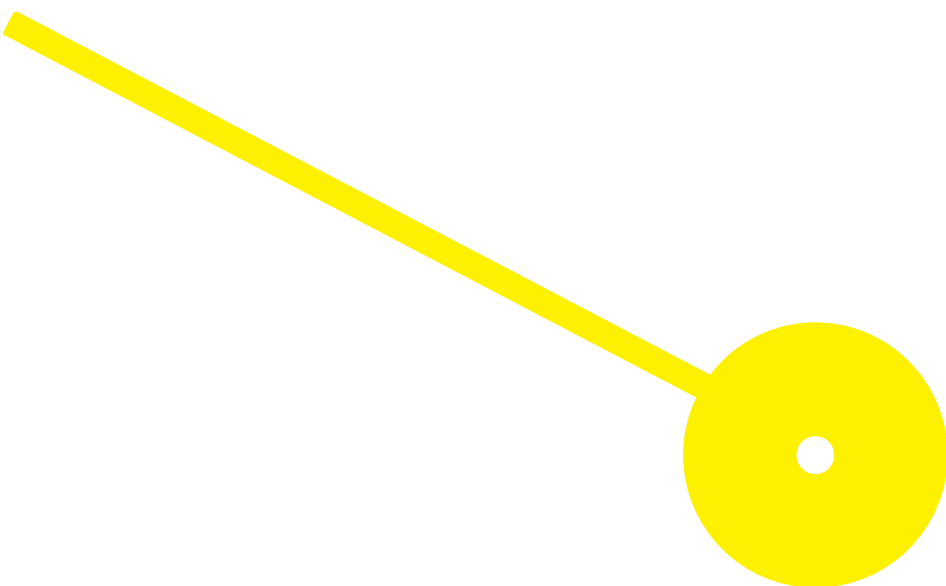




Prenatal inflammation and susceptibility to diseases: a systematic review on the first step of accelerated aging

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09/2024





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**Prenatal inflammation dysregulation and susceptibility to diseases:
a systematic review on the first step of accelerated aging**

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Dissertação apresentada para cumprimento dos requisitos necessários à obtenção do grau de Mestre em **Análises Clínicas e Saúde Pública** – Ramo de **Imunohemoterapia e Transplantação** pela Escola Superior de Saúde do Instituto Politécnico do Porto.

Agradecimentos

Este ano que passou foi uma montanha-russa de emoções, tanto a nível pessoal como profissional. A meu ver, o fruto deste projeto deve-se à influência de várias pessoas que, direta ou indiretamente, estiveram nele envolvidos. A todos, um sincero “obrigada”.

Este projeto é essencialmente dedicado à estrela que mais brilha no céu ao anoitecer. Alguém que viveu os seus últimos anos em sofrimento devido a uma doença crónica. Alguém que dizia “este será o meu último Natal” todos os anos desde que me lembro, exceto no último ano. Ao meu maior fã e apoiante, ao meu avô.

Resumo

Introdução: O aumento da esperança média de vida ao nascimento foi acompanhado com o aumento da incidência de doenças crónicas. A acumulação de inflamação crónica de baixo grau resulta em consequências detrimenais associadas à aceleração do envelhecimento. Para identificar quando se inicia, esta revisão foca-se na desregulação da inflamação pré-natal, procurando identificar se existe uma relação entre o desvio do padrão inflamatório durante a gestação e o desenvolvimento de doenças crónicas na vida adulta.

Métodos: A pesquisa de artigos foi efetuada em abril de 2024 nas bases *Pubmed*, *Web of Science* e *Embase*, usando *queries* semelhantes. Todos os dados obtidos foram geridos na plataforma *Microsoft Excel* e foram seguidas as *guidelines PRISMA*.

Resultados: Um total de 20 artigos foram incluídos para revisão, sendo na sua maioria estudos experimentais. Os biomarcadores mais enfatizados foram *IL-6*, *IL-1 β* e *TNF- α* e as doenças crónicas mais abordadas são associadas a desenvolvimento cerebral ou pulmonar, associado principalmente a nascimentos prematuros.

Conclusão: Existe uma clara influência da desregulação das citocinas na saúde do feto e no desenvolvimento de futuras doenças crónicas. Seria importante desenvolver estratégias de acompanhamento da taxa inflamatória no terceiro trimestre e prevenir que futuras gerações desenvolvam estas doenças.

Palavras-chave: *Aging, Prenatal inflammation, Chronic Diseases, Cytokines, Prenatal Exposure Delayed Effects.*

Abstract

Background: With increasing life expectancy, it came higher incidence of chronic illnesses. Throughout life, low chronic inflammation accumulates causing detrimental effects that accelerates aging. To identify where this inflammation begins, this review focused on inflammation before birth, searching for a relation between inflammation deviation during pregnancy and the development of chronic diseases.

Methods: The search was conducted in April 2024 in PubMed, Embase and Web of Science databases, using similar queries. All the data was handled in Microsoft Excel and PRISMA guidelines were implemented.

Results: A total of 20 articles were included for analyze, mostly experimental studies. The most emphasized biomarkers were IL-6, IL-1 β e TNF- α , and the most referenced were associated with brain and pulmonary fetal development, in relation to preterm birth.

Conclusions: There is a clear influence of cytokines unbalance in the health of the fetus and future chronic diseases development. It would be important to develop strategies to follow pregnancies throughout this final trimester to intervene and allow full development or measure inflammation to prevent future generations from this reality.

Keywords: Aging, Prenatal inflammation, Chronic Diseases, Cytokines, Prenatal Exposure Delayed Effects.

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1. Introduction

In the last century, societies have faced an unprecedented increase in life expectancy, however, the extension of lifespan has not been paralleled by an equivalent improvement in healthspan, the period of time free from any age-associated condition or disease (1). According to "Our Life Expectancy" website, the average life expectancy after birth, 100 years ago, was 32 years worldwide (2), which means that it has more than doubled in the last century, with a life expectancy after birth of 73,4 years, in 2023, which is an extremely short time in the evolutionary scale. This unbalance has led to a significant rise in the prevalence of chronic diseases, posing deep challenges for healthcare systems and quality of life of aging populations. Understanding this topic is fundamental to develop prevention methods and strategies to enhance the quality of those extended life years (3).

Interestingly, there are common underpinnings between aging and chronic diseases (4,5). Thus, it becomes instrumental to understand what the aging process is, when does it start and how it shapes disease trajectories. This is crucial to develop strategies able to model adaptive processes upwards and, at the same time, downregulate the chronic detrimental ones, throughout life.

Recently, the concept of inflammation has been presented as the missing link between aging and chronic diseases development (6,7) i.e., the older the organism is, more likely it will lead to dysregulated inflammation, increasing susceptibility to tissue damage and to develop chronic diseases (8), and concomitantly, resulting in decreased quality of life at older ages (9). Therefore, many studies related to aging focus on understanding its fundamental mechanisms to translate in improved healthspan trajectories. (10).

To learn more about the relation between aging and inflammation, this study will focus on their temporal origins, to understand when does inflammation start to accelerate biological age, and how it affects long-term systemic homeostasis.

1.1. Aging

The definition of aging is still ground of active discussions in the scientific community. It was first hypothesized that aging is a consequence from a genetic program within the genes (11), in contrast by other schools of thought who now are more confident that aging is a mere consequence of the accumulation of errors and loss in adaptability from internal and external

damage (12). Concordant to both sides, aging presents itself as a multi-factorial complex process worthy of being studied, not to only to extend lifespan but, more importantly, to augment healthspan (1).

This process results in progressive changes to organisms, affecting biological processes and the normal function of tissues but, more importantly, it affects human life in different ways (13).

As an example, with increased life expectancy uncoupled by healthspan has led to an accumulation of diseases related to aging – chronic diseases such as cardiovascular diseases, neurodegenerative disorders and a multitude variety of cancers (4,14). This is believed to be caused by the single most important risk factor: increased biological aging (15). But what leads to biological age acceleration? Although, this remains elusive, the main characteristics of accelerated biological aging individuals, are related to immunological alterations, chronic inflammation and decreased cellular repair capacity, which together, contribute to increased vulnerability of organisms for dysfunction and chronic diseases (16,17).

Thus, it is reasonable to speculate that individuals can be stratified based on inflammation-driven acceleration of biological age (18). Moreover, understanding the origins of inflammation may lead to important clues on the true nature of biological aging.

1.1.1. Chronological age

When discussing aging, it is important to discriminate whether or not, the focus is on chronological or biological aging, since biological age has an extra layer of relevance.

