INCIDENCE AND RISK FACTORS OF PREECLAMPSIA IN RAMATHIBODI HOSPITAL

KORRAVARN YODMAI

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE
(HUMAN REPRODUCTION AND POPULATION PLANNING)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2007

Thesis
Entitled

INCIDENCE AND RISK FACTORS OF PREECLMAPSIA IN RAMATHIBODI HOSPITAL

Korravarn Yodmai
.....

Miss. Korravarn Yodmai
Candidate

Somsak Suthutvoravut
.....

Assoc.Prof.Somsak Suthutvoravut,
M.D., Dip. Thai Board of Ob.&Gyn.,
Dip. Field Epidemiology (C.D.C.)
Major-Advisor

Sanya Patrachai
.....

Asst.Prof.Sanya Patrachai,
M.D., Dip. Thai Board of Ob.&Gyn.,
M.P.H.
Co-Advisor

V. Singhakajen
.....

Assoc.Prof.Vajira Singhakajen,
B.A.(Stat.), LL.B.,
M.A.(Demography),
Co-Advisor

Svasti
.....

Prof.M.R.Jisnuson Svasti,Ph.D.
Dean
Faculty of Graduate Studies

Somsak Suthutvoravut
.....

Assoc.Prof.Somsak Suthutvoravut,
M.D., Dip. Thai Board of Ob.&Gyn.,
Dip. Field Epidemiology (C.D.C.)
Chair
Master of Science Programme in
Human Reproduction and Population
Planning
Faculty of Medicine
Ramathibodi Hospital

Thesis
Entitled

INCIDENCE AND RISK FACTORS OF PREECLMAPSIA IN RAMATHIBODI HOSPITAL

was submitted to the Faculty of Graduate Studies, Mahidol University for the degree of Master of Science (Human Reproduction and Population Planning)
on
May 17, 2007

Korravarn Yodmai
.....
Miss.Korravarn Yodmai
Candidate

A Chittacharoen
.....
Prof.Apichart Chittacharoen,
M.D., Dip. Thai Board of Ob.&Gyn.,
Chair

V. Singhakajen
.....
Assoc.Prof.Vajira Singhakajen,
B.A.(Stat.), LL.B.,
M.A.(Demography),
Member

Somsak Suthutvoravut
.....
Assoc.Prof.Somsak Suthutvoravut,
M.D., Dip. Thai Board of Ob.&Gyn.,
Dip. Field Epidemiology (C.D.C.)
Member

Somsak W.
.....
Dr.Somsak Wachirachaikan
M.D., Dip. Thai Board of Ob.&Gyn.,
Member

Sanya Patrachai
.....
Asst.Prof.Sanya Patrachai,
M.D., Dip. Thai Board of Ob.&Gyn.,
M.P.H.
Member

Svasti
.....
Prof.M.R.Jisnuson Svasti,
Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

Rajata Rajatanavin
.....
Prof.Rajata Rajatanavin,
M.D., F.A.C.E.,
Dean
Faculty of Medicine
Ramathibodi Hospital
Mahidol University

ACKNOWLEDGEMENTS

This thesis would never have been completed without the support and advice of the following persons to whom I would like to express my heartfelt thanks for their valuable assistance.

I would like to express my great gratitude to Associate Professor Somsak Suthutvoravut, my major advisor who provided clear guidance with intellectual direction to my thesis.

I am very grateful to my co – advisor, Assistance Professor Sanya Patrachai and Associate professor Vajira SinghakaJen for their kindness and valuable advice.

Finally, I received whole-heart encouragement and complete support from everyone in my family, without them this research could not have been complete.

Korravarn Yodmai

INCIDENCE AND RISK FACTORS OF PREECLAMPSIA IN RAMATHIBODI HOSPITAL

KORRAVARN YODMAI 4837940 RAHP/M

M.Sc. (HUMAM REPRODUCTION AND POPULATION PLANNING)

THESIS ADVISORS: SOMSAK SUTHUTVORAVUT, M.D., DIP.THAI BOARD OF OB & GYN, Dip. FIELD EPIDEMIOLOGY (C.D.C.) SANYA PATRACHAI, M.D.,DIP. THAI BOARD OF OB & GYN, M.P.H, VAJARA SINGHAKAJEN, B.A., (STAT), LL.B, M.A.(DEMOG.)

ABSTRACT

The first part of this study is a historical cohort study with the objective to determine the incidence of preeclampsia among nulliparous women who came to register for the first time at the antenatal care booking unit Ramathibodi Hospital, Thailand during 1 January – 30 December 2005. The second part is a case – control study with the objective to determine risk factors of preeclampsia. During the study period, there were 2,543 pregnant women who came to register for the first time. For those who failed to follow up attempt to contact was done by mail or telephone. Overall, 68.7 percentage of women who registered had known outcomes of pregnancy (65.7% delivery, 3.1% abortion). Descriptive statistics were number and percentage. Analytical statistics including odds ratio with 95% confidence intervals, chi – square test, and logistic regression were used to determine risk and association of factors and preeclampsia. SPSS/PC$^+$ program was used for statistical analysis.

The results of the study showed that the incidence of preeclampsia was 4.9% (3.4% mild preeclampsia and 1.5% severe preeclampsia). The case - control study included 82 cases of preeclampsia and 82 cases of control. The controls were selected from pregnant women who came to register on the same day just after the preeclampsia cases. The significantly associated factors were maternal age more than 30 years old, occupation of house-wife, body mass index (BMI) at first ANC visit more than 25 kg/m^2, and mean gain weight of 0.5 kg/wk or more than ($p < 0.05$).

In conclusion, incidence of preeclampsia in Ramathibodi Hospital is comparable to other studies. Risk factors of preeclampsia could be applied in screening pregnant women and to advise them and prepare services to prevent and treat risk of or development of preeclampsia.

KEY WORD: INCIDENCE / RISK FACTORS / PREECLAMPSIA

68 pp.

อุบัติการณ์ และ ปัจจัยเสี่ยงที่มีความสัมพันธ์กับการเกิดภาวะ preeclampsia ในโรงพยาบาลรามาธิบดี (INCIDENCE AND RISK FACTORS OF PREECLAMPSIA IN RAMATHIBODI HOSPITAL)

กรวรรณ ยอดไม้ 4837940 RAHP / M

วท.ม. (การเจริญพันธุ์และวางแผนประชากร)

คณะกรรมการควบคุมวิทยานิพนธ์ ; สมศักดิ์ สุทัศน์วรวุฒิ, พ.บ. ว.ว.(สูติ นรีเวช) สัญญา ภัทราชัย, พ.บ. ว.ว. (สูติ นรีเวช) วชิระ สิงห์หคเชน, สค.ม (ประชากรศาสตร์)

บทคัดย่อ

ส่วนแรกของการศึกษาครั้งนี้เป็น การศึกษาแบบ historical cohort study ซึ่งวัตถุประสงค์เพื่อศึกษาอุบัติการณ์ของการเกิดภาวะ preeclampsia ของหญิงตั้งครรภ์แรกที่มาลงทะเบียนฝากครรภ์ ที่โรงพยาบาลรามาธิบดี ช่วงวันที่ 1 มกราคม ถึง 30 ธันวาคม 2548 ส่วนที่สอง เป็นการศึกษาแบบ case control ซึ่งมีวัตถุประสงค์เพื่อศึกษาปัจจัยเสี่ยงต่อการเกิดภาวะ preeclampsia ในช่วงที่ทำการศึกษามีหญิงตั้งครรภ์แรก มาลงทะเบียนครั้งแรกในการฝากครรภ์จำนวน 2,543 ราย และในจำนวนนี้มีที่ไม่ทราบการคลอดและการแท้ง ได้มีการติดตามโดยการส่งจดหมาย และโทรศัพท์ไปสอบถามเพิ่มเติม สรุปโดยรวมพบว่า ร้อยละ 68.9 ทราบผลการคลอดและแท้ง โดยร้อยละ 65.7 ทราบผลการคลอด และ ร้อนละ 3.1 แท้งบุตรก่อนอายุครรภ์ 20 สัปดาห์ สถิติที่ใช้ ได้แก่ สถิติพรรณนา ประกอบไปด้วย จำนวน และร้อยละ และสถิติวิเคราะห์ ประกอบด้วย odds ratio, 95% confidence interval, chi – square และ logistic regression เพื่อหาปัจจัยเสี่ยงที่มีความสัมพันธ์กับภาวะ preeclampsia โดยใช้โปรแกรม SPSS/ PC^+ ในการวิเคราะห์ข้อมูล

ผลการศึกษาพบว่า มีหญิงตั้งครรภ์จำนวน 82 คน เกิดภาวะ preeclampsia ดังนั้น อุบัติการณ์ของการเกิดภาวะ preeclampsia ในโรงพยาบาลรามาธิบดี เท่ากับ ร้อยละ 4.9 โดยร้อยละ 3.4 เป็นชนิดไม่รุนแรง (mild preeclampsia) และร้อยละ 1.5 เป็นแบบชนิดรุนแรง (severe preeclampsia) และการศึกษา case control ประกอบด้วยหญิงตั้งครรภ์ที่มีและไม่มีภาวะ preeclampsia จำนวน 82 คน เท่าๆกันสตรีที่ไม่มีภาวะ preeclampsia เลือกจากหญิงตั้งครรภ์ที่มาฝากครรภ์ในวันเดียวกัน และต่อหลังจาก หญิงตั้งครรภ์ที่มีภาวะ preeclampsia ทันที พบว่า หญิงตั้งครรภ์ที่มีอายุมากกว่า30ปี, แม่บ้าน, ดัชนีมวลกายเมื่อมาฝากครรภ์ครั้งแรกมากกว่า 25 กิโลกรัมต่อตารางเมตร, และน้ำหนักเฉลี่ยที่เพิ่มขึ้นมากกว่า 0.5กิโลกรัมต่อสัปดาห์ มีความสัมพันธ์กับการเกิดภาวะ preeclampsia อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$)

โดยสรุป อุบัติการณ์การเกิดภาวะ preeclampsia ในโรงพยาบาลรามาธิบดี ใกล้เคียงกับการศึกษาอื่นๆ ปัจจัยเสี่ยงที่มีความสัมพันธ์กับภาวะ preeclampsia สามารถนำไปจำแนกหญิงตั้งครรภ์ ให้คำแนะนำและเตรียมการดูแลและป้องกันรักษาความเสี่ยง และการเกิดภาวะ preeclampsia ได้

68 หน้า

CONTENTS

CONTENTS (Conts.)

LIST OF TABLES

CHAPTER I
INTRODUCTION

Significance of Problem

Preeclampsia is a disorder that occurs only during pregnancy and the postpartum period and affects both the maternal and the unborn baby (1). Pre-eclampsia occurs in 6% of pregnancies, usually in the second or third trimester, and after the 32nd week (2). However, some women with rapidly advancing disease reported few symptoms. Preeclampsia and other hypertensive disorders of pregnancy are a leading global cause of maternal and infant illness and death. By conservation estimates, these disorders are responsible for 76,000 deaths each year (3).

However, around one in 2,000 cases of pre-eclampsia can develop into eclampsia, a potentially lethal condition for both mother and baby. Eclampsia is a severe form of preeclampsia. Women with eclampsia have seizures resulting from the condition. Eclampsia occurs in about one in 1,600 pregnancies and develops near the end of pregnancy, in most cases. HELLP syndrome is a complication of severe preeclampsia or eclampsia. HELLP syndrome is a group of physical changes including the breakdown of red blood cells, changes in the liver and low platelets (3).

Eclampsia complicates 1 in 2,000 maternities in the United Kingdom and carries a maternal mortality of 1.8 percentages. The HELLP syndrome is more common, probably about 1 in 50 maternities, but may be as dangerous as eclampsia itself. These two major maternal crises can present unheralded prodromal signs of preeclampsia. Cerebral hemorrhage is a lesion that can kill women with preeclampsia or eclampsia (4).

In 1983, the Ministry of Public Health of Thailand reported that pregnancy-induced hypertension or preeclampsia was an important condition which was a leading cause of maternal deaths in the country, after hemorrhage and infection (5).

The cases of maternal deaths reported by the Ministry of Pubic Health during 1989-1993 indicated that hemorrhage and infective were the first and second leading causes of death and preeclampsia was the third. Reported statistics on preeclampsia in

Thailand were different due to studies arising from difference groups of population and survey periods (5).

One problem of the statistics of incidence of pregnancy – induced hypertension or preeclampsia is the research design of study. Most reports were cross sectional study which included or excluded referred cases which resulted in distortion of incidence or prevalence of the disease.

Pregnant women who wish to delivery their babies in Ramathibodi Hospital have to come to register at the booking unit during early pregnancy and come to antenatal care visit in the hospital. Because of well organized and complete system of antenatal care visits and their record, if is possible to do a cohort study to determinate the more accurate incidence of preeclampsia among middle classes Thai pregnant women.

Objective of the study: To study

1. Incidence of preeclampsia among nulliparous women who came to register at the antenatal booking unit Ramathibodi Hospital.

2. Factors associated with preeclampsia. Factors included were maternal age, occupation, birth place, present illness, hematocrit at registration, body mass index at first the antenatal visit, mean weight gain during the antenatal visits and multiple pregnancies.

Hypothesis:

Those factors which were significantly association with preeclampsia included maternal age, occupation, birth place, present illness, hematocrit at antenatal care visit, body mass index at first the antenatal visit, mean weight gain during pregnancy and multiple pregnancies.

Scope of the study:

The study recruited pregnant women who came to register at the antenatal booking unit Ramathibodi Hospital during 1st January to 30th December 2005. Their

outcome of pregnancy were them follow. Risk factors of preeclampsia were done by case-control study by recording case of preeclampsia and control of non-preeclampsia.

Definition of terms:

1. Age was calculated from the present year minus year at birth.

2. Body mass index (BMI) was calculated from weight divided by height square. Measurement of weight and height at the initial prenatal visit.

$$BMI = \frac{\text{weight (kg)}}{\text{Height (m)}^2}$$

3. Multiple pregnancies are number of baby of labor.

4. Mean body weight gain is defined as weight of pregnant women gained during the pregnancy: weight on the date of delivery minus her weight at the first the antenatal booking unit.

5. Hematocrit is defined as blood concentration (gm %) measurement at the first antenatal booking unit.

6. History present of illness is history of chronic disease previous pregnancy.

7. Occupation was type of occupation during pregnancy.

8. Preeclampsia:

Preeclampsia is a common problem during pregnancy, affecting up to one in seven pregnant women around the world. This condition is defined by high blood pressure and excess protein in the urine after 20 weeks of pregnancy. It may also be called toxemia or pregnancy-induced hypertension.

Diagnosis by The committee on terminology American college of obstricians and gynecologists (ACOG)

1. Hypertension is defined as either:

1.1 Systolic blood pressure more than 140 mmHg

1.2 Diastolic blood pressure more than 100 mmHg

1.3 A rise in systolic blood pressure of at least 30 mmHg

1.4 A rise in diastolic blood pressure of at least 15 mmHg

Blood pressure elevation should be documented on at least two occasions 6 hour or more apart.

