EVALUATION OF RETINAL NERVE FIBRE LAYER AND MACULAR THICKNESS IN PATIENTS WITH HYPERTENSIVE DISORDER IN PREGNANCY

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

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TABLE OF CONTENTS

CHAPTER 2: STUDY OBJECTIVES AND HYPOTHESIS

CHAPTER 3: MANUSCRIPT

CHAPTER 4: STUDY PROTOCOL

CHAPTER 5: APPENDICESS

LIST OF ABBREVIATION

BP	Blood pressure
DBP	Diastolic blood pressure
DVP	Deep vessel plexus
GH	Gestational hypertension
HDP	Hypertensive disorder in pregnancy
HELLP	Haemolysis, elevated liver enzyme, low platelet
HPT	Hypertension
ICAM	intracellular adhesion molecule
ISSHP	International Society for the Study of Hypertension in Pregnancy
MAP	Mean arterial pressure
NICE	National Institute for Health and Care Excellence
NO	Nitrous oxide
NOR	National Obstetric Registry
OCT	Optical coherence tomography
PE	Pre-eclampsia
PGI	Prostaglandin I
PGI2	Prostacyclin inhibitor 2
RNFL	Retinal nerve fibre layer
SBP	Systolic blood pressure
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
sFlt-1	Soluble fms-like tyrosine kinase-1
sEng	Soluble endoglin
SVP	Superficial vessel plexus

SPSS	Statistical Package for Social Sciences
VEGF	Vascular endothelial growth factor

ABSTRAK

Objektif: Kajian ini adalah untuk mengukur ketebalan lapisan saraf retina (RNFL) dan makula di kalangan pesakit darah tinggi semasa mengandung atau "Hypertensive disorder in pregnancy" (HDP) berbanding wanita mengandung yang sihat pada trimester ketiga.

Kaedah kajian: Perbandingan "cross-sectional" telah dijalankan di Hospital Universiti Sains Malaysia, melibatkan seramai 200 orang pesakit HDP dan 50 orang wanita mengandung sihat sebagai kawalan. Peserta yang memenuhi syarat kajian diperiksa dan menjalani ujian Tomografi Koheren Optikal (OCT) pada mata kanan. Ketebalan RNFL dan makula diukur dan dianalisa menggunakan SPSS 26.0.

Keputusan: Terdapat penipisan pada lapisan RNFL dan makula dikalangan pesakit HDP berbanding wanita mengandung sihat. Bagi golongan 'pre-eclampsia' penipisan adalah pada bahagian purata dan atas RNFL, manakala bagi golongan 'gestational hypertension' penipisan RNFL adalah ketara pada kuadrant purata, atas dan bawah. Bagi golongan pesakit darah tinggi kronik semasa mengandung, penipisan RNFL dilihat pada bahagian purata manakala bagi golongan 'chronic hypertension with superimposed pre-eclampsia', penipisan RNFL ketara di bahagian purata dan atas. Kedua-dua golongan 'gestational hypertension' dan 'chronic hypertension with superimposed pre-eclampsia', menunjukan penipisan makula yang ketara pada bahagian 'temporal' luar dengan bacaan 251.00µm dan 251.11µm masing-masing; dan bawah luar makula dengan bacaan 259.53 µm bagi golongan terakhir.Analisa 'Regression' menunjukkan tiada hubungkait antara

tekanan darah dan bilangan ubat darah tinggi dengan purata ketebalan RNFL dan makula di kalangan pesakit HDP.

Kesimpulan: Pesakit HDP menunjukkan penipisan RNFL dan makula berbanding subjek kawalan. Tiada hubung kait didapati di antara bacaan tekanan darah dan bilangan ubat dengan ketebalan lapisan RNFL dan macula di kalangan pesakit HDP.

Kata kunci: Darah tinggi semasa mengandung , ketebalan RNFL, ketebalan makula

ABSTRACT

Objective: Evaluate retinal nerve fibre layer (RNFL) and macular thickness in patients with hypertensive disorder in pregnancy (HDP) compared to healthy pregnant control in third trimester.

