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Chapter

From Pregnancy Loss to COVID 19 Cytokine Storm: A Matter of Inflammation and Coagulation

Fortunato Vesce

'Dosis facit venenum!'
Paracelso

Abstract

Large scientific evidence achieved during the second half of the past century points to a leading role of inflammation in the pathogenic mechanism of the main pregnancy complications, such as abortion, pregnancy loss, premature delivery, infection, fetal encephalopathy, enterocolitis, pulmonary hyaline membrane diseases and death. Thinking about pregnancy inflammation, one must refer today to the umbalance of the normal mediators of organic functions: cytokins, peptides, nucleosides, prostanoids. Indeed, according to the order and quantity of their release, they are involved either in physiology or in pathology of pregnancy. At this regard, it has been shown that Th1-type immunity is incompatible with successful pregnancy. Regulation of the mediators of maternal functions is largely under fetal genetic control. Assessment of the fetal role derives from studies showing an umbalance of cytokines and plasminogen activator system, an increase of endothelin, a downregulation of adenosine receptors, in the fetal compartment, in aneuploid pregnancies. The resulting functional deviations deal with inflammation, imfection, coagulation, impaired utero-placental perfusion, possibly leading to fetal demise and ominus maternal complications. SARS-COV-2 infection, on the other hand, is characterized by a similar umbalance of the inflammatory mediators, leading to hyperactivation of a type-1 lymphobyte T-helper response, which ends in a possibly fatal cytokine storm syndrome. While SARS-COV-2 infection recognizes a viral etiology, the cause of pregnancy inflammation must be recognized in the inability of the fetus to control the maternal immune response. Therefore, the preventive measures are quite different, although both benefit of a similar anti-inflammatory, antibiotic and anti-coagulant therapy.

Keywords: pregnancy inflammation, abortion, FIRS, SARS-COV-2, IL-6, viral pneumonia, cytokine storm

1. Introduction

Inflammation was defined in ancient times as *'rubor, calor, tumor, dolor and functio laesa'*: redness, heat, swelling, pain and functional impairment. However, in the large majority of the cases, this pathologic process starts before the onset of the clinical signs and symptoms, as a result of an unbalanced release of the

mediators of tissue functions, among which cytokines and prostanoids. Such a release can be triggered by physical, chemical, metabolic, endocrine, infectious as well as mechanical events. Nevertheless, many normal functions are regulated by the same mediators that in other circumstances give rise to inflammation. Among physiological functions ovulation, menstruation, implantation of the product of conception, delivery, healing of the placental site and involution of the puerperal uterus are included. For instance, as regards the onset of parturition, we have shown that receptor ligands for the inflammatory peptide N-formyl-methionyl-leucyl-phenylalanine (fMLP) are present in amniotic fluid. Their levels do not vary during gestation, while they are significantly increased by labour, along with the expression of fMLP receptor in amnion tissue, thus indicating a modulation of the fMLP system by the events of physiological labour, and/or viceversa [1–3]. A detailed knowledge of cytokine and prostanoids involved in the regulation of normal pregnancy is needed to better understand the role of inflammatory mediators in the pathogenic mechanism of gestational complications.

At this regard it must first be considered that the trophoblast itself, i.e. the peripheral part of the product of conception, regulates implantation and placentation. These are a consequence of membrane ligands and receptors, hormone and local factor release by fetal and maternal tissues. There are two kinds of trophoblast, villous and extravillous, the first devoted to fetal-maternal nutrients and gas exchanges, and the second to adhesion of the placenta to the uterine wall and to the modulation of uterine arteries. Indeed, invasion of the uterine spiral arteries by extravillous throphoblast occurs, aimed at progressively increasing the perfusion of the intervillous space. A derangement of this stuctural and functional process leads to different types of complications, including pregnancy loss and maternal life-threatening disease.

In the past it was believed that these vascular changes occurred within the first half of pregnancy, but today it must be admitted that they last until the moment of delivery. From this point of view, pregnancy must be considered an endocrine mediated vascular phenomenon, regulated by cytokines mainly derived from the extra-villous trophobalst itself [4].

