

Infectious and environmental placental insults: from underlying biological pathways to diagnostics and treatments

Samuel Chenge¹, Harrison Ngunjiri², Bernard N. Kanoji^{2,3}, Amanda N. Sferruzzi-Perri⁴, Francis M. Kobia^{1,2,3,*}

¹Department of Medical Microbiology and Laboratory Sciences, Jomo Kenyatta University of Agriculture and Technology, Juja, off Thika road, P. O. Box 62000-00200 Nairobi, Kenya

²Directorate of Research and Innovation, Mount Kenya University, General Kago road, P.O. Box 342-01000, Thika, Kenya

³Centre for Malaria Elimination, Mount Kenya University, General Kago road, P.O. Box 342-01000, Thika, Kenya

⁴Department of Physiology, Development and Neuroscience, Centre for Trophoblast Research, University of Cambridge, Downing Street, Cambridge CB2 3EG, United Kingdom

*Corresponding author. Centre for Malaria Elimination, Mount Kenya University, P.O. Box 342-01000, Thika, Kenya. E-mail: kobiafrancis.m@gmail.com

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Abstract

Because the placenta is bathed in maternal blood, it is exposed to infectious agents and chemicals that may be present in the mother's circulation. Such exposures, which do not necessarily equate with transmission to the fetus, may primarily cause placental injury, thereby impairing placental function. Recent research has improved our understanding of the mechanisms by which some infectious agents are transmitted to the fetus, as well as the mechanisms underlying their impact on fetal outcomes. However, less is known about the impact of placental infection on placental structure and function, or the mechanisms underlying infection-driven placental pathogenesis. Moreover, recent studies indicate that noninfectious environmental agents accumulate in the placenta, but their impacts on placental function and fetal outcomes are unknown. Critically, diagnosing placental insults during pregnancy is very difficult and currently, this is possible only through postpartum placental examination. Here, with emphasis on humans, we discuss what is known about the impact of infectious and chemical agents on placental physiology and function, particularly in the absence of maternal–fetal transmission, and highlight knowledge gaps with potential implications for diagnosis and intervention against placental pathologies.

Keywords: placental health, placental infections, placental environmental insults, pregnancy outcomes, cell signaling

Introduction

The placenta fulfills several key functions for the fetus, including oxygen and nutrient transport, fetal metabolic waste elimination via the maternal circulation, and endocrine roles (Cindrova-Davies and Sferruzzi-Perri 2022). Consequently, impaired placental function has adverse effects on the fetus, including low birth weight, premature birth, and stillbirth. Placental dysfunction may also predispose the fetus to adverse health outcomes in adult life, such as diabetes, cardiovascular disorders, and psychiatric problems (Knöfler et al. 2019). Structurally, the maternofetal interface consists of the maternal decidua (a maternal membrane that lines the uterus) and the placenta, a specialized fetal organ (Cindrova-Davies and Sferruzzi-Perri 2022). In early pregnancy, the trophoblast cells (specialized placental cells) invade the decidua and fuse to form the syncytiotrophoblast, which executes the placenta's transport and barrier functions (Renaud and Jayarajah 2022). During the first trimester, chorionic villi (finger-like placenta projections) develop and are covered by the syncytiotrophoblast (Cindrova-Davies and Sferruzzi-Perri 2022, Megli and Coyne 2022). The space between chorionic villi (intervillous space) provides an expansive vascular space where the syncytiotrophoblast is bathed in maternal blood, which is supplied through modification of the uterine microvascular system by the invasive extravillous trophoblast (He et al. 2017, Cindrova-Davies

and Sferruzzi-Perri 2022). Thus, being the point of contact between the mother and the fetus, the placental intervillous space is continuously exposed to maternal blood-borne pathogens and environmental factors, such as chemicals (Fig. 1). Placental injuries resulting from such factors are hard to diagnose and treat during pregnancy and are only detectable via postpartum histological examination of the placenta, which cannot inform clinical decisions aimed at improving fetal outcomes during gestation. With emphasis on sub-Saharan Africa, we discuss the pathogens and environmental factors known to access the placenta (Fig. 2), their burdens, their known and/or potential impacts on maternal and child health, and their diagnostic challenges. We also highlight potential areas for future research that may inform the development of sensitive diagnostics and interventions against placental dysfunction.

