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Impact of maternal nutrition in viral infections during pregnancy

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A B S T R A C T

Other than being a physiological process, pregnancy is a condition characterized by major adaptations of maternal endocrine and metabolic homeostasis that are necessary to accommodate the fetoplacental unit. Unfortunately, all these systemic, cellular, and molecular changes in maternal physiology also make the mother and the fetus more prone to adverse outcomes, including numerous alterations arising from viral infections. Common infections during pregnancy that have long been recognized as congenitally and perinatally transmissible to newborns include toxoplasmosis, rubella, cytomegalovirus, and herpes simplex viruses (originally coined as ToRCH infections). In addition, enterovirus, parvovirus B19, hepatitis virus, varicella-zoster virus, human immunodeficiency virus, Zika and Dengue virus, and, more recently, coronavirus infections including Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) infections (especially the novel SARS-CoV-2 responsible for the ongoing COVID-19 pandemic), constitute relevant targets for current research on maternal-fetal interactions in viral infections during pregnancy. Appropriate maternal education from preconception to the early postnatal period is crucial to promote healthy pregnancies in general and to prevent and/or reduce the impact of viral infections in particular. Specifically, an adequate lifestyle based on proper nutrition plans and feeding interventions, whenever possible, might be crucial to reduce the risk of virus-related gestational diseases and accompanying complications in later life. Here we aim to provide an overview of the emerging literature addressing the impact of nutrition in the context of potentially harmful viral infections during pregnancy.

1. Introduction

Pregnancy itself is a physiological process that aims to provide an optimal environment for proper development of the fetus. However, drastic adaptations of maternal physiology during gestation to accommodate the fetoplacental unit make the preconception-pregnancy-postpartum period especially prone to adverse maternal/fetal outcomes. The risk does not end with the delivery of the placenta but includes long-term complications that may appear later in life [1–5]. Although many reports concerning pregnancy-related diseases focus on abnormal placentation, excessive gestational weight gain, maternal obesity and its related complications, gestational diabetes mellitus, preeclampsia, or intrauterine growth restriction [6,7], infections can also arise that impede a healthy pregnancy and lead to complications for the mother, the fetoplacental unit, and the baby after delivery [8].

Successful health promotion during pregnancy requires an adequate maternal education spanning from before conception to the early postnatal period [9]. In this sense, encouraging a healthy lifestyle, especially based on moderate physical activity and proper nutrition plans, might be crucial to reduce the risk of gestational diseases and related complications in later life [10,11]. The aim of this review is to provide an overview of the benefits of a healthy diet and lifestyle for successful

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pregnancies, then focusing on the impact of nutrition in the context of potentially harmful viral infections during pregnancy.

2. Maternal nutrition and lifestyle for healthy pregnancies

Recent reviews highlight the importance of healthy lifestyle habits for preventing gestational diseases and reducing the risk of birth defects, impaired fetal development and in utero fetal programming [5,10,12,13]. Moderate physical activity during all stages of pregnancy has proven effective beyond obvious benefits on muscle tone and function [14]. While some intervention studies recommend an average of 30 min of exercise per day [10], guidelines on duration, frequency and intensity of physical activity for pregnant women might differ among countries [15].

There is consensus on the relationship between obesity and poor perinatal outcomes, including gestational diabetes mellitus, pre-eclampsia, and large for gestational age infants; therefore, many health programs rely on weight loss, when advisable, and recommendations for proper nutrition throughout pregnancy and beyond. Thus, appropriate gestational weight gain must ideally be preceded by an optimal starting point (i.e., advisable pre-pregnancy weight, with body mass index (BMI) between 18.5 and 24.9 kg/m^2), and energy intake in late pregnancy (when sedentary behaviors are more likely to occur) should not exceed 10% of that in non-pregnant women [12]. A healthy maternal diet rich in vegetables, fruit, legumes, olive oil, nuts and fish should promote the equilibrated intake of proteins, high-quality fats (essential and poly-unsaturated fatty acids), and fiber-rich carbohydrates with low glycemic index [16–18]. Minor constituents such as minerals and vitamins (e.g., iron, calcium, zinc, iodine, folate, vitamin D and carotenoids) are highly sensitive to deficiencies during pregnancy and are routinely administered in the form of dietary supplements to support the processes of gestation and breastfeeding [18–20] (Fig. 1).

Recent data suggest that viral infections may contribute to the pathophysiology of maternal obesity and/or gestational diabetes mellitus [21,22]. Risk factors for influenza or acute respiratory viral infections include age, chronic somatic diseases, and pregnancy, with higher risk in obese patients and those with circulatory and respiratory disorders [23]. Intrauterine effects of maternal obesity upon immune or respiratory development might explain the reason why these infants are associated with increased risk of cough, wheeze, and lower respiratory tract infection [24]. There is growing evidence that epigenetic mechanisms (e.g., DNA methylation, histone modifications, exosome-derived microRNAs) can be responsible for this nutritional programming in utero that affect the infants' immunocompetence in the early stages of life [25,26] Concerning COVID-19 disease, where malnutrition and trace element deficiency affect the course of infection, obesity is a prognostic risk factor that associates with worse outcomes [27]. Indeed, maternal obesity has emerged as a key risk factor increasing the susceptibility of pregnant women to severe COVID-19 disease [28]. Therefore, it is important to highlight the relevance of nutritional status as a critical point in the host's response to infections, therapies, and vaccines.