Methodology: Comparative cross-sectional study conducted in Hospital Universiti Sains Malaysia with 200 HDP participants and 50 controls recruited. Clinically stable participants who fulfilled criteria with normal ocular examinations were subjected to optical coherent tomography (OCT) of the right eye. RNFL and macular thickness were evaluated and analysed using SPSS 26.0.

Results: Thinner mean RNFL and macular quadrants in HDP groups compared to control were observed; after controlling potential cofounders. Pre-eclampsia showed significant thinning at average and superior RNFL quadrants while, gestational hypertension group showed thinning at average, superior and inferior RNFL regions. Chronic hypertension group showed thinner average RNFL, while chronic hypertension with superimposed pre-eclampsia showed significant thinning at average and superior RNFL quadrants. Thinner outer temporal macular region observed in both gestational and chronic hypertension with superimposed pre-eclampsia groups with mean of 251.00µm and 251.11µm respectively. The latter group also showed thinner outer inferior macular of 259.53µm. Regression analysis between blood pressure (BP) and number of antihypertensive medications with average RNFL and macular thickness showed no significant associations.

Conclusion: Mean RNFL thickness was significantly lower in the all HDP groups while macular thickness was significantly lower in the gestational hypertension and chronic hypertension with superimposed pre-eclampsia group. Blood pressure and number of medications showed no significant associations with RNFL and macular thickness.

Keywords: Hypertensive disorder in pregnancy (HDP), RNFL thickness, macular thickness

CHAPTER 1:

INTRODUCTION

1.1 Hypertensive disorder in pregnancy

Hypertensive disorder in pregnancy (HDP) is a multisystem group of disorders where hypertension is the main aetiology. It is one of the most common medical disorder encountered during pregnancy.

1.1.1 Physiological changes in pregnancy

In normal pregnancy, there is an invasion of foetal uteroplacental tissue to maternal uterine wall. The trophoblastic tissue reaches the uterine maternal spiral artery through invasion of decidua and maternal myometrium segment by end of first trimester. This lead to maternal immunological tolerance to foetal allograft and degeneration of tunica intima of spiral artery causing vasodilation with increased intervillous blood flow (Karthikeyan and Lip, 2007).

During pregnancy sustained increase in maternal oestrogen and progesterone levels inhibit hypothalamus-pituitary axis to support the growing foetus. This will lead to physiological maternal changes including the cardiovascular, pulmonary, renal, metabolic, hormonal, immunologic and hematologic system to prepare the body for an increase metabolic demand to support pregnancy and later for parturition (Sanghavi *et al*., 2014; Soma-pillay *et al*., 2016; Troiano, 2018).

Maternal intra and extracellular fluid volume also increase throughout pregnancy. Blood plasma volume increases by 45% to approximately 1.2 litre to 1.6 litre above non-pregnant values that peaks at third trimester (Troiano, 2018).

Although there is increase in fluid volume, the blood pressure remains normal. Maternal vasodilation that are mediated by potent substances such as nitrous oxide (NO) and prostaglandin I (PGI), leads to 25 – 30% reduction in peripheral vascular resistance from baseline that peaks at second trimester (Soma-pillay *et al*., 2016). This is coupled with an increase in cardiac output due to increase in stroke volume and change in maternal heart rate. This leads to maternal blood pressure reduces 25% from baseline and reach nadir at second trimester. The blood pressure returns to initial baseline level at third trimester onwards (Sanghavi *et al*., 2014; Soma-pillay *et al*., 2016)

Meanwhile, physiological maternal haematological changes throughout normal pregnancy includes haemodilution due to initial fall in haemoglobin level despite increase plasma volume. The red blood cells level gradually increases up to 40% due to increase erythropoiesis in a healthy pregnancy (Chandra *et al*., 2012). Pregnancy state also tilts the balance of coagulation system in favour of clotting where there is an increase in concentration of clotting factors including factor VIII, IX, X and fibrinogen level with reduction in level of anticoagulant such as antithrombin and fibrinolytic activity. Thus, predisposing pregnant women to thrombosis and this effect is more pronounced in condition like HDP (Abdo *et al*., 2014; Soma-pillay *et al*., 2016).

