



Stress-Sensitive Regulators of Fetal Neurodevelopment in HIV and Preeclampsia: An Immunocytochemical Appraisal of Placental OGT and T4 Levels

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Abstract

Preeclampsia and HIV are a significant burden to maternal health globally, especially in low-middle income countries such as South Africa. In the KwaZulu-Natal province, SA antenatal HIV prevalence is 41.1%, while PE is 12%. PE and HIV infections are maternal stress and inflammation that impact placental function and fetal development. Therefore, this study investigated the impact of the comorbidity of PE and HIV on placental stress and neurodevelopment. Placentae were obtained from four cohorts of pregnant women: normotensive HIV negative, normotensive HIV positive, preeclamptic HIV negative, and preeclamptic HIV positive. The placental tissue sections were immunostained for OGT and T4. Our findings showed that the maternal weight, diastolic, and systolic blood pressures (BP) were higher in PE vs. the normotensive groups, irrespective of HIV status. In addition, significant changes were noticed in the placental weight, fetoplacental ratio, and placental efficiency coefficient. Our findings showed that the maternal weight, diastolic, and systolic blood pressures (BP) were statistically higher in the PE compared to the normotensive. No significant differences were observed between HIV positive and HIV negative groups. In addition, significant changes were noticed in the placental weight, fetoplacental ratio, and placental coefficient. Furthermore, considerable upregulation in the placental expression of OGT in both the conducting and exchange villi of PE and concomitant downregulation in HIV-positive patients compared with Normotensive and HIV-negative individuals, respectively. Our results provide inferential evidence on the dysregulation of OGT in the comorbidity of PE and HIV. This may mediate a compromised programmed outcome of an adverse maternal environment during pregnancy and consequently affect fetal development.

Keywords Preeclampsia · HIV/AIDS · Placenta · OGT · T4

Introduction

During pregnancy, mothers undergo stress and anxiety that affect fetal neurodevelopment, significantly increasing the lifetime risk of neurodevelopmental disorders in the offspring (Bleker et al. 2019). More specifically, dysregulation

of dopamine receptor number and the function of the hypothalamic–pituitary–adrenal (HPA) axis have been reported (Bergman et al. 2007).

Preeclampsia development is a common source of maternal stress, affecting about 4.6% of women worldwide (Yang et al. 2021). Human immunodeficiency virus (HIV) infections/Acquired immune disorder syndrome (AIDS) is a major public health challenge and the leading cause of mortality in sub-Saharan Africa. In South Africa (SA), the leading cause of maternal mortality is HIV infection (34.5%), with hypertension in pregnancy (14.8%) remaining the leading direct cause of death in pregnancy. In the province of KwaZulu-Natal, SA, the antenatal prevalence of HIV infection (41.1%) is unacceptably high; hence, HIV infection comorbid with preeclampsia presents a serious problem to obstetricians (Naidoo 2021). The increased risk of adverse pregnancy outcomes impacts

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infant health. For example, several observational studies found that maternal HIV infection increases the risks of stillbirth, neonatal death, low birth weight, preterm birth, and small for gestational age (Ndirangu et al. 2012; González et al. 2017; Santosa et al. 2019; Arab et al. 2017; Xiao et al. 2015). Moreover, varying degrees of impaired cognitive, language, and motor development occur in children exposed to HIV particularly in low-resource settings, such as SA (Le Doaré, Bland, and Newell 2012; McHenry et al. 2018; Sherr et al. 2014; Stanzi et al. 2018).

Both preeclampsia and HIV infection induces placental stress that reduces placental growth during pregnancy, which impacts the gene expression profiles of offspring. O-linked *N*-acetylglucosamine transferase (OGT) is one of the genes impacted, and, in conditions of maternal stress, offspring show reduced OGT expression in the labyrinth region of the brain. A genome-wide array screen identified OGT as a cellular stress marker crucial for neurodevelopment during pregnancy. The OGT level in mothers exposed to prenatal stress is significantly lower. Furthermore, its expression was affected by gender, being higher in males than female offspring. This extent of expression may corroborate the higher rates of neurodevelopmental disorders in males (Howerton et al. 2013). There are undoubtedly shreds of evidence indicating the pivotal role of O-GlcNAcylation in the brain. O-GlcNAc modification is most common in the brain and is crucial for neuronal survival and neuronal and synaptic function in the mature brain. Most importantly, many studies have demonstrated that genetic or pharmacological manipulation of O-GlcNAcylation remarkably alters neuronal and synaptic functions in the brain. Our understanding of O-GlcNAcylation in the brain and neurodevelopment continues to evolve rapidly; as we advance, new technologies will allow us to dissect the molecular mechanisms by utilizing state of the art O-GlcNAcylation that determine normal neurodevelopment and disease-specific pathology (Lee et al. 2021).

In addition to OGT, the hypothalamus-pituitary-thyroid (HPT) axis is also a stress-sensitive system involved in prenatal neurodevelopment. Thyroid hormones (TH) mediate numerous maturational signals necessary for neonatal survival (Shallie and Naicker 2019). As fetal thyroid hormone production does not commence until mid-gestation, the mother is the primary source of TH to the fetus during early fetal development (Moog et al. 2017). Maternal TH enters and leaves the placenta via a series of transporters. These hormones are metabolized through sulfation, glucuronidation, and deiodination within the placenta. Insufficient maternal TH in early pregnancy is associated with a wide range of largely irreversible cognitive and motor deficits, growth retardation, and speech and hearing defects. Notably, dysregulation of TH receptors and their transporters imply their contribution to the pathogenesis

and pathophysiology of neurodevelopmental defects (Adu-Gyamfi et al. 2020).

Since the placenta is an endocrine tissue that functions as an essential mediator in response to the intrauterine milieu, it may also serve as a biomarker of PE development. Furthermore, maternal stress is a known risk factor for neurodevelopmental disorders, including schizophrenia, and often exhibits a sex bias in presentation rates, age of onset, and symptom severity. This study examines the association of HIV/AIDS and preeclampsia, commodities with fetal-placental parameters, and placental expression/accumulation of OGT and the thyroid hormone T4. It has the potential to identify indicators of stress-induced metabolic and neurodevelopmental disorders associated with the comorbidity of HIV and PE.

Materials and Methods

Study Population

Post-institutional ethical (BCA 338/17) and hospital regulatory permission for this retrospective study, written informed consent was obtained from all participants. HIV-positive and HIV-negative preeclamptic and normotensive pregnant women were recruited from a large regional hospital in eThekweni, South Africa.