Infectious placental pathologies

Several infectious agents directly infect the placenta and in some cases, are transmitted to the fetus (Table 1). However, even without transmission to the fetus, the presence of pathogens at the maternofetal interface can disrupt placenta development and morphology (Garcia et al. 1985, Genest et al. 1996, Tawevisit et al. 2021, Mimura et al. 2022), injure the placenta and impair

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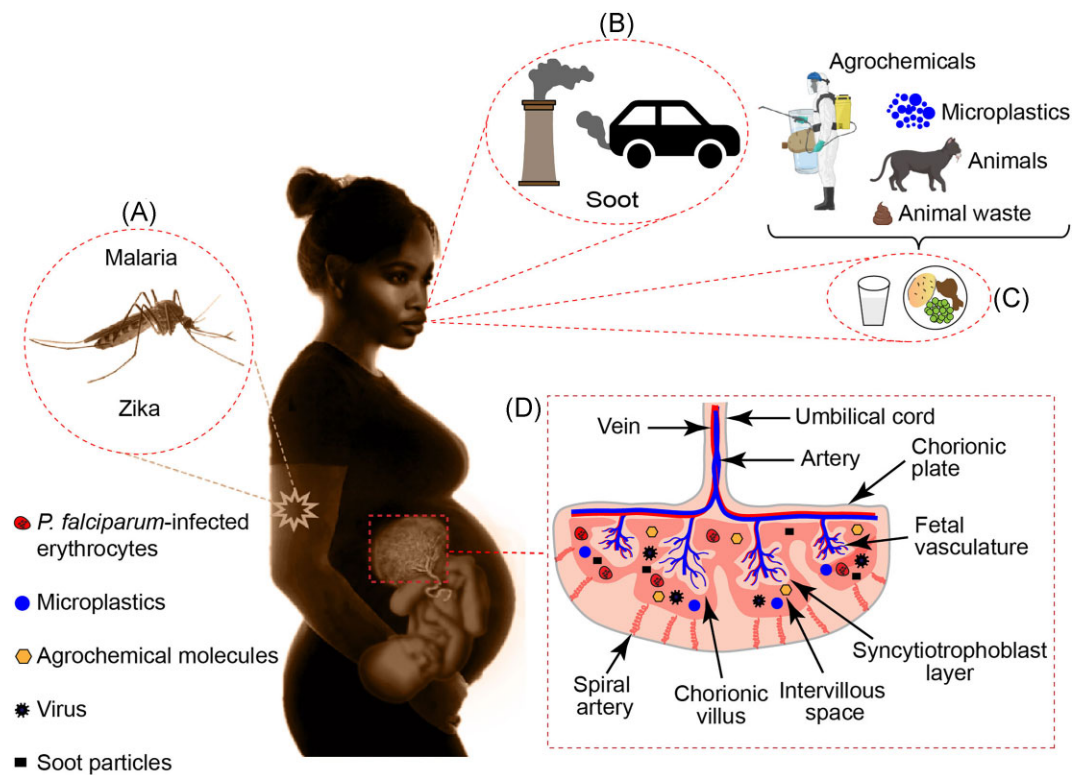


Figure 1. Schematic representation of exposure to infectious agents and chemicals during pregnancy and their routes of transmission to the placenta. Insect bites, e.g. mosquitoes (A), human activity products, e.g. agrochemicals and microplastics (B), and contaminated food (C), expose pregnant women (adapted from Kobia et al. 2022) to vector-borne pathogens, environmental chemical factors, and food-borne pathogens, which access the placenta and accumulate in placental intervillous spaces (D). Importantly, even without accessing fetal circulation, infectious and environmental placental insults may adversely affect the fetus by causing placental dysfunction.

Table 1. The main agents that are known to access the maternofetal interface.

| | Agent | Presence in human placenta | Transmission to fetus | Reference |
|----------------------|----------------------------------|----------------------------|-----------------------|---|
| Infectious | Cytomegalovirus | Yes | Yes | Lanzieri et al. (2017), Uenaka et al. (2019) |
| | Rubella | Unknown | Yes | Patel et al. (2020) |
| | <i>L. monocytogenes</i> | Yes | Yes | Parkash et al. (1998), Lecuit et al. (2004), Madjunkov et al. (2017), Megli and Coyne (2022) |
| | <i>T. pallidum</i> | Yes | Yes | Qureshi et al. (1993), Genest et al. (1996), WHO (2022) |
| | <i>T. gondii</i> | Yes | Yes | Li et al. (2014), Milne et al. (2020), Pinto-Ferreira et al. (2020) |
| | <i>P. falciparum</i> | Yes | Limited evidence | Wang et al. (2021) |
| | SARS-CoV-2 | Yes | Yes (rare) | Facchetti et al. (2020), Hecht et al. (2020), Debelenko et al. (2021), Lu-Culligan et al. (2021), Argueta et al. (2022) |
| | Fungal agents | Yes (rare) | Yes (rare) | Delprado et al. (1982), Bliss et al. (2008), Obermair et al. (2020), Shazniza Shaaya et al. (2021) |
| Environmental | Phthalates | Yes | Yes | Liang et al. (2022) |
| | Polycyclic aromatic hydrocarbons | Yes | Yes | Agarwal et al. (2020) |
| | Microplastics | Yes | Unknown | Braun et al. (2021), Ragusa et al. (2021, 2022a,b), Zhu et al. (2022) |
| | Soot | Yes | Yes | Bongaerts et al. (2022) |
| | Agrochemicals | Yes | Yes | Saxena et al. (1981), Lopez-Espinosa et al. (2007), Nanes et al. (2014), Anand and Taneja (2020), Mathiesen et al. (2020) |

Note: presence in human placenta refers to pathogen observation in naturally infected/exposed human placenta and not nonhuman hosts or experimental contexts.