2. Proteinuria is defined as 300 mg/l or more of protein in a 24 hour urine collection or protein urine 1+ or more by dipstick.

The diagnosis of preeclampsia is based on blood pressure criteria with proteinuria or edema or both are present.

Classification of hypertension in pregnancy by ACOG

Pregnancy-induced hypertension (PIH) is defined as hypertension during pregnancy and divided in to:

1. Preeclampsia is defined as hypertension after 20 week's gestation concurrent with proteinuria or pitting edema of 1+ after bed rest 12 hours or complicated. Preeclampsia is divided into:

1.1. Mild preeclampsia is defined as a systolic blood pressure not over than 160 mmHg or diastolic blood pressure not over than 110 mmHg concurrent with proteinuria less than 5gm per lit in 24-hour urine or 1+ - 2+ proteinuria on dipstick.

1.2. Severe preeclampsia is defined as hypertension and one or more of following complication:

1.2.1. Blood pressure equate to or grater than 160 mmHg systolic or equate to or grater 110 mmHg diastolic, record on two occasions at least 6 hours apart with patient in bed rest.

1.2.2. Proteinuria of 5 grams or more in 24-hours or 3^{+}- 4^{+} proteins on dipstick.

1.2.3. Oliguria

1.2.4. Cerebral or visual disturbances

1.2.5. Epigastric pain

1.2.6. Pulmonary edema or cyanosis

1.2.7. Increase of liver enzyme or jaundice

1.2.8. Serum creatinine level more than 1.6 mg/ 100 ml

1.2.9. A platelet count of fewer than 100 x 10^3 /m^3

2. Eclampsia is defined as preeclampsia plus the development of generalized tonic-clonic seizures not caused by coincidental neurological disorders.

3. Gestational hypertension has high blood pressure, but no excess protein in their urine. In most cases, the high blood pressure is mild and occurs in the later stages of pregnancy. About one in four women with gestational hypertension go on to develop Preeclampsia.

4. Chronic hypertension is high blood pressure that appears before 20 weeks of pregnancy or lasts more than 12 weeks after delivery. In some cases, women know they have chronic high blood pressure before they become pregnant. But, in many cases, women with long-standing high blood pressure are not evaluated for the problem before they become pregnant. Their high blood pressure is discovered only during prenatal care, but because blood pressure is often low in early pregnancy, it may not be detected initially. Chronic high blood pressure is not caused by pregnancy. If it does not disappear after delivery, you probably had it all along and were never diagnosed.

5. Transient hypertension is defined as the development of an elevated blood pressure during pregnancy after 20 week of gestation or in the first 24 hours postpartum without other signs of preeclampsia or preexisting hypertension. The blood pressure must return to normal within 10 days after delivery.

CHAPTER II

LITERATURE REVEIW

In this chapter, concepts and theories on the preeclampsia were presented. The presentation will be organized into different topics as follow:

1. Definition of preeclampsia
2. Pathology of preeclampsia
3. Diagnosis of preeclampsia
4. Treatments of preeclampsia
5. Related researches of risk factors of preeclampsia

Definition of preeclampsia

Preeclampsia is a multisystemic, pregnancy-specific disorder that is diagnosed by new-onset hypertension and proteinuria after 20 weeks' gestation. It is a leading cause of maternal and infant morbidity and mortality worldwide, yet its etiology remains unclear (6).

Pathology of preeclampsia

Pathophysiologies of the condition remain unclear. It is likely, however, that inadequate placental perfusion resulting from inadequate placental invasion precipitates the release of some form of chemical trigger which, in susceptible mothers, leads to endothelial damage, metabolic changes and a form of inflammatory response (7).

In normal pregnancy there is increased biosynthesis of eicosanoids – particularly prostacyclin (PGI2), a vasodilator with platelet inhibitory properties, and thromboxane A2, a vasoconstrictor with a tendency to stimulate platelet aggregation. As both usually increase in proportion to each other, there is a net neutralization and

homeostasis is maintained. This homeostasis is disrupted in pre-eclampsia because of a relative deficiency in prostacyclin due either to a decrease in its synthesis and/or an increase in the production of thromboxane A2. This imbalance leads to vasoconstriction, hypertension, and platelet stimulation. These observations form the theoretical basis behind the use of low-dose aspirin, a prostaglandin inhibitor, in preventing pre-eclampsia. The dose of aspirin required to inhibit thromboxane synthesis is less than that required for prostacyclin inhibition and it should, in theory, therefore reduce the vascular and thrombotic effects (8).

Normal pregnancy is also associated with an increase in angiotensin II, a potent vasoconstrictor, yet despite this it is usual in pregnancy for the peripheral vascular resistance to fall. This appears to be because of a resistance to effects of angiotensin II in normal pregnancy, a phenomenon which seems to be lost in women who are destined to develop preeclampsia. This suggests that abnormalities in the renin-angiotensin-aldosterone system may play a role in the pathogenesis of the condition. Most agree that it seems unlikely, however, that derangements in this system are the primary cause of the pre-eclampsia (8).

In addition to these changes, there also appears to be some form of inflammatory process. There is an increase in the pro-inflammatory cytokines, evidence of neutrophil activation, and an increase in substances capable of causing inflammatory damage, particularly proteases and oxygen radicals. These are also recognized to damage vessel walls. Other systemic metabolic changes include hypertriglyceridaemia and a significant increase in free fatty acids, both associated with acute atherosis (9).

Some of these metabolic changes may cause endothelial damage, which in turn promotes platelet adhesion, stimulates clotting activity and disturbs the normal physiological modulation of vascular tone, further amplifying the response. The resulting secondary damage to other organs gives rise to the clinical features of gestational hypertension, pre-eclampsia, eclampsia and the HELLP syndrome (6).

In normal pregnancy trophoblastic invasion of the maternal spiral arteries causes the diameter of these arteries to increase around five-fold, converting the supply from a high resistance low flow system to one with a low resistance and high flow. In pre-eclampsia adequate invasion does not seem to occur, or is limited to the

decidual portions of the vessels, and the result is inadequate placental blood flow. Inadequate placental invasion is also associated with fetal growth restriction, but not all those with this form of growth restriction develop pre-eclampsia (7).

As the degree of trophoblastic invasion is regulated by the maternal decidual barrier, probably by the action of a specific form of leucocyte, it has been suggested that the primary aetiological factor in pre-eclampsia may be immunological in origin. The predominance of pre-eclampsia in first pregnancies, and the protective effect of parity, further supports an immunological mechanism but the exact nature of this has yet to be elucidated. Nonetheless inadequate placental invasion certainly occurs and may be the trigger to release some factor, or alter the level of some factor, which brings about a response in a susceptible mother. Currently sFlt-1 upregulated in response to placental hypoxia and sEng upregulated in response to cell-surface Eng in conjunction are considered the most likely candidates (9).

Central Nervous System (6)

Tissues are capable of regulating their own blood flow; this process is known as autoregulation. Cerebral perfusion is maintained by autoregulation at a constant level of about 55 mL/min/100 g at a wide range of blood pressures. However, blood pressure may rise to levels at which autoregulation cannot function. When this occurs, the endothelial tight junctions open, causing plasma and red blood cells to leak into the extravascular space. This may result in petechial hemorrhage or gross intracranial hemorrhage. The upper limit of autoregulation varies from one person to another; eg, chronic hypertension may cause medial hypertrophy of the cerebral vessels, resulting in a shift of the curve to the right . This explains the paradox of 2 patients with equally severe hypertension who have markedly different clinical presentations. The young primigravida whose blood pressure is normally 110/70 mm Hg may convulse with a blood pressure of 180/120 mm Hg, while a chronic hypertensive may be asymptomatic or have only a headache at the same pressure.

The mechanism of the cerebral damage in eclampsia is unclear. The pathologic findings are similar to those of hypertensive encephalopathy. These abnormalities include fibrinoid necrosis and thrombosis of arterioles, microinfarcts, and petechial hemorrhages. In both hypertensive encephalopathy and eclampsia, the lesions are

widely distributed throughout the brain, but the brainstem is more severely affected in the former, while the cortex is more severely affected in the latter. Other differences in the two conditions are that eclampsia may be seen in the absence of hypertension and that retinal hemorrhages and infarcts are rare in eclampsia. Two theories have been proposed to explain the pathogenesis of hypertensive encephalopathy, vasospasm, and forced dilation. In the first, vasospasm causes local ischemia, arteriolar necrosis, and disruption of the blood-brain barrier. According to the second, as blood pressure rises above the limit of autoregulation, cerebral vasodilation occurs. Initially, some vessel segments dilate, and some remain constricted. Overdistention of the dilated segments results in necrosis of the medial muscle fibers and damage to the vessel wall. It is possible that both mechanisms are operant.

The presence of cerebral edema in preeclampsia-eclampsia is controversial. One set of researchers stated that cerebral edema was not present in eclamptic patients when autopsy was performed within 1 hour of death and that such edema was a late postmortem change. In contrast, some others found generalized cerebral edema in some autopsy specimens and confirmed increased intracranial pressure in eclamptics with prolonged coma (> 6 hours). Early studies of cerebrospinal fluid opening pressure showed elevated pressures; however, more recent studies have failed to confirm this.

Head computed tomographic (CT) scans in women with eclampsia have shown abnormalities in about one-third. By using fourth-generation equipment and with a short interval from seizure to CT scan, abnormalities may be detected in half the patients. The main findings are focal hypodensities in the white matter in the posterior half of the cerebral hemispheres with occasional lesions in the gray matter, temporal lobes, and brainstem. One researcher suggested that these areas of radiographic hypodensity represented petechial hemorrhages accompanied by local edema. Subarachnoid or intraventricular hemorrhages may be seen in the most severe cases.

Magnetic resonance imaging (MRI) is more sensitive at demonstrating abnormalities than CT scan, but it is not as widely available. T2-weighed MRI scans show high signal in the cortical and subcortical white matter. Most of the abnormalities lie in the occipital and parietal areas in watershed areas where the anterior, middle, and posterior circulations meet. Basal ganglia and brainstem abnormalities occur in more critically ill patients.

Cerebral angiography has been performed in a few patients with eclampsia, revealing diffuse arterial vasoconstriction.

Electroencephalograms (EEGs) show nonspecific abnormalities in about 75% of patients after eclamptic seizures. The pattern is usually a diffuse slowing of activity (theta or delta waves), sometimes with focal slow activity and occasional paroxysmal spike activity. These abnormalities may be seen in other conditions, such as hypoxia, renal disease, polycythemia, hypocalcemia, and water intoxication. The electroencephalographic pattern is unaffected by magnesium sulfate. It gradually returns to normal 6-8 weeks postpartum. Uncomplicated eclampsia causes no permanent neurologic deficit.

Eyes (6)

Both serous retinal detachment and cortical blindness may occur.

Pulmonary System (6)

Pulmonary edema may occur with severe preeclampsia or eclampsia. It may be cardiogenic or noncardiogenic and usually occurs postpartum (11). In some cases it may be related to excessive fluid administration or to delayed mobilization of extravascular fluid (10). It may also be related to decreased plasma colloid oncotic pressure from proteinuria, use of crystalloids to replace blood loss, and decreased hepatic synthesis of albumin. Pulmonary edema is particularly common in patients with underlying chronic hypertension and hypertensive heart disease, which may be manifested by systolic dysfunction, diastolic dysfunction, or both. Aspiration of gastric contents is one of the most dreaded complications of eclamptic seizures. This may result in death because of asphyxia from particulate matter plugging major airways or in chemical pneumonitis from aspirated gastric acid. Aspiration may cause various types of pneumonia, ranging from patchy pneumonitis to full-blown adult respiratory distress syndrome.

Cardiovascular System (6)

Plasma volume is reduced in patients with preeclampsia. Normal physiologic volume expansion does not occur, possibly because of generalized vasoconstriction,

capillary leak, or some other factor. Because the cause of the reduced volume is unknown, management is controversial. One theory is that the decreased volume is a primary event causing a chronic shocklike state. Hypertension is thought to be the result of release of a pressor substance from the hypoperfused uterus or of compensatory secretion of catecholamines. Proponents of this theory advocate avoidance of diuretics and use of volume expanders. Another theory is that decreased volume is secondary to vasoconstriction. Proponents of this theory advocate the use of vasodilators and warn that volume expanders may aggravate hypertension or cause pulmonary edema.

Studies using the Swan-Ganz catheter have demonstrated a spectrum of hemodynamic findings in preeclampsia ranging from a low-output, high-resistance state to a high-output, low-resistance state (13). One study found a low wedge pressure, low cardiac output, and high systemic vascular resistance in untreated nulliparous preeclamptic women, while patients who received various therapies and were usually referred, a wide range of hemodynamics was found (14). The conclusion was that the untreated preeclamptic patient was significantly volume-depleted and that the wide spectrum of hemodynamic findings in the treated group resulted from prior therapy and the presence of other variables such as labor, multiparity, and preexisting hypertension.

In another study of a heterogeneous population of pretreated and nonpretreated patients, a generally consistent profile emerged. Preeclampsia was in general a high cardiac output state associated with an inappropriately high peripheral resistance. Although the systemic vascular resistance was within the normal range for pregnancy, it was still inappropriately high for the elevated cardiac output. The failure of the circulation to dilate in the setting of increasing cardiac output appeared to be a characteristic feature of preeclampsia. The normal wedge and central venous pressures found in their study suggested venoconstriction with central relocation of intravascular volume if the generally accepted reports of decreased plasma volume in preeclampsia are correct. They postulated splanchnic venoconstriction as the mechanism of this volume shift.

Normal pregnant women are resistant to the vasoconstrictor effects of angiotensin II. Pregnant women require about 21/2 times the amount of angiotensin II

required by no pregnant women to raise the diastolic blood pressure 20 mm Hg. Patients who will develop superimposed preeclampsia lose their refractoriness to angiotensin II many weeks before hypertension develops. These patients may be identified as early as 18-24 weeks' gestation by infusion of angiotensin II.

Normal pregnant women lose their refractoriness to angiotensin II after treatment with prostaglandin synthetase inhibitors such as aspirin or indomethacin; this suggests that prostaglandin is involved in mediating vascular reactivity to angiotensin II in pregnancy. Refractoriness to angiotensin II can be restored in patients with preeclampsia by the administration of theophylline, a phosphodiesterase inhibitor that increases intracellular levels of cAMP. Therefore, prostaglandins synthesized in the arteriole may modulate vascular reactivity to angiotensin II by altering the intracellular level of cAMP in vascular smooth muscle.

Liver (6)

The spectrum of liver disease in preeclampsia is broad, ranging from subclinical involvement with the only manifestation being fibrin deposition along the hepatic sinusoids to rupture of the liver. Within these extremes lie the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) and hepatic infarction.

Kidneys (6)

The characteristic lesion of preeclampsia, glomeruloendotheliosis, is a swelling of the glomerular capillary endothelium that causes decreased glomerular perfusion and glomerular filtration rate. Fibrin split products have been found on the basement membrane by some observers, who have suggested that intravascular coagulation may be secondary to thromboplastin released from the placenta. However, the fibrin split products are found infrequently and only in small amounts. Other investigators have detected IgM, IgG, and complement in the glomeruli of some patients and have suggested an immunologic mechanism. Serial renal biopsies have shown that the lesion is totally reversible over about 6 weeks.