Sampling Strategy

In the primary study, purposive sampling was used as per the inclusion and exclusion criteria.

Exclusion Criteria

Women with gestational diabetes, chronic diabetes, chronic renal disease, sickle cell disease, cardiac disease, chronic hypertension, pre-existing seizure disorders, antiphospholipid antibody syndrome, abruption placentae, chorioamnionitis, eclampsia, polycystic ovarian syndrome, thyroid disorder, no antenatal care, unknown HIV status, and those who declined to give informed consent.

Inclusion Criteria

Preeclampsia is defined as a new-onset systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on two occasions at least 4 h apart, presenting after 20 weeks gestation. Preeclampsia is further defined by proteinuria, thrombocytopenia, renal insufficiency, impaired hepatic function, pulmonary edema, or new-onset headache (Wisner 2019).

Sample Size

At delivery, placentae were obtained from 76 pregnant women, divided into preeclamptic (PE) and normotensive (N) cohorts ($n = 38$ each). These cohorts were further sub-stratified by HIV status ($n = 19$) into PE HIV negative (PE-), and PE HIV positive (PE+), normotensive pregnant HIV negative (N-), normotensive HIV positive (N+) groups.

The fetoplacental ratio is defined as the fetal birth weight to placental weight. The typical ratio is 1:7 (Lurie et al. 1999). In comparison, the placental coefficient is defined as the placental weight ratio to fetal weight. It usually is between 0.10 and 0.18 (Jakó et al. 2019).

Methods

Phosphate (10%) buffered formalin-fixed placental tissue were dehydrated and processed for routine immunocytochemistry using conventional techniques before embedding in paraffin wax. 3 μ m of placental tissue was sectioned on a rotary microtome (Leica RM 2135, Germany) and collected on adhesive-coated slides. The sections were deparaffinized and rehydrated in descending ethanol concentration series prior to immunostaining with the Dako Envision Flex detection system kit (K800021; Dako, Denmark). Tissue sections were incubated at 97 °C in preheated target-retrieval solution for 20 min. The slides were immunostained with a rabbit polyclonal 11 β -HSD2 antibody for 20 min. A goat horseradish peroxidase-conjugated secondary antibody was added for 20 min, followed by 3,3'-diaminobenzidine as the chromogen, and counterstained with Mayer's hematoxylin. The primary antibody was replaced with a buffer and a non-immune serum of the same IgG class as the primary to serve as a buffer and negative control.

Morphometric Image Analysis

Placental tissue was viewed, captured, and processed with an Axioscope A1 microscope (Carl Zeiss, 22 Germany). Four fields of view per slide for villi type (*i.e.*, exchange and conducting) were selected at an initial magnification of 20x. Images were analyzed with the 'Fiji' version of ImageJ from the NIH (USA). The OGT immunostaining (brown chromogen) within the villi were quantified. The optical density of OGT was calculated by transforming the intensity numbers obtained via ImageJ to an optical density (OD) with the formula $OD = \log(\text{max intensity}/\text{mean intensity})$, where maximum intensity for 8-bit images = 255.

Statistical Analysis

The data obtained were analyzed using GraphPad Prism, version 7 (California, USA). Descriptive statistics are presented as mean $\pm$ standard deviation. In addition, parametric statistics (T-test and the one-way ANOVA test) was used to determine the difference between and across study groups. Statistical significance was determined at a p-value of <0.05.

Results

Clinical Characteristics and Demographic Data

Table 1 summarizes the demographics of the study population.

Maternal age and diastolic and systolic blood pressures (BPs) were statistically higher in the preeclamptic than the normotensive subjects (age- $p < 0.01$; BP $p < 0.001$). No significant differences were noted for maternal weight and gestational age ($p > 0.05$) between preeclamptic and normotensive women (Table 1).

The mean fetoplacental ratio was 7.12 compared to 6.26, 6.40 compared to 5.80 in the NT- vs NT+ and PE+ groups, respectively. The difference between NT- and NT+ was statistically significant ($p < 0.05$) (Table 2).

Table 1 Demographic and clinical characteristics of the study population

	N-	N +	PE-	PE +
Number (n)	19	19	19	19
Maternal age (years)	19.00 $\pm$ 5.26	29.24 $\pm$ 6.65	28.59 $\pm$ 6.70	30.61 $\pm$ 5.96
Gestational age (weeks)	38.76 $\pm$ 1.64	38.00 $\pm$ 1.90	36.58 $\pm$ 5.50	37.05 $\pm$ 6.00
Maternal Weight(kg)	69.26 $\pm$ 8.83	69.86 $\pm$ 12.06	79.54 $\pm$ 14.93	79.19 $\pm$ 18.22
Systolic BP (mmHg)	112.50 $\pm$ 14.09	107.40 $\pm$ 14.46	158.90 $\pm$ 19.83	158.70 $\pm$ 16.43
Diastolic BP (mmHg)	68.18 $\pm$ 10.62	67.76 $\pm$ 11.27	102.7 $\pm$ 10.35	102.60 $\pm$ 9.20

The values are presented as mean $\pm$ standard deviation; $n = 76$; Blood Pressure (BP) Normotensive HIV negative (N-); Normotensive HIV positive (N+); Preeclamptic HIV negative (PE-); Preeclamptic HIV positive (PE+)

Table 2 Maternal BMI, Foetal/placental ratio, Placental weight, and coefficient

Variables	N– Mean ± SD	N+ Mean ± SD	PE– Mean ± SD	PE+ Mean ± SD	P value
Placental weight (g)	459.4 ± 76.6	494.3 ± 90.2	560.9 ± 81.8	473.6 ± 68.2	P < 0.01**
Fetal Birth Weight (g)	3226 ± 491.0	3182 ± 519.2	2993 ± 479.1	2902 ± 506.2	P > 0.05
Maternal BMI	30.57 ± 5.5	30.02 ± 5.6	31.75 ± 5.8	30.57 ± 5.8	P > 0.05
BW/PW (Foetal-placenta ratio)	7.18 ± 1.4	6.26 ± 1.2	6.40 ± 1.5	5.80 ± 1.0	P < 0.001***
PW/BW (Placental coefficient)	0.15 ± 0.03	0.17 ± 0.04	0.16 ± 0.03	0.18 ± 0.03	P < 0.01**

SD, standard deviation n; g, grams; BW/PW, birth weight/placental weight ratio; PW/ BW, placental weight/birth weight ratio. 1-way ANOVA * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

The mean placental coefficient was normal with no significant differences across groups [0.15 ± 0.03 (N–) vs 0.17 ± 0.04 (N+) vs 0.16 ± 0.03 (PE–) vs 0.18 ± 0.03 (PE+)]. Additionally, the BMI was lower in the HIV+ vs HIV– groups, albeit non-significant (Table 2).

