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# The Influence Of Maternal Infections On Congenital Heart Defect

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***Abstract***

Congenital heart defects (CHDs) contribute significantly to heightened infant mortality rates. This review explores the intricate link between maternal infections and CHDs, emphasizing diverse factors influencing fetal development, such as bacterial, fungal, protozoan and viral agents. These infections pose reproductive health risks, potentially leading to complications like prematurity, stillbirth and heart defect to the fetus. The TORCH acronym (Toxoplasma, Other infections, Rubella, Cytomegalovirus, Herpes simplex) identifies infectious teratogens related to congenital issues, emphasizing vertical transmission through the placenta or ascending from the vagina. Rubella and Cytomegalovirus play a significant role in heart defects, particularly when maternal infections amplify CHD risk during pregnancy. Specific scrutiny is placed on Rubella and Cytomegalovirus for their impact on pregnancy outcomes and potential links to congenital heart defects, with preventive strategies discussed, including vaccination and antiviral therapy. The timing and severity of these infections are pivotal in determining their impact on fetal heart development. Environmental exposures and maternal nutrition are critical factors influencing fetal development. Maternal undernutrition in low- and middle-income countries associates with adverse pregnancy outcomes, including congenital heart defects. Emphasizing the importance of maintaining a nutritious maternal diet, rich in essential nutrients, is crucial for improved fetal health and successful pregnancy outcomes. This

review offers insights into preventive measures and underscores the need for continued research to enhance prenatal care strategies.

***Keywords: Congenital heart defects; environmental exposure; Maternal-fetal health; Maternal infections; Nutrition; Pregnancy complications; Vertical transmission.***



## INTRODUCTION

Infections pose a substantial risk to human reproductive health, exerting the potential to lead to severe complications that significantly impact pregnancy outcomes. These complications include prematurity, stillbirth and the transmission of infections to the developing fetus, resulting in congenital infections and subsequent severe diseases [1]. Alberman and Stanley, along with Goldenberg et al., have emphasized the need for extensive research to explore the intricate connection between pregnancy outcomes and maternal colonization by a diverse range of microorganisms, including bacteria, fungi, protozoa and viruses. Understanding the dynamics of maternal colonization is crucial in comprehending how these infections may influence fetal development and impact the health of the newborn [2] [3].

Calado and dos Anjos Pires, further underscore the gravity of infections acquired either in utero or during the birthing process, contributing significantly to fetal and neonatal mortality. This not only influences immediate outcomes but also has lasting effects on early and subsequent child morbidity. The implications of maternal infections extend beyond the prenatal period, affecting the health and well-being of the child into infancy and childhood. This emphasizes the importance of identifying and addressing infections during pregnancy to mitigate their potential long-term consequences [4].

Building on these insights, Balalau et al., have defined infectious teratogens using the widely accepted acronym TORCH. This acronym encompasses specific infectious agents that pose a particular threat during pregnancy: Toxoplasma, Other infections, Rubella, Cytomegalovirus, and Herpes Simplex. Recognizing and categorizing these infections are essential steps in developing targeted strategies for prevention, diagnosis and treatment, particularly as they relate to congenital anomalies and developmental issues in newborns [5].

Moreover, Tanimura and Yamada, have highlighted a potential avenue for intervention in the form of early antiviral treatment. Their findings suggest that timely administration of antiviral medications can lead to improvements in neurological outcomes for symptomatic infants with congenital infections. This underscores the crucial role of prenatal detection in identifying newborns at elevated risk and initiating appropriate interventions to mitigate the impact of these infections on the developing child. The emphasis on prenatal detection emphasizes the need for effective screening programs and early interventions to enhance the overall health outcomes for infants at risk of congenital infections [6].

*Transmission of maternal infection*

Identifying the myriad factors influencing the transmission of maternal infections to the fetus and their potential to cause stillbirth is a critical aspect of understanding pregnancy outcomes. McClure and Goldenberg, in their research, underscored the diverse range of pathogens that play a role in shaping these outcomes [7]. The complexity lies in the various routes through which these infections can reach the developing fetus, each presenting unique challenges and implications for maternal and fetal health. Emphasizing the routes of transmission, Moore et al., highlighted that organisms can reach the fetus through vertical transmission, either via the placenta or by ascending from the vagina across the membranes into the amniotic fluid [8].

Vertical transmission, as defined by DeSilva et al., Boyle et al., and Christianson et al., involves the direct infection of the fetus from the maternal host and stands as a significant contributor to morbidity and mortality in pregnancy. This mode of transmission underscores the intimate connection between the maternal and fetal circulatory systems, which serves as both a pathway for vital nutrients and, unfortunately, a conduit for potential pathogens that can adversely affect fetal development. The severe outcomes for the fetus resulting from bacterial, viral and parasitic infections have been noted by these authors, highlighting the wide-ranging impact that maternal infections can have on fetal well-being [9, 10, 11]. Understanding the specific nature of these infections is crucial for tailoring effective preventive and therapeutic strategies during pregnancy. Additionally, Spinillo et al., observed that infections can reach the placenta and membranes through ascending bacteria from the birth canal or via hematogenous spread of bacteria, viruses and protozoa. This dual mechanism of transmission underscores the vulnerability of the fetal environment to infections originating from both the maternal reproductive tract and systemic circulation. Furthermore, these microorganisms can trigger maternal and fetal inflammatory reactions, often associated with specific anatomopathological findings. The

inflammatory responses may contribute to complications such as preterm birth, stillbirth, or other adverse pregnancy outcomes [12].

