Inflammation Research
https://doi.org/10.1007/s00011-018-1190-3

Inflammation Research

REVIEW

# Pre-eclampsia: the role of highly active antiretroviral therapy and immune markers

Wendy N. Phoswa[1] · Thajasvarie Naicker[2] · Veron Ramsuran[3,4] · Jagidesa Moodley[5]

Received: 22 August 2018 / Revised: 26 September 2018 / Accepted: 27 September 2018


## Abstract

**Purpose of the review** This review highlights the role immune cells and markers such as natural killer (NK) cells, cytokines and human leukocyte antigen (HLA-G) play in predisposing HIV-infected women who are on HAART to develop PE, thus contributing to a better understanding and early diagnosis of PE with a subsequent reduction in maternal foetal and neonatal deaths.

**Recent findings** Pregnant women infected with the Human Immunodeficiency Virus (HIV) have a 25% risk of mother to child transmission. This risk, however, decreases to 2% if the women is on treatment. Highly active antiretroviral therapy (HAART) is the recommended treatment for both pregnant and non-pregnant women infected with HIV. Treatment with HAART is reported to potentiate predisposition to the development of hypertensive disorders of pregnancy such as pre-eclampsia (PE). Pre-eclampsia accounts for 7–10% of abnormal pregnancies worldwide. Studies demonstrate that pregnant women with HIV have PE at lower frequencies than uninfected women, however, the converse is observed upon HAART initiation. HIV-infected women on HAART exhibit a greater tendency to develop PE, emanating from immune reconstitution induced by HAART.

**Summary** There is paucity of information as to the pathogenesis of PE upon HAART initiation and there are, therefore, controversial data as to whether HAART predisposes women to a lower, equal or higher risk of PE development compared to the general population, further investigations on the impact of HIV infection and HAART on the immune response and rate of PE development in HIV infected pregnant women are urgently needed.

**Keywords** Highly active antiretroviral therapy · Human immunodeficiency virus · Immune markers · Pre-eclampsia · Pregnancy

## Introduction

Pre-eclampsia is a pregnancy specific disorder that effects 3–17% of pregnancies world-wide [1]. It is the leading cause of both maternal and neonatal morbidity and mortality in low and middle income countries (LIMCs) [1–3]. Pre-eclampsia presents with elevated blood pressure, i.e., systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, and proteinuria (> 300 mg/24 h) at or after 20 weeks of gestation in a previously normotensive woman [4–6]. Pre-eclampsia may be classified by gestational age into early (< 33weeks + 6 days) or late (> 34 weeks + 0 days) onset PE [7]. Early onset pre-eclampsia (EOPE) has a prevalence rate of 0.3–12% and has a higher risk of maternal and fetal complications than late onset pre-eclampsia (LOPE). It is associated with extensive overall endothelial and villous/vascular lesions of the

Responsible Editor: John Di Battista.

✉ Wendy N. Phoswa
phoswawendy@gmail.com

1 Discipline of Obstetrics and Gynaecology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

2 Optics and Imaging Centre, University of KwaZulu-Natal, Durban, South Africa

3 KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP), School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa

4 Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa

5 Women's Health and HIV Research Group, University of KwaZulu-Natal, Durban, South Africa

Published online: 01 October 2018

placenta [8]. Late onset pre-eclampsia has a prevalence of 2.7%, with minimal placental pathological changes which induces maternal inflammatory response leading to the development of PE, eclampsia and maternal death [9, 10].

The exact cause of PE remains unknown. Risk factors for PE include nulliparity, multi-fetal gestations, previous history of hypertensive disorders of pregnancy, [(gestational hypertension, PE, severe PE, eclampsia, chronic hypertension and the HELLP syndrome (haemolysis, elevated enzymes and low platelets)], obesity, diabetes mellitus, connective tissue disorders like systemic lupus erythematosus and anti-phospholipid antibodies, African American ethnicity [11, 12] and immune maladaptation [13]. The frequency of PE may also be affected by immunosuppressive conditions, such as HIV infection and acquired immunodeficiency syndrome (AIDS) [14]. In addition highly active antiretroviral therapy (HAART) has been reported to alter the maternal immune response and leads to the development of pre-eclampsia in HIV infected pregnancies [15–17].

## Highly active antiretroviral therapy on the risk of pre-eclampsia development: HIV infected pregnancies

HIV/AIDS, are major global causes of disease and death [18]. Approximately 17.4 million women worldwide are HIV infected [19], many of whom are of childbearing age [20].The current recommended treatment for HIV infection in pregnant and non-pregnant women is HAART [14]. The use of HAART in pregnancy is important for the reduction of perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and pre-exposure and post-exposure prophylaxis of the infant [21]. However, it has been reported that HAART may predispose HIV-infected pregnant women to PE development [22]. The rate of PE is reported to be lower in HIV-infected pregnancies [16]. HIV-infected women have been reported to have a significantly higher risk of PE development compared to HIV-uninfected women [23]. However, the risk of PE increases with HAART administration which induces immune reconstitution induced by HAART and results in PE development [23]. In the pre-HAART era, PE was an uncommon disorder of pregnancy in HIV-infected women and its occurrence was less frequent (none of 61 who presented before 1994; $p = 0.0087$) compared to the general population (12 pre-eclamptics in 214 HIV-uninfected women) [24, 25]. However, with the routine use of HAART, the reported incidence of PE in HIV-infected women is reported to have escalated to a level similar to that of HIV-uninfected women. A cohort study conducted by Wimalasundera et al. has shown that there was no significant difference between the rate of PE in HIV-1-infected women on treatment and uninfected controls (12 of 214; $p = 0{\cdot}2$) [25]. In agreement, three independent cohort studies conducted in the United States and Europe also showed no difference in the risk of PE development in HIV-infected HAART treated vs HIV-uninfected pregnant women [26–28]. In contrast, a cohort study from Brazil demonstrated a significantly lower risk of PE development in HAART treated women compared to HIV-uninfected women [29]. These findings are further corroborated in another study that demonstrated that HIV-infected women on HAART are not predisposed to PE development [30]. Interestingly, a survey of 36 hospitals from 11 European countries has identified PE as the most common pregnancy complication in women receiving HAART [31]. Similar findings were observed in a retrospective secondary analysis study done in South Africa by Sebitloane et al. who reported that treatment with HAART reduced the protective effect against the development of PE [17]. In addition, Suy et al. demonstrated a low rate of PE among HIV-infected women not receiving HAART, suggesting that HIV-infected treatment naïve women are at a lower risk of PE development than HIV-uninfected women [32].There are, therefore, controversial data as to whether HAART predisposes women to a lower, equal or higher risk of PE development compared to the general population, further investigations on the impact of HIV infection and HAART on the immune response and rate of PE development in HIV-infected pregnant women are urgently needed.