Morphometric Image Analysis of OGT Immunostaining

Immunostaining of OGT revealed distinct stained conducting villi (Fig. 1) and exchange villi (Fig. 2). There was a significant increase in the optical density of OGT immunostaining in the PE groups, irrespective of HIV status, in both the syncytiotrophoblast of stem (conducting) villi ($p < 0.01$) and terminal (exchange) villi ($p < 0.05$) of normotensive individuals when compared with PE patients (Figs. 3a and 4a).

Significant decreases in optical density (used to estimate the intensity or amount of protein expression) of OGT were observed in both exchange ($p > 0.05$) and conducting ($p < 0.001$) villi in HIV-positive compared to HIV-negative Individuals (Figs. 3b and 4b).

Figure 3c and 4c show OD results for syncytiotrophoblast OGT immunostaining across all the groups. Significant differences were observed after One-way ANOVA analyses in the exchange villi [$F(3, 74) = 28.51$, $p < 0.0001$] and in the conducting villi [$F(3, 74) = 17.25$, $p < 0.0001$] among the groups. Significant downregulation in of OGT was observed in the NT+ when compared to the NT– ($p < 0.0001$) and PE+ in the conducting ($p < 0.001$) and exchange villi ($p < 0.01$). OGT signal was significantly lower in the PE– group when compared with the NT– group ($p < 0.05$), whereas it was significantly greater in the PE+ group when compared with the PE– group ($p < 0.0001$).

Fig. 1 Photomicrographs of OGT immunostained placental conducting villi across all the study groups. Preeclamptic HIV positive (PE+); Preeclamptic HIV negative (PE–); normotensive HIV positive (NT+); normotensive HIV negative (NT–); A, arteriole; S, syncytiotrophoblast; Magnification: 400 μ m

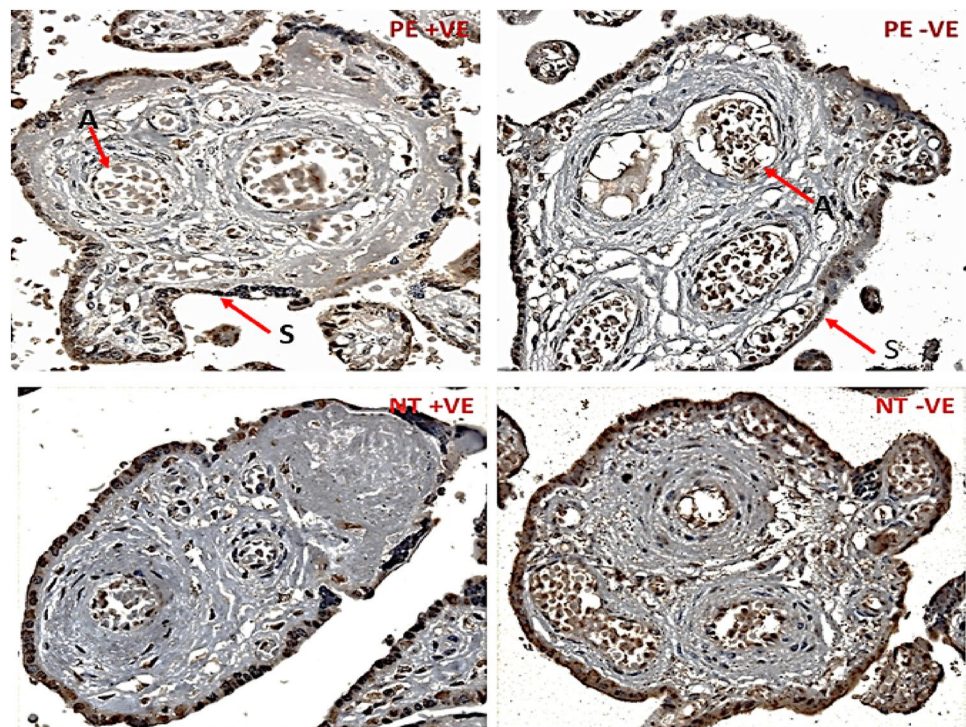


Fig. 2 Photomicrographs of OGT Immunostained placental exchange villi across all the study groups. Preeclamptic HIV positive (PE+); Preeclamptic HIV negative (PE-); normotensive HIV positive (NT+); normotensive HIV negative (NT-); A, arteriole; S, syncytiotrophoblast; Magnification: 400 μ m