*Incidence and Prevalence*

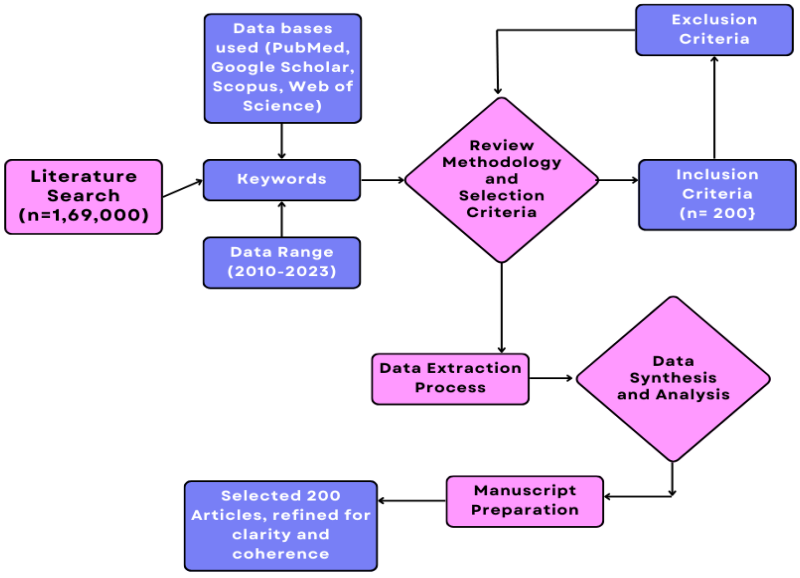
Woodd S L et al., emphasized that infections are a significant and preventable contributor to maternal morbidity, with pregnancy-related sepsis constituting 11% of maternal deaths [13]. Turbadkar et al., 30.4% of pregnant women were found to exhibit Rubella IgM antibodies, aligning with similar research in Mumbai where the prevalence was 26%. Additionally, a seropositive rate of 8.4% for CMV IgM was reported in women with Bad Obstetric Histories (BOH) [14]. Building on these findings, the World Health Organization estimated that, approximately 100,000 children worldwide are born with congenital rubella syndrome in 2021, marked by congenital cataract, microphthalmia, cardiac defects and sensorineural deafness [15].

Emphasizing the persistent challenge of adverse pregnancy outcomes, Lawn et al., underscored the high stillbirth rates, especially prevalent in low-middle income countries (LMIC), where approximately 98% of the estimated 3 million third-trimester stillbirths occur annually [16]. McClure et al., further pointed out that maternal infections likely play a crucial role in stillbirths, particularly in sub-Saharan Africa and South Asia, where the burden is most pronounced [17]. Providing additional insights, Seale et al., detailed the prevalence of neonatal infections in regions such as sub-Saharan Africa, South Asia and Latin America, highlighting a 9.8% case fatality risk associated with potential severe bacterial infections in the first month of life [18].

In India, the seroprevalence rates of toxoplasmosis exhibit significant variability across different regions, ranging from 26% in Delhi and 41.75% in its neighboring areas (Akoijam BS et al.,) to a substantial 77% in the sub-Himalayan parts of the country [19, 20]. In alignment with the concept presented by Neu et al., and Stegmann and Carey, organisms implicated in congenital conditions are encompassed in the TORCH complex, with the TORCH acronym representing Toxoplasma gondii. This concept also underscores that other infections, such as Rubella, Cytomegalovirus, and Herpes viruses, have been identified as contributors to stillbirths, perinatal morbidity and 2%–3% of all congenital anomalies [21, 22].

## MATERIALS AND METHODS

This comprehensive review thoroughly examines the intricate interplay of environmental factors, specifically maternal infections, in the development of congenital heart defects (CHDs). By utilizing keywords such as "Congenital heart defects," "Maternal infections," "Vertical transmission," "Pregnancy complications," "Environmental exposure," "Maternal nutrition," and "Maternal-fetal health," we systematically explored databases including PubMed, Google Scholar, Scopus and Web of Science, covering studies published until the knowledge cut-off date in January 2023. The analysis of 48 selected articles from an initial pool of 200 underscores complex relationships among genetic factors and environmental risks. The review emphasizes the significant role of maternal infections as potential triggers for CHDs, with multiple revisions ensuring adherence to scientific writing standards.




**Flow Chart 1: Illustrating Systematic Methods for Maternal Infections on CHDs**

**Factors causing maternal infections**

Maternal infections during pregnancy can be caused by various factors, including:

***Pathogens:*** Robbins JR and Bakardjiev AI, have provided insights into the transfer of pathogens from mother to fetus, highlighting two specific sites within the human placenta where this exchange takes place. In their observations, they note that, maternal cells directly interact with specialized fetal cells known as trophoblasts. The first site of interaction occurs at the uterine implantation site, where maternal immune and endothelial cells are in close proximity to extra villous trophoblasts. The second site involves maternal blood surrounding the syncytiotrophoblast (SYN), another layer of cells in the placenta. The placenta's trophoblasts facilitate the transfer of substances, including pathogens, between maternal and fetal circulatory systems at key locations, playing a crucial role in maternal-fetal transmission [23].

Building on this understanding, Richardson et al., have demonstrated that pathogens can exploit different routes to access the uterus and infect the developing fetus. Among these routes, hematogenous transmission through the placenta is identified as one of the most common mechanisms. In this process, microorganisms are able to travel through the maternal bloodstream and cross the placental barrier, thereby gaining access to the fetal circulatory system. Additionally, ascending transmission is highlighted, where microorganisms traverse the reproductive tract of the pregnant woman to reach the developing fetus [24].

***Environmental exposures:*** Environmental chemicals can significantly impact development, growth and reproduction by mimicking hormones or interacting with hormone receptors [25]. Gonzalez-Casanova et al., suggest that prenatal exposure to pollutants, including mold, lead, pesticides, tobacco and air pollutants may affect cognitive development [26]. O'Toole et al., additionally note a positive association between environmental risks, particularly tobacco smoke and increased cardiovascular morbidity and mortality. Animal studies indicate that tobacco smoke triggers endothelial dysfunction, prothrombotic responses and exacerbates atherogenesis and myocardial ischemic injury, with similar mechanisms possibly activated by other pollutants or food components [27]. Kalisch-Smith et al., emphasized the significant association between congenital heart defects (CHD) and environmental exposures. The development of CHD is shaped by a combination of environmental factors, oligogenic influences, and gene–environment interactions. The environmental origins of CHD have been strongly supported for nearly 80 years [28]. In 1941, Gregg NM provided substantial evidence for the environmental hypothesis by illustrating that maternal rubella infection could result in a range of birth defects, including CHD [29].

