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The serum level of haem oxygenase-1 enzyme in pre-eclampsia and normal pregnancy: A comparative study

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Abstract

Haem oxygenase-1 (HO-1) contributes to the antioxidant capacity of several organ systems and this is important in pre-eclampsia where anti-angiogenic factors, systemic inflammation and oxidative stress predominate. This study aimed to determine the serum levels of HO-1 in pre-eclampsia and normotensive pregnant women and investigate the relationship between it and severity of pre-eclampsia. This was an analytical cross-sectional study that involved 240 consenting pregnant women over a period of 8 months. Of these, 120 women who were diagnosed with pre-eclampsia from a viable gestational age of 28weeks were consecutively recruited as cases; while 120 normotensive pregnant women matched with age and gestational age were recruited as controls. Their serum HO-1 levels were assayed by the double-sandwich antibody Enzyme Linked Immunosorbent Assay. Values were compared between the two groups and correlated to the severity of pre-eclampsia. There was no significant difference in the median levels of HO-1 in pre-eclampsia [3.23 (3.0 – 3.5) ng/ml] and normotensive pregnancies [2.88 (2.2 – 3.3) ng/ml], $p>0.05$. Median levels of HO-1was however significantly higher in severe pre-eclampsia [4.43 (4.0 – 4.6) ng/ml] compared to mild pre-eclampsia [2.80 (2.3 – 3.2) ng/ml] and normotensive pregnant controls ($p<0.05$). Serum HO-1 levels showed a positive correlation with mean arterial blood pressure in severe

pre-eclampsia. It was concluded that women with severe pre-eclampsia had higher levels of serum HO-1anda positive correlation with disease severity.

Keywords: Haem oxygenase 1, pre-eclampsia, oxidative stress

Introduction

Pre-eclampsia remains a major cause of perinatal and maternal morbidity and mortality. It is rapidly progressive, multi-systemic and characterized by widespread endothelial damage with a clinical presentation of hypertension[1,2] and one or more of the following: proteinuria, maternal organ dysfunction (including renal, hepatic, hematological, or neurological complications), or foetal growth restriction, after 20 weeks gestation.[3] it is a major cause of preterm delivery with its attendant complications.[1,4] pre-eclampsia is mild in 75% of cases and severe in 25% of them.[5]it could be early onset- occurring before 34weeks gestational age, late onset if it occurs after 34weeks or postpartum.[3,6] globally, the incidence rate of pre-eclampsia stands at 3 - 10%, and maybe as high as 10 – 18% in developing countries including nigeria.[7] the prevalence in an institution based study of lagos stands at 7.6%.[8] it accounts for the death of 76,000 women and 500,000 babies per year.[9] The aetiology of this pregnancy specific disease and the mechanisms responsible for its pathogenesis have not been fully understood, making prevention and cure an ongoing challenge.[10,11]central to its pathogenesis is placental ischemia/hypoxia which is thought to lead to widespread activation of the maternal vascular endothelium, resulting in enhanced formation of endothelin and superoxide, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide and carbon monoxide.[1,12,13]

Recent studies are exploring the role of haem oxygenase enzyme (HO-1), an anti-inflammatory enzyme system, in combating the oxidative stress, vasoactive and angiostatic substances that may be responsible for the pathology seen in pre-eclampsia. It is suggested that its levels may be altered in the disease entity.[1,11,13,14,15]The haem oxygenase system is now known to be an important stress response pathway. Its metabolites carbon monoxide (CO) and bilirubin are known to exert protective functions on the vascular endothelium. CO is a potent vasodilator while bilirubin is an antimetabolite; both of which may have a local vasodilatory and protective effect in the foeto-placental vasculature.[16]

Most of the studies done on HO-1 have been on placental explants. This study however, was conducted on human sera because the HO-1 enzyme activities against angiostatic molecules are not limited to the placentae. The study aimed to determine the serum level of HO-1 in pregnancies complicated by pre-eclampsia and it is hoped that the findings may contribute to the understanding and management of the disease.

