A COMPARISON OF THE CALCULATED CREATININE CLEARANCE LEVEL BETWEEN GESTATIONAL HYPERTENSION AND CHRONIC HYPERTENSION DURING PREGNANCY AND POSTPARTUM

by

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TABLE OF CONTENTS

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AKI	Acute Kidney Injury
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ARB	Angiotensin II Receptor Blockers
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
DBP	Diastolic Blood Pressure
ESRD	End-Stage Renal Disease
ESRF	End-Stage Renal Failure
GFR	Glomerular Filtration Rate
IQR	Inter quartile Range
MDRD	Modification of Diet in Renal Disease
OR	Odd Ratio
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
USM	Universiti Sains Malaysia

LIST OF SYMBOLS

$1-\beta$	Power
A	Level of significance
N	Sample
$<$	Less than
$>$	More than
$\geq$	More than or equal to
$\approx$	Approximately
$=$	Equal
%	Percentage
Σ	Standard Deviation
Δ	Estimated difference from population mean
Y	Dependent variable
$\hat{Y}$	Predicted value
E	Residual
H_0	Null hypothesis
H_A	Alternative hypothesis

PERBANDINGAN TAHAP KIRAAN PELEPASAN KREATININA ANTARA HIPERTENSI GESTASI DAN HIPERTENSI KRONIK SEMASA HAMIL DAN SELEPAS BERSALIN

ABSTRAK

Pengenalan: Frekuensi individu yang didiagnosis hipertensi di seluruh dunia kira-kira sehingga 10% daripada semua kehamilan, dan ia juga salah satu punca utama morbiditi dan kematian semasa kehamilan. Hipertensi semasa hamil boleh menyebabkan komplikasi jangka panjang selepas beberapa tahun. Hipertensi semasa mengandung juga sangat berkaitan dengan penyakit buah pinggang tahap akhir. **Tujuan**: Kajian ini membandingkan tahap pengurangan kiraan pelepasan kreatinina antara pesakit hipertensi gestasi dan hipertensi kronik daripada kehamilan hingga selepas bersalin. Kajian ini bertujuan untuk menilai tahap perbezaan min kiraan pelepasan kreatinina dikira dalam kumpulan (hipertensi gestasi dan hipertensi kronik), perbezaan min kiraan pelepasan kreatinina antara kumpulan tanpa mengira masa dan perbezaan min pelepasan kreatinina dikira antara kumpulan berdasarkan masa. **Kaedah:** Satu kajian prospektif telah dilakukan ke atas pesakit dengan hipertensi gestasi dan hipertensi kronik di Hospital Universiti Sains Malaysia. Kajian ini membandingkan pengurangan tahap kiraan pelepasan kreatinina di antara pesakit hipertensi gestasi dan kronik. Seramai 10 peserta dari setiap kumpulan telah diambil pada trimester ketiga kehamilan dari Klinik Obstetrik & Gynecologi, Hospital USM. Peserta kajian telah bersetuju dan maklumat peserta telah diambil dari rekod perubatan pada trimester ketiga kehamilan. Peserta memgambil darah bagi ujian fungsi buah pinggang untuk setiap temujanji

pada trimester ketiga, enam minggu selepas bersalin dan 12 minggu selepas bersalin. Pelepasan kreatinina dikira dengan menggunakan formula "Modification of Diet in Renal Disease'. Analisis Kovarians Ukuran Berulang telah digunakan dan pembolehubah berat lahir bayi dan usia gestasi semasa melahirkan telah dikawal. **Keputusan**: Keputusan kajian menunjukkan perbezaan yang signifikan dalam perbandingan 1 (trimester ketiga kehamilan-enam minggu selepas bersalin; perbezaan min: 25.99; 95% CI: 19.84, 32.14; p <0.001) dan perbandingan 2 (trimester ketiga kehamilan-12 minggu selepas bersalin: perbezaan min: 23.66; 95% CI: 9.63, 37.64; p = 0.003) dalam kumpulan hipertensi gestatasi. Semua perbandingan masa di kalangan peserta hipertensi kronik adalah signifikan. Terdapat perbezaan yang signifikan dalam perbandingan 1 (trimester ketiga kehamilan-enam minggu selepas bersalin; perbezaan min: 27.02; 95% CI: 18.15, 35.90; p <0.001), perbandingan 2 (trimester ketiga kehamilan-12 minggu selepas bersalin: perbezaan min: 28.85; 95% CI: 20.75, 36.96; p <0.001) dan perbandingan 3 (enam minggu selepas bersalin-12 minggu selepas bersalin: perbezaan min: 1.83; 95% CI: 0.41, 3.25; p = 0.015). Untuk hasil interaksi, terdapat perbezaan yang signifikan pelepasan kreatinin dikira pada 12 minggu selepas bersalin (p = 0.026). Untuk perbandingan lain, tidak ada perbezaan yang signifikan untuk min kiraan pelepasan kreatinina antara dua kumpulan. Apabila membandingkan tahap kiraan pelepasan kreatinina daripada trimester ketiga dan 12 minggu selepas bersalin, hipertensi kronik menunjukkan kemerosotan tahap kiraan pelepasan kreatinina yang lebih besar dengan perbezaan min 28.85 ml / min. Pesakit dengan hipertensi gestatasi mempunyai peningkatan dalam kiraan pelepasan kreatinina pada 12 minggu selepas bersalin tetapi tahap kiraan pelepasan kreatinin dalam hipertensi kronik cenderung berkurangan 1.83 ml / min pada 12 minggu selepas bersalin. **Kesimpulan:** Pemeriksaan berkala semasa postpartum terutamanya terhadap fungsi buah pinggang adalah digalakkan di kalangan wanita yang mempunyai

sejarah hipertensi semasa mengandung kerana ia adalah salah satu daripada isu penting yang perlu dipertimbangkan kerana berisiko untuk mempunyai penyakit buah pinggang beberapa tahun selepas mengandung.

