPS)] or other toxic metabolite from microbes, and indirect pathway induced by various proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-8. Pre-eclampsia is a pathological condition of the pregnancy characterized by an increase of circulating proinflammatory cytokines that can induced directly an augmentation of PCT.

Increased levels of sPCT are, however, attenuated by the release of IFN-γ in response to viral infections, and non-infectious inflammatory stimuli, such as autoimmune disease and chronic inflammatory processes, are much less pronounced, rarely exceeding 0·5 ng/ml [21,22]. Interestingly, during these processes, the mature CT peptide concentration either does not increase or is only slightly augmented [16,23].

Several studies have shown that, in patients with sepsis, higher PCT levels are associated with a greater risk of progression to severe sepsis and septic shock, worsening the survival prognosis. Local bacterial infections and

abscesses do not significantly raise PCT levels [22,24,25]. PCT levels fall with successful treatment of severe bacterial infection and severe non-infectious inflammatory stimuli [4]. Persistent or recurrent PCT elevation in the latter setting should prompt suspicion of secondary infection.

PCT levels may also be elevated in medullary thyroid carcinoma [26] and small-cell lung carcinoma [27], paralytic/vascular ileus exhibiting paraneoplastic production [28] and renal failure [29]. PCT, although useful in bacterial sepsis, has no value in the assessment of fungal or viral infections and shows no response to intracellular microorganisms (i.e. *Mycoplasma*) or in local infections with no systemic response [30]. Similar to CRP, clinical conditions associated with high baseline PCT levels include burns, major surgery and systemic inflammatory processes [30]. PCT can also be used in the guidance of antibiotic therapy. Optimizing antibiotic therapy is important at an individual patient-level but can also minimize emergence of antibiotic resistance [31].

The studies conducted to date are starting to clarify the pathways involved in PCT expression, but little is known about the functions that this prohormone performs at a paracrine and systemic level.

PCT biological functions

The physiological importance and regulation of PCT production are not well understood. Several hypotheses suggest that PCT may be involved in the calcium metabolism, cytokine network and modulation of nitric oxide (NO) synthesis, as well as pain-relieving effects [32]. There are no enzymes in the plasma to break down PCT. Therefore, if PCT enters the circulation it remains unchanged, with a half-life of approximately 30 h, with no evidence of sPCT binding to any cellular receptors [32].

PCT is able to induce, in peripheral blood cells, an increase of proinflammatory cytokine levels, such as IL-6, TNF-α and IL-1β, in a dose-dependent manner [33]. Despite this, and further evidence [34,35], the PCT proinflammatory characteristics are not yet unanimously accepted.

In vascular smooth muscle cells, Hoffmann and co-workers showed an inhibitory effect of PCT on lipopolysaccharide (LPS)-mediated TNF-α synthesis at the transcriptional level [36]. Monneret *et al.* demonstrated that a simultaneous incubation of human whole blood cells with LPS and PCT led to the suppression of LPS-induced production of TNF-α, but the prohormone had no effect on LPS-induced IL-1, IL-6 and IL-8 [37]. Consequently, in this series of studies, PCT was proposed to exhibit an anti-inflammatory effect. The explanation for this apparent contradiction could be that PCT can act as a proinflammatory modulator on the cells that have previously been primed by inflammatory cytokines or LPS [38]. Thus, it appears that cellular targets of PCTs' actions are multiple, including both leukocytes and non-hematopoietic cells.

PCT impair the function and viability of human hepatocytes and endothelium and exert general cytotoxicity *in vitro* [39,40]. PCT with TNF-α induces endothelial barrier disruption and (at concentrations of 0·02 ng/ml) reduces endothelial cell migration and *in-vitro* tube formation. The mechanisms are unclear and need further investigation [39].

The synthesis of PCT by peripheral blood monocytes and tissue macrophages

The amount of macrophages that can contribute to plasmatic levels of PCT is not fully understood. There are few studies on the production of PCT by human macrophages in culture: Linscheid *et al.* has revealed that after 5 days of culture macrophages did not express either calcitonin or calcitonin gene-related peptide (CGRP)-1 mRNA after stimulation with several proinflammatory factors [41]. The study demonstrated the capability of peripheral blood mononuclear cells (PBMCs) to secrete PCT only after an adherence to endothelial cells or plastic surfaces. Other studies showed the synthesis of PCT by PBMCs with contrasting results [5], due perhaps to the fact that within the PBMC population we have immune cells deriving from very different precursors. The presence of PCT has been previously observed by Oberhoffer and colleagues in freshly isolated PBMCs both at transcriptional and translational levels [42]. Herget-Rosenthal *et al.* described a correlation between PBMCs and PCT expression and the concentration of PCT in the blood from controls and patients with advanced chronic kidney disease [43]. Moreover, Balog *et al.* showed that Gram-positive bacteria have the TNF-inducing ability to elevate the intracellular content of PCT in human monocytes [19].

