Review Article

Gestational Inflammation: Its Foetal Control and the Proper Therapeutic Approach

Fortunato Vesce[1]

1. University of Ferrara, Italy

Inflammation triggers coagulation. Gestational Inflammation with its vascular implications is the cause of the major obstetric complications, from sporadic and recurrent miscarriage, to foetal growth restriction, premature delivery with all its nefarious perinatal sequels, up to the most dramatic scenarios of foetal and maternal death: it is neither adequately diagnosed nor promptly and exhaustively counteracted by current obstetrics.

Controlling gestational inflammation in normal pregnancy is primarily a foetus's job. The vast majority of aneuploid foetuses are unable to control normal gestational inflammation, and are therefore spontaneously aborted. Euploid foetuses may be unable to control normal gestational inflammation, and in this case they are aborted, or suffer from the inflammatory complications of advanced pregnancy.

This article reports a selection of the best scientific evidence on gestational inflammation. It also analyses the current therapeutic approach, with particular regard to the use of glucocorticoids throughout pregnancy.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Premise

It is worth to consider in advance that pregnancy is made possible thanks to an invasion of maternal endometrium by the trophoblast surrounding the blastocyst. Such invasion generates a cellular reaction[1], the nature of which is primarily of an inflammatory type. It belongs to the cellular branch of the immune response, leaving perfectly operative the humoral one.

A favorable outcome is only possible if the thetrophoblast is able to turn off the inflammatory endometrial reaction it itself has caused. This means that the physiological pregnancy is largely under foetal control. Foetuses (i.e. trophoblast) unable to properly modulate the local maternal reaction sign their own death warrant.

The physiological role of the 'inflammatory mediators'

The normal evolution of pregnancy is the result of deep vascular changes in the maternal organism under the control of foetal mediators. According to their prevalent action, a taxonomic classification can divide these mediators into inflammatory and anti-inflammatory. However, they are known to play either role, depending on the cell type and the circumstances of their involvement, in response to the activation of the actors of the opposite function. Indeed, the so-called 'inflammatory' ones primarily regulate physiological functions, such as ovulation, menstruation, labor and many others. In search of scientific evidences of the physiologic role of such mediators, the receptor ligands for the inflammatory peptide N-formyl-methionyl-leucyl-phenylalanine (fMLP) were found to be present in amniotic fluid. Their concentration increases with labor, while fMLP receptors are expressed in amnion tissue[2][3][4][5]. So, what are these inflammatory mediators for? Can normal labor be considered an inflammatory process? Not entirely. Certainly, it often presents with pain, heat, functional impairment, like it may happen during menstruation: and to some externt labor can be considered a delayed menstruation, as Gustavii pointed out a long time ago[6].

Is fMLP involved in the control of menstruation as well? After all, understanding the physiological role of these mediators is not a simple matter of measurement. fMLP is only one among many chemotactic factors able to modulate cytokines, including IL-1 alpha and IL-1 beta gene expression and IL-6 secretion, which in turn are known to modulate inflammation[7].

Therefore, it should be interesting to explore the behavior of the peptide in the genesis of premature labor and foetal systemic inflammation, a syndrome preceded by an increase of IL6 concentration in the foetal compartment. However, even if that were the case, it would be a drop in the ocean! A large network of gestational cytokunes, chemokines, peptides and prostanoids have been investigated in both experimental and clinical conditions, with sometimes controversial results. Nevertheless, over the course of half a century, the inflammatory nature of the major complications of pregnancy has been widely recognized at least on a pathological level, if not on a clinical one.

In this article the concept of gestational inflammation will be discussed in its broadest sense, from the natural maternal immune response, to its physiological control by the foetus, up to its harmful pathological deviations. Furthermore, the therapeutic approach will be analyzed with particular attention to the balance of the mediators that trigger inflammation, thus paving the way for infection, and to the use of glucocorticoids for the prevention of pregnancy loss.

A look at the nature and mechanism of gestational inflammation

Between the two endpoints of conception and delivery, the process of placentation takes place, during which the maternal and foetal immune systems interact with each other. This occurs through the release of specific mediators of opposite function, the maternal ones being more addressed towards inflammation, whereas the foetal ones act against it. The earliest stage of the foetal-maternal competition occurs at the beginning of blastocyst implantation in the uterine mucosa. Mainstreams clinicians are customed considering such an early stage separately from advanced pregnancy, when the foetus is now capable of extrauterine life. Nevertheless, both from a biological and clinical point of view, the functional evolution of the trophoblast must be considered a unitary and continuous process until delivery. Indeed, the same inflammatory deviation of its function that triggers miscarriage, later can leads to premature birth, chorioamnionitis, nefarious perinatal complications, up to the loss of both the foetus and the mother.

During the three-days travel from the tube to the uterine cavity the product of conception does not need to come into contact with the maternal blood, since everything he needs is already in his baggage. Later, when the throphoblast cells reach the mucosa, they differenziate into two types, respectively called extra-villous and villous. The first type is responsible for structural and functional changes in the maternal vessels[5]. It penetrates the uterine arterioles and distrupts their wall, causing the leakage of blood in which the chorionic villi are immersed to drain increasing quantities of nutrients and oxigen.