A COMPARISON OF THE CALCULATED CREATININE CLEARANCE BETWEEN GESTATIONAL HYPERTENSION AND CHRONIC HYPERTENSION DURING PREGNANCY TO POSTPARTUM

ABSTRACT

Introduction: Hypertension is present in approximately up to 10% of all pregnancies worldwide, and also one of the leading causes of morbidity and mortality in pregnancy. Hypertensive disorders during pregnancy may cause the long-term complications and consequences after a decade having hypertension during pregnancy. Hypertensive disorders during pregnancy is also highly associated with end-stage renal disease. **Objective**: This study compared the reduction of creatinine clearance level between gestational and chronic hypertension patient from pregnancy to post-delivery. This study aimed to assess the level of mean difference of calculated creatinine clearance within group (gestational hypertension and chronic hypertension), the mean difference of calculated creatinine clearance between groups regardless of time and the mean difference of calculated creatinine clearance between groups based on time. **Methods:** A prospective cohort study was performed on patients with gestational and chronic hypertension at Hospital Universiti Sains Malaysia. The total of 10 pregnant mothers from each group were recruited during their third trimester of pregnancy from Obstetrics & Gynaecology Clinic of Hospital USM. The patients were consented and medical record was reviewed at recruitment (third trimester). Patients had the blood taking of renal function test for every visit at third trimester, six weeks after delivery and 12 weeks

after delivery. The creatinine clearance was calculated by using Modification of Diet in Renal Disease formula. Repeated Measure ANCOVA analysis was applied with birth weight and gestational age at delivery were controlled. **Results:** For within group analysis, there was a significant difference of mean calculated creatinine clearance within gestational hypertension and chronic hypertension based on time after controlling potential covariates (birthweight and gestational age at delivery) ($F=21.59$, $p=0.002$). Multiple comparisons was performed with adjusted α based on Bonferroni correction. The results showed that there were significant differences in pair 1 (third trimester-six weeks postpartum; mean difference: 25.99; 95% CI: 19.84, 32.14; $p<0.001$) and pair 2 (third trimester-12 weeks postpartum: mean difference: 23.66; 95% CI: 9.63, 37.64; $p=0.003$) in gestational hypertension group. In the meantime, all comparison groups were significant in chronic hypertension participants. Multiple comparisons showed that there were significant differences in pair 1 (third trimester-six weeks postpartum; mean difference: 27.02; 95% CI: 18.15, 35.90; $p<0.001$), pair 2 (third trimester-12 weeks postpartum: mean difference: 28.85; 95% CI: 20.75, 36.96, $p<0.001$) and pair 3 (six weeks postpartum-12 weeks postpartum: mean difference: 1.83; 95% CI: 0.41, 3.25; $p=0.015$). Meanwhile, there was no significant difference of mean calculated creatinine clearance between gestational hypertension and chronic hypertension ($F=1.59$, $p=0.266$) regardless of time. For time-treatment interaction results in repeated measure ANOVA analysis, there was no significant difference of mean calculated creatinine clearance between groups based on time ($F= 0.56$, $p= 0.579$). But, we still proceed to multiple comparison to determine if there was a significant difference for each time. From the results, there was a significant difference of calculated creatinine clearance at 12 weeks postpartum ($p=0.023$). For other measurement, there was no significant difference of mean creatinine clearance between this two groups. When comparing the creatinine clearance from third

trimester to 12 weeks postpartum, chronic hypertension group showed a big reduction of calculated creatinine clearance with mean difference of 28.85 ml/min. Patient with gestational hypertension had increase in creatinine clearance at 12 weeks postpartum but the creatinine clearance level in chronic hypertension tend to decrease by 1.83 ml/min at 12 weeks postpartum. **Conclusion:** The regular check-up during postpartum especially on renal function is encouraged in women with a history of hypertensive disorders in pregnancy as it is one of the important issues to consider due to the chance of having renal disorder after several years of pregnancy.

CHAPTER 1

INTRODUCTION

1.1 Hypertensive Disorders during Pregnancy

1.2 Burden of Hypertension Disorder during Pregnancy

Hypertension is present in approximately up to 10% of all pregnancies worldwide, and also one of the leading causes of morbidity and mortality in pregnancy (Duley, 2009). Since 2001, the prevalence of hypertensive disorders has been increasing among delivery hospitalizations (Duley, 2009).

In the United States, the prevalence of hypertension is 5 to 10% in pregnant women, which is the second leading cause of the maternal death (Sibai *et al.*, 2005). According to a study that had been done in Kuala Lumpur, 4.41% patients had pregnancy-induced hypertension during pregnancy and 7.14% of all pregnancies died from preeclampsia in 2008 (Ismail, 2008).

Hypertensive disorders during pregnancy increase up to 15% of maternal mortality in both industrialised and developing countries (Arulkumaran *et al.*, 2004).The outcomes that contributes to hypertensive disorders during pregnancy include small for gestational age infants, maternal and perinatal mortality, and preterm labour (Macdonald-Wallis *et al.*, 2012). In the low outcome countries, the leading causes of mortality among hypertensive disorders women are pregnancy and childbirth complication (Duley, 2009). Otherwise, women with hypertensive disorders will increase the chance of getting acute renal failure (Mehrabadi *et al.*, 2014).