1.1.2 Pathophysiology of HDP

In HDP the uteroplacental trophoblastic invasion of maternal uterine spiral arteries is abnormal and defective. Henceforth, the maternal spiral artery remains muscular, small calibre and responsive to vasoconstrictive influence that reduce blood flow to the uteroplacental bed (Fisher *et al*., 2016). The placenta hypoperfusion leads to subsequent placental hypoxia. This will initiate a consequence of events where widespread endothelial cell dysfunction occur that causes a detrimental condition including vasospasm, hyper coagulopathy and multiorgan dysfunction. The underlying cause for poor initial placental invasion however remains unclear (Karthikeyan and Lip, 2007).

Previous study has associated that certain inheritable abnormal maternal genes to be more susceptible to develop HDP such as mutation in angiotensinogen T235 and the factor V Leiden alleles (Karthikeyan and Lip, 2007). Physiologically, angiotensinogen (AGT) is known to regulate blood pressure control, fluid volume balance and vascular smooth muscle remodelling. In T235 variant of AGT, there is hypovolemia as seen in HDP as compared to increase fluid volume in normal pregnancy. There are defective arteries changes, with vascular smooth muscle cell proliferation and athetotic remodelling of vessels. Meanwhile, mutation of factor V Leiden prevents normal degradation of activated Factor V that leads to molecules retain their procoagulant activity, thus predisposing women to thromboembolism in pregnancy (Lumbers and Pringle, 2021). Placental bed biopsy in HDP women showed excessive upregulation inflammatory mediators including I-CAM and tumour necrosis factor-α expression; causing trophoblast apoptosis and defective in spiral arteries invasion (Labarrere *et al*., 2018).

As the endothelium is important in the modulation of vascular tone, disturbance of endothelial cells leads to alterations in the production of several vasoactive compounds producing a vasoconstricted state. Placental production of the vasoconstrictor mediators including thromboxane A2, soluble vascular endothelial growth factor (VEGF) receptor-1, soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng), which caused multiorgan maternal endothelial dysfunction are increased, while vasodilators compound production such as plasma prostacyclin (PGI2) and nitric oxide (NO) are reduced (Karthikeyan and Lip, 2007; Kumasawa *et al*., 2019). Impaired endothelial function is evidenced by maternal systemic hypertension, oedema and proteinuria. Endothelial dysfunction may also stimulate platelet and neutrophil activation thus making the already smaller maternal vessel more prone to further thromboembolism and hypoxia (Tagetti and Fava, 2020).

1.1.3 Classification of HDP

According to International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines 2018, HDP can be classified into a few subgroups, including; gestational hypertension, pre-eclampsia, eclampsia, chronic hypertension and chronic hypertension with superimposed preeclampsia.

Gestational hypertension is diagnosed when there is a blood pressure of more than 140/90 mmHg recorded after 20 weeks of gestation, without any significant proteinuria, while pre-eclampsia is diagnosed when there is de novo hypertension diagnosed after 20 weeks of gestation with presence of significant proteinuria. Proteinuria is considered significant if urine protein collected in 24-hour urine is more than 300mg / 24 hours or protein in

urine is 2+ or more than 1g/dL. Pre-eclampsia can be associated with symptoms that reflect severity of the disease particularly with presence of HELLP syndrome. HELLP syndrome is a group of signs and symptoms mainly haemolysis, elevated liver enzymes, low platelet counts, headache, epigastric discomfort or worsening oedema that indicates disease progression. Meanwhile, eclampsia is a condition where patient develop fitting episode at any time throughout pregnancy that is associated with high blood pressure. Chronic hypertension is defined as hypertension that had begun prior to conception of pregnancy and remain persistent even after six weeks of postpartum. Another group of HDP is chronic hypertension with superimposed pre-eclampsia where there is worsening of chronic hypertension during pregnancy by evidence of raised blood pressure or presence of significant proteinuria (Brown *et al*., 2018; Walle *et al*., 2019).

