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Risk factors for the progression from gestational hypertension to preeclampsia

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RÉSUMÉ

Objectif: L'objectif de cette étude est de déterminer les facteurs prédictifs de la progression de l'hypertension gestationnelle (HG) en prééclampsie (PE), parmi les femmes qui initialement présentaient une HG, en créant un modèle qui puisse prédire cette progression. **Protocole expérimental:** C'est une étude de cohorte rétrospective de 280 patientes présentant initialement une hypertension gestationnelle; 189 patientes ont évolué vers une PE, 91 sont restées avec une hypertension gestationnelle jusqu'à l'accouchement. Les données ont été comparées par une analyse du Chi deux, un test exact de Fisher, une analyse de la variance, une analyse de régression logistique univariée et multivariée, lorsque applicable. **Résultats:** Trois facteurs prédictifs significatifs (un antécédent de PE, un taux d'acide urique et l'âge gestationnel lors de la détection de l'HG) étaient associés à la progression de l'HG en PE dans une analyse de régression logistique multivariée. Un modèle de prédiction multivarié a été développé, avec une sensibilité = 81.5%, spécificité = 84.6%, valeur prédictive positive = 91.7%, et valeur prédictive négative = 68.8%. **Conclusions:** Une hypertension gestationnelle précoce, une histoire de prééclampsie antérieure et le taux d'acide urique sont des variables associés à la progression de l'hypertension gestationnelle vers la prééclampsie. Notre modèle utilise de simples facteurs prédictifs disponibles lors des soins de routine périnataux; qui ont raisonnablement de bons paramètres de validité pour prévoir la probabilité de progression de l'hypertension gestationnelle en prééclampsie; qui peuvent fournir un outil simple utile dans la gestion du risque de patientes présentant une hypertension gestationnelle.

Mots clés: Sensibilité, Spécificité, Modèle de prédiction multivarié, Age gestationnel, Antécédent de prééclampsie, Acide urique.

ABSTRACT

Objective: Little is known on why some women with gestational hypertension (GH) progress to preeclampsia (PE) while others do not. The objective of this study was to throw light on the predictors of progression to PE, among women who initially present with GH and to create a model which could predict this progression. **Research design:** This was a retrospective cohort study of 280 patients with an initial presentation of GH; 189 patients progressed to PE, and 91 patients remained as GH until delivery. Data were compared by Chi square or Fisher exact tests, analysis of variance and by univariable and multivariable logistic regression analysis where applicable. **Results:** In the multivariable logistic regression analysis, three significant predictors were associated with progression from GH to PE: prior history of PE, uric acid level and gestational age at GH presentation. A multivariable prediction model was developed, with sensitivity = 81.5%, specificity = 84.6%, positive predictive value = 91.7%, and negative predictive = 68.8%. **Conclusions:** Early onset GH, prior history of PE and uric acid level are variables associated with the progression from GH to PE. Our model uses simple predictors available in routine perinatal care and has reasonably good validity parameters for predicting the probability of progression from GH to PE, which may provide a useful simple tool in the risk management of patients with gestational hypertension.

Key words: Sensitivity, Specificity, Multivariable predictive model, Gestational age, Prior preeclampsia history, Uric acid.

TABLE OF CONTENTS

LIST OF TABLES 36

LIST OF FIGURES 47

LIST OF ABBREVIATION

ALT: Alanine aminotransferase

aOR: Adjusted odds ratio

ASSHP: Australasian Society for the Study of Hypertension in Pregnancy

AST: Aspartate aminotransferase

BMI: Body Mass Index

BP: Blood pressure

exp: Exponent

GA: Gestational age

GA_LT36: Gestational age at GH onset, being coded as: < 36 weeks = 1, ≥36 weeks = 0

GH: Gestational hypertension

GH-PE: Preeclampsia progression from gestational hypertension

HELLP syndrome: Hemolysis, Elevated Liver enzymes, and Low Platelets

IDDM: Insulin Dependent Diabetes Mellitus

ISSHP: International Society for the Study of Hypertension in Pregnancy

IUGR: Intrauterine growth restriction

LDH: Lactic acid dehydrogenase

NICU: Neonatal Intensive Care Unit

NPV: Negative predictive value

OR: Odds ratio

P: Probability of GH to progress to PE

PAPE: Past history of PE, being coded as: Yes = 1, No = 0

PE: Preeclampsia

PlGF: Placental Growth Factor

PPV: Positive predictive value

ROC curve: Receiver-operator characteristic curve

SD: Standard deviation

sFlt-1 (sVEGFR1): soluble Fms-like tyrosine kinase 1

SGA: Small for gestational age, birth weight below the 10^{th} percentile for gestational age

URA: Uric acid

URA_GE300: Uric acid level at GH onset, being coded as: < 300 µmol/L = 0, ≥300 µmol/L = 1

VEGF: Vascular Endothelial Growth Factor

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1. Literature review

1.1. Introduction

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal and neonatal morbidity and mortality in worldwide countries. An estimated one-third of all maternal deaths in Canada are caused by hypertensive disorders, a trend that has changed little since the early 1970s.[1] Pregnant women with hypertension, either newly diagnosed or pre-existing, remain at risk for severe complications such as abruptio placenta, cerebrovascular disorders, end-organ failure and disseminated intravascular coagulation.[2-7] As well, the fetus is at risk for intrauterine growth restriction (IUGR), prematurity and intrauterine death.[2;5;8;9]

Despite recent advances in our understanding of the pathophysiology and treatment of hypertensive disorders in pregnancy, confusion abounds in the literature regarding the definitions and classifications of such disorders.

Hypertensive disorders in pregnancy affect about 6 to 10 % of all pregnancies and remain a major cause of maternal and neonatal mortality and morbidity worldwide. In developed countries, preeclampsia primarily affects fetal and neonatal well-being through intrauterine growth restriction (IUGR), preterm birth and low birth weight. A significant component of neonatal morbidity is attributed to preterm delivery undertaken to prevent further deterioration in the fetus and mother.[10] In fact, about 15% of all preterm births are indicated deliveries for preeclampsia.[11] Preterm birth has been associated with increased risks of neonatal mortality and long-term neurological disability. Preeclampsia also increases the risk of intrauterine growth restriction (IUGR). Growth restricted babies not only have an increased risk of acute problems but, more alarmingly, IUGR may confer a long-term burden in future cardiovascular risk.[12;13]

From a public health perspective, it is of concern that the rate of preeclampsia has

increased by 40% between 1990 and 1999 in a study report,[14] probably the result of a rise in the number of older mothers and multiple births, conditions that predispose to preeclampsia.

1.2. Classification of Hypertensive Disorders in Pregnancy

Classification of hypertensive disorders in pregnancy has varied in the past and led to some confusion in both the clinical management and research efforts toward the etiology of these disorders. The most recent classification recommended by the National High Blood Pressure Education Program[15] is as follows.

- Preeclampsia / Eclampsia;
- Gestational hypertension;
- Chronic hypertension;
- Preeclampsia superimposed on chronic hypertension.

These categories identify disorders with different epidemiological characteristics, pathophysiology, and risks for mother and baby. Previous terminology such as Pregnancy-induced hypertension has been gradually abandoned.[16] These categories are summarized below.

1.2.1. Preeclampsia

Preeclampsia is defined as the de novo appearance of hypertension (systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg), accompanied by new-onset proteinuria, defined as ≥300 mg per 24 hours; occurring after 20 weeks of gestational age. Previous definitions included edema, but this sign is non-specific and is observed in many normotensive pregnant women. Thus, edema is no longer considered to be part of the diagnostic criteria for preeclampsia. Likewise, previous criteria in which a rise of 30 mmHg in systolic pressure and/or 15 mmHg in diastolic pressure were considered diagnostic have been eliminated as too non-specific, identifying up to 25% of

pregnant women.[17] In addition, probably because of this lack of specificity, it is very difficult to demonstrate an excess of morbidity in these women.[17] As proteinuria may be a late manifestation of preeclampsia, it should be suspected when de novo high blood pressure is accompanied by headache, abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes. It is prudent to treat such patients as if they may develop preeclampsia later.

Eclampsia occurs when preeclampsia progresses to a life-threatening convulsive phase. Such convulsions usually occur after mid-pregnancy or during delivery, but as many as one third of eclamptic convulsions occur during the first 48 hours after delivery.

In fact, in the era of adequate blood pressure control, preeclampsia-associated mortality is most commonly due to either hepatic necrosis or adult respiratory distress syndrome, both of which are the consequences of systemic inflammation.[18]

1.2.2. Gestational hypertension

Gestational hypertension is defined as increased blood pressure (> 140 mmHg systolic or > 90 mmHg diastolic pressure) first diagnosed after 20 weeks' gestation and not accompanied by proteinuria. Gestational hypertension may later satisfy diagnostic criteria for preeclampsia if accompanied by proteinuria ($\geq$ 300 mg/24 hrs) during pregnancy. However, in many cases proteinuria never occurs, the course is relatively benign, and the blood pressure normalizes after delivery.

1.2.3. Chronic hypertension

Chronic hypertension refers to an elevated blood pressure in the mother that predated the pregnancy. It can be diagnosed when elevated blood pressure is detected before the 20th week of gestation and can also be diagnosed retrospectively when hypertension fails to normalize within 6 weeks of delivery. Blood pressure generally falls in the first and second trimesters; therefore women with high blood pressure before the

20th week of gestation are assumed to have pre-existing hypertension. Chronic hypertension may also not have been recognized before the pregnancy. The absence of clinical data to guide medical treatment strategies is particularly disconcerting because women with chronic hypertension are at increased risk of superimposed preeclampsia (15-25%), preterm delivery, fetal growth restriction or demise, abruptio placenta, congestive heart failure, and acute renal failure. There is no evidence that treatment of chronic hypertension reduces the probability of developing preeclampsia and its complications in this high risk group.

1.2.4. Preeclampsia superimposed on chronic hypertension

The outcome for mothers and infants with preeclampsia superimposed on existing hypertension is worse than with de novo preeclampsia.[11] Women with chronic hypertension have a 15 to 25% risk of developing preeclampsia during pregnancy. It is sometimes difficult to establish a differential diagnosis between the deterioration of chronic hypertension and the onset of preeclampsia. A rapid increase in proteinuria or the development of laboratory signs suggesting organ damage, such as elevated liver enzymes or thrombocytopenia, can help in diagnosing preeclampsia.

All women with raised blood pressure must be carefully monitored for the associated features of preeclampsia.

1.3. Preeclampsia: Current Concepts

1.3.1. History

Eclampsia was described by Celsus in 100 AD as seizures during pregnancy that abated with delivery.[19] For the ensuing 2000 years, eclampsia was considered to be a pregnancy-specific seizure disorder. It was not until the mid-1800s that the similarity of the edematous eclamptic woman and the dropsic patient with Bright's disease (acute glomerulonephritis) stimulated clinicians to determine whether women with eclampsia,

like individuals with Bright's disease, had protein in their urine. Protein was indeed present in the urine of eclamptic women. Furthermore, it was recognized that the proteinuria usually antedated the seizures. In another 50 years, it was possible to measure blood pressure noninvasively. Again, the association between increased blood pressure and eclampsia was recognized, as was the fact that the hypertension also antedated the seizures.[19] It soon became evident that hypertension and proteinuria during pregnancy, even without seizures, identified a woman with the potential for a rapidly progressive life-threatening disorder and a fetus at increased risk for stillbirth. These two findings of renal dysfunction and hypertension guided research for more than 80 years. It was not until about 10 years ago that investigators began focusing on the pathophysiology and multiple systemic manifestations of preeclampsia.