3. Microbiome and immunity during pregnancy

Once considered a sterile organ, the uterus and accompanying structures of the upper female reproductive tract seem to harbor a specific microbiota, which could have reached the site via structural changes in the cervix barrier throughout the menstrual cycle [10]. The total biomass shaping the uterine (or endometrial) microbiome, however, is much smaller than that of the lower tract. Therefore, special care should be taken to avoid contamination with vaginal specimens when trying to isolate bacteria of presumed superior origin, because endometrial samples are normally collected transcervically [29]. *Lactobacillus* dominance has been reported by some authors following this route of uterine access, especially from women undergoing in vitro

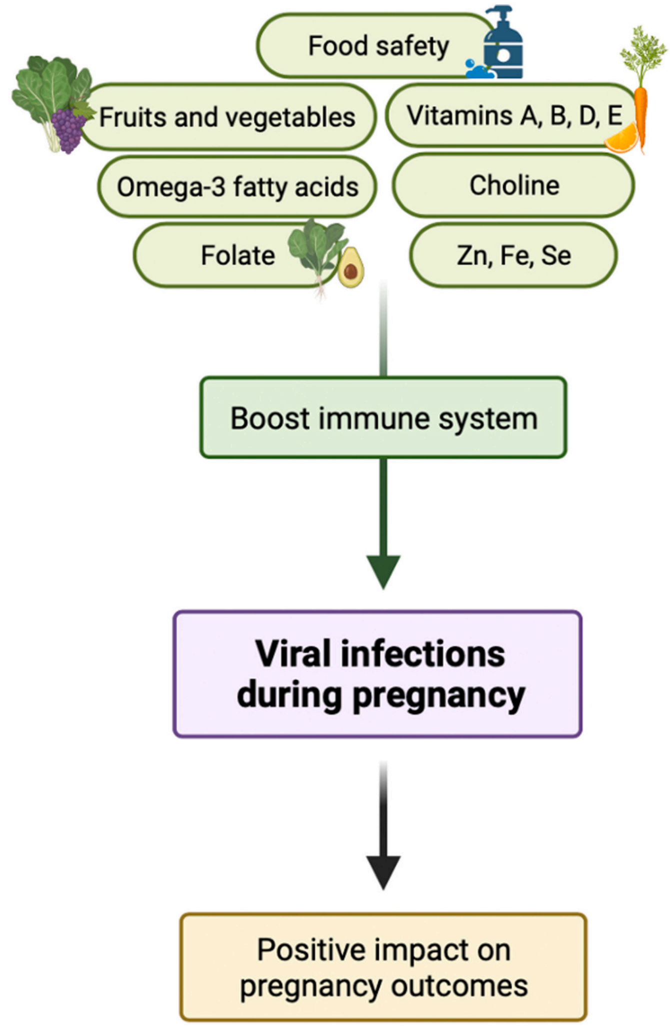

Fig. 1. Programs/interventions for a healthy pregnancy. Food hygiene and a healthy lifestyle based on adequate nutrition plans can reduce the risk of gestational diseases and subsequent related complications. A balanced diet composed of functional foods such as fruits and vegetables, including enough intake of micronutrients (e.g., vitamins, iron, zinc, and selenium), can support the physiological immune system for a full-term pregnancy and improve viral infections and treatment outcomes. Proper intake of omega-3 polyunsaturated fatty acids might help reduce the excessive inflammatory response related to some viral infections that compromise pregnancy outcomes, and choline supplements might also improve adverse fetal effects produced by respiratory virus infection.

fertilization procedures [30–32]. On the other hand, studies using endometrial biopsies, less subjected to contamination with microbiota of vaginal/cervical origin (e.g., following C-sections or hysterectomy), found significant quantities of other bacteria, including *Acinetobacter*, *Pseudomonas*, *Sphingobium*, and *Vagococcus* [33,34].

Even though the current data does not provide sufficient evidence that a real 'core uterine microbiome' exists, variations in the relative proportion of endometrial microorganisms have been linked to lower rate of success in assisted reproduction programs, as well as to gynecological disturbances ranging from dysfunctional uterine bleeding to endometrial cancer [35]. In addition, considering that hormonal, metabolic and immunological changes during pregnancy affect those microbial communities located in the vagina, oral cavity or gastrointestinal tract [10], it is not surprising that these changes also influence the specific profile of the microbiota in the endometrium, if any. The same reasoning is extensive to placental microbiota and in utero fetal colonization, where the presence of bacteria reported in amniotic fluid, umbilical cord blood, and meconium is not exempt from controversy arising from sample contamination [36].

Most (if not all) immune cells possess receptors for sex hormones. Therefore, as gestation proceeds and steroid hormone levels increase, estrogen and progesterone-mediated signaling modulate the immune response at different levels, including the respiratory and nervous systems. In fact, estrogen receptors play an important role in the pathophysiology of some autoimmune diseases, where symptoms are relieved during pregnancy [37]. This is why pregnancy tends to be considered as a state of transient immunosuppression that, on the other hand, make the mother and the fetoplacental unit more susceptible to microbial infections including viruses, bacteria, or fungi. Infectious episodes during this critical period increase the risk of adverse maternal/fetal outcomes including preeclampsia/eclampsia, recurrent miscarriage, intrauterine growth restriction, and premature delivery [38]. Intrauterine infections are estimated to be responsible for 25–40% of premature births [39]. Even if the placental barrier prevents a virus from reaching the fetus, the sole response of the mother's immune system might have a negative impact on proper fetal development [40].

During pregnancy, changes in the morphology and environment of the vaginal mucosa modulate the innate immunity mechanisms of the lower genital tract, which helps the normal microbiome resist external pathogens and maintains vaginal homeostasis [41,42]. The increased function of innate immune response components (e.g., phagocytic action of monocytes, neutrophils, and dendritic cells) might compensate for a lower T-cell and natural killer (NK) cell function [43,44]; otherwise, it would be difficult for a woman to survive her own pregnancy, indeed. Concerning the uterine decidua, NK cells that produce significant quantities of interferon gamma (IFN-γ) predominate at this level [38]. IFN-γ then stimulates T-cells and B lymphocytes to secrete cytokines and antibodies, and macrophages and neutrophil cells to release antimicrobial peptides [45]. Modulation of the balance between M1/M2 macrophages also occurs during pregnancy [46].

At the maternal-fetal interface, trophoblast cells also exert immunomodulatory actions, including Toll-like receptor-mediated recognition of microorganisms and subsequent recruitment of white blood cells [47]. In addition, acquired immunity mechanisms in the placenta include antiviral and anti-parasite actions derived from cytokine production and cytotoxic effects of CD4+ and CD8+ T-cells [48,49]. Amniotic fluid also contains different innate immune cells [50,51], and the phagocytic function of fetal innate immune cells seem quite similar to that of adults, despite a weaker presentation antigen ability [52]. Under normal conditions, neonatal T-cells show a Th2-dominant response and decreased IFN-γ production, which then reverses in the postnatal period to eventually achieve a 'mature' Th1-dominant pattern of response typical of adult life [53].