As in any other vascular district of the body, this generates an inflammatory reaction, aimed at reducing blood leakage by means of vasoconstrition and coagulation. The activation of such a natural response would appeare to hinder the ultimate goal of a normal birth, but in physiological pregnancy this is not the case. In fact, the foetal immune system takes over the maternal one, to preserve optimal placental perfusion until chldbirth. In its competition with the maternal immune system, foetal self-defense is essentially accomplished by counteracting vasoconstriction and blood coagulation. For this purpose extravillous trophoblast cells progressively eliminate the smooth muscle from the wall of the spiral artery

up to its myometrial tract. The consequent vasodilatory effect produces a continuous, low-resistance blood flow. At the same time coagulation is prevented by replacing the endothelial lining of the vascular intima with trophoblastic cells. In this way, the local maternal platelet activation does not take place, and the thrombosis is not triggered.

These structural changes of the uterine arterioles were clearly described by Harold Fox in his classic text entitled 'Pathology of the Placenta'[8].

At the same time the trophoblastic cells directly produce functional mediators[5], and stimulate the release of many others by maternal platelets, as well as by immune and other cells. Therefore it is right to state that pregnancy is directly under the control of the foetus itself: *foetus faber fortunae sua*e!

On the other hand, contrary to some unproven opinions, the maternal immunity against infectious diseases remains fully operative throughout pregnancy. The idea of an assumptive "fragility" of the pregnant woman is completely devoid of any scientific basis. It derives solely from the hypothesis that the foetus should be 'rejected', because the mother's immune system does not recognizes its paternal genetic component. According to this opinion, maternal tolerance would be accomplished through a reduction of the humoral immunity, thus leading to an increased risk of infection. A corollary of this unproven risk should be the need to resort to vaccines, whose number is continuously increasing, and whose efficacy and safety have never been reliably investigated. Instead, contrary to the opinion of an increased risk of serious infections accredited by World Health Organization, the admission rate to Intensive Care Unit is significantly lower for pregnant women. Moreover, no increased need for ventilatory support, nor a greater likelihood of severe outcomes and maternal death compared to either the general population or non-pregnant women of reproductive age is reported. Only a higher rate of hospitalization is registered, rightly ascribed to a better care for motherhood[9].

Surprisingly, however, the above data have been interpreted in the opposite meaning by others[10]. To give a greater credence to an increased risk of maternal death, these Authors go back to the 1918 flu pandemic, an era when the therapeutic efficacy of antibiotics, anticoagulants and anti-inflammatory drugs was unknown!

Unfortunately, however, vaccination, by definition entails inflannation, thus strenghtening the normal maternal cellular immune reaction[11], with a consequent increased risk of foetal demise. It is the author's opinion that, given the current uncertainties, it may be best to exercise caution regarding vaccinations during pregnancy until more research is available.

Foetal-maternal regulation of immune and vascular function

Many of the pregnancy-related mediators of the cellular functions are secreted by two subpopulations of lymphocytes (Th1 and Th2) derived from the functionally undiscriminated type (Th0). Th1-type produces mainly interleukins (IL-1, IL-2, IL-12, IL-15, IL-18), interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), known to mediate cellular immunity. Th2 produces IL-4, IL-5, IL-6, IL-10, IL-13 and granulocyte-macrophage colony stimulating factor (GM-CSF), which control the humoral response[12][13]. Moreover, Th2 cytokines prevent Th1 cytokine secretion[14].

The pro-inflammatory/anti-inflammatory cytokine ratio, is enhanced in preeclampsia. It is probably associated to an excessive production of inflammatory agents, among which IL-12[15]. Placental ischemia, consequent to poor spiral artery remodeling[16], enhanced Th1/Th2 ratio[17] and pro-angiogenic/anti-angiogenic factor imbalance[18] may promote inflammatory changes through the release of Th-1 cytokines and ROS with consequent endothelial dysfunction, leading to the release of humoral factors responsible for the clinical symptoms of preeclampsia[19].

As for the gestational evolution of cytokine balance, based on circulating levels of interferon-gamma (IFN-gamma) and interleukin-6 (IL-6) as Th1 and Th2 biomarkers respectively, the variation of their ratio was investigated in the maternal blood of 35 women from 10 to 40 weeks of pregnancy. It is important to note that IFN-gamma levels decrease with gestational age, whereas those of IL-6 increase. The IFN-gamma/IL-6 ratio switches around the 19th week of pregnancy. Therefore the Authors suggest that the Th1 bias may be prevailing at the beginning of pregnancy, balanced in the middle and supplanted by the Th2 bias at the end[20].

These results should be taken into account when the cytokines are tested for statistical or diagnostic purposes.

Many other factors are involved in the differentiation and specializzation of trophoblastic cells from implantation to delivery. During early pregnancy, low oxygen is reported to prevent trophoblast differentiation towards an invasive phenotype. Low oxygen effects are mediated by hypoxia inducible factor-1 (HIF-1alpha subunit), whose expression parallels that of transforming growth factor-beta3 (TGFbeta3), an inhibitor of early trophoblast differentiation[21][22].

Abnormalities in TGF-β3 expression are associated with preeclampsia and it has been demonstrated that down-regulation of this growth factor restores the invasive capability of preeclamptic trophoblast

cells[23].

A crucial role for optimal foetal oxigenation and growth is exerted by prostacyclin ($PGI_{2)}$, a prostanoid with vasodilatory and anticoagulant function. It is produced by both the mother and the foetus for the entire duration of pregnancy. Placental cells in culture synthesize and release PGI_2. Its production appears to increase with gestational age, so that preterm and term placental PGI_2 production is significantly greater than that in first-trimester.

Notably, synthesis of PGI_2 is inhibited by the cyclo-oxygenase inhibitors indomethacin and aspirin, a potentially dangerous effect, considering the wide clinical use of these drugs[24].