***Social and Behavioral Factors:*** Volkow ND et al., highlighted the increasing trend of women reporting marijuana use, either for recreational purposes or to manage pregnancy-related nausea and vomiting [30]. Metz and Stickrath, observed that marijuana, the most commonly used illicit drug during pregnancy, exhibits prevalence rates ranging from 3% to 30% across different populations [31]. It freely crosses the placenta and is present in breast milk. Considering the effects on fetal development, Behrooz L et al., pointed out that, maternal prenatal smoking can adversely affect fetal development, particularly with respiratory implications [32]. While postnatal smoke exposure is a recognized risk factor for respiratory infections, the independent effects of prenatal smoking, apart from postnatal exposure, are less well-established. Smoking influences maternal immunity, predisposing individuals to infection and inflammation [33].

***Sexual Transmission:*** According to the World Health Organization (WHO), Neisseria gonorrhoeae (NG), Chlamydia trachomatis (CT) and Treponema pallidum (TP) significantly contribute to the global burden of treatable bacterial sexually transmitted infections (STIs), with nearly a quarter of a billion new cases reported annually [34]. Maternal infection with these conditions has been linked to neonatal infections such as conjunctivitis (CT, NG), pneumonia (CT) and disseminated infection (TP, NG). TP, in particular, may have devastating consequences, including multi-organ involvement, failure to thrive and neonatal death (Silveira MF et al., Woods CR, Hammerschlag MR, Walker DG and Walker GJ, Walker GJ and Walker DG, Woods CR, Woods CR) [35, 36, 37, 38, 39, 40, 41]. Studies conducted by Silveira MF et al., Woods CR (2005) and Hammerschlag MR (2011), revealed that, untreated chlamydial and gonococcal infections can have serious consequences in pregnant women, potentially leading to fetal loss, premature rupture of membranes and preterm labor and delivery [35, 36, 37]. Emphasizing the importance of addressing these challenges, Workowski K A , highlighted the need for new, more effective treatment regimens, highly sensitive tests for asymptomatic infection, improved counseling for patients and their sexual partners and the development of new vaccines for sexually transmitted pathogens to achieve broader public health goals and enhance sexual and reproductive health [42].

***Maternal Immune Status:*** Langel SN et al., emphasize the pivotal role of bolstering immunity within the maternal-neonatal dyad, a process facilitated by both transplacental transfer and breast milk secretion. This enhancement is crucial for protecting developing offspring from pathogens both before and after birth,

influencing susceptibility to infections, and shaping responsiveness to immunization across generations. This strategic approach holds significant promise for public health [43].

Sukumaran et al., report that, maternal immunization during pregnancy plays a key role in providing protective maternal antibodies against infectious diseases to the fetus before birth. However, the current practice is limited to vaccines like Tdap and seasonal influenza, primarily due to the safety profile of inactivated vaccines. Live vaccines, which carry potential fetal risks, are not recommended [44].

***Medications:*** During pregnancy, around 80% of women use medications, with some drugs posing potential risks for congenital anomalies (CAs), as highlighted by Bakker et al., and Jentink et al., [45, 46]. Pregnant women are typically excluded from pre-authorization studies, underscoring the importance of post-authorization research, particularly utilizing pregnancy medication exposure registries, to assess the risks and benefits of medications during pregnancy [47, 48]. Fisher et al., discovered that, maternal hypertension and antihypertensive use elevate the risk of specific congenital heart defects (CHDs) like PVS, VSD-PM, ASD2 and CoA [49]. Moreover, Van Gelder et al., found that physiological changes in early pregnancy leading to gestational hypertension and pre-eclampsia may contribute to major birth defects such as CHDs and hypospadias [50]. Despite the potential risks, Van Zutphen et al., concluded that maintaining treatment during pregnancy is crucial for maternal and fetal health; however, consensus is lacking on the necessity of medication use for mild to moderate hypertension during pregnancy [51].

***Maternal Nutrition:*** R Elango and RO Ball, G Saccone and V Berghella and A Mousa emphasize the importance of maintaining a nutritious maternal diet, incorporating vegetables, fruits, legumes, olive oil, nuts and fish to achieve a balanced intake of proteins, high-quality fats (essential and polyunsaturated fatty acids) and fiber-rich carbohydrates with a low glycemic index [52, 53, 54]. Lowensohn et al., assert that a nutrient-rich maternal diet before and during pregnancy is linked to improved fetal health, appropriate birth weight and increased rates of maternal and infant survival [55]. According to Black RE et al., maternal undernutrition in low- and middle-income countries (LMICs) significantly hinders successful pregnancy outcomes, contributing to 800,000 neonatal deaths annually [56]. Wu et al., discovered that maternal malnutrition during gestation impairs embryonic and fetal growth, leading to adverse outcomes such as intrauterine growth restriction (IUGR), low birthweight, preterm birth and birth defects (e.g., neural tube defects and iodine deficiency disorders) [57]. Encouraging supplements and fortified foods ensures adequate nutrient supply for both mother and fetus [58]. Building on these findings, Lowensohn et al., further emphasize that physicians treating pregnant women should be prepared to advise on a healthy diet for the benefit of the fetus [55].

***Nutritional Deficiencies:*** Maternal and child health relies heavily on nutrition. Beyond inadequate maternal nutrition, factors such as biology, socioeconomic conditions, teenage pregnancy, short interpregnancy intervals and demographics also influence birth outcomes [59]. Fall CH et al., noted that, multiple nutrient deficiencies are commonly observed in low socioeconomic status populations [60]. Recognizing the broader impact, Bhutta ZA et al., highlighted the risks associated with poor maternal outcomes, including maternal mortality, anemia, hypertension, bleeding and postpartum complications. These factors contribute to adverse fetal outcomes, encompassing low birth weight, preterm birth and growth issues significant contributors to neonatal deaths unrelated to congenital malformations [61].