1.2 Prevalence of Kidney Diseases among Hypertensive Pregnant Women

Many studies reported long-term complications and consequences after a decade having hypertension during pregnancy (Nisell *et al.*, 1995; Männistö *et al.*, 2013a; Asad and Garovic, 2014). Women with chronic hypertension contribute a leading factor of getting preeclampsia during pregnancy that can cause chronic kidney disease (Szczech *et al.*, 2014). The previous researchers mostly discuss on the blood pressure in pregnancy but to highlight the relationship between hypertension and kidney problem is also important. Hypertensive disorders usually resolve after delivery, but many recent studies show that hypertension is highly associated with End-Stage Renal Disease (Bellamy *et al.*, 2007; Männistö *et al.*, 2013b).

According to a study that conducted at the Institute of Medical Sciences, Banaras Hindu University, 1.39% patients with chronic hypertension had renal artery stenosis (Prakash *et al.*, 2006). Many recent studies show that hypertension is highly associated with cardiovascular disease and end-stage renal disease (Bellamy *et al.*, 2007). The main secondary causes of chronic hypertension in pregnancy include coarctation of the aorta, renal artery stenosis , chronic kidney disease, and systemic disease with renal involvement (Lowe *et al.*, 2015). Women with chronic hypertension are at high risk of developing preeclampsia which contribute end-stage renal failure later on (Relative Risk=4.3, 95% Confidence Interval=3.5-5.6) (Lowe *et al.*, 2015).

The Odd Ratio for acute kidney injury (AKI) was 9.9 (95% CI 8.4–11.6) among women with chronic hypertension while 2.2 (95% CI 1.7–2.9) among women with gestational hypertension. The largest expected population-attributable fractions were detected for eclampsia/severe preeclampsia tailed by chronic hypertension (OR: 10.7, 95% CI: 9.0–

12.5) and the least for gestational hypertension (OR: 1.8, 95% CI: 0.9–2.8) (Kuklina *et al.*, 2009). Gilbert *et al* (2007) reported the relationship of chronic hypertension and severe complications during and after pregnancy. The complications include the cardiovascular disease and renal disease. A study conducted in Finland showed that the gestational hypertension women increase the risk of developing the kidney disease later on compared to normotensive women (Hazard Ratio: 1.91, 95% CI: 1.18–3.09) ; the researchers also proved that chronic hypertension was the second highest percentage that getting CKD after 40 years follow up (Männistö *et al.*, 2013b).

Hypertension in pregnancy is associated with renal complications (Asad and Garovic, 2014). Asad and Garovic (2014) reported that hypertensive pregnancy disorders had significant 9.38 HR of developing CKD and ESRD compared to those without hypertensive pregnancy disorders. Besides, women who previously had a hypertensive disorder pregnancy had a cardiovascular or renal disease in the average of six years (Asad and Garovic, 2014). In that case, treatment and further management for patient with hypertensive pregnancy disorders should be considered to prevent the consequences later on (Asad and Garovic, 2014). A study conducted at Swedish University Hospital reported that women with gestational hypertension had significantly increased the chance of getting microalbuminuria and chronic hypertension after seven years follow-up (Nisell *et al.*, 1995). The presence of hypertension during pregnancy is also highly associated with renal disease (Nisell *et al.*, 1995).

1.3 Pathogenesis of Kidney Disease in Hypertensive Pregnant Women

The kidney plays an important part in the adaptive physiology of the pregnant woman, so it will presenting some renal function alterations found in hypertensive women (Machado *et al.*, 2012). Hypertension is the most common medical complication of pregnancy and also can continue from pregnancy to postpartum. Pregnancy is a condition of chronic volume and sodium overload that leads to increased cardiac output, edema, and blood pressure elevation (Ghuman *et al.*, 2009). During delivery, accumulated sodium is rapidly reduced, and it may take up to two months for the salt and water homoeostasis to return to antepartum levels (Ghuman *et al.*, 2009). If patients have underlying conditions such as hypertension, kidney or heart disease, the pattern of physiologic return to the pre-pregnant state may be impaired (Ghuman *et al.*, 2009).

Prakash *et al.* (2006) reported that renal function was normal in 25% of chronic hypertension patients while 9.72% of chronic hypertension patients had a severe renal failure with serum creatinine more than 3 mg/dl. Most of the patients had mild renal insufficiency for chronic hypertension patients during pregnancy with four of seven patients had advanced renal failure required haemodialysis. The risk factors that favour an increased risk for renal progression for those who have essential hypertension was gout, a diuretic agent used, obesity and ageing (Johnson *et al.*, 2005). Women with hypertension disorders during pregnancy was significantly associated with the development CKD where the HR was 9.3 of getting chronic kidney disease and ESRD compared to healthy women (Wang *et al.*, 2013).

An increase of SBP is related to greater chances of a fast decrease of renal function (Strevens, 2002; Shlipak *et al.*, 2005). Hanratty *et al.* (2011) reported that blood pressure

is associated with the incident of CKD. For those who have SBP more than 120 mmHg will increase the risk of getting CKD (Hanratty *et al.*, 2011). Other than that, rapid declination of renal function was associated with the higher blood pressure (Vupputuri *et al.*, 2003). The cooperation of multidisciplinary team obstetricians and nephrologists is important to maintain the normal blood pressure in women with renal impairment and protect the kidney from further worsening (Taylor *et al.*, 2014).