Rami and co-workers demonstrated the capability of human macrophages cultured to synthesize PCT after 7 days of culture under basal conditions; the researchers also demonstrated the incapacity of human macrophages to respond to LPS in terms of PCT expression and production when they are not polarized to M1 macrophages [44]. In this article they have analysed, for the first time, the PCT expression by macrophages cultured in gravid serum, demonstrating a hampered capability to respond to LPS [44].

PCT as a marker of sepsis during pregnancy

Although PCT continues to be found increasingly useful in modern clinical practice, there are only a few published data on PCT in pregnancy [45,46]. As we have already described, PCT seems to be a useful biomarker for severe

bacterial infections, and this could also be the case in the obstetrics and gynecology field, but the use of PCT as a marker of sepsis during pregnancy is controversial, as the general reference values for PCT in pregnancy have not been currently established. More data are needed to also support the use of PCT in obstetrics and gynecology [31], because reference intervals (RIs) for this prohormone, which are essential for clinical decision-making, are lacking. The existing RIs for PCT are mainly based on general adults, not involving pregnant women. A Swiss study provides reference values for PCT during the third trimester, at delivery and in the immediate postpartum period [47]. A recent Chinese study, aimed to establish reference intervals for PCT in healthy pregnant women in the Chinese population, indicated that the serum PCT levels are significantly higher in pregnant *versus* non-pregnant women, and this increase is particularly evident postpartum [48]. These observations can be justified by the placental production of PCT, due to the physiological synthesis by trophoblast and stromal cell of the decidua, as demonstrated by Agostinis and colleagues in a recent article [49].

Several studies have indicated that pregnant serum PCT is not relevant to predict spontaneous preterm birth [50] or for maternal bacterial infection in pregnancy [31]; for instance, during chorioamnionitis PCT is more likely to be released by the fetus rather than by placental tissue [51], indicating that it cannot be a good marker for maternal infection. All these investigations concur to validate the observations that gravid condition (pregnancy hormones and immunity state) can render the main PCT producers resistant to LPS activation. Rami and co-workers, in effect, demonstrated that macrophages cultured in gravid serum, when stimulated with LPS, significantly decrease the level of mRNA for PCT [44]. This effect is due probably to progesterone, because after LPS stimulation progesterone also down-regulates the expression on PCT in human macrophages

Table 1. Summary of the studies aimed to understand if procalcitonin (PCT) is a pre-eclampsia (PE) diagnostic, predictive and/or prognostic marker of PE

Study	Results	Significance
Agostinis *et al.* (2018) (n = 30 PE and 30 HP; predictive study; n = 13 PE and 13 HP)	Diagnostic marker: yes Predictive marker: no	$P < 0{\cdot}005$
Uckan and Sahin (2018) (n = 30 PE and 30 HP)	Diagnostic marker: yes	$P < 0{\cdot}001$
Jannesari and Kazemi (2017) (n =59 PE and 50 HP)	Diagnostic marker: yes	$P < 0{\cdot}001$
Duckworth *et al.* (2016) (n = 143 PE and 280 HP)	Diagnostic marker: yes Predictive marker: no	PCT does not represent a useful diagnostic test for determining the development of PE within 14 days ($P > 0{\cdot}001$)
Birdir *et al.* (2015) (n = 35 PE and 100 HP)	Diagnostic marker: yes Predictive marker: no	PCT does not represent a predictive marker for PE ($P > 0{\cdot}001$)
Artunc-Ulkumen *et al.* (2015) (n =40 PE and 40 HP)	Diagnostic marker: yes Predictive marker: yes	PCT concentrations were significantly higher in PE group ($P = 0{\cdot}001$) and levels were correlated with the severity of the PE. PCT can be used for screening test for PE due to high sensitivity ($P < 0{\cdot}001$)
Lucy *et al.* (2013) (n = 287 women)	Predictive marker: no	PCT does not represent a useful diagnostic test for determining the development of PE within 14 days ($P > 0{\cdot}001$)
Kucukgoz Gulec *et al.* (2012) (n = 64 PE and 33 HP)	Diagnostic marker: yes	$P < 0{\cdot}001$
Can *et al.* (2011) (n = 72 PE and 33 HP)	Diagnostic marker: yes	$P < 0{\cdot}001$
Montagnana *et al.* (2008) (n = 24 PE and 12 with hypertension but without proteinuria)	PCT is a useful prognostic marker of the PE severity	PCT level in the severe PE group was significantly higher than in the mild PE and hypertensive groups. They concluded that rather than being a simple marker, PCT is an inflammatory mediator (such as cytokine)

HP = healthy pregnant.

while 17-β-estradiol increases and human chorionic gonadotropin has no effect [44].