1.3.2. Epidemiological characteristics

The epidemiology of preeclampsia is complicated by differences in definitions and inaccuracy of diagnosis. A single blood-pressure reading of 140/90 mm Hg or above is not uncommon in pregnancy and was reported in nearly 40% of pregnant women in one study.[20] Such a finding carries little risk to the mother or fetus. Persistent hypertension is diagnosed if an abnormal reading is found on two occasions at least 4h apart.[21] The type of hypertension can be further defined on the basis of other clinical signs, particularly proteinuria and abnormalities of coagulation.[22]

Differences in diagnostic criteria and poor record keeping make it virtually impossible to compare the frequency of preeclampsia in different populations from routinely collected data. It is clear that death rates from the disorder are higher in developing countries; however, this need not indicate increased disease frequency. Death from preeclampsia is largely preventable by appropriate care. Death rates are primarily a marker of quality of care rather than disease frequency. There is a suggestion of an increased risk of preeclampsia in black women. Although the disorder appears to be more common in young women, when the "first pregnancy effect" is controlled for,

preeclampsia is actually more frequent in older women.[23]

Preeclampsia is twice as common in primigravid women than in women having second or later pregnancies.[24] However, with a change of partner, the risk in a multiparous woman increases; this effect suggests that primipaternity is important. Some men seem to have an increased risk of fathering a preeclamptic pregnancy.[25] Women who become pregnant with donor eggs have a higher frequency of preeclampsia than women pregnant with their own eggs;[26] this finding suggests that any new fetal factors are important, not necessarily those of paternal origin.

1.3.3. Pathophysiology

Preeclampsia is the result of an initial placental trigger, and a maternal systemic reaction that produces the clinical signs and symptoms of the disorder.[27] In 2005, Redman[28] reviewed some new and interesting advances in understanding preeclampsia, include the conception of placental preeclampsia and maternal preeclampsia. Placental preeclampsia progress with preclinical stage, which characteristics as poor placentation, inhibited trophoblast invasion and poorly remodeled arteries. Whereas maternal preeclampsia has the characteristic as more an abnormal maternal response problem than an abnormal pregnancy, such as maternal arterial disease, hypertension, obesity or diabetes.

1.3.3.1. Placental trigger

Preeclampsia occurs only in the presence of a placenta. Although it can be associated with a failure of the normal invasion of trophoblast cells, leading to maladaptation of maternal spiral arterioles,[29] it can also be associated with hyperplacentation disorders such as diabetes, hydatidiform mole, and multiple pregnancy. The maternal arterioles are the source of blood supply to the fetus, and maladaptation of these vessels can interfere with normal villous development. In some cases, compensation

can occur, but, in others, poor villous development results in placental insufficiency.[30] Secondary damage, such as fibrin deposition and thrombosis can then occur within the placenta. These features are found in cases of placental insufficiency, whether preeclampsia is present or not.[31] Not all women with the potential placental trigger develop preeclampsia; therefore the maternal response appears to be a decisive factor in the development of systemic disease.

1.3.3.2. Maternal response

Although preeclampsia is said to be a vascular endothelial disorder,[32] it is a multisystem disorder with various forms. This variation could be due to different vascular beds being affected to varying degrees, but later research has shown that there is a strong maternal inflammatory response.[27] Although this response has been described in the placental bed,[33] there is far broader immunological systemic activity.[27] These changes may explain many of the clinical signs, including the endothelial-cell dysfunction.

Because preeclampsia is diagnosed by the presence of hypertension and proteinuria, the remaining systemic features can vary from mild cases with little systemic involvement, to multiorgan failure in severe cases. How extensively the disease develops depends on various modifying factors, which could be genetic or environmental in origin.

1.3.3.3. Hereditary factors

The epidemiological features of preeclampsia suggest a genetic basis for the disorder. Preeclampsia is more common in daughters of preeclamptic women[34] and in pregnancies fathered by sons of preeclamptic women,[35] suggesting the involvement of both maternal and fetal genes in the syndrome.

Preeclampsia can be familial.[36] However, various groups have studied the genetic basis of this disorder and no consistent results have been obtained. A single preeclampsia gene is unlikely; there are probably several modifier genes interacting with environmental

factors to determine whether an individual woman may develop the disease.[37] There have been conflicting results for the genes that encode angiotensinogen, superoxide dismutase, tumour necrosis factor α, methylenetetrahydrofolate reductase, factor V Leiden, and endothelial nitric oxide synthase. These studies concentrated on maternal genetics and ignored the potential paternal and fetal influences.[25] The results of large multicentre studies with the use of modern chip technology for genome scanning with multiple microsatellite markers are awaited to clarify the role of genetics in the pathophysiology of preeclampsia.[37] In addition, genetic markers of the disease would be useful not only in identifying relevant molecules but also would facilitate longitudinal studies of pathogenesis.

1.3.4. Subclassification of Preeclampsia

Preeclampsia / eclampsia is a maternal syndrome that probably arises through multiple pathways. It varies from the usually evanescent disease of preeclampsia at term to the severe disease most commonly developing remote from term. There is some evidence to support its subclassfication on the basis of gestational age at disease onset.

1.3.4.1. Preeclampsia: Current classification

Most recently, guidelines for the diagnosis and management of preeclampsia have been produced by the Canadian Hypertension Society,[21] the US National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy,[38] and the Australasian Society for the study of hypertension in Pregnancy (ASSHP),[39] as well as International Society for the Study of Hypertension in Pregnancy (ISSHP).[40] Later in 2002, Pridjian G[41] published an article, summarized preeclampsia classification as follows:

1. **Mild preeclampsia** is defined as a blood pressure (BP) of 140 / 90 mm Hg or higher with proteinuria of 0.3 to 5 g/day; the evidence of other organ dysfunction is

not present. The importance of making this diagnosis is related to the fact that maternal and fetal surveillance are subsequently increased. New onset hypertension in pregnancy or gestational hypertension should also be followed carefully because 10% of eclampsia occurs before significant proteinuria.[42] Forerunners to the diagnosis of mild preeclampsia include the sudden onset of weight gain or edema, and an increase in blood pressure.

2. **Severe preeclampsia** is defined as a systolic blood pressure greater than or equal to 160 mm Hg or a diastolic blood pressure greater than or equal to 110 mm Hg or if hypertension is complicated by significant proteinuria (>=5 g/day), or by evidence of end-organ damage. The following signs and symptoms, although variably present, are associated with severe preeclampsia: headache, visual disturbances, confusion, right upper quadrant or epigastric pain, impaired liver function, proteinuria, oliguria, pulmonary edema, microangiopathic hemolytic anemia, thrombocytopenia, oligohydramnios, and fetal intrauterine growth restriction (IUGR).

While dichotomizing preeclampsia in this way presumably differentiates women with lower risk from those with higher risk for perinatal outcomes, the definition allows no "shades of gray".

All classifications are predicated on the occurrence of hypertension, proteinuria and other organ dysfunction, none of which is present in 10% of women within 1 week prior to their first eclamptic seizure.[43] Also, gestational age at presentation is not a criterion for diagnosis, severity, or subclassification.

1.3.4.2. Early or late-onset preeclampsia

That gestational age has not been accounted for in any of the current classification systems is a major problem. It is the most important clinical variable in predicting both maternal and perinatal outcomes. Early-onset preeclampsia represents considerable additional maternal risk, as maternal mortality has been reported to be 20-fold higher

when preeclampsia onset is less than 32 weeks' gestation than when preeclampsia occurs at term.[44] In addition, data indicate that early onset preeclampsia may be a qualitatively different disease. This is supported by observations that the pathophysiology of early-onset preeclampsia differs from late-onset disease, in terms of neutrophil function[45] and cytokine levels.[45-47] Also, there is compelling epidemiologic evidence that early-onset disease (defined as onset earlier than 28 weeks) is associated with a greater risk for recurrence in later pregnancies,[48] and an increased risk for later cardiovascular disease and death.[49-53] Being delivered at less than 37 weeks' gestation by a mother whose pregnancy was complicated by preeclampsia increases the lifetime hazard for death from cardiovascular disease by 7.1 (crude odds ratio)[51] to 8.1[52] fold. Furthermore, the concurrence of intrauterine growth restriction, preeclampsia, and preterm birth (<37 weeks' gestation) confers an adjusted hazard ratio for cardiovascular death of 16.1[51] compared with normotensive pregnancies of appropriately grown fetuses at term.

Von Dadelszen[45] reported in 2002 that a greater than 50% chance of survival for a fetus delivered of a woman with preeclampsia is attained when the gestational age at delivery is $\geq 27^{+}$ weeks' and/or the birthweight ≥600 g. Also, Xiong et al[54] reported that early-onset preeclampsia, but not preeclampsia arising at term, is an important predictor of intrauterine growth restriction (IUGR). In fact, recent data suggest that IUGR is a function of preeclampsia arising before 37 weeks' gestation.[54] Furthermore, there is an increase in large babies among women with preeclampsia delivering after 37 weeks' gestation.[55]

For these reasons, women with early-onset preeclampsia may provide the most homogeneous data for differentiating the changes of preeclampsia from those of normal pregnancy.

1.3.5. Maternal-Fetal Interactions in Preeclampsia

An important question which remains unanswered is "how does reduced placental perfusion result in the maternal preeclampsia syndrome?" It is clear that reduced perfusion alone is not sufficient to explain preeclampsia. Intrauterine growth restriction may be the result of reduced placental perfusion. However, many women with a growth-restricted fetus do not develop preeclampsia, and a small percentage of preeclamptic women have large fetuses. In addition, implantation defects including failure to remodel blood vessels that supply the placenta (a characteristic of preeclampsia) are present in pregnancies with fetal growth restriction[56] and in one-third of pregnancies ending in spontaneous preterm births.[57] This has led some to postulate that reduced placental perfusion must interact with maternal factors to result in the maternal preeclampsia syndrome. These factors are posited to be genetic, behavioral, or environmental.

The fetal syndrome is manifested by intrauterine growth restriction, fetal acidemia, and increased risk for both perinatal morbidity and mortality, particularly due to the risk of prematurity.[58]

1.3.6. Preeclampsia: Clinical features

1.3.6.1. Risk factors

A variety of risk factors for preeclampsia have been identified,[2;59] such as nulliparity, extremes of maternal age, family history of preeclampsia, history of preeclampsia in a previous pregnancy, preexisting hypertension or renal disease, uric acid level, diabetes mellitus, multiple gestation, hydatidiform mole and hydrops fetalis. Certain of these risk factors could potentially be useful for identifying patients for prophylactic therapy, but many patients develop the disease with no risk factors other than nulliparity.[59]

1.3.6.2. Clinical manifestations of preeclampsia

Hypertension, edema and proteinuria remain the most important clinical hallmarks of the condition.[2] Blood pressure should be measured with the patient in the sitting position after five minutes of rest.[2] By convention, the blood pressure should be documented to be abnormal on at least two separate occasions, four or more hours apart.

The loss of serum protein and the increase in capillary endothelial permeability lead to a decrease in intravascular volume and increased tissue edema.[60] Edema is not required for the diagnosis of preeclampsia. Indeed, it is common in many healthy pregnant women: edema of the face or hands is reported in 64% of normotensive women, whereas as many as 40% of women with eclampsia have no edema before the onset of convulsions. While it is difficult to distinguish the harmless, physiologic edema of pregnancy from the edema of preeclampsia, suspicion should be raised if pedal edema (1+ or greater) does not resolve with overnight rest, in the presence of edema of the face and hands, and edema associated with more than 2 kg of weight gain in a week.[2;61]

Proteinuria is somewhat easier to define and interpret than edema. Excretion of greater than 300 mg of protein per 24 hours is considered abnormal; this usually correlates with reading of "1+" or greater by dipstick examination[2] and is generally associated with the classic pathological finding of glomeruloendotheliosis,[62] which is not permanent but recovers after delivery. Detection of mild proteinuria on dipstick examination ("1+" or greater) should prompt a 24-hour urine collection if there is clinical suspicion of toxemia and if the results will alter clinical management. The detection of heavy ("2+" or greater) proteinuria is almost always pathologic in the absence of urinary tract infection or heavy vaginal contamination.[2] The presence of proteinuria confirms the diagnosis of preeclampsia and the concomitant increase in risk for both mother and fetus.[63] The risk is related simply to the presence of proteinuria; it is not affected by the absolute value of the increase in urinary protein excretion.[64]

Several body systems are involved in the pathologic changes of preeclampsia. In the central nervous system, cerebral edema is associated with convulsions and can be seen on

computer tomography and magnetic resonance imaging. Cerebral edema may antedate eclampsia, because occipital lobe blindness can occur in the absence of eclampsia and is completely reversible. Certain signs and symptoms in the gastrointestinal, cardiovascular and renal system are both common and nonspecific.