However, aging, broadly speaking, refers to chronological age, which is the numeric value of time measured after one's birth. As individuals age chronologically, they are more susceptible to become distinct and develop certain types of age-related diseases. Driving these different paths, are exposures to both internal factors, such as dysregulated immune system, oxidative damage, among others, and external factors, such as dietary patterns and environmental exposure (19).

The immune system dysregulation commonly involves age-related biases in molecular and cellular processes, and thus, decreased optimal function. The result is impaired ability to resolve infections or eliminate cancer cells or establishing a persistent inflammatory microenvironment (15). Moreover, since the clearance of senescence cells is impaired, this contributes to the establishment of an inflammatory microenvironment as well (20). The persistent inflammatory state, driven by what is called immunosenescence, results in a low-grade chronic inflammation

across tissues and presents itself as a critical event in the onset and progression of age-related diseases (4,21).

Although chronological age presents a higher risk for developing chronic illnesses, some older individuals do not exhibit any diseases nor appear with declining healthspan. Thus, the origin of this variability is closely linked to biological aging rate and so, it becomes highly relevant to understand and measure biological age, as a defining factor for predisposition for dysfunction and disease.

1.1.2. Biological age

While chronological age is a measurement of the time, that has elapsed since birth, biological age reflects the physiological and functional state of an organism, which may differ significantly from its chronological age. This variable metric is assessed by measurements developed using aging biomarkers, which are indicators that estimate the biological age of a cell, tissue or organism (22). Interestingly, recent findings have shown that biological age can differ between organs within the same organism due to genetic susceptibility, lifestyle and environmental exposure (23).

The aging clocks, which are biological quantifications of specific functions in association with an individual chronological age, are a strong example of successful biomarkers of aging. This measure is built from an algorithm design to estimate an individual's biological age (24), which provides information on health status, identifies tissues in need for preventative care, and stratifies individuals at higher risks for diseases development (25). One of the most common used is the epigenetic clock, using DNA methylation patterns that capture the cumulative impact of various aging processes at the molecular and cellular level (26). These epigenetic changes alter gene expression and may contribute to accelerated aging, and are captured by the epigenetic clocks, such as the Horvath clock (27).

Also, individuals seem to age their organs at different paces, the idea of ageotypes (see below) can be used as accurate predictors of health and longevity (28), meaning that they can be applied to identify the specific accelerated aging tissues across individuals, to help shaping novel public health policies according to personalized needs. This debuts preventive medicine, more focus on prevention, rather than the commonly adopted reactive medicine. Furthermore, understanding the fundamental process of biological age, and its origins will help to tailor interventions to timely compress tissue dysfunction and chronic diseases (29).

A recent study stated that inflammation can be used as a biomarker of aging, i.e., proteomic inflammatory aging clock (*iAge*), as it was strongly associated with damage accumulation and, consequently, diseases development such as frailty and cardiovascular disease (30,31). This clearly illustrates, the strong connection between the proinflammatory state and biological age acceleration. As a matter of fact, low-grade chronic inflammation also known as inflammaging (32), can contribute to cellular damage, and immune system dysregulation, playing a critical role in the loss of homeostasis (19,21).

In a different study, a machine learning model approach using plasma proteomics data was used to show that close to 20% of people experience accelerated biological aging in a single organ, increasing its risk for chronic diseases development and mortality risk (33). Adding to this, recent years have shown that the functional performance of several tissues in the human body varies across individuals, for example, some may be cardioagers, i.e. who suffer from accelerated age of the cardiovascular system (34), while others are described by renal agers, i.e., who display kidney accelerated biological age (35). These differences across individuals, put them at risk for cardiovascular disease or chronic kidney disease, respectively. This suggests that different individuals show different trajectories of biological age, but what how and when were these differences set?

Another study demonstrated that proteomic aging can be used to predict age-related functional status, multimorbidity and mortality risk across populations (30). The data also introduced "age gaps", deviation from chronological age, as a metric to describe patterns of heart, brain, kidney and liver aging, that can be used in the future to provide insights into disease progression(33), which has been validated in another study that aging is distinct across different organ systems (36).

To sum up, inflammation is an important link between the molecular and cellular processes in chronic diseases and accelerated biological age (14,37).

2. Pregnancy: the first step towards aging

In order to avoid the accumulation of a multi-stage process of aging, the search for its beginning has motivated a paradigm shift. The first published research was in 2004, suggesting that microenvironment during develop could predispose individuals to age-related diseases (38), followed by Gluckman et al 2004, introducing the idea of fetal programming with late life outcomes (39). Recently, the ground zero theory of aging proposed a model where it states that

both organismal life and aging begin closer to mid-embryogenesis (40). During the third week of gestation, gastrulation occurs, a critical process in the early stages of pregnancy in which an embryo alters its structure, called the gastrula, reaching at this stage, the lowest point of biological age. The ground zero theory of aging thus proposes that this is the moment where aging begins (41). Allison and colleagues stated that the process of aging is connected to early developments in the womb, by finding that mothers supplemented with antioxidants during late pregnancy contributed to healthy aging in adulthood (42), emphasizing the connection between development and aging.

At the early stages of pregnancy, during developmental gastrulation, amniotic fluid consists of a filtrate of maternal blood. For this reason, it is possible to correlate the embryonic environment with the maternal state (43), since everything the mother has been exposed to, can cross the placenta and enter the amniotic fluid by diffusion. For example, upon maternal high consumption of mutagenic compounds, such as tobacco, alcohol, or drugs, the embryo will be negatively affected (44,45), namely in placental function and in fetal growth (46).

Studies using animal models have also shown that IL-6 present in the mother's blood can directly cross the placenta and cause behavioural issues in the offspring (47). This is likely due to inflammatory signalling pathway that crosses the placenta, leading to altered epigenetic mechanisms (48), which results in fetal DNA methylation deviations (49). The last pathway presents a huge weight to the investigation of aging due to its crucial role in later disease development (50).

There are several hormones and immunological molecules in a delicate balance throughout pregnancy, not only to sustain a healthy process, but also to avoid any mechanism of defence that may become overactivated and attack the embryo (51). This sensitive environment grants a mechanism to dodge unwanted immune responses against the allogenic fetus by protecting the embryo against infections without rejecting it as a foreign object (52).

To protect the fetus from rejection, there are many mechanisms involved, such as the expression of HLA-G by the placenta, inhibiting the cytotoxicity of the NK cells by preventing their activation, and activating the T reg cells, which are responsible for maintaining immunological tolerance against paternal antigens (53–56).

When the main hormones of the female reproductive system, estrogen and progesterone, are at their peak during ovulation, they align with a perfect microenvironment for egg fecundation and, and if that does not occur, the menstrual phase begins. In case of fecundation, there are a

group of cytokines that are released, stimulating the ovaries to continue producing these hormones (51,57). Progesterone is essential to prepare the uterine wall for the embryo implantation, and to prevent uterine contractions that would otherwise cause rejection of the embryo and consequently, pregnancy loss. On the other hand, estrogen allows vascularization of the endometrium for a bigger blood supply to the placenta and uterine growth (57) and contributes to regulation of the innate immune function, reducing pro-inflammatory cytokines, such as IL-6 (58,59).

When it comes to cytokines, they modulate the maternal immune response to avoid rejection of the half-allogenic embryo, who is identified by the maternal immune system as non-self. The leukemia inhibitor factor (LIF) will then promote the trophoblasts to invade the endometrium and integrins, as link proteins, will attach it to the uterine wall (60).

These molecules will play their role in the pregnancy process as a whole, working to the same aim: a successful pregnancy, from fecundation to delivery (61,62).

However, external stimuli such as lifestyle, infections, tobacco consumption, alcohol intake and dietary patters can influence inflammation patterns and interfere with the embryo development which has different levels of phenotypes depending on the development phase (32,44,63).

2.1.1. First trimester

Early pregnancy is a very delicate phase of development since more than half of the natural pregnancy-losses are caused by chromosomal abnormalities, anatomic uterine abnormalities and immunological dysregulation (43,51,64,65). As a well-orchestrated process, there is at first, an elevation of cytokines production that aims to ease the invasion of trophoblasts into the uterine wall and help rearranging the endometrium for placental establishment (66).

The array of predominant cytokines in the first trimester are of pro-inflammatory nature, providing a controlled local inflammatory environment, with interleukins such as IL-1 β , IL-2, IL-6, interferon-gamma (IFN- γ) and tumoral necrosis factor-alfa (TNF- α) (67).