Trophoblast regulation is needed because the rupture of the spiral arterioles, with consequent dripping of the maternal blood in which the nutrition villi are immersed, in any other tissue except the uterine wall would trigger an inflammatory reaction aimed at coagulating the blood to stop hemorrhage. How is it possible that this defense mechanism is not activated in physiological pregnancy? As it will be explained, the reason is that extravillous trophoblast itself has the task of transforming the natural maternal TH-1 inflammatory reaction into an anti-inflammatory condition of the TH-2 type [5]. The lack of this transformation, in fact, leads to pregnancy loss and to other complications, such as premature birth, gestosis, fetal growth restriction and related postnatal syndromes [5]. For instance, as regards fetal growth, peripheral mononuclear cells stimulated with trophoblast antigens [6] as well as with mitogen [7] in pregnant women with fetal growth restriction produce higher levels of the pro-inflammatory cytokines IFNγ, TNFα, IL-8, IL-12, IL-18, IL-23 and lower anti-inflammatory cytokines IL-4, IL-10, IL-13 compared with pregnant women with normal fetal growth.

2. The misunderstood concept of ‘maternal tolerance’

Although the scientific literature of the last few decades already contains evidence of the leading role of inflammatory cytokines in the mechanisms of pregnancy complications, it has not yet been completely understood by mainstream

medicine. As a consequence the protective role of glucocorticoids administration is neglected or totally ignored.

Moreover, it has not been understood that physiological pregnancy does not compromise the general immunity of the maternal organism. At this regard, attempts to credit the hypothesis of a reduced maternal immune response are frequently made. A theory of maternal-fetal tolerance proposed that a 'temporary state of maternal immunosuppression' is vital to allow successful implantation and development of the product of conception [8, 9].

Subsequently, a tightly regulated balance between inflammatory and tolerogenic states during the "immune chronology" of normal pregnancy has been affirmed [10–14]. It is claimed that a pro-inflammatory environment predominates during early trophoblast invasion and at parturition, while it turns to anti-inflammatory during the second and third trimesters to allow fetal growth [15].

All true! What needs to be understood is the real nature of this changes. Indeed, it must be clear that it is absolutely wrong to speak of inflammation when a physiological function such as implantation or childbirth is triggered by the same mediators that, in pathologic conditions, would cause inflammation. Their derangement may trigger inflammation: *dosis facit venenum*, as Paracelso stated! It is also reported that dysregulation of immune cells at the level of maternal decidua is implicated in severe complications, including recurrent miscarriage, pre-eclampsia, fetal growth restriction, chorioamnionitis, and preterm birth [16–23].

It is therefore very important to understand the nature of the so called 'maternal tolerance' towards the product of conception, in order to avoid dangerous conclusions. Indeed, it is wrongly claimed that a corollary of this maternal tolerance implies an increased susceptibility to infection during pregnancy. In turn, this misinterpretation has generated the belief that pregnancy carries a high risk of severe flu syndrome which must be prevented by vaccination!

In order to better understand the terms of this matter, it must be briefly recalled that normally the changes in maternal immune system occur only at the uteroplacental level, upon the direct action of the trophoblast. The features of these changes have nothing in common with the immune response to infections. As for the entire maternal organism, the integrity of the immune system is perfectly maintained. Both branches of immunity, that is, the humoral and the cellular, are fully operational during normal pregnancy. A clear example of the integrity of humoral immunity is represented, for instance, by maternal-fetal isoimmunization, i.e. Rh disease. In this pathologic condition the maternal immune system activates the production of antibodies against Rh positive fetal red blood cells leading to anemia, erythroblastosis and possibly to fetal death.