The consequences of maternal nutritional deficiencies extend to both the mother and the developing fetus. Examples of various maternal nutritional deficiencies are listed in the table below:

| Deficiency | Effects on the Fetus | Symptoms | Reference |
|---|---|---|---|
| **Vitamin A Deficiency** | Effects on several fetal organs and on the fetal skeleton | Night Blindness | [62, 63] |
| **Folate (Vitamin B9) Deficiency** | Neural tube defects, cognitive decline | Depression and neuropathy | [64] |
| **Iron Deficiency** | Intrauterine growth retardation, prematurity, feto-placental miss ratio and higher risk for peripartum blood transfusion | Anemia | [65] |
| **Calcium Deficiency** | Impact on bone health | Fractures, osteoporosis, chronic disease risk | [66, 67] |
| **Vitamin D Deficiency** | Muscle weakness and bone pain, increased risk of fractures | Rickets in children and osteomalacia and osteoporosis in adults | [68, 69,70,71] |
| **Iodine Deficiency** | Impaired brain development in the child, with effects on cognitive and motor function, hearing and speech. | Decreased IQ, goiter, hypothyroidism and hyperthyroidism | [72, 73] |
| **Zinc Deficiency** | Influences fetal growth, preterm birth necrotizing enterocolitis, chronic lung disease and retinopathy | Alopecia, diarrhea, skin lesions, taste disorders, loss of appetite, impaired immune function and neuropsychiatric changes and growth retardation, | [74, 75] |

**Table 1: Examples of various maternal nutritional deficiencies.**

**Different types of maternal infections**

Infectious diseases significantly contribute to morbidity and mortality in children globally. According to the World Health Organization and the classification by Chan M & Smith M A, these diseases are caused by bacteria, viruses, fungi, or parasites invading body tissues or releasing toxins that disrupt normal functions. The body's inflammatory response is triggered to combat the invading microorganisms [76, 77]. Unfortunately, infections or the inflammatory reactions to them can lead to detrimental outcomes such as preterm delivery, birth defects, developmental delays, or stillbirths.

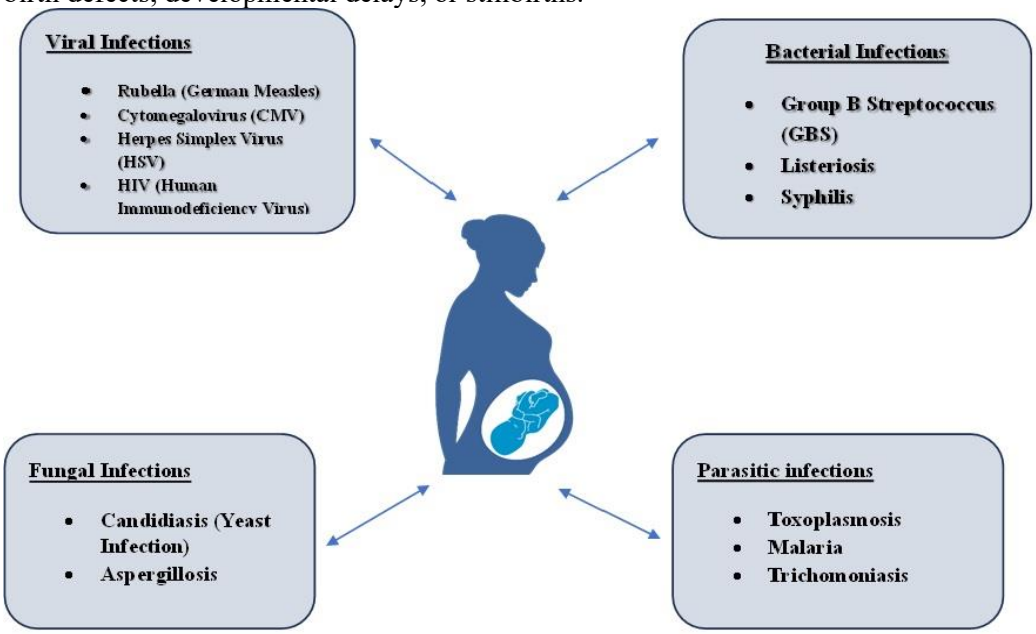



**Figure No:1 Figure illustrating different types of maternal infection**

## I. VIRAL INFECTIONS

Silasi M et al., highlighted that, traditionally viral infections during pregnancy were considered mostly harmless, with exceptions like herpes virus. However, recent outbreaks, including Ebola and other epidemics and pandemics, have revealed that pregnant women face worse outcomes than the general population and non-pregnant women, including preterm labor and adverse fetal effects [78]. Racicot K and Mor G emphasized that some viruses can directly infect the fetus at specific gestational times, while others target only the placenta. Both scenarios may lead to severe birth defects or pregnancy loss [79]. Thomas J R et al., identified that maternally derived immune cell types in close proximity to the fetus-derived placenta provide an additional layer of immune protection [80]. Mate A et al., discovered that, appropriate maternal education from preconception to the early postnatal period is crucial for promoting healthy pregnancies and preventing/reducing the impact of viral infections. This involves maintaining an adequate lifestyle through proper nutrition plans and feeding interventions whenever possible, which may be crucial in reducing the risk of virus-related gestational diseases and associated complications in later life [81].
Various types of viral infections can affect pregnant women and they are:

***Rubella (German Measles)***
Rubella was initially identified as the virus causing birth defects [77]. Studies by O'Leary S T et al., revealed that, rubella virus, belonging to the togavirus family and genus Rubivirus, finds humans as the sole reservoir for infection [82]. Thompson KM et al., noted that, the gestational age during maternal rubella infection

influences the likelihood and severity of outcomes, with early pregnancy infections increasing the risks of spontaneous termination (miscarriage), fetal death (stillbirth), birth defects and reduced survival for live-born infants [83]. Outside of pregnancy, rubella is generally a mild, self-limited infection [84]. However, maternal rubella infection in the first trimester can be catastrophic, resulting in fetal death or the birth of an infant with congenital anomalies known as congenital rubella syndrome. Webster WS , further added on that, damage to blood vessel walls and heart linings is directly responsible for cardiovascular, central nervous system (CNS), hearing and other systemic defects, as well as growth restriction in congenital rubella syndrome. Deafness, cardiovascular and neurological damage and retinopathy are more prevalent if infection occurs within the first 16 weeks of gestation but become rare thereafter [85]. Kimberlin DW, stressed the importance of universal childhood immunization and vaccination of all susceptible individuals with rubella vaccine to reduce virus circulation, crucial for preventing both rubella and congenital rubella syndrome [86].