Regarding these cytokines, they can also compromise pregnancy viability if unbalanced. Previous studies on TNF- α have found that, when amplified, it is associated with pregnancy loss (68). It has also been found that, within a certain context, anti-inflammatory cytokines are produced by villous cytotrophoblast, such as IL-1 β and IL-8, with increased gestational age (69), which might be a mechanism to balance the inflammatory scale in this first stage of pregnancy.

Following this coordinated inflammation period, is the formation of the embryo's main organs and systems, i.e., the heart is fully developed and starts beating, the core of the brain and spine are formed (70). This emphasizes the importance of controlled adaptative inflammation that is instrumental in assisting first trimester development.

2.1.2. Second trimester

By the 13th week, the fetus enters a stage of growth and further development, having its main systems already formed. This is the case for the bones that begin to harden, allowing bone marrow to assist in hematopoiesis, and the immunologic systems to mature, beginning the production of T and B-cells (71). To sustain the embryo growth there is the requirement for higher blood volume to satisfy its nutrient's necessity (72). With the increased production of red blood cells, the iron is consumed rapidly, which explains why it is common to see pregnant women displaying conditions of iron deficiency.

Interestingly, during the second trimester, there is also fine-tuned changes in the inflammatory landscape being, however, quite distinct from the previous trimester. This means that the surrounding environment, during the second trimester is mainly constituted by anti-inflammatory molecules, with a strong presence of interleukin-10 (IL-10), interleukin-4 (IL-4) and Transforming Growth Factor - beta (TGF- β) (66).

This anti-inflammatory environment is crucial for fetal growth and development by ensuring safety for the fetus. The cytokines described, modulate the maternal immune response and sustain tolerance, vital for reducing the risk for preeclampsia or abortion and retaining a healthy pregnancy (73).

2.1.3. Third trimester

During the last stage of pregnancy, there is a return of the pro-inflammatory environment to prepare for the ultimate stage: delivery. These cytokines work together to mature the uterus (74), fetal membranes form the uterine wall and to prepare it for continuous contractions to expel the baby through the vaginal canal.

Other than that, there is also an adjustment to the immunological response to maintain the equilibrium between protection and tolerance. A balance between cytokines in this phase is necessary for labor development. Cytokines IL-6, IL-1, IL-8 and TNF- α play a key role to increase

uterine contractability and cervical remodelling, helping in collagen breakdown to ease tissue changes and accommodate a suitable delivery process (75).

A cytokines unbalance has been linked to problems in pregnancy and childbirth, such as increased TGF- β linked to preeclampsia (76), and decreased IFN- γ associated with active labor (77), leading to pre-term labor.

In last stage of development, the brain develops rapidly with a faster neuronal myelination, and the lungs mature to sustain the first breath. The fetus immunological system starts to develop and to prepare for life outside the womb (78). In the past few years, IL-6 upregulation, above optimal thresholds, was shown to be linked to cognitive developmental alterations and behaviour disorders in early life (47), supporting the idea that there is a susceptibility for cognitive impairment and potentially psychiatric disorders in relation to utero environment (79,80), i.e. autism spectrum disorder and attention-deficit and hyperactivity disorder (ADHD) (48).

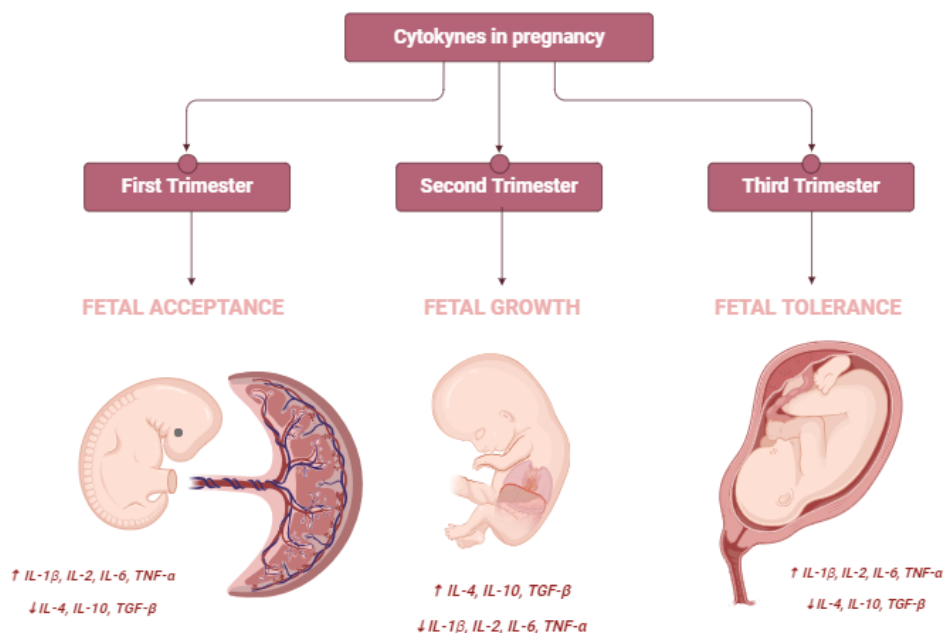


Figure 1 – Cytokine's role in pregnancy development throughout each trimester. Pro-inflammatory cytokines are more evident in the first and third trimester, to implement pregnancy and to prepare for childbirth, while anti-inflammatory cytokines are necessary in the second trimester to allow fetal growth.

Accordingly, it is clear that pro-inflammatory cytokines help to mediate not only late-stage tissue development such as brain neuronal myelination or lung maturation, but also to prepare the proper setting for delivery by increasing uterine contractability and cervical remodelling for childbirth, as presented in *Figure 1*.

2.2. Inflammation as a double edge sword

An important feature of the immune system relates to inflammation modelling as a defence mechanism (81). Inflammation is a response to a specific *stimulus* at a particular location, meaning that different *stimuli* can cause different responses: although most *stimuli* are caused by physical injuries, they can also be triggered by infections, allergic or autoimmune diseases, or due to environmental factors or nutritional imbalances (82).

Nonetheless, there are common mechanisms of the innate immune system such as a recognition of the *stimulus*, followed by activation of proliferation of dedicated immune cells, primed for pro-inflammatory actions, as well as to increased vasodilation and permeability. For example, the neutrophils are attracted, via cytokines produced by mastocytes and endothelial cells, to the primary lesion location and, after activation, they play an active role in healing and replacing old tissue with healthier tissue(83). The phagocytes digest the pathogens or damaged cells, producing reactive oxygen species (ROS) followed by resolution of inflammation (84). This is commonly an acute short-term inflammation confined to the injury site, decreasing after the issue is resolved.

However, to every rule there are exceptions. In some cases, where the inflammation endures after resolution, this results in a residual low-grade inflammation that, if persistent, becomes chronic with severe outcomes to the organism. For example, a recent study showed that inflammatory aged B cells, from the adaptative system, can contribute to an inflamed microenvironment and drive cancer progression, namely B cell lymphoma (85).

Chronic inflammation is linked to many of the hallmarks of aging. It is responsible for DNA damage which results in poor control of the immune system. Thus, since inflammation is a common underpinning between aging and chronic diseases, assessing its origins and locations can be used to identify the most at-risk individuals for those diseases. In fact, the aforementioned inflammatory aging clock (iAge) was based on patterns of systemic age-related inflammation for early detection of age-related clinical phenotypes, tracking accelerated aging (18).

Some diseases caused by this can be atherosclerosis, diabetes or any autoimmune disease. As such, this type of inflammation can also be described as detrimental inflammation.

2.2.1. Detrimental inflammation

In previous studies, low-grade chronic inflammation has been set as a common link in chronic diseases and aging, which motivate research on the origins of detrimental inflammation and its full impact in healthspan and lifespan.

As mentioned before, *inflammaging* can persist even after the trigger is suspended, resulting in long-term consequences. An uncontrolled inflammatory response can have negative effects at the organismal level, playing the opposite role of what it was supposed to: harm instead of protective adaptation.

According to Saavedra and colleagues, chronic inflammation follows cellular senescence, microbiome composition imbalance, exhausted immune cells, and mitochondria-induced epigenetics alterations (86) just to mention a few. This suggests hypersensitive of the immune system to become pro-inflammatory as the organism ages.

The continuous chronic inflammatory conditions in the organism might be a result of a failed inflammation resolution, with abnormal infiltration of immune cells that aim to resolve an unsolvable problem, but by failing so, leads to an ever-increasing inflammatory microenvironment, culminating in extensive tissue damage and fibrosis (87).

