

# The Elusive Role of Placental Macrophages: The Hofbauer Cell

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## Keywords

Placenta · Macrophages · Hofbauer cells · Human immunodeficiency virus · ZIKA

## Abstract

In this review, we discuss the often overlooked tissue-resident fetal macrophages, Hofbauer cells, which are found within the chorionic villi of the human placenta. Hofbauer cells have been shown to have a phenotype associated with regulatory and anti-inflammatory functions. They are thought to play a crucial role in the regulation of pregnancy and in the maintenance of a homeostatic environment that is crucial for fetal development. Even though the numbers of these macrophages are some of the most abundant immune cells in the human placenta, which are sustained throughout pregnancy, there are very few studies that have identified their origin, their phenotype, and functions and why they are maintained throughout gestation. It is not yet understood how Hofbauer cells may change in function throughout normal pregnancy, and especially in those complicated by maternal gestational diabetes, preeclampsia, and viral infec-

tions, such as Zika, cytomegalovirus, and human immunodeficiency virus. We review what is known about the origin of these macrophages and explore how common complications of pregnancy dysregulate these cells leading to adverse birth outcomes in humans. Our synthesis sheds light on areas for human studies that can further define these innate regulatory cells.

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## Introduction

Macrophages are tissue-resident immune cells in the same way as fibroblasts, MAIT cells, and Langerhans cells and perform crucial immunological functions such as antigen presentation, phagocytosis, cytokine secretion, and coordination of innate and adaptive immune responses [1]. Macrophages play a role in virtually every aspect of an organism's biology, from development and homeostasis to tissue repair, as well as immune responses to pathogens. They are a heterogeneous population of immune

cells that constantly change their functional state in response to changes in tissue physiology or environmental challenges [2]. The plasticity of these cells allows them to respond to various environmental signals and change their phenotype and physiology in response to cytokines and microbial signals [3]. Historically, tissue-resident macrophages were believed to be continuously replenished by blood-circulating monocytes that originate from progenitors in adult bone marrow. This concept was central in defining the “mononuclear phagocyte system” that grouped together precursors of monocytes in the bone marrow, monocytes in peripheral blood, and macrophages in the tissues [4, 5]. However, advanced techniques for studying cellular ontogeny showed that the homeostatic contribution of peripheral blood monocytes to tissue-resident macrophage populations may be confined to specific tissues such as gut, dermis, and the heart with tissue-specific turnover rates. Alternatively, most tissue-resident macrophages arise from embryonic precursors prior to birth and maintain themselves locally throughout adulthood, independent of circulating monocytes [6, 7].

The chorionic villi of placental mammals has conspicuous macrophages known as the Hofbauer cells, which are considered fetal in origin [8]. Three-dimensional studies and histological analyses of human placental villous tissue show that Hofbauer cells are large (10–30  $\mu\text{m}$ ), pleomorphic, highly vacuolated with granular cytoplasm [9–11]. They are found within the fetal villi of the placenta from the first trimester of pregnancy until birth [12], and histological analyses show their location to be close to fetal vessels and trophoblasts, making them likely candidates for placental development and homeostasis [13]. These macrophages were named after an American gynecologist, J. Isfred Isidore Hofbauer (1879–1961); however, little is known about his research or work. (online suppl. Fig. 1 shows the only known portrait of J. Isfred Isidore Hofbauer, courtesy of Rubenstein Rare Book and Manuscript Library of Duke University, for all online suppl. material, see [www.karger.com/doi/10.1159/000/497416](http://www.karger.com/doi/10.1159/000/497416)). Although their origin has yet to be fully established, some studies have proposed that during the first trimester of pregnancy, they originate from mesenchymal progenitor cells [14–16], while the existence of transitional forms between monocytes and macrophages in the second and third trimester suggests that they differentiate from circulating monocytes of the fetus [17, 18]. Takahashi and colleagues reported that primitive macrophages appear as early as day 10 of gestation in the blood vessels of the chorionic villi of the mouse placenta, and that these macrophages enter the chorionic