In any case, although estrogen/progesterone-mediated regulation of different immune components has been widely investigated in vitro, an integrated action on the complex maternal immune system remains to be elucidated. Basic research on animal models represents here a useful complement/alternative to epidemiological studies in pregnant women, where controlled experimental conditions and extensive sample collection represent an obvious impediment [37].

4. Common viral infections during pregnancy

Without causing unnecessary anxiety and prescribing potentially harmful treatments to pregnant women, infections during pregnancy should be carefully monitored because potential sequelae are often underestimated [54]. The group of maternal infections traditionally known to be transmitted to newborns congenital and perinatally was coined with the acronym ToRCH, which stands for Toxoplasmosis, Rubella, Cytomegalovirus (CMV), and Herpes simplex virus (HSV) [55]. Nowadays, the definition of TORCH infections has been expanded and the "O" include "Other" congenital infections that can reach the fetus via transplacental route, or be transmitted to the neonate in the peripartum or postpartum (via breastfeeding) periods; that is the case of bacterial syphilis and listeriosis, trypanosomiasis, and viral infections including enterovirus, parvovirus B19, hepatitis virus, varicella-zoster virus (VZV), human immunodeficiency virus (HIV), and Zika virus (ZIKV), among others [56,57] (Fig. 2). The declaration of the novel coronavirus (COVID-19) outbreak as a pandemic in 2020 [58] has triggered an obvious intensive research in the field, and some authors claim that SARS-CoV-2 infection should also be included within TORCH entities [59].

CMV infection, whether primary or due to reinfections with latent CMV or different CMV strains, is one of the most common condition responsible for fetal/neonatal complications [60]. Influenza-like symptoms, if any, are generally mild in the mother. However, transplacental viral transmission is associated with intrauterine growth restriction, neurodevelopmental disorders, hepatitis, and hematological alterations [60–62]. Worryingly, hearing deficits might appear in the long term even when no signs of illness are present at birth [63].

The inclusion of rubella vaccines in regular vaccination programs has reduced the incidence of congenital rubella syndrome, although long-term immunity might be questionable in some cases and reinfections have been reported [64]. Infections are usually non-severe and non-specific but are associated with severe visual and hearing abnormalities, especially if occurring in the first trimester [54].

Subclinical HSV-1/2 infections are usual among the general population due to viral latency in peripheral neurons [65]. In addition, 2–3% of pregnancies present with primary HSV infection, although most cases are free of significant symptoms [66]. On the other hand, miscarriage and congenital anomalies including encephalitis might occur if the virus reaches the fetus, especially in the first half of pregnancy [67]. Surveillance of primary infection with active genital herpes at term is very important to reduce the risk of viral shedding in the birth canal, and Caesarean delivery is recommended in such cases [66,68].

A frequent rash-causing disease in school-aged children (normally preceded by flu-like symptoms), parvovirus B19 infection is commonly known as "fifth disease" or "slapped cheek disease" [69]. Transplacental infection from contagious mother (representing up to 10% of pregnancies during biennial epidemics) can occur throughout pregnancy, although fetal risk is highest in the first trimester [70,71]. Complications include spontaneous abortions and fetal hydrops secondary to hematological and cardiac alterations [72,73].

Vertical transmission of VZV is small compared with other viruses but fetal infections might be present in 10–15% of maternal chickenpox. Although clinical manifestations are generally mild, if any, potential fetal complications are characterized by intrauterine growth restriction, microcephaly, limb hypoplasia, and convulsions [74–76]. Complicated infection also increases the risk of maternal respiratory, hemorrhagic, or neurological outcomes [54].

ZIKV and Dengue virus are mosquito-borne flavivirus sharing similar vectors. Originally reported in Africa, a significant rise of microcephaly cases in Brazil was recently attributed to ZIKV, and the infection has been a notifiable disease for the last 5 years [77]. Congenital ZKV infection might present with microcephaly-derived structural and functional abnormalities in the central nervous system, visual and hearing disturbances, heart disease, and severe arthrogryposis (multiple joint contractures) [78–80]. Dengue, which is also transmitted by mosquitos of the *Aedes* genus, induces fever and hemorrhagic signs in pregnant women, including epistaxis and metrorrhagia; this might lead ultimately to abortion or early delivery with high maternal mortality rates. Complications like prematurity and neonatal infection have also been encountered in fetuses born to infected pregnant women [81].

Despite combined antiretroviral therapy (cART) is available to stop the progression and to prevent vertical transmission of the disease, infant HIV infection remains an important global health issue [82]. Congenital transplacental infection accounts for most of HIV transmission in children, although they can also be infected during delivery or through breastfeeding. Many clinical manifestations are nonspecific