Indeed, as patients with recurrent miscarriage have significantly increased platelet aggregation in response to arachidonic acid, the use of aspirin in the management of this condition is suggested[25]. Therefore, aspirin is expected to hinder thromboxane on the one hand, thus counteracting the formation of the platelet thrrombus, but also to inhibit prostacyclin production on the other, in this way promoting vasoconstriction and thrombosis. Indeed, the action of prostacyclin is normally counterbalanced by tromboxane (TxA2), a prostanoid responsible for vasoconstriction and thrombosis, which is released by various cells, among which endothelial, macrophages and neutrophyls. The enhancement of tromboxane release is the natural consequence of inflammation. The maternal inflammatory response is not limited to platelet activation, but widely affects other tissues, among which the endothelial lining of uterine arteries. Women whose pregnancies end in abortion have higher output of 2,3-dinor-TxB_2 (a tromboxane metabilite) and lower excretion of 2,3-dinor-6-keto-$PGF_{1\alpha}$ (a prostacyclin metabolite), with a lower ratio of prostacyclin to thromboxane, indicating a thromboxane dominance and prostacyclin deficiency compared with women whose pregnancies proceede to term[26].

These data underline the importance of a balanced prostacyclin/tromboxane ratio in pregnancy.

In apparent contrast with the evidences that increased platelet aggregation is a cause of severe complications, among which increased miscarriage rate, pre-eclampsia and pregnancy loss, reduced platelet aggregation in response to adenosine diphosphate, and thrombin receptor activating peptide was reported in patients with history of recurrent miscarriage in comparison with those of the same group who subsequently have successful pregnancies. Women with subsequent miscarriages also have a trend towards reduced platelet aggregation in response to epinephrine[27].

However, it must be onsidered that in vivo platelets disfunction is a complex process than cannot be simply reduced to more or less experimental in vitro aggregation.

Further questions regarding platelet dysfunction concern the complexity of the maternal inflammatory response and the adequacy of the adopted therapy. As it will be seen later, the ability of aspirin to inhibit thormboxane formation in vitro does not provide any significant clinical advantage in terms of live birth rate and foetal well-being.

Potential causes of enhanced gestational inflammation

Once the prevalent inflammatory nature of major obstetric complications is understood, its prevailing causes must be carefully considered. In this regard, the current attitude is to look for maternal infectious, immune and genetic causes.

As for the first, the stubborn search for potential pathogens appears to be no longer necessary, since the foetus inhability to turn off the maternal immune reaction - unleashed by himself - is sufficient to explain even the most serious consequences. After all, free mother-to-child transmission of viruses and their specific antibodies has been reported in normal pregnancy[28][29]. Moreover, HPV infection is rare in chorionic villi, and is not related to abortion[30]. As for Ureaplasma parvum and urealiticum, Mycoplasma genitalium and hominis and clamydia tracomatis, their DNA sequences are found with similar frequency in periferal blood mononuclear cells of spontaneous and volontary aborters[31]. On the other hand, it is logical to believe that the mere presence of viruses and bacteria is not a sufficient cause of disease, because it is known that healthy carriers do exist. The independence of the onset of inflammation from pathogens is indirectly demonstrated in the above mentioned ‘syndrome of the systemic foetal inflammatory response’ (Romero – Gomez Syndrome)[32]. In this condition high levels of foetal IL6 are found in the foetal compartment before the onset of premature birth symptoms, suggesting the existence of foetal cytokine umbalance preceding the eventual infection. Nevertheless, the widely held belief that inflammation is triggered by infection is claimed on the basis of the curative effect of antibiotics. However it has been shown that, in the absence of infection, Ampicillin is able to inhibit amniotic Prostaglandin E and IL6 release, in this way directly counteracting inflammation[33][34].

Furthermore it is reported that Ceftriaxone and Gentamicin exert the same action although to a lesser extent. On the contrary, Tetracycline and Erytromycine do not influence the prostanoid output. The inhibitory (i.e. anti-inflammatory) effect of Ampicillin is potentiated in an additive manner by Ceftriaxone, reduced by Gentamycyn and eliminated by Tetracycline and Erytromicin[35].

These data should open a serious debat on the current interpretation of healing from antibiotics: is it the result of their direct anti-inflammatory action rather than the anti-bacterial one? Or: in what extent it is the result of both?

Autoimmune syndromes and diseases of the maternal connective tissue are a well known cause of recurrent miscarriage. Nevertheless, successful pregnancy is possible, although at the cost of an increased risk of complications[36].

The foetal-maternal genetic control of gestational inflammation

A large number of maternal and foetal cells produce immune mediators, but a clear assessment of their role in the genesis of different gestational situations has not been yet sufficiently clarified. While the role of the maternal immune system is beyond question, its control by the foetus still awaits to be adequately understoood. Indeed, there is much evidence to suggest that the foetus itself governs the balance of gestational immunity. The above mentioned Romero-Gomez Syndrome, for example, indicates that the foetal inflammatory state may not be triggered by infection. Accordingly, it has been also postulated that successful pregnancy induces an immune bias towards Th2 immunity, and a Th2 cytokines imbalance is believed to cause intrauterine growth restriction and foetal death. Further evidence points to a foetal role in triggering increased or umbalanced release of pro-inflammatory mediators. Indeed, maternal peripheral mononuclear cells stimulated with trophoblast antigens from growth restricted foetuses produce higher levels of pro-inflammatory cytokines compared with normally grown foetuses[37][38][39].

Growth restriction, therefore, can be considered a consequence of low utero-placental perfusion caused by vasoconstriction and thrombosis of uterine spiral arterioles, i.e. by the normal maternal inflammatory response, which growth-restricted foetuses lack the ability to switch off. This foetal idiopathic inhability may well be one cause of the shift towards Th1-type immunity[39] which is a reported caise of 'unexplained' pregnancy failure.