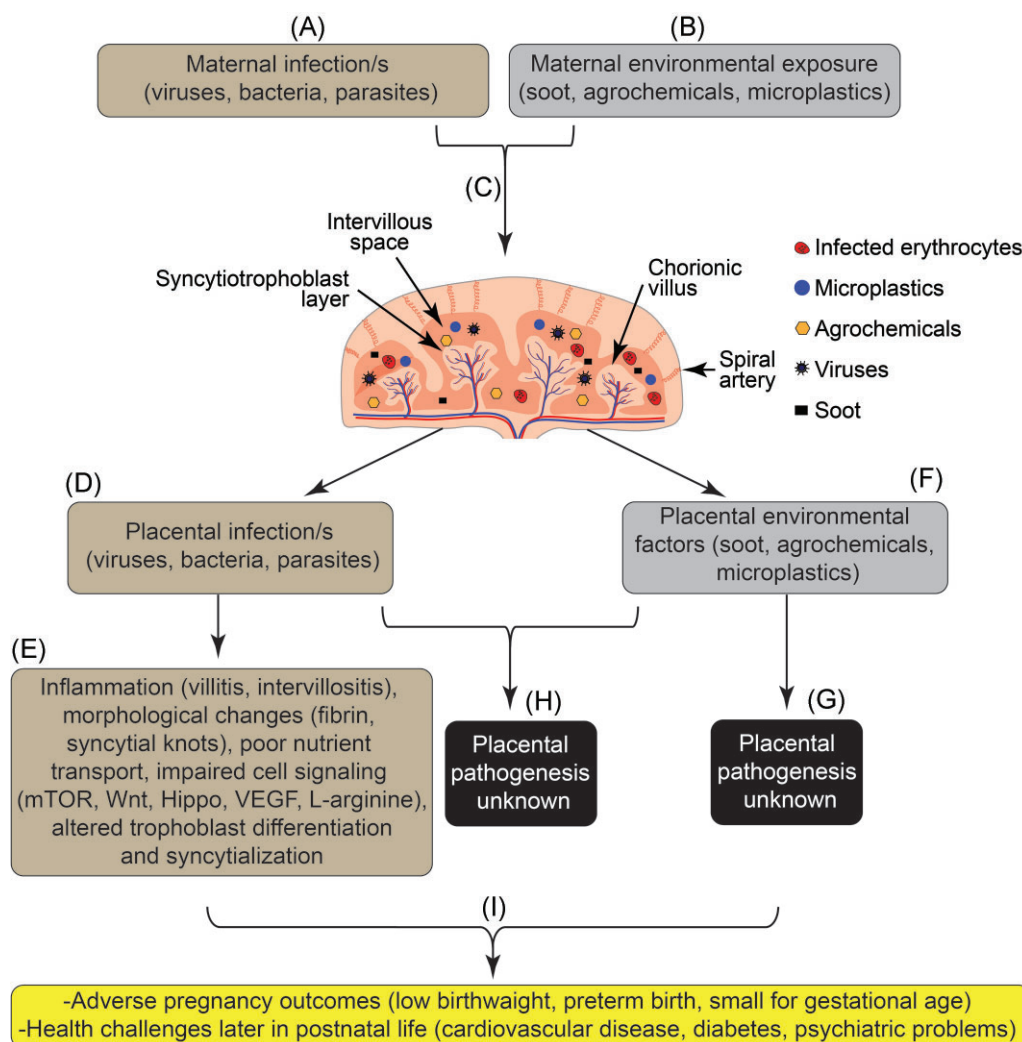


Figure 2. Summary of the impact of placental infections and environmental factors on pregnancy outcomes and well-being in later postnatal life. Upon accessing placental intervillous spaces (A)–(C), pathogens cause placental infections, which trigger several pathogenic processes (D) and (E). Environmental factors also accumulate in the placenta (F), but little is known about their impact on placental function when occurring alone or in combination with placental infections (G) and (H). Still, infectious and environmental placental insults are associated with adverse pregnancy outcomes and health challenges in later postnatal life (I). mTOR: mechanistic target of rapamycin and VEGF: vascular endothelial growth factor.

placental function (Parkash et al. 1998, Lecuit et al. 2004, Pereira et al. 2014, Debelenko et al. 2021, Ernst et al. 2021, Gestrich et al. 2021, Linehan et al. 2021, Roberts et al. 2021, Argueta et al. 2022, Glynn et al. 2022, Stensvold et al. 2022), and cause adverse fetal outcomes (Pereira et al. 2014, Page et al. 2019, Zakama et al. 2020, Schwartz et al. 2021, Shende et al. 2021) (summarized in Fig. 3). However, less is known about the mechanisms through which placental infections affect placental health, function, and fetal outcomes. Below we discuss current knowledge of the cellular and molecular processes underlying the placental pathobiology of the main pathogens known to infect the placenta.