Currently, there are very few studies done on the incidence of PE in HIV-associated pregnancies; most of the current studies indicating low rate of PE in HIV-positive HAART treated women are representative of studies done in different racial groups, e.g. (Whites, Black, Asian), and from these groups; the number of studies in the white ethnic women were found to be greater than in studies in other racial groups [29, 30, 32]. Pre-eclampsia is reported to be more prevalent in Black, Indian, and Pakistani women [33]. Therefore, more studies investigating the incidence of PE in HIV-associated pregnancies needs to be conducted in these ethnic groups to reduce bias.

In the province of KwaZulu-Natal in South Africa, the prevalence of HIV infection amongst pregnant women is 40% [34]. Pre-eclampsia is also a common disorder in this province (12%) [35]. Although controversial reports have been published on what causes an increase in the risk of PE in HIV-infected women on HAART, recent evidence points towards the immune restoration induced by HAART which predisposes HIV-infected women to PE development [15]. Other reports suggest that this predisposition is believed to emanate from a direct toxic effect on the liver rather than immune restoration [36].

This review will focus on the role of HAART on the risk of PE development by highlighting immune markers involved in HIV associated pre-eclampsia and normotensive

pregnancies. Understanding the role of immune markers that predispose HIV-infected women to PE when initiated on HAART treatment is necessary for early diagnosis of PE and its management to reduce maternal and foetal deaths. Table 1 lists studies that have reported on the prevalence of PE in HIV-infected pregnancies.

## Pathogenesis of pre-eclampsia

There is general agreement that the pathogenesis of PE originates from the presence of placenta [37]. Various environmental and genetic factors are also implicated. Nonetheless, an imbalance in immunological factors initiates the cascade of events that cause impaired placentation [29, 38]. Immune maladaptation during implantation may result in poor trophoblast invasion which then leads to poor spiral artery remodeling within the myometrium which leads to insufficient placental perfusion with resultant placental ischemia or hypoxia [5]. The hypoxic placenta releases pathogenic factors such as (Th1 cytokines, proteolytic enzymes, and free radical species) into the maternal circulation that contributes to vascular endothelial dysfunction that leads to the second stage of the disorder or the maternal syndrome [13]. This pathognomonic endothelial vascular dysfunction contributes to the development of maternal hypertension, proteinuria and other clinical manifestations of the disorder such as maternal renal insufficiency, liver involvement, neurological or haematological complications, utero-placental dysfunction and/or foetal growth restriction [39, 40].

## Immune maladaptation

### Role of major histocompatibility complex (MHC) in placentation

During placentation, the major histocompatibility complex (MHC) antigens on trophoblast cells play a crucial role in maintaining the maternal–foetal tolerance. The MHC antigens are divided into classical class I antigens: (HLA-A, -B and -C) and non-classical class I antigens (HLA-E, -F and -G) [41]. Invasive extravillous cytotrophoblast cells express HLA-C, -E, -F and -G antigens [41, 42]. These antigens interact with maternal immune cells in the decidua, especially the uterine natural killer (uNK) cells enabling successful placental development. Moreover, the interaction with uNK cells is mediated through the binding of cytotrophoblast antigens (HLA-C, -E, -F and -G) to their appropriate receptors on the NK cells [41].

The HLA-C, -E, -F and -G antigens on EVTs interact with the maternal immune cell receptors (CD94/NKG2A and KIR2DL4) enabling successful maternal–foetal tolerance during pregnancy [43]. Importantly, the binding of HLA-G with the uterine cell receptors stimulates the production of pro-inflammatory and immune-regulatory cytokines, together with factors involved in the control of angiogenesis, which are believed to be important in spiral artery remodelling [44]. Moreover the interaction of trophoblast cells lacking HLA-G with the uterine natural killer cells leads to their lysis [45] with consequential reduced trophoblast cell invasion [46, 47]. Additionally, this may also result in chronic immune activation which then causes the development of PE [43, 48].

### The role of human leukocyte antigen (HLA-G) in pregnancy and HIV infection

Human leukocyte antigen (HLA-G) is an important non-classical immuno-regulatory molecule which has seven isoforms including HLA-G1, HLA-G2, HLA-G3, HLA-G4, HLA-G5, HLA-G-6 and HLA-G7; with HLA-G1, HLA-G2, HLA-G3, and HLA-G4 isoforms been soluble [49]. This molecule plays a pivotal role in maternal–foetal tolerance during pregnancy and is also expressed in malignant transformation, autoimmune and inflammatory diseases, transplantation and infectious diseases. During pregnancy the HLA-G molecules react with NK cells and T-cell inhibitory receptors such as KIR, KIR2DL4, LILRB1, LILRB2, ILT-2 and ILT-4, thus protecting the foetal trophoblast cells from maternal uterine natural killer cell invasion [50, 51]. The inhibition of NK and T cells creates an anti-inflammatory environment, due to a release of cytokines such as interleukin 10 (IL-10), that upregulates HLA-G [52] and mediates successful trophoblast invasion.

HLA-G expression in cells is known to be upregulated following human cytomegalovirus (CMV) and HIV infection [53–55]. The expression of the HLA-G molecule in the early stage of HIV infection and its progression is well documented. During HIV-1 infection, the HLA-G1 isoform is downregulated via a *Vpu*-dependent mechanism, which recognizes a double lysine residue in positions 4 and 5 of the C terminus [56]. Also the HLA-G1 isoform has the ability to present viral peptides to CD8 + T lymphocytes [57]; therefore, the recognition of HIV-1 infected cells by CD8 + T lymphocytes could depend on the expression of HLA-G1 [56].

In contrast, Lozano et al., report a high surface expression of HLA-G on monocytes and on some T lymphocytes in HIV positive patients with or without antiretroviral treatment. These authors hypothesize that this upregulation of HLA-G was induced by HIV-1, [54]. Alternatively this increase may be caused indirectly as a consequence of high levels of IL-10 expression [52].

Donaghy et al. observed high circulating levels of soluble HLA-G (sHLA-G) in HIV-1-infected individuals and

**Table 1** A comprehensive list of studies in this review examining the prevalence of pre-eclampsia in HIV-infected treated, non-treated and non-infected women