Once the foetus' inability to properly control the maternal inflammatory reaction has been recognized, we must find out where it originates from. To answer this question the mediators of inflammation, coagulation and vascular function released by aneuploid foetuses was investtigated, in order to verify whether an increased or umbalanced output could justify their high abortion rate.

A raised amniotic fluid level of endothelin, a potent vasoconstrictor, was found in the presence of aneuploidy compared to normal pregnancies[40]. Moreover, abnormality of the plasminogen activation

system was reported in aneuploid pregnancies, possibly ieading to impaired utero-placental perfusion, thus to abortion, foetal growth restriction and death[41]. Accordingly, amniotic fluid of Down Syndrome pregnancies display increased TGF-beta activity and lacked IL-2 immunoactivity[42]. Moreover, down-regulation of adhesion molecules such as integrin-α, and upregulation of MMP-9 are riported in trisomy 21, with possible impairement in trophoblast function. These alterations may be responsible for the increase in cytotrophoblast apoptosis[43]. Further amniotic fluid abnormalities in aneuploid pregnancies are an increase of interleukin-6 ($P = 0.034$) and a decrease of interleukin-8 ($P < \text{or} = 0.0001$)[44].

In addition, the receptoors of adenosine, a pro-angiogenic nucleoside, were investigated in 71 first trimester chorionic villi samples and cultured mesenchymal cells from euploid and trisomy 21 pregnancies. Overall, the adenosine transduction cascade appears to be disturbed in Trisomy 21 through reduced expression of A_{2B} and A_1A receptors[45].

All these anomalies of mediators of inflammation, coagulation and vascular function are a cause of foetal growth restriction, malformation and death, thus leading to the high rate of aneuploid pregnancy loss.

If the above reported evidences speak in favor of a foetal genetic cause for the lack of a proper control of immune and vascular function in the presence of aneuploidy, what can be said for euploidy?

Progress in genetic polymorphisms research answers this question. Genetic polymorphism means that the structure or nucleotide arrangement of the same gene may vary between individuals. The variations are compatible with life, and may affect numerous genes, including those associated with angiogenesis, thrombogenesis and immune response[46].

Maternal common inflammatory polymorphisms entail an increased risk of recurrent miscarriage and preterm birth[47][48]. Consistent with the increased risk of preterm birth that inflammatory polimorphysms entail, a decreased risk is reported for the anti-inflammatory ones[49].

Furthermore, maternal polymorphisms of the immunoregulatory genes IL10, MBL2, TNFRSF6 and TGFB1 influence the susceptibility to chorioamnionitis and other unfavorable pregnancy outcomes [50].

While maternal polymorphisms are widely studied, the same cannot be said for the foetal ones. This reflect the current and often erroneous opinion that adverse pregnancy events are attributable to maternal pathological conditions. On the contrary, since both the maternal and foetal immune systems modulate the utero-placental function, foetal genetic polymorfisms have the same importance as maternal ones in determining the fate of the pregnancy.

Clinical implications of the foetal-maternal immune system mutual modulation

The evidence reported above is only a small part of the large amount of data in the scientific literature on cytokine modulation in pregnancy. As mentioned in the introduction, the maternal inflammatory response is not in itself a pathological event, as far as the foetus is able to counteract it. It turns into pathology only when the spatial-temporal production of inflammatory cytokunes is uncontrolled, and the Th1 foetal-maternal immune response takes over the Th2 one[51].

So, slowly, the idea of counteracting inflammation has made his way into the minds of obstetricians. It must be said however that the maternal immune reaction to trophoblast invasion is not currently seen as a possible cause of miscarriage. According to mainstream obstetrics, the most accredited causes are maternal diseases, including connective tissue chronic inflammation, thronbophilia and infection. Indeed, an increased risk of miscarriage and other complications are registered in the presence of such pathologic conditions. Nevertheless, physiological pregnancy, albeit less frequently, can occur in these patients, thus confirming the opinion that a better genetic polymorphism of the new foetus may be able to control the maternal immune system.

Ignoring the possible role of gestational inflammation in the genesis of obstetrical complications, current obstetrics does not effectively counteract it. Therapy is still basically anchored to weak measures dating back to the first half of the last century: robust doses of progesterone, weak doses of aspirin and in some cases ineffective glucocorticoids.

Progesterone

Progestagens are prescribed routinely for the protection of early and late pregnancy. Initially the reason for their use was the maintenance of electrical and mechanical quiescence of the nyometrium. As for their utility, the need of progesterone action on the endometrium for implantation is known and beyond question. It is worthwhile to recall that around the end of last century a combination hydroxiprogesterone caproate plus estradiol valerate was approved for cure of threatened miscarriage[52] as well as for osteopenia due to hypogonadism[53][54], for stimulation of breast enlargement[55] and also for contraception[56]! However, so far there is no clinical evidence of real efficacy in protecting pregnancy against severe inflammatory complications. Only in 2007 the estro-progestin combination was withdrown from the italian market. Nevertheless, new potential indications

to progesterone administration are produced by the tireless scientifical research, among which a possible anti-inflammatory action that should make its use suitable against miscarriage[57]. Fortunately, however, the real usefulness of progestogens in the prevention of obstetric complications is slowly coming out. According to FIGO Good Practice Reccomendations[58], evidence on the use of progesterone for prevention of recurrent miscarriage demonstrates no significant difference in live birth rates compared to placebo. Similarly, a recent meta-analysis on seven randomised trials involving 5,682 women, concluded that progestogens probably make little or no difference to live birth rate for women with threatened or recurrent miscarriage[59]. Furthermore, the method of pessary administration of 400 mg vaginal progesterone for threatened miscarriage does not increase live birth-rate[60]. Although other Authors seem to interpret the reccomentations of the guidelines in a more reassuring way[61], a further meta-analysis confirmed that progestogens probably make little or no difference to live birth rate for women with threatened or recurrent miscarriage[62].