In the lack of a reliable demonstration of an increased incidence of flu and other infectious diseases during pregnancy, one may believe that, although active in Rh disease, the production of antibodies against viruses and bacteria is hindered. On the contrary, in fifty years of my personal clinical experience, I have never detected symptoms or signs of a reduced or ineffective maternal immune reactivity against infection, nor an increased incidence of infectious diseases in normal pregnancy. Moreover, looking at the scientific literature my conviction has been largely confirmed. Hundreds of articles including thousand of patients have been recently examined as far as flu is concerned. Contrary to the opinion of an increased risk and serious complications accredited by World Health Organization (WHO), a significantly lower risk of admission to Intensive Care Unit was registered for pregnant women. Moreover, no significant difference between pregnant and non-pregnant patients was registered, as regards mechanical ventilatory support. Pregnancy did not carry a greater likelihood of maternal death or other severe outcomes compared to either the general population or non-pregnant women of reproductive age. The only

difference between pregnant and non-pregnant was a higher risk of hospitalization in the first, that the Authors correctly ascribed to a better care for motherhood [24].

Surprisingly, however, the above data have been interpreted in the opposite meaning by others, which also reported a disproportionaly high mortality rate in the flu pandemic of 1918 [25]. However, that was before the era of antibiotics, anticoagulants and anti-inflammatory drugs (the safety, preventive and therapeutic power of which is unfortunately still poorly understood today!).

3. How do infections affect pregnancy?

A further aspect of the matter is the influence of infections on the outcome of pregnancy. Indeed, an increased incidence of adverse events following viral infection would speak in favor of a preventive vaccination aimed at protecting pregnancy and the newborn future life.

It has been reported that infectious agents are potentially involved in about 40% of spontaneous abortion [26–28]. On the contrary, recent research failed to show an increased incidence of several infections in spontaneous abortion. The free mother–to-child transmission of the three oncogenic viruses, BKPyV, JCPyV and SV40 has been shown by detecting DNA sequences and specific IgG antibodies in mothers and their offspring in normal pregnancy [29]. The incidence of Human Papilloma Virus (HPV) infection is not increased in spontaneous abortion, and the overall prevalence of serum anti-HPV16 IgG antibodies was found to be 30% in patients with normal pregnancy and 37.5% in those with spontaneous abortion ($p > 0.05$), thus indicating a normal, or even better humoral immunity in the latter [30].

Rubella virus, varicella-zoster, human immunodeficiency virus, adenovirus, cytomegalovirus, herpes simplex virus, human parvovirus, Epstein–Barr virus, enterovirus and respiratory syncitial virus have all been found in amniotic fluid samples, but their mere presence has never been associated with negative human pregnancy outcome [31–34]. Based on the above evidences, it should appear that the gestational setting of human female immune system is towards a better protection against infectious diseases compared to non-pregnant.

Interestingly, however, it has been shown that viral experimental infection of pregnant mice predisposed to the effects of bacterial endotoxin [35]: it is an observation of extraordinary importance to better understand the pathogenesis of bacterial infections. Indeed, it explains that the bacteria normally present in their saprophytic state can become pathogenic as a consequence of a previously produced inflammation.

Accordingly, the onset of human preterm labor is preceded by a systemic fetal inflammation, before the appearance of clinical signs of maternal or fetal infection [36, 37]. It has been stated that an amniotic concentration of IL6 above 11 ng/ml is related to, and defines, the Systemic Fetal Inflammatory Response Syndrome, that is followed by premature birth and by utero-placental infection, with all the postnatal sequelae, including encephalopathy, enterocolitis and the pulmonary hyaline membrane disease.

Of particular importance is to consider what could be the origin of fetal inflammation, in the absence of maternal chronic inflammatory disease, pathogens and clinical signs of infection. Indeed, in primates the events leading to premature delivery seem to progress from experimental intrauterine infection to pro-inflammatory cytokine activation and prostaglandin production, thus triggering myometrial contractions [38–40]. In humans, instead, also the mere inflammation of the chorio-decidual interface is mentioned as a primum movens producing a cascade of cytokines that result in an inflammatory response [41].

Therefore the question is: when gestational inflammation is not bacterial- or viral-induced, where does it come from?

4. Chromosomal abnormalities and genetic inflammatory polymorphisms as a cause of pregnancy inflammation and coagulation

In the absence of chronic maternal inflammatory dysease, the cases with IL-6 rise preceding infection would speak in favor of a functional inflammation arising from the fetus itself. In such cases, based on the above mentioned role of extravillous trophoblast in the control of the local maternal cellular immune response, it can be admitted that the shift from TH-1 to TH-2 type of maternal immunity, normally resulting from the fetal release of an adequate amount and quality of TH-2 mediators, did not take place, due to a failure of the trophoblast to correctly balance cytokines.