Blood (6)

Most patients with preeclampsia-eclampsia have normal clotting studies. In some, a spectrum of abnormalities may be found, ranging from isolated thrombocytopenia to microangiopathic hemolytic anemia to disseminated intravascular coagulation (DIC). Thrombocytopenia is the most common abnormality; a count of less than 150,000/uL is found in 15-20% of patients. Fibrinogen levels are actually elevated in preeclamptic women as compared with normotensive patients. Low fibrinogen levels in preeclampsia-eclampsia are usually associated with abruptio placentae or fetal demise. Elevated fibrin split products are seen in 20% of patients (usually in the range of 10-40 uL/mL). Microangiopathic hemolytic anemia without other signs of DIC may be seen in about 5% of patients, and evidence of DIC is also present in about 5%. In the past, DIC was thought to be the cause of preeclampsia; now it is regarded as a sequela of the disease.

The HELLP syndrome describes patients with hemolytic anemia, elevated liver enzymes, and low platelet count. Criteria for the diagnosis at the authors' institution are schistocytes on the peripheral blood smear, lactic dehydrogenase > 600 U/L, total bilirubin > 1.2 mg/dL, aspartate aminotransferase > 70 U/L, and platelet count < 100,000/mm3. This syndrome is present in about 10% of patients with severe preeclampsia-eclampsia. It is frequently seen in Caucasian patients with delay in diagnosis or delivery and in patients with abruptio placentae. The syndrome may occur remote from term (eg, at 31 weeks) and with no elevation of blood pressure. The syndrome is frequently misdiagnosed as hepatitis, gallbladder disease, idiopathic thrombocytopenic purpura, or thrombotic thrombocytopenic purpura. Most hematologic abnormalities return to normal within 2-3 days after delivery, but thrombocytopenia may persist for a week.

Endocrine System

The role of the renin-angiotensin-aldosterone system in the regulation of blood pressure during normal and hypertensive pregnancy has not been clearly defined. In normal pregnancy, estrogen's effect on the liver markedly increases production of renin substrate. This increases plasma renin activity, plasma renin concentration, and angiotensin II levels. Plasma aldosterone levels rise even higher than can be accounted

for by the prevailing plasma renin activity. Despite the high plasma concentration of aldosterone, there is no blood pressure increase or hypokalemia in normal pregnancy; indeed, blood pressure falls in the midtrimester. This may be due to counterregulatory factors such as the natriuretic effect of progesterone or activation of vasodepressor systems such as kinins or prostaglandins (6).

Interpreting renin, angiotensin, and aldosterone levels in studies of preeclampsia is difficult because of differences in the definition of preeclampsia (parity, degree of proteinuria, early- or late-onset disease), differences in taking of blood samples (values may be affected by bed rest, sodium intake, labor, etc), and differences in assay techniques. In the majority of studies, renin, angiotensin, and aldosterone are all suppressed in preeclampsia, but they are still above nonpregnant levels. The available evidence suggests that the renin-angiotensin system is only secondarily involved in preeclampsia (10).

Atrial natriuretic peptide (ANP) is a volume regulatory hormone synthesized by cardiac myocytes, which has potent natriuretic, diuretic, and vasorelaxant properties. ANP secretion is stimulated by increased atrial pressure and alterations in sodium balance. Elevated concentrations of ANP accompany pathologic states characterized by fluid overload such as Cirrhosis, congestive heart failure, and chronic renal failure. However, ANP is elevated in preeclampsia, a disorder supposedly characterized by hypovolemia. It is even elevated in the second trimester before the onset of clinical evidence of preeclampsia. The mechanism for the elevation is unknown. It may be that endothelin or another vasoactive peptide is stimulating release of ANP. It may also be that the widely accepted concept of central hypovolemia in preeclampsia is incorrect (10).

Catecholamines (11)

Urinary and blood catecholamine levels are the same in normotensive pregnant women, women with preeclampsia, and nonpregnant controls. However, it cannot be ruled out that sympathetic activity is of pathogenetic importance for initiation or maintenance of hypertension in patients with preeclampsia. Catecholamine levels increase during labor, presumably owing to stress. The vascular refractoriness to

catecholamines is lacking in preeclampsia, as is the refractoriness to other endogenous vasopressors such as antidiuretic hormone and angiotensin II.

Prostacyclin (6, 10)

Prostacyclin is a prostaglandin discovered in 1976. It increases intracellular cAMP in smooth muscle cells and platelets resulting in vasodilator and platelet antiaggregatory effects. Its half-life is about 3 minutes, breaking down in plasma to 6-keto-PGF1α, which is stable and can be measured as an indication of prostacyclin levels. These plasma levels are low, indicating that prostacyclin acts physiologically at the local level rather than as a circulating hormone.

Prostacyclin is made primarily in the endothelial cell from arachidonic acid, catalyzed by the enzyme cyclooxygenase. Cyclooxygenase can be inhibited by aspirin-like drugs. Mechanical or chemical perturbation of the endothelial cell membrane stimulates formation and release of prostacyclin. For example, pulsatile pressure or chemicals such as bradykinin or thrombin stimulate prostacyclin generation in the vessel wall.

Thromboxane A2 generated by platelets from arachidonic acid via cyclooxygenase induces vasoconstriction and platelet aggregation. Thus, prostacyclin and thromboxane have opposing roles in regulating platelet-vessel wall interaction.

Aspirin irreversibly inhibits cyclooxygenase. Cyclooxygenase must be produced continuously by endothelial cells, because they recover their ability to synthesize prostacyclin within a few hours after a dose of aspirin. On the other hand, platelets do not have a nucleus and therefore cannot make fresh cyclooxygenase. Thromboxane synthesis recovers only as new platelets enter the circulation. Platelet life span is about 1 week. Thus, daily treatment with low-dose aspirin results in chronic inhibition of thromboxane metabolites and decreased excretion of prostacyclin metabolites in preeclamptic patients. Low-dose aspirin therapy is aimed at restoring the presumed thromboxane-prostacyclin imbalance in preeclampsia.

Nitric Oxide (6)

Nitric oxide (NO) is an endogenous vasodilator and inhibitor of platelet aggregation and acts synergistically with prostacyclin (15). It is produced by

endothelial cells from L-arginine. Synthesis can be inhibited by arginine analogs such as NG-monomethyl-L-arginine and NG-nitro-L-arginine. Intravenous injection of one of these inhibitors into rats, rabbits, or guinea pigs causes an immediate rise in blood pressure that is reversed by L-arginine. This indicates that continual basal release of NO from endothelial cells keeps the vasculature in a dilated state. NO acts only in the immediate vicinity of the cell that releases it. Any that escapes into the bloodstream decays chemically to form nitrite or is immediately inactivated by hemoglobin.

NO plays an important role in several pathologic processes. It is one of the mediators of hypotension in septic shock. A deficiency of NO contributes to the cause of hypertension and Atherosclerosis. Currently it is thought that the NO system may be more important than the prostaglandins in the pathogenesis of preeclampsia. Chronic blockade of the endogenous NO system produces a model of hypertension and renal damage in pregnant and nonpregnant rats. Some studies have shown that there is decreased excretion of NO in the urine of pregnant preeclamptic women, but whether NO plays an important pathophysiologic role in the development of preeclampsia remains unknown.

Endothelin-1 (10)

In addition to the relaxing factors prostacyclin and NO, the vascular endothelium releases vasoconstrictor substances. The vasoconstrictor endothelin was discovered in 1988. There are 3 different isopeptides: endothelin 1, 2, and 3. Endothelin-1 is the only endothelin manufactured by endothelial cells. Endothelins are also synthesized by kidney cells and nervous tissue. There are widespread endothelin-binding sites including those in the brain, lung, kidney, adrenal, spleen, intestine, and placenta. It is thought that endothelins act as endogenous agonists of dihydropyridine-sensitive calcium channels. The most striking property of endothelin-1 is its long-lasting vasoconstrictor action. It is 10 times more potent than angiotensin II. Endothelin may play a role in constriction of placental vessels after delivery and may regulate closure of the ductus arteriosus in the newborn. The mitogenic effects of endothelin-1 may cause vascular wall hypertrophy in Atherosclerosis and hypertension. Endothelin-1 may play a role in renal vasoconstriction in acute renal

failure. A 3-fold elevation of plasma endothelin 1 and 2 has been found in women with preeclampsia compared with gestation-matched controls.

One hypothesis is that prostacyclin is an antiplatelet and vasodilator mechanism held in reserve to reinforce the NO system when endothelial damage occurs. Lack of NO may be a causative factor in hypertension. Endothelin-1 is released by endothelial cells to constrict the underlying smooth muscle in an emergency such as laceration. Excess endothelin-1 may also be involved in the genesis of hypertension.

Placenta (6)

In normal pregnancy, the proliferating trophoblast invades the decidua and the adjacent myometrium in 2 forms: interstitial and endovascular. The role of the interstitial form is not clear but it may serve to anchor the placenta. The endovascular trophoblastic cells invade the maternal spiral arteries, where they replace the endothelium and destroy the medial elastic and muscular tissue of the arterial wall. The arterial wall is replaced by fibrinoid material. This process is complete by the end of the first trimester, at which time it extends to the deciduomyometrial junction. There appears to be a resting phase in the process until 14 to 16 weeks' gestation, when a second wave of trophoblastic invasion extends down the lumen of the spiral arteries to their origin from the radial arteries deep in the myometrium. The same process is then repeated, ie, replacement of the endothelium, destruction of the medial musculoelastic tissue, and fibrinoid change in the vessel wall. The end result is that the thin-walled, muscular spiral arteries are converted to saclike, flaccid uteroplacental vessels, which passively dilate to accommodate the greatly augmented blood flow required in pregnancy.

Preeclampsia develops following a partial failure in the process of placentation. First, not all the spiral arteries of the placental bed are invaded by trophoblast. Second, in those arteries that are invaded, the first phase of trophoblastic invasion occurs normally, but the second phase does not occur, and the myometrial portions of the spiral arteries retain their reactive musculoelastic walls.

In addition, acute atherosis (a lesion similar to Atherosclerosis) develops in the myometrial segments of the spiral arteries of patients with preeclampsia The lesion is

characterized by fibrinoid necrosis of the arterial wall, the presence of lipid and lipophages in the damaged wall, and a mononuclear cell infiltrate around the damaged vessel. Acute atherosis may progress to vessel obliteration with corresponding areas of placental infarction.

Thus, in preeclampsia there is an area of vascular resistance in the spiral artery because of failure of the second wave of trophoblastic invasion. In addition, acute atherosis further compromises the vascular lumen. Consequently, the fetus is subjected to poor intervillous blood flow from the time of early gestation; this may result in intrauterine growth retardation or stillbirth. Antihypertensive therapy may be detrimental because peripheral vasodilatation may further reduce the already compromised placental blood flow. Representation of the relationship between cerebral blood flow and mean arterial blood pressure. Cerebral blood flow normally remains constant at mean arterial pressures of 60-140 mm Hg. In chronically hypertensive patients, medial hypertrophy causes the lower and upper limits of autoregulation to be shifted to higher blood pressure values.The placental bed in normal and preeclamptic pregnancy. In preeclampsia, the physiologic changes in the uteroplacental arteries do not extend beyond the deciduomyometrial junction, leaving a constricting segment between the radial artery and the decidual portions.

Diagnosis of preeclampsia

The National high blood pressure education program's working group clinical classification schema has but four categories (6):

1. Chronic hypertension

Defined as hypertension (≥ 140 / 90 mmHg) present and observable prior to conception or diagnosed before the 20^{th} week of gestation. In addition high blood pressure presenting in late pregnancy which persists beyond the 42^{nd} day postpartum is also classified as chronic hypertension.

2. Preeclampsia – Eclampsia

The diagnosis of preeclampsia is determined by de novo increase in blood pressure accompanied by proteinuria, edema, or both.

2.1. Here hypertension is diagnosed by:

2.1.1. A sustained rise in systolic blood pressure of 30 mmHg or more over baseline

2.1.2. A sustained rise of at least 15 mmHg in diastolic blood pressure over baseline

2.1.3. A sustained systolic blood pressure of at least 140 mmHg

2.1.4. A sustained diastolic blood pressure of 90 mmHg or more

These values must be present at two measurements obtained 6 hours apart to ensure that the elevation is a sustained increase and not simply a response to stress. The first two criteria, concerned with an interval rise rather than an absolute level, are most informative in patients with borderline BP levels.

2.2.Proteinuria is defined as a qualitative measurement of 1+ (30mg / dl), or ≥ 300 mg in urine 24 hour collections.

Preeclampsia occurs as a spectrum but is arbitrarily divided into mild and severe forms. This terminology is useful for descriptive purposes but does not indicate "difference diseases" nor should it indicate arbitrary cut – off point for therapy. Severe preeclampsia is diagnosed when the following criteria (or ominous signs and symptoms) are present:

1). Blood pressure ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic, record on two or more occasions 6 hours apart, with the patient resting in bed

2). Proteinuria of 5 g/24 hours or 3 or 4 plus qualitatively

3). Oliguria (500 ml/ 24 hours)

4). Cerebral or visual disturbances

5). Epigastria pain

6). Pulmonary edema or cyanosis

Eclampsia is a severe form of pregnancy -induced hypertension and the occurrence of seizures in a preeclampsia patient that can not be attributed to other causes. HELLP syndrome is a complication of severe preeclampsia or eclampsia. HELLP syndrome is a group of physical changes including the breakdown of red

blood cells, changes in the liver and low platelets (cells found in the blood that are needed to help the blood to clot in order to control bleeding).

3. Preeclampsia superimposed upon chronic hypertension

There is ample evidence that preeclampsia may occur in women already hypertension and that the prognosis for mother and fetus is much worse than with either condition alone. The Working Group recommended that the diagnosis be made on the basis of increases of blood pressure (increments of or exceeding 30 mmHg systolic and 15 mmHg diastolic, or 20 mmHg arterial pressures) together with the appearance of abnormal proteinuria or generalized edema.

4. Transient hypertension

Transient hypertension is defined as the development of an elevated blood pressure during pregnancy after 20 week of gestation or in the first 24 hours postpartum without other signs of preeclampsia or preexisting hypertension. The blood pressure must return to normal within 10 days after delivery.

Treatments of preeclampsia

Early recognition is the key to treatment. This requires careful attention to the details of prenatal care - especially subtle changes in blood pressure and weight. The objectives are to prolong pregnancy if possible, to allow fetal lung maturity while preventing progression to severe disease and eclampsia. The critical factors are the gestational age of the fetus, fetal pulmonary maturity status, and the severity of maternal disease. Preeclampsia-eclampsia at 36 weeks or more of gestation is managed by delivery regardless of how mild the disease is judged to be. Prior to 36 weeks, severe preeclampsia-eclampsia requires delivery except in unusual circumstances associated with extreme fetal prematurity, in which case prolongation of pregnancy may be attempted. Epigastric pain, thrombocytopenia, and visual disturbances are strong indications for delivery of the fetus. For mild to moderate preeclampsia-eclampsia, bed rest is the cornerstone of therapy. This increases central blood flow to the kidneys, heart, brain, liver, and placenta and may stabilize or even improve the degree of preeclampsia-eclampsia for a period of time (8).