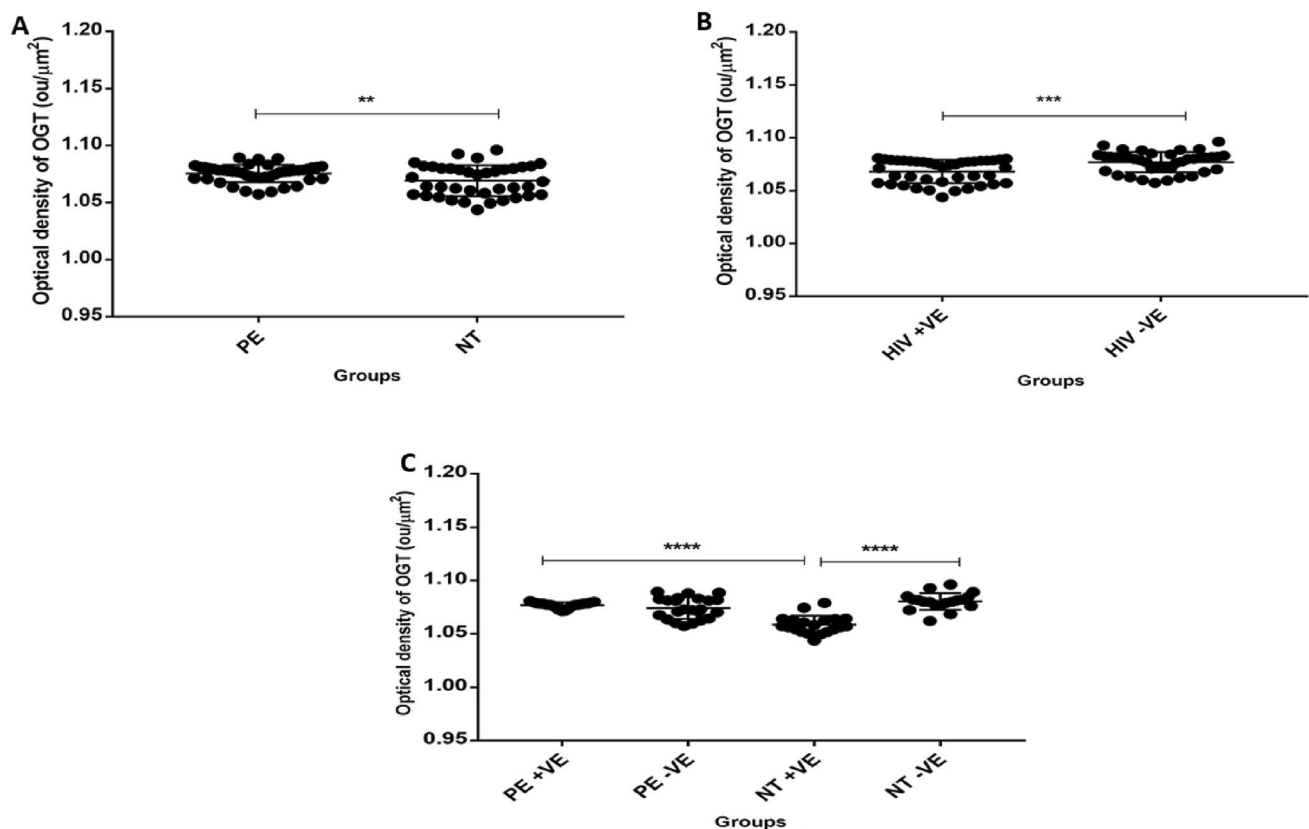
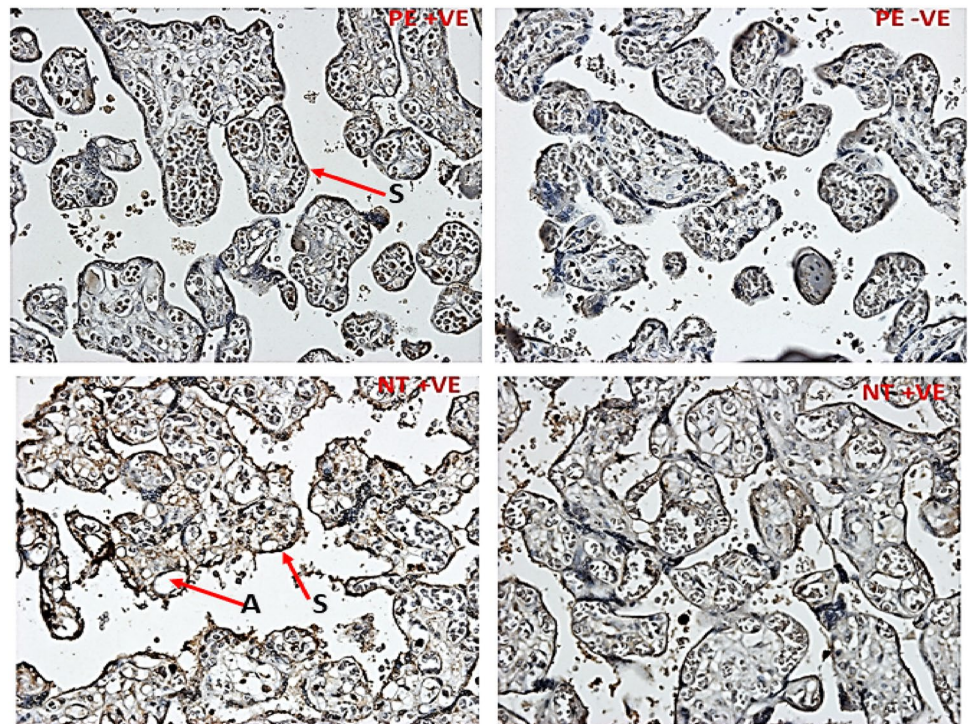


Fig. 3 Image analysis of placental conducting villi immunostained with OGT **A** Normotensive versus Preeclamptic mothers; **B** HIV negative versus HIV positive mothers and **C** Preeclamptic HIV negative (PE -), Preeclamptic HIV positive (PE+), Normotensive HIV

negative (NT -) and Normotensive HIV positive (NT+). Data are presented as mean $\pm$ SD. ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