1.4 Prevalence of Kidney Disease

The permanent loss of renal function is one of the major public health problem (Ong-ajyooth *et al.*, 2009; Ingsathit *et al.*, 2010). The prevalence of kidney disease and ESRD is growing worldwide. In US, the estimated prevalence of CKD was 16.8% while 12.1-17.5% in Asia (Hooi *et al.*, 2005). The incidence and prevalence of patients with ESRD had dialysis in Malaysia increased from 88 and 325 per million population (pmp) in 2001 to 170 and 762 pmp in 2009 respectively (Hooi *et al.*, 2005).

Malaysia is a prominent country in the world with diabetic nephropathy needing dialysis (Hooi *et al.*, 2005). In 2005, 15,000 patients were on dialysis and 2000 patients had a kidney transplant (Hooi *et al.*, 2005).

1.5 Burden of Kidney Disease

The rising number of ESRD causes an economic and social burden on the healthcare system. According to the Ministry of Health, based on economic calculation, the cost of dialysis was RM 2500 per month while it was 1.7 times higher in the US for stage 3 and stage 4 CKD compared to stage 1 CKD. In Malaysia, the price increase by 2.6 times higher in patients with stage 4 CKD (Hooi *et al.*, 2005).

The burden of kidney disease is demonstrated by economic, social and medical aspects. The burden of kidney disease is not only life-threatening complications but significantly affects patients' quality of life (Karopadi *et al.*, 2013). Diabetes is one of the factors that mainly contributes to the increasing incidence of ESRD accounting for 58% of new patients accepted for dialysis (Goh *et al.*, 2014). In Malaysia, from the year 1980-2002, the number of patients with transplant and dialysis approached 400 rates per million population (Hooi *et al.*, 2005). Besides, the new dialysis case increased to 2,538 patients in 2004.

Globally, the health care expenses per year for one person requiring dialysis are between $150,000-$200,000 and will exceed $1 trillion this decade. In developed countries like United Kingdom, US and Australia, only 1% of the population needs dialysis or a transplant. However, they consume up to 5% of health care costs. The outcome of patient with dialysis is also poor, and the annual mortality exceeding 25% (Karopadi *et al.*, 2013).

The total cost for haemodialysis is RM33,642 per patient for a year and RM 31,635 for peritoneal dialysis (Hooi *et al.*, 2005). Annually, the amount of haemodialysis conducted reached 402 to 23,000 procedures per year while 70 to 2,300 for peritoneal dialysis per year (Hooi *et al.*, 2005). The mean cost for each haemodialysis treatment is RM169 with the range from RM79.61-RM475.79. For the peritoneal dialysis treatment, the range indicated from RM1,400-RM3,200 per month for one patient with the average of RM2,186 (Hooi *et al.*, 2005). The mean of life years saved for haemodialysis is 10.96 years and 5.21 years for peritoneal dialysis (Hooi *et al.*, 2005). The total cost per life year saved for both haemodialysis and peritoneal dialysis treatment is RM33,642 and RM31,635 respectively (Hooi *et al.*, 2005). The budget for equipment, property,

construction, expenses, and staff was higher for haemodialysis while the budget was higher on peritoneal dialysis for consumables and hospitalization (Hooi *et al.*, 2005).

1.6 Justification of the Study

This study highlights the importance of monitoring hypertension during and after postpartum period. No published study in Malaysia had been done on this topic yet. No study in Malaysia compares the creatinine clearance between gestational and chronic hypertension. There is only a study conducted in Malaysia by the Department of Obstetrics & Gynaecology, University of Malaya Medical Centre that compared the plasma creatinine and on underlying pathogenesis of preeclampsia and pregnancy-induced hypertension (Yelumalai *et al.*, 2010). Thus, this study provides some beneficial information regarding the creatinine clearance value on antenatal and postpartum hypertensive among patients in Hospital USM, Kubang Kerian.

In this study, the pattern of declination of calculated creatinine clearance for non-proteinuria patient was examined. This study was conducted to compare the creatinine clearance between patients with gestational hypertension and chronic hypertension at third trimester, six weeks postpartum, and 12 weeks postpartum. It provides more knowledge on postpartum hypertension and calculated creatinine clearance level that later help in identifying the relation of kidney problem and hypertension on top of improving the management of postpartum hypertensive in future. The consideration of taking renal function as the part of management of hypertensive pregnant as to prevent the long-term consequences especially CKD. Besides, this study also can help physicians to set the best timing in justifying further investigation and management for renal disease during postpartum especially on the duration of follow-up. The follow-up of hypertensive

disorders women after delivery is crucial to detect the complication and underlying disease and also to reduce the mortality and morbidity. Many researchers concentrated on hypertension during pregnancy and how to manage the patient with this complication preceding to delivery (Duley *et al.*, 2007) but the actual prevalence of hypertension after delivery is difficult to identify because of limited information or research on this problem. This matter was reported by the Confidential Enquiries into Maternal Deaths in the United Kingdom, where 10% of maternal deaths caused by hypertensive disorders of pregnancy was during postpartum period (Magee *et al.*, 2005). The failure of obstetricians to link clear goals for follow-up after delivery in high risk patients are showed by the 50% failure rate (Webster *et al.*, 2001). It is recommending to have multiple visits during two to six weeks after delivery depends on defining what is the reason to achieve for every visit (Webster *et al.*, 2001).

1.7 Research Questions

1. Is there any significant mean difference of calculated creatinine clearance levels within gestational and chronic hypertension based on three months follow-up when birth weight and gestational ages at delivery are controlled?
2. Is there any significant mean difference of calculated creatinine clearance levels between gestational and chronic hypertension regardless of three months follow-up when birth weight and gestational ages at delivery are controlled?
3. Is there any significant mean difference of calculated creatinine clearance levels between gestational and chronic hypertension concerning three months follow-up when birth weight and gestational ages at delivery are controlled?