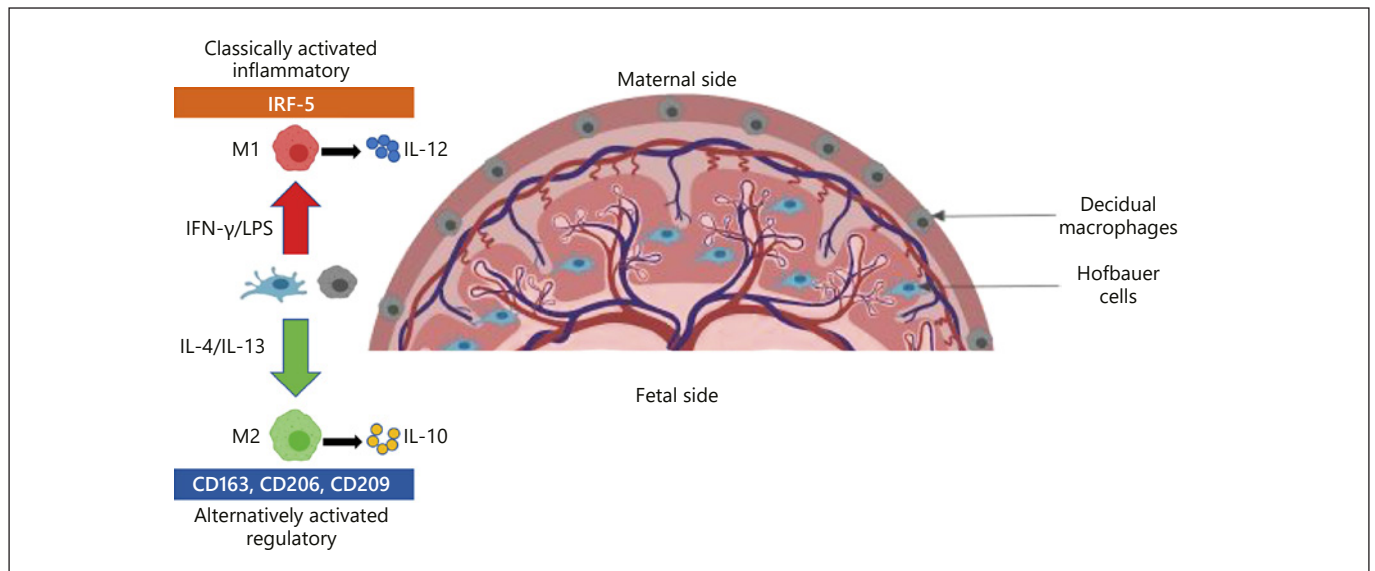
villous mesenchymal stroma and ingest fluid-like stromal materials to transform into Hofbauer cells [19]. Using chromogenic in situ hybridization for Y-chromosome (DYZ1), Kim and colleagues showed that placental villous tissues from male neonates had chromogenic in situ hybridization+ signals from Y chromosome in most macrophages, but not in lymphocytes, suggesting that most macrophages were of fetal origin [20].

Hofbauer cells are targets of a number of viruses and other pathogens at the maternal–fetal interface [21–23]. Better characterized are decidual macrophages, which are the second most abundant immune cell type in the uterine decidua after decidual natural killer cells [24, 25]. No studies appear to exist that directly compare the numbers and function of HCs and decidual macrophages. In fact, characterizing the role of Hofbauer cells in protecting the fetus and maintaining tolerance has somehow been neglected, especially when there is an adverse pregnancy outcome.

## Results

### *Classical and Alternative Polarization of Hofbauer Cells*

The functional maturation of macrophages was described in a manner similar to the well-characterized concept of T helper type 1 and type 2 polarization of effector T cells [26, 27]. They have been classified as M1 (classically activated) and M2 (alternatively activated) macrophages [28, 29], with M1-like macrophages secreting pro-inflammatory cytokines and mediating resistance to pathogens, but also contributing to tissue destruction; while M2 macrophages secrete anti-inflammatory cytokines and promote tissue repair and remodeling [29, 30]. However, this paradigm of macrophage activation is simplistic, especially in humans [2]. This definition only considered the effects of particular stimuli on macrophage polarization, neglecting complex mechanisms that leads to macrophage activation in different tissues. A great variety of intermediates have been described based on their plasticity and adaptability [3] so that this concept may need to be revised. However, a comprehensive classification that will consider in vitro stimulus activation, cell origin, tissue microenvironment, pathology, and time is still required [2]. One M1-like phenotype has been described and compared to several M2 phenotypes, such as M2a, M2b, M2c, and M2d [31, 32], where M2b macrophages share characteristics with M1-like macrophages [33]. Each of the M2 macrophage subtypes differs in a