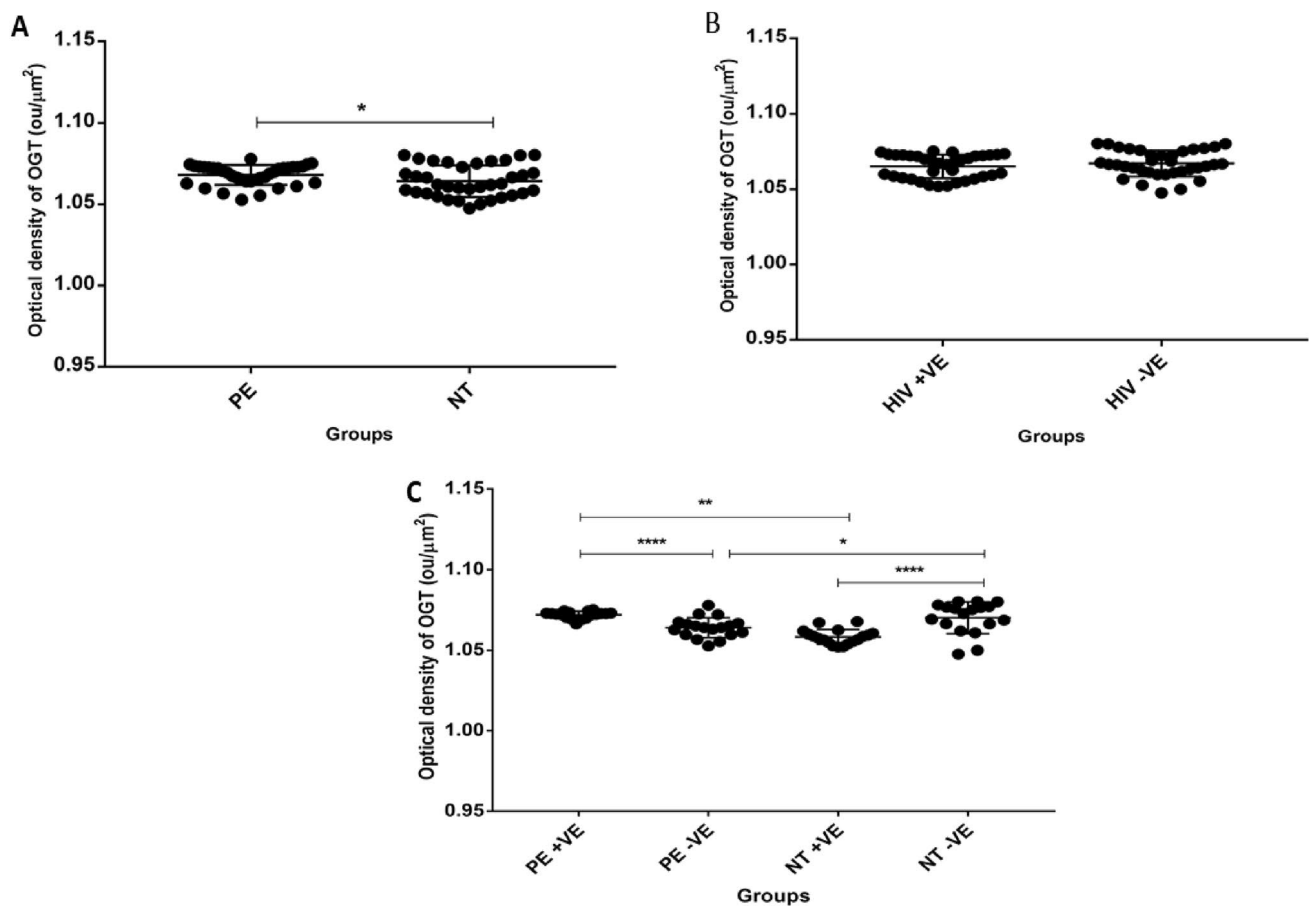


Fig. 4 Image analysis of placental exchange villi immunostained with OGT **A** Normotensive versus Preeclamptic mothers; **B** HIV negative versus HIV positive mothers and **C** Preeclamptic HIV negative (PE

-VE), Preeclamptic HIV positive (PE + VE), Normotensive HIV negative (NT -VE) and Normotensive HIV positive (NT + VE). Data are presented as mean $\pm$ SD. * $p < 0.05$; ** $p < 0.01$; **** $p < 0.0001$

Placental T4 Immunostaining

Immunostaining of T4 revealed distinct stained conducting villi (Fig. 5) and exchange villi (Fig. 6). Immunostaining of placental tissue sections for the thyroid hormone T4 revealed a significant decrease in placental T4 in PE vs. the NT groups, irrespective of HIV status. T4 was significantly reduced within the syncytiotrophoblast of both the stem (conducting) ($p < 0.05$) and terminal (exchange) ($p < 0.0001$) villi of PE compared to normotensive groups (Figs. 7a and 8a). T4 immunoexpression was also downregulated in both conducting (groups (Figs. 7b and 8b).

Based on one-way ANOVA analyses, there were significant differences [$F(3, 74) = 17.49$, $p < 0.05$] in T4 levels in exchange villi and [$F(3, 74) = 18.47$, $p < 0.0001$] in the conducting villi across the groups. Significantly lower levels of T4 immunoexpression were detected in NT + VE versus NT -VE villi ($p < 0.0001$) and in PE -VE versus NT -VE in both the conducting ($p < 0.0001$) and exchange villi ($p < 0.0001$). We also observed significant downregulation

in the expression of T4 and in the conducting ($p < 0.0001$) and exchange ($p < 0.001$) villi, respectively, of the comorbid (PE + VE) patients when compared with villi in the NT -VE group (Figs. 7c and 8c).

Discussion

The placenta serves many functions during pregnancy that are vital to the health and development of the fetus. However, maternal stresses such as infection and disruptions to metabolic homeostasis and immune tolerance may adversely affect placental function (Elliot and Crespi 2006; Croy et al. 2009). Our results demonstrate a significant dysregulation of two stress-sensitive molecules, OGT and T4, with potentially severe implications for the developing fetus.

Although the association between maternal stress and fetal neurodevelopmental disorders is well documented, the factors determining vulnerability to HIV infection and PE are unknown. Our results display a significant

Fig. 5 Photomicrographs of T4 immunostained placental conducting villi across all the study groups. Preeclamptic HIV positive (PE+); Preeclamptic HIV negative (PE-); normotensive HIV positive (NT+); normotensive HIV negative (NT-); A, arteriole; S, syncytiotrophoblast; Magnification: 400 μ m