1.8 General Objective

To compare the calculated creatinine clearance level between gestational and chronic hypertension in pregnant women.

1.9 Specific Objectives:

1. To compare the mean of calculated creatinine clearance levels within gestational and chronic hypertension based on three months follow-up when birth weight and gestational ages at delivery were controlled.
2. To compare the mean of calculated creatinine clearance levels between gestational and chronic hypertension regardless of three months follow-up when birth weight and gestational ages at delivery were controlled.
3. To compare the mean of calculated creatinine clearance levels between gestational and chronic hypertension concerning three months follow up when birth weight and gestational ages at delivery were controlled.

1.10 Research Hypotheses

1. There is a significant mean difference of calculated creatinine clearance levels within gestational and chronic hypertension based on three months follow-up when birth weight and gestational ages at delivery were controlled.
2. There is a significant mean difference of calculated creatinine clearance levels between gestational and chronic hypertension regardless of three months follow-up when birth weight, gestational ages at delivery and length of diagnosed were controlled.

3. There is a significant mean difference of calculated creatinine clearance levels between gestational and chronic hypertension concerning three months follow-up when birthweight and gestational ages at delivery were controlled.

CHAPTER 2

LITERATURE REVIEW

All the literature search related to gestational hypertension, chronic hypertension, serum creatinine level, creatinine clearance level and renal function test was widely done. Only articles in English were selected and the search engines used were PubMed, Science Direct, and Google Scholar. The keywords with the of used Boolean operators (AND/OR) were: "creatinine clearance" or "GFR" during "pregnancy" and "postpartum", "creatinine clearance" reduction or "GFR" from pregnancy to postpartum in chronic hypertension women and "creatinine clearance" or "GFR" reduction from pregnancy to postpartum in "gestational hypertension women" or "pregnancy-induced hypertension". All the literature search published from 2005 to 2015 were included.

2.1. Hypertension in Pregnancy

Hypertension is defined as SBP more than 140 mm Hg and/or diastolic blood pressure more than 90 mm Hg during pregnancy (Prakash *et al.*, 2006). There is no longer known as hypertension when the DBP increase by 15 mmHg and SBP increase by 30 mmHg more than baseline BP if the entire values are still below 140/90 mmHg (Bavanandan *et al.*, 2013). Table 2.1 shows the definition and classification of hypertension in pregnancy based on Malaysia Clinical Practice Guideline for management of hypertension.

Table 2.1 Definition and classification of hypertension in pregnancy

Classification	Definition
Chronic hypertension	Hypertension is present before the conception or before 20th week of gestation or starting hypertension in late gestation but fails to resolve at postpartum
Preeclampsia-eclampsia	It is detected in the hypertension after 20th week of gestation, and one or more of the following: • Significant proteinuria. • Renal insufficiency: serum creatinine more than 90 micromol/l or oliguria. • Liver disease • Neurological problems: convulsions (eclampsia) hyperreflexia with severe headaches or clonus, persistent visual turbulences (scotoma). • Haematological instabilities: thrombocytopenia, coagulopathy, haemolysis. • Fetal growth restriction.
Superimposed preeclampsia	Diagnosed in women with chronic hypertension following this criteria: • Detected proteinuria after 20-week gestation • A sudden rise in the severity of hypertension • Presence of features of preeclampsia-eclampsia, • A sudden incline in proteinuria in women who have prior proteinuria early in gestation
Gestational hypertension	Hypertension diagnosed for the first time after 20 weeks of gestation. The definition is changed to "temporary" when blood pressure stabilizes at postpartum.

Source: (Bavanandan *et al.*, 2013)

2.2 Assessment for Hypertensive Pregnant Women

Preeclampsia should be assessed in any woman with a new onset hypertension when 20 weeks gestation. The assessment and management of this patient must be appropriate (Lowe *et al.*, 2015). The urgent hospital admission should be considered if patients diagnosed preeclampsia have the threatening signs and symptoms of severe hypertension, epigastric pain, headache, nausea and vomiting (Vijgen *et al.*, 2010).

At each investigation instead of diagnosing hypertension in pregnancy, the clinician should consider the woman's symptoms, laboratory investigations and foetal health (Lowe *et al.*, 2015). Table 2.2 shows further laboratory investigation in hypertensive women during pregnancy.

Table 2.2 The laboratory investigation in hypertensive women during pregnancy

	Modality	**Frequency**
Chronic Hypertension	Assess for proteinuria	Each visit
	Blood test for preeclampsia (FBC, electrolytes and creatinine, LFT)	If rapid increase in BP or new proteinuria
Gestational Hypertension	Assess for proteinuria	At time of diagnosis: if non-protein uric repeat daily (ignore the assessment once proteinuria has been detected)
	Blood test for preeclampsia (FBC, electrolytes and creatinine, LFT)	Twice weekly or more regularly if unstable

Source: (Lowe *et al.*, 2015)

2.3 Management of Hypertension Disorders during Pregnancy

Antihypertensive treatment should be on-going in all women with a systolic blood pressure of greater than or equal to 160mm Hg or a diastolic blood pressure greater than or equal to 110 mm Hg (Lowe *et al.*, 2015). Hypertensive pregnant women should be brought up to an obstetrician for further investigation and management.

The basic choices of the drug are still labetalol and methyldopa (Bavanandan *et al.*, 2013). Intravenous hydralazine or Intravenous labetalol or oral nifedipine are used in the occurrence of severe hypertensive crisis to lower the BP in pregnant women. Otherwise,

to reduce the risk of severe gestational hypertension, 1.5 g/day of high calcium supplement can be taken (Bavanandan *et al.*, 2013).