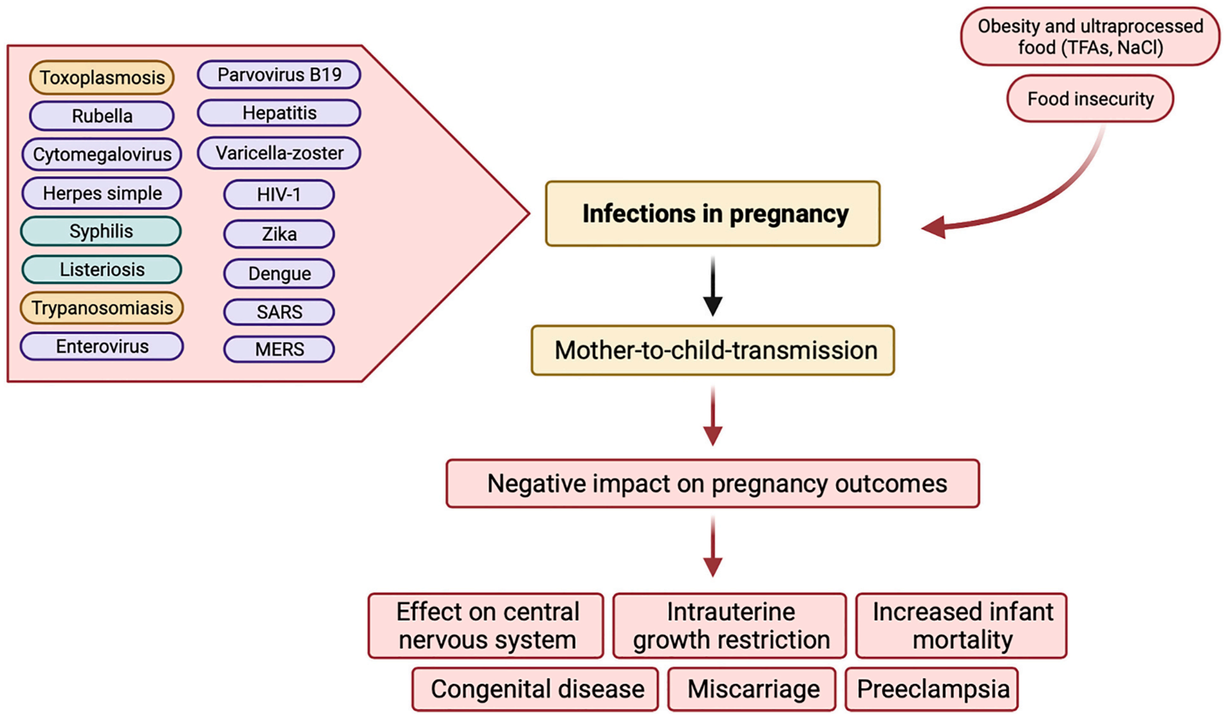

Fig. 2. Impact of common pregnancy infections on mother-to-child-transmission. Maternal infections transmitted to newborns congenital and perinatally are classically known as ToRCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) infections. In addition, parasitic trypanosomiasis, bacterial syphilis and listeriosis, and viral infections including enterovirus, parvovirus B19, hepatitis virus, varicella-zoster virus, human immunodeficiency virus (HIV), Zika and Dengue virus, and, more recently, coronavirus infections including Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) infections, can also experiment transplacental/peripartum/postpartum mother-to-child transmission with negative consequences. In addition, food insecurity and subsequent poor nutritional status can result in adverse health consequences, especially in virus-infected pregnant women. Excessive trans-fatty acids (TFAs) and salt (NaCl) intake from regular consumption of ultra-processed foods during pregnancy might also result in poorer outcomes during viral infections.

and include lymphadenopathy, microcephaly, hepatomegaly and splenomegaly, and signs of accompanying bacterial/fungal/viral infections [57]. HIV-infected women show higher risk of small for gestational age newborns, preterm birth, and stillbirth [83]. Furthermore, the early initiation of cART recommended in current guidelines [84] is not without teratogenic effects [85–87].

Extensive literature on COVID-19 pandemic in recent months include numerous review articles concerning the novel, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the context of pregnancy [59,88–93]. Based on prior agreement that pregnant women are more vulnerable to recent coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS), they were immediately given especial consideration as the COVID-19 pandemic was advancing [94–97], and phone/online consultations began to replace much routine antenatal care whenever possible [98,99]. Some conclusions drawn so far point to higher risk of severe maternal disease during pregnancy, compared with the general population, and plausible (although not confirmed) vertical transmission with uncertain mechanisms [100]. Increased inflammatory response (e.g., augmented IL-6 secretion) in severe cases could potentially increase the risk of miscarriage, preterm labor, stillbirth, intrauterine growth restriction, early-onset preeclampsia, neurodevelopment disturbances, and neurosensory deficits in later life [91,101,102], although such conclusions cannot yet be extrapolated. The presence of the virus in breast milk is still uncertain and women are currently advised to breastfeed whenever possible, even if they tested positive during the postpartum period [93]. Specific mechanism of SARS-CoV-2 infection and current treatment strategies are discussed in other papers in this Special Issue. Classical and non-classical epigenetic mechanisms must also be taking into account, especially considering their relevance in the pathogenesis of other respiratory diseases [103,104] In any case, larger population studies are still needed to elucidate whether progesterone-mediated modulation of the immune response during pregnancy results in exacerbated susceptibility/morbidity or may, on the contrary, protect against SARS-CoV-2 infection.

5. Viral infections in pregnancy in the context of food insecurity

Food insecurity exists when there is limited availability of healthy nutrients leading to poor nutritional status, with development of general undernutrition and protein, energy and micronutrient deficiencies [105]. This status might contribute to higher morbidity and mortality rates, which is worsened in pregnant and breastfeeding women because of their increased nutritional demands [106].

Viral infections during pregnancy might lead to structural and functional changes affecting the mother, the fetoplacental unit, and the neonate. For instance, infection with human CMV is related to intrauterine growth restriction and miscarriage [107]. As mentioned above, there is demonstrated transmission from mothers to fetuses or neonates; vertical transmission can either occur transplacentally during gestation or be transvaginal during parturition. Some evidence on breastmilk transmission has also been reported [108]. CMV infection is more common in the third trimester, where it is associated with a 70% risk of mother-to-child transmission [109]. CMV infection can result in severe damage in the fetus, including neurological consequences such as periventricular calcifications, microcephaly, visual impairment, sensorineural hearing loss, neurodevelopmental delay, and hepatomegaly [108–110]. Necrosis and oedema have been found in placentas of women infected with CMV, these changes being associated with the severity of congenital disease symptoms in the fetus [111].

ZKV infections in pregnant women can also be vertically transmitted via the placenta, leading to congenital Zika syndrome [112]. The risk of congenital Zika infection is highest early in pregnancy (first trimester) [113]. Infants infected with ZKV develop important damage on various tissues including the central nervous system; this results in intrauterine growth retardation with stillbirths, and increased infant mortality 2 to 3 days postpartum [114]. Zika RNA has also been found in breast milk of ZKV-infected mothers [115].

As mentioned above, transmission of HIV from mother to children can occur during pregnancy, childbirth, and breastfeeding. Several studies suggest that most (50–80%) of the vertical transmission of HIV takes place around the time of birth [116]. When HIV crosses the placenta, it produces changes in the feto-maternal unit with defective maturation of syncytiotrophoblasts, which might lead to fetal growth restriction or preeclampsia [117].