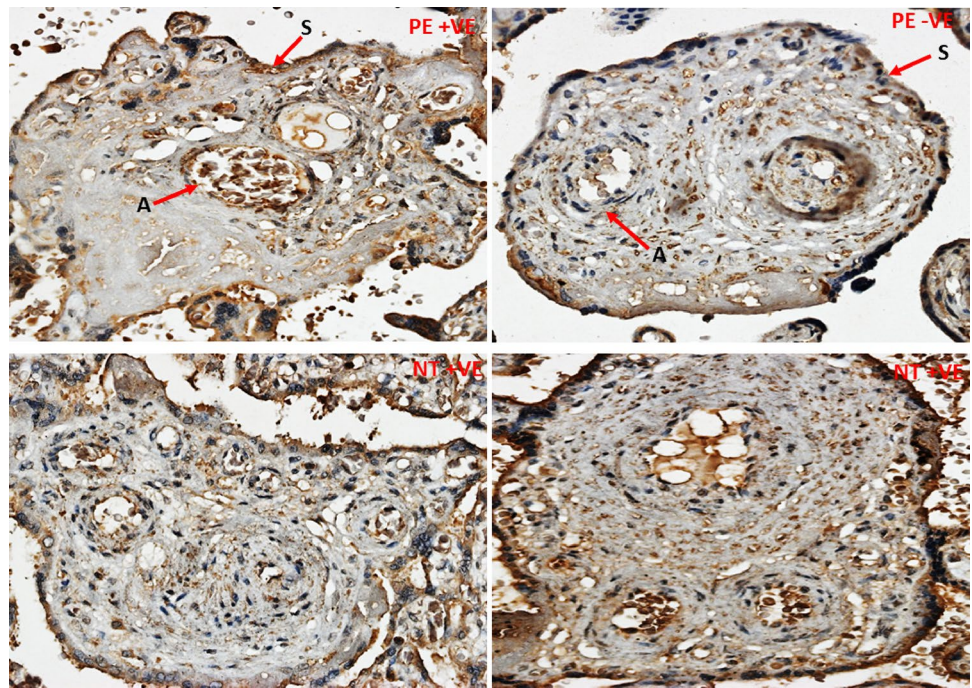
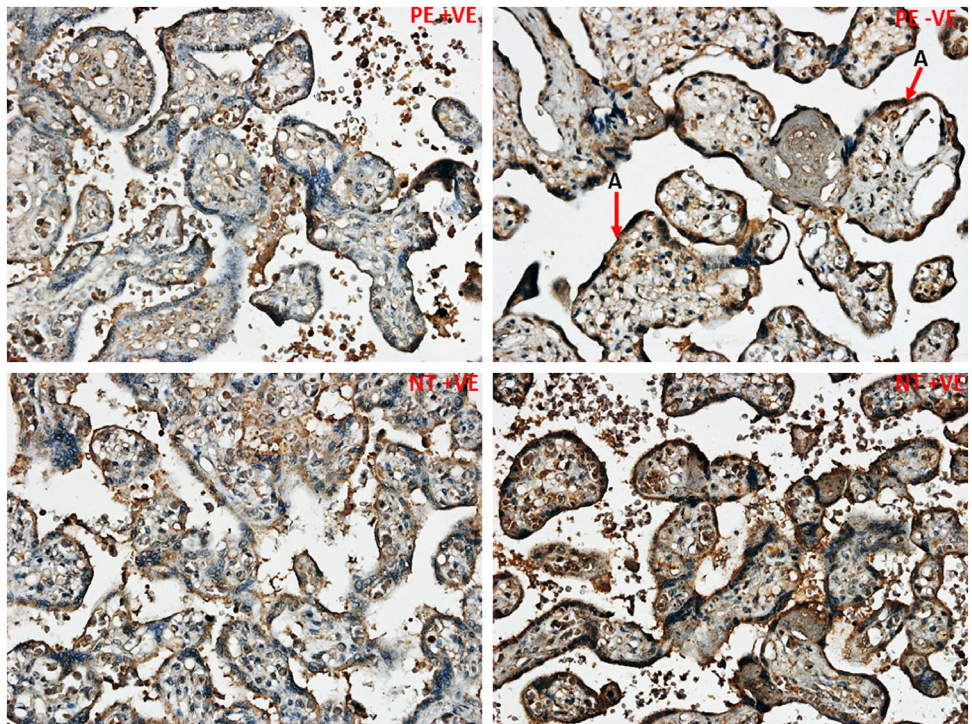


Fig. 6 Photomicrographs of T4 immunostained placental exchange villi across all the study groups. Preeclamptic HIV positive (PE + VE); Preeclamptic HIV negative (PE -VE); normotensive HIV positive (NT + VE); normotensive HIV negative (NT -VE); A, arteriole; S, syncytiotrophoblast; Magnification: 400 μ m



downregulation of placental OGT immunoexpression in HIV infection and PE. Several signaling pathways modulate essential placentation processes whilst specific proteins that regulate placental function target glycosylation with O-linked β -N-acetylglucosamine (O-GlcNAc) or O-GlcNAcylation. This reversible post-translational modification

on nuclear and cytoplasmic proteins is mainly controlled by O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA). O-GlcNAcylation has been implicated as a modulator of proteins in physiological and pathological conditions, and more recently, O-GlcNAc was shown to modulate placental proteins (Lima et al. 2018). Of note, O-GlcNAcylation serves