It should seem instead that Vaginal micronized progesterone, may increase the live birth rate for women with a history of one or more previous miscarriages and early pregnancy bleeding: thus progesterone shows inconsistent behavior in relation to the administration route. However, as regards the efficacy limited to cases with early bleeding, one possible explanation could be that some of them may not be true cases of threatened abortion: the blood may come from the decidua parietalis. Indeed, it is known that in early pregnancy the gestational sac does not occupy the entire uterine cavity, and there are women that may experience mild bleeding during the period of missed menstruation until late in the second trimester: this has little or nothing to do with threatened miscarriage. Strictly speaking, bleeding should be considered a sign of threatened abortion only when it is caused by the disruption of the normal relationship between chorionic villi and uterine spiral arterioles. In a previous randomized multicenter trial in which 400 mg vaginal progesterone was given twice daily to patients with history of recurrent miscarriage from a positive pregnancy test until 12 weeks, there was no significant difference for live birth after 24 weeks compared to placebo[63]. Nevertheless, the National Institute for Health and Care EXcellence (NICE) recommend to offer vaginal micronised progesterone 400 mg twice daily until 16 completed weeks to pregnant women with vaginal bleeding and history of one previous miscarriage. Actually, a single miscarriage can be due to causes that do not beenefit from progesterone, such as occasional aneuploidy. Moreover, the duration of the therapy is questioned. It has been highlighted that the increase in live birth rate at 34 weeks is only 3%; it is registered only in women with 3 previous miscarriages, and the beneficial effect occurs at 9 weeks gestation, i.e. at the time of the shift in

progesterone production from the corpus luteum to the placenta. This suggests that there is no need of the hormone supplementation until the 16 week. The need to investigate the long term effects of progesterone on brain development has also been highlighted[64].

The American College of Obstetrics and Gynecology Clinical Guidance for prevention of recurrent premature birth by progesterone supplementation was recently updated. Quoting Conde-Agudelo and Romero[65], the Committy states that vaginal progesterone may be prescribed in women with history of preterm birth, singleton pregnancy and a shortened cervix. On the contrary, prevention of recurrent preterm birth between 20 and 37 weeks gestation with ntramuscular administration of 17-OHP is not supparted by the current body of evidence, and therefore it is not approved by the FDA[66]. At this regard, the American College Committy notes that the FDA decision does not appear to be based on "safety concerns", and "does not provide any basis for evaluating potential progesterone efficacy in a subset of the general population": in other words, it seems that the Committy wants to distance itself from the FDA's position. However, the Committy, does not seem at all surprised by the difference in efficacy of progesterone, which appears to be mild via the vaginal route, but is completely absent via the systemic route. It is not easy to figure out the reason of the intramuscolar route failure, considering the prompt hematogenous spread to all organs and tissues, including the vagina. Finally, one would expect that, by inhibiting myometrial contraction, progesterone administered before cervical shortening would be more effective than after the process has already begun. In addition, the concern of the American Committy for the apparent indifference of FDA as regards safety and potential efficacy on population subsets seems to be misplaced, because it may be relevant to research, but not yet to clinical care. How can these incongruity be explained? It would seem that proven clinical efficacy is still an essential condition for autorising the administration of a drug to the human population.

Further attempts to support the mild action of progesterone have been made by combining the therapy with cerclage. However, the hormone is supposed to counteract the increased myometrial contractility triggered by gestational inflammation, while the surgical thightening of the cervix can only be effective in the absence of inflammatory myometrial contractions. Therefore, an eventually increased efficacy of this combined approach requires that patients with two different pathogenc mechanisms are mixed in the study population. Nevertheless, a trial speaks in favor of an increased efficacy of combined progesterone and cerclage in singleton gestation compared to each of the two ssingle therapies[67][68]. On the contrary, a meta-analysis evaluating both the vaginal and intramuscolar route of progesterone

combined with cerclage and pessary in tween pregnancies with short cervical length reported no reduction of preterm birth < 34 weeks of gestation[69].

Overall, the efficacy of progesterone in the management of miscarriage, premature birth, pregnancy loss and related complications appears to be uncertain or weak, and does notjustify its widespread and undiscriminate prescription.

Aspirin

The pathogenic link between inflammation and thrombosis, and their role in obstetric complications guided some clinical preventive strategies. As above mentioned, thromboxane A2 is released from platelets, macrophages, neutrophils, trophoblast and endothelial cells, as a consequence of tissue injury and inflammation. In addition, it Is also reported to augment cellular immune responses and inflammatory tissue injury[70]. Vasocontriction and platelet aggregation caused by the prevalent action of tromboxane are attenuated by aspirin, whose inhibitory action is supposed not to extend to prostacyclin. Therefore, Based on the known deficiency in prostacyclin and overproduction of tromboxane A2 in women with hystory of recurrent miscarriage, 50 mg aspirin were daily given throughout pregnancy to 66 patients. The therapy was able to decrease Tromboxane A2 production without influence on Prostacycline concentration, but no improvement of live birth rate was observed[71]. Low dose aspirin was also recommended for prevention and cure of preeclampsia because the disease is characterized by an imbalance of the tromboxane/prostacyclin ratio, due to increased thromboxane production.