| Author | Country | Design | Cohort size | Adjustment | Prevalence of pre-eclampsia: main findings |
|---|---|---|---|---|---|
| [25] | United Kingdom | Matched cohort | $N=428$<br>*214 HIV+women* (mono therapy, dual therapy, triple ART and untreated)<br>*214 HIV– women* | Age, parity (primiparous $n=132$, multiparous $n=296$), ethnicity (African $n=348$, White $n=76$, Asian $n=4$), gestation (weeks), diagnosis, blood pressure (mm Hg), proteinuria, platelets ($10^9$/L), creatinine (μmol/L), alanine transaminase (IU/L), CD4, CD8, HIV-1 RNA (copies/mL), antiretrovirals, NRTI | *Lower risk of pre-eclampsia* in non-treated HIV positive women (none of 61 who presented before 1994; $p=0.0087$) or on mono or dual therapy (one of 77; 1%; $p=0.018$) than triple ART treated HIV positive women (8 of 76; odds ratio 15.3, 95% CI 0.9–270, $p=0.0087$)<br>*No difference in risk of pre-eclampsia* between treated HIV positive women and HIV negative controls (12 of 214; $p=0.2$) |
| [29] | Spain | Cohort | $N=1831$<br>*123 HIV+women* (mono or HAART)<br>*1708 HIV− women* | Age, ethnic groups [(Black $n=30$, White $n=102$, and Mulatto $n=68$)], parity (Primiparous $n=54$, and Multiparous $n=146$), therapy, CD4, HIV-1 RNA (copies/ml) | *Lower risk of preeclampsia* in HIV positive women on mono or triple therapy (0.8% $n=1$) as compared to controls (10.6% $n=182$) ($P=0:0017$) |
| [32] | Brazil | Cohort | $N=8768$<br>*From 1985 until July 2003 472 HIV+women*<br>*8296 HIV– women* | Age, parity (Nulliparity $n=5291$ Multiparity $n=3949$), race (White $n=7855$, non-white $n=1385$), tobacco smoking, intravenous drug use, no. foetuses, median known duration of HIV infection [months (IQR)], median CD4 cell count [cells/ml (IQR)], antiretroviral therapy prior to pregnancy [No. (%)], antiretroviral therapy during pregnancy [No. (%)] | *Higher risk of pre-eclampsia* in treated HIV positive women compared to HIV negative women |
| [26] | United States | Cross-sectional | $N=4{,}513{,}890$ HIV + women: 6143 in 1994, 6235 in 2003<br>HIV− women: 4,283,347 in 1994, 4,507,655 in 2003 | Age, insurance type, hospital location, drug abuse, anemia, urinary tract infection, sexually transmitted infections, clinically relevant comorbidities | *No difference in* hospitalization rates for preeclampsia between HIV positive women (no treatment information) and HIV negative women |
| [28] | Netherlands | Matched cohort | $N=339$<br>*143 HIV+women*<br>*196 HIV−women* | Age, parity (No previous births $n=147$ One previous birth $n=103$, two or more previous births $n=89$, ethnicity (white $n=69$, Black $n=244$, other $n=26$), year of delivery, drug abuse, tobacco use, CD4 count, HAART use before pregnancy, HAART in first trimester, HAART with PI | *No difference in risk of pre-eclampsia* between treated HIV positive women and HIV-negative controls |
| [27] | United States | Matched cohort | $N=453$<br>151 *HIV+women*<br>302 *HIV– women* | Age, parity, ethnicity, year of delivery, insurance type, hospital location, mode of delivery, drug abuse, tobacco use, co-morbidities (e.g. chronic hypertension), HAART | *No difference in risk* between treated HIV positive women and HIV negative women when tobacco and cocaine use were adjusted for |
| [30] | Toronto | Matched cohort | $N=364$<br>*91 HIV+women*<br>*273 HIV− women* | Age, parity $n=\%$ (primiparity $n=55$, multiple pregnancy $n=55$ Race $n=\%$ (White $n=52.9$, Black $n=27.4$, Other $n=19.7$, mode of delivery, drug abuse, tobacco use, history of PE, chronic hypertension, urinary tract infection, sexually transmitted infections, diabetes mellitus | No difference in risk between treated HIV positive women and HIV negative women in the odds of preeclampsia (3.3% vs. 5.1%; adjusted odds ratio [aOR] 0.59; 95% CI 0.11–3.08) |

speculated that this elevation of HLA-G was dependent on the release of the membrane-bound isoform thereby inducing immune tolerance [58]. In keeping with the findings of Donaghy and colleagues, Murdaca et al. also reported elevated serum levels of sHLA-G in HIV-infected individuals [59]. These results correlate with parameters of immunological and virological response to antiretroviral treatment, and the authors report decreased levels of sHLA-G in patients in whom the replication of HIV-1 was suppressed during HAART treatment. Levels of sHLA-G remain elevated in women with high levels of HIV-RNA after 36 months of receiving antiretroviral therapy. The elevated serum sHLA-G may depend on the increased production of cytokines during HIV-1 infection, contribute to the immunosuppressive state of the HIV-1-positive individuals and facilitate their progression to AIDS [59].

Additionally, Lajoie et al. performed a longitudinal study evaluating sHLA-G plasma levels in HIV-1-infected patients with different rates of clinical progression to determine whether sHLA-G expression was associated with HIV-1 expansion. The findings of this study indicated elevated levels of sHLA-G in the early stages of HIV-1 infection, whereas in the chronic stage, in untreated normal progressor, and in long-term progressor the sHLA-G levels were restored to normality, as a result of the immune system's ability to control the HIV-1 infection. Furthermore, they concluded that sHLA-G elevation in HIV infection was associated with disease progression. Although HLAG has been shown to play a role in the immune system during HIV infection, there is a paucity of data interrogating the role of HLA-G in HIV associated pregnant women receiving HAART.

## Natural killer cells

During normal pregnancy the maternal decidua consists of a unique subset of immune cell populations such as macrophages, NK cells, and regulatory T cells which express human leukocyte antigens that actively contribute to the tolerance and function of the placenta [60–63]. It has been reported that 70% of decidual leukocytes are NK cells, 20–25% are macrophages and 1.7% are dendritic cells [64–66]. Hence this maternal immune tolerance involves crucial interaction between maternal immune cells (helper and cytotoxic T lymphocytes, regulatory T cells, macrophages, dendritic cells and uNK cells) in recognizing and accepting the foetal antigens and facilitating placental growth.

Natural killer cells are crucial components of the innate immune system. NK cells can be classified into two subsets, depending on their immunophenotype and function: $CD56^{dim}$ and $CD56^{bright}$. $CD56^{dim}$ constitutes 90% of the total NK cell population in peripheral blood [67].

### Uterine natural killer cells

The majority of uNK cells are similar to tissue-resident NK and a small subset of peripheral NK cells express CD56 but not CD16 and $CD3^{-}$ [68]. Uterine natural killer cells are less cytotoxic and produce large amounts of cytokines compared to peripheral NK cells. Uterine natural killer cells located within the non-pregnant endometrium are called endometrial NK cells whilst in the decidua are called decidual NK (dNK) cells. Decidual NK cells constitute the major lymphocyte population in the uterus during early gestation with a decrease after 20 weeks of gestation when trophoblast invasion is complete [69]. They produce transforming growth factor-beta (TGF-β) and other angiogenic factors such as angiopoietin (Ang) 1, Ang 2, vascular endothelial growth factor (VEGF), and placental growth factor (PlGF) [70, 71]. These factors induce and support the invasion of the extravillous trophoblasts into the maternal spiral arteries to achieve the remodelling of the spiral arteries required for adequate placental perfusion [45, 72].