1.3.6.3. Laboratory abnormalities in preeclampsia

Many controversies exist concerning the use of laboratory testing for early diagnosis of preeclampsia.

A decrease in blood volume can occur in preeclampsia, can lead to maternal haemoconcentration and is associated with an increased risk of intrauterine growth restriction.[63]

Several abnormalities of the coagulation system can occur in preeclampsia. These include changes in platelets, the coagulation cascade and in the fibrinolytic systems. Their common pathophysiology is likely vascular endothelial damage or activation. Studies of platelet function in preeclampsia suggest increased activation, decreased numbers, and shorter lifespan.[65;66] In normal pregnancy, the platelet count can fall below 200×10^9/L because of the normal maternal blood-volume expansion. In preeclampsia, the platelet count falls further and may be an indication of progressive disease.[63] This fall is a result of both increased consumption and intravascular destruction. Associated coagulation abnormalities are likely if the count is below 100×10^9/L.[67] A low platelet count is one component of the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), which carries a particular risk to the mother.[68] Fay[69] reported that declining platelet counts were more significant than the absolute level.

Uric acid levels normally fall in pregnancy because renal excretion increases, so comparing the pregnant patient's uric acid with reference values for nonpregnant patients may be falsely reassuring.[2;69] Renal perfusion in preeclampsia is less than in normal pregnant women, trending toward the degree of perfusion observed in the nonpregnant state as the disease worsens. Uric acid excretion in preeclampsia is decreased

predominately due to its enhanced tubular reabsorption and decreased renal clearance[70] resulting in a higher than normal plasma levels.[71] Plasma uric acid levels generally correlate with severity of disease,[72] and high levels have been associated with poor fetal outcome.[73] Roberts[59] reported that the serum uric acid concentration 'is a particularly sensitive marker of preeclampsia available to clinicians'. The mean uric acid level of normal pregnant women is 3.8 mg/dL (228 μmol/L), whereas it is 6.7 mg/dL (402 μmol/L) in preeclampsia, with levels reaching 9.0 mg/dL (540 μmol/L) in severe disease.[74]

Liver involvement in preeclampsia is variable but is the cause of the upper epigastric pain commonly seen in the disorder. The liver swells as a result of local edema secondary to inflammatory infiltrates and obstructed blood flow in the sinusoids. Haemorrhage can occur beneath the liver capsule and may be so extensive as to cause rupture of the capsule into the peritoneal cavity. If a haematoma or haemorrhage is suspected, the liver should be examined by ultrasonography.[75] Liver involvement can be assessed by measurement of alanine aminotransferase and aspartate aminotransferase activities in serum: they increase in preeclampsia as a result of leakage across cell membranes. Increases in these enzymes are part of the HELLP syndrome.[68] With substantial liver involvement there are coagulation abnormalities that result from hepatic dysfunction. Disseminated intravascular coagulation is a rare complication of preeclampsia in the absence of placental abruption.[76]

Renal function is generally maintained in preeclampsia until the late stage. In normal pregnancy, there is an increase in creatinine clearance with a concomitant decrease in serum creatinine and urea concentrations. If creatinine concentrations are high early in the disease process, underlying renal disease should be suspected. In severe disease, increases in serum creatinine can be seen and are associated with worsening outcome.[77] Acute renal failure is now rare in preeclampsia in more developed countries;[78] most cases are associated with haemorrhage or sepsis. Most cases of renal failure are due to acute tubular necrosis, and most patients recover with no long-term renal impairment.[78] Acute

cortical necrosis, a permanent cause of renal failure, occurs in less than 4% of all cases of renal failure in preeclampsia.[79]

In recent years, generalized systemic inflammatory response has been reported, of which endothelial dysfunction is an important component[80]. In 2004, Levine[81] reported in a nested case control study that excess circulating soluble fms-like tyrosine kinase 1 (sFlt-1, also referred as sVEGFR1), an antiangiogenic protein, which released by hypoxic and dysfunctional placenta, binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), preventing their interaction with endothelial receptors on the cell surface and inducing endothelial dysfunction, before clinical signs of preeclampsia appeared. The levels of serum sFlt-1 increased and PIGF decreased earlier and more pronounced in the pregnant women who progressed to preeclampsia later than that of normotensive women, whose levels of serum sFlt-1 moderately elevated and PIGF decreased during the last two moths of pregnancy. In 2006, Levine[82] also reported that serum soluble endoglin, another antiangiogenic protein, increased markedly 2-3 months earlier than clinical preeclampsia onset.

Table X summarizes the literature on laboratory abnormalities in relation to the severity of preeclampsia.[41;83] The cut offs are only provided as reference guidelines for research and clinical management.

1.3.6.4. Maternal risk factors for progression from non-proteinuric gestational hypertension to preeclampsia

To a large extent, the etiology of preeclampsia remains poorly understood. During the last fifteen years, many clinical, biophysical and biochemical tests have been proposed for the identification of women who are at increased risk for developing preeclampsia.[81-86]

Some previous research provides insight into risk factors for preeclampsia and gestational hypertension, and more specifically concerning risk factors for the progression from gestational hypertension without proteinuria to preeclampsia.

In 1998, Ros[87] reported type 1 diabetes (OR = 5.98), gestational diabetes (OR = 3.11) and twin birth (OR = 4.17) as significant risk factors for preeclampsia, whereas the associations between these variables and the risk of gestational hypertension were weaker and nonsignificant. Obese women (Body mass index > 29) had an increased risk of both gestational hypertension (OR = 4.85) and preeclampsia (OR = 5.19).[87] Some studies have reported that uric acid levels are significantly elevated in women with gestational hypertension and preeclampsia as compared to normotensive pregnant women.[88;89] Women who developed preeclampsia following gestational hypertension presented earlier than those who remained with gestational hypertension until delivery. In a retrospective study, prior miscarriage, serum albumin, high hematocrit, creatinine and uric acid were associated with an increased likelihood of progression from gestational hypertension to preeclampsia.[90] It has been suggested that the serum uric acid concentration is "the most sensitive indicator of preeclampsia available to clinicians."[59] Among women with gestational hypertension of pregnancy, the likelihood ratio of developing preeclampsia with a serum uric acid value of 5.5 mg/dL (330 μmol/L) or higher was 1.41.[88]

The onset of abnormal uric acid clearance precedes any measurable decrease in the glomerular filtration rate.[91] In addition, histological studies performed on renal biopsy specimens suggest that hyperuricemia correlates with the presence of glomerular lesions that characterize preeclampsia.[92] Increased oxidative stress and formation of reactive oxygen species have been proposed as another contributing source of the hyperuricemia noted in preeclampsia.[93] Furthermore, several investigators have documented a correlation between hyperuricemia and both the severity of disease and neonatal morbidity.[94-96] In fact, one study found serum uric acid concentration to be a better predictor of low birth weight than blood pressure.[97]

In summary, current reports about the risk factors for progression from gestational hypertension to preeclampsia are few and results are inconsistent. Several factors, such as gestational diabetes, twin birth, early gestational age at the onset of gestational hypertension, prior miscarriage, high hematocrit, serum albumin, creatinine and uric acid have been reported to be risk factors.

2. Thesis project

2.1. Rationale and objectives for current study

Hypertensive disorders in pregnancy affect about 6 to 10 % of all pregnancies and remain a major cause of maternal and neonatal mortality and morbidity worldwide.

According to the classification recommended by the National High Blood Pressure Education Program,[15] hypertension during pregnancy is categorized as follows: preeclampsia (PE) / eclampsia, gestational hypertension (GH), the continued presence of chronic hypertension, and the superimposition of preeclampsia on chronic hypertension. These categories identify disorders with different epidemiological characteristics, pathophysiology and risks for mother and baby.[38]

Gestational hypertension (GH) is usually defined as an elevated blood pressure (BP) arising after 20 weeks of gestation in the absence of significant proteinuria, and is generally characterized by more favourable maternal and fetal outcomes than is preeclampsia.[98] Woman with gestational hypertension may progress to preeclampsia. However, in many cases proteinuria never occurs, the course is relatively benign and blood pressure normalizes after delivery.

Preeclampsia (PE) is a complex multi-system disorder of human pregnancy, with an incidence of 2-5%. It is characterized by elevated BP occurs which after 20 weeks of gestation, accompanied by new-onset of significant proteinuria. Other maternal organ dysfunctions may be associated, such as renal impairment, liver dysfunction or abnormalities of coagulation (thrombocytopenia, disseminated intravascular coagulation).[2;99-101] This is a far more serious disorder with potentially more severe consequences for both mother and fetus, such as preterm delivery, fetal growth retardation, and perinatal mortality.

Hypertension is usually the first clinical feature of preeclampsia, before the onset of proteinuria in most cases. At first presentation, it is often difficult to know if a pregnant woman with new hypertension will remain in that state or progress to preeclampsia. As the outcomes of these disorders are different, it is mandatory to treat each case as emerging preeclampsia. On the other hand, most women with gestational hypertension may be managed safely as outpatients, and it would be helpful to know both the absolute risk of progression from gestational hypertension to preeclampsia, and the factors at initial presentation which predict this progression.

Up to now, the etiology of preeclampsia remains poorly understood. In recent years, some clinical, biophysical, and biochemical tests have been suggested or reviewed to identify women who are at increased risk for the development of preeclampsia,[81-83;85;86] especially rising circulating levels of soluble fms-like tyrosine kinase 1 (sFlt1) and ratios of sFlt1/PlGF (placental growth factor) before the onset of preeclampsia. However, some of these tests are invasive, whereas others require expensive techniques or special expertise that precludes their utility in routine screening. It is well recognized that pregnant women with multiple fetuses, previous preeclampsia/eclampsia, insulin-dependent diabetes, and previous poor pregnancy outcomes are at increased risk for preeclampsia.[102;103] In 2000, Odegard [104] reported in a population based, nested case control study that women with preeclampsia in a previous pregnancy had a strongly increased risk of severe preeclampsia and early onset disease. In a case control study, maternal age above 26 years, multiparity, and no prenatal care were reported to be risk factors for the development of eclampsia.[105]

Study objectives: It remains unknown exactly what factors predict the progression from gestational hypertension to preeclampsia. The objectives of this study were:

1) To explore differences in sociodemographic and obstetrical characteristics between women with gestational hypertension who progressed to preeclampsia and those who remained in the gestational hypertensive state until delivery.

2) Among women who presented with gestational hypertension, to assess individual

predictors of progression to preeclampsia.

3) To create a multivariable prediction model for the progression from gestational hypertension to preeclampsia based on commonly available prenatal clinical and lab testing data and to assess the sensitivity, specificity, positive predictive value and negative predictive value of this model.

The study variables were those that can be identified at their initial presentation with gestational hypertension by the already available clinical and/or laboratory features. Such a study may help to uncover important clinical features that could facilitate early prediction of progression from gestational hypertension to preeclampsia, enhance the effectiveness of care and minimize the risk of potentially serious maternal and neonatal complications.

2.2. METHODS

2.2.1. Definitions

Gestational hypertension is defined as the onset of hypertension (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) after 20 weeks of gestation which returned to normal within 3 months of delivery, without or with proteinuria of no greater than trace levels. Hypertension in these women is confirmed after either overnight rest in hospital or following repeated BP measurements during the next few days visit.

Preeclampsia is defined as a systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥90 mmHg with proteinuria ≥300 mg in a 24-hour urine collection or 1+ on dipstick urinalysis in two samples taken 6 hours apart if 24 hour urine was unavailable. Eclampsia is diagnosed when convulsions occur in a woman with preeclampsia.