With regard to SARS-CoV-2, its effect on pregnant women and its impact on pregnancy outcome is not fully known, as already mentioned. Whereas some authors did not find enough evidence of vertical transmission, SARS-CoV-2 has been detected in some cases in amniotic fluid, cord blood and placenta, although the presence of the virus was not associated with any maternal or neonatal feature [118]. The small viral load found in the placenta does not seem to induce a relevant inflammatory response, which suggests that the placenta is not a preferential target and may be a protective barrier against this coronavirus [119,120].

Food insecurity is always dangerous and can result in adverse health consequences in different groups, especially in women and children. The impact of food insecurity becomes even greater in the context of viral infection (Fig. 2). Thus, malnutrition is related to increased risk of HIV transmission and a lower response to HIV treatment [121,122]. Experimental studies have shown an association between malnutrition and adverse pregnancy outcomes in women infected with HIV [105,123]. Changes in maternal weight gain during pregnancy, low birth weight, and preterm delivery have been found in malnourished pregnant women infected with HIV [124]; these alterations could be prevented in some cases by multivitamin supplementation [125,126], thus confirming the association of food insecurity with poor health outcomes in pregnant women infected by the virus.

Additionally, reports have recently shown the impact of food insecurity in the setting of the COVID-19 pandemic [127,128]. Indeed, this pandemic might potentially lead to greater food insecurity worldwide and increase the risk of chronic undernutrition and infectious diseases in children and pregnant women; risk factors might then appear that worsen the prognosis of patients infected with SARS-CoV-2 [129]. This status is known as syndemic paradigm [130], in which two or more coexistent situations may act synergistically and produce a complex disaster in a given population [131]. Therefore, there is a strong relationship between food insecurity and viral infections that make pregnant women especially vulnerable [132,133].

6. Optimal nutrition and prevention of mother-to-child-transmission (PMTCT)

Mother to child viral transmission is responsible for at least 90% of new childhood infections today. Therefore, the implementation of potent programs/interventions that ensure an optimal prevention of mother-to-child transmission (PMTCT) is crucial to reduce infant infections [134,135].

PMTCT interventions should be programmed during pregnancy, labor, delivery, and breastfeeding. Many studies have been published in this regard in the context of HIV. Following the recommendations of the World Health Organization (WHO) [134], different studies have reported the beneficial effects of antiretrovirals in HIV-infected pregnant women and infants, as well as their ability to reduce HIV transmission [121,136,137]. Strategies were created in 2016 to eliminate vertical transmission of HIV, syphilis, and hepatitis B by 2030.

Poor nutrition leads to increased susceptibility to infection [116,138], making pregnant women more prone to MTCT (Fig. 2). Because an adequate intake of macro and micronutrients is required to achieve a healthy pregnancy [10], some studies (albeit limited) focused on the relevance of optimal nutrition and its benefits in MTCT. Nutritional interventions in the context of PMTCT might be decisive not only to protect the health of both mother and children but also to reduce viral MTCT.

Recently, BourBour et al., demonstrated that a balanced diet composed of protein, omega-3 fatty acids, vitamin A, vitamin D, vitamin E, vitamin B1, vitamin B6, vitamin B12, vitamin C, iron, zinc, and selenium can improve COVID-19 infection and treatment outcomes [139] (Fig. 1). These results might be extensible to MTCT in other viral contexts. However, large clinical trials are needed to confirm such an assumption.

Multivitamin supplementation decreased adverse pregnancy outcomes in pregnant women infected with HIV, which might result in reduced MTCT [126]. Moreover, a recent clinical trial has shown the beneficial effect of maternal vitamin D supplementation during pregnancy and lactation to prevent acute respiratory infections in infants, suggesting vitamin D as a candidate to decrease viral MTCT [140]. Freedman et al. also found that choline supplements might improve the adverse fetal effects arising from respiratory virus infection and maternal inflammation [141]. In the same way, similar supplementations could be beneficial for proper fetal development in COVID-19 infection.

7. Feeding interventions (nutrient supplements) to improve fetal growth during viral infections

The crucial importance of maternal diet and the role of macronutrients and micronutrients for a healthy pregnancy [10] support feeding interventions, targeting food security and balanced systemic nutrient levels, as a key to a successful pregnancy. Primary interventions should focus on food hygiene; relevant infections (not only of viral origin) may be avoided by cleaning food surfaces properly and by following safe food handling practices, such as processing at high temperatures before consumption [142,143]. As easy as they may seem, some developing countries lack the necessary measures to implement these recommendations. Although it is well-known that viruses cannot multiply in food products, it is true that food, water, and other contaminated environments can spread viruses and aggravate pregnancy outcomes [144]. Among the main viruses that can be transmitted to humans through infected food or water are rotavirus, enterovirus, sapovirus, astrovirus, norovirus, adenovirus, and hepatitis A (HAV)/hepatitis E (HEV) viruses [145,146].

Feeding interventions must be considered as a strategy to get an optimal nutritional status in pregnancies with viral infections to avoid problems related to fetal growth. Some authors claim the need to develop nutritional strategies in common (i.e., TORCH) infections known to present with fetal growth deficits [147–149]. Moreover, malnutrition can confer a greater predisposition to viral infections during pregnancy, including HEV [150] or SARS-CoV-2 [151].

7.1. Macronutrients

Proper intake of omega-3 polyunsaturated fatty acids (n-3 PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), might constitute an effective intervention to reduce virus-related inflammation that compromises pregnancy outcomes (Fig. 1). Madore et al. [152] showed that n-3 PUFAs act as powerful immunomodulators due to their anti-inflammatory properties, which could reduce neurological disorders (e.g., autism) related to viral infection during pregnancy. Similarly, n-3 PUFAs might also be worth exploring during pregnancy to counteract the aggressive inflammatory response associated with SARS-CoV-2 infection [93,153]. Interestingly, prenatal supplementation with PUFAs has been associated with reduced allergic outcomes after birth through epigenetic modulation of genes that regulate T-cell differentiation, whereas no such effect was observed when supplemented to infants [25,26]. Changes in histone acetylation triggered by n-3 PUFAs might be responsible for proper postnatal polarization of T-cells towards the Th1 phenotype, among other epigenetic changes that contribute to immune maturation [53,154]. Moreover, consumption of n-3 PUFAs has been helpful in reducing triglycerides levels during HIV infection [155], which could also be a healthy strategy during pregnancy. On the other hand, the lack of specific information on the modulation of carbohydrate/protein intake in pregnancies with viral infections suggests following the general indications for normal pregnancies; that is, obtaining these components from a diet rich in functional foods such as fruits, vegetables, legumes, and fiber [10].