In order to confirm this opinion, it was right to investigate the physiological modulators of vascular functions and coagulation, as well as the behavior of cytochines and prostanoids involved in inflammation and smooth muscle contraction, in the fetal compartment of pregnancies with fetal aneuploidy. The reason to chose aneuploid pregnancies was that very often they end in abortion and, therefore, an imbalance of these mediators can be expected.

Accordingly, a significantly increased level of amniotic fluid IL-6, and a decreased IL-8 level in the presence of fetal aneuploidy at the 17th week of pregnancy was registered, while IL-6 concentration was reduced in the maternal blood [42].

Morover, the comparison between euploid and aneuploid pregnancies with respect to maternal serum and amniotic fluid levels of the components of the plasminogen system, showed significantly higher serum levels of urokinase plasminogen activator and its complexed form with type-1 inhibitor in aneuploidy. In addition, in amniotic fluid, tissue plasminogen activator was significantly lower in aneuploidy, whereas type-1 inhibitor was significantly higher in the cases with minor chromosomal abnormalities. In addition, the complexed form of urokinase plasminogen activator with its type-1 inhibitor was 7,53 times higher in aneuploidy [43].

With the aim to shed light on the regulation of the vascular function in pregnancies complicated by fetal chromosomal abnormalities, the potent vasoconstrictor peptide endothelin and the proangiogenic nucleoside adenosine were investigated. Amniotic fluid levels of endothelin-1 were significantly increased in pregnancies with fetal aneuploidy at the 17th gestational week [44]. As regards the adenosine transduction cascade, it is disturbed in Trisomy 21. Indeed, compared to euploid, reduced adenosine receptors, A [1] and A(2B) expression was revealed in chorionic villi and mesenchimal cells [45]. It was suggested that these vascular anomalies may lead to fetal growth restriction, malformation and abortion, well known features of aneuploid pregnancies.

These results, indicative of an umbalance of cytokines, along with abnormalities of vascular function and coagulation in fetal aneuploidies suggest that the related gestational complications may arise from the fetus itself. They support the opinion that the high incidence of miscarriage observed in chromosomal abnormalities can be interpreted as a consequence of inflammation, vascular function impairment and coagulation.

However they may also occur in euploid pregnancy, as possible expressions of fetal genetic inflammatory polymorphisms. These, indeed, are reported to be responsible for harmful inflammatory response in those who possess them. Accordingly, it has been demonstrated that maternal polymorphisms in genes IL-10, MBL, TNFRSF6 and TGFB1 may influence susceptibility to chorioamnionitis [46].

Furthermore, polymorphisms that increase the magnitude or the duration of the inflammatory response are associated with an increased risk of preterm birth, while those decreasing the inflammatory response are associated with a lower risk [47]. Moreover, an investigation on six cytokine genes associated with inflammation, namely IL-1α, IL-1ß, IL-2, IL-6, TNF, and lymphotoxin α, led to the conclusion that common genetic variants in proinflammatory cytokine genes do increase the risk for spontaneous preterm birth [48].

5. Therapy of cytokine umbalance

5.1 Antibiotics

Once it was established that the major obstetric complications arise from an inflammatory process of maternal or fetal origin, the next step was to establish the best way to prevent and cure it.