### Natural killer cell receptors

The function of NK cells is controlled by a wide range of receptors that are expressed on the cell surface. These receptors are either inhibitory or activating in nature. The family of inhibitory receptors consists consist of: (1) the killer immunoglobulin-like receptors (KIRs) or Ig-like receptors (CD158), which recognize mainly HLA-A, HLA-B, and HLA-C expressed in any host cell; (2) the C type lectin receptors (CD94/NKG2), which recognizes the non-classical MHC molecule, HLA-E and (3) leukocyte inhibitory receptors (LIR1, LAIR-1) [73]. On the other hand, the activating receptors are; the natural cytotoxicity receptors (NKp30, NKp44, NKp46), C type lectin receptors (NKG2D, CD94-NKG2C), and Ig-like receptors (2B4) [72, 74, 75].

#### Natural killer cells receptors in normal and pre-eclamptic pregnancy

During normal pregnancy, the interaction between the maternal natural killer cells and fetal cells occur via cytotrophoblast MHC antigen recognising and accepting maternal NK cells inhibitory receptors, thus preventing the killing of trophoblast cells. However, in PE NK cell expression is altered leading to abnormal trophoblast cells invasion. Bachmayer et al. reported that levels of inhibitory NKG2A and activating NKG2C are higher in PE compared to normotensive healthy pregnant women.

They concluded that the peripheral NK cell pool is altered in women with PE with enhanced NKG2A and NKG2C levels on NK cells [76].

### The role of NK cells in HIV infection and the risk of pre-eclampsia

NK cells are $CD3^-$ multifunctional effector lymphocytes based on levels of CD56 and CD16 expression [77]. About 90% of peripheral blood NK cells are $CD56^{dim}$ and express high levels of the FcγRIIIA receptor (CD16); the other (10%) of peripheral blood NK cells are $CD56^{bright}$ and express low levels or an absence of CD16 [78].

$CD56^{dim}$ are mostly cytotoxic upon activation, thereby releasing pro-apoptotic cytoplasmic granules composed of granzymes and perforins. $CD56^{dim}$ NK cells can also induce cytolysis via induction of Fas/FasL-dependent or TRAIL-dependent apoptotic signals. In addition, a minority of NK cells (CD16) binds to the constant (Fc) domain of IgG antibodies that can bind to viral antigens expressed on the surface of infected cells. This antibody conjugation of NK-cell and antibody-coated target cell, strongly mediates NK-cell activation, referred to as antibody-dependent cell-mediated cytotoxicity (ADCC) [74]. Interestingly, the $CD56^{bright}$ NK cells have a limited cytotoxic capacity and is more abundantly found within lymph nodes [79]. These NK cells act by producing pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-10, certain chemokines. They play a role in modulating other subsets of lymphocytes, thereby regulating dendritic cell maturation, differentiation of helper T cells, and B- and T-cell-specific immune responses [80, 81]. However, during HIV infection NK cells are generally downregulated or inhibited and are unable to target infected or transformed cells thereby leading to uncontrolled viral replication. Mela and Goodier report a decreased expression of NKG2A on peripheral NK cells of HIV-1 infected individuals [82]. Although the role of NK cells in HIV infection is well described, its function in HIV associated PE has produced debatable results [83].

#### Role of HAART on NK cells and risk of pre-eclampsia development

The use of highly active antiretroviral therapy (HAART) suppresses HIV-1 viremia by restoring the ability of NK cells to secrete CC-chemokines which suppress endogenous HIV-1 replication by non-cytolytic mechanisms [84]. However, this has a negative impact during pregnancy as NK cell activation may lead to dysregulation of trophoblast invasion and may result in chronic immune activation which is associated with PE development.

## Cytokines

### Cytokine production in normal and pre-eclamptic pregnancies

In normal pregnancy, the placenta causes a shift from the pro-inflammatory (Th1) to anti-inflammatory (Th2) immune response [85]. It has been proposed that the placenta is a Th2 organ that stimulates the production of Th2 cytokines [86]. In pathological pregnancies such as PE, spontaneous abortions and intrauterine growth restriction (IUGR), the regulation of the maternal immune system is further altered and the shift to the Th2 immune response does not occur leading to elevated Th1 immune response [87]. This is usually due to an ischemic placenta which is unable to cause a shift from a Th1 to Th2 immune response.

Data on the shift from Th2 to Th1 immune state observed in PE is conflicting [88, 89]. Several authors have reported increased levels of IL-6 in PE [90–92]. Greer et al., has reported increased plasma levels of IL-6, but normal concentrations of IL-8 in PE [90] while Olusi et al., reported significantly lower IL-6 and IL-8 levels in PE compared to normal pregnancy [88]. Similarly, Hentschke et al., also reported increased soluble IL-6 receptors in PE [91]. In addition, Udenze et al., reported increased levels of IL-6 and TNF- α in PE [92]. In contrast, Ozier et al., found no difference in the levels of IL-6 and TNF- α in PE [93]. Interestingly, previous studies have shown increased IFN-γ and decreased levels of IL-4 in PE [94–97]. The severe pre-eclamptic state is associated with high levels of pro-inflammatory cytokines IL-8, IL-6, and IFN-γ, whereas normotensive pregnancy evolves with high levels of the regulatory cytokine IL-10. Similarly, previous studies report high levels of IL-10 in healthy pregnant women [98–102], suggesting that successful pregnancy reflects a predominance of regulatory cytokines. Studies in mice revealed that IL-10 deficiency in early pregnancy affects trophoblast growth and differentiation, causing placental failure and abortion [103]. IL-10 also increases the resistance of trophoblasts to Fas-mediated apoptosis [104]. Inhibition of IL-10 by passive immunization (with monoclonal antibody to IL-10) during early gestation increases blood pressure in pregnant baboons [105]. Therefore, it may be hypothesized that decreased IL-10 production is associated with a predisposition to PE development [106–108].

The pathophysiology of PE may be induced by the presence of Th17 cells. These are relatively novel CD4 + lymphocyte subpopulations, which are characterized by their secretion of IL-17. This cytokine interacts with inflammatory factors to amplify the small vascular inflammatory

reactions of the placenta, damage vascular endothelial cells, increase the permeability of blood vessels, and release large numbers of oxygen free radicals. Together, these constitute the pathological basis of the clinical manifestations of PE, including hypertension, vascular spasms, oedema, and proteinuria [109].

Gergely et al. previously demonstrated that Th17 cells were elevated in PE compared with healthy pregnant women [110]. These findings were confirmed by Cornelius et al., who found that an infusion of IL-17 inhibitor given to a PE rat model significantly decreases blood pressure and placental oxidative stress [111]. Similarly, Wallace et al. also found that both Th17 cells and IL-17 were significantly elevated in the reduced uterine perfusion pressure (RUPP) rat model of PE [112]. The authors further concluded that blockage of IL-17 significantly decreased placental ROS emanating from the placental ischemia in RUPP rats, indicating that increased levels IL-17 is associated with PE-related conditions [112].