Table 1 – Main cytokines involved in inflammatory processes and their functions.
Adapted from Chen et al. 2018 (83)

Cytokine	Family	Main sources	Function
IL-1 β	IL-1	Macrophages, monocytes	Pro-inflammation, proliferation, apoptosis, differentiation
IL-4	IL-4	Th-cells	Anti-inflammation, T-cell and B-cell proliferation, B-cell differentiation
IL-6	IL-6	Macrophages, T-cells, adipocyte	Pro-inflammation, differentiation, cytokine production
IL-8	CXC	Macrophages, epithelial cells, endothelial cells	Pro-inflammation, chemotaxis, angiogenesis
IL-10	IL-10	Monocytes, T-cells, B-cells	Anti-inflammation, inhibition of the pro-inflammatory cytokines
IL-12	IL-12	Dendritic cells, macrophages, neutrophils	Pro-inflammation, cell differentiation, activates NK cell
IL-11	IL-6	Fibroblasts, neurons, epithelial cells	Anti-inflammation, differentiation, induces acute phase protein
TNF- α	TNF	Macrophages, NK cells, CD4 ⁺ lymphocytes, adipocyte	Pro-inflammation, cytokine production, cell proliferation, apoptosis, anti-infection
IFN- γ	INF	T-cells, NK cells, NKT cells	Pro-inflammation, innate, adaptive immunity anti-viral
GM-CSF	IL-4	T-cells, macrophages, fibroblasts	Pro-inflammation, macrophage activation, increase neutrophil and monocyte function
TGF- β	TGF	Macrophages, T cells	Anti-inflammation, inhibition of pro-inflammatory cytokine production

There are many molecules involved, notably:

- Cytokines – signalling proteins produced by different cells to model inflammation (66);
- Chemokines – cytokines specialised in drawing immune cells, such as IL-6;
- Prostaglandins – lipidic molecules that controls inflammation by managing its consequences, such as prostaglandin E2 (PGE2);
- Complement proteins – promote inflammation by amplifying its response, such as C3a;
- Mediators, such as histamine, among others.

This review will emphasize cytokines as shown in *Table 1*.

As a conclusion, detrimental inflammation differs from acute adaptative inflammation for its persistence and extent, i.e., when the levels are optimal, they serve many physiological processes but when dysregulated, they contribute to damage and, in some cases, even pregnancy loss, as shown on *Figure 2*.

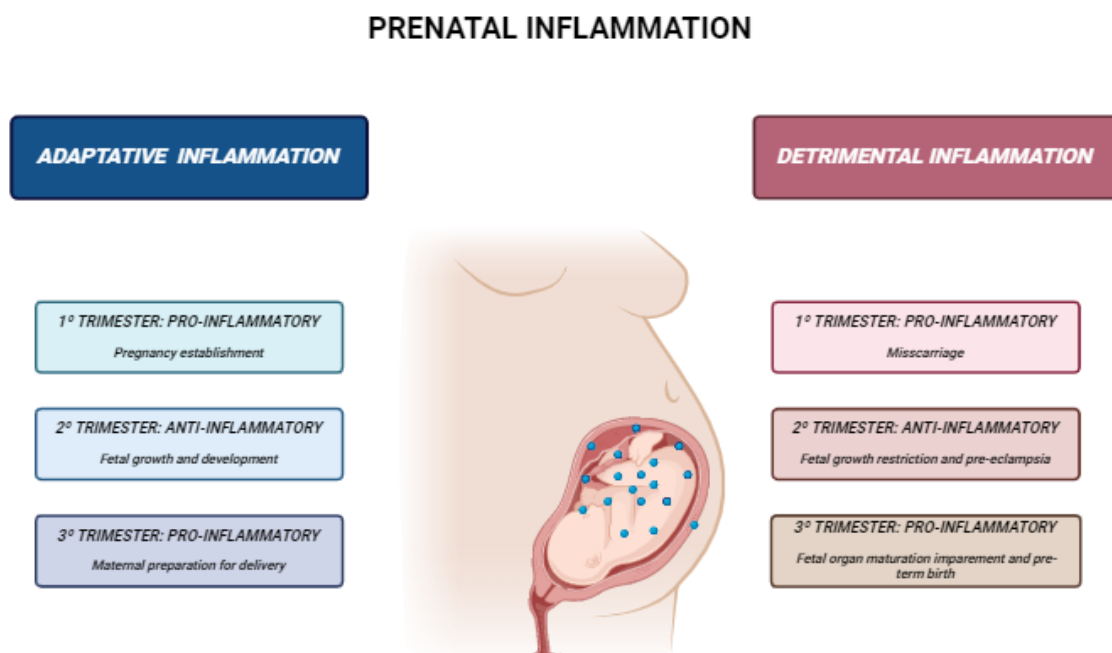


Figure 2 – Importance of inflammation balance throughout pregnancy. According with the dosage of cytokines in each trimester, the ideal pattern of inflammation will allow a pregnancy development while unbalance will cause detrimental inflammation, resulting in pregnancy complications and higher disease susceptibility for the fetus.

The prolonged inflammatory state is associated with many chronic diseases' formation. This imbalance between pro-inflammatory and anti-inflammatory signals can do more harm than good, hence its importance to manage for preventing and treating inflammation-related diseases both in the short and long-term.

2.3. Inflammation as the link between pregnancy and accelerated biological age

Along this review, the importance of inflammation for a living organism from prenatal stages of development to older ages has been established. It has been demonstrated that cytokines can both serve as immunological trackers of aging, e.g. aging clocks, and immunological indicators for a healthy pregnancy. So, how do cytokines behave as a predictive marker for development of chronic diseases?

Interleukin-6 (IL-6) is a cytokine, produced by macrophages and lymphocytes, and occasionally by endothelial cells, that aims in promoting inflammation. IL-6 is also involved in uterine remodelling for embryo acceptance, facilitating implantation, and in childbirth induction by increasing the production of prostaglandins and oxytocin (61). However, when dislocated from optimal levels, IL-6 is associated with pregnancy complications, such as premature birth (88), neurocognitive dysfunction (89) and preeclampsia (90,91).

Similarly, the IL-8 is involved in embryo implantation and birth induction, but it is especially important in maternal-fetal communication and placenta formation (61). As a chemokine, IL-8 can attract inflammatory cells, which can be both good or bad, depending on the context and gestational stage, and has similar complications to IL-6, when altered. When out of the optimal range, it can also cause intrauterine growth restriction and, in some cases, gestational diabetes *mellitus*, induced through heightened inflammation, initiated by microbial dysbiosis (92).

To activate the immune cells, TNF- α has a major role in response to infections serving as a cytokine responsible for maintaining the proinflammatory microenvironment. TNF- α also plays a fundamental task in embryonic implantation in the uterine wall but if dysregulated may lead to miscarriage (66).

Moreover, IFN- γ is pleiotropic molecule and has been widely described for a multitude of roles by engaging in innate and adaptative immune system. Its role in aging process has been documented and discussed in a study stating that a lower IFN response is associated with extended lifespan in aging models, such as mice and *Drosophila* (93). It is produced not only by antigen presenting cells (APCs) but also by other immune cells, such as T Cells and NK cells, and

has a profound role in adaptive processes for example neural differentiation. However, when exacerbated becomes detrimental and it can play a role in neuroinflammation causing degenerative disorders, like Alzheimer's and Parkinson's Diseases (94). IFN- γ can indirectly influence the IL-6 production by a positive feedback loop (95), and it has been shown that when both IL-6 and IFN- γ levels are increased, it creates a pro-inflammatory microenvironment that can negatively impact the cognitive and behaviour development (96) and ultimately result in pregnancy lost (52).

IL-1 β is a proinflammatory cytokine involved in modulation of immune responses that favours growth of the fetus. However, just like any other cytokine, when unbalanced, it triggers extensive inflammatory responses and compromises the maternal-fetal immune tolerance axis (65). Along with TNF- α , IL-1 β stimulates the PAPP- α protein, important for fetal development and growth, and also modulates insulin-like growth factor 1 (IGF1), a protein with a similar structure to insulin that promotes immune tolerance to the fetus (97). Interestingly, when low, it associates with fetal growth restriction, preterm birth, pre-eclampsia (98) and Down's syndrome (99).

To conclude, cytokines that are commonly linked to biological age acceleration are also found in the pregnancy development. It has been established that early inflammation can influence biological aging by accelerating its rate and, in some cases, it has been linked to the progression of chronic diseases.