**Fig. 1.** Anatomical location of decidual macrophages and Hofbauer cells in the placenta. M1 macrophages are distinguished by the lack of expression of M2 markers. M1 macrophages secrete high levels of IL-12 while M2 macrophages secrete high levels of the IL-10 cytokine upon polarization.

number of aspects such as expression of certain surface molecules, cytokine secretion, and function [3]. Although oversimplified, the M1/M2 paradigm provides a useful framework, especially for specific immune responses. Defining the phenotype of HCs within this spectrum of macrophage polarity will illuminate the functional role of these cells in the placenta. Do HCs express M1-like markers, as they protect the fetus from maternally transmitted infections, or do they express an M2-like phenotype, to promote tolerance? Or, do these cells coexpress M1/M2 markers depending on the role being played at any given time?

Figure 1 shows the location of Hofbauer cells and decidual macrophages in the chorionic villi and the decidua of the placenta, respectively. Based on the M1/M2 macrophage polarization paradigm, IL-4 or IL-13 would polarize these macrophages toward a regulatory, M2 phenotype that is characterized by the expression of the scavenger receptor, CD163; mannose receptor, CD206; DC-SIGN, CD209; and secretion of IL-10. Whereas, IFN- $\gamma$  or LPS would polarize these macrophages toward a proinflammatory, M1 phenotype that is characterized by the lack of expression of markers associated with the M2 phenotype, IRF-5 expression and high secretion of proinflammatory cytokines, such as IL-12 [34–37]. Apart from placental-tissue localization, there are no specific markers to distinguish decidual macrophages from HCs and all other human tissue macrophages. To understand

the developmental nature of macrophages in the placenta, and hence how they contribute to maternal–fetal tolerance, there is a need to distinguish between these macrophage populations.

#### *The Role of Hofbauer Cells in Pregnancy*

During pregnancy, the fetus with both maternal and paternal alleles develops within an active maternal immune system without succumbing to immunological rejection [38, 39]. Medawar [40] proposed the presence of immunological tolerance toward the semi-allogeneic fetus that facilitates pregnancy; however, this mechanism is yet to be fully understood. Macrophages have been shown to play a role in regulating pregnancy [41], promote tolerance toward the semi-allogeneic fetus [42], and maintain a homeostatic environment crucial for normal fetal development [38, 43]. In a study aimed at investigating the antigenic phenotype of Hofbauer cells from first- and third-trimester placentas, Goldstein and colleagues showed that these villous stromal macrophages were numerically higher than other villous stromal mononuclear cells and that their phenotype was different from that of macrophages from other tissues. They also showed that the Hofbauer cells possessed surface expression of CD4 and suggested that these cells may serve as a portal of entry, or a reservoir, of human immunodeficiency virus (HIV) in placentas from viremic mothers [44], as will be discussed more in depth.

Hofbauer cells, like other macrophages, express the 3 IgG Fc $\gamma$  receptors (Fc $\gamma$ R): Fc $\gamma$ RI (CD64), Fc $\gamma$ RII (CD32), and Fc $\gamma$ RIII (CD16) [45] and also the pan-macrophage marker, CD68 [46]. They are thought to have an immunoregulatory phenotype consistent with that of M2 anti-inflammatory macrophages, and several studies have shown that Hofbauer cells can be stimulated by glucocorticoids [47] and IL-10 [43] to express CD163, CD206, and CD209 [43], while secreting IL-10 and TGF- $\beta$  [48]. Hofbauer cells have also been reported to constitute a mixture of M2a, M2b, and M2c macrophages that differ in marker surface expression, cytokine secretion and functions [49], reinforcing the concept of a regulatory rather than inflammatory role of these cells. There is limited information on the role of these cells in placental physiology; however, there have been suggestions that they may play a role in transport of nutrients within the villous stroma and in transmission of antibodies from the mother to fetus through the surface expression of Fc receptors [50–52]. Hofbauer cells have also been associated with numerous complications of pregnancy such as chorioamnionitis (CA), miscarriage, and preterm birth [53]. The potential role of HCs in the pathophysiology of complications of pregnancy such as villitis of unknown etiology and histological CA, has been discussed by Tang et al. [53]; however, there is very little information on the effect of other common complications of pregnancy and maternal infections on HC phenotypic polarity and gene expression. The polarity and function of maternal decidual macrophages have been reviewed by Brown et al. [54] and others [55] and will not be featured in this review. Rather, we will focus on the impact of common complications of pregnancy; CA, preeclampsia (PE), and gestational diabetes mellitus (GDM) on the phenotype and function of Hofbauer cells and their role in the vertical transmission of congenital viral infections such as Zika virus (ZIKV), HIV, and cytomegalovirus (CMV). We also highlight gaps in knowledge about Hofbauer cells and contradictory findings of studies on their dysregulation in pathological pregnancies.