Patient that was nulliparous, had previous history of HDP or at lower education level is at an increased risk to develop HDP. Meanwhile, mothers with gestational diabetes, obese with body mass index more than 29, multiple pregnancy and history of smoking are associated with an increased severity of HDP (Wagnew *et al*., 2020; Barton *et al*., 2020).

1.2 Prevalence of HDP

Report by WHO regarding Global Burden Disease Report showed hypertension was responsible for a total of 6-10 % of all diseases effecting pregnancy and represent 13% of all maternal deaths worldwide (Abalos *et al*., 2014). HDP burden differ between region with rate of 1.8% in the Middle East, 4.5% in the Americas region, 2-2.5% in South East Asia and 8% in Sub-Saharan region (Abalos *et al*, 2014; Gemechu and Assefa, 2020).

It affects 4.3-10% from all deliveries in Malaysia according to National Obstetric Registry (NOR) 2012. Specifically, in Kelantan state it affects 3.64% from 13,066 deliveries in 2011 and 3.52% out of 10,955 deliveries in 2012 (Jeganathan, 2012). Local data from Hospital Universiti Sains Malaysia in 2018-2020 showed an increasing trend of HDP where 2281 from 28,603 women develop HDP throughout their pregnancy.

Maternal death due to HDP differ between region where high income and develop countries fair slightly better with rate of 12.9% maternal death compare to developing countries with 14% deaths each year (Say *et al*., 2006). Ten years analysis in South East Asia region showed maternal death due to HDP rank second as the most common cause following haemorrhage of 29.9% with rate of 14.5% (Say *et al*., 2006; Khan *et al*., 2006). A review done from 1997-2008 in Malaysia recorded a total of 238 maternal deaths reported related to hypertension which accounts for an average incidence rate of 13.56% each year (Jeganathan, 2012).

Hypertensive disorder in pregnancy also carries a significant risk of maternal and foetal morbidity. Pre-eclampsia especially is known to contribute to 5% (1 in 20) risk of stillbirth, 50% risk of preterm deliveries, 14-19% risk of term birth and 20-25% risk of preterm birth to have small-for-gestational-age babies of less than tenth centile of birth weight for gestation. (Kintiraki *et al*., 2015)

Meanwhile, the most common maternal complications related to hypertensive disorder in pregnancy includes progression to eclampsia at 3.24% followed by postpartum haemorrhage at 0.83% and abruptio placenta at 1.08% (NICE , 2010; Osungbade and Ige, 2011; Jeganathan, 2012). Lower income countries showed the highest rate of eclampsia compared to high and middle income countries (Abalos *et al*., 2014). The risk is higher if patient develop severe hypertension earlier in pregnancy, higher pregnancy body mass index, similar episode of pre-eclampsia in previous pregnancy, had history of previous miscarriage or if patient is having multiple pregnancy (Wong *et al*., 2013; Shen *et al*., 2017).

Hypertensive disorder in pregnancy posed a long-term effect towards maternal health. Constriction in maternal arteriolar and dilation of venular calibre remains even after delivery that is associated with increase lifetime risk to develop chronic hypertension (3.7 times) in 14 years, ischemic heart disease (2.16 times) in 12 years, stroke (1.81 times) in 10 years, and venous thromboembolism (1.87 times) in 5 years. (Benschop *et al*., 2017).

Women with HDP also have higher future relative risk to develop chronic kidney disease and metabolic syndrome compare to normal populations (Pouta *et al*., 2004; Turbeville and Sasser, 2020). Previous study has proposed that early microvascular changes in retinal nerve fibre layers thickness and vessels reflects similar vascular dysfunction in visceral organ vascular beds that correlates with future risk of mothers to develop chronic hypertension, diabetes, renal and cardiovascular disease even before the target organ damage occur (Farrah *et al*., 2020).