## Cytokine production in HIV associated pre-eclampsia

A similar shift from Th1 to Th2 cytokines has been reported during the progression of HIV disease, which is counteracted with the usage of HAART [113]. A study by Maharaj et al. demonstrated that both normotensive and pre-eclamptic HIV infected pregnant women on HAART display lower Th1 cytokine levels (IL-2, TNF-α, and IL-6, and IFN-γ) than both PE and normotensive uninfected pregnant women [15]. Their study also showed lower Th1 levels in HIV-infected pre-eclamptics on HAART when compared to HIV-uninfected pre-eclamptic and no differences in Th1 (IL-2, TNF-α, IFN-γ or IL-6) in PE when compared to normotensive pregnant women. In addition, they found that there was no differences in the Th1 immune response in pre-eclamptic HIV-infected and non-infected women when compared to HIV-infected and non-infected normotensive pregnant women [15]. This might suggest that PE development in HIV-infected women who are on HAART might not be due to immune reconstitution, but might be due to another pathway; since it has been mentioned that HAART medication results in the synthesis and secretion of retinol-binding proteins that lead to reduction in serum retinol concentrations, which is associated with PE development [36].

Despite conflicting results with regards the risk of PE development in HIV infected pregnant women; another study found that the high levels of Th1 cytokines in HIV-infected HAART treated pregnant women when compared to HIV-uninfected pregnant or non-pregnant women [114]. From Alonso et al. findings it was shown that Th1 immune response is induced in HIV-infected treated pregnancies and reduced in HIV-uninfected pregnant and non-pregnant individuals. This suggested that HAART treatment might predispose HIV-infected women to PE development by upregulating the Th1 immune response in HIV-infected pregnant women [114] (Fig. 1).

## Conclusion

It is evident that PE is less common in HIV-infected treatment naïve pregnancies; however, most studies have shown that the risk of PE development in HIV-infected women is greater in those receiving HAART. Therefore, more studies are required to confirm immune reconstitution following HAART usage and whether it is a risk indicator for PE development.

This review highlighted immune markers that play a role in predisposing HIV infected pregnant women on HAART treatment to PE development. Both HIV and PE have a high prevalence within South Africa and both are identified as

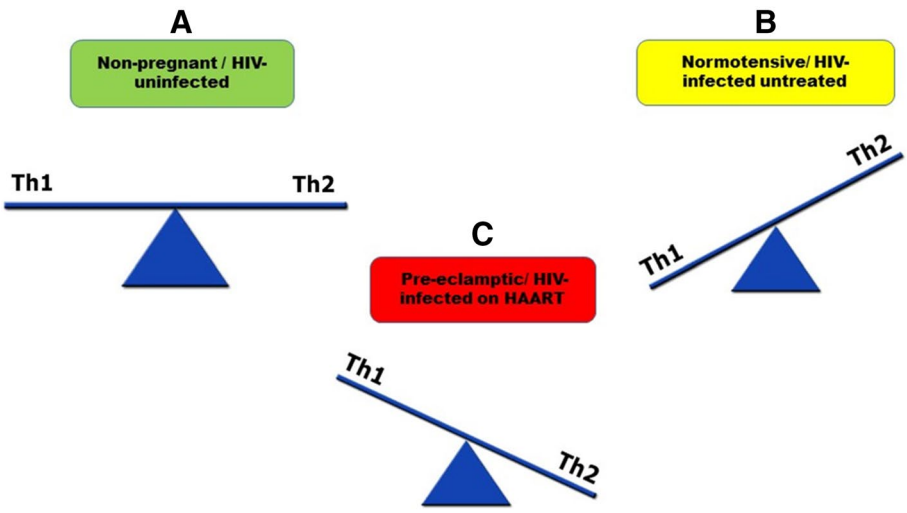


**Fig. 1** Schematic diagram representing pro-inflammatory (Th1) and anti-inflammatory (Th2) cytokine balance in **a** non-pregnant or HIV-uninfected, **b** normotensive or HIV-infected untreated and **c** pre-eclamptic or HIV-infected on HAART. **a** Shows a balance in the distribution of Th1 and Th2. In **b** there is an imbalance of cytokines with more Th2 release than Th1. This imbalance increases of HIV infection in untreated women. In **c** Th1 levels are higher than Th2, therefore, this predisposes HIV-infected HAART treated women to pre-eclampsia development

immune related. Amongst the selected and highlighted immune markers in this review; NK cells, cytokines, and HLA-G are shown to play a crucial role in both HIV and PE pathogenesis. However, there are significant gaps in knowledge and a fair amount of research still needs to be done to determine the involvement of these immune markers in the development of PE in HIV associated pregnancies.

## Future research

More research much concentrate on the immune reconstitution induced by HAART to identify immune markers associated with the risk of involved in PE development in pregnant women on HAART. This will assist with early diagnosis of PE in HIV-infected women who are on HAART treatment.