#### *Impact of Common Complications of Pregnancy on Hofbauer Cells*

##### *Chorioamnionitis*

CA is an acute inflammation of placental membranes and the chorion due to microbial infections such as *Escherichia coli* and *Group B Streptococcus* [56–58]. Elevated levels of proinflammatory cytokines during CA-specific immune responses are associated with disease in the fetal pulmonary system and brain damage, making CA a risk

factor for neonatal morbidity and mortality [59]. Although the pathophysiology of CA is yet to be elucidated, it is believed to be a consequence of the disturbed immune homeostasis in the placenta associated with Hofbauer cells.

There is a contradictory evidence for the effect of CA on the polarization of Hofbauer cells. Joerink et al. [60], suggested that maternal allergen sensitization and the presence of CA have no effect on the phenotype of Hofbauer cells; however, phenotypic and genetic studies have reported impaired function of Hofbauer cells during CA infection [61]. In line with this study, Vinnars et al. [62] had earlier reported that there is a drastic decrease in the number of CD68+ (pan-macrophage marker) Hofbauer cells in the presence of CA compared to healthy controls. Conversely, Hung et al. [63] and Toti et al. [64] showed that the number of CD68+ Hofbauer cells of placentas complicated by CA is increased. We suggest that the discrepancies may be due to differences in quantification and propose that a stringent standardized method should be used to quantify immunohistochemistry and immunofluorescence data. There is also very little information on the impact of altered numbers and/or regulation of selected macrophage markers by CA.

##### *Gestational Diabetes Mellitus*

GDM is maternal hyperglycemia due to insulin resistance that develops during pregnancy to create a glucose gradient necessary for the supply of energy and nutrients to the developing fetus [65, 66]. GDM prevalence ranges from 3 to 20% in pregnant women [67] and is associated with chronic low-grade inflammation of the placenta [68, 69]. Sisino et al. [70] reported that in pregnant rats receiving streptozotocin during pregnancy, diabetes alters the normal phenotype of HCs from an M2 anti-inflammatory regulatory phenotype to a proinflammatory phenotype. A recent pilot study by Schlieffsteiner et al. [71] contradicts these findings as they reported that HCs maintain an anti-inflammatory M2 phenotype despite the presence of GDM in humans. During inflammatory diseases of the placenta, such as villitis of unknown etiology, there is increased infiltration of the chorionic villi by Hofbauer cells [20, 72], a phenomenon similarly reported in pregnancies complicated by GDM [73]. However, the role and function that Hofbauer cells play or are involved in these conditions are unclear.

##### *Preeclampsia*

PE is a placental disorder of unknown etiology, and it is likely that aberrant immune activation plays a role in its pathogenesis [74]. It is characterized by hyperten-



sion (>140/90 mm Hg) after 20 weeks of gestation and proteinuria (>300 mg/L per day) [75]. Its prevalence ranges from 5 to 10% globally, making it one of the leading causes of morbidity and mortality in mother and child [76]. Przybyl et al. [77] reported that CD74, a human leukocyte antigen class II histocompatibility antigen- $\gamma$  chain, is downregulated on Hofbauer cells in the presence of PE. They suggested that this downregulation alters macrophage polarization from an immunoregulatory M2 phenotype toward a proinflammatory signature affecting essential macrophage-trophoblast crosstalk [77]. It has been reported that the number of Hofbauer cells is significantly decreased in the presence of PE and that the CD209+ HCs from pregnancies with PE secrete less IL-10 than those from normal pregnancies [78]. These data suggest that PE affects an essential immune regulatory role of Hofbauer cells in maternal-fetal tolerance. More studies are needed to investigate the bidirectional effects of PE and Hofbauer cells, and the role of these cells in regulating pregnancies is complicated by PE.