Methodology

This study was conducted in the department of obstetrics and gynecology of the lagos state university teaching hospital (lasuth), ikeja, lagos between January and august 2021. It was a cross-sectional study involving women with pre-eclampsia as study group and healthy normotensive pregnant women as controls. Ethical approval was obtained from our institution's ethics and research committee. We determined the sample size by using the formula for single proportion with prevalence rate of 7.6%[8] each, amounting to 120 per group including 10% attrition. All consecutive pregnant women who were diagnosed with preeclampsia (study) using the revised international society for the study of

hypertension (isshp) criteria[3] together with normotensive (controls) who presented at the antenatal clinics and emergency room of the hospital and fulfilled the inclusion criteria were recruited after due counselling, and informed consent was taken to participate in this study.

Pre-eclampsia was defined as an elevated blood pressure of 140/90mmhg and above, developing after 20-week gestation with one or more of the following: proteinuria (the presence of 0.3g or more of protein in a 24-hour urine collection; usually corresponds with 1+ or greater on a urine dipstick test), maternal organ dysfunction (including renal, hepatic, hematological, or neurological complications) or foetal growth restriction.[3]pre-eclampsia is severe when systolic blood pressure is 160mmhg and above, or diastolic blood pressure of 110mmhg and above or both combined; or a mean arterial blood pressure [calculated as systolic bp + (diastolic bp ×2)/3] of 110mmhg and above.[17] the presence of maternal organ dysfunction, foetal growth restriction and foetal death were also considered as markers of severity.[17]

All participants were recruited at diagnosis from a viable gestational age of 28 weeks and the control which consisted of normotensive pregnant women were matched at the time of recruitment with maternal and gestational age.

Those excluded from this study included pregnant women with any of the following conditions: chronic hypertension, chronic renal disease, eclampsia, diabetes mellitus, multiple pregnancy, sickle cell disease, human immunodeficiency virus infection (hiv) or acquired immune deficiency syndrome (aids), infections, patient on antiplatelet agents like aspirin and those on calcium supplements, patients in labor, patients who smoke cigarette and those who declined participation.

Relevant information was obtained from each patient into a structured proforma. Blood pressure was measured with appropriate cuff-size automated sphygmomanometer with participants in sitting position. About 5 ml of venous blood sample was obtained from the antecubital vein of all participants via routine aseptic phlebotomy into plain vacutainer specimen bottle. Samples were processed to obtain the supernatant serum into numbered cryovials and kept at -20^{o}c till batch analysis. Serum haem oxygenase-1 (ho-1) determination was done by quantitative double-sandwich antibody enzyme linked immunosorbent assay (elisa) technique with the commercially manufactured kit by my BioSource laboratories inc, san diego, ca 92195-3308, USA. The average value of ho-1 in pregnancy is 3.04ng/ml (2.41 – 4.39).[18]sensitivity of the kit: minimum detectable ho-1 up to 0.06ng/ml. Detection range: 0.312ng/ml – 20ng/ml specificity: no significant cross-reactivity or interference between human ho-1 and analogues. The data were analyzed using statistical package for social sciences version 26 (spss ibm chicago). Descriptive statistics, tables, charts and graphs were used for data presentation. Numeric data which are normally distributed such as gestational age and birth weight were summarized using the mean and standard deviation, while data that are not normally distributed such as haem oxygenase-1 was presented using median and interquartile range. Continuous variables between the two groups were compared using the independent student t test when normally distributed while mann-whitney u test was used for comparison when skewed. Kruskal wallis was used in comparing median haem oxygenase-1 in more than two groups.

Categorical variables were compared using the chi square test. Linear correlation between numeric variables was carried out using spearman correlation. The level of statistical significance was set atp < 0.05.