***Cytomegalovirus (CMV)***

Cytomegalovirus (CMV), a prevalent worldwide DNA herpesvirus, is commonly transmitted through sexual activity and contact with young children during pregnancy [87]. Britt W, found that, the risk of congenital CMV infection associated with primary maternal infection during pregnancy is estimated to be between 30 and 40% [88]. While most healthy children and adults infected with CMV remain asymptomatic, those who do experience symptoms typically manifest common illness indicators such as fever, sore throat, fatigue and swollen glands. However, CMV can lead to severe illness in pregnant women, their infants, individuals caring for children and those who are immunocompromised [77]. Khan et al., documented aortic root dilatation in two congenitally infected CMV patients after excluding other common causes of ascending aorta dilatation [89]. Additionally, Sakaguchi et al., reported dilated cardiomyopathy and signs of congestive heart failure in a 2-month-old infant associated with perinatal congenital CMV infection [90]. Another study by Manzoor et al., detailed a case of tetralogy of Fallot in a 3-month-old infant, revealing a previously unidentified congenital CMV infection [91].

Despite the absence of a licensed CMV vaccine, suggested preventive measures, such as good hygiene practices and avoiding intimate contact with young children (e.g., kissing on the mouth and sharing utensils), have been proposed to prevent maternal primary CMV infection during pregnancy, though this approach remains an unproven method for reducing the risk of congenital CMV infection [87].

***Herpes Simplex Virus (HSV)***

Herpes simplex virus (HSV) infections are widespread globally, affecting a substantial portion of the human population, as reported by Looker et al., [92, 93]. Mustafa et al., specified that HSV-1 is responsible for orofacial and genital infections, while HSV-2 primarily causes genital infections [94]. According to James et al., an estimated 3.7 billion people worldwide were seropositive for HSV-1 and nearly 500 million for HSV-2 in 2016 [95].

Knipe and Howley, noted that HSV-1 is typically acquired early in life through the orolabial mucosa, while HSV-2 infections commonly occur later through sexual transmission [96]. Although vertical transmission during pregnancy is rare, occurring in less than 1% of cases, Hammad and Konje, asserted that the risk of intrapartum vertical transmission is high for individuals with active lesions or asymptomatic shedding. Neonates exposed to HSV during childbirth may suffer severe consequences, including disseminated, central nervous system, and skin, eye mouth/mucous disease, or even face mortality [97].

Lee and Nair, revealed that to minimize the risk of vertical transmission, vaginal delivery should be avoided if there are active genital lesions outside the first trimester. However, in the first trimester, they suggested attempting vaginal birth despite the presence of active lesions. Notably, there is currently no established guidance for the prophylactic treatment of non-genital HSV-1 during pregnancy [98].

***Human Immunodeficiency Virus (HIV)***

The global HIV pandemic profoundly impacts 36.9 million individuals, including 1.5 million pregnant women, with a significant burden of 91% in the sub-Saharan Africa region, leading to poor perinatal outcomes, as disclosed by Wedi et al., [99]. Deeks et al., reported that, HIV transmission occurs through contact with infected body fluids, involving mucosal tissue, blood, or broken skin [100]. Spector and Ellington et al., underscored diverse mechanisms of HIV transmission from mother to offspring, encompassing in utero transplacental transport, intrapartum transmission and breastfeeding. High maternal viral load stands as the primary risk factor for both in utero and intrapartum mother-to-child HIV transmission, with additional risks linked to viral phenotype, advanced HIV-1-related illness/AIDS, maternal co-infections, prolonged rupture of amniotic membranes and genetic polymorphisms affecting virus entry or immune responses [101, 102].

Current antiviral treatments, such as combination antiretroviral therapy (cART) with three active drugs from two or more classes, can reduce HIV-related illness, extend lifespan and prevent transmission [103]. Key advancements in public health include male medical circumcision, antiretrovirals for preventing mother-to-child transmission and treatment in HIV-positive individuals to prevent transmission, as well as pre-exposure prophylaxis. Ongoing research explores additional prevention methods, such as vaccines and vaginal microbicides [104].

| Viral infection | Effect on mother | Outcome of fetus | Symptoms | Prevention | Reference |
|---|---|---|---|---|---|
| **Varicella-Zoster Virus (Chickenpox)** | Shingles in Pregnancy, bacterial sepsis, pneumonia, encephalitis and haemorrhage | Congenital abnormalities (congenital varicella syndrome) | Fever, continued development of new skin vesicles for >5 days and involvement of the lungs, liver and brain. | Live attenuated varicella vaccine | [105, 106] |
| **Hepatitis B and C** | Liver Complications, vertical transmission risk | Chronic viral hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) | Fever, jaundice, abdominal pain, nausea and vomiting lasting 2 to 3 months | HBsAg vaccine | [107] |
| **Influenza (Flu)** | Changes in the immune, heart, and lung functions during pregnancy. | Risk of stillbirth | Chills, cough, sneezing and weakness | Flu vaccinations | [108, 109] |
| **Zika Virus** | Guillain-Barre Syndrome, | Microcephaly and birth defects, neurological complications | Fever and a slight headache, dizziness, joint pain/edema | Individual protection from mosquito bites and vector control | [110] |
| **Parvovirus B19 (Fifth Disease)** | Anemia | Spontaneous abortions, fetal anemia, heart failure, fetal hydrops, and/or fetal demis | Viremia, fever, malaise and myalgia | No vaccine or antiviral is available | [111] |
| **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)** | Mild pneumonia, respiratory failure, septic shock and multiple organ dysfunction or failure | Vertical Transmission, mild respiratory difficulty and sporadic cough | Self-reported fever, fatigue, dry cough, myalgia and dyspnea | Antibiotic treatment | [112, 113] |
| **Chikungunya** | Joint pain of abrupt onset, high fever and rash | Stillbirth, fetal loss | Oedema of lower limbs, inflammation of the right achilles tendon, alopecia | DENV vaccine, ZIKV vaccine | [114, 115, 116, 117] |