## Compliance with ethical standards

**Conflict of interest** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References


1. Loewendorf AI, Nguyen TA, Yesayan MN, Kahn DA. Preeclampsia is characterized by fetal NK cell activation and a reduction in regulatory T cells. Am J Reprod Immunol. 2015;74:258–67.
2. Duhig KE, Shennan AH. Recent advances in the diagnosis and management of pre-eclampsia. F1000prime Rep. 2015;7:24.
3. Saleem S, McClure EM, Goudar SS, Patel A, Esamai F, Garces A, et al. A prospective study of maternal, fetal and neonatal deaths in low-and middle-income countries. Bull World Health Organ. 2014;92:605–12.
4. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. The Lancet. 2005;365:785–99.
5. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. The Lancet. 2010;376:631–44.
6. English FA, Kenny LC, McCarthy FP. Risk factors and effective management of preeclampsia. Integr Blood Press Control. 2015;8:7.
7. Magee LA, Kenny L, Karumanchi SA, McCarthy F, Saito S, Hall DR, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis and management recommendations for international practice 2018. Pregnancy Hypertens. 2018;72:24–43.
8. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol. 2014;10:466.
9. Lisonkova S, Joseph K. Incidence of preeclampsia: risk factors and outcomes associated with early-versus late-onset disease. Am J Obstet Gynecol. 2013;209:544 (**e1–e12**).
10. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph K. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol. 2014;124:771–81.
11. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. J Pregnancy. 2012;2012:586578. https://doi.org/10.1155/2012/586578.
12. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330:565.
13. Dekker GA, Sibai BM. Etiology and pathogenesis of preeclampsia: current concepts. Am J Obstet Gynecol. 1998;179:1359–75.
14. Landi B, Bezzeccheri V, Guerra B, Piemontese M, Cervi F, Cecchi L, et al. HIV infection in pregnancy and the risk of gestational hypertension and preeclampsia. World J Cardiovasc Dis. 2014;4:257.
15. Maharaj NR, Phulukdaree A, Nagiah S, Ramkaran P, Tiloke C, Chuturgoon AA. Pro-inflammatory cytokine levels in HIV infected and uninfected pregnant women with and without preeclampsia. PLoS One. 2017;12:e0170063.
16. Kalumba V, Moodley J, Naidoo T. Is the prevalence of pre-eclampsia affected by HIV/AIDS? A retrospective case-control study: cardiovascular topics. Cardiovasc J Afr. 2013;24:24–7.
17. Sebitloane HM, Moodley J, Sartorius B. Associations between HIV, highly active anti-retroviral therapy, and hypertensive disorders of pregnancy among maternal deaths in South Africa 2011–2013. Int J Gynecol Obstet. 2017;136:195–9.
18. Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. PLoS Med. 2010;7:e1000229.
19. Organization WH. Global summary of the AIDS epidemic 2014. Hämtad från. http://www.who.int/hiv/data/2012_epi_core_en.png (2013).
20. Ono E, dos Santos A, Machado DM, Succi RCdM, Amed AM, Salomao R, et al. Immunologic features of HIV-1-infected women on HAART at delivery. Cytom Part B: Clin Cytom. 2008;74:236–43.
21. Townsend CL, Tookey PA, Newell M-L, Cortina-Borja M. Antiretroviral therapy in pregnancy: balancing the risk of preterm delivery with prevention of mother-to-child HIV transmission. Antivir Ther. 2010;15:775.
22. Browne JL, Schrier VJ, Grobbee DE, Peters SA, Klipstein-Grobusch K. HIV, antiretroviral therapy, and hypertensive disorders in pregnancy: a systematic review and meta-analysis. JAIDS J Acquir Immune Defic Syndr. 2015;70:91–8.
23. Sansone M, Sarno L, Saccone G, Berghella V, Maruotti GM, Migliucci A, et al. Risk of preeclampsia in human immunodeficiency virus–infected pregnant women. Obstet Gynecol. 2016;127:1027–32.
24. Stratton P, Tuomala RE, Abboud R, Rodriguez E, Rich K, Pitt J, et al. Obstetric and newborn outcomes in a cohort of HIV-infected pregnant women: a report of the women and infants transmission study. J Acquir Immune Defic Syndr Hum Retrovirology. 1999;20:179–86.
25. Wimalasundera R, Larbalestier N, Smith J, De Ruiter A, Thom SM, Hughes A, et al. Pre-eclampsia, antiretroviral therapy, and immune reconstitution. The Lancet. 2002;360:1152–4.
26. Kourtis AP, Bansil P, McPheeters M, Meikle SF, Posner SF, Jamieson DJ. Hospitalizations of pregnant HIV-infected women in the USA prior to and during the era of HAART, 1994–2003. AIDS. 2006;20:1823–31.
27. Haeri S, Shauer M, Dale M, Leslie J, Baker AM, Saddlemire S, et al. Obstetric and newborn infant outcomes in human immunodeficiency virus-infected women who receive highly active antiretroviral therapy. Am J Obstet Gynecol. 2009;201:315, e1–e5.
28. Boer K, Nellen J, Patel D, Timmermans S, Tempelman C, Wibaut M, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG: Int J Obstet Gynaecol. 2007;114:148–55.
29. Mattar R, Amed AM, Lindsey PC, Sass N, Daher S. Preeclampsia and HIV infection. Eur J Obstet Gynecol Reprod Biol. 2004;117:240–1.