Anthropometric parameters of the baby, such as birth weight, height and head circumference were measured shortly after delivery. Gestational age was based on the last menstrual period, and verified by first-trimester or early second-trimester ultrasound

when available. If the date of the last menstrual period was not consistent with the result of ultrasound examination, gestational age was based solely on the first-trimester or early second-trimester ultrasound findings.

Small-for-gestational-age (SGA) was defined as birth weight below the 10th percentile for gestational age according to the recently published Canadian sex-specific fetal growth reference values based on infants born in 1994-96.[106]

2.2.2. Research design

This was a historical prospective cohort study, based on maternal and perinatal records of women who received obstetric care and delivered at Hôpital Sainte-Justine in the period between March 2001 and June 2003 inclusive.

In this study, we firstly identified patients based on computerized obstetric delivery records at the department of obstetrics and gynecology. Thereafter, we used these patients' personnel identification information to further access to the paper-formatted medical charts, to extract the information of maternal sociodemographic, obstetrical and clinical characteristics. Regarding to the detail items extracted from medical charts, please refer to ANNEXES – Information Extraction Form (page: xii).

Inclusion criteria: Women with a singleton pregnancy who were diagnosed as having gestational hypertension without proteinuria at the initial presentation, either at the time of hospitalization or at an outpatient prenatal visit.

Exclusion criteria: Hypertensive patients were excluded if they had

1) Multiple gestations, e.g. twins, triplets, quadruplets
2) Chronic hypertension
3) Renal disease
4) Acute or chronic hepatitis

The medical charts of the women presenting with gestational hypertension were reviewed to confirm whether they were eligible according to these criteria.

2.2.3. Clinical and laboratory data

Our study was approved by the hospital ethics review board. Data abstraction and data cleaning were performed by Yuquan Wu and double checked by another research student in the prenatal research unit of Hôpital Sainte-Justine.

The following clinical and laboratory data at initial presentation with gestational hypertension were obtained from the hospital records: maternal age, gravidity, parity, smoking status, diabetes (gestational or pre-existing), prior spontaneous miscarriage (obtained from patient history alone, therapeutic terminations excluded); prior preterm birth, previous preeclampsia and gestational hypertension history (multiparity only); hemoglobin, hematocrit, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, uric acid (URA) and lactic acid dehydrogenase (LDH). The laboratory data concerning other time-points (before GH diagnosed, after GH diagnosed but prior to admission for delivery, at admission, after admission prior to delivery, delivery and after delivery) were also collected when it was recorded in the patient's medical chart.

Blood pressure (BP) and gestational age (GA) concerning the following time points were transcribed from the hospital medical charts: when the diagnosis of gestational hypertension was first made, at the time of diagnosis of preeclampsia (if applicable), at the time of admission to hospital for delivery, at the time of delivery and after delivery during hospitalization.

Other clinical and laboratory data include highest measured 24h proteinuria (mg/24h) after gestational hypertension onset, number of days of hospitalization during admission for delivery, mode of the delivery, infant birth weight (g), height (cm), head circumference (cm), placental abruption, fetal NICU admission and placental weight.

In patients initially diagnosed as having gestational hypertension, clinical and laboratory measures at first presentation of gestational hypertension were compared between those who progressed to preeclampsia and those who remained with a diagnosis of gestational hypertension until delivery.

Women were treated with various antihypertensives (catapres, labetalol, clonidine, methyldopa, nifedipine, etc.) aiming to maintain systolic BP 110-140 mmHg and diastolic BP 80-90 mmHg.

2.2.4. Dependent and independent variables

The primary dependent variable was progression from gestational hypertension to preeclampsia. The factors that were potentially associated with this progression were referred as independent or predictive variables. We assessed the sensitivity, specificity, positive predictive value and negative predictive value of this model.

Independent variables were sociodemographic, obstetrical and laboratorial characteristics of the patient at the time of initial presentation with gestational hypertension. These included: gestational age at GH onset, maternal age, smoked, number of prenatal visits, primigravidity, nulliparity, prior history of gestational hypertension, prior history of preeclampsia, history of miscarriage, history of preterm birth or diabetes; also the following independent variables being measured at the initial presentation with gestational hypertension: systolic and diastolic blood pressure, hemoglobin, hematocrit, platelet count, liver enzymes (alanine aminotransferase, aspartate aminotransferase), serum creatinine, uric acid, and lactic acid dehydrogenase levels. Because of the information of mother's height missing in about 1/3 medical charts (GH group: 32 cases, GH-PE group: 58 cases), body mass index (BMI) between the groups was not compared and not studied in multivariable logistic regression model.

We also conducted a descriptive analysis for certain clinical outcomes other than the main outcome of interest, according to the present or absent of progression to preeclampsia.

As well, we documented gestational age at delivery, small for gestational age (SGA) (according to the criteria of published Canadian fetal growth reference values based on infants born in 1994-96[106], birthweight below the tenth centile for gestational age), and certain obstetrical and neonatal outcome indicators.

2.2.5. Statistic analysis

Differences in continuous variables were tested by analysis of variance. Chi square and Fisher exact tests were used for testing the difference between groups in categorical variables.

Univariable logistic regression analysis was employed at first to evaluate individual clinical and laboratory variables as potentially significant predictors for progression from gestational hypertension to preeclampsia. Subsequently, multivariable logistic regression analysis was employed to evaluate the effect of one variable controlling for other co-variables. We used the STEPWISE routine as the model selection method. This algorithm specifies 0.05 as the critical alpha level for entering a variable into the model and 0.10 as the significance level for a variable to remain in the model.

For most continuous variables, because standard deviation (SD) was pretty large and one crude unit of change (e.g. serum uric acid: 1 μmol/L) is clinically meaningless, we used one standard deviation (SD: 56.1 μmol/L for serum uric acid) as the unit increase to calculate its crude or adjusted odds ratio, 95% confidence interval and P-values.

The sensitivities and specificities of the variables which had significant associations with the outcome (progression from gestational hypertension to preeclampsia) in a multivariable logistic regression analysis were also explored. This was followed by the development of a receiver-operator characteristic (ROC) curve to determine a suitable cut-off value for creating a model which used dichotomous variables, and calculating the model's sensitivity, specificity, positive predictive value (PPV) and negative predictive

value (NPV), as well as the probability of progression to preeclampsia from gestational hypertension under various possible common clinical combinations of these variables. We calculated different predicted sensitivities and specificities under various cut-off points of probabilities of progression from gestational hypertension to preeclampsia in the multivariable logistic regression model and depicted the relevant ROC curve. The exploratory analysis (Table VIII, Fig. 4) suggested that a cut-off value of the predicted probability of 50% or 60% was associated with a good sensitivity and specificity (Fig. 4). If a patient's predicted probability of progression from gestational hypertension to preeclampsia was more than 50% in the logistic predictive model, then this woman was considered as having a positive test result (progressed to preeclampsia from gestational hypertension) for calculating the sensitivity, specificity, positive predictive value and negative predictive value of this logit model.

Statistical analysis was performed using SAS software (version 9.0, SAS Institute, Cary, NC).

2.3. RESULTS

Because of the small number of patients with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count, 14 cases) and eclampsia (2 cases), these cases were combined with preeclampsia cases into a single group, hereafter referred to as "preeclampsia" in this study.

In all, 298 women were identified as having gestational hypertension at initial presentation and either progressed to preeclampsia or remained gestational hypertension until delivery. Women with multiple pregnancies (14 cases) were excluded from the analysis, mainly because this variable is a potentially confounding variable known to be associated with both preeclampsia or gestational hypertension and birth weight.

Of these identified patients, medical records were available for further review in 99% of cases. Two records of patients with gestational hypertension were excluded as there were insufficient data available for this study.

Pregnancies complicated by chronic hypertension and preeclampsia superimposed on chronic hypertension were excluded. Patients with renal disease or other secondary causes of hypertension were also excluded, 2 patients with hepatitis B were also excluded from the later research analysis, mainly because their elevated liver enzymes influenced the analysis of liver enzymes predictors (alanine aminotransferase, aspartate aminotransferase) for progression from gestational hypertension to preeclampsia, leaving a total of 280 patients in the study.

Of the 280 women with the initial diagnosis of gestational hypertension at the first presentation, 189 (65%) went on to develop preeclampsia.

Table I summarizes comparisons of maternal demographic and obstetric characteristics between the gestational hypertension group and the preeclampsia group. Systolic BP and diastolic BP at admission for delivery and delivery were higher in women who progressed to preeclampsia (GH-PE group) than among those who remained with a diagnosis of gestational hypertension until delivery (GH group). The proportion with a prior history of preeclampsia was two times higher in GH-PE group than in the GH group.

There were no significant differences between groups in maternal age, or proportions who were primigravid, nulliparous, smoked, had a past history of diabetes, miscarriage, preterm birth or prior history of gestational hypertension.

The proportion undergoing cesarean delivery in GH-PE group was twice of that observed in the GH group. The number of days of maternal hospitalization was also longer in the GH-PE group than in the GH group. The number of prenatal visits between GH and GH-PE groups was similar.

Table II summarize the differences in maternal clinical characteristics at initial presentation with gestational hypertension and neonatal outcomes between these two

groups. Women who progressed from gestational hypertension to preeclampsia (GH-PE group) presented earlier with gestational hypertension (32±4 wks *vs* 38±2 wks) and were delivered earlier (35±4 wks *vs* 38±2 wks) with higher rates of fetal intrauterine growth restriction (IUGR) (27% *vs* 14%) and lower neonatal anthropometric parameters (birth weight, height and head circumference). Fetal NICU admission was more frequent in the GH-PE group than those who remained gestational hypertension until delivery (GH group) (30% *vs* 3%).

The level of uric acid (URA) at presentation with gestational hypertension was significantly higher (mean difference=31 μmol/L) in the GH-PE group than in GH group, whereas the levels of hemoglobin, hematocrit, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine and lactic acid dehydrogenase (LDH) which were measured at time point of gestational hypertension onset were not significantly different between the GH-PE group and the GH group. There were no significant differences in systolic or diastolic blood pressure at the initial presentation with gestational hypertension between the GH-PE and GH groups (Table II).

Univariable logistic regression analysis showed that a prior history of preeclampsia, serum uric acid level and gestational age at first presentation with gestational hypertension were significantly associated with the progression from gestational hypertension to preeclampsia (Table III). Independent variables which had no significant association with the progression to preeclampsia from gestational hypertension, included maternal age, primigravidity, nulliparity, smoking status and prior history of gestational hypertension, diabetes, history of miscarriage and history of preterm birth, as well as the following variables measured at first presentation with gestational hypertension: systolic and diastolic blood pressure, hemoglobin, hematocrit, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine and serum lactic acid dehydrogenase (LDH).

In the multivariable logistic regression analysis, the parameters which were significantly associated with progression from gestational hypertension to preeclampsia

were prior preeclampsia history, uric acid level and gestational age at initial presentation with gestational hypertension. Adjusted odds ratios of these variables were slightly higher compared to the crude ORs in univariable logistic regression analysis (Table IV). This was especially true for prior history of preeclampsia, where the OR increased from 2.74 to 3.43 after adjusting for other variables. As regards serum uric acid concentration measured at first presentation with gestational hypertension, the odds ratio was 1.78 if we applied one standard deviation value of uric acid as the unit increase (56.1 μmol/L) in the model (Table IV).

The test properties of serum uric acid and gestational age at first presentation with gestational hypertension were assessed by examining sensitivity and specificity values over different cutoff values (Table V) and by graphing receiver-operator characteristic (ROC) curves, respectively (Fig.1, Fig.2).

From Fig.1, a break point on the ROC curves for a gestational age of 36 weeks appears to be reasonably sensitive (81%) and specific (86%). We note from Figure 2 that serum uric acid could not achieve more than 80% for either sensitivity or specificity. The level of 300 μmol/L (56%, 64%, respectively) appears to be the best cut-off value to distinguish women who progressed to preeclampsia from those who remained with a diagnosis of gestational hypertension until delivery.