2.3.1. Deviation of inflammation during fetal development leads to disease trajectories

IL-6 and TNF- α have been identified as the major mediators of inflammation during pregnancy, having a higher impact on pregnancy outcome when unbalanced, especially in correlation with the neurological diseases in the third trimester, as stated in the previous chapters (61,89). The fetal lung development is finalised post-birth, which makes it vulnerable to external and environmental factors and becomes particularly vulnerable to hypoxia (100). Some studies have also suggested that chronic obstructive pulmonary disease (COPD) and asthma, either have their start during fetal development or upon early childhood (100,101), but both seem to be connected to maternal habits and environmental exposures. However, altered immunological responses related inflammation, subsequently increase the risk for COPD throughout the life course (102,103).

In fact, a study from 2020 found that mothers with asthma have immune cells with SMAD3 hypermethylation and as well as increased secretion of IL-1 β , unlike healthy mothers. It was also

described, that above normal range, the exposure to IL-5 during fetal development can alter the efficiency of neurocin-1, a neurotransmitter crucial for neural development and synaptogenesis, that suggests fetal programming can be influenced by the mother immunological pattern during pregnancy (104).

In this context, the most discussed exposures in the literature are dietary patterns, nutrients, supplements intake and smoking habits (102), that were linked to increased cytokines production and poor T CD8+ adaptive immunity upon infection (105). Regarding dietary patterns, a diet based on animal high protein and low fiber, has been frequently associated with elevated inflammation markers while Mediterranean diet with reduced ones (87).

In a different study, prenatal and postnatal inflammation was linked to cortisol levels in preterm infants at 18 months, which may indicate reprogramming of the Hypothalamic-Pituitary-Adrenal Axis (HPA axis), an interactive system for homeostasis maintenance and stress management, that, due to early inflammatory stress (106), may impact later life outcomes such as psychiatric disorders (107), inflammatory chronic diseases (108) or even accelerated aging (109).

2.3.2. Does fetal exposure to detrimental inflammation accelerate biological aging later in life?

As mentioned above, biological aging acceleration may occur after chronic low-grade inflammation. However, it is not yet fully understood when biological aging begins let alone how it is triggered.

There is growing evidence that associate prenatal inflammation to an accelerated biological aging in offsprings (110), for example, accelerated epigenetic aging has been found in individuals exposed to high levels of inflammation in utero (111). Epigenetic changes include altered DNA methylation patterns, commonly associated with an increased risk of developing chronic diseases, such as chronic obstructive pulmonary disease (COPD) (103).

Understanding the molecular and cellular mechanisms involved in a balanced immunological microenvironment could potentially help to develop therapeutic opportunities to promote healthy pregnancies (42), and by doing so, modulate life trajectories towards decelerated biological age rate and concomitantly lower risk for the development of inflammatory chronic diseases. Other studies have established correlations between fetal exposure and the development of late life diseases; however, not only few have quantifications of the inflammation during pregnancy but

also, there are many variables that were not accounted for (mainly lifestyle and genetic susceptibilities) which posits a challenge for accurate interpretation and meaning.

2.4. Objectives

In this review, we aim to summarise and analyse available evidence of studies focused on inflammation during the prenatal stages, in both clinical trial and experimental studies, to shed light on what might be the first inflammatory trigger to accelerated aging in adult life and increased risk for chronic diseases.

It is aimed that the results shown and discussed in this systematic review might offer a new framework and stimulate discussions to develop preventive strategies to control accelerated biological aging rates during pregnancy and extend healthspan trajectories.

3. Materials and methods

The present study consists of a systematic review of literature. This review will be focusing on analysing and systematising available evidence in research databases, on the effect of inflammation exposure during gestation in the susceptibility of diseases and biological aging. It was conducted and written according to the *Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)* guidelines.

The PubMed, Web of Science and Embase databases were searched and conducted in April 2024 with languages limited to English, using the queries presented in *Table 2*. In the PubMed database, it was applied the filters "Clinical Trial" and "Randomized Controlled Trial" to exclude the reviews and systematic reviews due to many results, to allow a simpler analyse.

Table 2 – Query used for each database.

Databases	Chosen Query	Articles (n)
PubMed	"Inflammation"[Mesh] AND "Pregnancy"[Mesh] AND ("Chronic Disease"[Mesh] OR "Disease Models, Animal"[Mesh] OR "Fetal Development"[Mesh])	41
Web of Science	"Inflammation"[Mesh] AND "Pregnancy"[Mesh] AND ("Chronic Disease"[Mesh] OR "Disease Models, Animal"[Mesh] OR "Fetal Development"[Mesh])	74
Embase (HOST)	"Inflammation" AND "Chronic Diseases" AND ("Prenatal Exposure Delayed Effects" OR "Fetal Development")	37
	Total:	152

3.1. Inclusion and exclusion criteria

All the data was extracted from the selected databases to *Microsoft Excel* software to allow easier analyse. At first, the titles and abstracts were read to select the eligible articles that met the inclusion criteria. Afterwords, the full articles were read, and the exclusion criteria were applied to select the final articles for revision. The inclusion and exclusion criteria used for selection is shown on *Table 3*.

Table 3 – Eligible criteria for selection of articles.

Inclusion criteria	Exclusion criteria
1. Human or animal sampling from the gestation period, including maternal blood, umbilical cord blood or other embryonic material;	1. Duplicates removal;
2. Inflammation quantification;	2. Review and systematic reviews papers, meta-analyses and conference proceedings exclusion;
3. Biological aging acceleration;	3. Articles where at least one of the following inflammation factors were not evaluated: IL-1 β , IL-4, IL-6, IL-8, TNF- α , IFN- γ or TGF- β .
4. Chronic diseases development and/or related to "in utero" exposure;	4. Written in any other language rather than English.

After search, it was retrieved 152 publications for review. When applying the inclusion criteria, it was found that:

- 17 articles verified the inclusion criteria 1;
- 14 articles verified the inclusion criteria 2;
- 5 articles verified the inclusion criteria 3;
- 28 articles verified the inclusion criteria 4; and
- 41 articles verified two or more of the inclusion mentioned above.

The selection criteria mentioned above was applied to the retrieved articles, and the PRISMA flow diagram can be found in *Figure 3*.

In total, 105 articles verified the inclusion criteria defined by this study.

As expected, most of the excluded articles were due to exclusion criteria 2 and 3, once this topic on inflammation has been highlighted in the past years by investigators and community. Not many articles were published with numeric quantification of cytokines throughout gestation. After application of the exclusion criteria only 24 articles were found, and 20 articles were selected after risk of bias assessment.