Results

The socio-demographic characteristics of participants were similar in both groups as shown in table 1.the mean age was 30.38±4.5 years and 29.86±4.4 years in cases and control respectively (p=0.363). Majority (92.5%) of them were married. The difference in the booking status of the participants was significant with p<0.001. Nulliparous women constituted a larger proportion 110(45.8%) of the women studied but the difference in parity between the groups was not significant (p=0.280). tables 3 and 4 showed the comparison of median ho-1 levels among the groups. There was no significant difference in the median levels of ho-1 in all pre-eclampsia [3.23 (3.0 – 3.5) ng/ml] and normotensive pregnancies [2.88 (2.2 – 3.3) ng/ml], p>0.05. Median levels of ho-1was however significantly higher in severe pre-eclampsia [4.43 (4.0 – 4.6) ng/ml] compared to mild pre-eclampsia [2.80 (2.3 – 3.2) ng/ml] p<0.05. There was a positive correlation between serum ho-1 levels and mean arterial blood pressure in severe pre-eclampsia as depicted in fig.1. Fig 2 however showed a negative correlation between serum ho-1 levels and gestational age at delivery. Birth weight and apgar scores at 1 and 5 minutes were significantly lower in participants with severe pre-eclampsia compared to mild form (p<0.001) as shown in table 5. Participants with pre-eclampsia have significantly higher proportion 9(7.5%) of maternal complications compared to control (p<0.001), the commonest complication in pre-eclamptic patients being help syndrome.

Table 1: Sociodemographic characteristics of participants

	Pre-eclampsia (n=120)	Normal pregnancy (n=120)	Total	X^2	p-value
Age group (Years)					
21-25	21(17.5)	21(17.5)	42(17.5)	0.000	1.000
26-30	47(39.2)	47(39.2)	94(39.2)		
31-35	33(27.5)	33(27.5)	66(27.5)		
≥36	19(15.8)	19(15.8)	38(15.8)		
Mean ± SD	30.38±4.5	29.86±4.4		0.911**	0.363
Marital status					
Married	109(90.8)	113(94.2)	222(92.5)	0.961	0.327
Single	11(9.2)	7(5.8)	18(7.5)		
Parity					
Nulliparous	61(50.8)	49(40.8)	110(45.8)	2.546	0.280
Primiparous	40(33.3)	46(38.3)	86(35.8)		
Multiparous	19(15.8)	2(20.8)	44(18.3)		

**Independent student t test

Table 2: Pre-eclampsia characteristics among participants

Variable	Frequency (=120)	Percentage
Severity of pre-eclampsia		
Mild	57	47.5
Severe	63	52.5
Gestational age at diagnosis of pre-eclampsia		
Early gestational age (<34)	36	30.0
Late gestational age (≥34)	84	70.0

Table 3: Median comparison of Haem oxygenase 1 in all pre-eclampsia vs normotensive pregnancy

	Median (Q1-Q3)	U-value	p-value
Group			
Pre-eclampsia	3.23 (3.0-3.5)	1.930	0.053
Normal pregnancy	2.80 (2.2-3.3)		

U-Mann-Whitney U-value

Table 4: Median comparison of Haem oxygenase-1 in all the groups

	Median (Q1-Q3)	K-value	p-value
Group			
Normal pregnancy	2.88 (2.2-3.3)		
Mild Pre-eclampsia	2.80 (2.3-3.2)	10.381	0.035
Severe Pre-eclampsia	4.43 (4.0-4.6)		

K-Kruskal Wallis test

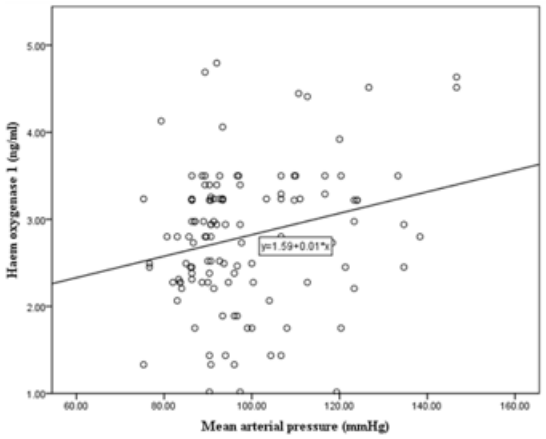
Table 5: Foetal outcomes according to severity of Pre-eclampsia