Table VI presents the results of the analysis of the Logit model, using the same variables as in the previous model (Table IV) but applying the observed cut-off values suggested from Table V, Fig.1 and Fig.2, to form another Logit model where all the variables in the model were dichotomous variables. We provided the relevant regression coefficients, adjusted ORs, 95% confidence interval and p values for calculating the different predicted probability (Table VII) when we applied various possible common combinations of these dichotomous variables identified in Table VI. The adjusted ORs of gestational age less than 36 weeks at gestational hypertension onset, past history of preeclampsia and uric acid level more than 300 umol/L measured at first presentation with gestational hypertension for the progression from gestational hypertension to

preeclampsia were 3.63, 3.21 and 2.66, respectively. The formula suggested by this prediction model was:

$$P = \frac{\exp(-1.34 + 1.29 \times GA\_LT36 + 0.98 \times URA\_GE300 + 1.17 \times PAPE)}{[1 + \exp(-1.34 + 1.29 \times GA\_LT36 + 0.98 \times URA\_GE300 + 1.17 \times PAPE)]}$$

Notes:

GA_LT36: gestational age at GH onset, < 36 weeks = 1, ≥36 weeks = 0.

URA_GE300: Uric acid level at GH onset, < 300 μmol/L = 0, ≥300 μmol/L = 1.

PAPE: Past history of preeclampsia, being coded as: Yes = 1, No = 0.

Example:

If a patient at first presentation with gestational hypertension had the following characteristics: Gestational age < 36 weeks, uric acid level > 300 μmol/L and a positive history of preeclampsia in a previous pregnancy,

then $P = \exp(-1.34 + 1.29 \times 1 + 0.98 \times 1 + 1.17 \times 1) / [1 + \exp(-1.34 + 1.29 \times 1 + 0.98 \times 1 + 1.17 \times 1)]$, → $P = \exp(2.10) / [1 + \exp(2.10)]$, → $P = 89\%$

Therefore, this pregnant woman would be estimated to have 89% probability of developing preeclampsia.

Different predicted probabilities for progression from gestational hypertension to preeclampsia according to various possible combinations of dichotomous variables identified in Table VI are listed in Table VII and plotted in Fig 3. For a pregnant woman presenting with gestational hypertension at less than 36 weeks and had prior preeclampsia history, but with serum uric acid level less than 300 umol/L, the probability of developing to preeclampsia would be 75%; whereas the probability would be 72% if the pregnant woman's gestational age less than 36 weeks and uric acid level more than 300 umol/L at first presentation with gestational hypertension, but without a past history of preeclampsia.

Table VIII lists relevant sensitivities and specificities using various cut-off points of probabilities of progression from gestational hypertension to preeclampsia. The corresponding ROC curve was plotted in Figure 4. The 50% or 60% cut-off values of the predicted probability in the model (Table VI) had reasonably good sensitivity and specificity (50% cut-off points: sensitivity=81.5, specificity=84.6; 60% cut-off points: sensitivity=78%, specificity=86.7), and the 50% cut-off point of the predicted probability seemed to be the best combination of sensitivity and specificity for prediction of progression from gestational hypertension to preeclampsia. Table IX lists the validity parameters of the model using the P = 0.50 as the cut-off point: sensitivity = 81.5%; specificity = 84.6%; agreement rate = 82.5%; positive predictive value (PPV) = 91.7% and negative predictive value (NPV) = 68.8%.

2.4. DISCUSSION

Until now, few studies had been reported on the topic of risk factors for the progression from gestational hypertension to preeclampsia, especially the different characteristics at the initial presentation with gestational hypertension for progression to preeclampsia *versus* remained gestational hypertension until delivery. We have established a model to predict this progression with reasonably good sensitivity, specificity, positive predictive value, and negative predictive value. We have explored the differences in characteristics at the time point of gestational hypertension onset between women who remained as gestational hypertension and those who progressed from gestational hypertension to preeclampsia. Our study focused on clinical, obstetrical and laboratory characteristics that are routinely available at the time of initial presentation with gestational hypertension. The present study provides new data on strategies for the identification of patients who will progress to preeclampsia from gestational hypertension.

Several studies[105;107;108] examined risk factors for the development of eclampsia, but these studies compared eclampsia either with preeclamptic controls or with non-preeclamptic controls, or with uncomplicated eclamptic controls (not complicated by

intracerebral hemorrhage, pulmonary edema, renal, hepatic, respiratory system dysfunction or HELLP syndrome). We investigated specifically the risk factors for the development of preeclampsia among patients whose initial presentation was gestational hypertension. Hypertension is the most common first presentation of preeclampsia[42] and the recording of raised blood pressure together with urinalysis for proteinuria are the major screening tests for detecting preeclampsia.

In epidemiologic studies, special attention should be paid to medical surveillance (or detection) bias, which occurs when the identification of the outcome is not independent of the knowledge of the exposure. In our study, we found no difference in the number of prenatal visits between patients who progressed from gestational hypertension to preeclampsia and those who remained as gestational hypertension until delivery (Table I). This suggests that medical surveillance between the preeclampsia group and the gestational hypertension group was similar, and the number of visits was not a risk factor for the progression from gestational hypertension to preeclampsia.

In univariable logistic regression analysis, variables such as gestational age at first presentation with gestational hypertension, previous preeclampsia and serum uric acid at initial presentation with gestational hypertension were significant risk factors for progression to preeclampsia from gestational hypertension (Table III). Multivariable logistic regression analysis confirmed these variables were influential maternal risk factors for the development of preeclampsia from gestational hypertension. Adjusted odds ratios of these variables were slightly higher than the crude ORs in univariable logistic regression analysis, especially for the past history of preeclampsia (adjusted OR = 3.43, crude OR = 2.74), suggesting that a past history of preeclampsia is an important risk factor in the progression from gestational hypertension to preeclampsia (Table IV).

Some studies reported that women who had preeclampsia in a first pregnancy have 5-8 times the risk of preeclampsia as that in a second pregnancy.[49;109-112] Our study indicated that women with gestational hypertension who had prior history of

preeclampsia have a 3 to 4-fold risk of progression to preeclampsia than those without a history of preeclampsia (Table IV).

It has been suggested that the serum uric acid level is "the most sensitive indicator of preeclampsia available to clinicians."[59] Plouin *et al.*[113] documented poor perinatal outcomes (including stillbirths and neonatal deaths) in pregnancies complicated by preeclampsia and elevated serum uric acid levels. In their study, 59% of women had serum uric acid levels ≥360 μmol/L in the group with poor perinatal outcomes compared to 20.3% in the group with favorable perinatal outcomes. Slemons and Bogert[114] were the first to report an association between serum uric acid concentration and preeclampsia in 1917. Later in 1934, Stander et al[115] first reported the correlation between serum uric acid level and severity of preeclampsia. Histological evidence from biopsy[116] reveals frequent renal involvement in cases of preeclampsia/eclampsia. Tubular function is the first to be involved and later in the disease process glomerular function is impaired. Uric acid is used as an indicator of disease severity in established preeclampsia and has been reported to be a better predictor for adverse perinatal outcome than blood pressure.[83] However, we did not find it to be an important factor for the severity of preeclampsia. In most patients, the increase in uric acid level seems to coincide with the increase in blood pressure, and precedes development of the proteinuric stage which is a sign of glomerular damage of the disease.[117] Uric acid concentrations have been used for early detection of preeclampsia, but not for hypertension[117]. However, the reported low sensitivity and specificity in most studies renders uric acid measurement unhelpful for widespread use of early detection of preeclampsia.[118]

Our data suggest that serum uric acid levels measured at initial presentation with gestational hypertension were significantly higher in women who developed preeclampsia than those who remained as gestational hypertension until delivery, although mean serum uric acid levels in these 2 groups were in the normal reference range (< 350 μmol/L). Serum uric acid levels were also significantly associated with progression from gestational hypertension to preeclampsia in a multivariable logistic regression analysis (Table IV). The odds of developing preeclampsia from gestational

hypertension increased by 78% for each standard deviation (56.1 μmol/L) increase in serum uric acid level measured at gestational hypertension onset. The cutoff value of 300 μmol/L is only moderately sensitive (56%) and specific (64%) (Table V, Fig 2) for predicting the development of preeclampsia from gestational hypertension, similar to those reported by Lim, KH[88]. Redman *et al.*[119] showed that serum uric acid levels ≥420 μmol/L were associated with significant perinatal mortality and maternal morbidity and were of great value when the diagnosis of preeclampsia was in doubt. Koike[120] also reported that the elevation of serum uric acid levels occurs earlier in twin gestations than in singletons and may serve as a useful early predictor of the development of preeclampsia.

There were significant differences in gestational age at initial presentation with gestational hypertension between those who developed preeclampsia from gestational hypertension and those who remained with gestational hypertension until delivery, the GH-PE group presenting significantly earlier than GH group (32±4 *vs* 38±2 weeks) (Table II). The optimal cutoff value for predicting preeclampsia progression from gestational hypertension was 36 weeks of gestational age at first presentation with gestational hypertension. Sensitivity and specificity were 81% and 86% (Table V, Fig 1), respectively. Women who are diagnosed earlier with gestational hypertension are more likely to develop preeclampsia.

The adjusted odds ratio for gestational age less than 36 weeks at gestational hypertension onset was highest among the variables in the model (aOR = 3.63) (Table VI), indicating this risk factor had the strongest association with the progression from gestational hypertension to preeclampsia. A prior history of preeclampsia was the second variable in importance on this progression (aOR = 3.21) (Table VI). If a pregnant woman who had a history of preeclampsia and presented gestational hypertension earlier than 36 weeks in the current pregnancy, she would have a very high probability to develop preeclampsia. Limited information is available regarding the risk of progression to preeclampsia from gestational hypertension according to gestational age at disease onset. Barton[121] in a prospective cohort study reported that among patients with a singleton

pregnancy between 24 and 35 week's gestation accompanied with mild gestational hypertension, nearly 50% ultimately developed preeclampsia and 10% progressed to severe disease, indicating early onset of mild gestational hypertension was associated with the progression to preeclampsia. This was also confirmed by Sanchez-Ramos[122] who reported that approximately 50% of women with mild preeclampsia remote from term (24-36 weeks) would develop severe preeclampsia.

The parameters of validity of our multivariable prediction model (sensitivity: 81.5%, Specificity: 84.6%, positive predictive value (PPV): 91.7%; negative predictive value (NPV): 68.8%) suggested it was likely a good model for predicting the progression to preeclampsia from gestational hypertension. It is clear from Table VIII and Figure 4 that, for this multivariable prediction model (Table VI), the predicted probability: 0.50 or 0.60 seemed to be a good cut-off value with respect to both sensitivity and specificity for predicting progression from gestational hypertension to preeclampsia. As preeclampsia is a disease with important clinical implications, we gave priority to sensitivity in selecting the cut-off value for the model.

To our knowledge, this is the first study designed to predict the progression from gestational hypertension to preeclampsia. Braun[123] in 1997 reported in a case control study that uric acid (URA), low density lipoproteins (LDL), phosphoglycerate kinase (PGK), mean platelet volume (MPV) and decreases in glyceraldehyde phosphate dehydrogenase (G3PD) were associated with preeclampsia compared with non-hypertensive pregnancies, and creating the following predictive model: Probability to develop preeclampsia = 0.7764 (URA) + 0.8086 (PGK) -0.7032 (G3PD) + 0.1399 (LDL) -0.2386 (MPV). However, their study is a comparison of preeclampsia *versus* healthy pregnant controls.

In our study, potential selection bias (Berksonian bias) must be acknowledged. Selection bias occurs when a systematic error emerges in the ascertainment of study subjects. Preeclampsia patients, especially severe preeclampsia patients, were often referred to our hospital for treatment, delivery and were therefore available for chart

review in our study. Some patients who presented with mild preeclampsia or gestational hypertension may be managed and delivered in other hospitals, and their profile may differ from patients included in our study.