#### Viral Permissiveness of Hofbauer Cells to ZIKV

Vertical transmission of a number of viruses such as ZIKV, rubella, CMV, herpes simplex virus, and HIV-1, from an infected mother to her developing fetus, suggests viral tropism for placental cells [79]. ZIKV is a mosquito-borne flavivirus, which can be vertically transmitted from an infected mother to her fetus [80, 81], causing adverse birth outcomes such as fetal brain abnormalities and microcephaly [82]. ZIKV-specific antigen was detected in Hofbauer cells and histiocytes in the intervillous space of a placenta from a mother with ZIKA [83]. During pregnancy, increased levels of proinflammatory cytokines such as IL-6, CXCL8 (IL-8), and TNF have been reported in the amniotic fluid, decidua, fetal membranes, and maternal serum [84, 85]. The mechanism by which ZIKV breaches the placental barrier is not clear, and ZIKV RNA has been detected in amniotic fluid and in fetal and newborn brain tissue [83, 86, 87]. Vertical transmission of the ZIKV to the human fetus is mediated through productive infection of Hofbauer cells [88, 89], leading to cell proliferation and hyperplasia of these cells in the second and third trimester [90]. Thus, placental inflammatory abnormalities are not a component of vertical transmission of the ZIKV *per se*.

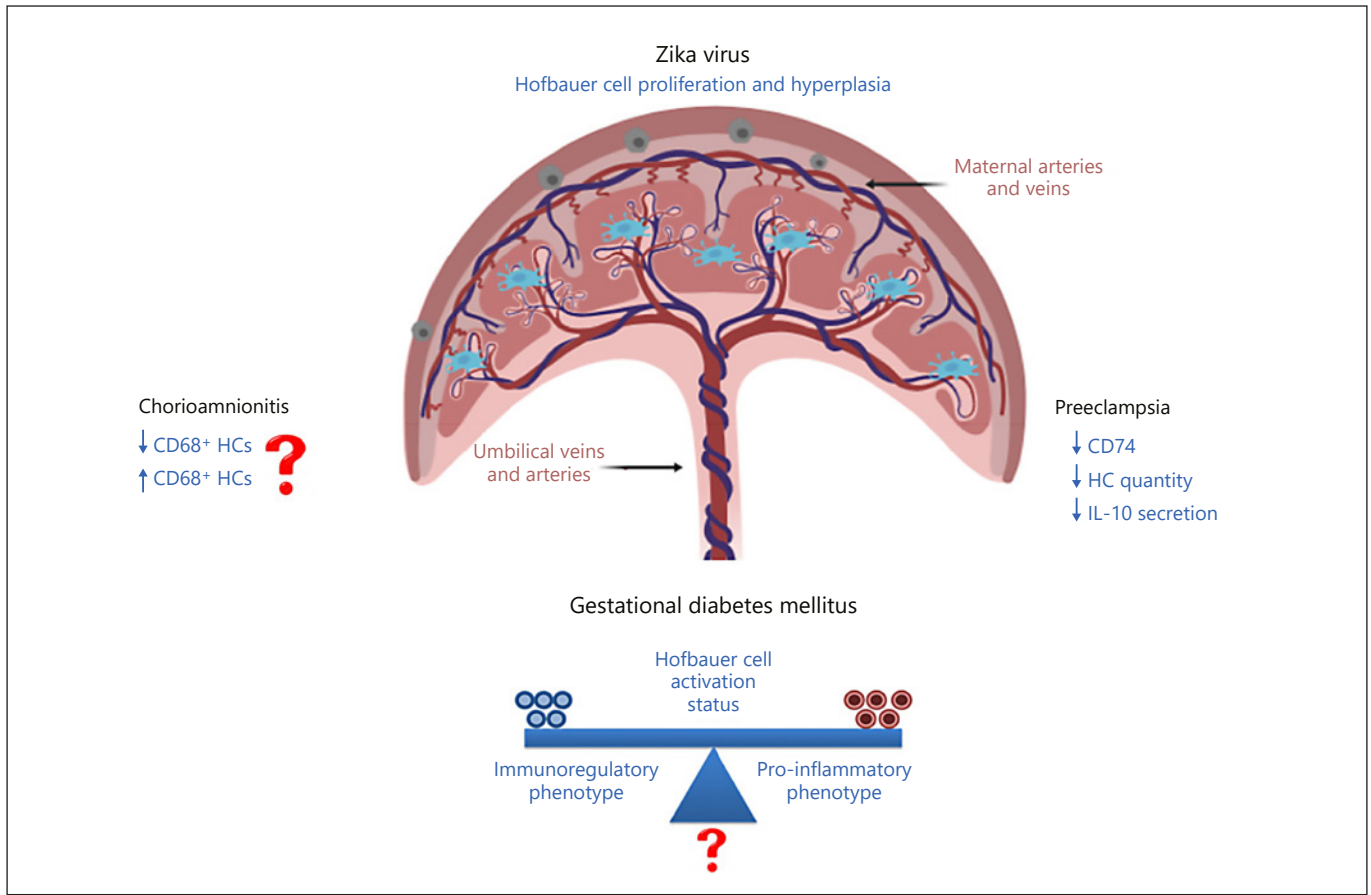
Quicke et al. [88] demonstrated that human placental Hofbauer cells are much more susceptible to productive ZIKV infection than autologous cytotrophoblasts. They showed that, upon infection, Hofbauer cells induce se-