Several clinical studies showed that ajunctive antibiotic therapy aimed at the delay of childbirth, even in absence of infection, in cases of so called 'idiopathic' threatened preterm delivery, was able to significantly prolong pregnancy [49, 50]. As some antibiotics influence the intracellular level of calcium [51] and phospholipase A2 [52], a calcium-dependent enzyme involved in the regulation of prostaglandin biosynthesis, the question of their possible direct anti-inflammatory action (i.e. independent of the antibacterial effect) was raised. Therefore the effect of ampicillin on the amnionic prostaglandin E2 release was tested, showing a significant dose dependent inhibitory action of the drug on the prostanoid output. Such a result suggested that its use in the therapy of premature labor is authorized even in the absence of infection [53]. Subsequently the inhibitory action of beta-lactamines was compared with that of other classes of antibiotics. Interestingly, it was found that Ceftriaxone and, to a lesser extent, Gentamicin significantly and reversibly inhibit both basal and arachidonic acid- or oxytocin-stimulated amnionic prostaglandin E release. On the contrary, Tetracycline and Erythromycin do not influence prostaglandin E output. The inhibitory effect of ampicillin is potentiated, in an additive manner, by Ceftriaxone, reduced by Gentamycin, and eliminated by Tetracycline and Erythromycin [54]. A further relevant aspect emerges from the research on the novel action of antibiotics mentioned above: the influence of ampicillin on IL-6, one of the TH-1 cytokines able to stimulate Prostaglandin E2 release. The effect of the drug was tested on amnion-like Wistar Institute Susan Hayflick (WISH) cells as well as in amniotic fluid of patients submitted to genetic amniocentesis during the 17th week of their singleton physiological pregnancy. At doses ranging from 10^{-7} to 10^{-4} M, ampicillin decreased IL-6 as well as PGE2 release from WISH cells. Moreover, IL-6 amniotic fluid levels sampled 4 hours after ampicillin administration proved significantly and strongly reduced when compared with those sampled either before or 12 hours after treatment [55].

The effects of the above antibiotics shed new light on their utility not only in the therapy of infection, but also in inflammatory conditions, which often precede it. Indeed, contrary to the widespread delay in the use of antibiotics for fear that they may favor the appearance of resistant bacterial strains (an event limited to particular cases, which can be solved by replacing the drug), those antinflammatory effects support the indication for the early or even preventive use of beta-lactamines, in order to suppress inflammation. Therefore, to this purpose, beta-lactamines can represent the first choise, aimed at preventing the infection of the inflammed tissue. It could be argued that there are other steroidal and non-steroidal drugs to fight inflammation. It's true. But inflammation has many little-known aspects, and here

one talks about the one that precedes and favors the infection, in which the anti-inflammatory action of antibiotics would logically seem preferable to that of drugs without bactericidal activity.

Based on the above considerations, the preventive use of beta-lactamines in invasive prenatal diagnosis was introduced four decedes ago at the obstetrical departement of Ferrara University Hospital. Indeed, amnicentesis, cordocentesis and chorionic villous biopsy, like any other surgical procedure, produce inflammation in the injured tissues: myometrium, decidua amnio-chorial membranes, placenta, obviously resulting in the release of TH1 cytokines and prostaglandins. The reason for choosing beta-lactamines is that they are more effective in reducing IL-6 and PGE2 release compared to other classes of antibiotics, and the in vitro and in vivo evidence already obtained was certainly sufficient to begin with. Later on, the first randomized controlled clinical trial showing the efficacy of antibiotic administration before amniocentesis in reducing the incidence of abortion and premature birth was published [56]. Azithromycin was used in this trial, probably due to its wide bactericidal effect. However it was subsequently shown that in pregnant rats the drug reduces the level of tumor necrosis factor TNF- α and increases that of IL-10, two cytokines with inflammatory and anti-inflammatory action, respectively [57]. It should be noted that the article suggests the use of azithromycin to prevent pregnancy loss 'infection- or endotoxin-dependent'. However, as it is shown in the Fetal Inflammatory Response Syndrome, inflammation may represent the condition preceding, and also leading to infection. Considering for instance the possible presence of predisposing factors to inflammation, like fetal or maternal genetic inflammatory polymorphisms, antibiotic use should not be limited to cure infection, but is also indicated to prevent and cure the preceding inflammation. It is our clinical opinion that the risk of producing resistant bacterial strains is overestimated, and therefore in half a century experience our strategy for prevention of pregnancy loss largely included preventive use of antibiotics.