**Table No 2: Effect of viral infection during pregnancy**

## II. BACTERIAL INFECTIONS

Bacterial infection, a widespread clinical condition affecting various organs and tissues, is highlighted by Xiao and Cai [118]. According to Fisher, bacteria can persist within hosts due to factors such as host immunosuppression, pathogen immune evasion and antibiotic ineffectiveness [119]. This persistence poses a considerable threat to human health, as noted by Deusenbery et al., with escalating antibiotic resistance contributing to significant morbidity and mortality. Therefore, the swift and effective identification and treatment of pathogenic bacteria are crucial in addressing this pressing issue [120].

### *Group B Streptococcus (GBS)*

Invasive Group B Streptococcus (GBS) infection, posing a persistent threat of morbidity and mortality, manifests as diverse clinical diseases, particularly impacting high-risk populations such as pregnant women, neonates and the elderly, with an increasing incidence in nonpregnant adults, as discovered by Raabe and Shane [121]. The estimated incidence of systemic invasive GBS disease in pregnant women is 0.38 cases per 1,000 pregnancies, with a worldwide case fatality rate of 0.2%, according to studies by Hall et al., [122]. Historically, S. agalactiae has been classified into nine serotypes based on the capsular polysaccharide, with a tenth serotype described by Slotved et al., as noted by Edwards and Baker [123, 124]. An Alberta, Canada study revealed that the most prevalent serotypes causing invasive GBS disease include III (20%), V (19%), Ia (19%), Ib (13%) and II (11%) [125].

Raabe and Shane emphasized that, these predominant serotypes causing disease exhibit regional variability and differ between invasive and colonizing isolates [121]. Syndromes arising from invasive GBS disease in adults include bacteremia without an identifiable focus and infections of the skin and soft tissues, as reported by Skoff et al., Chaiwarith et al., and Tazi et al., [126, 127, 128]. Ulett et al., identified an additional manifestation involving urinary tract infections associated with various GBS serotypes [129].

Penicillin G stands as the primary treatment for invasive GBS disease in adults, as noted by Edwards and Baker [124]. Kimberlin et al., established that Penicillin G monotherapy is recommended for addressing invasive GBS infection in infants, with dosing ranging from 250,000 to 450,000 units/kg/day for infants up to 7 days old and 450,000 to 500,000 units/kg/day for those older than 7 days [130]. Raabe and Shane, concluded that formulating and executing strategies to identify hosts, judiciously treat with narrow-spectrum antimicrobials and prevent invasive disease through vaccines are imperative in reducing the burden of Group B Streptococcus disease [121].

***Listeriosis***

Listeriosis, an infrequent foodborne illness caused by Listeria monocytogenes, is transmitted through the consumption of contaminated ready-to-eat food, long-shelf-life products, deli meats and soft cheeses, as reported by Madjunkov et al., [131]. This transmission pathway is corroborated by Schlech et al., and Mateus et al., who emphasized that, listeriosis can be spread through contaminated food, leading to cases and outbreaks [132, 133]. Goulet et al., documented that, the annual incidence of listeriosis worldwide ranges from 1 to 10 cases per million population [134].

Madjunkov et al., further noted that, Listeria predominantly affects immunocompromised patients, elderly individuals, pregnant women and neonates [131]. Pregnancy-related listeriosis increases the risk of fetal and neonatal mortality by approximately 21%, with infections more likely to occur in the third trimester (66%) than in the first trimester (3%), as highlighted by Wadhwa Desai et al., [135]. Maternofetal transmission of L. monocytogenes can lead to adverse outcomes such as amnion inflammation, amnionitis, preterm labor, stillbirths, spontaneous abortions, or severe disease with widespread microabscesses and granulomas (granulomatosis infantiseptica), as reported by Mylonakis et al., and Janakiraman [136, 137].

Confirming the severe consequences of listeriosis, Khsim et al. in 2022 emphasized its potential to result in miscarriage, spontaneous preterm labor and birth, stillbirth and congenital neonatal infections [138]. Wang et al., added that, pregnant women may exhibit symptoms similar to influenza, such as fever, headache, diarrhea, myalgia, or other digestive-related symptoms [139]. Symptoms typically manifest as fever and other flu-like symptoms, such as fatigue and first-line treatment involves intravenous amoxicillin or ampicillin, as concluded by Khsim et al., [138].

***Syphilis***

According to WHO, syphilis is annually diagnosed in approximately 1.5 million pregnant women, making it the most prevalent congenital infection worldwide and carrying significant consequences for both the mother and the developing fetus if left untreated [140, 141]. De Santis et al., explained that, syphilis caused by the spirochete Treponema pallidum, progresses through distinct phases—primary, secondary, latent and tertiary—without alteration in physical manifestations during pregnancy and transmissibility is possible at any stage [142].

Maternal syphilis is associated with a 21% increased risk of stillbirth, 6% increased risk of preterm delivery and a 9% increased risk of neonatal death, as discovered by Gomez et al., [143]. WHO affirmed that, approximately 50% of non-treated or inadequately treated pregnant women can transmit the disease to the conceptus, resulting in adverse outcomes such as stillbirth, neonatal death, prematurity, low birth weight, or congenital infection [144]. Uku et al., demonstrated a strong association, emphasizing that, babies born to mothers with syphilis should also receive penicillin treatment, underscoring the importance of comprehensive management to mitigate the risks associated with maternal syphilis and ensure the well-being of both the mother and the newborn [145].