Cytomegalovirus

Cytomegalovirus (CMV) has a high global prevalence (Zuhair et al. 2019). A meta-analysis revealed a CMV prevalence of 80%–93% in the general African population and 85%–94% among African women (Zuhair et al. 2019). It is the most common congenital infection and is associated with a neonatal mortality rate of 7%–12% and serious complications like neurodevelopmental

and hearing impairments (Lanzieri et al. 2017, Akpan and Pillarisetty 2022).

Placental CMV has been observed through immunodetection of CMV's immediate early genes 1 and 2 and CMV's DNA-binding protein (Uenaka et al. 2019). Although the molecular and cellular pathways underlying CMV placental pathobiology are not fully understood, *in vitro* studies using placental cell lines indicate that CMV may impair invasion by extravillous trophoblast cells by downregulating matrix metalloproteinases (Tao et al. 2011). Studies using human primary extravillous trophoblast cells and extravillous trophoblast-like cell lines indicate that CMV infection inhibits their proliferation and invasion by suppressing Hippo and WNT signaling pathways (van Zuylen et al. 2016, Kong et al. 2021). There are also data showing that CMV may dysregulate several other cellular pathways thought to influence pregnancy outcomes, including apoptosis, cytokines, the class I major histocompatibility pathway, and the kynurenine pathway (Njue et al. 2021). These findings highlight the risks placental CMV poses to the well-being of the fetus even without fetal infection. However, because these findings are from *in vitro* studies, further work is needed to