On the other hand, attempts to treat preeclampsia by direct prostacyclin administration yelded poor results[72].

However, current evidence does not support low-dose aspirin for the prevention of miscarriage, fetal growth restriction, stillbirth and preterm birth[73].

As regards the milfd effectiveness of aspirin, it must be considered that gestational inflammation cannot be reduced to the simple increase of thromboxane: it involves a series of mediators of cellular immunity that may be insensitive to the COX2 inhibitory action of aspirin: it is logical to assume that a higher degree of inflammation requiress a stronger protection. It was therefore thought that this could somehow be obtained by combining aspirin with heparin.

Heparin

Ten years ago a meta-analysis evaluated nine studies that included 1228 women with a history of recurrent misvarriage, with or without inherited thrombophilia, treated with aspirin and/or heparin: no beneficial effect of the anticoagulant in studies at low risk of bias was found[74]. Soon after, thromboprophylaxis with 4000 IU/day low molecular weight heparin was tested in a prospective observational study on 150 women with a history of two or more first trimester miscarriage. Contrary to the result of the previous meta-analysys, live birth was achieved 85%, compared to 66% in the untreated control group[75]. Moreover, an increase in live birth rate has been reported by combining aspirin plus heparin in women with persistent antiphospholipid antibodies[76]. On the contrary, in a more recent international open-label, randomised controlled trial, low molecular weight heparin administered to women who had two or more pregnancy losses and confirmed inherited thrombophilia did not result in higher livebirth rates[77].

Glucocorticoids (GC)

Cortisone was used, in 1953, to treat hyperemesis gravidarum. 29 women were given 25 to 75 mg/day doses for 5 to 64 days, with complete remission of the symptoms within 36 hours, without any negative effect on the neonates[78]. Today glucocorticoids prescription is widespread during the mid- and late pregnancy, while little is known about its potential significance in early pregnancy. Stimulation of HCG secretion, suppression of uterine Natural killer cells and promotion of trophoblast growth/invasion have been reported among the positive effects, while the negative could be inhibition of cytokine-prostaglandin signalling, restriction of trophoblast invasion following up-regulation of plasminogen activation inhibitor-1, induction of apoptosis, and inhibition of embryonic and placental growth[79].

The clinical rationale for the use of GC in the management of the major obstetrics complications is simple: since all of them have an inflammatory pathogenesis, all of them may benefit from the complex anti-inflammatory action of these hormones. It could be argued that the other drugs mentioned above also exert a direct or indirect anti-inflammatory action, but their effectiveness is very limited. GC instead are known to control the mediators of cellular functions, among which IL-1, IL-6, IL-8, Tumor necrosis factor, Granulocyte-macrophage Colony-stimulating factor and Monocyte chemotactic protein-1 factor[80]. Their action is exerted also on cellular cytokine receptors, which are increased in some cell types, decreased in others[81]. Other examples of the regulatory actions of GC are down-regulation of the

expression of the cellular receptors that recognise a variety of pathogens, named Toll-like receptors[82] as well as suppression of pro-inflammatory and up-regulation of anti-inflammatory cytokines[83]. Moreover, betamethasone reverses the migration dysfunction induced by arginine-vasopressin in HTR8/Svneo trophoblastic cells by reverting the matrix metalloproteinase-9 associated inflammation. Therefore, since arginine-vasopressin secretion is elevated throughout gestation in pregnancies complicated by pre-eclampsia, the use of betamethasone has been suggested as a novel therapeutic strategy for this syndrome [84]. The above mentioned effects on cells, cytokines and receptors are indicative of the vast control that GC exert on body functions. Nevertheless, despite the logical and experimental premises of their anti-inflammatory effectivveness, they are rarely used in pregnancy with this specific purpose. Even when they clearly do exert it, the result of their application is interpreted differently. For example, the betamethasone life-saving prevention and cure of neonatal hialine membrane disease of the lung, is currently all attributed to little-known maturational processes. Actually, the hormone directly stimulates lecithin release from the human foetal membranes with a greater amnion response[85]. This complex action, recently confirmed in the rabbit lung, appears to be mediated by a molecular mechanism that causes a decrease of Forkhead box M1, a protein involved in lung development[86]. However a large part of the ominous perinatal complication of premature neonates that benefit from betamethasone, including respiratory distress, encephalopathy and necrotizing enterocolitis, is a direct consequence of inflammation rather than prematurity. Therefore, one should wonder to what extent the life-saving effect of betamethasone is attributable to the stimulated maturation as opposed to its powerful anti-inflammatory action.

Part of the caution in prescribing GC is due to the fear of adverse embryo-foetal malformative or maturation events, some of which have been produced experimentally in laboratory animals. As a consequence there is a widespread tendency to avoid prescribing in early pregnancy, or to resort to poorly effective types of these hormones. It is also believed that prednisolone does not reach the foetus, and therefore cannot cause adverse effects on it. This is a questionable belief, since steroids are fat-soluble, and therefore freely cross the cell membranes. Accordingly, placental 11β-HSD2 has been shown to metabolise beclomethasone, prednisolone, dexamethasone and betamethasone[87]. Despite the above mentioned prejudices, the use of GC, including fluorinated, is the mainstay for a variety of maternal and foetal pathologic conditions. Absolute indications are Addison syndrome and hypopituitarism. Furthermore, they are largely used in pregnant women with asthma, collagen disease, ulcerative colitis,

regional enteritis, and those needing immunosuppression. The most frequent foetal indications to their use are reported below.