1.3 Associated ocular changes in normal pregnancy

Multiorgan physiological changes during pregnancy commonly affects visual system. In normal pregnancy there has been reports regarding changes in maternal corneal sensitivity, increased in corneal thickness, altered visual function, retinal sensitivity, increased in retinal vessel density, increased capillary blood flow and reduced in intraocular pressure (Kızıltunç *et al*., 2020). It was attributed due to ocular tissue including cornea, lacrimal gland and chorio-retinal vascular complex have hormonal receptor that responds to oestrogen effect during normal pregnancy. Increased levels of oestrogen causes an elevation in nitrous oxide synthesis and reduction in endothelin-1 synthesis that leads to vasodilation and decrease in vascular resistance in ocular chorio-retinal tissue (Chanwimol *et al*., 2019). These ocular changes despite being mild and transient can aggravate pre-existing ocular disease or condition throughout pregnancy state.

1.3.1 Retina and optic nerve head changes in normal pregnancy

The retina and optic nerve head thickness is made not only of ganglion cell axon but also retinal vascular beds to maintain its healthy function. The retinal vascular beds originate from central retinal artery, that further divide into; 1) radial peripapillary capillary plexus (RPCP) that supply the nerve fibre layer, 2) superficial vascular plexus (SVP) located between the ganglion cell layer (GCL) and inner plexiform layer, 3) intermediate capillary plexus (ICP) located between the inner plexiform layer and inner nuclear layer, and 4) deep capillary plexus (DCP) located between inner nuclear layer and outer plexiform layer.

Collectively, RPCP and SVP is also known as superficial vascular complex (SVC), while the ICP and DCP known as deep vascular complex (DVC). These vessels supply the inner retina, including the retinal ganglion cells, while the outer retina derives oxygenation and nutrition from the choriocapillaris of the choroid (Campbell *et al*., 2017).

Previous studies have shown positive correlations between SVC, DVC and choroidal vascular density with retinal nerve fibre layer (RNFL) and macular thickness, that validate the role of these complex vascular plexus in maintaining RNFL health and thickness (Pournaras and Riva, 2013; Ciloglu *et al*., 2019; Courtie *et al*., 2020).

1.3.2 Ocular blood flow regulations

Blood flow regulation in ocular tissue mimic cerebral blood flow autoregulation. The retinal circulation has blood-retina barrier that is similar to blood brain barrier that stabilizes any extreme plasma changes (Hui *et al*., 2017). Thus, any abnormalities seen in retinal tissue might suggest similar changes in cerebrovascular system.

Retinal circulation however, differs slightly from choroidal vascular regulation, as it lacks sympathetic autonomic control. Retinal vascular system mainly depends on local vasogenic factors such as endothelin-1 that act on vascular pericytes to maintain stable ocular blood flow and perfusion. Thus any excessive increase or decrease in blood pressure can disturb the balance of the vasodilation and vasoconstrictive effect on vascular endothelium thus causing breakdown in this circulatory regulations (Luo *et al*., 2015).

The choroidal circulation autoregulation meanwhile depends on both sympathetic control and local vasogenic mediators. Previous studies have shown that pregnancy cause an increase in choroidal thickness due to hormonal effect that increase blood flow, reduce vascular resistance and vasodilatations (Luo *et al*., 2015; Jiang *et al*., 2019). In HDP patients however these circulation autoregulatory mechanism are defective thus causing retinopathy or RNFL and macular layer abnormalities.

1.4 Associated ocular changes in hypertensive disorder in pregnancy

Ocular involvement is fairly common in HDP. Patient may be asymptomatic or presented with ocular symptoms that include headache, blurring of vision, scotomas, photopsia , visual filed disturbance, diplopia or rarely blindness (Shah *et al*., 2015).