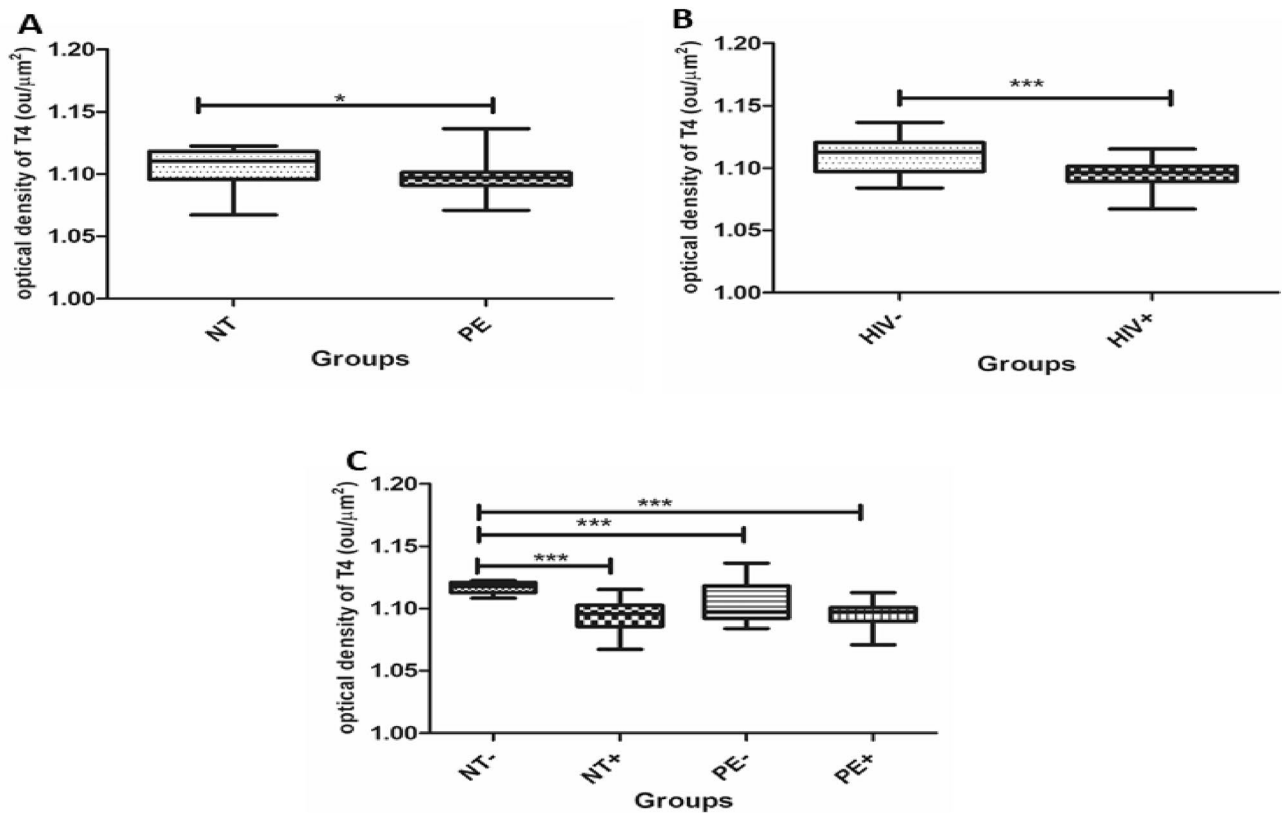


Fig. 7 Image analysis of placental conducting villi immunostained with T4. **A** Normotensive versus Preeclamptic mothers; **B** HIV negative versus HIV positive mothers and **C** Preeclamptic HIV negative

(PE -VE), Preeclamptic HIV positive (PE + VE), Normotensive HIV negative (NT -VE) and Normotensive HIV positive (NT + VE). Data are presented as mean $\pm$ SD. * $p < 0.05$; *** $p < 0.001$

as a critical tool in cell survival in conditions of elevated stress and cellular injury (Martinez et al. 2017). Furthermore, exposure to stress reduces placental growth, leading to maternal and fetal metabolic dysfunction and growth restriction during pregnancy (Lima et al. 2018).

The significant downregulation observed in the placental OGT of HIV patients may be attributed to the direct stress associated with HIV infection and/or to antiretroviral therapy (ARVs). Previous studies have shown mitochondrial DNA depletion, elevated OS levels, and apoptosis in the placenta of HIV-infected women receiving zidovudine-containing ART implicating secondary mitochondrial failure potentiating PE development and adverse perinatal outcomes (Hernández et al. 2017). In addition, chronic oxidative stress also occurs in humans infected with HIV (Shallie and Nai-cker 2019).

The observed downregulation in placental OGT in PE is indicative of oxidative stress. Placentae from women with preeclampsia have reduced antioxidant capacity compared to normal placentas (Wang and Walsh 1996; Walsh 1998). Furthermore, levels of antioxidants in blood from women with preeclampsia are reduced with oxidative modifications of proteins and lipoproteins (Hubel 1999; Rajmakers et al.

2004). Also, the degree to which the implantation and the conversion of the spiral arteries are deficient has been postulated to influence oxidative stress and endoplasmic reticulum (ER) stress. Oxidative stress disturbs the normal redox state of the cell, which causes toxic effects on all cellular components, including proteins, lipids, and DNA, and more severe oxidative stress can result in cell death (Valko et al. 2007). During ER stress, unfolded and misfolded proteins accumulate and activate ER stress-response pathways, also known as the unfolded protein response (UPR) (Yung et al. 2016). Preeclamptic placentas have been shown to accumulate clusters of misfolded proteins, and it is speculated that these aggregates may contribute to the pathophysiology of the disease. However, UPR activation is promiscuous as it can be activated in response to various stimuli. Although transient UPR activation serves a protective function, the chronic nature of cellular stress and stress-response activation in the CNS during HIV infection may overwhelm the buffering capacity of the ER.

Taken together, it appears that OGT expression may change according to the type and intensity of stress, either HIV infection or PE, experienced by the mother and affect offspring in a sexually dimorphic manner. Physiologically,

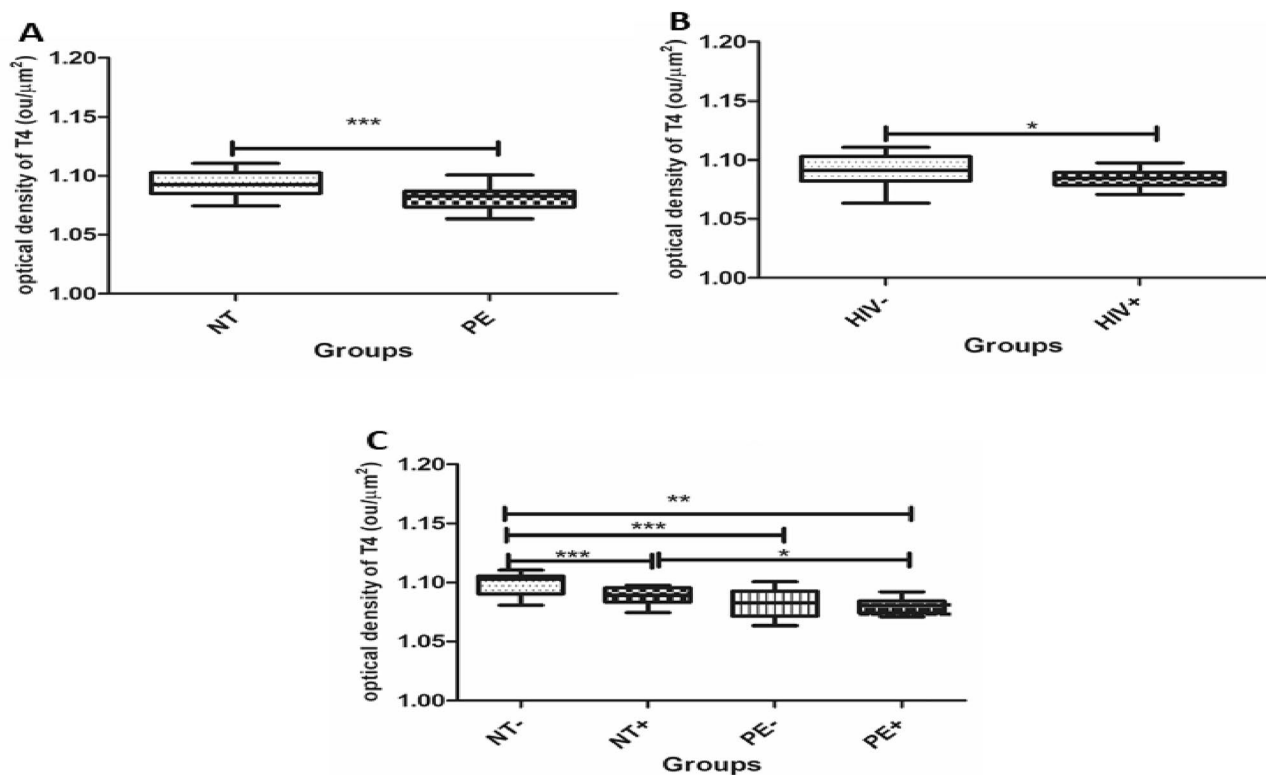


Fig. 8 Image analysis of placental exchange villi immunostained with OGT **A** Normotensive versus Preeclamptic mothers; **B** HIV negative versus HIV positive mothers and **C** Preeclamptic HIV negative (PE