30. Boyajian T, Shah PS, Murphy KE. Risk of preeclampsia in HIV-positive pregnant women receiving HAART: a matched cohort study. J Obstet Gynaecol Can. 2012;34:136–41.
31. Study EC. Pregnancy-related changes in the longer-term management of HIV-infected women in Europe. Eur J Obstet Gynecol Reprod Biol. 2003;111:3–8.
32. Suy A, Martínez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS. 2006;20:59–66.
33. Poon L, Kametas N, Chelemen T, Leal A, Nicolaides K. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. J Hum Hypertens. 2010;24:104.
34. Health Do. National antenatal sentinel HIV and syphilis prevalence survey in South Africa. Department of Health Pretoria; 2011.
35. Moodley J, Onyangunga O, Maharaj N. Hypertensive disorders in primigravid black South African women: a one-year descriptive analysis. Hypertens Pregnancy. 2016;35:529–35.
36. Mawson AR. Effects of antiretroviral therapy on occurrence of pre-eclampsia. The Lancet. 2003;361:347–8.
37. Redman C. Pre-eclampsia and the placenta. Placenta. 1991;12:301–8.
38. Eastabrook G, Brown M, Sargent I. The origins and end-organ consequence of pre-eclampsia. Best Pract Res Clin Obstet Gynaecol. 2011;25:435–47.
39. Palei AC, Spradley FT, Warrington JP, George EM, Granger JP. Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. Acta Physiol. 2013;208:224–33.
40. Mol BW, Roberts CT, Thangaratinam S, Magee LA, De Groot CJ, Hofmeyr GJ. Pre-eclampsia. The Lancet. 2016;387:999–1011.
41. Ishitani A, Sageshima N, Hatake K. The involvement of HLA-E and-F in pregnancy. J Reprod Immunol. 2006;69:101–13.
42. Hviid TVF. HLA-G in human reproduction: aspects of genetics, function and pregnancy complications. Hum Reprod Updat. 2005;12:209–32.
43. Sargent IL, Borzychowski AM, Redman CW. Immunoregulation in normal pregnancy and pre-eclampsia: an overview. Reprod Biomed Online. 2006;13:680–6.
44. Tabiasco J, Rabot M, Aguerre-Girr M, El Costa H, Berrebi A, Parant O, et al. Human decidual NK cells: unique phenotype and functional properties—a review. Placenta. 2006;27:34–9.
45. Ahn H, Park J, Gilman-Sachs A, Kwak-Kim J. Immunologic characteristics of preeclampsia, a comprehensive review. Am J Reprod Immunol. 2011;65:377–94.
46. Goldman-Wohl D, Ariel I, Greenfield C, Hochner-Celnikier D, Cross J, Fisher S, et al. Lack of human leukocyte antigen-G expression in extravillous trophoblasts is associated with pre-eclampsia. Mol Hum Reprod. 2000;6:88–95.
47. Hara N, Fujii T, Yamashita T, Kozuma S, Okai T, Taketani Y. Altered expression of human leukocyte antigen G (HLA-G) on extravillous trophoblasts in preeclampsia: immunohistological demonstration with anti-HLA-G specific antibody "87G" and anti-cytokeratin antibody "CAM5. 2". Am J Reprod Immunol. 1996;36:349–58.
48. Novotny S, Wallace K, Herse F, Moseley J, Darby M, Heath J, et al. $CD4^+$ T cells play a critical role in mediating hypertension in response to placental ischemia. J Hypertens. 2013;2:14873. https://doi.org/10.4172/2167-1095.1000116.
49. Paul P, Cabestre FA, Lefebvre S, Khalil-Daher I, Vazeux G, Quiles RMM, et al. Identification of HLA-G7 as a new splice variant of the HLA-G mRNA and expression of soluble HLA-G5,-G6, and-G7 transcripts in human transfected cells. Hum Immunol. 2000;61:1138–49.
50. Rouas-Freiss N, Marchal RE, Kirszenbaum M, Dausset J, Carosella ED. The α1 domain of HLA-G1 and HLA-G2 inhibits cytotoxicity induced by natural killer cells: is HLA-G the public ligand for natural killer cell inhibitory receptors? Proc Nat Acad Sci. 1997;94:5249–54.
51. Dahl M, Hviid TVF. Human leucocyte antigen class Ib molecules in pregnancy success and early pregnancy loss. Hum Reprod Update. 2011;18:92–109.
52. Moreau P, Adrian-Cabestre F, Menier C, Guiard V, Gourand L, Dausset J, et al. IL-10 selectively induces HLA-G expression in human trophoblasts and monocytes. Int Immunol. 1999;11:803–11.
53. Cabello A, Rivero A, Garcia MJ, Lozano JM, Torre-Cisneros J, González R, et al. HAART induces the expression of HLA-G on peripheral monocytes in HIV-1 infected individuals. Hum Immunol. 2003;64:1045–9.
54. Lozano JM, González R, Kindelán JM, Rouas-Freiss N, Caballos R, Dausset J, et al. Monocytes and T lymphocytes in HIV-1-positive patients express HLA-G molecule. AIDS. 2002;16:347–51.
55. Onno M, Pangault C, Le Friec G, Guilloux V, André P, Fauchet R. Modulation of HLA-G antigens expression by human cytomegalovirus: specific induction in activated macrophages harboring human cytomegalovirus infection. J Immunol. 2000;164:6426–34.
56. Derrien M, Pizzato N, Dolcini G, Menu E, Chaouat G, Lenfant F, et al. Human immunodeficiency virus 1 downregulates cell surface expression of the non-classical major histocompatibility class I molecule HLA-G1. J Gen Virol. 2004;85:1945–54.
57. Lenfant F, Pizzato N, Liang S, Davrinche C, Le Bouteiller P, Horuzsko A. Induction of HLA-G-restricted human cytomegalovirus pp65 (UL83)-specific cytotoxic T lymphocytes in HLA-G transgenic mice. J Gen Virol. 2003;84:307–17.
58. Donaghy L, Gros F, Amiot L, Mary C, Maillard A, Guiguen C, et al. Elevated levels of soluble non-classical major histocompatibility class I molecule human leucocyte antigen (HLA)-G in the blood of HIV-infected patients with or without visceral leishmaniasis. Clin Exp Immunol. 2007;147:236–40.
59. Murdaca G, Contini P, Setti M, Cagnati P, Lantieri F, Indiveri F, et al. Behavior of non-classical soluble HLA class G antigens in human immunodeficiency virus 1-infected patients before and after HAART: comparison with classical soluble HLA-A,-B,-C antigens and potential role in immune-reconstitution. Clin Immunol. 2009;133:238–44.
60. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol. 2004;5:266.
61. Zenclussen AC. CD4 + CD25 + T regulatory cells in murine pregnancy. J Reprod Immunol. 2005;65:101–10.
62. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63:425–33.
63. Racicot K, Kwon JY, Aldo P, Silasi M, Mor G. Understanding the complexity of the immune system during pregnancy. Am J Reprod Immunol. 2014;72:107–16.
64. Bulmer JN, Denise P, Ritson A. Immunoregulatory cells in human decidua: morphology, immunohistochemistry and function. Reprod Nutr Dév. 1988;28:1599–614.
65. Mor G, Straszewski-Chavez SL, Abrahams VM. Macrophage-trophoblast interactions. Placenta: Springer; 2006. pp. 149–63.
66. King A, Burrows T, Verma S, Hiby S, Loke Y. Human uterine lymphocytes. Hum Reprod Update. 1998;4:480–5.
67. Angelo LS, Banerjee PP, Monaco-Shawver L, Rosen JB, Makedonas G, Forbes LR, et al. Practical NK cell phenotyping and variability in healthy adults. Immunol Res. 2015;62:341–56.
68. Giuliani E, Parkin KL, Lessey BA, Young SL, Fazleabas AT. Characterization of uterine NK cells in women with infertility or recurrent pregnancy loss and associated endometriosis. Am J Reprod Immunol. 2014;72:262–9.