Foetal atrio-ventricular block

Isolated foetal complete atrio-ventricular block (AVB) is a condition that occurs in 1 of every 20,000 pregnancies. It results from lupus erythematosus, due to transplacental passage of maternal anti-Ro/SSA and/or anti-La/SSB antìbodies. However other rheumatic diseases, among which Sjogren syndrome may be involved, and even foetuses of asymptomatic women can be affected.

Complete AVB usually develops during gestational weeks 16 to 24, with a 15 to 30% foetal mortality rate, and two thirds of affected offspring requiring permanent pacing. The condition is associated with endocardial fibroelastosis and possible late-onset cardiomyopathy[88], fluorinated Gc such as dexamethasone or betamethasone, given to the mother before 16 weeks′ gestation, can prevent progression to third-degree AVB, alleviate cardiomyopathy[89], and reduce the risk of developing antibody-mediated congenital heart block in the offspring[90]. Moreover, by means of foetal kinetocardiograrn it has been shown that fluorinated steroids normalize atrioventricular conduction in first-degree AVB[91]. However, not all the above effects are confirmed, although there is agreement on the decreased risk of subsequent cardiomyopathy[91]. Adverse effects on the foetal central nervous system, lung, retina, and adrenal glands have been ascribed to fluorinated corticosteroids administration. However, since they are associated with premature or very low-birth-weight newborns, the poor outcome can hardly be ascribed to GCs: rather it should be accepted that, without treatment, those foetuses would never survive. Moreover, neurodevelopmental problems appear to be associated with postnatal rather than antenatal dexamethasone therapy. To avoid fluorinated steroids in women who previously had children with AVB or skin rash, intravenous immunoglobulin is suggested. In these patients, serial echocardiograms are needed to detect premature atrial contractions or moderate pericardial effusion, that might be a target of preventive steroidal therapy[92]. It is believed that in the presence of alarming symptoms, betamethasone is safer than dexamethasone[93].

A recent study evaluated long-term outcomes after antenatal betamethasone therapy for AVB prevention. Body weight and height of the fourteen children enrolled were within normal range, all had normal intelligence, and none had autism[94].

Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia is caused by the loss or decreased i activity of the enzymes involved in cortisol biosynthesis. In the vast majority of cases 21-hydroxylase deficiency is found due to mutations in the gene CYP21A2, located in the short arm of chromosome 6[95][96]. Congenital adrenal hyperplasia is a cause of physical and psychological virilization in affected females. Prenatal diagnosis is needed in pregnancies at risk, followed by GC administration in the positive cases. Chorionic villus sampling has been preferred because it can be performed at the 10th -12th week of gestation, much earlier than amniocentesis. A significant improvement is represented today by the noninvasive diagnosis using cell-free DNA in maternal plasma[97].

Dexamethasone administration to the pregnant mother is effective in reducing genital virilization. Data from large human studies show that dexametasone administered even before 10 weeks of gestation does not induce significant or enduring side effects neither in the mother nor in the foetus, and the newborns do not differ in weight, length, or head circumference from untreated unaffected newborns[98].

Cystic adenomatoid malformation of the lung

Cystic adenomatoid malformations of the foetal lung (CCAM) are rare ernbryonic developrnental abnormalities characterized by overgrowth of the terminal respiratory bronchioles at the expense of the saccular spaces. Although rare cases of spontaneous resolution are reported, CCAM are generally coupled with high incidence of fooetal or neonatal death. Several cases sre reported about the efficacy of betamethasone in the management of CCAM complicated by fetal hydrops. The standard dose of 12 mg, twice 24 hours apart, for prevention of hyaline membrane disease lead to the complete resolution of the condition. In a clinical study on eleven patients survival was 100% in foetuses with hydrops or a CCAM, and resolution of hydrops was seen in 80% of steroid-treated patients[99]. In some cases, however, despite the therapy and the resolution of hydrops, late intrauterine death occurred, suggesting that the malformation may have a preeminent role in the final outcome[100]. While negative clinical effects of betamethasone are not reported in these patients, it seems that the clinical assessment this pathologic condition requires a deeper clinical assessment[101].

Alloimune Thrombocytopenia

Alloimmune thrombocytopenia is analogous to the foetal/neonatal anaemia caused by haemolytic disease of the foetus and newborn. Foetal antigens, which are normally expressed on platelets from the 16th week of pregnancy, may cause maternal immunisation, so that foetal and placental transfer of IgG antibodies may lead to neonatal thrombocytopenia. It has been reported an increase in the fetal platelet count after maternal treatment with prednisone (1 O mg/daily) from 23 weeks gestation[102]. Alloimmune thrombocytopenia is cured today by intravenous immune globulin adrninistered by 24 weeks gestation to pregnant women at risk due to a previously affected infant. Immunoglobulin 1 g/kg weekly with or without oral dexarnethasone was first reported to lower the incidence of foetal cerebral hemorrage, increasing platelet count, compared to untreated patients. Dexarnethasone 3-5 mg/d augments the effect of immune globulin, although, in some patients, it was associated with oligohydramnios and foetal growth restriction. Prednisone can also be used to treat foetuses with an inadequate response to immune globulin alone, but presumably because of its lower anti-inflammatory action a dose of 60 mg/daily is required. Overall, weekly immune globulin 1 g/kg starting at 24 weeks′ gestation is the mainstay of therapy, while adjunctive corticosteroids is suggested in women who have failed prior treatments[103].