Management of preeclampsia depends upon its severity as well as the gestational age that it becomes clinically apparent.

Basic management objective for any pregnancy complication by preeclampsia are (6);

(1) Termination of pregnancy with the least possible trauma to mother and fetus

(2) Birth of an infant who subsequently thrives

(3) Completed restoration of health to the mother.

In certain cases of preeclampsia, especially in women at or near term, all three objectives are served equally well by induction of labor.

Traditionally, the timing of prenatal examinations has been scheduled at intervals of 4 weeks until 28 weeks, and then every 2 weeks until 36 weeks and weekly thereafter. Increases prenatal visits during the third trimester facilitate early detection of preeclampsia. Women with overt hypertension (≥ 140 / 90 mmHg) are frequently admitted to the hospital for 2 to 3 days to evaluate the severity of new - onset pregnancy hypertension. Those with persistent severe disease are observed closely and many are delivered. Conversely, women with mild disease are often managed as outpatient (7).

Bed rest may be attempted at home or in the hospital. Prior to making this decision, the provider should evaluate the six sites of involvement listed in Table 18-2 and make an assessment about the severity of disease.

Home management with bed rest may be attempted for patients with mild preeclampsia and a stable home situation. This requires homemaking assistance, rapid access to the hospital, a reliable patient, and the ability to obtain frequent blood pressure readings. A home health nurse can often provide frequent home visits and assessment.

Hospitalization is considered at least initially for women with new-onset hypertension if there is persistent or worsening hypertension or development of proteinuria. A systematic evaluation is instituted to include the following (6):

1. Detailed medical examination followed by daily scrutiny for clinical findings such as headache, visual disturbances, epigastric pain, and rapid weight gain.

2. Admittance weight and every day thereafter.
3. Admittance analysis for proteinuria and at least every 2 days thereafter.
4. Blood pressure reading in sitting position with an appropriate-size cuff every 4 hour, except between midnight and morning.
5. Measurement of plasma or serum creatinine, hematocrit, platelets, and serum liver enzyme, the frequency to be determined by the severity of hypertension
6. Frequent evaluation of fetal size and amniotic fluid volume either clinically or with sonography.

The only known treatment for eclampsia or advancing preeclampsia is delivery, either by induction or Caesarean section. However, post-partum pre-eclampsia may occur up to 6 weeks following delivery even if symptoms were not present during the pregnancy. Post-partum pre-eclampsia is dangerous to the health of the mother since she may ignore or dismiss symptoms as simple post-delivery headaches and edema. Hypertension can sometimes be controlled with anti-hypertensive medication, but any effect this might have on the progress of the underlying disease is unknown.

Magnesium sulphate

In some cases women with preeclampsia or eclampsia can be stabilized temporarily with magnesium sulphate intravenously to forestall seizures while steroid injections are administered to promote fetal lung maturation. Magnesium sulphate as a possible treatment was considered at least as far back as 1955, but only in recent years did its use in the UK replace the use of diazepam or phenytoin. Evidence for the use of magnesium sulphate came from the international MAGPIE study. When induced delivery needs to take place before 37 weeks gestation, it is accepted that there are additional risks to the baby from premature birth that will require additional monitoring and care (8).

Other investigated treatments

Studies into supplementation with antioxidant vitamins C and E found no change in preeclampsia rates. Drs. Padayatty and Levine with NIH in a "Letter to the

Editor" stated that the studies and another "Letter to the Editor" overlooked a key reason for the lack of vitamin C on the prevention of preeclampsia. Because plasma ascorbate concentrations were not reported, we estimated them from known data, the placebo and treatment groups in the study probably had similar plasma and tissue ascorbate concentrations. Doses of 1 g per day have little effect on plasma or intracellular ascorbate concentrations. Calcium supplementation in women with low-calcium diets found no change in preeclampsia rates but did find a decrease in the rate of severe preeclamptic complications. Aspirin supplementation is still being evaluated as to dosage, timing, and population and may provide a slight preventative benefit in some women, however significant research has been done on aspirin and the results thus far are unimpressive. There is insufficient evidence to recommend either exercise or bed rest as treatments. Studies of protein/calorie supplementation have found no effect on preeclampsia rates, and dietary protein restriction does not appear to increase preeclampsia rates (6).

Termination of pregnancy

Delivery is the only cure for preeclampsia. Headache, visual disturbances, or epigastric pain likely indicate that convulsions are imminent and Oliguria is another ominous sign. Severe preeclampsia demands anticonvulsant and usually antihypertensive therapy followed by delivery. Treatment is identical to that described subsequently for eclampsia. The prime objectives are to forestall convulsions, to prevent intracranial hemorrhage and serious damage to other vital organs, and to delivery a health infant (7, 8, and 9).

With severe preeclampsia that dose not improves after hospitalization, delivery is usually advisable for the welfare of both mother and fetus. Labor should be induced by intravenous oxytocin. Many clinicians favor preinduction cervical ripening with a prostaglandin or osmotic dilator. Whenever it appears that labor induction almost certainly will not succeed, or attempts at induction of labor have failed, cesarean delivery is indicated for more severe case of preeclampsia (7, 8, and 9).

Related researches of risk factors of preeclampsia

Maternal age

In 1974, Porapakkham S (11) studied an epidemiologic study of eclampsia 298 cases at Siriruj Hospital during 1967-1974. The results of study showed that there was an increase incidence of eclampsia among maternal age less than 20 years old and more than 35 years old.

In 1993, Thakkinstain A (12) studied factors associated with preeclampsia at Ramathibodi Hospital in 1993. The study design was a case – control study which selected 250 cases of hypertensive disorder in pregnancy comparing with 375 normotensive pregnant wonen. The result of study showed that maternal age less than 19 years old and maternal age more than 35 years old were associated with preeclampsia (OR = 3.21).

In 1995, Pichainarong N (13) studied risk factor of pregnancy – induce hypertension among 4 Maternal and Child Hospitals during 1993-1995, a cohort study of 1,760 gravidas. The result of study showed that maternal age of 30 years old or more was associated with preeclampsia.

In1997, Condé-Agudelo A, Kafury-Goeta AC (14) conducted a case- control study of risk factors of complicated eclampsia. The study in 24 pregnant women who had eclampsia and complication of intracerebral hemorrhage, pulmonary edema, renal, hepatic, or respiratory failure, disseminated intravascular coagulation, abrutioplacetae, pulmonary aspiration, and hemolysis with elevated liver enzymes and low platelets syndrome. The result of study showed that pregnant women aged 26 years old or more had more complications of eclampsia.

In 1999, Wonguppa R (15) studied risk factors associated with preeclampsia. The data was collected from admission and discharge maternal records, at the Police General Hospital during 1995 – 1999. The result of study showed that maternal age of 30 years old or more was significantly associated with preeclampsia.

In 2002, Dawson LM and associated (16) studied familial risk of preeclampsia in Newfoundland. They reviewed 5,173 obstetric charts from 10 hospitals, representing 99% of delivery on the island of Newfoundland for 1 year period from April 1996 – March 1997. The incidence of preeclampsia in nulliparous was 5.6%, and

in primiparous women was 7.9%. The result found that maternal age more than 35 years old was significantly associated with preeclampsia (RR = 1.9, 95% CI = 1.2 – 3.1).

In 2005, Duckitt K and Harrington D (17) studied risk factors of pre-eclampsia by systematic review of controlled studies published during 1966 – 2002. The results found that maternal age of more than 40 years old was significantly associated with preeclampsia (OR= 1.96, 95% CI 1.34 to 2.87).

In contrast in 1995, Sibai BM and associated (18) studied Risk factor for preeclampsia in healthy nulliparous women: a prospective multicenter study. This study reported that maternal age was not significantly associated with preeclampsia.

In 1996, Singhala K (19) studied factors associated with preeclampsia in pregnancy women admitted at Ramathibodi Hospital, 1994 – 1995. The study reported that maternal age was not significantly association with preeclampsia

Multiple pregnancies

In 1995, Coonrod DV and associated (20) studied risk factors for preeclampsia in twin pregnancies: a population – based cohort study. Methods are all twin pregnancies (3407) and approximately twice as many singletons (8287) were assembled using Washington state birth certificates from the period 1984 – 1988. The result showed that multiple pregnancies were significantly associated with preeclampsia (OR 3.5, 95% CI 3.0 – 4.2).

In 1998, Ros HS and associated (21) studied comparison of risk factors for preeclampsia and gestational hypertension in a population- base cohort study. The data were collected from The Swedish Medical Birth Register and include all nulliparas aged 34 years or less who gave birth at the University Hospital of Uppsala, Sweden, during 1987 -1993. Of these 10,666 women, 44% develop gestational hypertension, and 5.2% develop preeclampsia. The following risk factor was significantly associated with increased risk of preeclampsia that had twin birth (OR 4.17, 95% CI 2.30-7.55).

In 1991, Anourlu RI and associated (22) studied risk factors for preeclampsia in Lagos, Nigeria. A case – control study was conduced in a tertiary hospital in Nigeria during February 2001 – August 2002 to determine the risk factors for eclampsia. The

study showed that pregnant women who had multiple pregnancies was significantly associated with preeclampsia (OR = 2.71, 95% CI = 1.27-6.13).

In 2005, Duckitt K and Harrington D (17) reported that multiple pregnancies were significantly associated with preeclampsia (OR 2.93, 95% CI 2.04 to .21).

Body mass index at first visit

In 1991, Eskenazi B and associated (23) studied a multivariate analysis of risk factors for preeclampsia at Northern California Kaiser Permanente Medical Centers during 1984 - 1985. The result showed that preeclamptic women more likely to be of high body mass index (OR= 1.7, 95% CI = 1.2 to 6.2).

In 1993, Puthamont S (24) studied risk factors associated with preeclampsia in Rachavithi Hospital. This is a case - control study in 119 preeclamptic women. The result showed that body mass index more than 20 kg / m^2 was significantly associated with preeclampsia.

In 1995, Pichainarong N (13) studied risk factors of preeclampsia among 4 Maternal and Child Hospitals during 1993-1995. They reported that pregnant women who had body mass index more than 21 kg / m^2 was significantly associated with preeclampsia.

In 1998, Ros HS and associated (21) studied comparison of risk factors for preeclampsia and gestational hypertension in a population- base cohort study. Compared with underweight women (body mass index less than 19.8), obese women (body mass index more than 29) had increase risks of gestational hypertension (OR = 4.85, 95% CI = 1.97-11.92) and preeclampsia (OR = 5.19, 95% CI = 2.35 – 11.48).

In 1999, Thadhani R and associated (25) studied high body mass index and hypercholesterolemia to be risks of hypertensive disorders of pregnancy during 1991 to 1995. Women with pregravid body mass index over 30 kg/m2 was significantly associated with preeclampsia (OR = 2.1, 95% CI =1.0 to 4.6).

In 1999, Wonguppa R (15) studied risk factors associated with preeclampsia at the Police General Hospital during 1995 – 1999. The result of study showed that body mass index at first visit more than 21 kg / m^2 was significantly associated with preeclampsia.

In 2002, Duckitt K and Harrington D (17) studied risk factors for pre-eclampsia by systematic review of controlled studies published 1966 – 2002. The result showed that raised body mass index before pregnancy was significantly associated with preeclampsia (OR = 2.47, 95% CI = 1.66 to 3.67).

In 2004, Wolf M and associated (26) studied differential risk of hypertensive disorders of pregnancy among Hispanic women. The purpose of this study was to compare the risk of preeclampsia and gestational hypertension in a prospective cohort of normotensive, nulliparous Hispanic (n= 863) and non-Hispanic Caucasian women (n = 2,381). They received prenatal care and delivered at Massachusetts General Hospital during October 1998 – January 2002. The study showed that pregnant women who had body mass index at first prenatal visit significantly higher risk of preeclampsia (RR = 1.07, 95% CI = 1.04 – 1.10).

In 2001, Mireles C and associated (28) studied risk factors for preeclampsia/ eclampsia among working women in Mexico City. This study examined risk factors by population-base sampling. After adjusting for women whose pre-gestational weight of 55 kilogram or more were at increased risk factor associated with preeclampsia (OR = 2.02, 95% CI =1.34-3.04).

In 2005, Doherty DA and associated (27) studied pre-pregnancy body mass index and pregnancy outcome. The research method was pregnancy cohort recruited pregnancies between 16 and 18 weeks. The study showed that pre-pregnancy obesity (BMI > 30 kg / m^2) is a risk factors for gestational diabetes, preeclampsia, labor induction, cesarean for fetal distress, postpartum hemorrhage and neonatal hypoglycemic and need for resuscitation. Being underweight is a risk factor for fetal growth restriction.

In 2005, Rudra CL and Williams MA (29) studied BMI as a modifying factors in the relations between age at menarche, menstrual cycle characteristics, and risk of preeclampsia by case – control study from 1998 to 2002. Usual menstrual cycle characteristics among 286 preeclampsia cases and 471 normotensive controls were assessed using a structured interview during postpartum hospitalization. The study showed that pre – pregnancy BMI < 25 kg / m^2, preeclampsia risk was lower in those reporting cycles ≥ 36 days in length (adjusted OR = 0.78, 95% CI = 0.35 – 1.83) and menarche at ≥ 14 years (adjusted OR = 0.48, 95% CI = 0.28– 0.82). In contrast, among

overweight or obese women, preeclampsia risk was higher in those with long cycles (OR 3.11 95% CI 0.62 – 1.56) p (interaction) = 0.16) and late menarche (OR 1.53 95% CI 0.59 – 3.97) p (interaction) = 0.03)

In 2005, Carr DB and associated (30) studied a sister's risk and family history as a predictor of preeclampsia. The study design was population – based case – control study from Washington state birth certificates linked to hospital discharge records. Case were women with gestational hypertension 1611 cases or preeclampsia 1071 cases. Control was normotensive pregnancy (8041 pregnancies). All women delivered their first child during 1987 to 2002 and had a sister with a previous delivery in Washington State. Women who had BMI $\geq$ 25 kg/ m^2 was significantly associated with preeclampsia (OR = 1.9, 95% CI 1.3 – 3.0).

In 2006, Leeners B and associated (31) studied BMI as new aspects of classical risk factors for hypertensive disorders in pregnancy. At the beginning of pregnancy, BMI was measured in 1067 women with a history with hypertension diseases in pregnancy and 1063 controls. Diagnoses of hypertension disease in pregnancy were classified according to ISSHP (International society for the study of hypertension in pregnancy) and BMI according to WHO (World Health Organization) criteria. After verification of exclusion criteria and matching for confounders, 687 women with hypertension disease in pregnancy and 601 controls. The result found that the increase in BMI was significantly associated with an increase in the development of gestational hypertension (OR 1.1 95% CI 1.062 – 1.197), preeclampsia (OR 1.1 95% CI 1.055 – 1.144), but not for HELLP syndrome. According to WHO definitions, overweight women (BMI was 25 – 30 kg/ m^2) had a 2-fold (95% CI = 1.365-2.983) risk and obese women (BMI was 30 kg/ m^2 or more) had 3.2-fold (95% CI = 1.7- 5.909) risk of developing preeclampsia when compared with women of normal weight (BMI was 15.5-24 kg/ m^2).