As described previously, most published data about PCT in pregnancy concern the diagnostic and/or prognostic role of this prohormone in pre-eclampsia (PE) [52–55].

PCT as a biomarker of PE

Excessive inflammation at fetal–maternal interface has been associated with gestational complications such as preterm labour, intrauterine growth restriction and PE. In healthy pregnancy, immune regulatory mechanisms prevent excessive systemic inflammation; however, in PE, the regulation of immune responses is disrupted as a result of aberrant activation of innate immune cells [56,57].

PE is a multi-systemic disorder of human pregnancy, characterized by widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation, and can present as late as 4–6 weeks postpartum. It is clinically defined by hypertension and proteinuria, often characterized by elevated liver enzymes, thrombocytopenia with or without pathological edema [58].

The notion that the placenta is the origin of the pathogenic mechanisms on the basis of PE is now universally accepted [58]. Incomplete spiral artery remodeling is considered the initial step in the pathogenetic events leading to hypertension, proteinuria and associated maternal and fetal dysfunction.

As PE is a disorder that occurs around the 20th week of gestation, whereas placental damage begins as early

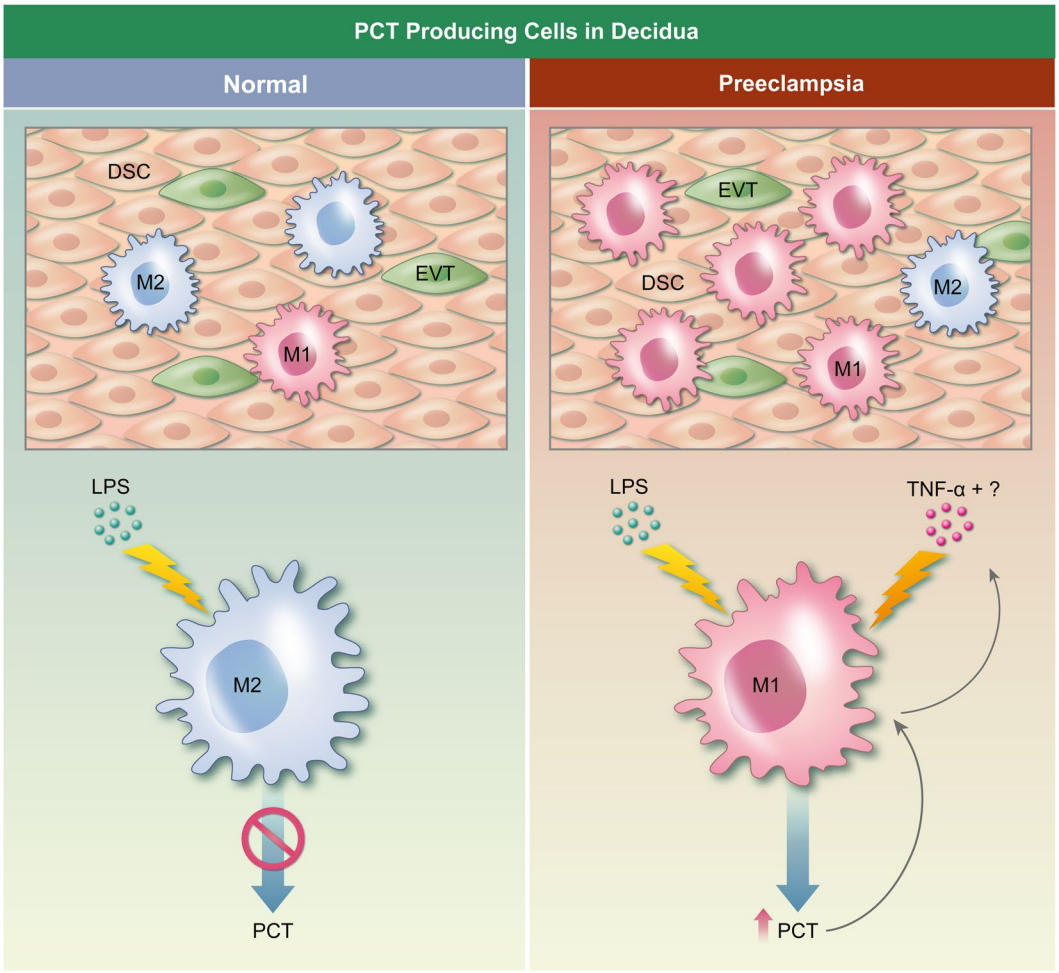

Fig. 3. Model of procalcitonin (PCT) synthesis by decidual cells in normal conditions and in pre-eclampsia. Decidual stromal cells (DSC), extravillous trophoblast (EVT) and macrophages (M) are able to produce PCT in decidua, but the contribution of M in pathological conditions is the most relevant (right panel), while in normal conditions pregnancy hormones block the macrophage response to lipopolysaccharide (LPS) in terms of PCT production (left panel). Tumor necrosis factor (TNF)-α is necessary for the up-regulation of PCT induced by pre-eclamptic sera on macrophages, but it probably requires co-operation with additional factors, still to be identified.