7.2. Micronutrients

The impact of micronutrients on immune function is well established. Thus, vitamins A, B, C, D, E and folate, and other trace elements such as zinc, iron, and selenium, among others (Fig. 1), play an optimal role in supporting the physiological immune system for a full-term pregnancy [10].

The reduction of vitamin D levels has been associated with higher risk of respiratory infections [156]. As mentioned above, Morris et al. [140] established a protocol of vitamin D supplementation during pregnancy and lactation to prevent subsequent acute respiratory infections during infancy. Taking vitamin D supplements has also been attributed a lower risk of respiratory events during pregnancy, such as wheezing [157]. Moreover, vitamin D deficiency is linked to the progression of viral diseases such as HIV [158], COVID-19 [159], or HBV/HCV [160], among others. Other vitamins or micronutrients have also been tested in this context alone or in combination. For instance, vitamin A showed promise in porcine epidemic diarrhea virus [161] and HIV [162], although a reduction in MTCT of HIV following vitamin A supplementation has not been demonstrated [163], and overdosing of vitamin A and E should be avoided in pregnant women [164]. Prenatal multivitamin intake (with or without vitamins A and E) has been reported to reduce the incidence of hypertension and other complications in pregnant women living with HIV [165,166]. All these findings might support the use of vitamin supplements in other viral infections, although overall studies have thus far been inconclusive.

Folic acid and its derivatives represent another widely recommended micronutrient during pregnancy (Fig. 1). In fact, folic acid supplementation might be among the main recommendations, not only for its benefits during normal pregnancies but also for the positive outcomes reported in different disorders, including pregnancies affected by HBV [167], ZKV [168], SARS-CoV-2 [169] and influenza viruses [170], among others. The beneficial effects might arise from the immunomodulatory properties [171,172] attributed to folic acid, including histone modifications that affect T-cell differentiation [25], with a reduction in pregnancy complications. Folic acid deficiency during pregnancy is known to produce neural tube defects and congenital heart diseases, and facilitates anemia, leukopenia, and thrombocytopenia [10]. On the other hand, since an overdose of folic acid might not always be safe in certain individuals [173], precautions should be taken to avoid complications when pregnant women have a viral infection. Therefore, recommendations in this context should include foods enriched in folic acid (e.g., green leafy vegetables, fruits, cereals, offal) and supplements with a controlled amount of folic acid.

Although micronutrient supplementation with iron [174] or zinc [175] should be monitored during pregnancy due to controversial effects, general recommendations regarding micronutrient deficits should always be considered to avoid harmful outcomes during viral infections.

8. Impact of ultra-processed foods in the setting of viral infections during pregnancy

Ultra-processed foods, defined as industrial formulations typically with 5 or more ingredients [176], are often energy-dense and nutrient-poor products that contain trans-fatty acids (TFAs) and toxic compounds released during food processing [177]. Obesity, diabetes mellitus, heart disease and cancer have been associated with the regular consumption of ultra-processed foods, and some authors claim regulation to avoid their addictive and toxic effects on human health [178]. Detrimental effects have been reported in different observational studies [179–182], including during pregnancy [183].

In relation to viral infections, inadequate nutrition could lead to malnourishment (understood as undernutrition or overweight/obesity) and increase the risk of infections [184], including influenza virus and SARS-CoV-2 [185]. Diets rich in ultra-processed foods can cause vitamin and mineral deficiencies and, consequently, alter the redox and inflammation status with consequences on the immune response; this may explain a higher susceptibility to some pathogens such as HIV [186], hepatitis virus [187] and SARS-CoV-2 under these circumstances [188].

Ultra-processed foods from Western societies are generally enriched in salt (sodium chloride), which has a negative impact on the function of immune cells and promotes the development of autoimmune diseases, among others [189]. Whereas some authors describe that high-salt diets disrupt the ability of NK cells and, therefore, prevent adequate immune defense against viruses [190], Zhang et al. [191] postulated that a such a diet can also act as an immunomodulator and help fight pathogens including viruses, bacteria, and parasites. Although there is general consensus on the role of high salt intake in exacerbating inflammatory and autoimmune diseases, the clinical guidelines of some countries do not yet consider a dietary salt restriction during pregnancy, surprisingly [192].

As mentioned, TFAs are common components of ultra-processed foods. TFA intake has been associated with higher risk of infertility, adverse effects on gestation and poor fetal outcomes [193]. Pro-inflammatory effects of TFAs from ultra-processed foods (e.g., fries and chips) have been associated with upregulation of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and other inflammatory biomarkers [194,195]. Excessive TFA intake following regular consumption of ultra-processed foods might have negative effects in pregnancies complicated with viral infections (Fig. 2), because TFAs can worsen the alterations induced by some viruses such as HBV [196], HCV [197], HIV [198], and perhaps SARVs-CoV-2 [199,200]. All these findings suggest that recommendations during pregnancy should consider avoiding excessive TFA intake from ultra-processed foods and promoting diets enriched in n-3 PUFAs instead, which have proven beneficial both in viral infections [201,202] and during pregnancy [203,204], as mentioned above. Nonetheless, since specific studies in this regard are still scarce, more research is warranted to demonstrate that consumption of ultra-processed foods induces a poor prognosis during pregnancy in a context of viral infection.