We have developed a multivariable prediction model with reasonably good validity parameters for predicting the progression from gestational hypertension to preeclampsia, based on common clinical and laboratory test results available in routine prenatal care. The model may be useful to the clinicians to stratify gestational hypertensive women's risk level according to their gestational age and uric acid level at first presentation with gestational hypertension, as well as whether there was a prior history of preeclampsia. For example, woman with onset of hypertension after 36 weeks of gestation, without other features of preeclampsia, has only a small risk of developing preeclampsia and can be managed safely as an outpatient.

Clinical monitoring of these risk factors in pregnancies complicated by gestational hypertension could provide an easy, inexpensive and helpful tool for identifying women with gestational hypertension at high risk of developing preeclampsia, therefore directing tertiary perinatal care to reduce the incidence of adverse perinatal outcomes. Some other potential risk factors for predicting the progression to preeclampsia, such as body mass index, sFlt-1, PIGF, VEGF and serum soluble endoglin, should be included in the study, as well as studied in the multivariable logistic regression model, to make the model more stabilized and valid. This study provides new method to investigate the progression to preeclampsia; further larger scale prospective studies which include more risk factors are warranted to test the efficacy of this model in predicting the progression to preeclampsia from gestational hypertension.

LIST OF TABLES

Table I. Comparison of maternal sociodemographic and obstetrical characteristics between patients with ***gestational hypertension*** (GH) and ***preeclampsia*** (GH-PE, progressed from gestational hypertension to preeclampsia)

Maternal information	**GH** *(N=91)*	**GH-PE** *(N=189)*
Maternal age (years)	30 ± 5	30 ± 6
Primigravidity (%)	48	40
Nulliparous (%)	68	63
Smoking (%)	12	11
Past history of diabetes (%)	3	4
Past history of miscarriage (%)	35	40
Past history of preterm birth (%)$^{+}$	17	20
Past history of preeclampsia (%)$^{+}$	17	38*
Past history of gestational hypertension (%)$^{+}$	38	52
Number of prenatal visits	8.5 ± 2	8.3 ± 2
Systolic BP at admission for delivery (mmHg)	145 ± 10	152 ± 15**
Diastolic BP at admission for delivery (mmHg)	86 ± 8	91 ± 10**
Systolic BP at delivery (mmHg)	142 ± 14	151 ± 15**
Diastolic BP at delivery (mmHg)	81 ±10	88 ±11**
Placental Abruption (%)	0	6*
Mode of delivery: Cesarean (%)	21	42**
Gestational age at preeclampsia onset (weeks)	-	34 ± 4
Gestational age at delivery (weeks)	38 ± 2	35 ± 4**
Days of hospitalization	4 ± 2	7 ± 5**

GH group: Gestational Hypertension
GH-PE group: Progression from gestational hypertension to preeclampsia

* Significant $P < 0.05$, * * Significant $P < 0.01$. $^{+}$ Multiparae only.
Values are given as **Mean ± SD** for continuous data.
BP: blood pressure

Table II. Comparison of maternal clinical characteristics at patients with gestational hypertension onset and neonatal outcomes between ***gestational hypertension*** (GH) and ***preeclampsia*** (GH-PE, progressed from gestational hypertension)

Clinical & lab data at GH presentation	**GH** *(N=91)*	**GH-PE** *(N=189)*
Gestational age at GH onset (weeks)	38 ± 2	32 ± 4**
Systolic BP at GH onset (mmHg)	147 ± 9	146 ± 9
Diastolic BP at GH onset (mmHg)	87 ± 8	86 ± 9
Hemoglobin at GH onset (g/dL)	122 ± 13	121 ± 11
Hematocrit at GH onset (%)	0.36 ± 0.03	0.36 ± 0.04
Platelet count at GH onset (10^9/L)	215 ± 69	211 ± 51
ALT at GH onset (U/L)	16 ± 5	18 ± 6
AST at GH onset (U/L)	24 ± 6	24 ± 6
Creatinine at GH onset (µmol/L)	58 ± 12	59 ± 11
Uric acid at GH onset (µmol/L)	271 ± 61	302 ± 50**
LDH at GH onset (U/L)	152 ± 23	149 ± 24
Neonatal outcome		
SGA (%)	14	27*
Birth weight (g)	3277 ± 642	2409 ± 957**
Infant height (cm)	51 ± 4	47 ± 5**
Infant head circumference (cm)	34 ± 2	32 ± 3**
NICU admission (%)	3	30**
Placental weight (g)	490 ± 100	430 ± 148**

GH group: Gestational Hypertension
GH-PE group: Progression from gestational hypertension to preeclampsia

* Significant $P < 0.05$, * * Significant $P < 0.01$. $^{+}$ Multiparae only.
Values are given as **Mean ± SD** for continuous data.
GH: gestational hypertension; **BP:** blood pressure; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **LDH:** lactic acid dehydrogenase; **SGA:** small for gestational age, birth weight below the 10^{th} percentile for gestational age.

Table III. Factors associated with progression from ***gestational hypertension*** to ***preeclampsia*** (Univariable logistic regression analysis)

Predictor	Crude Odds ratio	95% confidence interval	P value
Gestational age at GH onset (weeks)	0.52	0.45 — 0.62	< 0.0001
Uric acid level at GH onset (μmol/L)	1.78	1.36 — 2.32	< 0.0001
Past history of preeclampsia	2.74	1.02 — 7.40	0.0462
Past history of gestational hypertension	1.55	0.76 — 3.14	0.2255
Maternal age (years)	1.02	0.98 — 1.07	0.3842
Systolic BP at GH onset (mmHg)	0.84	0.65 — 1.07	0.1503
Diastolic BP at GH onset (mmHg)	0.82	0.64 — 1.06	0.1239
Hemoglobin at GH onset (g/dL)	0.88	0.69 — 1.14	0.3353
Hematocrit at GH onset	0.92	0.72 — 1.18	0.5116
Platelet count at GH onset	0.94	0.74 — 1.21	0.6373
ALT at GH onset (U/L)	1.25	0.96 — 1.64	0.1047
AST at GH onset (U/L)	1.17	0.90 — 1.53	0.2364

Table III. (Continued)

Predictor	Crude Odds ratio	95% confidence interval	P value
Creatinine at GH onset (μmol/L)	1.10	0.85 — 1.41	0.4718
LDH at GH onset (U/L)	0.89	0.69 — 1.14	0.3455
Primigravidity	0.70	0.43 — 1.16	0.1701
Nulliparous	0.81	0.48 — 1.38	0.4462
Smoking	0.91	0.42 — 1.98	0.8099
Past history of diabetes	1.30	0.34 — 5.01	0.7064
Past history of miscarriage	1.24	0.74 — 2.08	0.4168
Past history of preterm birth	1.13	0.42 — 3.05	0.8045

GH: gestational hypertension; **BP:** blood pressure; **ALT:** alanine aminotransferase;

AST: aspartate aminotransferase; **LDH:** lactic acid dehydrogenase

Note: In the univariable logistic regression analysis, the effect estimates are for per one standard deviation increase for the following independent continuous variables whose values measured at the initial presentation with gestational hypertension:

Uric acid (56.1 μmol/L); Systolic BP (8.6 mmHg); Diastolic BP (8.6 mmHg); Hemoglobin (11.6 g/dL);
Hematocrit (0.036 %); Platelet count (57.5 x 10^9/L); ALT (6.0 U/L); AST (6.0 U/L);
Creatinine (11.4 μmol/L); LDH (23.8 U/L)

Table IV. Factors significantly associated with progression from ***gestational hypertension*** to ***preeclampsia*** (Multivariable logistic regression analysis, variables selection method in the model: Stepwise)

Predictor	Adjusted Odds ratio	95% confidence interval	P value
Gestational age at GH onset (weeks)	0.53	0.44 — 0.62	< 0.0001
Past history of preeclampsia	3.43	1.02 — 11.60	0.0471
Uric acid level at GH onset (μmol/L)	1.78	1.26 — 2.51	0.0011

GH: gestational hypertension

Note: In the multivariable logistic regression analysis, unit of change for gestational age at GH onset: 1 week

Past history of PE was coded as: 1=Yes, 0=No

Unit of change for uric acid level at GH onset: one standard deviation (56.1 μmol/L).

Table V. Sensitivity and specificity for various gestational age and serum uric acid cut-off values at GH presentation for predicting progression from ***gestational hypertension*** to ***preeclampsia***

Parameter	Cutoff value	Sensitivity (%)	Specificity (%)
Gestational age at GH presentation (weeks)	30	30	99
	32	44	99
	34	60	97
	36	81	86
	38	94	59
	39	98	38
Uric acid at GH presentation (µmol/L)	220	92	25
	240	88	36
	260	83	45
	280	74	59
	300	56	64
	320	39	73
	340	29	84
	360	19	93

GH: gestational hypertension

Table VI. Multivariable logistic regression analysis for the progression from ***gestational hypertension*** to ***preeclampsia;*** using same variables in Table IV but changing these predicting variables to dichotomous variables, cut-off points suggested from Table V, Fig 1 and Fig 2

Predictor	Coefficients (B)	Odds ratio =Exp(B)	95% confidence interval	P value
Constant	-1.34			
Gestational age < 36 weeks at GH onset	1.29	3.63	1.61 — 6.26	< 0.001
Uric acid ≥300 µmol/L at GH onset	0.98	2.66	1.34 — 5.29	0.005
Past history of preeclampsia	1.17	3.21	1.01 — 11.60	0.048

GH: gestational hypertension

The logistic model: Logit (P) = -1.34 + 1.29 x GA_LT36 + 0.98 x URA_GE300 + 1.17 x PAPE

Therefore: **P = exp (-1.34 + 1.29 x GA_LT36 + 0.98 x URA_GE300 + 1.17 x PAPE) / [1 + exp (-1.34 + 1.29 x GA_LT36 + 0.98 x URA_GE300 + 1.17 x PAPE)]**

P: Probability to be preeclampsia progressed from gestational hypertension.

GA_LT36: gestational age at GH onset, being coded as: < 36 weeks = 1, ≥36 weeks = 0.

URA_GE300: Uric acid level at GH onset, being coded as: < 300 µmol/L = 0, ≥300 µmol/L = 1.

PAPE: Past history of PE, being coded as: Yes = 1, No = 0.

Table VII. Different predicted probabilities based on the multivariable logistic prediction model for progression from ***gestational hypertension*** to ***preeclampsia*** according to various common combinations of predicting variables values

Predicted Variables			Probability of progression to PE from GH
Gestational age < 36 wks at GH onset	**Uric acid ≥300 µmol/L at GH onset**	**Past history of PE**	
No	No	No	20%
No	***Yes***	No	41%
No	No	***Yes***	46%
Yes	No	No	58%
No	***Yes***	***Yes***	69%
Yes	***Yes***	No	72%
Yes	No	***Yes***	75%
Yes	***Yes***	***Yes***	89%

GH: gestational hypertension; **PE:** preeclampsia

Table VIII. Sensitivity and specificity values for predicting the progression from ***gestational hypertension*** to ***preeclampsia*** under various clinical scenarios using different P cut-off values in a multivariable logistic prediction model

(Note: A patient will be predicted to be '***GH-PE***' if the estimated probability is more than 30%, 40%, 50%, 60% or 70%, based on the multivariable logistic regression model in Table VI)

Parameter	Cutoff value of probabilities	Sensitivity (%)	Specificity (%)
All the variables in multivariable logistic regression model in Table VI	30%	92.1	46.1
	40%	89.4	54.0
	50%	81.5	84.6
	60%	78.0	86.7
	70%	71.0	92.3
	80%	48.2	95.7

Table IX. Predicted *versus* observed numbers of events based on the multivariable logistic model (Table VI) using P>0.50 as the cut-off value for predicting progression from ***gestational hypertension*** to ***preeclampsia***

Number Predicted	Number Observed	
	GH-PE	**GH**
GH-PE	154	14
GH	35	77

GH: gestational hypertension; **PE:** preeclampsia

Assumption: When a patient's probability of progression from gestational hypertension to preeclampsia > 50% in the multivariable logit analysis, then this woman would be predicted to be 'GH-PE' (progressed to preeclampsia later) in logistic predicted analysis model.