Prevalence of hypertensive retinopathy in HDP range from 13%-45% (Karki *et al*., 2010; Rasdi *et al*., 2011; Patel *et al*., 2018; Ranjan and Sinha, 2014). Hypertensive retinopathy changes include generalised arteriolar narrowing, arteriovenous nipping, silver wiring, cotton wool spots, retinal haemorrhages and papilloedema. These retinopathy changes can be classified according to Keith-Wagner and Baker classification, where; grade 1 have generalised arterioles attenuation, grade 2 have generalised arterioles attenuation with focal arteriolar attenuation, grade 3 have added haemorrhages, hard exudate or cotton wool spots, while grade 4 have all the mentioned symptoms including optic disc swelling. Most common hypertensive retinopathy changes seen was generalised arterioles attenuation (Bakhda, 2016).

Retinal pathologies that maybe associated with HDP other than hypertensive retinopathy changes include serous retinal detachment, central retinal vein occlusion, optic neuropathy or cortical blindness (Prabhu *et al*., 2018). However, more than 50% of HDP patient have no retinopathy and remain asymptomatic despite having microvascular changes (Neudofer *et al*., 2014).

In ophthalmology, the retina is unique as it is the only organ in human's body that allows for direct visualisation of retinal blood vessel and nerve axons that may reflect the early changes that occur in other part of human vessel and neuronal tissues. The retina is particularly vulnerable to change in hypertension during pregnancy; however, the eyes are rarely examined in hypertensive disorder in pregnancy unless there was an active eye complaint. Previous studies suggested that monitoring of retinal conditions in women with hypertensive disorder during pregnancy may detect any early changes that may predict poor maternal and foetal outcome (Reddy *et al*., 2003; Rasdi *et al*., 2011).

In pregnancy there is limitation in drug or investigation that is considered safe for maternal and foetal growth and well-being. Optical coherence tomography (OCT) is a non-invasive way to analyse the ocular changes in pregnancy. In spectral domain OCT, it uses light axial scan through ocular tissue and measure the reflected frequency differences thus it is an ideal method to evaluate any subtle retinal layer and optic nerve changes (Menke and Sturm, 2009).

1.5 Retinal nerve fibre layer in hypertensive disorder in pregnancy

The retinal nerve fibre layer (RNFL) is formed by retinal ganglion cell axons which form part of inner layer of retina. It received electrical signals from photoreceptors that pass-through the ganglion cells. At the optic disc, the RNFL bend and pass-through lamina cribrosa at scleral canal to form neuroretina rim of optic nerve. The RNFL is known as a sensitive and early indicator of structural damage (Grosso *et al*., 2005). Although standard automated perimetry has long been considered as gold standard for visual field measurement, it is believed that about 20 - 40% of the retinal ganglion cells are lost before any changes can be seen in perimetric assessment (Lupton *et al*., 2013). Thus, OCT scan is the new unrivalled way of detecting early retinal changes.

Thinner RNFL measurements have been found in a few conditions namely older age, Caucasians, myopia, glaucoma, medical diseases like diabetes, hypertension, obstructive sleep apnoea and several neurological diseases like Alzheimer, Parkinson and Multiple sclerosis (Lee *et al*., 2018; Chauhan *et al*., 2019; Rawat *et al*., 2020). Recent studies also showed thinner RNFL can be seen in patients with hypertension complicating pregnancy compared to healthy pregnant women (Atas *et al*., 2014; Arab *et al*., 2017).

In normal pregnancy, maternal RNFL commonly increase in thickness compared to non-pregnancy state. Demir et al., (2011) and Cankaya et al., (2013) observed that increment in maternal RNFL was highest during third trimester due to physiological changes and fluid retention caused by hormonal changes during pregnancy. However, although Demir et al., (2011) observed increment in both fovea and retinal nerve fibre layer thickness in healthy pregnant compare to healthy non-pregnant women, it was not statistically

significant. Other study also concluded that the difference in fovea thickness between healthy pregnant and healthy non-pregnant women although present, was transient (Ulusoy *et al*., 2015).