9. Modulation of microbiota for preventing viral infections during pregnancy

Microbial populations in the female reproductive system change during life, including in pregnancy [205]. The vaginal flora of pregnant women is composed of *Lactobacillus crispatus* and *L. iners*, *Gardnerella*, *Prevotella*, *Sneathia*, *Atopobium*, *Dialister*, and *Megasphaera* spp. [38]. An emergent concept of the significant but understudied components of microbiome, the virome, should also be considered. This includes viruses residing in or on the human body, which can either stipulate a defensive role or predispose us to imminent viral infections by their mutual crosstalk with bacteria. Bacteriophages, which might seem indifferent when it comes to causing human disease, play a major role in many infections by influencing the growth of bacterial communities [206]; in this way, a more diverse viral flora has been associated with unsuccessful pregnancies, and vice-versa [207].

As mentioned, intrauterine infection, whether bacterial or viral in nature, is strongly associated with adverse obstetric outcomes including an increased risk of miscarriage, premature birth and stillbirth, thus supporting epidemiological evidence that the pregnant population is at increased risk of severe illness and mortality from viral infections [208]. The interplay between the cervico-vaginal microbiota and the immune system cells is determinant to prevent infections by external pathogens, as well as to maintain an immune tolerant environment, particularly during pregnancy. Thus, women with poor *Lactobacillus* flora are more susceptible to sexually transmitted pathogens, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*. Loss of *Lactobacillus* is also present in cases of bacterial vaginosis (BV), where other bacteria such as *Escherichia coli*, *Staphylococcus* spp. [209], or *Gardnerella vaginalis* [210] begin to overgrow and become the dominant species.

Probiotics have beneficial effects during pregnancy, including moderation of diabetes, excessive weight gain, BV, and preeclampsia [10]. Therefore, this approach can be considered an interesting tool to optimize the vaginal flora. However, in a randomized, double blind, placebo-controlled trial with 304 women receiving oral capsules of a probiotic containing *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14, daily until the end of pregnancy, the authors found no evidence of a clear effect of oral probiotics on the composition of the vaginal microbiota during pregnancy [211].

Lactobacillus-dominant vaginal microbiotas have been associated with decreased risk of HIV-1 acquisition because the virus can be inactivated by elevated glycogen metabolism and subsequent lactic acid accumulation. Moreover, the risk of HIV-1 infection paralleled the severity of vaginal flora disturbance, with the highest risk of HIV-1 attributed to women with severe BV [212]. There is emerging evidence that the reduced presence of *Lactobacillus* spp., combined with a greater diversity of vaginal microbiota, is involved in the acquisition of human papillomavirus and in the persistence and development of

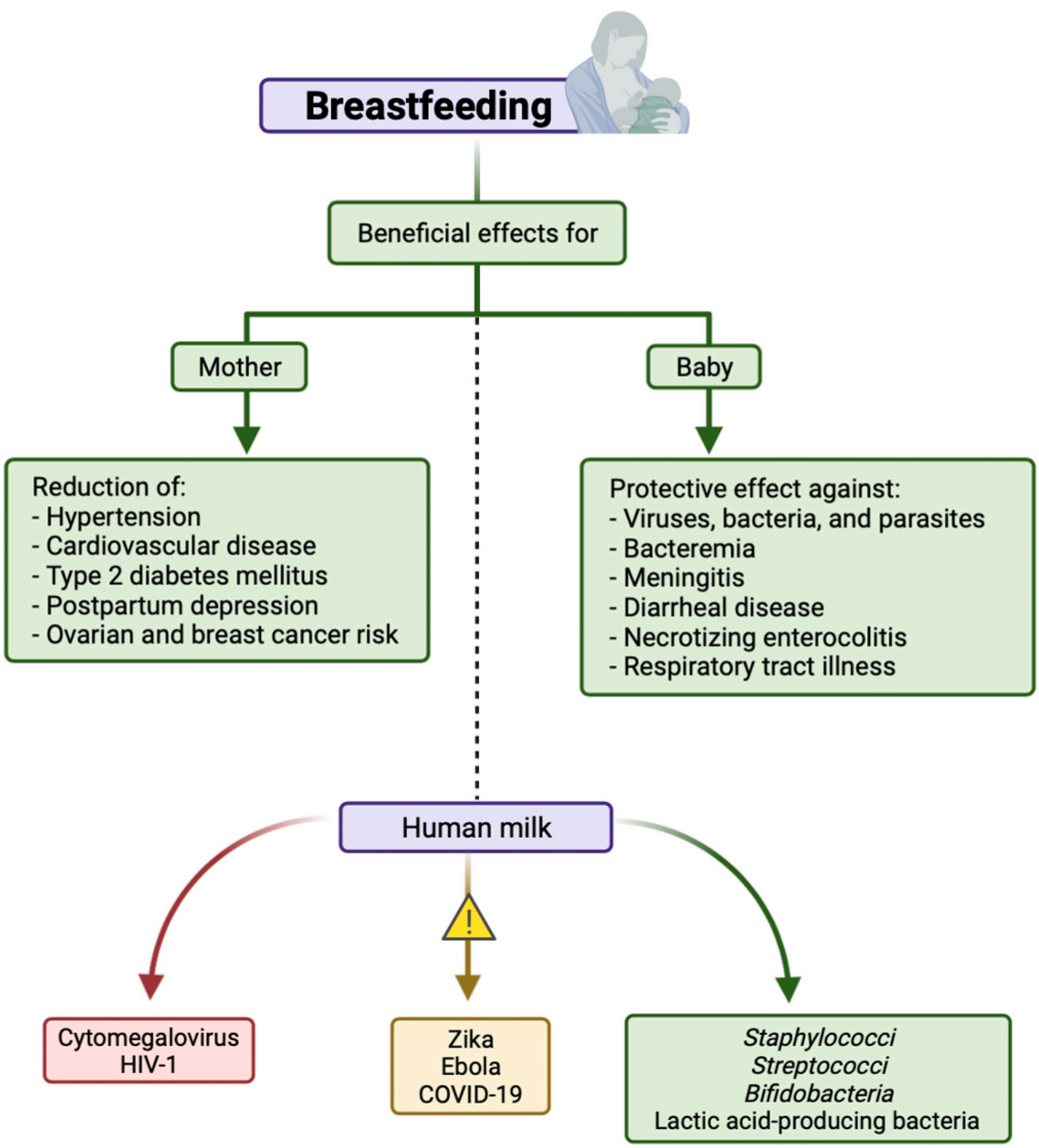

Fig. 3. Dual effects of breastfeeding. Beneficial effects of breastfeeding on the mother and the baby are depicted in green boxes/arrows. Human milk contains *staphylococci*, *streptococci*, *bifidobacteria*, and lactic acid-producing bacteria with positive contributions to the infant's immune system, as described in the text. However, although transmission through human milk is rare for most viruses, the high transmission rates of cytomegalovirus and human immunodeficiency virus (HIV) prevent lactation in such cases (red boxes/arrows). In turn, Zika and Ebola virus transmission through breast milk remains controversial at present, although suppression of breastfeeding is currently recommended. The implications of COVID-19 disease for pregnant women and newborns are under intense investigation; the presence of the virus in breast milk is still uncertain and women are currently advised to breastfeed whenever possible.

cervical precancer/cancer [213]. In the same way, BV increases the genital shedding of HSV-2 [214].