So, for the variables in the Table VI (multivariable logistic regression analysis)

Sensitivity: 154 / (154+35) = 81.5 %

Specificity: 77 / (77+14) = 84.6 %

Agreement rate: (154+77) / (154+14+35+77) = 82.5 %

Positive predictive value: 154 / (154+14) = 91.7 %

Negative predictive value: 77 / (77+35) = 68.8 %

For the different sensitivity and specificity values under various clinical scenarios, refer to Table VIII.

Table X. Laboratory abnormalities in relation to the severity of preeclampsia

	Mild Preeclampsia	Severe Preeclampsia
Proteinuria	> 300 mg in 24 hours	> 5000 mg in 24 hours
Serum creatinine levels	Elevated and ≤1.0 mg/ dL	> 1.0 mg/dL
AST*	Elevated and ≤70 U/L	> 70 U/L
Bilirubin	Elevated and ≤1.2 mg/dL	> 1.2 mg/dL
Uric acid	Elevated and ≤360 μmol/L	> 360 μmol/L
LDH*	Elevated and < 600 U/L	≥600 U/L
Platelet count	Decreased and ≥100,000 cells/mm^3	< 100,000 cells/mm^3

* AST = aspartate aminotransferase; LDH = lactate dehydrogenase.

LIST OF FIGURES

Fig 1: Receiver-operator characteristic curve for ***Gestational age at GH presentation*** in predicting the progression to ***preeclampsia***

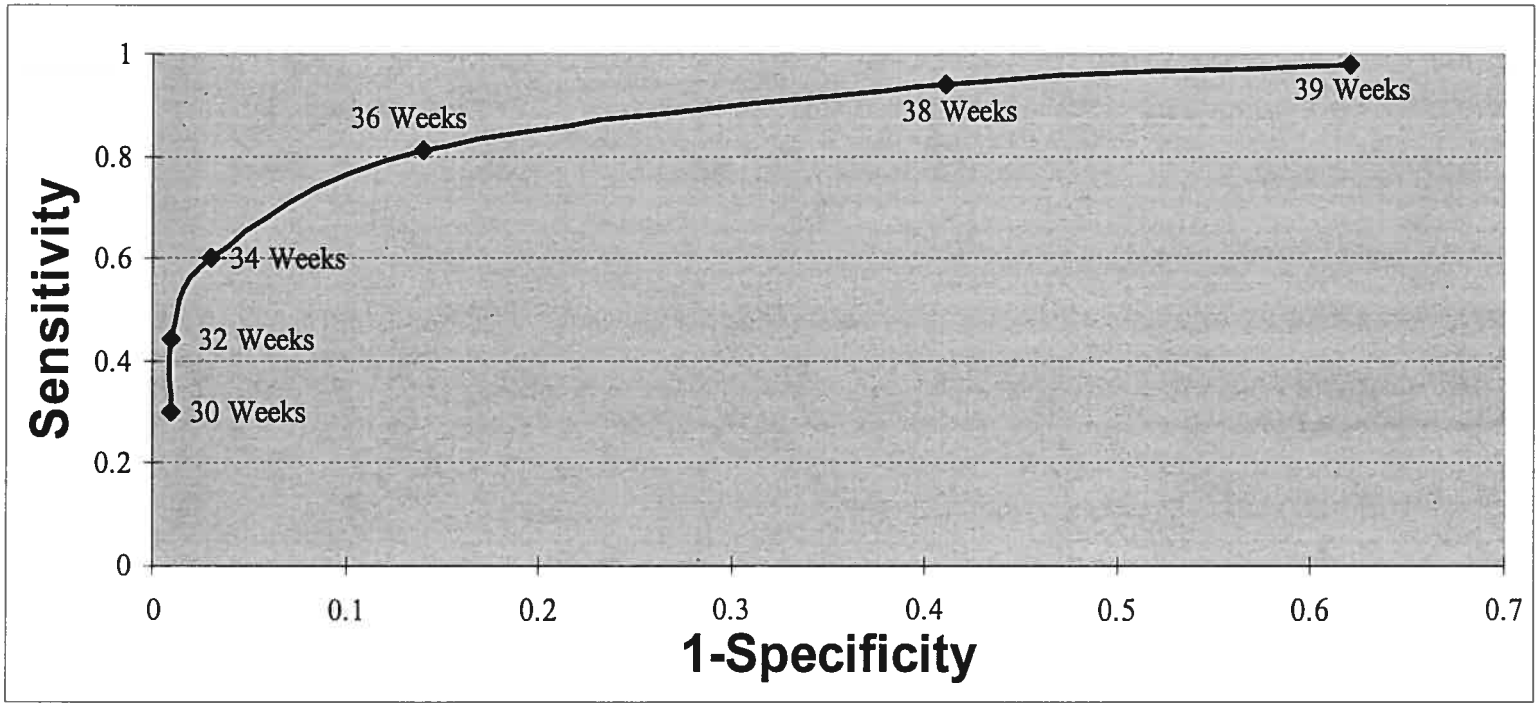


Fig 2: Receiver-operator characteristic curve for ***serum uric acid*** value in predicting the progression to ***preeclampsia***

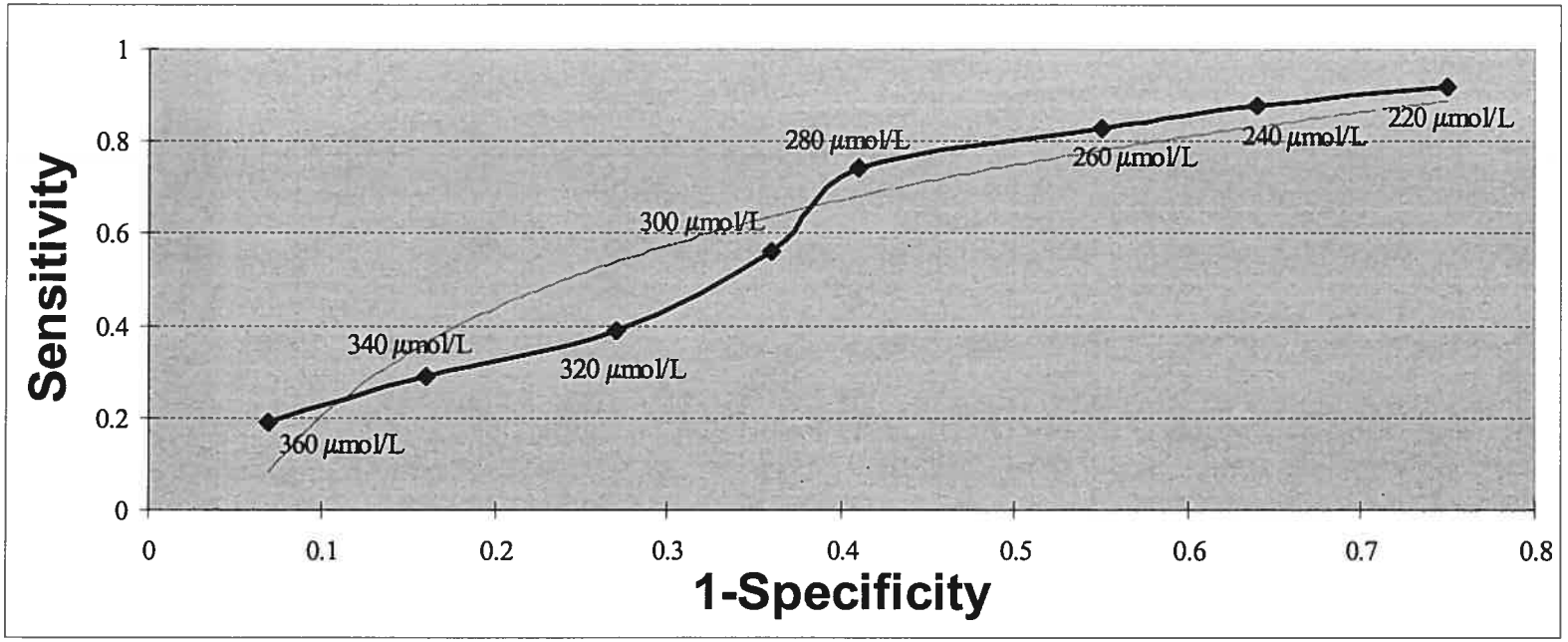
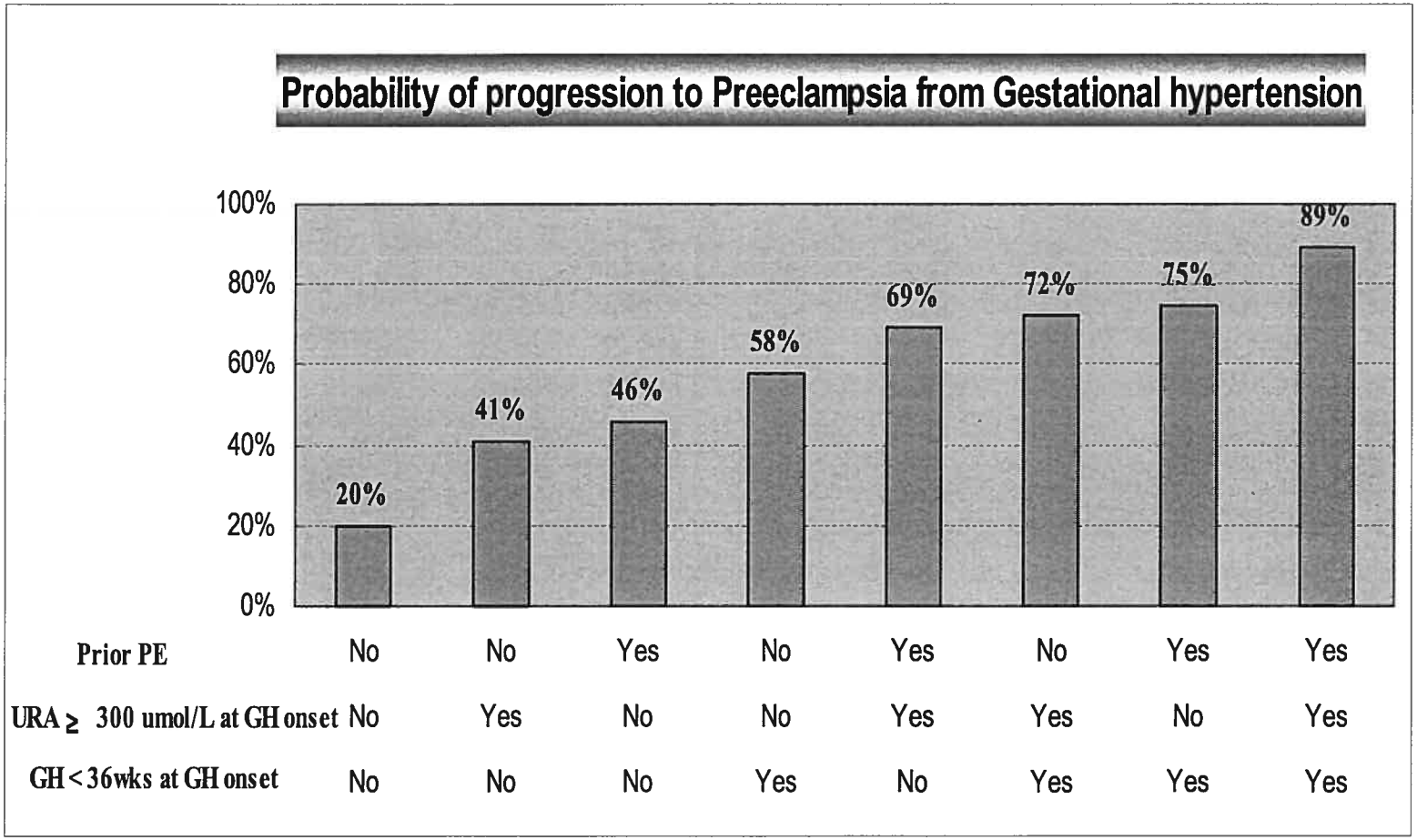
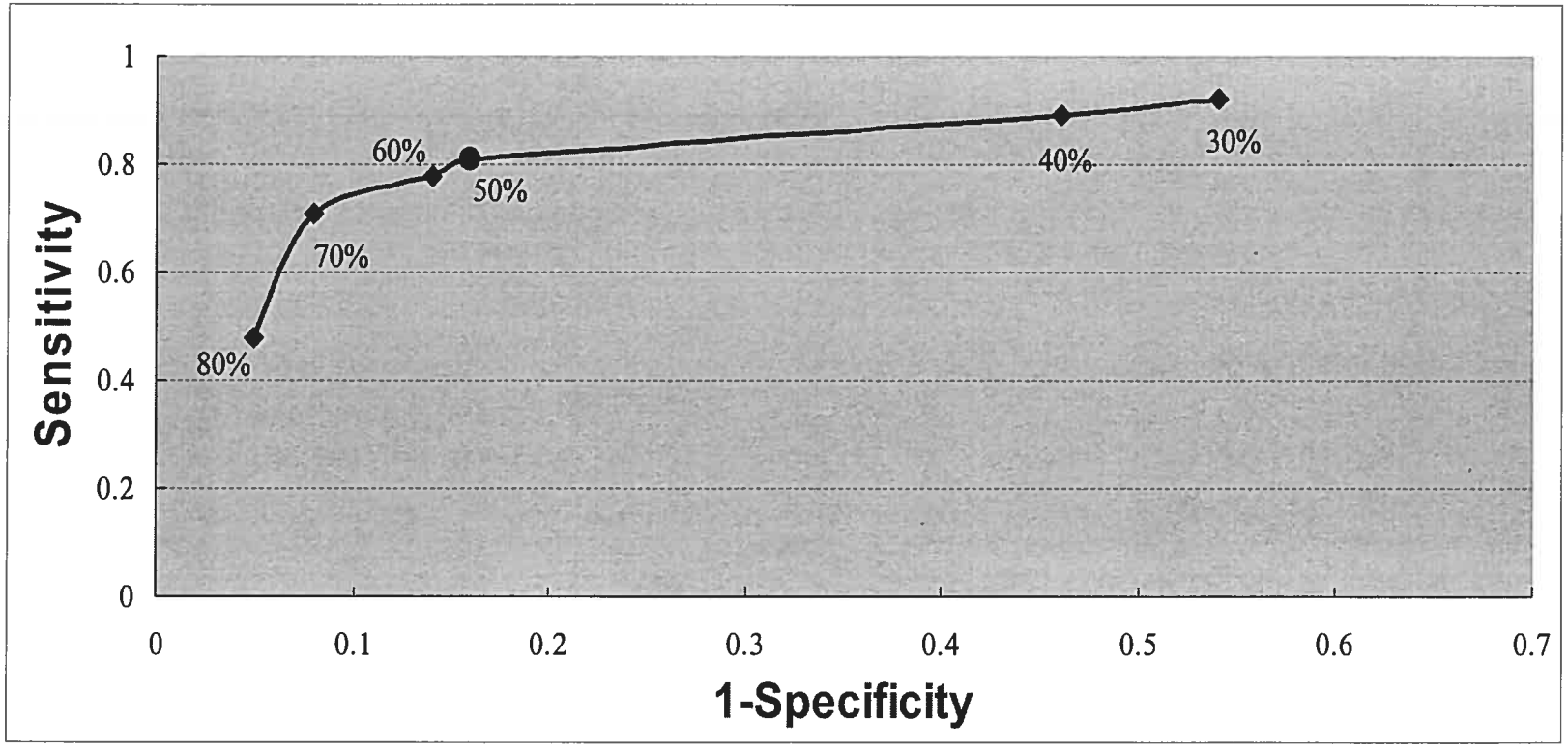