	Mild (n=57)	Severe (n=63)	t-value	p-value
Gestational age at delivery	36.35±1.2	35.25±2.6	2.576	**0.011**
APGAR score at 1 minutes	7.43±1.6	5.36±1.2	2.049	**0.037***
APGAR score at 5 minutes	8.40±1.2	6.73±2.1	4.433	**0.008***
Birth weight at delivery (Kg)	2.59±0.6	2.06±0.8	3.013	**0.003***

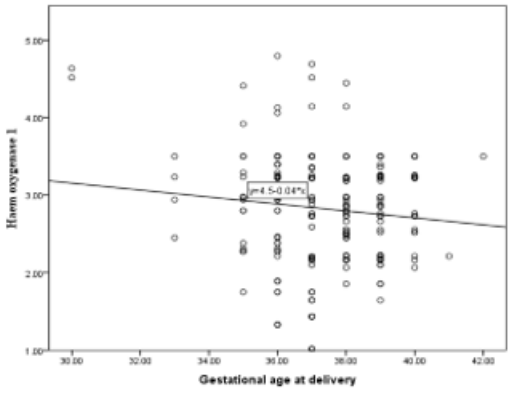
*p value significant

Table 6: Maternal complication among participants

	Pre-eclampsia (n=120)	Normal pregnancy (n=120)	Total	X^2	p-value
Maternal complication					
Present	9(7.5)	2(1.7)	11(4.6)	4.669	**0.031***
Absent	111(92.5)	118(98.3)	229(95.4)		
Type of maternal complication	n=9	n=2			
HELLP	4	0	4	2.394	0.031
AKI	3	0	3	1.954	0.058
Eclampsia	1	0	1	0.542	0.495
DIC	1	0	1	0.542	0.495
Pulmonary Edema	1	0	1	0.542	0.495
Post-partum haemorrhage	0	2	2	0.954	0.091



Spearman Correlation coefficient=0.454, p=0.029***Fig 1: Correlation between haem oxygenase-1 and severity of pre-eclampsia by Mean Arterial Pressure (MAP)**



Spearman Correlation coefficient= -0.198, p=0.030***Fig 2: Correlation between gestational age at delivery and haem oxygenase 1**

Discussion

This study did not show any significant difference with respect to the socio-demographic characteristics of the patients with pre-eclampsia and controls. The percentage of pregnant women diagnosed with pre-eclampsia who did not receive routine antenatal care was significantly more than their normotensive counterparts. This observation was similar to that documented by other authors in studies assessing the risk factors for pre-eclampsia.[7,8,5,19,20]

The median serum level of ho-1 in this study was within the reference range documented for normal pregnancy [3.04ng/ml (2.41-4.39)][18] in both cases and controls. It was observed that there was no significant difference in the serum level of ho-1 in mild pre-eclampsia [2.80ng/ml (2.3 – 3.2)] and normotensive controls [2.88ng/ml (2.2 – 3.3)]. This finding agrees with that reported by sand rim et.al. That ho-1 expression though increased in pregnancy compared to the non-pregnant, remains within normal range throughout the period of pregnancy.[21,22] the increase of ho-1 from the non-pregnant state(1.69ng/ml)[23] was thought to be due to its induction by the oxidative stress that accompanies the process of the pregnancy and immunology of placentation.[16,24] the absence of a recognized difference may be because the mechanism that leads to the release of the vasoactive substance and reactive oxygen species implicated in the pathogenesis of pre-eclampsia may not have developed in mild cases.[11,25] this may also explain why the foeto-maternal outcome in mild pre-eclampsia is similar to that of normotensive controls. The finding in this study however, differed from that documented by some other authors who found a reduction in ho-1 levels especially in severe pre-eclampsia. The difference may result from the difference in tissue/samples

analysed.[1,10,26, 27,28,29]