69. Lash G, Robson S, Bulmer J. Functional role of uterine natural killer (uNK) cells in human early pregnancy decidua. Placenta. 2010;31:87–92.
70. Moffett-King A. Natural killer cells and pregnancy. Nat Rev Immunol. 2002;2:656–63.
71. Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med. 2006;12:1065.
72. Mandal A, Viswanathan C. Natural killer cells: in health and disease. Hematol/Oncol Stem Cell Ther. 2015;8:47–55.
73. King A, Allan DS, Bowen M, Powis SJ, Joseph S, Verma S, et al. HLA-E is expressed on trophoblast and interacts with CD94/NKG2 receptors on decidual NK cells. Eur J Immunol. 2000;30:1623–31.
74. Wu J, Lanier LL. Natural killer cells and cancer. Adv Cancer Res. 2003;90:127–56.
75. Cerwenka A, Lanier LL. Natural killer cells, viruses and cancer. Nat Rev Immunol. 2001;1:41–9.
76. Bachmayer N, Sohlberg E, Sundström Y, Hamad RR, Berg L, Bremme K, et al. Women with pre-eclampsia have an altered NKG2A and NKG2C receptor expression on peripheral blood natural killer cells. Am J Reprod Immunol. 2009;62:147–57.
77. Poli A, Michel T, Thérésine M, Andres E, Hentges F, Zimmer J. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology. 2009;126:458–65.
78. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. 2001;22:633–40.
79. Ferlazzo G, Thomas D, Lin S-L, Goodman K, Morandi B, Muller WA, et al. The abundant NK cells in human secondary lymphoid tissues require activation to express killer cell Ig-like receptors and become cytolytic. J Immunol. 2004;172:1455–62.
80. Martín-Fontecha A, Thomsen LL, Brett S, Gerard C, Lipp M, Lanzavecchia A, et al. Induced recruitment of NK cells to lymph nodes provides IFN-γ for T H 1 priming. Nat Immunol. 2004;5:1260.
81. Mocikat R, Braumüller H, Gumy A, Egeter O, Ziegler H, Reusch U, et al. Natural killer cells activated by MHC class I low targets prime dendritic cells to induce protective CD8 T cell responses. Immunity. 2003;19:561–9.
82. Mela CM, Goodier MR. The contribution of cytomegalovirus to changes in NK cell receptor expression in HIV-1-infected individuals. J Infect Dis. 2007;195:158–9.
83. Conde-Agudelo A, Villar J, Lindheimer M. Maternal infection and risk of preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2008;198:7–22.
84. Kottilil S. Natural killer cells in HIV-1 infection: role of NK cell-mediated non-cytolytic mechanisms in pathogenesis of HIV-1 infection. Indian J Exp Biol. 2003;41:1219–25.
85. Laresgoiti-Servitje E, Gómez-López N, Olson DM. An immunological insight into the origins of pre-eclampsia. Hum Reprod Update. 2010;16:510–24.
86. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunol Today. 1993;14:353–6.
87. Hu W, Wang H, Wang Z, Huang H, Dong M. Elevated serum levels of interleukin-15 and interleukin-16 in preeclampsia. J Reprod Immunol. 2007;73:166–71.
88. Olusi SO, Diejomaoh M, Omu A, Abdulaziz A, Prabha K, George S. Interleukins in preeclampsia. Ann Saudi Med. 2000;20:4–7.
89. Adrián TR, Ruiz A, Vílchez RM, Estévez J, Atencio R. Interleukin-2 receptor serum concentrations in normal pregnancy and pre-eclampsia. Investig Clin. 2002;43:73–78.
90. Greer IA, Lyall F, Perera T, Boswell F, Macara LM. Increased concentrations of cytokines interleukin-6 and interleukin-1 receptor antagonist in plasma of women with preeclampsia: a mechanism for endothelial dysfunction? Obstet Gynecol. 1994;84:937–40.
91. Hentschke MR, Lucas LS, Krauspenhar B, Felix RP, Sussela AO, Berlesi F, et al. Increased levels of the soluble receptor of Interleukin-6 in patients with preeclampsia compared to normotensive pregnant women. Sci Medica. 2014;23:213–8.
92. Udenze I, Amadi C, Awolola N, Makwe CC. The role of cytokines as inflammatory mediators in preeclampsia. Pan Afr Med J. 2015;20(1).
93. Ozler A, Turgut A, Sak M, Evsen M, Soydinc H, Evliyaoglu O, et al. Serum levels of neopterin, tumor necrosis factor-alpha and Interleukin-6 in preeclampsia: relationship with disease severity. Eur Rev Med Pharmacol Sci. 2012;16:1707–12.
94. Arriaga-Pizano L, Jimenez-Zamudio L, Vadillo-Ortega F, Martinez-Flores A, Herrerias-Canedo T, Hernandez-Guerrero C. The predominant Th1 cytokine profile in maternal plasma of preeclamptic women is not reflected in the choriodecidual and fetal compartments. J Soc Gynecol Investig. 2005;12:335–42.
95. Mansouri R, Akbari F, Vodjgani M, Mahboudi F, Kalantar F, Mirahmadian M. Serum cytokines profiles in Iranian patients with preeclampsia. Iran J Immunol. 2007;4:179–85.
96. Molvarec A, Szarka A, Walentin S, Bekő G, Karádi I, Prohászka Z, et al. Serum leptin levels in relation to circulating cytokines, chemokines, adhesion molecules and angiogenic factors in normal pregnancy and preeclampsia. Reprod Biol Endocrinol. 2011;9:124.
97. Szarka A, Rigó J, Lázár L, Bekő G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunol. 2010;11:59.
98. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. Am J Reprod Immunol. 1998;40:102–11.
99. Hennessy A, Pilmore H, Simmons L, Painter D. A deficiency of placental IL-10 in preeclampsia. J Immunol. 1999;163:3491–5.
100. Makris A, Xu B, Yu B, Thornton C, Hennessy A. Placental deficiency of interleukin-10 (IL-10) in preeclampsia and its relationship to an IL10 promoter polymorphism. Placenta. 2006;27:445–51.
101. Sharma A, Satyam A, Sharma JB. Leptin, IL-10 and inflammatory markers (TNF-α, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. Am J Reprod Immunol. 2007;58:21–30.
102. Borekci B, Aksoy H, Al RA, Demircan B, Kadanali S. Maternal serum interleukin-10, interleukin-2 and interleukin-6 in pre-eclampsia and eclampsia. Am J Reprod Immunol. 2007;58:56–64.
103. Chaouat G, Meliani AA, Martal J, Raghupathy R, Elliott J, Elliot J, et al. IL-10 prevents naturally occurring fetal loss in the CBA x DBA/2 mating combination, and local defect in IL-10 production in this abortion-prone combination is corrected by in vivo injection of IFN-tau. J Immunol. 1995;154:4261–8.
104. Aschkenazi S, Straszewski S, Verwer KM, Foellmer H, Rutherford T, Mor G. Differential regulation and function of the Fas/Fas ligand system in human trophoblast cells. Biol Reprod. 2002;66:1853–61.
105. Orange S, Rasko JE, Thompson JF, Vaughan J, Olive E, Pedler M, et al. Interleukin-10 regulates arterial pressure in early primate pregnancy. Cytokine. 2005;29:176–85.
106. Teran E, Escudero C, Moya W, Flores M, Vallance P, Lopez-Jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with pre-eclampsia. Int J Gynecol Obstet. 2001;75:243–9.
107. Darmochwal-Kolarz D, Leszczynska-Gorzelak B, Rolinski J, Oleszczuk J. T helper 1-and T helper 2-type cytokine imbalance

in pregnant women with pre-eclampsia. Eur J Obstet Gynecol Reprod Biol. 1999;86:165–70.
108. Wilczyński JR, Tchórzewski H, Banasik M, Głowacka E, Wieczorek A, Lewkowicz P, et al. Lymphocyte subset distribution and cytokine secretion in third trimester decidua in normal pregnancy and preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2003;109:8–15.
109. Dhillion P, Wallace K, Herse F, Scott J, Wallukat G, Heath J, et al. IL-17-mediated oxidative stress is an important stimulator of AT1-AA and hypertension during pregnancy. Am J Physiol-Regul Integr Comp Physiol. 2012;303:R353–R8.
110. Toldi G, Rigó J, Stenczer B, Vásárhelyi B, Molvarec A. Increased prevalence of IL-17-producing peripheral blood lymphocytes in pre-eclampsia. Am J Reprod Immunol. 2011;66:223–9.
111. Cornelius DC, Hogg JP, Scott J, Wallace K, Herse F, Moseley J, et al. Administration of interleukin-17 soluble receptor C suppresses TH17 cells, oxidative stress, and hypertension in response to placental ischemia during Pregnancy novelty and significance. Hypertension. 2013;62:1068–73.
112. Wallace K, Richards S, Dhillon P, Weimer A, Edholm E-s, Bengten E, et al. CD4 + T-helper cells stimulated in response to placental ischemia mediate hypertension during pregnancy. Hypertension. 2011;57:949–55.
113. Fiore S, Newell M-L, Trabattoni D, Thorne C, Gray L, Savasi V, et al. Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women. J Reprod Immunol. 2006;70:143–50.
114. Alonso R, Resino S, Bellón J, Muñoz-Fernández M. Antiretroviral treatment induces a shift to type-2 cytokine responses in HIV-1 infected pregnant women. Eur Cytokine Netw. 2000;11:647–53.