Fig 3: Probability of progression to ***Preeclampsia*** from ***gestational hypertension*** in multivariable logistic regression analysis according to various common combinations of predicting variable values



GH: gestational hypertension; **PE:** preeclampsia; **URA:** uric acid

Fig 4: Receiver-operator characteristic curve for various predicted probability cut-off values based on a multivariable logistic prediction model (Table VI)



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ANNEXES

Information Extraction Form

Identification code |__|__|__|

Risk factors for the progression from GH to PE

HÔPITAL SAINTE-JUSTINE
Le centre hospitalierUniversitaire mère-enfant

Information Extraction Form

Investigators: Yuquan Wu
William D Fraser, MD
Zhong-Cheng Luo, Phd, MD

Diagnosis:

March 1, 2001 ~ June 2003

The number of medical charts: |__|__|__|__|__|__|__|__|
(Numéro du dossier hospitalier de la mère)

Baby Hospital Number: |__|__|__|__|__|__|__|__|
(Numéro du dossier hospitalier du bébé)

The date of Medical chart review: |__|__|__|__| / |__|__| / |__|__|

Identification code |__|__|__|

Risk factors for the progression from GH to PE

I. General Information

1. **Reasons de l'admission:**
   Complications de grossesse: _____
   Travail:
   Indication d'induction: _____
   Méthodes d'induction: _____

2. Date of Birth: |__|__|__|__| / |__|__| / |__|__| (yyyy/mm/dd)
   (Date de naissance)
3. Maternal age: |__|__| (years)
   (Âge)

4. Blood pressure **prior to** pregnancy BP: |__|__|__| / |__|__|__| mmHg
   Date: |__|__| / |__|__| / |__|__| (yy/mm/dd)
5. Mother's **pre-pregnancy** weight: |__|__|. |__|__|Kg or |__|__|__| lbs

6. Mother's **height**: |__|__|__| cm or |__| feet, |__|__| inches

7. **D.D.M**: |__|__| / |__|__| / |__|__| (yy/mm/dd) **D.P.A**: |__|__| / |__|__| / |__|__| (yy/mm/dd)

8. Date of **admission** for the delivery:
   |__|__| / |__|__| / |__|__| ___:___ GA: |__|__| weeks |__| days
   (yy/mm/dd)
9. Date of the **delivery**:
   |__|__| / |__|__| / |__|__| ___:___ GA: |__|__| weeks |__| days
   (yy/mm/dd)
10. The GA of the delivery was determined by:
    LMP|__|, ultrasound |__|, both|__|

11. **G**ravidity: |__| **P**arity: |__|

Identification code |__|__|__|

Risk factors for the progression from GH to PE

	Yes	No	Not indicated
12. Smoking during pregnancy	☐	☐	☐
If Yes, Detail :			
13. Alcohol (during pregnancy)	☐	☐	☐
If Yes, Detail :			
14. Drug dependent (Cocaine, Héroine, Marijuana, Autres)	☐	☐	☐
If Yes, Detail :			

15. Marital status: Married ☐ Conjoint de fait ☐
Unmarried / Divorced / Separat ☐ Other ☐ Specify:

II. Previous medical history

16. In the past history, whether there were following outcomes

1). In the **past** medical history

	Yes	No	Not indicated
• Diabetes mellitus	☐	☐	☐
- IDDM (Type I)	☐	☐	☐
- NIDDM (Type II)	☐	☐	☐
• Chronic renal diseases	☐	☐	☐
• Other disease:			

_____

2). In the **past** pregnant history

	Yes	No	Not indicated
• Multiple pregnancy	☐ Number: |__|	☐	☐
• Abortions	☐ Number: |__|	☐	☐
(therapeutic terminations excluded)			
• Preterm birth	☐ Number: |__|	☐	☐
• Stillbirth	☐ Number: |__|	☐	☐

Identification code |__|__|__|

Risk factors for the progression from GH to PE

- Preeclampsia ☐ GA : ☐ ☐
- Gestational hypertension ☐ GA : ☐ ☐
- GD (Gestational Diabetes) ☐ GA : ☐ ☐
- Other medical disorder ☐ ☐ ☐

Diagnosis :

III. Current Pregnancy

17. Prenatal visits:

1). The date of the **first** visit |__|__| / |__|__| / |__|__| (yy/mm/dd)

Or gestational age (GA) |__|__| wks |__| days

2). The number of prenatal visits

Total: |__|__|

18. Summary of perinatal information (record the relevant data when GH onset and PE onset , highest BP and proteinuria after GH presentation)

Period	**Date** (yy/mm/dd)	**Blood pressure** (mmHg)	***Proteinuria*** (0=no, T=trace, 1=1^{+}, 2=2^{+}, 3=3^{+}, 4=4^{+}, 9=none record)	***24h proteinuria*** (mg/24h)	***Hematuria*** (3-5 red cells) (yes = 1; no= 0)	**Hemoglobin** (g/dL) and **Hematocrit** (%) and **Platelet** (10^{9}/L)	**ALT** and **AST** (U/L)	**Creatine** (umol/L) and **(Uric Acid)** and **LDH** U/L)	**Maternal weight** (Kg)	**GA** (Weeks)
Before admission (Prenatal Visit)	(First Visit)									
Admission										
At hospital stay										
At delivery										
After delivery										

Identification code |__|__|__|

Risk factors for the progression from GH to PE

19. During the **admission**, whether there were

	Yes	No	
- GH (Gestational Hypertension)	☐	☐	
- PE (Preeclampsia)	☐	☐	
- Eclampsia	☐	☐	
- Acute renal failure	☐	☐	
- HELLP syndrome	☐	☐	
- Others	☐	☐	Specify:

20. The **earliest GA** when the diagnosis was made for **GH** (Gestational Hypertension)

GA: |__|__| wks |__| days Date: |__|__| / |__|__| / |__|__|
(yy/mm/dd)

21. The **earliest GA** when the diagnosis was made for **PE** (Preeclampsia)

GA: |__|__| wks |__| days Date: |__|__| / |__|__| / |__|__|
(yy/mm/dd)

22. During the pregnancy, **the highest proteinuria** of 24h urine collection:

|__|__|__|__| mg protein. GA: |__|__| wks |__| days

23. Therapy at hospital stay:

	Yes	No
- Magnesium sulfate	☐	☐
- Antihypertensive medications	☐	☐
- Corticosteroïds	☐	☐
- Antibiotics	☐	☐
- Others	☐	☐

24. Multiple pregnancy:

Single pregnancy |__| Twin pregnancy |__| Multiple pregnancy ≥3 |__|

Identification code |__|__|__|

Risk factors for the progression from GH to PE

25. Mode of the delivery

	Yes	No
Cesarean delivery	☐	☐
(a). mother indications	☐	☐
(b). fetal indications	☐	☐
Vaginal spontaneous	☐	☐
Vaginal assisted	☐	☐

26. Whether there were following maternal and fetal outcomes or information

	Yes	No	
1). Maternal information:			
• Gestational diabetes	☐	☐	GA :
• Premature rupture of membranes (≤37 wks)	☐	☐	GA :
• Labor induction	☐	☐	GA :
• Renal dysfunction : Oliguria (< 0.5 ml/kg/h or < 500 ml/24h)	☐	☐	Detail :
• Blood loss during delivery (> 500 ml)	☐	☐	Volume :
• Blood transfusion	☐	☐	

- Antenatal inpatient days |__|__| days
- Days hospitalized (mother) |__|__| days

	Yes	No	
2). Fetal information:			
o Placental abruption	☐	☐	GA :
o NICU admission	☐	☐	
o Other complications	☐	☐	Specify:
o Infant death (Stillbirth)	☐	☐	

Identification code |__|__|__|

IV. Infantile Information

27. General information of the infant

- ❖ Sex: Male |__| Female |__|
- ❖ Birth weight |__|__|__|__| grams
- ❖ Gestational age |__|__| weeks |__| days
- ❖ Baby's height |__|__|. |__| cm or |__|__|. |__| inches
- ❖ Head circumference of the infant: |__|__|. |__| cm or |__|__|. |__| inches
- ❖ APGAR score: 1 min |__|__| 5 min |__|__| 10 min |__|__|
- ❖ Placental weight |__|__|__|. |__| grams
- ❖ Days hospitalized (infant) |__|__| days

28. Infant status

	Yes	No	
- Live birth	☐	☐	
- Stillbirth	☐	☐	GA :
- Neonatal death	☐	☐	Days :