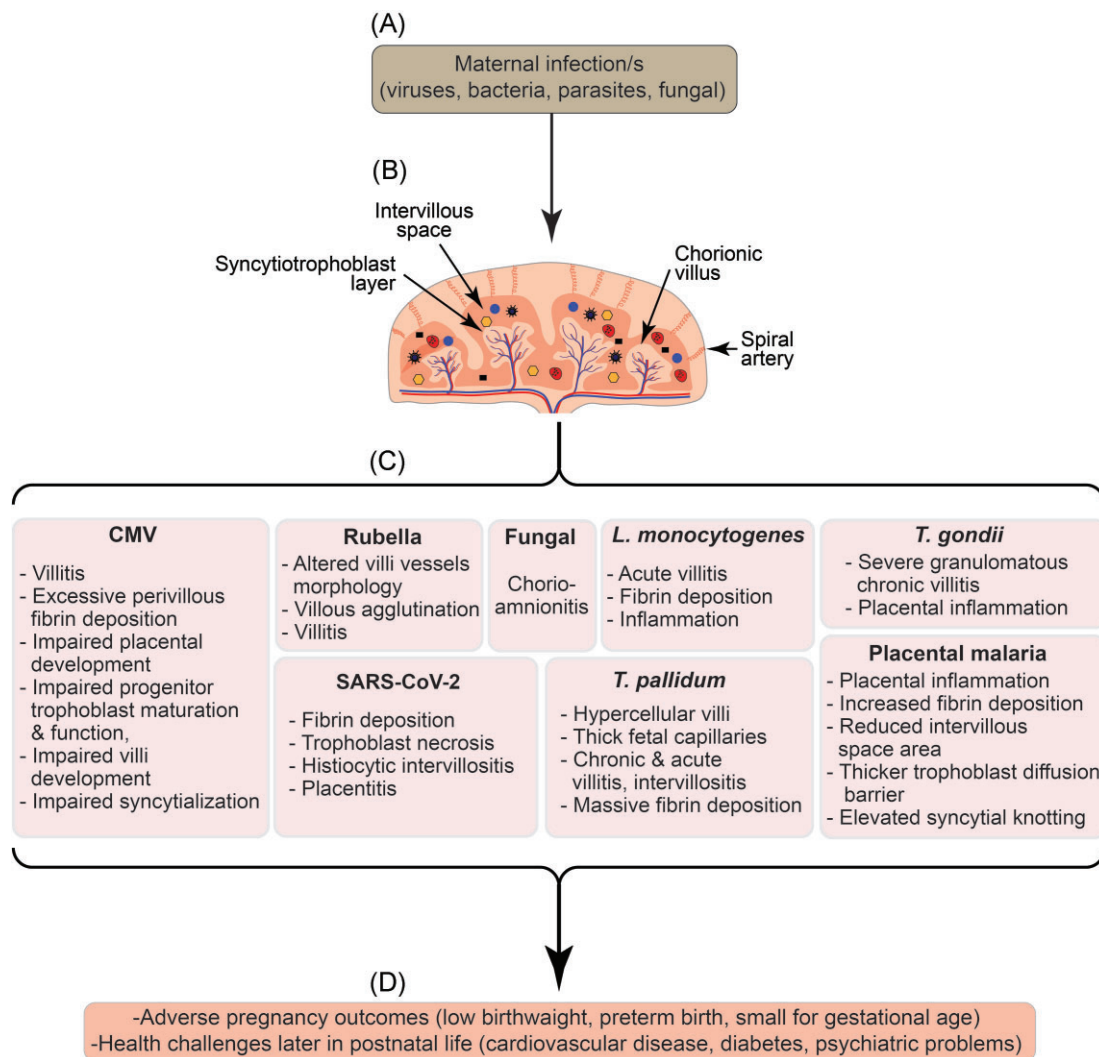


Figure 3. Summary of currently known pathohistological effects of placental infections. Upon infecting the placenta (A) and (B), infections trigger pathological processes that lead to various placental pathological outcomes (C), which result in poor pregnancy outcomes and health challenges later in postnatal life (D).

uncover strategies for diagnosing and intervening against CMV infection during pregnancy.

Rubella

Rubella, a generally mild disease caused by the rubella virus, presents with fever and a rash, and complications like arthritis, joint stiffness, and encephalitis (Winter and Moss 2022). In 2018, about 140 000 rubella cases were reported worldwide (Patel et al. 2020), although cases may be significantly undercounted due to high rates of asymptomatic infections (Winter and Moss 2022). Because the findings illustrating the effect of placental rubella on placental structure and possibly placental function (Table 1 and Fig. 3) are decades-old, comprehensive assessment of the impact of placenta leveraging advanced strategies like Click or tap here to enter text.high-resolution imaging (Laketa 2018) and placental stereological (Yong et al. 2022) analyses are warranted. Moreover, no studies have examined how rubella alters placental gene expression and cell signaling pathways, although transcriptional profiling of cultured primary fetal and adult endothelial cells has shown that rubella upregulates several proinflammatory chemokines (Geyer et al. 2016).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), a highly transmissible disease that mainly causes respiratory symptoms, although it can affect any organ system (White-Dzuro et al. 2020). As of 2022, the WHO estimated that two-thirds of the African population had been exposed to COVID-19, although 67% of the cases were asymptomatic (over two-thirds of Africans exposed to virus which causes COVID-19; WHO 2023). Pregnant women are reported to experience more severe COVID-19 complications than nonpregnant women, probably because of placental infection and a higher risk of viremia (having the virus in blood circulation) (Roberts et al. 2021, Villar et al. 2021). COVID-19 in pregnancy is associated with several complications, including preeclampsia, preterm birth, low placental weight, and a higher risk of miscarriage (Woodworth et al. 2020, Roberts et al. 2021, Rosenbloom et al. 2021, Villar et al. 2021, Balachandren et al. 2022, Radan et al. 2022). Because fetal infection with COVID-19 is rare, pregnancy complications likely result from placental infection (Table 1) and resulting placental injury (Fig. 3) (Roberts et al. 2021). The NIH/Eunice Kennedy Shriver National Institute of Child

Health and Human Development group of experts, therefore, recommends assessing SARS-CoV-2 presence and localization in placental tissue (Roberts et al. 2021). A recent study detected placental SARS-CoV-2 in 42% of the cases examined (Argueta et al. 2022), although others have reported lower rates or no placental SARS-CoV-2 (Facchetti et al. 2020, Hecht et al. 2020, Debelenko et al. 2021, Lu-Culligan et al. 2021).

SARS-CoV-2 infection of placental explants was associated with reduced expression of trophoblast and endothelial cell markers, and an upregulation of Hofbauer cells (fetal macrophages) markers, as well as proinflammatory and apoptotic factors (Argueta et al. 2022). However, these observations were made using term placentas. Additionally, it is not clear if the effects of COVID-19 on the placenta linger after maternal virus clearance, although some studies have observed placental injury and inflammation in placentas from mothers with past COVID-19 infection without detecting placental or neonatal SARS-CoV-2 (Debelenko et al. 2021, Lu-Culligan et al. 2021, Garcia-Flores et al. 2022). Taken together, these observations indicate that placental COVID-19 alters placental function, but further studies are needed to precisely detail the underlying mechanisms, especially in cases of asymptomatic infection. Moreover, the impact of repeat placental SARS-CoV-2 infection during pregnancy and their effects on placental health and function, and pregnancy outcomes is unclear. Studies are also needed to determine if COVID-19 vaccination protects from placental SARS-CoV-2.