In 1995, Sibai BM and associated (18) studied risk factor, pregnancy complication, and prevention of hypertensive disorders in women with pregravid diabetes mellitus. The result showed that previous weight of pregnancy was significantly associated with preeclampsia.

Mean weight gain

In 1976, Puthamont S (24) studied risk factors associated with preeclampsia in Rachavithi Hospital. The study showed that increase weight during pregnancy was more than 12 kilograms was significantly associated with preeclampsia.

In 1993, Thakkinstain A (12) studied factors associated with pregnancy-induce hypertension at Ramathibodi Hospital. The study showed that mean weight gain of 0.3 kg/wk or more was significantly associated with preeclampsia.

In 1995, Pichainarong N (13) studied risk factors of pregnancy – induce hypertension among 4 Maternal and Child Hospitals. The result found that the risk of preeclampsia increased among women with weight gain more than 0.3 kilograms per week.

In 1999, Wonguppa R (15) studied risk factors association with preeclampsia in pregnant women at the Police General Hospital during 1995 – 1999. The study showed that average weight gain during pregnancy more than 0.3 kilograms per week was significantly associated with preeclampsia.

History present of illness

In 1998, Ros HS and associated (21) studied comparison of risk factors for preeclampsia and gestational hypertension in a population- base cohort study at the University Hospital of Uppsala, Sweden, during 1987 -1993. The following risk factor were significantly associated with increased risk of preeclampsia; type 1 diabetes (OR = 5.58, 95% CI = 2.72-11.43) and gestational diabetes (OR = 3.11, 95% CI =1.61-6.00).

In 1995, Sibai BM and associated (18) studied risk factors, pregnancy complication, and prevention of hypertensive disorders in women with pregravid diabetes mellitus. The result showed that history present of illness was significantly associated with preeclampsia.

In 1998, Mahomed K and associated (32) studied risk factors for preeclampsia – eclampsia among Zimbabwean women: recurrence risk and familial tendency at Harare Maternity Hospital, Harare Zimbabwe during the period of June 1995 to April 1996. The result showed that pregnant women who had history of hypertension was significantly associated with preeclampsia and eclampsia.

In 1998, Bryson CL and associated (33) studied association between gestational diabetes and pregnancy – induce hypertension from 1992 – 1998 Washington state birth certificates and hospital discharge records to investigate this relation. The result showed that after adjustment for body mass index, age, ethnicity, parity, and adequacy of prenatal care, gestational diabetes was found to be associated with a significant 1.5 folds increase risk of severe and mild preeclampsia and a 1.4 folds increase in gestational hypertension. But no significant association was found between gestational diabetes and eclampsia.

In 1999, Wonguppa R (15) studied risk factors association with preeclampsia in pregnant women at the Police General Hospital during 1995 – 1999. The study showed that previous history of hypertension was significantly associated with preeclampsia.

In 1999, Thadhani R and associated (25) studied high body mass index and hypercholesterolemia: risk of hypertensive disorders of pregnancy during 1991 - 1995. The result showed that a history of elevated cholesterol was not significantly associated with the risk of preeclampsia (RR = 2.0, 95% CI = 1.2 to 3.3.).

In 2002, Dawson LM and associated (16) studied familial risk of preeclampsia in Newfoundland: A population – based study. This study reported that mother who had history of diabetic mellitus was significantly associated with preeclampsia (RR = 8.4, 95% CI = 3.0-23.8)

In 2002, Duckitt K and Harrington D (17) studied risk factor for pre-eclampsia during 1966 – 2002. The study showed that the risk of preeclampsia is increase in women with a previous history of preeclampsia (RR = 7.91, 95% CI = 5.85 to 8.83) and in those with antiphospholipids antibodies (RR = 9.72, 95% CI = 4.34 to 21.75) and pre-existing diabetes (RR = 3.56, 95% CI = 2.54 to 4.99). Individual studies show that risk is also increased with an interval of 10 years or more since a previous pregnancy, autoimmune disease, renal disease and chronic hypertension.

In 2002, Anourlu RI and associated (22) studied risk factors for preeclampsia in Lagos, Nigeria during February 2001 – August 2002. The study showed that pregnant women who had chronic hypertension was significantly associated with preeclampsia (OR = 2.21, 95% CI = 1.17-6.20).

In 2006, Mayer A and associated (34) studied chronic hypertension is an independent risk factor for preeclampsia and preterm delivery in women with rheumatologic diseases in a population – based study. The study showed that pregnant women who had history of rheumatologic disease had association with preeclampsia (OR = 3.05, 95% CI = 1.44 – 6.45).

Hematocrit at first visit

In 1996, Singhala K (19) studied factors associated with preeclampsia in pregnancy women admitted at Ramathibodi Hospital, 1994 – 1995. The result found that pregnant women who had hematocrit less than 30 gm% was not significantly associated with preeclampsia (OR = 1.53, 95% CI = 0.17 – 13.71).

In 1999, Wonguppa R (15) studied risk factors associated with preeclampsia in pregnant women at the Police General Hospital during 1995 – 1999. This study reported that hematocrit less than 30 gm% was not significantly associated with preeclampsia.

Occupation

In 1994, Irwin DE and associated (35) reported nulliparas employed in jobs involving high levels of physical activity were at significantly decreased risk of PIH compare to nulliparas working at low levels of physical activity (construction craftsmen, RR=0.37; unskilled labourers RR = 0.71).

In 1995, Spinillo A, and associated (36) studies the effect of work activity in pregnancy on the risk of severs preeclampsia by case-control study. They reported that clerical workers had a significantly lower risk of severe preeclampsia than women who were unemployed at the beginning of pregnancy. In addition, moderate/high physical activity at work was associated with 2-fold increase in the risk of severe preeclampsia compare to mild activity (OR=2.08, 95%CI 1.11, 3.88).

In 1996, Klonoff-Cohen HS and associated (37) reported working women had 2.3 time the risk of developing preeclampsia (95%CI=1.2-4.6) compared with nonworking women. Work-related psychosocial strain increased the risk of preeclampsia in this study.

In 2002, Higgins J R and associates (38) studied the relationship between maternal work, ambulatory blood pressure, and preeclampsia at the Rotunda Hospital (a large maternity hospital), Dublin, Ireland. They reported that the association between preeclampsia and maternal work remained significant (OR=5.5, 95%CI = 1.1, 15.2) compared with not working even after allowing for the confounding factors of age, smoking, BMI, and marital status.

Birth place

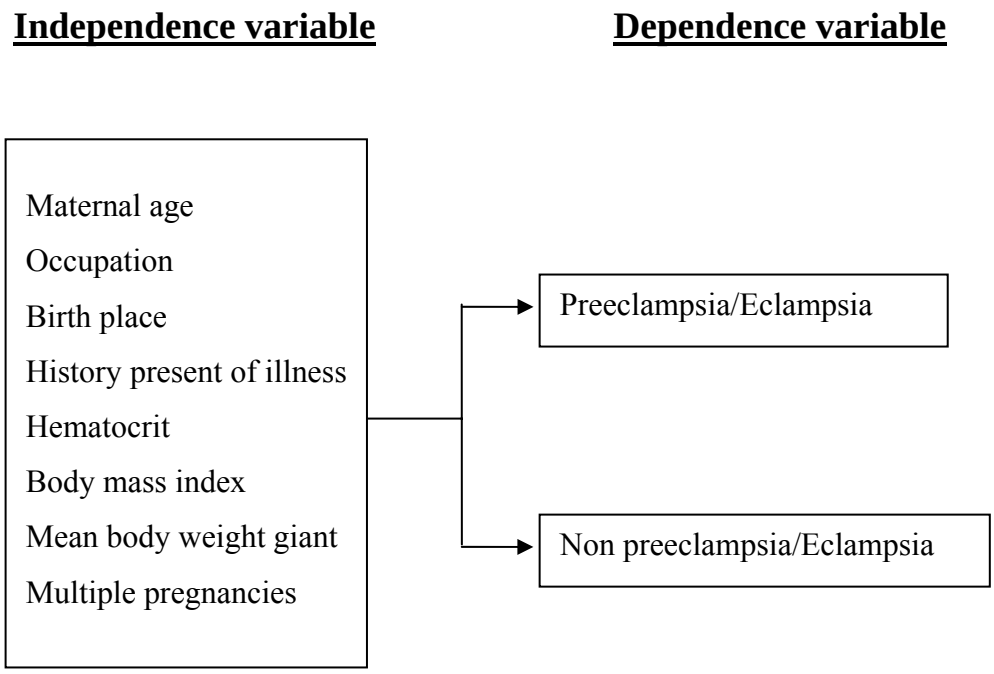
No direct study on association with birthplace and preeclampsia was found. But birthplace was found to be associated with some outcomes of pregnancy e.g. low birth weight.

In 1998, Fuentes-Afflick E and associated (39) studies maternal birth place, ethnicity, and low birth weight in California, 1992. They reported that the association between maternal birthplace and low birth weight varied by ethnicity.

In 2001, Faiz AS and associated (40) studies risk of abruptio placenta by regions of birth and residence among African-American women in the United States during 1995 - 1996. They suggested that place of residence rather than place of birth was associated with the risk of placental abruption and the prevalence of risk factors determined the rate of abruption.

In 2006, Zhu M and associated (41) studies maternal birthplace and major congenital malformatioms among New York Hispanics during 1993-2001. They reported that foreign-born Hispanic mothers had a slightly lower risk to delivery live-born singleton infants with major congenital malformations than did U.S. born Hispanic mothers.

CEPTUAL FRAMEWORK



CHAPTER III
METERIALS AND METHOD

Research design

This study comprised of two parts of study. The first part of this study is a historical cohort study with the objective to determine the incidence of preeclampsia among nulliparous women who came to register for the first time at the antenatal booking unit Ramathibodi Hospital during 1 January – 30 December 2005. The second part is case – control study with the objective to determine risk factors of preeclampsia.

Target Population

In the first part of study all the pregnant women who came to register from the first time at the antenatal booking unit Ramathibodi Hospital during 1 January – 30 December 2005. The name and hospital numbers of all pregnant were in the computerized records of the hospital.

The second part of the study was a case - control study. The cases were pregnant women who outcome of deliveries were know and who were diagnosed to be preeclampsia which was recorded in the computerized medical statistics of the hospital. The inclusion criteria of cases and controls were:

Cases:

1. The pregnancy women who came to register at the antenatal booking unit for first time at Ramathibodi Hospital during 1 January 2005 – 30 December 2005
2. They were nulliparous.
3. Outcome of delivery was known.
4. They were diagnosed of having preeclampsia from medical statistics of Ramathibodi Hospital or self report in women who delivered in other hospital.

Control:

The inclusion criteria of the controls were the same as cases except that they were not diagnosed as having preeclampsia and they registered at the antenatal booking unit just after the preeclampsia cases.

Sample Size Estimation

To collect all pregnant women who came to registered at the antenatal booking unit Ramathibodi Hospital on day to day basis, we included total cases of 1 year (during 1st January to 30th December 2005) to be our samples which totally were 2,543 cases.

Instrument

The instrument of this study was data record form which was constructed by the researcher according to the objectives. Data was collected from computerized, records of the antenatal booking unit, medical records and statistics from medical statistics unit of Ramathibodi Hospital.

Data Collection Procedure

The steps of data collection were as follow:

1. Submitting the research proposal for approval on human rights related to researches involving human subjects, based on the declaration of Helsinki form Ethical research committee of Faculty of medicine Ramathibodi Hospital. It received approval on 15 January 2007.
2. Outcome of delivery or abortion were recorded from medical statistics unit of Ramathibodi Hospital, computerized medical records form and delivery log book at the delivery unit, Ramathibodi Hospital.
3. Those women, whose outcome of delivery and abortion were not known, were followed by mail and telephone. Three weeks period was allowed for their responses. If there was no response, they were classified as loss to follow up.

Method of Data Analysis

1. Descriptive statistic: number and percentage
2. Analysis statistical:

- Univariate analysis; odds ratio, 95% confidence interval and p – value was used to compare each of the independent risk factors associated with preeclampsia.
- Multivariable analysis by logistic regression.
- SPSS^{+} PC program was used for statistical analysis.

CHAPTER IV
RESULTS

This study compared of 2 parts. The first part is a historical cohort study of incident a preeclampsia among nulliparous women in Ramathibodi Hospital. The second part is a case - control study with the objective to risk factors association with preeclampsia. The studied results were present as follow:

Objective1. Incidence of preeclampsia at Ramathibodi hospital

During 1 January – 30 December 2005 there were 5,288 pregnant women who came to register for the first time at the antenatal care booking unit Ramathibodi Hospital. Among these women, there were 2,543 nulliparous women (48.1%). This nulliparous woman were followed, 1,594 cases (62.7%) delivered in Ramathibodi Hospital and 53 cases (2.1%) of abortion before twenty weeks of gestational. Eight hundred ninety six pregnant women who lost to follow up were followed by telephone or mail. Seventy six cases (8.5%) responded. Seventy five cases responded outcome of there delivery and one case of abortion.

In conclusion among 2,543 cases of nulliparous women who registered at booking unit Ramathibodi Hospital, outcomes of pregnancy were knows in 1,723cases (67.8%), 1,669cases of delivery (65.6%) and 54 cases (2.1%) of abortion. The numbers of failed to follow up were 820 cases (32.2%).

Among 1,669 cases of nulliparous whose outcomes of deliveries were knows, there were 82 cases of preeclampsia. Incidence of preeclampsia among nulliparous women whose came to register the delivery at Ramathibodi Hospital was 4.9% (mild preeclampsia 3.4% and severe preeclampsia 1.5%).

Objective2. Factors associated with preeclampsia by case – control study

In this case - control study, it compared of 82 cases of preeclamptic women and 82 cases of non – preeclamptic women as controls. Eighty two cases of non preeclamptic women who severe as control was record by select .

1) Univariate Analysis

1.1 Odds ratio with 95% confidence interval

By using uinvariate analysis by chi-square test with odds ratio and 95% confidence intervals, factors which were found to be significantly associated with preeclampsia were maternal age, occupation, birth place, present illness, hematocrit at registered, body mass index at first the antenatal visit, mean weight gain during the antenatal visits and multiple pregnancies as show in table 1and 2

Maternal age

The lowest risk of preeclampsia was found among pregnant women of 21 – 25 years of age which was used as a reference group. When compare with reference group, the highest risk was found among women of 30 years or more had the odds ratio with 95% confidence intervals of 2.121 (0.880 – 5.375) which was not statistically significant.

Occupation

The lowest risk of preeclampsia was found among government officer who was used as reference group. When compare with reference group, the highest risk was found among house-wife had the odds ratio with 95% confidential interval of 3.148 (0.862-11.495) which was not statistically significant.