5.2 Lactoferrin

Nevertheless, alternative drugs may be used in the protection of pregnancy, when an antinflammatory action is indicated without the need of a anti-bacterial one. To this purpose we tested Lactoferrin (LF), an iron-binding glycoprotein with anti-inflammatory properties, which is normally present in human organism and is largely prescribed to cure anemia. We first reported that a vaginal compound containing 300 mg of LF, administered 4 hours before genetic amniocentesis, significantly decreases amniotic IL-6 concentration [58]. Subsequently we found that the same dose of the compound significantly down-regulates 17 pro-inflammatory amniotic cytokines among which IL-9, IL-15, IFN-γ, IP-10, TNF-α, IL-1α and MCP-3, while it up-regulates several among anti-inflammatory [59]. We also evaluated the effect of vaginal LF on amniotic fluid PGE2 level and MMP-TIMP system. We found that vaginal lactoferrin significantly lowers PGE 2, active MMP-9, and its inhibitor TIMP-1. Conversely, active MMP-2 and MMP-2/TIMP-2 molar ratio are increased, whilst TIMP-2 remains unchanged [60].

5.3 Glucocorticoids

Once recognized that the majority of relevant pregnancy complications are triggered by an inflammatory process, the preventive and curative role of glucocorticoids has been better clarified. The physiologic adrenal gland circadian production of glucocorticoids represents the first defense against inflammation, throughout the corticosteroid control of the mediators of cellular functions among which IL-1,

IL-6, IL-8, Tumor necrosis factor, granulocyte-macrophage colony-stimulating factor (G-CSF), monocyte chemotactic protein-1 (MCP-1) [61]. The complex action of glucocorticoids (GCs) is exerted also on cellular cytokine receptors, which are increased in some cell types, decreased in others [62, 63]. Examples of the regulatory actions of GCs are down-regulation of the expression of the cellular receptors that recognize a variety of pathogens (Toll-like receptors) [64], as well as suppression of pro-inflammatory and up-regulation of anti-inflammatory cytokines. This effect has been reported for dexamethasone in primary isolated murine liver cells [65]. Glucocorticoid inhibition of the human pro-IL-lβ gene by decreasing DNA binding of transactivators to the signal-responsive enhancer has been shown as well [66].

An important example of the complexity of these regulatory processes to be considered is that the glucocorticoid receptor (GR) can decrease TNF stimukated IL-6 transcription independently from GCs, as a protective mechanism against excessive inflammation [67]. Moreover GCs are reported to induce, rather than to inhibit, the secretion of the migration inhibitory factor (MIF) [68], thus counteracting its own inhibition of pro-inflammatory cytokine production.

In addition to the intricate network of stimulatory and inhibitory messengers and tissue distribution of receptors, the action of the GCs is subordinated to the enzyme that transforms cortisol into cortisone, thus inactivating it: 11-beta hydroxysteroid Dehydrogenase [69]. It is widely distributed in the uterus and placenta, in immune cells, skeletal muscle and heart, while it is reported to apparently lack in the fetal organism up to the advanced stages of its development. What can this lack possibly mean? Well, the first logical implication is that normal embryonic development does not fear the effect of cortisone up to the advanced stage of its maturation.

At this regard, there is one important point to clarify to the benefit of mainstream obstetrics, and it is the difference between 'maturation' and 'inflammation'. The concept of an improvement of fetal lung maturation by betamethasone was first expressed fifty years ago, to explain the decreased incidence of 'Hyaline Membrane Disease' of neonates following the hormone administration to their mothers the day before premature birth [70].

At that time the devastating influence of inflammation on pregnancy had not been sufficiently explored, and the 'Fetal Systemic Inflammatory Response Syndrome' had not been described. Therefore it was believed that the hyaline membrane disease was caused by prematurity, and the action of betamethasone was to induce a sort of pulmonary maturation. But today, the features of fetal inflammation leading to Hyaline Membrane Disease, Necrotising Enterocholitis and Encephalopathy are well known, and therefore to keep on talking of 'maturation' instead of inflammation, it is not only an incorrect opinion: it is also misleading. Indeed, such a misinterpretation impairs the correct preventive use of GCs throughout pregnancy. A deep update is therefore needed in order to renew the guidelines on a clinical basis rather than a mere statistical one, as usally done.