as the first trimester of pregnancy, one of the major challenges in the study of this syndrome is to find a predictive marker. At present, however, there are no plasmatic factors that can be considered PE markers with a predictive value. Perhaps for this reason, numerous studies have been carried out during the last 5 years to verify if the PCT could be an ideal candidate for this role. In Table 1 we report a summary of the studies that aimed to understand if PCT is a PE marker [49,52–55,59–63]. In general, we can deduce that PCT plasmatic levels are increased in PE and its levels correlate with the severity of the disease, but PCT has no predictive value.

In PE, the systemic maternal inflammatory response is enhanced and characterized by a generalized intravascular inflammatory reaction. Intravascular leukocytes, clotting and complement systems activation are involved in the pathogenesis of PE [64]. Several studies have reported higher levels of inflammatory cytokines in PE than those with normal pregnancies [64–67]. For example, IL-6 and TNF-α, potent inflammatory mediators associated with endothelial damage and oxidative stress, are increased in pre-eclamptic patients, whereas no difference in IL-1β was observed [67–69].

The increase of circulating proinflammatory cytokines in PE can be responsible for the augmentation of systemic PCT levels; furthermore, as we have previously discussed, increased PCT levels induce proinflammatory cytokine production that stimulates PCT release which, in turn, triggers the production of PCT itself, causing a positive loop of PCT secretion [5]. Another role that PCT could play in PE pathogenesis is connected with its cytotoxic activity on hepatocytes and endothelium [39,40]. Indeed, it is well known that peculiar characteristics of PE are endothelial dysfunction and liver damage [70]. Regarding the local role of the PCT at the fetal–maternal interface in PE, Agostinis *et al.* detected a strong increase in PCT mRNA expression in PE compared to normal placenta [49]. Even though trophoblast and decidual stromal and endothelial cells produce PCT under physiological conditions, they cannot be considered the unique cell types responsible for the observed phenomenon. Indeed, all tissue macrophages are certainly involved in PCT production in pre-eclamptic decidua, as demonstrated by co-localization of CD68 immunoreactivity with PCT. It is known that PE sera contain specific factors, such as cytokines or protein aggregates [67,71], that are able to modulate the synthesis of several proteins [72]. The main proinflammatory cytokine whose levels have been shown to increase in PE patients is TNF-α [67,73]. In particular, Agostinis and colleagues took advantage of an anti-TNF-α antibody, adalimumab, to hamper the activity of TNF-α [49]. Sera incubated with this antibody completely lose their ability to promote PCT up-regulation but, unexpectedly, TNF-α alone, used at the concentration found in PE sera, was completely ineffective while still able to increase the expression of IL-1β [49,73]. Similar findings were observed by Balog and co-workers, based on the observation that the anti-TNF-α antibody significantly decreased intracellular PCT production by leukocytes stimulated with *S. aureus* [19]. These data together suggest that TNF-α is necessary for the up-regulation of PCT, but it probably requires co-operation with additional factors still to be identified (Fig. 3).

Conclusions

On the basis of the analysis of the data present in the literature we can conclude that PCT, unlike the normal non-pregnant condition, is not relevant to predict maternal bacterial infection because pregnancy conditions (hormones and immunity state) can induce a resistance to LPS activation by the main PCT producers.

In PE, the local and the systemic increase of proinflammatory cytokines enhance PCT production by macrophages; this triggers a self-amplifying loop, in which PCT induces an increase of the proinflammatory cytokine production by macrophages. PCT, on its own, is able to induces direct damage acting on endothelium and consequently exacerbating the pre-eclamptic endothelial dysfunction.

Concerning the clinical and diagnostic importance of PCT, its serum levels can be considered a good diagnostic marker of PE, although PCT cannot be considered a predictive marker of PE onset. Furthermore, PCT emerges as a good prognostic marker of the severity of PE. However, further studies are necessary to confirm this observation.

Acknowledgements

The authors thank Berkan Vural for the English editing. This work was supported by grants from the Institute for Maternal and Child Health, IRCCS 'Burlo Garofolo', Trieste, Italy (RC 20/16, RC 23/18). Fondazione Cassa di Risparmio Trieste to R. B.

Disclosure

None to declare.

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