Birth place

The lowest risk of preeclampsia was found among pregnant women who had birth place was north which was used as reference group. When compare with reference group, the highest risk was found among pregnant women who had birth place was south which had the odds ratio with 95% confidential interval of 3.467 (0.791-15.197) which was not statistically significant.

History present of illness

The lowest risk of preeclampsia was found among pregnant women who had not history present of illness which was used as reference group. When compare with

reference group women who had history present of illness had the odds ratio with 95% confidential interval of 1.962 (0.689-5.586) which was not statistically significant

Hematocrit at registered

The lowest risk of preeclampsia was found among pregnant women hematocrit at registered 34-36 gm% which was used as reference group. When compare with reference group women who had hematocrit at registered was 39 gm% or more had the odds ratio with 95% confidential interval of 1.446 (0.483-4.330) which was not statistically significant

Body mass index at first the antenatal visit

The lowest risk of preeclampsia was found among pregnant women of body mass index at first the antenatal visit was 19-20 which was used as reference group. When compare with reference group, the highest risk was found among pregnant women of body mass index at first the antenatal visit was 25-26 which had the odds ratio with 95% confidential interval of 5.386 (1.602-18.110) which was statistically significant.

Mean weight gain at the antenatal visits

The lowest risk of preeclampsia was found among pregnant women of mean weight gain at the antenatal visits 0.30-0.39 which was used as reference group. When compare with reference group, the highest risk was found among pregnant women of mean weight gain at the antenatal visits 0.5 or more had the odds ratio with 95% confidential interval of 5.037 (1.993-12.732) which was statistically significant.

Multiple pregnancies

The lowest risk of preeclampsia was found among pregnant women who had singleton which was used as reference group. When compare with women who had twin or triple had the odds ratio with 95% confidential interval of 1.519 (0.247-9.338) which was not statistically significant

Table1: Odds ratio and 95% Confidence interval of risk factors

Factors	Cases (n = 82)		Controls (n=82)		OR	95%CI
	No.	(%)	No.	(%)		
Maternal age						
- ≤ 20	6	(50.0)	6	(50.0)	1.545	0.396-6.035
- 21 – 25	11	(39.3)	17	(60.7)	1.000	Ref.
- 26 – 30	27	(45.8)	32	(32.0)	1.304	0.522-3.256
- 31-35	30	(57.7)	22	(42.3)	2.576	0.989-6.710
- ≥ 36	8	(42.1)	11	(57.9)	1.374	0.407-4.641
Occupational						
- Government officer	10	(45.4)	12	(54.5)	2.083	0.330-13.145
- Labour	42	(46.7)	48	(53.5)	2.167	0.403-11.641
- Business	10	(55.6)	8	(44.4)	3.125	0.474-20.583
- House-wife	18	(66.7)	9	(33.3)	5.000	0.806-31.002
- Student	2	(18.6)	5	(71.4)	1.000	Ref.
Birth place						
- North east	20	(42.6)	27	(57.4)	1.605	0.520- 4.953
- North	6	(31.6)	13	(68.4)	1.000	Ref
- South	8	(61.5)	5	(38.5)	3.467	0.791-15.197
- Center	23	(57.5)	17	(42.5)	2.931	0.926- 9.283
- Bangkok	25	(55.6)	20	(44.4)	2.708	0.873- 8.401
Present illness						
- Yes	11	(64.7)	6	(35.3)	1.962	0.689-5.586
- No	71	(48.3)	76	(51.7)	1.000	Ref.

Table1: Odds ratio and 95% Confidence interval of risk factors (continuous)

Factors	**Cases (n = 82)**		**Controls (n=82)**			
	No.	**(%)**	**No.**	**(%)**	**OR**	**95%CI**
Hematocrit						
- < 33	16	(51.6)	15	(49.4)	1.200	0.513-2.808
- 34-36	32	(47.1)	36	(52.9)	1.000	Ref.
- 37-39	25	(51.0)	24	(49.0)	1.172	0.562-2.444
- > 39	9	(56.3)	7	(43.8)	1.446	0.483-4.330
Body mass index (kg /m^2)						
- < 19	6	(54.5)	5	(45.5)	2.486	0.646-9.563
- 19 - 20	14	(32.6)	29	(67.4)	1.000	Ref.
- 21 22	13	(48.1)	14	(51.9)	1.923	0.716-5.168
- 23 -24	18	(47.4)	20	(52.6)	1.864	0.757-4.591
- 25 26	13	(72.2)	5	(27.8)	5.386	1.602-18.110
- > 26	18	(66.70	9	(33.3)	4.143	1.489-11.527
Mean weight gain (kg / wk)						
- ≤ 0.29	22	(48.9)	23	51.1)	1.549	0.697-3.441
- 0.30-0.39	21	(38.2)	34	61.8)	1.000	Ref.
- 0.40-0.49	11	(40.7)	16	59.3)	1.113	0.434-2.852
- ≥ 0.50	28	(75.7)	9	24.3)	5.037	1.993-12.732
Multiple pregnancies						
- Singleton	79	(49.7)	80	(50.3)	1.519	0.247-9.338
- Twin/ Triple	3	(60.0)	2	(40.0)	1.000	Ref.

1.2 Risk factors as dichotomous variables.

When considering risk factors in table 1, in order to find a risk factor as a dichotomous variable, we reclassified those factors as follow. Maternal age as less than 30 years old and was 30 years old or more. Occupation as housewife or not. Birth place as north and north east or not. Present illness as yes or no. Hematocrit at registration as more 39 gm% or was 39 gm % or less than. Body mass index (BMI) at first antenatal visit as more than 25 kg /m^2. Mean weight gain during antenatal visit as 0.5 kilogram per week or less than o.5 kilogram per week. Multiple pregnancies as yes or no.

By using Chi – square test, odds ratio with 95% confidence interval, we analysis these risk factors as dichotomous variable. The result showed that factor which are significantly associated with preeclampsia were Maternal age over 30 years old, Body mass index (BMI) at first antenatal visit was more than 25 kg /m^2. Mean weight gain during antenatal visit was 0.5 kilograms per week. Birth place in the north or north east of Thailand was found to have significantly protective effect over preeclampsia (Table 2).

Table 2: The association between preeclampsia and risk factor by Univariate analysis

Factor	**Case (n =82)**		**Control (n =82)**			
	No.	**%**	**No.**	**%**	**OR**	**95%CI**
Maternal age						
- ≤ 30	44	(53.7)	55	(6.1)	2.051	1.029-4.087
- > 30	38	(46.3)	27	(32.9)		
Occupational as housewife						
- yes	18	(26.8)	9	(8.5)	2.281	0.958-5.433
- No	64	(73.2)	73	(91.5)		

Table 2: The association between preeclampsia and risk factor by Univariate analysis (continuous)

Factor	Case (n =82)		Control (n =82)			
	No.	**%**	**No.**	**%**	**OR**	**95%CI**
Birth place as north /north east						
- Yes	26	(39.4)	40	(60.6)	0.488	0.258-0.920
- No	56	(57.1)	42	(42.9)		
Present illness						
- Yes	11	(6.7)	6	(46.3)	1.962	0.689-5.586
- No	71	(43.3)	76	(3.7)		
Hematocrit						
- > 39 gm%	73	(89)	75	(91.5)	1.321	0.467-3.733
- < 39 gm%	9	(11)	7	(8.5)		
Body mass index (kg /m^2)						
- ≥ 25	31	(37.8)	14	(17.1)	2.952	1.425-6.115
- < 25	51	(62.2)	68	(82.9)		
Mean weight gain (kilogram per week)						
- ≥ 0.5	28	(34.1)	9	(11)	4.206	1.85-9.639
- < 0.5	54	(65.9)	73	(89)		
Multiple pregnancies						
- Yes	3	(1.8)	2	(1.2)	1.519	0.247-9.338
- No	79	(48.2)	80	(48.8)		

2) Logistic Regression analysis

By using logistic regression analysis, we input those variables as dichotomous variable in to the equation by stepwise method the statistics association factors were shown in table 3.

Listed by the magnitude of odds ratio the significant risk factors were mean weight gain during antenatal visit was 0.5 kilograms per week (OR= 5.178, 95% CI= 2.135 – 12.558). BMI at first visit was more than 25 kg /m^2 (OR= 3.091, 95% CI= 1.398 – 6.832). Maternal age more than 30 years old (OR= 2.844, 95% CI= 1.325 – 6.105) and occupation as housewife (OR= 2.651, 95% CI= 1.009 – 6.962). (Percentage Correct = 61.0)

Table 3: Association between risk factors and preeclampsia by multiple logistic regression

Risk factor	β	SE(β)	Exp.(β) (OR)	P-value	95%CI
Weight gain ≥ 0.5 kg/wk	1.644	0.452	5.178	<0.001*	2.135-12.558
BMI ≥ 25 kg /m^2	1.128	0.405	3.091	0.005*	1.398-6.832
Maternal age > 30 years	1.045	0.390	2.844	0.007*	1.325-6.105
House - wife	0.975	0.493	2.651	0.048*	1.009-6.962

P – Value < 0.05

CHAPTER V
DISCUSSION

The objectives of this study were to determine the incidence of preeclampsia among nulliparous women who came to register for the first time at the antenatal booking unit Ramathibodi Hospital during 1 January – 30 December 2005. The second part is case – control study with the objective to determine risk factors of preeclampsia. The discussion will be divided in to two sections as follow:

Part I. Research methodology

Part II. Research results

Part I. Research methodology

1. Research design

The research design of this study comprised of two parts of study.

The first part of the study was a historical cohort study which is appropriate for study of incidence rate. For historical cohort study cases were identified and their experience up to the present is obtained. This is a less common type of study because detailed records are often not available. This lack of data makes it difficult to be sure about an individual's level of exposure or even whether they did or did not develop the disease under study. However, if good data is available a retrospective cohort study can be extremely effective and relatively inexpensive. Detailed records are kept and updated annually. Advantages of historical cohort study are allowing complete information on the subject's exposure, including quality control of data, and experience there after. Provide a clear temporal sequence of exposure and disease, give an opportunity to study multiple outcomes related to a specific exposure, permit calculation of incidence rates (absolute risk) as well as relative risk, methodology and results are easily understood by non-epidemiologists and enable the study of relatively rare exposures. The disadvantages of historical cohort study were not suited for the study of rare diseases because a large number of subjects is required, exposure patterns, expensive to carry out because a large number of subjects is usually required,

baseline data may be sparse because the large number of subjects does not allow for long interviews (42,43).

In Ramathibodi Hospital, it was possible to identify pregnant women who came to register to deliver their babies and follow up of their outcomes was also relatively complete. Only 32.2% were failed to follow up after by mail or phone were attempted.

The second part of the study was a case-control study which is appropriate for study of risk factors of preeclampsia. The advantages of case-control study were that at permits the study of rare diseases, or with long latency between exposure and manifestation. The study can be launched and conducted over relatively short time periods, relatively inexpensive as compared to cohort studies. Study of multiple potential causes of disease is also possible. For disadvantages of case-control study were information on exposure and past history is primarily based on interview and may be subject to recall bias. Validation of information on exposure is difficult, or incomplete, or even impossible. The case cohort study concerned with one disease only, generally incomplete control of extraneous variables and choice of appropriate control group may be difficult (42, 43).

Population

The populations of this research were nulliparous women who came to register for the first time at the antenatal booking unit Ramathibodi Hospital during 1 January – 30 December 2005. They were followed to the end of pregnancy which was kept in the hospital data base. For those who failed to follow up, contact by phone or mail was done. Failed to follow up in this study was 32% which was acceptably.

Sample size

To collect all pregnant women who came to registered at the antenatal booking unit Ramathibodi Hospital on day to day basis, we included total cases of 1 year (during 1st January to 30th December 2005) to be our sample which totally were 2,543 cases.

Data collection

The instrument of this study was data record form which contrasted according to the objectives. Data was collected from computerized records of booking medical records. Follow up and outcome of pregnancy were obtained from who failed to follow up contact by phone or mail was done.

Part II. Research results

Objective1. Incidence of preeclampsia at Ramathibodi hospital

Incidence of preeclampsia among nulliparous women in Ramathibodi Hospital was 4.91% (mild preeclampsia 3.4% and severe preeclampsia 1.5%). The incidence of preeclampsia in this study was comparable with other study although using different research designs.

The incidence of preeclampsia is commonly reported to be about 5 percent, although remarkable variations are reported. The incidence is influenced by parity, with nulliparous women having a greater risk (7 to 10 percent) when compared with multiparous women. Palmer and associates reported that living at high altitude in Colorado increased the incidence of preeclampsia. Some investigators have concluded that socioeconomically advantage women have a lesser incidence of preeclampsia (44). However, Lawlor and colleagues did not observe this in an Aderdeen cohort of 3485 women (45).

The incidence of hypertensive disorders in healthy nulliparous women was carefully studied in trial of delivery calcium supplementation (46). Of 4302 nulliparous women delivered at or beyond 20 weeks, a fourth developed a pregnancy-related hypertensive disorder. When all nulliparas were considered, preeclampsia was diagnosed in 7.6 percent and severe disease developed in 3.3 percent. By contrast, Vatten and Skjærven reported an incidence of preeclampsia of 2.6 percent in more than 1.6 million Norwegian nulliparas (47).

The survivor of Word Health Organization reported that the incidence of preeclampsia was 7.5% and eclampsia was 0.9% (48).

In Thailand, the studies in 1998 by Siriraj Hospital reported that the incidence of preeclampsia was 4.8% (49).

Objective2. Factors association with preeclampsia by:

Several factors predisposing to the development of preeclampsia-eclampsia have been identified. They are important because we can use these factors in screening patients at high risk for special care and attention. Also, the presence or absence of predisposing factors can be helpful in differential diagnosis.

Maternal age

The result of uinvariate analysis showed that an increase of maternal age more than 30 years old increase the risk of preeclampsia by 2.9 times (95% confidence interval was 1.325 – 6. 105).

Several studies have found that hypertensive disorders in pregnancy, including preeclampsia are more common in women whose pregnancy occurs at an older maternal age. The age-specific incidences showed that girls in their early teens and women aged 35 or more are at increased risk. Saftlas and associated reported this observation in their nationally representative cross-sectional study of the US population (6). As well, it was the general impression of Hansen in a review of studies published before the earls 1980s (6). The risk for a woman over age 35 is about three- to fourfold higher than for a younger woman. Zhang and associated suggested that this effect may occur independent of misdiagnosed chronic hypertension, which is more common in older women, and may reflect collagen replacement of the normal muscle in the walls of myometrial arteries and atrophic changes in the vascular microstructure. The increased percentage of collagen and the undervascularization may then restrict luminal expansion and blood flow to the placenta (7).

In Thailand, this finding is in accordance with Thakkinstain A who studies preeclampsia at Ramathibodi Hospital reported that maternal age less than 19 years old and more than 35 years old was associated with preeclampsia (OR=3.21) (12). Similar results were found in two studies by Pichainarong N who studies risk factor as predictors of pregnancy – induce hypertension among 4 Maternal and Child Hospital during 1993-1995 (13) and Wonguppa R who studies preeclampsia at the Police General Hospital during 1995 – 1999 (15). Both studies reported that maternal age 30 years old or more was significantly associated with preeclampsia.