Recurrent Pregnancy Loss

As to maternal conditions that benefit from cortisone therapy, in addition to chronic inflammatory diseases with autoimmune character, a significant improvement of knowledge came from studies on the role of uterine natural killer cell (uNK) cytotoxicity in recurrent miscarriage. In early pregnancy there is an increase of uNK cells under the influence of steroids. They are believed to promote trophoblast growth and immune modulation at the foetal-maternal interface. Nevertheless, despite their presumptive physiological role, uterine and peripheral NK are involved in recurrent miscarriage and pregnancy los, and their toxicity participates in the rejection of the product of conception[104]. GC are abie to suppress in vitro NK and other inflammatory cells cytolytic activity and their tumor necrosis factor-alfa production[105]. It is worth to analyze the case of a patient with history of 19 consecutive miscarriages, in whom an high number of uNK had been found. She was first observed folIowing 14 miscarriages between the 8th and the I 0th gestational week. The remote medical history and the following investigation screen were negative: hormone profile, viral screen (toxoplasmosis, cytomegalovirus, hepatitis and herpes simplex virus), autoimmune screen (anti-DNA, mitochondrial and thyroid antibodies), full blood count, random blood sugar, karyotype analysis of both parents, ultrasound scan of the uterus,

hysteroscopy, antiphospholipid syndrome screen including IgG and IgM anticardiolipin antibody titres and dilute Russell viper venom time, Leiden factor V gene mutation, prothrombin gene mutation, methyltetrahydrofolate reductase mutation, antithrombin III deficiency, and activated protein C resistance. The mid-luteal level of uNK was the highest the Author had ever recorded. Pre-conceptual prednisolone 5 mg/daily was prescribed, leading to five further early losses. Therefore, a dose of 20 mg/daily preconceptual prednisolone was prescribed for 6 months prior lo conception. The hormone administration was stopped at the 5th week of her twentieth gestation. The pregnancy was complicated by foetal growth restriction and oligohydramnios. A caesarean section was performed at 33 weeks, with the birth of a 1484 g female in good conditions[106]. This was an unexplained result in the opinion of the Authors, although it is largely justified by the intensive regulatory action of the glucocorticoids on cellular and humoral immunity. In the absence of other maternal causes of miscarriage, the above mentioned foetal inhability to turn off maternal gestational inflammation may be considered a possible cause of the recurrent miscarriages in this patient. Moreover, the foetal growth restriction shows that, despite the high dose administered, the hormone was not able to completely remove the utero-placental vascular compromise produced by gestational inflammation. It has been suggested that estrogens and GCs could act directly on uNK cells through their receptors, influencing gene transcription at the decidual level. In addition, they down regulate inflammatory cytokine production by a variety of other cells[107]. Although immunoglobulins are reported to be almost equally effective as prednisolone in suppressing in vitro NK cell cytolytic activìty, it must be recalled that GC immuno-modulation is the result of a specific and complex action involving different cellular types and a large numberof cytokines and prostanoids.

A combination of prednisone, aspirin, folate, and progesterone has been reported to be associated with a higher live birth rate and a better foetal outcome compared with no treatment[108]. On the other hand, it has been also reported that elevated plasma cortisol concentration in early pregnancy may predict subsequent risk of pre-term labour with apparent mediatory role for increased placentaI CRH output[109]. Nevertheless, the eventual clinical relevance of this finding remains to be established. However, Nk percentage and cytotoxitity is not the only feature of gestational inflammation, since Th1/Th2 ratio imbalance is enough to trigger it. It follows that the measurement of this ratio in the maternal and foetal compartment is essential for the early diagnosis of potentially fatal complications.

Low-dose betamethasone alone througout pregnancy for prevention of gestational early and late inflammatory complications has been reported in patients with history of recurrent miscarriage[110][111][112]. According to the Authors, this therapy, named ‘Irpinia Resolution’, showed a greater efficacy in terms

of live birth rate and neonatal well-being compared to other treatments. The patients in their clinical studies, due to history of 2 to 10 previous miscarriages or pregnancy loss, had been already studied with laboratory tests and operative hysteroscopies for the search of endometrial inflammatory cells, and treated with surgical excision of uterine fibroids or endometriosis foci. In addition, they had been cured with variable doses of single or combined drugs, including progesterone, aspirin, heparin and prednisolone. Therefore, they were assigned to low-dose betamethasone therapy without further investigation and regardless of the results of previous tests. In the opinion of the Authors, there are three main reasons for the better perfoormance of low-dose betamethasone (usually 0,5 mg/daily until delivery): first, the well known greater anti-inflammatory activity of fluorinated GC compared to prednisolone; second, their resistance to inactivation by 11-beta-hydroxysteroid-dehydrogenase; third, their broad action against all aspects of the complex process of cellular and humoral inflammation. Thanks to these characteristics, betamethasone exerts its action precisely where it is required, that is at the level of the chorionic villi and maternal decidua, where gestational inflammation is triggered and produces its first effects.

Based on these evidences, these Autors encourage clinicians to adopt the 'Irpinia Resolution' for prevention of gestational inflammation in single cases, without fear of foetal and maternal adverse events. Once the potential of this therapy has been sufficiently confirmed in selected cases, further validation by means of case-control trials comparing treated with non treated patients would be welcome before directing it to the general population.

Concluding remarks

Uncontrolled Gestational Inflammation is the cause of the major obstetric complications, including euploid and aneuploid sporadic and recurrent miscarriage, foetal growth restriction, premature birth, up to perinatal and maternal death.

Recognize that major obstetric complications are due to the failure of the foetus to control gestational inflammation, is not a common mental attitude among clinicians. It is the Author's opinion that a greater diagnostic effort on the foetal causes, and more effective anti-inflammatory steroid therapy, would significantly improve live birth rate and perinatal well-being, meeting the expectations of the women who suffer from the recurrent denial of their motherhood.

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.