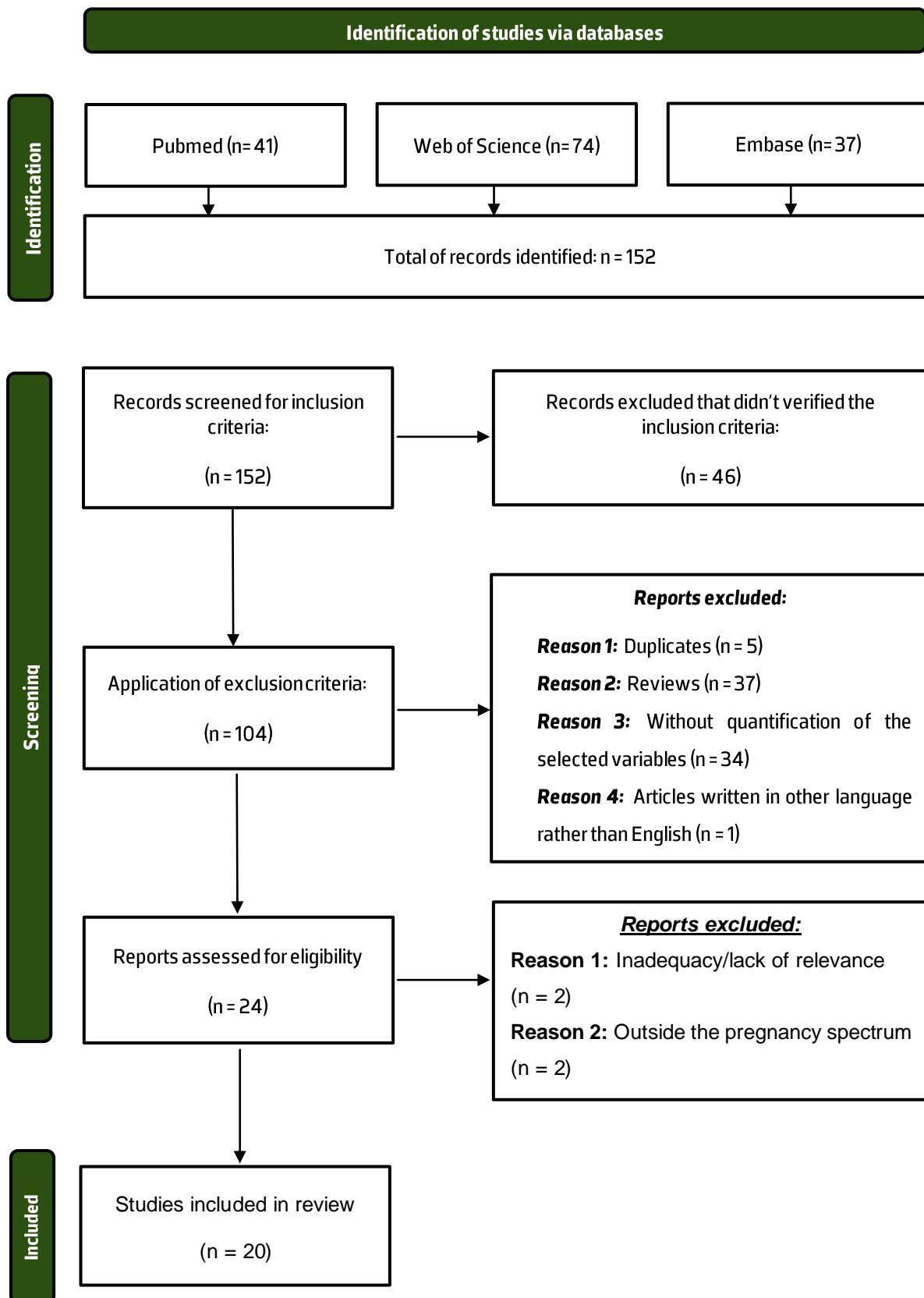


Figure 3 – Flow diagram for studies selection. Adapted from PRISMA.

3.2. Review development

The strategy of the article's development was set in January 2024 and included six main steps:

1. Select the topic and comprehensive reading of the subject;
2. PICO formulation: define the main question of investigation – “What is the Effect of inflammaging in organisms during their fetal development and in what way does it interfere in chronic diseases susceptibility?”;
3. Define search criteria and articles selection;
4. Database search and inclusion/exclusion criteria application;
5. Quality assessment and exclusion of the non-robust articles;
6. Writing.

3.3. Assessment of Risk of Bias

After criteria application, the *QUADRAS-2* was used to evaluate the risk of bias of the selected studies for review. This tool consists in a framework for critically analyse the main domains of bias by identifying bias sources and classification each study according to its risk. This step is crucial to validate and transmit confidence to this review conclusion, conferring a robust and impartial evidence presentation (112).

After summarizing the articles in the excel table, the main parameters of each study were evaluated, and four were excluded due to inadequacy to this reviews goal (113,114) and for being outside of the pregnancy spectrum (115,116).

4. Results

The selected criteria retrieved a total of 20 studies to be included in this systematic review, and the main characteristics of each study can be found in *Table 4*.

Half of the studies retrieved, consist in experimental studies, both in humans and animals, and the remaining are mostly observational studies, with publication year between 1997 and 2022. Among these studies, the sample sizes ranges from 35 to 927 individuals, with 7 studies without sample quantification information. Regarding the intervention duration, it ranges up to 8 years in a longitudinal study, with follow-up of offspring to evaluate diseases occurrence.

The experimental studies consisted mainly of prenatal inflammation induction with LPS, bacteria or use of a predisposed population to diseases, with only one study using a cytokine to induce inflammation.

Regarding the biological sample used, most studies relied on umbilical blood after birth (seven studies), histological process (six studies) or both (six studies), but a few also resorted with maternal blood (three studies) for comparative context. The most evaluated cytokines were TNF- α (twelve studies), IL-6 (ten studies) and IL-1 β (ten studies). Some other measured cytokines include IL-8 (5 studies), IL-10 (5 studies), IFN- γ (3 studies), IL-4 (2 studies), IL-2 (2 studies) and TGF- β (1 study).

Most of these studies focus on a specific disease or condition, with 7 studies evaluating inflammation relation in lung development, three studies on mother's obesity effects on inflammatory cytokine's production, two studies on psychological or cognitive dysfunction in result from prenatal inflammation, one on heart conditions in association with inflammatory discrepancies and one on predisposition for intestinal microbiome impact related to maternal inflammation. Eight studies evaluated inflammation in a general level.

Table 4 – Summarized results.

Reference	Study Design	Study Participants	Intervention	Results
Abioye, et al. 2018 (117)	Randomized Clinical Study	358 Pregnant women between 12 and 16 weeks infected with <i>Schistosoma japonicum</i>	Randomized administration of praziquantel, followed by blood samples at 32 weeks and after birth	Inflammatory anaemia in pregnancy did not have a significant impact on biomarkers after treatment with praziquantel
Takahashi, et al. 2015 (118)	Transversal Observational Study	122 newborns: 85 Preterm and 37 full-term	Cord blood collection	TGF β 1 is related to birth weight and gestational age (GA). Low levels were associated with chronic lung disease
Gantar, et al. 2013 (119)	Prospective Observational Study	129 newborns with GA < 30 weeks	Umbilical cord blood collection and gastric aspirate to measure IL-6 and IL-8. Pulmonary function tests conducted at 8 years of age	Preterm newborns showed reduced pulmonary function. IL-8 appeared to be relevant in early airway remodelling
Matoba, et al. 2009 (120)	Retrospective observational study	927 births grouped into GA < 32 weeks, 33 < GA < 36 weeks, and GA > 37 weeks	Quantification of 27 immunological biomarkers	Increased biomarkers included IL-2, IL-8, and TNF- α and decreased included IL-1 β
Hemmerling, et al. 2014 (121)	Experimental study in an animal model	Mice with genetic predisposition to ileitis and colitis, and controls without this predisposition	Maternal inflammation was induced using genetically modified mice that exhibit chronic inflammation	Disease severity is independent from maternal inflammation
Stouch, et al. 2016 (122)	Experimental study in an animal model	Mice fetus exposed to inflammatory conditions	Intra-amniotic injection of IL-1 β to induce inflammation in order to evaluate the inflammatory response and the abnormal development of fetal airways	Exposure to IL-1 β increased pro-inflammatory cytokines associated with changes in pulmonary morphology
Collins, et al. 2010 (123)	Experimental study in an animal model	Sheep fetus	Intra-amniotic injection of <i>Ureaplasma parvum</i> at 110, 117, or 121 days of gestation	Exposure to <i>Ureaplasma parvum</i> causes a mild acute inflammatory response in fetal lungs, with increased TNF- α and IL-10
Tissieres, et al. 2012 (74)	Experimental study	69 individuals: 24 newborns under 28 weeks, 25 newborns between 28 and 32 weeks and 20 adults	Umbilical cord blood was analysed to assess immune receptors, the cytokine response to bacteria, and opsonophagocytic capacity in association with IFN- γ	ELBW newborns showed a reduced inflammatory response to LPS and whole bacteria. Ex vivo treatment with IFN- γ reversed the defects in innate immune response

Table 4 – Summarized results (Cont.)

Reference	Study Design	Study Participants	Intervention	Results
Stouch, et al. 2014 (124)	Experimental study in an animal model	Transgenic C57BL/6 mice and IKFM mice	Fetal lung macrophages were stimulated with LPS, followed by IL-4 and IL-13 measurement	Fetal lung macrophages responded to LPS and the cytokines IL-4 and IL-13 similarly to adults. Activation increased the expression of pro-inflammatory genes and reduced the response to IL-4 and IL-13
Stewart, et al. 2007 (125)	Longitudinal observational study	60 pregnant women in under and over a BMI of 30 kg/m ²	Measurements of biomarkers of inflammation throughout pregnancy, and post-partum	The obese group had higher levels of IL-6, TNF- α , and the PAI-1/PAI-2 ratio indicates chronic endothelial activation and inflammation.
Mayor, et al. 2015 (126)	Experimental study in animal models	55 CR7/B16 mice: 30 high-fat diet and 25 in a normal diet	Gene and protein expression analyse and histological evaluation of the fetal lungs	These fetuses showed reduced structural development of the lungs, indicating impaired maturation.
Perdu, et al. 2015 (127)	Experimental study in an animal model	45 mice: obese female (BMI \geq 30 kg/m ²) and 45 controls	Uterine NK cells were isolated from uterine tissues for subsequent analysis	Obese females showed increased expression of genes related to metabolism and inflammatory stress
Levitona, et al. 2011 (128)	observational study	834 newborns born before the 28th week of gestation	The main intervention involved analysing the placentas and measuring inflammatory proteins in the newborns' blood	Inflammation in the umbilical cord was associated with elevated concentrations of inflammatory proteins in the blood of newborns
Hong, et al. 2006 (129)	Experimental study	Rats with glucocerebrosidase deficiency (< 4% of normal)	Analyse of pro-inflammatory cytokines, nitric oxide (NO) production, and reactive oxygen species (ROS) of brain samples	Increased levels of IL-1, IL-6, and TNF- α Gaucher rat's brains, and elevated IL-6 and TNF- α when treated with a glucocerebrosidase
Keelan, et al. 2015 (130)	Case-control study	98 pregnant women, but only 51 placentas were sampled	Ingestion of n-3 PUFAs (primarily DHA and EPA) from the 20th week of gestation	The expression of inflammatory cytokines PTGS2, IL1 β , IL6, and IL10 was not altered, however, there was an increase in TNF- α expression in the placenta
Kimya, et al. 1997 (131)	observational study	35 pregnant women: 10 who developed pre-eclampsia and 25 uncomplicated pregnancies	Blood samples were taken at various gestational weeks to measure levels of IL-1 α , IL-1 β and IL-1r	IL-1ra levels were significantly higher in the pre-eclampsia group, with 100% negative predictivity and sensitivity at 20-25 weeks

Table 4 – Summarized results (Cont.)