But this is in contrast with the study of Sibai B M and associated who studied risk factors associated with preeclampsia in healthy nulliparous women from five centers in USA and found no significant association between maternal age and preeclampsia (18). The study of Singhala K. in Ramathibodi Hospital in 1995 also reported that maternal age was no statistically significant association with preeclampsia (19).

Occupation

The study showed that house-wife is associated with preeclampsia with adjust odds ratio of 2.651(95% CI= 1.009 – 6.962).

The report by Higgins J R and associates in 2001, studied the relationship between maternal work, ambulatory blood pressure, and preeclampsia. Among 933 healthy normotensive primigravidas recruited from the antenatal clinics of the Rotunda hospital (a large maternity hospital), Dublin, Ireland. They reported that the association between preeclampsia and maternal work remained significant (OR=5.5, 95%CI = 1.1, 15.2) compared with not working even after allowing for the confounding factors of age, smoking, BMI, and marital status (38).

The result was also with the studies by Spinillo A, and associated who studies that the effect of work activity in pregnancy on the risk of severs preeclampsia by case-control study. They reported that clerical workers had a significantly lower risk of severe preeclampsia than women who were unemployed at the beginning of pregnancy. In addition, moderate/high physical activity at work was associated with 2-fold increase in the risk of severe preeclampsia compare to mild activity (OR=2.08, 95%CI 1.11, 3.88) (36). In addition to stress from physical works, there well also studies demonstrated that works of mild activities also increase risk of preeclampsia. The study by Irwin DE and associated who reported that nulliparas employed in jobs involving high levels of physical activity were at significantly decrease risk of PIH compare to nulliparas working at low levels of physical activity (construction craftsmen, RR=0.37; unskilled labourers RR = 0.71) (35). And similar with the study by Klonoff-Cohen HS and associated who reported that working women had 2.3 time the risk of developing preeclampsia (95%CI=1.2-4.6) compared with nonworking

women. Work-related psychosocial strain increased the risk of preeclampsia in this study (37).

This study demonstrated that occupation as house-wife was significantly associated with preeclampsia. Our study emphasized on the burden of psychological stress. Occupation as house wife was defined as no outside jobs thus most of them did not have their own income. In developing countries like Thailand that most socioeconomic static is at lower level, the living without payment and dependency on other's income may be stressful especially among younger aged, newly-wed and nulliparous. The psychological stress may be a predisposing factor of preeclampsia to be examined in the future.

The explanation for the association between work and preeclampsia is unknown, but it has been suggested that the stress of work leads to an increased release of catecholamines and a daylong sympathetic response that increases blood pressure. Sympathetic overactivity has recently been reported in preeclampsia.

Body mass index

The study confirmed the association between increase body mass index and risk of preeclampsia. After controlling the other effects, the result showed that body mass index at first visit of 25 kg / m^2 or more is an important risk factor for preeclampsia, with an adjusted odds ratio of 3.091 (95%CI=1.398 – 6.832) when compared with body mass index at first visit less than 25.

Several more studies confirmed the long-suspected association between baseline body size and preeclampsia with relative risk estimates ranging from 2.3 to 5.5, depending on the definition of weight used. Wolf and associated described the relationship between maternal weight (or body mass index) among 6270 consecutively delivered gravid women. Among women whose body mass index (BMI) was in the 90^{th} percentile or greater, the relative risk of preeclampsia was 2.3 (26). Eskenazi and associated in a carefully designed study of 139 preeclamptic cases and 132 controls, found that a BMI of 25.8 carried a 2.7-fold in creased risk for preeclampsia after controlling for other factor (23). In addition, a recent analysis of data from the Maternal Fetal Medicine Network shows higher rates of preeclampsia with increasing levels of overweight. In that study, overweight was only associated with preeclampsia

and not with gestational hypertension. Adiposity may also contribute to the relationships among other maternal predispositions such as hypertension, diabetes, race, and preeclampsia.

The results for obesity were consistent. Sibai M and associated found a higher risk of preeclampsia in women with a substantially elevated BMI (26 to 34.9 kg/m^2 , and over 35 kg/m^2) measured at the time of randomization (18). The similar results were found in studies by Carr DB and associate, Leeners B who reported that pregnant women who have body mass index of 25 kg/m^2 or more were high risk to have preeclampsia (30, 31). Ros HS and associated who studies comparison of risk factors for preeclampsia and gestational hypertension during 1987 – 1993 as a population-based cohort study, when compared with BMI < 19.8 kg/m^2, BMI of 29 kg/ m^2 had increase risks of preeclampsia (21). Thadhani R reported pregravid body mass index over30 kg/m^2 was associated with preeclampsia (35).

In Thailand, the similar results were found in several studies by Puthamont S, Pichainarong N, and Wonguppa R who reported that body mass index at first visit more than 20 kg / m^2 had significant association with preeclampsia (13, 15, and 24).

Obesity might also act through insulin resistance or increased sympathetic activity, both of which have been associated with hypertensive disorders of pregnancy (50, 51). Investigators have also postulated that abnormal lipid metabolism and hyperlipidemia, which are often associated with obesity, are responsible for the physiologic alterations of vasoactive mediators leading to hypertension during pregnancy (52, 53, and 54).

Several lines of evidence support the association between abnormal lipid metabolism and the systemic manifestations of preeclampsia. First, women with preeclampsia have higher serum lipid levels compared with pregnant controls (55, 56, 57, 58, and 59). In one recent study, first-trimester serum total cholesterol levels were significantly elevated in the 11 women who subsequently developed preeclampsia but not in the 26 women who developed isolated pregnancy-induced hypertension. Second, placental vessels of affected women had atherosclerotic-like changes, including deposition of fibriniod material and foam cell (60, 61). Third, byproducts of lipid peroxidation are elevated in women with preeclampsia (62, 63), and these byproducts might be associated with endothelial cell damage and vasoconstriction (62,

64). Levels of endothelin, a potent vasoconstrictor, are also higher in these women (65), and elevated serum cholesterol is associated with elevated endothelin activity in animals (66). Finally, elevate lipid level is a component of insulin resistance syndrome (67), and insulin resistance is associated with preeclampsia (68, 69). Therefore, elevated cholesterol level before pregnancy could render a woman susceptible to the deleterious systemic manifestation of preeclampsia during pregnancy.

Mean weight gain

An increase of mean weight gain during pregnancy increased the risk of preeclampsia. This study showed that mean weight gain more than 0.5 kg/wk is an important risk factor for preeclampsia, with an adjusted odds ratio of 5.178 (95% CI was 2.135-12.558).

This finding is in accordance with the study of Puthamont S who studied risk factors association with preeclampsia at Ratchavithi hospital as a case control study of 119 preeclamptic women. Her study showed that increase weight gain during pregnancy more than 12 kilograms was significantly associated with preeclampsia (OR=2.74) (30). Thakkinstain A who studied factors associated with preeclampsia at Ramathibodi hospital also found that mean weight gain ≥ 0.3 kg/wk was association with preeclampsia (OR= 7.17) (18) The similar results were found in study by Pichainarong N who studied risk factor of preeclampsia among 4 maternal and child hospital during 1993 – 1995 (19) and the study of Wonguppa R who studied risk factors association with preeclampsia in the Police General hospital during 1995 to 1999 (21).

But the result of this was study in contrast with the study of Singhala K who found that pregnant women who had average weight gain greater than or equal to 0.38 kg / week was not association with preeclampsia (25).

Birth place

By using univariate analysis, the result showed that birth place of north or north east of Thailand were found to have significantly protective effect against preeclampsia (OR= 0.488, 95% CI = 0.258-0.920). No other studies support this finding.

Effect of birthplace on maternal health were documented by Fuentes-Afflick E and associated who studies maternal birth place, ethnicity, and low birth weight in California, 1992. They reported that the association between maternal birthplace and low birth weight varied by ethnicity (39). Faiz AS and associated who studies risk of abruptio placenta by regions of birth and residence among African-American women in the United States during 1995 - 1996. They suggested that place of residence rather than place of birth was associated with the risk of placental abrution and the prevalence of risk factors determined the rate of abrution (40). Zhu M and associated studies maternal birthplace and major congenital malformatioms among New York Hispanics during 1993-2001. They reported that foreign-born Hispanic mothers had a slightly lower risk to delivery live-born singleton infants with major congenital malformations than did U.S. born Hispanic mothers (41).

CHAPTER VI
CONCLUSION AND RECOMMENDATION

Conclusion

Preeclampsia is a disorder that occurs only during pregnancy and the postpartum period and affects both the maternal and the unborn baby. Affecting at least 5 – 8 % of all pregnancies, preeclampsia and other hypertensive disorders of pregnancy are a leading global cause of maternal and infant illness and death. By conservation estimates, these disorders are responsible for 76,000 deaths each year (1).

Preeclampsia is a rapidly progressive condition characterized by high blood pressure and the presence of protein in the urine after 20 weeks. Swelling, sudden weight gain, headaches and changes in vision are important symptoms: however, some women with rapidly advancing disease report few symptoms (2). However, around one in 2,000 cases of pre-eclampsia can develop into eclampsia, a potentially lethal condition for both mother and baby. Eclampsia is a severe from of pregnancy induced hypertension. Women with eclampsia have seizures resulting from the condition. Eclampsia occurs in about one in 1,600 pregnancies and develops near the end of pregnancy, in most cases. HELLP syndrome is a complication of severe preeclampsia or eclampsia. HELLP syndrome is a group of physical changes including the breakdown of red blood cells, changes in the liver and low platelets (3).

Eclampsia complicates 1 in 2,000 maternities in the United Kingdom and carries a maternal mortality of 1.8 percentages. The HELLP syndrome is more common, probably about 1 in 50 maternities, but may be as dangerous as eclampsia itself. These two major maternal crises can present unheralded by prodromal signs of preeclampsia. Cerebral hemorrhage is a lesion that can kill women with preeclampsia or eclampsia (4).

In 1983, the Ministry of Public Health of Thailand reported that pregnancy-induced hypertension or preeclampsia was an important condition which was a leading cause of maternal deaths in the country, after hemorrhage and infection. The cases of

maternal deaths reported by the Ministry of Pubic Health during 1989-1993 indicated that obstructed labor and hemorrhage were the first and second leading causes of death and preeclampsia was the third. Reported statistics on preeclampsia in Thailand were different due to studies arising from difference groups of population and survey periods (5).

One problem of the statistics of incidence of pregnancy – induce hypertension or preeclampsia is the type of study. Most reports were cross sectional study which included or excluded referred cases which resulted in distortion of incidence or prevalence

The first part of this study is historical cohort study with the objective to determine the incidence of preeclampsia among nulliparous women who came to register for the first time at antenatal care booking unite Ramathibodi hospital during 1 January – 30 December 2005. The second part is case – control study with the objective to determine risk factors of preeclampsia. During the study period, there were 2,543 pregnant women who came to register for the first time. For those who loss to follow up attempt to contact was done by mail or telephone.

Descriptive statistics were number and percentage. Analytical statistics including odds ratio with 95% confidence intervals, chi – square test, and logistic regression were used to determine risk and association of factors and preeclampsia $SPSS^{+}$ PC program was used for statistical analysis.

The results of this study found that 68.7% of women who registered had known outcomes of pregnancy (65.7% delivery, 3.1% abortion). Percentage to loss to follow up was 32.2%. Among 1,670 nulliparous women 4.9% had preeclampsia. (3.4 of mild preeclampsia and 1.5 of severe preeclampsia). The case control study included 82 cases of preeclampsia and 82 cases of control. The controls were selected from pregnant women who came to register on the same day just after the cases. The significantly associated factors were maternal age more than 30 years old, BMI at first booking more than 25 kg/m^2, mean gain weight during antenatal visits more than 0.5 kg/wk (p-value < 0.05) and housewife when statistically analysis by logistic regression.

Recommendation for application

1. Set up program and education for women or teenage to control weight and avoid obesity.
2. Set up program and education for pregnant women to control weight during pregnant.
3. Recommendation for housewives to avoid or decreases both physical and mental stress during pregnancy.

Recommendation for further research

1. Incidence and risk factor of preeclampsia in prospective cohort study.
2. Study effects occupation stress both physical and emotional or risk of preeclampsia.
3. Study effect of birth place and preeclampsia.

REFERENCES

1. Ventura SJ, Martin JA, Curtin SC, Mathews TJ, Park MM. Birth: final data for 1998. National Vital Statistics Reports Vol 48, No 3. Hyattsville: MD, National Center Health Statistic; 2000.
2. Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987 – 1990. Obstet Gynecol 1996: 88; 161 – 7.
3. Pipkin FB. Risk factors for preeclampsia. Eng J Med 2001: 344; 34-40.
4. Douglas KA, Redman CWG. Eclampsia in the United Kingdom. BMJ 1994 Nov: 309(26); 1395 – 400.
5. Division of Public Health Statistic. Public Health Statistics. Thailand. Office of The Permanent Secretary Ministry of public Health. 1993.
6. Lindheimer MD, Roberts JM, Cunningham FG. Chesley's Hypertensive Disorders in pregnancy 2nd ed. London: Appleton&Lange; 1999.
7. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap L, Wenstrom KD. Williams Obstetrics, 22nded. New York: McGraw-Hill; 2005.
8. Chesley LC, Wynn RM. Hypertensive Disorders in Pregnancy. New York: Appleton-century-Crofts; 1978.
9. Mabie, William C., Sibai BM. Hypertensive States of Pregnancy. In Current Obstetric and Gynecologic Diagnosis and Treatment, ed. Alan H. DeCherney and Martin L. Pernoll. Norwalk, CT: Appleton & Lange, 1994.
10. Brody SA, Ueland K, Kase N (editor). Endocrine disorders in pregnancy. New York. Appleton & Lange. 1989.
11. Porapakkham S. An epidemiologic study of eclampsia 298 cases at Siriruj Hospital during 1967-1974. Obstet Gynecol 1974: 54; 26-30.
12. อัมรินทร์ ทักขิญเสถียร. ปัจจัยที่มีความสัมพันธ์กับภาวะความดันโลหิตสูง เนื่องจาก การตั้งครรภ์ในโรงพยาบาลรามาธิบดี 2535 เปรียบเทียบแบบ logical regression & discriminate analysis [วิทยานิพนธ์ปริญญาวิทยาศาสตรมหาบัณฑิต สาขาชีวสถิติ]. กรุงเทพ: บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล; 2536.