cretion of type I interferon, other proinflammatory cytokines, and upregulation of antiviral gene expression [88]. Their findings corresponded to those of Jurado et al. [89], Simoni et al. [91], and others [92]. However, these studies did not demonstrate the phenotypic changes or shift in activation status of Hofbauer cells that may be associated with abnormal functions of Hofbauer cells upon ZIKV infection. ZIKV infection has been shown to be enhanced by preexisting anti-flavivirus immunity through IgG engagement of the Fc $\gamma$ R [93]. This antibody-dependent enhancement of infection has also been reported in other flaviviridae, such as dengue virus [94, 95]. Although there is evidence of *in vitro* Hofbauer cells infection by ZIKV, the mechanisms by which the virus reaches these cells in the villi and how it is further transmitted to the fetal circulation needs further investigation. Phenotypic and functional changes of Hofbauer cells upon ZIKV infection have not yet been fully elucidated [90, 91, 96].

#### Human Immunodeficiency Virus-1

The large burden of HIV infection in sub-saharan Africa, where adolescent girls and young women between the ages of 15 and 24 years are bearing the brunt of the epidemic [97], has resulted in most HIV-1-infected pregnant women being placed on combination antiretroviral therapy (ART). These women show a high prevalence of aggravated PE [98] and adverse birth outcomes, including fetal death, preterm births [99, 100], and small-for-gestational age infants [100–102]. Whether Hofbauer cells are determinants of these adverse birth outcomes is not understood. The phenotype of Hofbauer cells favors productive infection with HIV-1 [52] and the 15–30% [103] vertical transmission rate, prior to prevention of mother-to-child transmission with ART, is testimony to this. *In vivo* [104] and *in vitro* [48] studies confirmed that Hofbauer cells are indeed targets of HIV-1.

During maternal HIV-1 infection, antibody- and cell-associated virions, cell-free virions, and maternal broadly neutralizing antibodies cross the placental barrier to interact with Hofbauer cells prior to entering the fetal circulation [105]. However, whether Hofbauer cells are involved in facilitating *in utero* HIV infection is unclear as these cells have proved to be invariably infected *in vitro* [106], where it has been shown that they can limit HIV-1 replication by the induction of immunoregulatory cytokines [48]. These cells also possess intrinsic adaptations that facilitate the sequestration of HIV-1 that may serve as a protective viral reservoir allowing for antiretroviral (ARV) drug entry in utero and



**Fig. 2.** The impact of common complications (Preeclampsia, Gestational Diabetes Mellitus [GDM] and Chorioamnionitis [CA]) of pregnancy and viral infections (Zika) on the quantity, phenotype

and function of Hofbauer cells. “?” denotes unknown or poorly defined and arrows represent either up- or down-regulated.

potentially the inactivation of the virus [106]. Therefore, how Hofbauer cells play a role in utero in protecting or mediating HIV-1 transmission is unclear. Various studies have demonstrated the permissiveness of Hofbauer cells to HIV-1 infection [107]; however, there are few data on the effect of HIV-1 and/or ARV drugs on the phenotype and function of these cells. Further investigation of the involvement of Hofbauer cells in HIV infection may shed light on the ability of these macrophages to inhibit or facilitate viral transmission, which can be relevant to understand other maternally acquired viruses.