Among chronic hypertension women, a preconception psychotherapy and regulation of treatment should be done. They may require an adjustment in the type of anti-hypertensive drug used before pregnancy. Drugs like Angiotensin II receptor blockers (ARB), Angiotensin converting enzyme (ACE), and thiazide diuretics are related to foetal abnormality so that they are contraindicated in pregnancy (Bavanandan *et al.*, 2013).

Patients with hypertensive disorder are suggested to bed rest in order to accelerate the uterine blood flow and stimulate nutrition to the foetus. The sitting position is the recommended position for outpatient blood pressure checking (Shah, 2007). Table 2.3 until table 2.5 show the antihypertensive drug treatment used in pregnancy and postpartum, dose and side effects.

Table 2.3 Guidelines for selecting antihypertensive drug treatment in pregnancy

Drug	Dose	Action	Contra-indications	Practise Points
Methyldopa	250-750mg tds 75-300µg tds	Central	Depression	Slow onset of action over 24H, dry mouth, depression, sedation, blurred vision
Clonidine	-	-	-	Withdrawal effects: rebound hypertension
Labetalol	100-400mg q8h	β Blocker with mild alpha vasodilator effect	Asthma, chronic airways limitation	Bradycardia, bronchospasm, headache, nausea, scalp tingling (resolves within 24H)
Oxprenolol	20-160mg q8h	-	-	-
Nifedipine	20mg-60mg slow release bd	Ca channel antagonist	Aortic stenosis	Severe headache in first 24 hours Flushing, tachycardia, peripheral oedema, constipation
Prazosin	0.5-5 mg q8h	α blocker	-	Orthostatic Hypotension (especially after first dose)
Hydralazine	25-50 mg q8h	Vasodilator	-	Flushing, headache, nausea, lupus-like syndrome

Source: (Lowe *et al.*, 2015)

Table 2.4 The most frequently used agents to stabilize blood pressure ≥ 160/110 mmHg

Agent	Dose	Onset	Peak	Duration
Labetalol	Start with 20 mg IV; Repeat 20 to 80 mg IV q 30 min, or 1 to 2 mg/min, max 300 mg (then switch to oral)	5 min	30 min	4 hr
Nifedipine	5 to 10 mg capsule to be swallowed, or bitten then swallowed, every 30 min	5 to 10 min	30 min	≈6 hr
Hydralazine	Start with 5mg IV; repeat 5 to 10 mg IV every 30 min, or 0.5 to 10 mg/hr IV, to a maximum of 20 mg IV (or 30 mg IM)	5 min	30 min	

Source: (Benton *et al.*, 2011; Bavanandan *et al.*, 2013)

Table 2.5 The drug used for postpartum hypertension

	Labetalol	Hydralazine	Nifedipine
Dose	100mg bd (oral): 20mg/h iv infusion, doubled every 30min: max 2.4g daily (oral) or 160mg/h iv infusion	200-300μg/min iv infusion: maintenance dose 50-150 μg/min iv infusion	10 mg bd orally, adjusted according to response to a maximum dose of 60mg daily in divided doses
Side-effects	Postural hypotension, Dizziness, tiredness, headache, rashes, scalp tingling, difficulty in micturition, gastrointestinal symptoms, liver damage	Headaches, nausea, sweating, arrhythmias, precipitation of angina, anxiety, restlessness, hyper-reflexia	Tachycardia, palpitations, dizziness, flushing, headache, rash, pruritus, urticarial, nausea, diarrhoea, constipation, eye pain, depression
Safe in breastfeeding	Yes	Yes (but monitor infant)	Yes

Source: (Chandiramani *et al.*, 2007)

The timing of delivery at 37 weeks of gestation and above among gestational hypertension women should be discussed by the physician. But there is no enough evidence to make a suggestion to deliver less than 37 weeks of gestation for women with

gestational hypertension unless they are diagnosed to have preeclampsia (Magee *et al.*, 2014). Meanwhile, chronic hypertension women who had no complication and healthy at 37 weeks of gestation and above should be considered to deliver at 38 to 39 weeks of gestation (Magee *et al.*, 2014). Vaginal delivery should be considered for women with hypertension during pregnancy, but caesarean delivery is compulsory when there is obstetric complications (Magee *et al.*, 2014). The use of ripening agents with prostaglandins makes the vaginal delivery more possible (Shah, 2007).

2.4 Management of Hypertension Disorders during Postpartum

Hypertensive disorder women are advised to have their blood pressure frequently checked at a local clinic if there is a delay in their hospital appointment. The dose of the antihypertensive drug should be slowly decreased and not suddenly stop for these patients (Bavanandan *et al.*, 2013). For women with gestational hypertension, the antihypertensive drug is given approximately one week at postpartum (Bavanandan *et al.*, 2013). Women with chronic hypertension will need a long duration of antihypertensive treatment in pregnancy and blood pressure usually start to normalize six weeks after delivery (Lowe *et al.*, 2015). Women with unstable blood pressure and established hypertension after delivery may require a medication tuning. Besides, non-steroidal inflammatory drugs should not be given if the hypertension is difficult to control during postpartum because of the occurrence of AKI or CKD, or thrombocytopenia (Lowe *et al.*, 2015). Meanwhile, not all the established hypertension women will require treatment during pregnancy. Basically, for those who have the highest risk of preterm labour and multiparous women will need treatment because of the elevation of the serum urate concentration (Lowe *et al.*, 2015).