13. Pichainarong N. Risk factor as predictors of pregnancy – induce hypertension among 4 maternal and child hospital during 1993-1995. [Ph.D.thesis in Epidemiology]. Bangkok: Factory of Graduate Studies, Mahidol University; 1995.
14. Condé-Agudelo A, Kafury-Goeta AC. Case- control study of risk factor for complicated eclampsia. Obstet Gynecol. 1997: 78; 56- 60.
15. Wonguppa R. Risk factors association with preeclampsia [Ms.thesis in Epidemiology]. Bangkok: Factory of Graduate Studies, Mahidol University; 1999.
16. Dawson LM, Parfrey PS, Hefferton D, Dicks EL, Cooper MJ, Young D, et. al. Familial risk of preeclampsia in Newfoundland: A population – based study. J Am Soc Nephrol 2002: 13; 1901-6.
17. Duckitt K, Harrington D. Risk factor for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005: 330; 565-9.
18. Sibai BM, Gordon T, Thom E, Caritis SN, Klebanoff M, Mc Nellis D, et al. Risk factor for preeclampsia in healthy nulliparous women: a prospective multicenter study. Units. Am J Obstet Gynecol 1995: 172; 642 – 648.
19. กชพร สิงหะหล้า. ปัจจัยที่มีความสัมพันธ์กับภาวะ preeclampsia ในหญิงตั้งครรภ์ ที่เข้ารับการรักษาที่ โรงพยาบาลรามาธิบดี ระหว่างปี พ.ศ.2535 – 2539 [วิทยานิพนธ์ปริญญาวิทยาศาตรมหาบัญฑิต สาขาการเจริญพันธุ์ และวางแผน ประชากร] . กรุงเทพฯ: บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล; 2539.
20. Coonrod DV, Hickok DE, Zhu K, Easterling TR, Daling JR. Risk factor for preeclampsia in twin pregnancies: a population – based cohort study. Am Obstet Gynecol 1995: 85; 645 – 50.
21. Ros H.S, Cnattingius S, Lipworth. Comparison of risk factor for preeclampsia and gestational hypertension in a population- base cohort study. Am J Epidemiol 1998: 147; 1062 - 70.
22. Anourlu RI, Iwuala NC, and Odum C U. Risk factors for preeclampsia in Lagos, Nigeria. Aust. N.Z. j. Obstet. Gynaecol 2005; 45: 278-82.
23. Eskenazi B, Fenster L, Sidney S: A multivariate analysis of risk factor for preeclampsia. JAMA 1991: 266; 237-241.

24. ศิรินันท์ พุทธมนต์. ปัจจัยที่มีความสัมพันธ์กับการเกิดภาวะ preeclampsia กรณีศึกษา เฉพาะผู้ป่วยโรงพยาบาลราชวิถี [วิทยานิพนธ์ปริญญาวิทยาศาสตรมหาบัณฑิต สาขาชีวสถิติ]. กรุงเทพ: บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล. 2533.

25. Thadhani R, Hunter DJ, Solomon CG. High body mass index and hypercholesterolemia: Risk of hypertensive disorders of pregnancy. Am J Obstet Gynecol 1999: 94; 543-50.

26. Wolf M, Shah A, Jimenez-Kimble R, Sauk J, Ecker JL, and Thadhani R. Differential risk of hypertensive disorders of pregnancy among Hispanic Women. J AM Soc Nephrol 2004: 15; 1330-8.

27. Doherty DA, Magann EF, Francis J, Morrison JC, Newnham JP. Pre-pregnancy body mass index and pregnancy outcome. Int J Obstet Gynecol 2006: 95 (3); 242 – 7.

28. Mireles C, Harlow, Sanchez-Carrillo, and Nunez. Risk factor for preeclampsia/ eclampsia among working women in Mexico City. Am J Paediatr Perinat Epidemiol 2001: 15; 40 – 6.

29. Rudra CL, Williams MA. BMI as a modifying factor in the relations between age at menarche, menstrual cycle characteristics, and risk of preeclampsia. Gynecol Endocrinol 2005: 21 (4); 200 – 5.

30. Carr DB, Epplein M, Johnson Co, Easterling TR, Critchlow CW. A Sister's risk: family history as a predictor of preeclampsia. Am J Obstet Gynecol 2005: 193; 965 – 72.

31. Leeners B, Rath W, Kuse S, Irawan C, Imthurn B, Neumaier-Wagner P. BMI: new aspects of a classical risk factor for hypertensive disorders in pregnancy. Clin Sci (Lond) 2006 Jul: 111(1); 81-6.

32. Mahomed K, Williams MA, Woelk GB, Jenkins-Woelk L, Mudzamiri S, Madzime S, et. al. Risk factors for preeclampsia – eclampsia among Zimbabwean women: recurrence risk and familial tendency towards hypertension. Obstet Gynaecol 1998: 18; 218 – 22.

33. Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between gestational diabetes and pregnancy – induced hypertension. Am J Epidemiol 2003: 158 (12); 1148 – 53.

34. Mayer A. Erez O, Novack L, Bashiri A, Wiznitzer A, Mazor M. Chronic hypertension is an independent risk factor for preeclampsia and preterm delivery in women with rheumatologic diseases: A population – based study. Eur J Obstet Gynecol Reprod Biol 2006: 45; 45-9.
35. Irwin DE, Savitz DA, St Andre KA, Hertz-Picciotto I. Study of occupational risk factor for pregnancy-induced hypertension among active duty enlisted Navy personnel. Am J Ind Med. 1994: 25; 349 - 59.
36. Spinillo A, Capuzz E, Colonna L, Piazzi G, Nicola S, Baltaro F. The effect of work activity in pregnancy on the risk of severe preeclampsia. Aust N Z J obstet Gynaecol 1995 Nov: 35 (4): 380-5.
37. Klonoff-Cohen HS, Cross JL, Pieper CF. Job stress and Preeclampsia. Epidemiology 1996: 7(3); 245 – 9.
38. Higgins J R, Walshe JJ, Conroy RM, Darling RN. The relation between maternal work, ambulatory blood pressure, and pregnancy hypertension. J Epidemiol Community Health 2002: 56; 389 – 93.
39. Fuent – Afflick E, Hessol Na, Perez – Stable EJ. Maternal birth place, Ethnicity, and low birth weight in California. Arch Pediatr Adolesc Med 1998: 152; 1105-12.
40. Faiz AS, Demissie K, Ananth CV, Rhoads GG. Risk of abruption placetae by regions of birth and residence among African – American women in the United States. Ethn Health 2001: 6; 247 – 53.
41. Zhu M, Charlotte D, Lin S. Maternal birthplace and major congenital malformations anong New York Hispanics. Birth Defects Res Clin Mol Teratol 2006: 76; 467 – 73.
42. Meirik O. Cohort and case-control studies. Switzerland: Epidemiological research, Word Health Organization; 2006.
43. Farmer R, Lawrenson R. Lecture notes: Epidemiology and public health Medicine, 5th. Australia: Blackwell Publishing; 2004.
44. Palmer SK, Moore LG, Young DA. Altered blood pressure and increased preeclampsia at high altitude (3100meters) in Colorado. Am J Obster Gynecol 1999: 180 (5); 1161-8.

45. Lawlor DA, Morton SM, Nitsch D, Leon DA, Esterlitz JR, Sibai B, Curet LB, et al. Association between childhood and adult hood socioeconomic position and pregnancy induced hypertension: results from the Aberdeen children of the 1950s cohort study. J Epidemiol Community Health 2005: 59; 49- 55.

46. Hauth JC, Ewell MG, Levine RJ. Pregnancy outcomes in healthy nulliparas who developed hypertension. Obstet Gynecol 2000: 95; 24-8.

47. Vatten IJ, Skærven R. Is pre-eclampsia more that one disease?. Br J Obstet Gynaecol 2004: 111 (4); 298 -302.

48. World Health Organization International Collaborative study of hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension. Am J Gynecol 1998; 158: 80-3.

49. สถิติประจำปี พ.ศ. 2541 สาขาวิชาวิจัยสถิติ-รายงาน ภาควิชาสูติศาสตร์-นารี คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล.

50. Weidmann P, de Courten M, Boehlen L, Shaw S. The pathogenesis of hypertension in obese subjects. Drugs1993: 446 (Suppl 2); 197-208.

51. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia-a state of sympathetic overactivity. N Engl J med. 1997: 335; 1480-5.

52. Stone JL, Lockwood CJ, Berkowitz GS, Alvares M, Lapinski R, Berkowitz RL. Risk factors for severe preeclampsia. Obstet Gynaecol 1994: 83; 357-61.

53. Cnattingius S, bergstrom R, Lipworth L, Kramer Ms. Pregnancy weight and the risk of advers pregnancy outcome. N Engl J med. 1998: 338; 147-52.

54. Murai JT, Muzykanskiy E, Taylor RN. Maternal and fetal modulators of lipid metabolism correlate with the development of preeclampsia. Metabolism 1997: 46; 963-7.

55. Gratacos E, Casals E, Sanllehy C, Cararach V, Alonso PL, Fortuny A. Variation in lipid levels during pregnancy with different type of hypertension. Acta OIbstet Gynaecol Scand.1996: 75; 896-901.

56. Vigne J, Murai JT, Arbogast BW, Jia W, Fisher SJ, Taylor RN. Elevated nonesterfied fatty acid concentration in severe preeclampsia shift the

isoelectric characteristics ofd plasma albumin. J Clin Endocrinol Metab 1997: 682; 3786-92.

57. Potter JM, Nessel PJ. The hyperlipidemia of pregnancy in normal and complication pregnancies. Am J Obstet Gynaecol 1979: 133; 165-70.
58. Kaaja R, Tikkanen MJ, Viinikka L, Ylikorkala O. Serum lipoproteina insulin, and urinary prostanoid metabolites in normal and hypertensive pregnant women. Obstet Gynaecol 1995: 85; 353-6.
59. Lorentzen B, Drevon CA, Endresen MJ, Henrikesen T. Fatty acid pattern of esterfied anf free fatty acids in sera of women with and preeclamptic pregnancy. Br J Obstet Gyneacol. 1995: 102; 530-7.
60. Roberts JM, Redman CW. Preeclampsia: More than pregnancy induced hypertension. Lancet. 1993: 341; 1447-51.
61. Sattar N, Gaw A, Packard CJ, Greer IA. Potential pathogenic role of aberrant lipoprotein and fatty acid metabolism in preeclampsia. . Br J Obstet Gyneacol 1996: 103; 614-20.
62. Hubel CA, Roberts JM, Taylor RN, Musci TJ, Rogers GM, McLaughlin MK. Lipid peroxidation in pregnancy: new perspective on preeclampsia, Am J Obstet Gynaecol 1989: 79; 1025-34.
63. Branch DW, Mitchell MD, Miller E, Palinski W, Witztum JL. Preeclampsia and serum antibodies to oxidation low-dencity lipoprotein. Laucet 1994: 343; 645-6.
64. Roberts JM, Taylor RN, Goldfein A. A clinical and biochemical evidence of endothelial cell dysfunction in the pregnancy syndrome preeclampsia. Am J hypertens 1991:4; 700-8.
65. Clark BA, Halvorson L, Sachs B, Epstein FH. Plasm endothelin levels in preeclampsia: Elevation and correlation with uric acid level and renal impairment. Am J obstet Gynaecol 1992: 166; 962-8.
66. Lerman A, Webster MW, Chesebro JH, Edwords WD, Wei CM, Fuster V, et al. Circulating and tissue endothelin immunoreactivity in hypercholesterolimic pigs. Circulation 1993: 8; 2923-8.
67. Winocour PH, Kaluvya S, Brown L, Farrer M, Millar JP, Neil AW, et al. The association of difference measures of inssulinemia with vascular factors

of health normoglycemic, normotensive, non-obese men and women. Q J Med. 1991: 79; 536-60.

68. Laivuori H, Tikkanen MJ, Ylikorkala O, hyperinsulin 17 years after preeclampsia first pregnancy. J clin Endocrino metab 1996: 81; 2908-11.
69. Lorentza B, Birkeland KI, Ender sen MJ, Henriksen T. Glucose intolerance in women with preeclampsia. Acta Obstet Gynaecol 1998: 77; 22-7.

APPENDIX

คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล
ถนนพระราม 6 กทม. 10400
โทร. (662) 354-7275, 201-1296 โทรสาร (662) 354-7233

Faculty of Medicine, Ramathibodi Hospital, Mahidol University
Rama VI Road, Bangkok 10400, Thailand
Tel. (662) 354-7275, 201-1296 Fax (662) 354-7233

Documentary Proof of Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects Faculty of Medicine, Ramathibodi Hospital, Mahidol University

MURA2006/436

Title of Project	Incidence and Risk Factor of Preeclampsia in Ramathibodi Hospital
Protocol Number	ID 12-49-15
Principal Investigator	Assoc. Prof. Somsak Suthutvoravit, M.D.
Official Address	Department of Obstetrics and Gynecology Faculty of Medicine, Ramathibodi Hospital Mahidol University

The aforementioned project has been reviewed and approved by Committee on Human Rights Related to Researches Involving Human Subjects, based on the Declaration of Helsinki.

Signature of Secretary Committee on Human Rights Related to Researches Involving Human Subjects	..... Assoc. Prof. Duangrurdee Wattanasirichaigoon, M.D.
Signature of Chairman Committee on Human Rights Related to Researches Involving Human Subjects	..... Prof. Boonsong Ongphiphadhanakul, M.D.
Date of Approval	January 15, 2007

DATA RECORD FORM

Incidence and risk factors of preeclampsia in Ramathibodi Hospital

---

1. Hospital number……..
2. วันที่มาฝากครรภ์……..
3. วันที่มาคลอด……..
4. สถานที่คลอด……..
5. Diagnosis
   - o Normal
   - o Mild preeclampsia
   - o Sever preeclampsia
   - o Eclampsia
6. อาชีพ
   - o ราชการ / รัฐวิสาหกิจ / เอกชน
   - o ผู้ใช้แรงงาน (กรรมกร)
   - o ธุรกิจส่วนตัว
   - o แม่บ้าน
   - o นักเรียน/ นักศึกษา
   - o อื่นๆ……..
7. สถานที่เกิด
   - o ภาคเหนือ
   - o ภาคตะวันออกเฉียงเหนือ
   - o ภาคใต้
   - o ภาคกลาง
   - o กรุงเทพและปริมณฑล

8. อายุของหญิงตั้งครรภ์เมื่อคลอด

- o < 20
- o 20 – 25
- o 26 -30
- o 31 – 35
- o 36 – 40
- o ≥ 40

9. ประวัติการเจ็บป่วยในอดีต

- o ไม่มี
- o มี ได้แก่
  - o DM
  - o Autoimmune disease
  - o Chronic hypertension
  - o Others.....

10. Hematocritครั้งแรกที่มาฝากครรภ์.....…gm%

11. น้ำหนักครั้งแรกที่มาลงชื่อฝากครรภ์……....kg

12. ส่วนสูง…….……..cm

13. น้ำหนักที่คลอด…….……...kg

14. อายุครรภ์เมื่อมาฝากครรภ์…….....weeks

15. อายุครรภ์เมื่อคลอด……..……..weeks

BIOGRAPHY

NAME	Miss Korravarn Yodmai
DETE OF BIRTH	June 8th, 1981
PLACE OF BIRTH	Roi Et, Thailand
INSTITUTION ATTENDED	Saint Louis College, 2000 – 2004: Bachelor of Nursing Science Mahidol University, 2005 – 2007: Master of Science (Human Reproduction and Population Planning)
POSITION & OFFICE	2004 – 2005, Bangkok 9 International, Bangkok, Thailand. Position: Regular nurse