Listeria monocytogenes

Listeria monocytogenes (*L. monocytogenes*) is the food-borne pathogen that causes listeriosis and available data indicate that in Africa, its incidence varies across food types and countries, and is particularly high in animal products (Dufailu et al. 2021). Although in healthy adults listeriosis does not result in severe disease, pregnant women are 18 times more likely to get listeriosis than non-pregnant women (Madjunkov et al. 2017). A recent French study found that almost all cases of listeriosis in pregnancy were associated with poor pregnancy outcomes, including preterm birth and miscarriage (Charlier et al. 2017).

The presence of *L. monocytogenes* in the placenta can adversely affect pregnancy outcomes even without fetal infection (Fig. 3). A recent study using cultured human trophoblast cells found that (Johnson et al. 2021) infection of primary human trophoblast cells with *L. monocytogenes* triggered strong proinflammatory responses and factors that recruit maternal leukocytes (Johnson et al. 2021). Infection of Hofbauer cells isolated from healthy human term placentas with *L. monocytogenes* also promoted a proinflammatory profile and infected Hofbauer cells spread *L. monocytogenes* to cultured primary human trophoblast cells and primary human umbilical vein endothelial cells (Azari et al. 2021). A mouse study found that placental *L. monocytogenes* resulted in the upregulation of several eicosanoids, which trigger inflammation as well as regulate the timing of labor (Conner et al. 2022). Mouse experiments have also shown that infection by *L. monocytogenes* inactivates mitogen-activated protein kinase signaling and leads to a loss of specific trophoblast cells (trophoblast giant cells) (Hashino et al. 2015).

Treponema pallidum

Treponema pallidum, the bacteria that causes syphilis, is mostly transmitted sexually and globally, around six million syphilis cases are recorded each year (Kojima and Klausner 2018). In Africa, the prevalence of syphilis ranges from about 1%–4.5%

(Kojima and Klausner 2018). Although many syphilis-associated poor pregnancy outcomes are caused by fetal infection (Table 1), syphilis can also adversely affect fetal outcomes through placental infection (Fig. 3). However, knowledge of the molecular and cellular impacts of placental syphilis is very limited.

Toxoplasma gondii

Toxoplasma gondii, the intracellular protozoan that causes toxoplasmosis, infects about 30% of the world's population but its seroprevalence reaches up to 90% in some demographic groups of Africa (Milne et al. 2020). Humans acquire *T. gondii* mainly through contact with contaminated animals, their contaminated feces, or consumption of contaminated food (Attias et al. 2020). Although *T. gondii* transmission to the fetus (Table 1) causes severe adverse pregnancy outcomes (Milne et al. 2020). Studies indicate that most *T. gondii* infections during pregnancy may reach the placenta but fail to breach the barrier. Indeed, *in vitro* studies found that the syncytiotrophoblast limits *T. gondii* infection by restricting its attachment to the placenta surface and/or blocking its intracellular replication (Ander et al. 2018). Importantly, cases of placental *T. gondii* in the absence of detectable maternal *T. gondii* infection have been reported (Matin et al. 2017, Stensvold et al. 2022). While placental *T. gondii* is associated with placental injury (Fig. 3), few studies have assessed the underlying mechanisms. The presence of *T. gondii*, induces the upregulation of immune genes by trophoblast cells (Ander et al. 2018), which promote the migration and activation of inflammatory macrophages (Dogan et al. 2011). However, detailed studies are needed to establish the effects of *T. gondii* on human placental health and function in the absence of fetal infection, as well as to uncover the mechanisms underlying its placental pathobiology.

Placental malaria

Malaria complications range from mild (e.g. fever, chills, and headache) to severe (e.g. acidosis and cerebral malaria) (Milner 2018). However, because residents of malaria-endemic regions possess partial immunity to malaria, many cases are asymptomatic (Heinemann et al. 2020). Pregnant women are more susceptible to malaria infection, which is associated with several fetal adverse outcomes (Rogerson 2017). These effects are mainly caused by placental malaria, which results from the accumulation of *Plasmodium falciparum*-infected red blood cells in the placenta (Wang et al. 2021). Because fetal malaria is rare (Table 1), the adverse effects of placental malaria on fetal outcomes are mainly attributed to placental injuries (Fig. 3). A study using placental samples from Malawi and cultured human primary trophoblast found that placental malaria is linked to reduced growth signaling (mTOR signaling) and decreased (Dimasuay et al. 2017). Another Malawian study associated placental malaria with reduced levels of L-arginine (a vasodilator precursor), and increased levels of nitric dimethylarginine (a vasodilator inhibitor), which might have implications for placental perfusion (McDonald et al. 2018). A study involving a Tanzanian cohort found that placental malaria has the potential to upregulate soluble vascular endothelial growth factor receptor (Muehlenbachs et al. 2006), which inhibits angiogenesis. Finally, a study involving a Malawian cohort with malaria infection in pregnancy and a mouse model found that placental malaria disrupts signaling mechanisms that control placental vascularization (Tran et al. 2021). A proteomics study that used placentas from a Brazilian cohort and a mouse model of malaria reported that placental malaria may alter multiple pathways, including those linked to oxidative stress and

apoptosis (Kawahara et al. 2019). However, (Kawahara et al. 2019) further studies are needed to understand how malaria impacts placental function to illuminate novel strategies for detecting and treating placental malaria during pregnancy.