It is important to follow-up the patients after six weeks to make sure determination or resolution of pregnancy-related changes and further ongoing care needed. It is advisable to follow-up the high-risk patients within three to six months (Julius *et al.*, 2006). This care included further investigation and management of renal disease (Lowe *et al.*, 2015). It is also important to ensure normalization of blood pressure during postpartum in women with uncertain blood pressure control before pregnancy (Lowe *et al.*, 2015). Women with persistent hypertension not previously assessed should undergo routine work-up according to standard regimens (Lowe *et al.*, 2015).

2.5 Renal Function in Hypertensive Pregnant Women

A serum creatinine determination for creatinine clearance estimation is very important to screen renal disease (Snyder and Pendergraph, 2005). A laboratory tests used to evaluate and monitor organ function over time during pregnancy are urine volume, creatinine, protein in the urine, and albumin (Magee *et al.*, 2014). Department of Obstetrics & Gynaecology, University of Malaya Medical Center reported the results on the renal function among hypertensive disorder women at the early pregnancy, late pregnancy and six weeks of postpartum. There were a significant mean differences of plasma creatinine between pre-eclampsia and normal pregnant women in all three measurements. There was also a significant mean difference of plasma creatinine between pregnancy-induced hypertension and normal pregnant women during late pregnancy (Yelumalai *et al.*, 2010). Based on a study conducted in Sweden, the creatinine clearance was significantly higher in women with preeclampsia compared to women with gestational hypertension (Strevens, 2002).

Parity does affect the renal function due to increase age and comorbid of the maternal (Wang *et al.*, 2011). For women who delivered at age more than 30 years had significantly increased the HR of chronic renal failure by 2.52 compared to women who delivered at age 25 years (Kuo *et al.*, 2012). The increasing age at the first birth will increase the risk of chronic renal failure death (Kuo *et al.*, 2012). In five cohort study population, older women have less schooling and higher parity because of educated women are likely to delay pregnancy for career reasons (Fall *et al.*, 2015). Many underlying diseases like hypertension, diabetes and obesity were associated complication during pregnancy in older women (Fall *et al.*, 2015). Baby birth weight is one of the associated factors of decreasing the renal function and increase the risk of end stage renal disease. Women with preterm birth low birthweight increase the risk of getting end stage renal disease (Wang *et al.*, 2013; Wu *et al.*, 2014). It was also reported that the blood pressure levels during common pregnancy is associated with gestational age, race, BMI and parity (Strevens, 2002).

2.6 Creatinine Clearance during Pregnancy

Pregnancy is related to the changes in the hormone that affects the renal function. Creatinine clearance will increase in pregnancy due to the increase of ultrafiltration capacity and reduced of average colloid osmotic pressure (Hussein and Lafayette, 2014). The kidneys size will increase up to 1 cm during pregnancy, and the most remarkable changes can be found in the urinary tract (Podymow and August, 2007). The changes of renal hemodynamic can be seen at the end of the first trimester when both GFR and renal plasma flow increase by 50% (Podymow and August, 2007). Measurement of kidney function and proteinuria are the most important and act as early standard detection of subclinical pathology in recognizing the renal disease. The choice of medications and the

changes of hormone and hemodynamic changes in pregnancy must be considered to assess renal function in pregnancy (Maynard and Thadhani, 2009). The normal value of serum creatinine (umol/L) during the third trimester of pregnancy is in the range 35 to 80 (Brenner, 2004).

The level of GFR usually will increase during pregnancy due to the decrease in serum creatinine concentration. The average falls by 0.4 mg/dl to a pregnancy range of 0.4-0.8 mg/dl (Fischer, 2007). Hence, although a serum creatinine of 1.0 mg/dl is a normal range for non-pregnant woman, it reveals the renal damage in a pregnant woman (Maynard and Thadhani, 2009). During pregnancy, creatinine clearance was found 40% higher compared with non-pregnant women (Hussein and Lafayette, 2014). Then, it will decline to normal non-pregnant level one month after delivery (Hussein and Lafayette, 2014). The renal plasma flow and creatinine clearance will change because of the exceeding renal plasma flow compared to the creatinine clearance in the early pregnancy (Hussein and Lafayette, 2014). The filtration fraction is slightly lower in non-pregnant controls (Hussein and Lafayette, 2014). The renal plasma flow falls toward non-pregnant levels between week 12 and third trimester while the creatinine clearance will usually normalize after 4-6 weeks postpartum (Odutayo and Hladunewich, 2012). Figure 2.1 shows the trend of GFR, RPF and FF during and post-delivery in normal pregnant women.

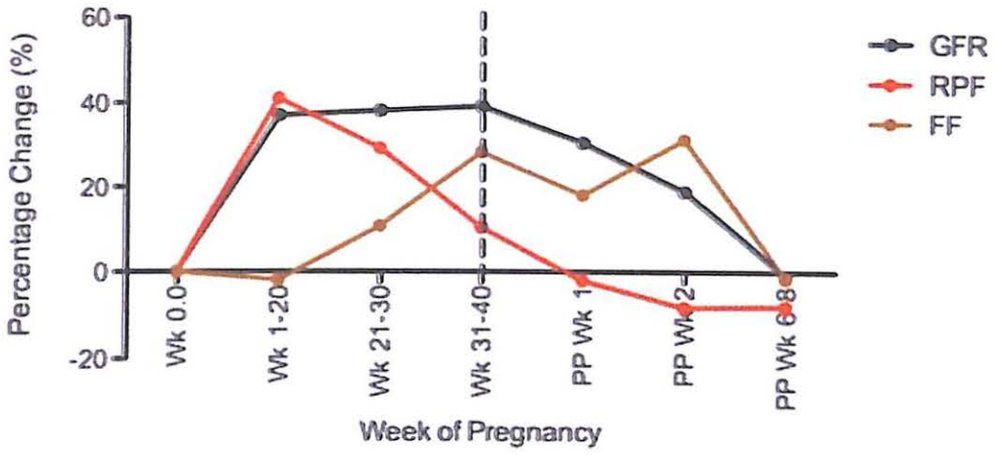

Figure 2.1 GFR, RPF and FF trends in normal pregnant women from pregnancy to postpartum (GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction)