Although the median serum levels of ho-1 were comparable between normotensive and those with mild pre-eclampsia in this study, levels in those with severe pre-eclampsia was significantly higher [4.43ng/ml (4.0 – 4.6)].this was similar to the findings by eide et al who documented an increase in ho-1 level in both the decidual and serum of patients with severe pre-eclampsia but normal values in mild pre-eclampsia and normotensives.[30]from figure 1, the levels of serum ho-1 were higher in mothers whose babies were delivered earlier than 34weeks compared to later and the difference was significant at p value = 0.030. Similar observation was documented by wantania et. Al in bali where higher levels of serum ho-1 were observed with delivery at gestation age<34weeks compared with >34weeks.wantania et al also found elevated serum ho-1 levels in cases with severe pre-eclampsia compared to those with mild pre-eclampsia and healthy pregnant women as documented in our current study. Pre-eclampsia is associated with increased oxidative stress which is not localized to the placenta but disseminated in the maternal circulation, and it is a component of the systemic inflammatory response.[31] the mechanism is such that enzyme ho-1 is rapidly up-regulated by oxidative stress and induction of ho-1 may protect cells by catalyzing pro-oxidant metalloporphyrin's, such as haem, to bile pigments (biliverdin, bilirubin) with free radical scavenging capabilities and anti-oxidant properties.[18,32]vitoratos et al in a hospital based study in greece also observed that severe pre-eclampsia group had significantly higher serum ho-1 levels antepartum compared to the mild pre-eclampsia and normotensive groups (5.50±1.54 vs. 3.04±0.72 ng/ml, p=0.0003, and 5.50±1.54 vs. 3.12±1.57 ng/ml, p=0.002, respectively). They also reported that there was a rapid reduction in serum ho-1 postpartum to normal levels in normal pregnancy compared to the pre-eclamptics.[32] this suggests that chronic oxidative stress may be involved in the pathogenesis of severe pre-eclampsia and subsequent endothelial dysfunction observed later in those affected by it.[13]

A positive correlation between severity of pre-eclampsia by mean arterial pressure (map) and serum level of ho-1 was observed in this study. This is in agreement with a similar study by vitoratos and colleagues. They observed that ho-1 was positively correlated with mean arterial pressure in pre-eclampsia.[32] granger and George in their systematic review of several articles on ho-1 studies acknowledged that serum ho-1 rises with increasing mean arterial pressure in severe pre-eclampsia.[13,15] eide et al. Also found a similar parallel correlation between serum ho1 levels and mean blood pressure in pre-eclampsia cases.[30] although in our study, levels of serum ho-1 correlated positively with mean blood pressure among cases of severe pre-eclampsia, we failed to demonstrate such a significant correlation in mild pre-eclampsia and control groups. Venditte et al found a negative correlation in their own study.[27]

Additionally, it was observed in this study that higher levels of ho-1 were associated with earlier gestational age in patients with pre-eclampsia. This negative correlation shows the possibilities of overwhelming oxidative stress in severe pre-eclampsia leading to decision to deliver the baby early since the pathology may progress and ultimately lead to foeto-maternal complications. In general, foeto-maternal outcome vis-à-vis mode of delivery, apgar scores, birth weight, nicu admission and perinatal death were better in controls than cases.

Conclusion

This study showed that there was no significant statistical difference in the serum levels of ho-1 enzyme in all who hadpre-eclampsia and normotensive pregnancies, it however demonstrated higher serum levels of haem oxygenase-1 enzyme in severe pre-eclampsia compared to mild pre-eclampsia and normotensive pregnancies. It also showed a positive correlation between ho-1 levels and severity of pre-eclampsia.