Fungal infections

Up to 75% of women experience at least one vaginal fungal infection in their lifetime (Willems et al. 2020), and the risk of infection tends to rise during pregnancy (Aguin and Sobel 2015). Vaginal fungal infections are mainly caused by the overgrowth of members of the *Candida* genus, with *Candida albicans* accounting for > 90% of the cases (Willems et al. 2020). Although the impact of vaginal fungal infection on fetal outcomes is not fully established, a Nigerian study associated vaginal candidiasis with an increased risk of preterm birth (Sule-Odu et al. 2020). Japanese and Australian studies have associated *Candida*-induced inflammation of the placental chorion (chorioamnionitis) with poor fetal outcomes, although chorioamnionitis is rare (Maki et al. 2017). Although fetal infection with *C. albicans* has been reported (Table 1), the mechanisms by which fungal infections affect fetal outcomes are unclear. Studies have reported fungal colonization of the human umbilical cord surface and placenta (Delprado et al. 1982, Obermair et al. 2020, Shazniza Shaaya et al. 2021) but such cases are very rare and the effects on placental structure and function are unknown. Thus, comprehensive studies are needed to determine the molecular and cellular processes that might be altered in the presence of placental fungal infections.

Environmental factors affecting placental health

Environmental factors like phthalates, microplastics, polycyclic aromatic hydrocarbons, and pesticides have been observed in the placenta and fetus (Table 1), but their impact on placental physiology and function is unclear. Below we summarize what is known about the presence of environmental factors in the placenta and highlight key questions that warrant investigation. A better understanding of the placental pathobiology of environmental factors may unveil strategies for diagnosing and intervening against them during pregnancy.

Phthalates

Phthalates are a group of widely used plasticizers with several biological effects, including adverse endocrine and metabolic effects (Casale and Rice 2022). Because of their presence in everyday products, including in food packaging, cosmetics, and pharmaceutical products, humans are routinely exposed to phthalates (Lapehn et al. 2023). Phthalate exposure during pregnancy has been associated with adverse pregnancy outcomes, such as hormonal disruptions (Lapehn et al. 2023), preterm birth (Welch et al. 2022), and low birth weight in American (Ferguson et al. 2022), European (De Cock et al. 2016, Lenters et al. 2016), and Chinese (Zhang et al. 2009) cohorts. However, studies on phthalates exposure in African cohorts and their effects on pregnancy outcomes are lacking. Exposure of trophoblast-like cells (Abou-Kheir et al. 2017) and cultured primary syncytiotrophoblast cells to mono(2-ethylhexyl) phthalate led to the differential expression of several genes, including inflammatory factors (Lapehn et al. 2023). A French study also found that exposure to phthalates during pregnancy altered DNA methylation profiles of the placenta (Jedynak et al. 2022), although the impact of the changes on gene expression and pregnancy outcomes was not determined. Studies using

cells, human placentas, and mouse models indicate that phthalates alter lipid metabolism, hormone production, and inflammatory processes (Martínez-Razo et al. 2021).

Microplastics

Microplastics, plastic degradation products with diameters of <5 mm, are widely distributed in air, drinking water, and food (Koelmans et al. 2019). Although data on microplastic pollution in Africa are scant, it may be high, especially in aquatic ecosystems (Okeke et al. 2022). Although microplastics have been observed in the placenta (Table 1), this is a very new line of inquiry, and studies are needed to establish the following: (i) the incidence of placental microplastics across geographical regions, economic backgrounds, and lifestyles, (ii) if the levels of placental microplastics change across gestation, (iii) if the accumulation of microplastics in the placenta varies with the type of plastic, and (iv) the impact of microplastics on placental biology at the molecular and cellular levels, morphology, and function.