The physiological increment in RNFL was however not seen in pre-eclampsia patients. Arab et al., (2017) studied retinal nerve fibre layer thickness in 35 pregnant women with mild to moderate pre-eclampsia, 70 pregnant women with severe pre-eclampsia and eclampsia and 44 healthy pregnant women. This study concluded thinner RNFL layer parameters in pre-eclamptic compared to healthy pregnant women group. Atas et al., (2014) showed similar results in a cross-sectional study on pregnant women over 28 weeks gestation. The study was done in 3 groups; group 1 consist of 27 pregnant women with mild pre-eclampsia, group 2 consist of 25 healthy pregnant women, and group 3 consist of 26 healthy non-pregnant women. Atas et al., (2014) concluded that macular, retinal nerve fibre layer and choroidal thickness increased in both pre-eclampsia and healthy pregnant women compared to healthy non-pregnant control group. The increment however was smaller in pre-eclampsia group compared to healthy pregnant group. The mean macular thickness for pre-eclampsia, healthy pregnant and healthy non-pregnant group was 211.09 (12.93) µm, 215.86 (17.08) µm and 229.81 (34.51) µm respectively, while mean RNFL thickness was 102.45 (8.69) µm, 104.77 (10.64) µm, and 97.65 (12.27) µm respectively.

There was however lack of study regarding RNFL thickness in other HDP group including gestational hypertension, chronic hypertension and chronic hypertension with superimposed pre-eclampsia groups.

1.6 Macular thickness in hypertensive disorder in pregnancy

Macular thickness is contributed by not only vascular plexus complexes and ganglion cells but also healthy nerve fibre layers that contributed up to 30% to 35% of total macular thickness (Guedes *et al*., 2003; Ito *et al*., 2019). Thus, any changes and reduction in macular thickness is postulated to reflect reduction in retinal ganglion cells and retinal nerve fibre layer atrophy.

Pregnancy is known to cause an increased in macular thickness due to hormonal changes and fluid retention. Both Cankaya et al., (2013) and Demir et al., (2011) noted significant increase in macular thickness of 287.95 (95.50) µm and 236.12 (27.28) µm respectively compared to healthy non-pregnant women of only 192.100 (58.61) µm and 224.62 (21.19) µm. However, in women with hypertensive disorder in pregnancy, this increment during pregnancy is less compared to other healthy pregnant women. This was postulated due to vasospasm and endothelial dysfunction that effect vessel calibre in women with hypertensive disorder.

Study by Atas et al., (2014) noted that the macular thickness in pre-eclampsia group was 211.09 (12.93) µm which was higher compare to healthy non-pregnant women group, however it was much lower compare to the healthy pregnant women group of 215.86(17.08) µm.

There is currently limited report that study the association between macular and retinal nerve fibre layer thickness in hypertensive disorder effecting pregnancy.

1.7 Rationale of study

Hypertensive disorder in pregnancy is a multisystemic disorder with widespread maternal endothelial dysfunction. Visual system is commonly affected in HDP. Thus, it is postulated that there will be difference in retinal nerve fibre and macular thickness in patients with hypertensive disorder in pregnancy as compared to healthy pregnant women.

This study will look into a wider range of disease subgroup within hypertensive disorder in pregnancy, mainly between gestational hypertension, pre-eclampsia, chronic hypertensive, chronic hypertension with superimposed pre-eclampsia and healthy pregnant women control groups; for any significant difference of RNFL and macular thickness. At the best of the author's knowledge there is currently limited research that study and compare the RNFL and macular thickness within all groups of hypertensive disorder in pregnancy as two previous studies were limited to a focused group of preeclampsia.

Although visual system is commonly affected in HDP, most patients remain asymptomatic. Thus, this study aims to evaluate any early and subclinical retinal and macular layer thickness changes in patients without overt retinopathy.

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