Limitation of this study

Measurements of ho-1 levels were performed only once during pregnancy. Repeated measurements on weekly or monthly basis in a cohort study, preferably starting before pre-eclampsia develops may allow a better assessment of the temporal changes and may explain the interaction further. Secondly, the exclusion of pre-eclamptic within the gestational ages 20 to 27 weeks might have affected the outcome and conclusion.

Recommendation

This was a cross-sectional study that identified serum ho-1 as a possible marker of severity for pre-eclampsia. Its serial measurement may be employed in monitoring patients especially when they present as mild disease, thereby giving a clue to when they become severe as ho-1 levels increase and preparation made for delivery. This may help achieve a modest increase in gestational age. Further clinical studies with larger number of patients and serial measurements during the course of the gestation are necessary to evaluate the exact role of ho-1 in both healthy pregnancies and those complicated by pre-eclampsia.

References

1. Ahmed AS, Cudmore MJ. Can the biology of VEGF and haem oxygenases help solve pre-eclampsia? Biochem Soc Trans. 2009;37(6):1237–42.
2. Rundra P, Basak S, Patil D, Latoo MY. Recent Advances In Management Of Pre-Eclampsia. Br J Med Pract. 2011;4(3):433–5.
3. Duhig K, Vandermolen B, Shennan A. Recent advances in the diagnosis and management of pre-eclampsia. F1000Research. 2019;8(242):1–8.
4. Jason JS, Waugh S, Marie C S. Dewhurst's textbook of obstetrics and gynaecology. 9th ed. Edmonds DK, editor. Hypertensive Disorders. New Jersey: Wiley-Blackwell; 2018. 73–82 p.
5. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. Am J Obstet Gynecol. 2004;190(6):1520–6.
6. American College of Obstetricians and Gynecologists. Preeclampsia and High Blood Pressure During Pregnancy. Pregnancy patient resources. 2003.
7. Osungbade KO, Ige OK. Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. J Pregnancy. 2011;2011(11):481–95.
8. Anorlu RI, Iwuala NC, Odum CU. Risk factors for pre-eclampsia in Lagos, Nigeria. Aust New Zeal J Obstet Gynaecol. 2005;45(4):278–82.
9. FIGO releases new Guidelines to combat pre-eclampsia [Internet]. FIGO Newsletter. 2019. p. 1–3. Available from: https://www.figo.org/preeclampsia-guidelines
10. Phipps E, Prasanna D, Brima W, Jim B.

Preeclampsia: Updates in pathogenesis, definitions, and guidelines. Clin J Am Soc Nephrol. 2016;11(6):1102–13.