Reference	Study Design	Study Participants	Intervention	Results
Gantar, et al. 2011 (132)	Observational Study	115 premature newborns under 30 weeks	Prenatal steroid treatment followed by histological examination, and IL-6 and IL-8 measurements	There was no significant difference in the presence of chorioamnionitis and levels of IL-6 and IL-8 between infants who developed BPD and those who did not
Liu, et al. 2022 (133)	Experimental study in an animal model	Pregnant female mice and their offspring	Chronic inflammation inducement with IL-1 β during pregnancy	CD45+ leukocyte infiltration increased in the placenta and reduced fetal viability. There was an increase in the expression of CD8 cells, but no significant changes in CD4 and FoxP3
Matoba, et al. 2011 (134)	Cohort study	74 SGA births and 319 births	Relating 27 umbilical cord blood immune biomarkers with small gestational age (SGA)	Biomarkers were selectively associated with SGA status, showing lower levels of log IL-1 β log BDNF and log NT-3
Ni, et al. 2022 (135)	Experimental study in an animal model	Male offspring CD-1 mice	Exposing pregnant mice to LPS to induce prenatal inflammatory exposure. The male offspring were later subjected to different environments	Cognitive decline was verified, and exposure to LPS caused increased IL-6, IL-1 β , TNF- α . Long-term EE exposure reduced these cytokine levels. LPS exposure caused higher NGPF2 and lower PSD-95, related with cognitive decline

5. Discussion

As established at the beginning, inflammation is an important link to biological aging acceleration, which has been hypothesized to begin in the womb. In this review, the cytokines information on prenatal stages of development was presented and analyzed to evaluate if pregnancy can be the beginning and the trigger point for chronic diseases susceptibility. Even though that was not the goal of those studies, their results provide meaningful premises for this field of expertise.

5.1. Biomarker role in the diagnostic of chronic diseases

As mentioned before, the most common biomarkers were $\text{TNF-}\alpha$, $\text{IL-1}\beta$ and IL-6 , present in more than half of the selected studies. There are many studies on these cytokines in adult populations to study aging. However, this study will show if the same cytokines, in a younger age, can have the same impact, or be the cause of certain diseases.

5.1.1. Brain development

The first study of this review concluded that maternal anaemia does not have a significant impact on the iron stores in the offspring (117), indicating that iron regulation mechanisms can protect the fetus from maternal inflammation, mechanism which are dependent of IL-6 . Other studies have previously indicated that iron restriction could be presented during gestation as a causal effect from inflammation (72). In this example, IL-6 stimulates hepcidin production in an inflammatory state reducing the iron availability in the blood, contributing to inflammatory anaemia. Overall, this micronutrient is also essential for brain development. Fetal iron status has also been associated with early chronic psychological stress and subsequent immune system changes (136), hypothesizing that maternal deviation of the HPA axis can lead to IL-6 increased, followed by iron decreased, ultimately leading to an impaired neurological development of the offspring (108).

In Hong et al. 2006, the chronic maternal inflammation is also addressed, suggesting that pro-inflammatory environments in the mother can predispose their descendants to immunological disorders in long term (129). By blocking glucocerebrosidase, Gaucher mice brain cells showed increased nitric oxide and reactive oxygen species (ROS), known for neuronal degeneration and cognitive deficit. This study used Gaucher mice, with a glucocerebrosidase deficiency, allowed to verify that an increase of pro-inflammatory cytokines, $\text{IL-1}\beta$, IL-6 and $\text{Tnf-}\alpha$, suggesting increased

neuroinflammation activation, commonly associated with neurodegenerative disorders, such as Alzheimer's disease. Following that thought, this study suggests that inflammation plays a critical role in disease progression, especially in the fetal development context (129).

A cognitive decline has been associated with prenatal inflammation exposure in Ni et al. 2022, by inducing an inflammatory environment with lipopolysaccharides (LPS), showing increased NGPF2 expression and decreased PSD-95 expression in the hippocampus (135). It suggests that prenatal inflammatory exposure led to an age-relative cognitive decline, associated with increased IL-6, IL-1 β , TNF- α . However environmental enrichment, meant to simulate natural conditions these animals would have in their habitat, appears to decrease these cytokines levels. The same results have been presented by Zhang et al. 2022, suggesting that gestational inflammation can cause learning and impairment developments, alleviated by environmental enrichment, by decreasing stress susceptibility (137).

This relation of neuroinflammation and neurodegenerative disorders susceptibility has been previously established in the first chapter, adding that fetal programming can be influenced by the mother immunological pattern during pregnancy (104).

5.1.2. Pulmonary development

In a study inducing a prenatal pro-inflammatory environment using rIL-1 β , it was proposed a fetal immune system reprogramming, presented by T cell dysfunction and dysregulated immune responses (133). The results of this study showed an increased CD45+ leukocytes infiltration in the placenta, as expected by the IL-1 β consequences, and reduced fetal viability and increased CD 8+ T expression in fetal liver cells (133). According to this study, females born from an adverse pro-inflammatory uterine microenvironment have higher efficiency of immune response than males. The authors believe that it suggests a predisposition for individuals to immune disorders such as allergic diseases, autoimmune conditions, and asthma (133). Although there are not many studies on allergic diseases, several studies focus on pulmonary development impairment in causation to an increased maternal pro-inflammation.

Among the included studies evaluating pulmonary consequences of prenatal inflammation, there was not a common denominator under the scope, with many cytokines being evaluated. Collins et al. 2010 concluded that respiratory complications in preterm neonates can be associated with intrauterine infections, finding increased mRNA levels of TNF- α and IL-10, but no significant alteration in mRNA levels IL-6 and IL-1 β . In concordance, plasmatic IL-6 was not

significantly associated with decreased pulmonary function (118,119,132) but IL-1 β (122) and IL-8 (119) were so. On the other hand, Gantar et al. 2011 showed that IL-8 was not significantly associated with bronchopulmonary dysplasia (132), in line with the nature of these cytokines, that can be pro and anti-inflammatory according to the environment where they lay (138).

Stouch et al. 2016 induced prenatal inflammation in mice with the injection of IL-1 β and showed inflammasome activation and fetal pulmonary morphology alteration, with increased cellular density (122). This study suggests a role of the inflammasome in the pathogenesis of respiratory diseases in younger ages and identifies IL-1 β as the main inflammatory mediator impairing pulmonary development because the morphogenesis is maintained when this cytokine was inhibited (122).

Interestingly, Takahashi, et al. 2015 described that TGF- β 1 and TGF- β 2 levels are regulated independently of other cytokines and are not influenced by them. These cytokines appeared to have a tight influence on the pulmonary development, presenting low levels when associated with chronic lung disease in preterm infants, and high levels with PDA, *patent ductus arteriosus*, a heart defect (118). TGF- β family is commonly associated with cellular degeneration capacity when lower while higher levels of this pleiotropic cytokines are linked to senescence and aging associated disorders, such as Alzheimer (139).

Although those studies did not follow-up the intervenient for new disease assessment, the study from Gantar et al. 2013 did follow up after 8 years. In this study, umbilical cord blood samples were retrieved to measure IL-6 and IL-8, and, at 8 years old, pulmonary function test were conducted. The results show reduced pulmonary function in preterm children - negative relationship between IL-8 and forced expiratory flow and forced expiratory volume per second/forced vital capacity (134). By showing an impaired pulmonary capacity, it suggests that IL-8 in the third trimester can be a sign for premature lung and airway remodelling, once this cytokine is commonly increased in the second trimester but not in the third.