Further example of the somewhat contradictory reciprocal influence of the mediators of inflammation, is that the pro-inflammatory cytokines, IL-1 and TNF-α included, up-regulate 11-β-hydroxysteroid-dehydrogenase mRNA in different cell types. Finally, GCs themselves stimulate the enzyme, appearently as an attempt to impaire their own anti-inflammatory effect.

Such complex influences are of particular relevance in understanding the nature of a balanced protective action against pregnancy loss. They indicate that the behavior of GCs in the regulation of inflammatory processes is far more complex than our limited knowledge can imagine: once recognized the number and function of the involved mediators, it is impossible to establish the precise order of their activation. The clinical protective action of glucocorticoids can only be assessed by

the *'ex juvantibus'* criterion: that is, case by case, from the benefit obtained following their administration.

6. Other therapies

The COVID pandemic found health systems around the world unprepared. The technical-scientific committees of epidemiologists and virologists failed to consider therapeutic strategies, limiting the advice only to preventive measures, such as face masks, lockdown and quarantena. However, alongside hundreds of thousands of dead there have been happy islands where patients have been properly cared. Hyperimmune serum transfusions from recovered patients proved effective in saving many human lives [71]. Their efficacy depends on a direct neutralization of the virus, by preventing its entry into the cell. Attempts have been made to reduce the level of IL-6 by administering its antagonist 'tocilizumab' [72]. However, to look for a single drug capable of balancing the intricate network of stormy cytokines is a legitimate but naive hope: lowering the level of just one cytokine while that of many others remains high does not make much sense. Therefore the attention of researchers should turn to drugs capable of restoring the balance of cytokines as a whole, reducing the level of the inflammatory ones and increasing that of the anti-inflammatory, as happens with cortisone and lactoferrin.

A similar approach recently suggested the use of α-1-antitrypsin (AAT), a serine protease inhibitor providing a defense against the digestion of healty tissue by proteolitic enzymes. Interestingly, AAT blood level is very high during inflammation, as well as in advanced pregnancy, while its deficiency causes inflammation and viral infections. AAT therapy has been appruved for treatment of chronic obstructive pulmonary disease [73], and there is no reason not to test it, even as a preventive measure, in a serious emergency as that of the current pandemic.

7. Pregnancy and COVID 19 *'cytokine storm'*

During the first few years of my residency, cases of unrecognized 'pregnancy cytokine storm' were not uncommon. The pathological condition in which they occurred, in advanced gestational age, was called *'gestosis syndrome'*. Today it is improperly called *pre-eclampsia*, due to a possible complication (rare, and not the worst): tonic–clonic convulsions. More common are the sequelae of vascular pathology: *abruptio placentae*, and disseminated intravascular coagulation. These are the consequence of the inflammation triggered by the cytokine unbalance, that, once become extreme, is called 'storm'. In more advanced Obstetric Units, these ominous complications virtually disappeared because their premises are identified and taken care of before the onset of cytokine stormy release. This represents the rationale of low dose betamethasone therapy throughout the entire course of pregnancy for preventing pregnancy loss and elated complications [74–77]. Conversely, when cytokines trigger intravasal coagulation at the utero-placental level, the fetus dies, just as an adult dies from pulmonary vessels coagulation triggered by COVID 19 cytokine storm. Indeed, both deaths are caused by suffocation, because the placenta is the lung through which the fetus breathes.

A virus does not kill by itself: it does so through inflammation and coagulation, two perfectly curable pathologies as long as they are treated in time, that is, at their first onset. Unfortunately, in the management of COVID-19 pandemic, Health Services, overlooking the pathogenesis, focused on preventive measures rather than cure the disease.

Filtering facepiece respirators (FFRs) as well common face masks were core of the world health strategy. However, there is little evidence that by wearing a medical mask and washing hands provides significant protection against COVID 19 contagion. To the best of our knowledge, there is no randomized controlled clinical trial that demonstrate the efficacy of face masks in preventing the contagion. After all, it is logical to observe that the masks are not watertight, and therefore viruses can escape around everywhere. The belief of a possible efficacy, derived from the 123 years old '*Flugge's droplets*' account [78], still ignores that the virus remaines viable in aerosols over 3 hours [79], and therefore a delayed infection is likely to occur even long after a loose interaction with a carrier.