## III. FUNGAL INFECTIONS

Enoch et al., determined that invasive fungal infections (IFI) pose a growing global concern, with invasive candidiasis and candidemia accounting for the majority of cases [146]. Cutaneous infections and infestations are particularly common among children and adolescents, as Alter et al., uncovered, emphasizing the prevalence of fungal infections affecting the skin and mucous membranes across all age groups. Despite the challenges posed by IFIs, mortality rates for most of these infections have generally decreased [147]. This

improvement is attributed to advancements in medical technology, enhanced care of central venous catheters (CVCs), improved diagnostics and the implementation of more effective preemptive therapy and prophylaxis, as highlighted by Enoch et al., [146].

***Candidiasis (Yeast Infection)***

Vulvovaginal candidiasis (VVC), commonly known as a yeast infection, is a prevalent gynecologic condition affecting 3 out of 4 women during their lifetimes, as noted by Soong and Einarson [148]. According to Aguin and Sobel, prevalence studies indicate that Candida species colonize the vagina in at least 20% of all women, with the rate increasing to 30% during pregnancy. Among clinically significant species, Candida albicans, including C. glabrata, C. parapsilosis, C. krusei and C. dubliniensis, C. albicans is considered the most crucial [149].

Despite therapeutic advances, candidiasis, often caused by C. albicans, remains common, affecting newborns, immunocompromised individuals (such as AIDS patients) and those receiving broad-spectrum antibiotics, as pointed out by Hani et al.,. Most clinicians, particularly during pregnancy, avoid long-term suppressive therapy with oral azoles for recurrent vaginal candidiasis (RVVC) [150]. Instead, they prefer addressing individual symptomatic episodes with a 7-day course of topical imidazole vaginally to minimize systemic exposure to medications, as recommended by Aguin and Sobel [149].

***Aspergillosis***

Among over 250 Aspergillus species, fewer than 40 are recognized for causing infections in humans, with Aspergillus fumigatus being the most prevalent and associated with serious, invasive diseases [151]. Jenks and Hoenigl, noted that infections caused by Aspergillus spp. continue to be linked with elevated morbidity and mortality rates. In immunocompetent hosts, innate immune mechanisms usually eliminate conidia, making Aspergillus fumigatus a relatively weak pathogen, resulting in uncommon clinical syndromes like aspergilloma and allergic bronchopulmonary aspergillosis [152].

Sehgal et al., reported that, two-thirds of their subjects experienced asthma or an allergic bronchopulmonary aspergillosis exacerbation during pregnancy, with most occurrences in the first two trimesters [153]. Historically, treatment focused on dampening the inflammatory response using prolonged courses of oral glucocorticosteroids, as identified by Tracy et al., [154]. However, recent concerns about steroid toxicity and the availability of new treatment modalities have led to trials of oral azoles, inhaled amphotericin, pulse intravenous steroids, and subcutaneously-injected anti-IgE monoclonal antibody omalizumab, all of which show evidence of efficacy and reduced toxicity, as reported by Sehgal et al., [153].

Patel et al., summarized that, drugs used for treating allergic bronchopulmonary aspergillosis (ABPA) include systemic glucocorticoids, antifungal agents and biologics, each carrying its own benefits and drawbacks. The evolving understanding of treatment options reflects a shift towards minimizing toxicity while maintaining efficacy in managing Aspergillus-related infections [154].

## IV. PARASITIC INFECTIONS

Parasites have traditionally been viewed as a significant menace warranting eradication [155]. According to Mahande A M & Mahande M J, parasitic infections during pregnancy have been linked to an elevated risk of pregnancy complications and unfavorable outcomes in resource-limited settings [156]. Taylor SM et al., supplement this by noting that, pregnant women often experience parasitic infections due to compromised immune systems, potentially impacting various physiological processes [157]. Timely identification and appropriate treatment during pregnancy are imperative to prevent adverse pregnancy outcomes and complications [157]. Enhancing public health education and socio-economic status could be instrumental in mitigating the risk of parasitic infections among pregnant women in the region, as asserted by Ahenkorah B et al., underlining the importance of proactive measures beyond individual medical interventions [158].

***Toxoplasmosis***

Toxoplasmosis, a prevalent chronic infection caused by the Toxoplasma gondii parasite, is a significant concern during pregnancy [159]. Contracting Toxoplasma gondii in its acute form during pregnancy can lead to significant adverse consequences for mothers, fetuses and newborns [160]. Variations in the incidence and prevalence of this infection across different geographical areas have been revealed, with seroprevalence among reproductive-age women in developed countries with temperate climates ranging from 10 to 50% [161]. Tropical regions, particularly in communities exposed to contaminated soil, undercooked meat, or unfiltered water, exhibit a higher prevalence, reaching up to 80% [162].

Various sources of Toxoplasma gondii infection have been highlighted, including the ingestion of raw or undercooked meats containing parasite tissue cysts, sporulation of oocysts through the consumption of contaminated vegetables and water and accidental ingestion of contaminated soil [163]. Vertical transmission from pregnant women with primary infections to their fetuses can lead to congenital toxoplasmosis (CT). Symptomatic patients typically manifest mild and non-specific symptoms such as fever, chills, sweats, headaches, myalgia, pharyngitis, lymphadenopathy, hepatosplenomegaly and/or a diffuse non-pruritic maculopapular rash [159]. Congenital toxoplasmosis cases may progress to miscarriage, neurological and visual abnormalities, or be asymptomatic at birth with the development of late clinical manifestations [164].
Confirmation of congenital infection involves serology with the identification of IgG and IgM antibodies against T. gondii and the avidity test (Villard O et al.,), along with the detection of Toxoplasma DNA in the amniotic fluid through polymerase chain reaction (PCR) (Vidigal PVT et al.,. The comprehensive understanding of the epidemiology, transmission, and clinical manifestations of toxoplasmosis underscores the importance of timely diagnosis and appropriate management during pregnancy [165, 166].