These results are in agreement with inflammation being a strong variable at play for the development of the lungs in the third trimester. Authors have also identified that some aspects need to be taken into consideration, that is to say lower gestation age, need for mechanical ventilation or resuscitation post birth, risk factors for bronchopulmonary dysplasia (132). In a study using mice lung cells to study pulmonary maturation, it was found that the activation of the macrophages increases the expression of pro-inflammatory genes, potentially contributing for

the pathogenesis of neonatal pulmonary inflammatory disease, along with lower sensitivity to anti-inflammatory signalling such as IL-4 and IL-13 (124).

However, given the rise of the incidence of pulmonary diseases in younger groups over the last decades, it suggests a growing influence of external variables that compromise general public health. For example, early-onset of lung diseases triggers might include environmental pollutants, prevented from industrial emissions and toxins, as well as tobacco use, physical negligence and poor dietary patterns based on fast foods and low proteins. However, when supplementing during pregnancy with fats with beneficial health value, did not show interleukins alteration, but increased TNF- α expression fourteen-fold in the placenta (130).

In Mayor et al. 2015, an impaired fetal lung development was observed in response of a maternal high fat diet. This study shows a 35% decrease in cell proliferation index in fetal lungs, and increased pulmonary glycogen content, indicating impaired maturation. Curiously, the placenta showed an increased IL-1 β in the fetal side and a decreased in GR gene expression by 50% (126). According to the authors, both contribute to inhibit lung development and increased the risk for chronic pulmonary disease, however, no correlation was established between the two.

5.1.3. Heart development

A maternal high fat diet was also associated with chronic low-grade inflammation and higher risk for heart disease, along with poor pregnancy outcomes (127). In this study, uterine NK cells from obese females showed significant functional and molecular alterations (through TNF- α and IFN- γ cytokines), with increased expression of genes related to metabolism and inflammatory stress, which may influence placental development and pregnancy outcomes (127).

It has been hypothesized that obese mothers could cause development of predispose microbiome to obesity, by identifying an altered *Bacillota/Bacteroidota* ratio and reduced levels of obesity biomarkers (140). Other studies have showed that maternal inflammation did not alter the diversity and composition of the microbiome in the offspring (121).

By studying inflammation patterns from beginning of gestation till right after birth, obese women show high levels of IL-6, TNF- α , and the PAI-1/PAI-2 ratio in the first trimester, indicating chronic endothelial activation and inflammation (125). This endothelial activation can be measured by endocan protein, and studies on women with pre-eclampsia have shown higher concentrations of this protein when in comparison with women with healthy pregnancies (141).

It has been discussed in other reviews that preeclampsia in pregnancy can lead to perinatal mortality and long-term cardiovascular risks for both mother and fetus (142), also shown by Carr et al. 2001 that women in the high-risk group for preeclampsia have a higher cardiac output, suggesting hyperdynamic circulation and endothelial activation early in pregnancy. This study also shows that a preventive treatment with atenolol have demonstrated a slower rise in TNF- α (143). Other that TNF- α (144), IL-1 β also demonstrates a potential as a biomarker for preeclampsia in higher risk groups. However, that study was unable to measure IL-1 β due to low concentration and IL-1ra (interleukin-1 receptor antagonist) showed 100% negative predictivity and 100% sensitivity in diagnosing preeclampsia (131). Taking into consideration that this study was from 1997, it is most likely that the methodology wasn't as precise and new measures in the same conditions should be made to verify its legitimacy.

5.2. Maternal inflammation as a biomarker of aging

In the general context IL-1 β appear to have a significant value in prenatal care as a predictive biomarker. Measuring log IL-1 β , the lower ratio was associated with small gestational age births, indicating probable fetal growth restriction, while other cytokines didn't prove any association (134). This condition as also been associated with higher levels TNF- α , IL-1 β , and IFN- γ , causing a hypoxic amniotic environment (145), suitable for low chronic inflammation that might affect the fetus in his adult life.

In the other hand, when mapping a vast group of inflammatory biomarkers across gestational age in cord blood samples, it was found that IL-1 β was a decreased biomarker in preterm birth, while IL-2, IL-4 IL-8 and TNF- α were increased (120). This antagonism results between studies could either represent low quality measurements (when discussing older studies results) or variability in samples, due to genetics or environmental causes. Interestingly, IL-6 shows no significative associations.

In Weimann et al. 1997 it was shown that higher levels of IL-6 in neonates are associated when they present infections (sepsis), but not as significantly in pre-term neonates, who have lower capacity to respond to infections (146), and was increased twice in in prenatal stress. As a consequence of prenatal maternal stress, higher IL-6 concentration was associated with depression and anxiety in adolescence (147), conditions that have been previously associated with prenatal inflammation in the first chapter. Similarly to this study, Tissieres et al. 2012 reported a compromised immune response of preterm neonates, exhibiting a higher risk to

develop bacterial sepsis (74). Following ex-vivo administration of interferon- γ proved effective in reversing these immune defects, suggesting a promising therapeutic approach to enhance immunity. This collaborates with the fact that maternal inflammation should be taken into consideration during check-up points in pregnancy so that, if necessary, interventions could be made to prevent further diseases or decreased probability of occurrence. To collaborate with this thought, Leviton et al. 2011 assessed the persistence of postnatal systemic inflammation in newborns associated with umbilical cord inflammation, indicating fetal inflammation (128). If not bypassed, this inflammation could persist as low-grade chronic inflammation and become detrimental over the years, increasing susceptibility to develop chronic diseases in adulthood.

5.3. Correlation between cytokines and diseases susceptibility

As expected, the main cytokines mentioned in previous studies consisted in IL-6, IL-8, IL-1 β and TNF- α . Results show that there might be an association between those biomarkers and chronic diseases, as hypothesized. Although there were not enough data on the second trimester of pregnancy, it is clear that there is an inflammatory pattern that can be change with dietary patterns, physical health and environmental factors, as described beforehand.

IL-6 showed an important role in the development of neurological diseases, and higher levels when subjected with maternal obesity or the presence of overall infection. This evidence aligns with first trimester inflammatory patterns, as a consequence of pre-conceptional pro-inflammatory diet or disorders – an unhealthy diet before pregnancy increases maternal inflammation and oxidative stress during pregnancy (148).

The second trimester, crucial for fetal growth, is more commonly associated with fetal growth restriction or deficient develop, as shown on lung maturation and neurodegenerative disorders. IL-1 β has frequently linked to pulmonary diseases and, for a healthy pregnancy, this cytokine is not commonly increased in the second trimester.

It has been notable that most included studies focused their study's sampling on women who had pre-term births. As importantly, the third trimester is closely related to pulmonary maturation, and chronic inflammation has a huge effect on fetal programming. This step is fundamental for a full development, and avoiding pre-term births due to unregulated inflammation could lead to a lower susceptibility to develop chronic diseases. Other than that, external factors should also be taken into consideration.

Overall, this review underscores the role of prenatal inflammation in long-term health outcomes and/or susceptibilities, providing a foundation for future investigations and potential interventions.

5.4. Limitations and therapeutical implications

Given the nature of the selected studies for this review, it diminished the possibility of generalizing the data, by including both human and animal samples, from different origins (such as maternal blood and fetal tissues). Due to the complexity of the human biology and taking into consideration that genetics and environmental factors have a high impact on people, causing a high variability in data.

6. Conclusions

Prenatal inflammation is crucial for a successful healthy pregnancy, playing a role in implantation and tolerance. However, persistence of altered inflammatory cytokines level can disrupt fetal development. Throughout this review, the importance of maternal inflammation in the offspring's health in a long-term effect, was established. Studies indicate a strong association between biomarkers commonly used to measure biological age acceleration in early "indicators of diagnostic" of chronic diseases in adulthood, such as pulmonary disfunctions or cognitive disorders.

Results variability demonstrate a complex interaction between cytokines, influence of genetics and conditioning by environmental factors, resulting in epigenetic modifications that persist into adulthood, increasing the risk of age-related diseases. Other than that, those cytokines can disrupt critical processes in the fetus, such as neurodevelopment. Monitoring and potentially intervening in pregnant women with elevated inflammation levels, or at a low-grade chronic inflammatory pattern, are necessary to prevent predisposition of the offspring to accelerated biological aging and chronic inflammation later in life.

This review aimed to offer valuable insights into inflammatory mechanisms during prenatal development, which was successfully achieved given the data on the articles. However, further studies of larger sample sizes and direct objective of investigating aging are necessary to be one step closer to decreasing the risk for chronic diseases at birth.

Funding

This research received no external funding.

Informed Consent Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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