In addition, there are many unresolved questions regarding the spread of this disease. The theory of the *'patient number 1'*, in Italy at first identified at Codogno (Lombardia), was nullified by the demonstration of the presence of anti-COVID-19 antibodies in the blood of healthy donors collected before the start of the pandemic. This observation suggests not only that the spread of the virus occurs in a silent way, but also that the virus is not able by itself to produce a deadly disease. For that to happen, concurrent pathologic conditions are required, some of which are well known, some others still unknown.

As reported above, the free transmission of viruses through the air, as well through other routes is well known, and scientifically confirmed. Obviously, the mere presence of viruses does not necessarily imply that the carriers must get sick: it is the well known condition of 'healty carriers'. On the other hand their absence does not exclude that the viruses can meet the same subjects in later periods of their life. The onset of the disease requires the concurrence of a compromised immune response.

In addition to the above considerations on the free and unrele nting circulation of all viral particles, COVID-19 included, the Italian experience in the unsuccessful management of the pandemic also speaks against the effectiveness of medical masks. In Italy, from North to South and all the way to the islands, everyone was forced to wear a mask, but the large majority of deaths were concentrated in four of the northern Regions: Piemonte, Lombardia, Veneto and Emilia Romagna. These are the most industrialized, rich and polluted Italian regions, which are regarded soundest as far the Italian healthcare system is concerned. However, precisely those regions reported the highest death rates, compared to all other Italian regions and other nations as well. In spite of wearing medical masks, a large number of Italian physicians and health workers died, most of which in the above mentioned regions. Further to that, at the beginning of the lockdown, a few hundred Italian citizens fled from north to south of the country, being accused of spreading the infection in the southern regions, but this did not happen at all. A surveillance study performed among healthcare workers at the 'Infectious Diseases Cotugno Hospital' in Naples, showed a very low prevalence of the COVID-19 infection among health care workers: the reason was that healthy subjects scrupulously follow protected and obligatory paths, and wear overalls and helmets that completely isolate them from the surrounding environment full of viruses [80].

The efficacy of the measures adopted at Cotugno Hospital therefore explains the little or no utility of simple masks in preventing the contagion. At the same time, Cotugno's experience demonstrates that concentrating a large number of carriers of high viral load in a limited space, without adopting the correct precautions is a serious mistake. How to proliferate subjects with a high viral load? Simple: instead of treating adequately the early symptoms of illness, leave them at home a few weeks with high fever and without effective medical treatment, then hospitalize them when the high viral load boosts inflammation up to the level of asphyxia due to pulmonary thrombosis.

8. Concluding remarks

Death from COVID 19 infection reiterates the same pathogenic mechanism of fetal and maternal death in pregnancy: it is a matter of inflammation triggered by umbalanced cytokines and coagulation in the lung, the same that happens in pregnancy, starting at the utero-placental level. In the first the cause is the virus, in the second is the fetus itself, as it is explained in the above reported literature.

In both cases, the cause cannot be eliminated.

The cure, instead, exists: it is the same in both conditions and is very effective. The rationale for management is not to fight the cause, but to cure the disease, i.e. inflammation, and consequent overlapping bacterial infection and thrombosis.

Therapeutic agents include cortison and eventually other non-steroidal drugs against inflammation, antibiotics against superimposed bacterial infection and heparin against thrombosis. However, it can be stated: no cytokine umbalance = no inflammation, no inflammation = no infection = no intravascular coagulation. Moreover, it must be stressed that the treatment is all the more effective the earlier it is started. The same therapy that can be effective if started at the first onset of symptoms, becomes 'compassionate' if started when inflammation and thrombosis are already in an advanced stage [81, 82].

Author details

Fortunato Vesce
Obstetric and Ginecology Unit, Ferrara University, Italy

*Address all correspondence to: ves@unife.it

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