Source: (Odutayo and Hladunewich, 2012)

2.7 Physiology of Hypertensive Disorder during Pregnancy

The important of monitoring the patients with chronic hypertension in pregnancy is because they have the higher incidence of getting the superimposed preeclampsia. Thus, the prospective studies of chronic hypertensive may be helpful in clarifying early complication which are important in the pathophysiology of preeclampsia. In most women with chronic hypertension, creatinine clearance is normally increase during pregnancy, but will decrease when superimposed preeclampsia is developed (Roberts *et al.*, 2009).

In women with pregnancy-induced hypertension, the creatinine clearance level will slightly decrease during pregnancy compared to normal pregnancy (Odutayo and Hladunewich, 2012). Meanwhile, the creatinine clearance was significantly low to 91 ml/min in women with preeclampsia compared to a value of 148 ml/min in healthy women (Odutayo and Hladunewich, 2012). This reduction is because of two phenomena. The first is because of the low protein concentration in plasma that enters the glomerular

microcirculation and the second is because of the renal plasma flow elevation (Odutayo and Hladunewich, 2012).

2.8 Pathogenesis of Kidney Disease in Hypertensive Pregnant Women

The kidney plays an important part in the adaptive physiology of the pregnant woman, so it will presenting some alterations found in hypertensive women (Machado *et al.*, 2012). Hypertension is the most common medical complication of pregnancy and also can persevere from pregnancy to postpartum. Pregnancy is a condition of chronic volume and sodium overload that leads to increased cardiac output, oedema, and blood pressure elevation (Ghuman *et al.*, 2009). During delivery, accumulated sodium is rapidly reduced, and it may take up to 2 months for the salt and water homoeostasis to return to antepartum levels (Ghuman *et al.*, 2009). If patients have underlying conditions such as hypertension, kidney or heart disease, the pattern of physiologic return to the pre-pregnant state may be impaired (Ghuman *et al.*, 2009). Prakash *et al.* (2006) reported that renal function was normal in 25% of chronic hypertension patients while 9.72% of chronic hypertension patients had a severe renal failure with serum creatinine more than 3 mg/dl.

Most of the patients had mild renal insufficiency for chronic hypertension patients during pregnancy with four of seven patients had advanced renal failure required haemodialysis. The risk factors that favour an increased risk for renal progression for those who have essential hypertension was gout, a diuretic agent used, obesity and ageing (Johnson *et al.*, 2005). Women with hypertension disorders during pregnancy was significantly associated with the development CKD where the HR was 9.3 of getting CKD and ESRD compared to healthy women (Wang *et al.*, 2013). The cooperation of multidisciplinary team obstetricians and nephrologists is important to maintain the normal blood pressure

in women with renal impairment and protect the kidney from further worsening (Taylor *et al.*, 2014).

An increase of SBP is related to greater chances of a fast decrease of renal function (Strevens, 2002; Shlipak *et al.*, 2005). Hanratty *et al.* (2011) reported that blood pressure is associated with the incident of CKD. For those who have SBP more than 120 mmHg will increase the risk of getting CKD (Hanratty *et al.*, 2011). Other than that, one study found that those who was higher treated blood pressure was related to prompt renal function decline (Vupputuri *et al.*, 2003).

2.9 Calculation of Creatinine Clearance

Serum creatinine level and creatinine clearance tests are used to indicate renal function. The rate of creatinine clearance is the indication of the kidneys' ability to filter the blood. The decrease value of creatinine clearance shows the poor renal function (Brenner, 2004). There are two main methods of creatinine tests to measure kidney function (Brenner, 2004):

- Creatinine clearance can be accurately determined by assessing the amount of creatinine present in a sample of urine collected over 24 hours. This method needs a person to urinate completely in a container for one day to test for the amount of creatinine in the urine. This method is inconvenient to assess the creatinine clearance, but it may be necessary to diagnose some kidney conditions.
- GFR can be estimated using only blood level of creatinine, which is calculated by using a formula. Different formulas are available, which take into account age, sex, and sometimes weight and ethnicity. The higher the blood creatinine level, the lower the estimated GFR and creatinine clearance.

For practical reasons, the blood test estimation method for GFR is used far more often than the 24-hour urine collection test for creatinine clearance.The calculated creatinine clearance is also a good estimate of GFR, but it becomes imprecise when a patient's body mass is considerably outside the normal range (for example, morbid obesity or severe malnutrition) or when renal function is very decreased (i.e. GFR <20 mL/min). In this study, Modification of Diet in Renal Disease (MDRD) formula was used because it was more convenience and practical to apply compare to measured creatinine clearance (Brenner, 2004). It is a standard clinical method to estimates GFR using a combination of serum markers and clinical parameters (Maynard and Thadhani, 2009). The formula for MDRD eGFR is calculated in ml/min/1.73m^2 (Maynard and Thadhani, 2009):

$$175 \times (\text{Serum Creatinine} / 88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$$

2.10 Conceptual Framework

Figure 2.2 shows the conceptual framework of this study. Calculated creatinine clearance of participants with gestational and chronic hypertension were evaluated at third trimester, six weeks postpartum and 12 weeks postpartum.