Despite the available guidelines that allow prenatal diagnosis and management of TORCH infections, little is known about the management of other viral infections linked to undesirable pregnancy outcomes [93]. In a mouse study investigating the role of the gut microbiota in the most prominent vectors of flavivirus transmission, oral antibiotics seem to increase the susceptibility and severity of symptoms in West Nile virus, Dengue, and ZKV infections [215]. It is important to better understand the dynamics of virus-host interactions and potential differences in susceptibility and reactivity among the population. The ability of different strains of lactic acid-producing bacteria to prevent or ameliorate different viral infections has been illustrated, for instance, in Ebola virus and CMV, where decreased severity and duration of upper respiratory tract infection or gastroenteritis has recently been reported [216].

Few studies dealing with microbiota and COVID-19 are still available. The use of pre- and probiotics to restore gut homeostasis can also be considered as a strategy that might limit the exacerbated immune response and avoid mitochondrial stress during the course of the disease [217].

10. Viral infections and breastfeeding

Overall, breastfeeding is beneficial for both mother and baby (Fig. 3). In the former, it can help reduce ovarian and breast cancer risk, postpartum depression, hypertension, cardiovascular disease, and type 2 diabetes mellitus. Breast milk is also recommended as the optimal source of nutrition in infants, at least during the first six months of life [218]. Due to its protective effect against different pathogens (viruses, bacteria, and parasites) and clinical entities (e.g., bacteremia, meningitis, necrotizing enterocolitis, respiratory tract illness or diarrheal disease), breast milk is considered one of the most important factors in protecting infants against the morbidity and mortality of infectious diseases [219].

Human milk contains *staphylococci*, *streptococci*, *bifidobacteria*, and lactic acid-producing bacteria (Fig. 3). *Lactobacillus* (which has beneficial effects as mentioned above) can be transported from the mother's intestine to the fetal intestine through breast milk [38]. Breastfeeding contributes to the infant's immune protection by favoring the growth of nonpathogenic flora growth, promoting the development of respiratory and intestinal mucosal barriers, or by means of specific factors against individual microorganisms [219]. It is also noteworthy that breast milk contains exosomes that carry a variety of microRNAs capable of inducing epigenetic modulation of immune system components [25,26].

As already discussed, the transmission of most significant viral infections in newborn or infants can occur transplacentally or intrapartum. The transmission risk from mother to child varies significantly depending on whether the infection occurs during pregnancy or while breastfeeding (e.g., HSV, HIV-1, CMV, HBV). Transmission through breast milk is rare for most viruses; the exceptionally high rate of transmission of CMV or HIV-1 (Fig. 3) might be due to continuous exposure during the lactation period (from months to years). Exposure to CMV-positive blood products or human milk (from donor or mother) should be avoided in CMV-seronegative or premature infants [219]. Interestingly, a recent meta-analysis indicates that the risk of perinatal transmission of HBV from carrier mothers may not increase after adequate immunoprophylaxis in the infants [220].

Nowadays, there are still controversies regarding ZKV transmission through breast milk [221] (Fig. 3). In this context, human milk should be considered as a potentially infectious fluid despite the fact there are no documented studies of long-term complications in infants with suspected, probable, or confirmed ZKV transmission through breastfeeding. Therefore, it is necessary to weigh the benefits of breastfeeding against the probability of virus transmission [222].

Although the transmission of Ebola virus disease through breastfeeding has not been firmly established (Fig. 3), the World Health Organization recommends suppression of this practice in all situations [223]. Children born to suspected or confirmed cases of Ebola virus disease should be separated from the breastfeeding woman and given a breastmilk substitute as needed.

The repercussions of COVID-19 for pregnant women and newborns are still not well known [224]. As mentioned above, direct breastfeeding is advisable in the case of asymptomatic or paucisymptomatic COVID-19-positive mothers under strict infection control measures; if the mother is too ill to care for the newborn, they should be handled separately and the latter should be fed with fresh breast milk [225].

11. Conclusion

Maintaining healthy lifestyle habits during pregnancy can help prevent diseases of pregnancy and decrease the risk of impaired fetal development and complications in later life. Following conception, substantial adaptations of maternal physiology occur to accommodate the fetoplacental unit. Consequently, women of childbearing age are especially susceptible to different conditions, including viral infections, which might impact the course of pregnancy and lead to complications and potential sequelae affecting themselves, the developing fetus, and the baby after delivery. A growing number of viruses beyond the original TORCH syndrome are known to cause infections with potential congenital and perinatal transmission. In this context, a healthy lifestyle based on adequate nutrition plans might be crucial to reduce the risk of gestational diseases and subsequent related complications. Maternal food insecurity is related to increased transmission risk and lower response to antiviral therapies, whereas feeding interventions can help reduce adverse pregnancy outcomes and improve proper fetal development during viral infections. On the other hand, maternal pre-pregnancy obesity is also associated with poor perinatal outcomes, including gestational diabetes mellitus and gestational diabesity [226], and preeclampsia, which can worsen in the setting of concomitant viral infections; therefore, many health programs rely on weight loss, when advisable, and recommendations for proper nutrition throughout pregnancy and beyond. The impact of breastfeeding on mother-to-child viral transmission should always be carefully monitored, including the ongoing SARS-CoV-2 pandemic where the presence of the virus in breast milk is still uncertain.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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