Now with successful prevention of mother-to-child transmission programs, where viral transmission has been reduced to 1–2% [108, 109], there is concern that maternal–fetal tolerance may be disrupted by ARV drugs per se. As discussed above, widespread use of ARV drugs has been associated with adverse birth outcomes preva-

lent among HIV-1-infected women on ART [99, 100]. Whether ARV drugs have teratogenic effects via Hofbauer cells dysfunction remains unknown.

#### Human Cytomegalovirus

Human CMV (HCMV) is among the leading causes of congenital infections globally [110]. It is a prevalent species-specific herpes virus that causes asymptomatic infections in healthy individuals but leads to sensorineural hearing and neurodevelopmental delay in infants [111] and increased morbidity and mortality in immunocompromised individuals [112]. HCMV can be transmitted from an infected mother to her developing fetus through the placenta [113, 114] and is a major cause of intrauterine growth restriction [115]. The mechanisms involved in transplacental HCMV transmission are poorly understood. Maternal infections with HCMV during pregnancy are associated with high risk of viral

**Table 1.** Lack of consensus in the literature on the impact of complications of pregnancy and maternal viral infection on HC

Pregnancy complication	Effect on HCs	References
Chorioamnionitis	Decrease in numbers	[62]
Chorioamnionitis	Increase in numbers	[63, 64]
Chorioamnionitis	No effect on polarization status	[60]
Gestational diabetes mellitus	Acquisition of a proinflammatory phenotype	[70]
Gestational diabetes mellitus	Maintain an anti-inflammatory phenotype	[71]
Preeclampsia	Downregulation of CD74 and acquisition of a proinflammatory phenotype	[77]
Preeclampsia	Decrease in numbers	[78]
ZIKV infection	Proliferation and hyperplasia	[90]
ZIKV infection	IFN & antiviral gene induction	[88]
HIV infection	Induction of immune-modulatory cytokines	[48]

transmission to the fetus [111], where primary HCMV transmission from mother to child during gestation is 35–40% [116]. El Costa et al. [117] proposed that transmission of viruses is facilitated by either the hemotogenous spread to the placenta or by cellular transfer from the maternal decidua to the anchoring placental villi in early pregnancy.

A number of studies have reported the ability of HCMV to infect monocytes, macrophages, and their progenitors [118, 119], suggesting that the macrophage lineage provides long-lived reservoirs for HCMV latency [120, 121]. At the maternal–fetal interface, HCMV has been shown to induce a distinct decidual tissue innate immune response and to dysregulate tolerance [122]. A better understanding of innate immune mechanisms at the maternal–fetal interface that modulates transplacental transmission of viruses is important to define, so that adverse birth outcomes that are associated with these infections can be prevented. Figure 2 highlights the lack of consensus and gaps in knowledge (denoted by “?”) from studies showing the impact of pregnancy complications and viral diseases on Hofbauer cell quantity, phenotype, and function. The lack of consensus in the literature is summarized in Table 1.

## Conclusion

The origin and role of Hofbauer cells at the maternal–fetal interface and in the promotion of tolerance and regulation of pregnancy are not clear, and their function during gestation warrants further investigation. What contributes to the elusive nature of these cells is their apparent ability to adapt to their microenvironment, including the

placenta – and likely shape the link between mother and fetus. The selective role of Hofbauer cells to different viruses highlights their pleiotropic nature and a possible gatekeeping role in determining which viral infections are congenital in the newborn infant. How Hofbauer cells appear to be relatively resistant to HIV, as opposed to Zika, remains an evolutionary and developmental enigma. We propose that identifying a biomarker of Hofbauer cell dysfunction associated with various maternal infections during pregnancy will allow for the development of placental interventions to mitigate adverse birth outcomes and improve the health of both mother and her newborn infant.

## Statement of Ethics

The authors have no ethical conflicts to disclose.

## Disclosure Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

M.Z.Z. conceived the review; M.Z.Z., F.O.M., S.G., and C.M.G. wrote the review.

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