-VE), Preeclamptic HIV positive (PE+VE), Normotensive HIV negative (NT-VE) and Normotensive HIV positive (NT+VE). Data are presented as mean $\pm$ SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

the placentae of stressed individuals have lower basal OGT expression than normal individuals. A previous study reported that early prenatal stress (EPS), a key risk factor for neurodevelopmental disorders, produces a marked reduction in male placental tissue OGT. Although our data do not include fetal sex, we observed consistent downregulation of OGT in placental tissue from women with PE.

The maternal thyroid hormones triiodothyronine (T3) and thyroxine (T4) are essential for the normal growth and development of the fetus. Their bioavailability in utero depends on the development of the fetal hypothalamic–pituitary–thyroid gland axis, the abundance of maternal thyroid hormones, and the transporters and deiodinases that influence tissue levels of the bioactive hormone. In comparison, fetal T4 and T3 concentrations are affected by gestational age, nutritional and endocrine conditions in utero, and placental permeability to maternal thyroid hormones, which vary among placental morphology species (Forhead and Fowden 2014). Normal pregnancy, HIV infection, and preeclampsia have been associated with hypothyroxinemia leading to biochemical hypothyroidism (Sardana, Nanda, and Kharb 2009). In our study, we report a significant dysregulation in the placental accumulation of T4 within the syncytiotrophoblast, which could represent effects on maternal T4 production or

placental uptake from maternal blood. Maternal T4 has also been shown to accumulate in the extracellular matrix.

The increased prevalence of thyroid disease amongst HIV patients compared to the general population is established (Ji et al. 2016), and hypothyroidism have been reported before the existence of HAART, which suggests that factors autonomous of the ARV medication are involved. In addition, opportunistic pathogens induce irreversible destruction of thyroid organs, thereby hindering function (Collazos et al. 2003; Zavascki et al. 2007; Kiertiburanakul et al. 2003; Jinno et al. 2012). Alternatively, drugs used to treat opportunistic infections may be responsible for hypothyroidism in HIV infection; rifampin promotes the reduction of peripheral thyroid hormone via hepatic microsomal enzymes (Sellmeyer and Grunfeld 1996; Etzel et al. 1992).

Conversely, there is no difference in the incidence of hypothyroidism between HAART and HAART naïve patients. The mechanism responsible for developing hypothyroidism and the progressive use of HAART remains unclear and necessitates further investigations (Ibrahim et al. 2019). Nevertheless, the manifestations of thyroid problems include both functional disturbances and pathological changes. Thyroid hormones are essential for many metabolic

activities in the body; their dysregulation can decrease the standard of life of HIV patients (Collazos et al. 2003).

In our study, TH levels correlated with the severity and outcome of preeclampsia. Thyroid hormones regulate neurodevelopment, probably from early fetal life onwards, and may be responsible for preterm birth in preeclampsia.

Thyroid hormones are intricately involved in the developing fetal brain REF. The fetal central nervous system is sensitive to the maternal thyroid status. Therefore, critical amounts of maternal T3 and T4 must be transported across the placenta to the fetus to ensure the proper development of the brain throughout ontogeny. Severe mental retardation can occur due to compromised iodine intake or thyroid disease (Pemberton et al. 2005).

TH deficiency, especially during the early critical embryonic stages of development, impacts not only the brain's molecular and functional pathways of the brain but also on the morphology of brain regions such as the cerebral cortex, hippocampus, and cerebellum (Gould et al. 1991; El-Bakry et al. 2010; Shallie and Naicker 2019). Additional abnormalities observed and attributed to maternal hypothyroidism include limited growth of axons and dendrites, decreased and abnormal neuronal connectivity, myelin deficits, and reduction in synaptic densities (Opazo et al. 2008). In contrast, hyperthyroidism accelerates neurodevelopmental procedures, leading to premature proliferation and cell differentiation. This establishes a shorter cell cycle duration reflected in decreased brain tissue and body weight, degeneration in brain matter, and premature termination of cerebellar processes (Shallie and Naicker 2019).

Identifying thyroid hormones and thyroid screening during pregnancy may alleviate the occurrence and serve as a timely intervention and appropriate measures for possible thyroid hormone administration in preterm infants. Although additional studies are needed to define how placental OGT impacts the epigenomic landscape responsible for healthy-*in-utero* development, the stress induced by HIV and PE leads to altered placental gene expression.

Conclusions

The comorbidity of HIV and PE resulted in significant downregulation in the placental levels of OGT and T4, which underscore the severity of stress associated with these two conditions in pregnancy. The outcomes validate the significance of the placenta as an active mediator between the maternal milieu and fetal development and demonstrate that sex differences in placental genetic and epigenetic patterning are critical in this process. Furthermore, our findings provide inferential evidence that trans-placental signals are involved in fetal programming. Therefore, utilizing the trans-placental signals to determine neurodevelopmental vulnerability

will bring us closer to understanding how neurodevelopmental diseases arise. Large-scale multicentric studies are required to determine the association and mechanism of thyroid abnormality in preeclamptic women by examining sexual dimorphism, focusing on gene expression and RNA sequencing.

Author contributions PDS, TN and NRN conceived and designed the study. PDS processed the samples. All authors participated in the data analysis and manuscript preparation. All authors read the final version of the manuscript.

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Data availability All data generated or analysed during this study are included in this published article.

Declarations

Conflicts of interest The authors declare no competing financial interests. The Department of Health and the institutional Biomedical Research Ethics Committee (Reference Number: BE 183/17) granted permission for this study. The study was conducted per the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Kwazulu-Natal, South Africa, and the University of Missouri Kansas City.

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