11. Palei AC, Spradley FT, Warrington JP, George EM, Granger JP. Pathophysiology of Hypertension in Preeclampsia: A lesson in Intergrative physiology. Acta Physiol. 2013;208(3):224–33.
12. Linzke N, Schumacher A, Woidacki K, Croy BA, Zenclussen AC. Carbon monoxide promotes proliferation of uterine natural killer cells and remodeling of spiral arteries in pregnant hypertensive heme oxygenase-1 mutant mice. Hypertension. 2014;63(3):580–8.
13. George EM, Granger JP. Heme oxygenase in pregnancy and preeclampsia. Curr Opin Nephrol Hypertens. 2013;22(2):1–12.
14. Cudmore M, Ahmad S, Al-Ani B, Fujisawa T, Coxall H, Chudasama K, et al. Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. Circulation. 2007;115(13):1789–97.
15. George EM, Warrington JP, Spradley FT, Palei AC, Granger JP. The heme oxygenases: Important regulators of pregnancy and preeclampsia. Am J Physiol - Regul Integr Comp Physiol. 2014;307(7):769–77.
16. Schumacher A, Zenclussen AC. Effects of heme oxygenase-1 on innate and adaptive immune responses promoting pregnancy success and allograft tolerance. Front Pharmacol. 2015;5(1):1–10.
17. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertens. 2013;3(1):44–7.
18. Wantania JJ, Homenta C, Kepel BJ. Relationship of Heme Oxygenase-1 (HO-1) Level with Onset and Severity in Normotensive Pregnancy and Severe Preeclampsia. Bali Med J. 2016;5(1):118.
19. Ekele BA, Bello SO, Adamu AN. Clusters of eclampsia in a Nigerian teaching hospital. Int J Gynecol Obstet. 2007;96(1):62–6.
20. Rabiu KA, Adewunmi AA, Ottun TA, Akinlusi FM, Adebanjo AA, Alausa TG. Risk factors for maternal mortality associated with eclampsia presenting at a nigerian tertiary hospital. Int J Womens Health. 2018;10:715–21.
21. Sandrim VC, Caldeira-Dias M, Bettiol H, Barbieri MA, Cardoso VC, Cavalli RC. Circulating heme oxygenase-1: Not a predictor of preeclampsia but highly expressed in pregnant women who subsequently develop severe preeclampsia. Oxid Med Cell Longev. 2018;2018(1):10–4.
22. Tong S, Kaitu'u-Lino TJ, Onda K, Beard S, Hastie R, Binder NK, et al. Heme oxygenase-1 is not decreased in preeclamptic placenta and does not negatively regulate placental soluble fms-like tyrosine kinase-1 or soluble endoglin secretion. Hypertension. 2015;66(5):1073–81.
23. Mateo I, Infante J, Sanchez-Juan P, I G-G, Combarros O. Serum heme oxygenase-1 levels are increased in Parkinsons disease but not in Alzheimers disease. Acta Neurol Scand. 2010;121(3):136–8.
24. Zenclussen ML, Linzke N, Schumacher A, Fest S, Meyer N, Casalis PA, et al. Heme oxygenase-1

is critically involved in placentation , spiral artery remodeling , and blood pressure regulation during murine pregnancy. Front Pharmacol. 2015;5(1):1–10.

25. Wong RJ, Zhao H, Stevenson DK. A deficiency in haem oxygenase-1 induces foetal growth restriction by placental vasculature defects. Acta Paediatr Int J Paediatr. 2012;101(8):827–34.
26. Zenclussen AC, Lim E, Knoeller S, Knackstedt M, Hertwig K, Hagen E, et al. Heme oxygenases in pregnancy II: HO-2 is downregulated in human pathologic pregnancies. Am J Reprod Immunol. 2003;50(1):66–76.
27. Venditti CC, Smith GN. Involvement of the heme oxygenase system in the development of preeclampsia and as a possible therapeutic target. Women's Heal. 2014;10(6):623–43.
28. Ahmed A, Rahman M, Zhang X, Acevedo CH, Nijjar S, Rushton I, et al. Induction of placental heme oxygenase-1 is protective against TNFalpha-induced cytotoxicity and promotes vessel relaxation. Mol Med. 2000;6(5):391–409.
29. George EM, Cockrell K, Aranay M, Csongradi E, Stec DE, Granger JP. Induction of heme oxygenase 1 attenuates placental ischemia-induced hypertension. Hypertension. 2011;57(5):941–8.
30. Eide IP, Isaksen C V., Salvesen KÅ, Langaas M, Schønberg SA, Austgulen R. Decidual expression and maternal serum levels of heme oxygenase 1 are increased in pre-eclampsia. Acta Obstet Gynecol Scand. 2008;87(3):272–9.
31. Barber A, Robson S, Myatt L, Bulmer J, Lyall F. Heme oxygenase expression in human placenta and placental bed: reduced expression of placenta endothelial HO-2 in preeclampsia and fetal growth restriction. FASEB J. 2001;15(7):1158–68.
32. Stocker R, Yamamoto Y, Mcdonagh AF, Glazer AN, Ames BN. Bilirubin Is an Antioxidant of Possible Physiological Importance. Sci. 1984;2(1):4–7.