***Malaria***

Malaria, a severe disease caused by parasites of the Plasmodium genus, is transmitted to humans through the bite of an infected female Anopheles mosquito [167]. Despite global efforts, malaria remains a significant public health concern, affecting 3.3 billion people in 97 countries, resulting in an estimated 200 million cases and approximately 600,000 deaths [168]. Pregnant women are particularly susceptible to malaria infections, posing risks to both maternal and fetal health [169]. The consequences of malaria during pregnancy include anemia, stillbirth, low birth weight and increased risks of maternal and fetal mortality [170].
In semi-immune women, malaria can lead to maternal anemia, while the developing fetus may experience stillbirth, premature delivery and fetal growth restriction [170]. Feeney M E, highlighted the variability in infants' responses to prenatal malaria exposure, with some developing T-cell tolerance, potentially explaining the increased childhood malaria risk [171]. The complex life cycle of these parasites involves transmission between mosquito vectors and vertebrate hosts [172].
Factors contributing to the resurgence of malaria include the emergence of drug-resistant parasite strains, the spread of insecticide-resistant mosquito strains and the absence of licensed and proven-effective malaria vaccines [172]. Duffy P E & Patrick Gorres J, reported a significant development in malaria vaccine research in 2015 when the European Medicines Agency favorably reviewed the pre-erythrocytic Plasmodium falciparum candidate RTS,S. This marked a milestone as it became the first human anti-parasite vaccine to pass regulatory scrutiny and was introduced into national pilot programs [173].

***Trichomoniasis***

Trichomoniasis is recognized as the most prevalent non-viral sexually transmitted infection (STI) globally [174]. In the United States, the Centers for Disease Control and Prevention, reports an estimated 3.7 million individuals affected by the infection, with only 30% exhibiting symptoms [175]. Trichomoniasis is associated with significantly heightened risks of HIV acquisition and transmission, as well as pregnancy complications, including preterm delivery, pelvic inflammatory disease (PID) among HIV-infected women and other conditions [176]. Symptoms in women typically include vaginal discharge, painful intercourse, urinary tract infection symptoms, vaginal itching, or pelvic pain [177]. Factors such as poor personal hygiene, multiple sexual partners, low socioeconomic status and underdevelopment have been linked to a high incidence of trichomoniasis [178].
The recommended treatment is a single dose (2 g) of metronidazole (MTZ) for both the index patient and their sexual partners. However, Kissinger P, underscores the challenge of high rates of retest positivity after single-dose treatment, likely stemming from clinical resistance rather than re-infection and/or drug resistance [179]. Treatment heavily relies on one class of drugs, the 5-nitroimidazoles, raising concerns about the potential emergence of widespread drug resistance. The evolving understanding of trichomoniasis highlights the need for comprehensive strategies to address its prevalence and potential challenges in treatment [180].

**Association between infections and congenital heart defects**

Congenital heart disease (CHD) represents a significant health concern, characterized by structural anomalies in the fetal heart during pregnancy. Roger VL et al., identify it as the leading cause of mortality among birth defects [181, 182]. Gorini F et al., highlighted the critical period for the vulnerable development of the fetal cardiovascular system, particularly during the second to eighth weeks of pregnancy, as a key time for the onset of CHD [183]. The historical teratogenic impact of the rubella virus on fetal cardiovascular development, as reported by Gregg NM, in 1941, initiated subsequent investigations into the correlation between maternal

rubella infection and the risk of CHD. Studies by Oster ME et al., Jenkins KJ et al., and Campbell M, have contributed to understanding this association [184, 185, 186]. Adams Waldorf KM and McAdams RM, further establish rubella virus, herpesvirus and cytomegalovirus as human teratogens capable of causing a spectrum of birth defects, including CHDs, when acquired in early pregnancy [187].

Jenkins KJ et al., identify various risk factors for CHD, including rubella, retinoic acid and specific drug use. Notably, there is an intriguing proposition that maternal viral infections during pregnancy may elevate the risk of offspring developing CHDs [185]. Li M et al., highlighted the association between maternal influenza during the second and third months of pregnancy and an increased risk for CHDs, particularly septal defects and conotruncal defects. Interestingly, the use of influenza medication might mitigate these associations [188]. Thinkhamrop J et al., conclude that, prophylactic antibiotic use in the second and third trimesters, as assessed through randomized controlled trials, does not show an increased risk of congenital abnormalities, although there is a recognition of insufficient evidence to comprehensively evaluate potential fetal harm [189].

The environmental contribution to CHD is underscored by studies focusing on exposure to physical, chemical and biological factors before or during pregnancy for both mothers and fathers. Autti-Ramo et al., found associated links between maternal alcohol and smoking and cardiac defects [190]. Ou Y et al., investigations in the Guangdong population reveals significant associations between CHDs and maternal chemical exposure, living in newly renovated rooms, residential proximity to main traffic, paternal smoking, and maternal occupation as a manual worker. Perinatal factors, such as antibiotic use, maternal fever, diabetes, influenza and threatened abortion, are identified as additional risk factors for CHDs. Additional investigation is required to assess the connection between maternal infections during pregnancy and the heightened risk of congenital heart defects (CHD) in offspring [191].

## CONCLUSION

The intricate link between maternal infections and congenital heart defects (CHDs), highlighting diverse factors influencing fetal development, from bacterial, fungal, protozoan to viral agents. Notably, infections like Rubella and Cytomegalovirus present significant risks, potentially causing complications such as prematurity, stillbirth and fetal heart defects. The TORCH acronym identifies infectious teratogens, underscoring the importance of preventive measures like vaccination and antiviral therapy. Environmental exposures and maternal nutrition also play vital roles in fetal development, with maternal undernutrition in low- and middle-income countries associated with adverse pregnancy outcomes, including CHDs. Promoting a nutritious maternal diet is crucial for optimal fetal health and successful pregnancies. The review offers insights into preventive strategies and emphasizes the ongoing need for research to enhance prenatal care. Understanding the impact of maternal infections on CHDs is crucial for effective public health interventions, ultimately improving maternal and fetal well-being.

## CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

## AUTHOR'S CONTRIBUTIONS

All authors contributed to data analysis, drafting and revising of the paper and agreed to be responsible for all the aspects of this work

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