Soot

Soot is a major byproduct of many human activities, like the use of petroleum-based fuels and biomass burning, and is associated with various health complications, including cancer, and respiratory and cardiovascular diseases (Niranjan and Thakur 2017). In Africa, soot exposure is particularly high due to the widespread use of dry wood and kerosene as cooking fuel (Eputai et al. 2022). Epidemiological studies in Uganda and Tanzania have reported an association between household air pollution from wood-based cooking fuel and poor pregnancy outcomes like stillbirth and low birth weight (Wylie et al. 2017, Eputai et al. 2022). However, little is known about the impact of soot on fetal well-being and recent reports that soot reaches the fetus (Bongaerts et al. 2022) have been controversial (Bongaerts et al. 2021, Holder et al. 2021), emphasizing the need for further studies. The possibility that soot affects placental physiology and function is supported by observations from *in vitro* experiments showing that exposing a trophoblast-like cell line to fine particulate matter air pollution triggers inflammation, endoplasmic reticulum stress, and growth suppression (Familarì et al. 2019). However, rigorous studies are urgently needed to determine the following: (i) the presence and amount of soot in placentas from women living in areas with high levels of environmental air pollution, such as those living in crowded industrial areas and those that routinely use wood-based cooking fuel, (ii) whether placental soot levels vary across gestation, (iii) whether placental soot levels vary with the source and, (iv) the impact of soot on placental physiology, morphology, and function.

Agrochemicals

Agrochemicals, including pesticides, insecticides, and herbicides are widely used at high volumes and pose significant risks to human health (Tudi et al. 2022). A study in an agricultural region of California associated exposure to high agropesticide levels with an elevated risk of adverse pregnancy outcomes, including preterm birth, low birth weight, and congenital anomalies (Larsen et al. 2017). Moreover, prenatal exposure to pesticides has been linked with holoprosencephaly (failure of correct fetal brain hemisphere separation) (Addissie et al. 2020), low fetal weight and length (Ferguson et al. 2019), fetal immune disruption (Prahel et al. 2021), and preeclampsia (Enderle et al. 2021), although the underlying mechanisms are not clear. Although several pesticides have been detected in the placenta (Table 1) the mechanistic impact of agrochemicals on placental health and function is unknown and

studies are needed to establish; (i) which pesticides accumulate in the placenta, (ii) whether pesticide accumulation in the placenta varies across gestation, and (iii) the impact of pesticides on placental morphology and function, as well as the molecular and cellular pathways by which such changes occur.

Challenges in studying placental pathologies

The main barriers to the study of placental pathologies are the inaccessibility of the placenta during pregnancy, the lack of animal models that faithfully recapitulate the structure (Furukawa et al. 2014) or biology (Schmidt et al. 2015) of the human placenta, and the difficulty in fully replicating human infections in experimental animals (Brehm et al. 2013). However, as the placenta is uniquely available for examination after delivery, it can provide valuable insights into how placental pathologies affect fetal outcomes and health in later life. This is especially important because it offers the opportunity to study human placental pathologies in the contexts that they occur, such as the geographical regions where specific infectious diseases are endemic. Moreover, term primary trophoblast and explants can be used to study placental function (Yang et al. 2022). To study the impact of placental infections during the early stages of pregnancy, first-trimester placentas obtained after elective pregnancy terminations can also be used (Turco et al. 2018), although these face significant ethical and regulatory hurdles. Dual perfusion of isolated human placental lobules may also be used to study placental physiology following challenges with infectious/environmental factors (Pollitti et al. 1996, Brownbill et al. 2018).

Another challenge relates to the high likelihood of pregnant women experiencing several infectious and environmental risks simultaneously. Thus, ideally, studies should investigate placental insults individually, as well as in combination with other infectious and/or environmental factors. Also, given the relatively high rate of undernutrition among pregnant women in sub-Saharan Africa (Desyibelew and Dadi 2019), where possible, studies should consider the impact of poor nutrition. When coupled with highly sensitive transcriptomic (Nuss et al. 2017), proteomic (Beltran et al. 2017), and microscopic imaging (Laketa 2018) technologies, these strategies can uncover crucial insights into the mechanisms underlying placental pathologies. Such knowledge is critically needed for the development of effective strategies for the diagnosis and treatment of placental pathologies in sub-Saharan Africa and other low-resource settings.

Conclusion

The placenta is important for well-being at the fetal, neonate, and later stages of life. Current evidence indicates that during pregnancy, infectious agents and chemicals can accumulate in the placenta. However, little is known about the impact of such insults on placental structure and function or the molecular mechanisms underlying their placental pathogenesis (Fig. 2). Importantly, there are no ways of detecting and managing placental injuries during pregnancy. Future studies should seek to uncover molecular and cellular processes that are altered by various agents that accumulate in the placenta. Moreover, correlating molecular changes (RNA or protein) identified in affected placentas with corresponding molecular alterations in the maternal circulation has the potential to identify novel biomarkers and intervention targets against placental injuries during pregnancy (Yong

et al. 2022). Identifying such targets promises significant gains in ongoing efforts to improve pregnancy outcomes and well-being in postnatal life in resource-constrained, high-burden settings of sub-Saharan Africa.

Authors' contributions

Samuel Chenge (Writing – original draft), Harrison Ngure (Writing – original draft), Bernard N. Kanoi (Writing – original draft, Writing – review & editing), Amanda N. Sferruzzi-Perri (Writing – original draft, Writing – review & editing), and Francis M. Kobia (Conceptualization, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing)

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