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Prediction of hypertensive disorders in pregnancy by combined uterine artery Doppler, serum biomarkers and maternal characteristics

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Ce mémoire intitulé:

Prediction of hypertensive disorders of pregnancy by combined uterine artery Doppler, serum markers and maternal characteristics

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Résumé

Objectif: Évaluer l'efficacité du dépistage de l'hypertension gestationnelle par les caractéristiques démographiques maternelles, les biomarqueurs sériques et le Doppler de l'artère utérine au premier et au deuxième trimestre de grossesse. Élaborer des modèles prédictifs de l'hypertension gestationnelle fondées sur ces paramètres.

Methods: Il s'agit d'une étude prospective de cohorte incluant 598 femmes nullipares. Le Doppler utérin a été étudié par échographie transabdominale entre 11 +0 à 13 +6 semaines (1er trimestre) et entre 17 +0 à 21 +6 semaines (2^{e} trimestre). Tous les échantillons de sérum pour la mesure de plusieurs biomarqueurs placentaires ont été recueillis au 1er trimestre. Les caractéristiques démographiques maternelles ont été enregistrées en même temps. Des courbes ROC et les valeurs prédictives ont été utilisés pour analyser la puissance prédictive des paramètres ci-dessus. Différentes combinaisons et leurs modèles de régression logistique ont été également analysés.

Résultats: Parmi 598 femmes, on a observé 20 pré-éclampsies (3,3%), 7 pré-éclampsies précoces (1,2%), 52 cas d'hypertension gestationnelle (8,7%) , 10 cas d'hypertension gestationnelle avant 37 semaines (1,7%). L'index de pulsatilité des artères utérines au 2^{e} trimestre est le meilleur prédicteur. En analyse de régression logistique multivariée, la meilleure valeur prédictive au 1er et au 2e trimestre a été obtenue pour la prévision de la pré-éclampsie précoce. Le dépistage combiné a montré des résultats nettement meilleurs comparés avec les paramètres maternels ou Doppler seuls.

Conclusion: Comme seul marqueur, le Doppler utérin du deuxième trimestre a la meilleure prédictive pour l'hypertension, la naissance prématurée et la restriction de croissance. La combinaison des caractéristiques démographiques maternelles, des biomarqueurs sériques maternels et du Doppler utérin améliore l'efficacité du dépistage, en particulier pour la pré-éclampsie nécessitant un accouchement prématuré.

Mot clés: Hypertension gestationnelle, Doppler utérins, Biomarqueurs sériques maternels, Caractéristiques démographiques maternelles, Dépistage, Modèle prédictif Multivarié.

Abstract

Objective: To evaluate the screening efficacy of maternal demographic characteristics, serum biomarkers and uterine artery Doppler (uaD) during the first and the second trimester for the hypertensive disorders of pregnancy. To elaborate prediction models of these diseases based on the combination of selected maternal demographic characteristics, maternal serum biomarkers and uaD indexes.

Methods: This is a prospective pregnant cohort study of 598 singleton nulliparous consecutive women. UaD investigation was performed by transabdominal sonography between 11+0 and 13+6 weeks, and between 17+0 and 21+6 weeks. All the serum samples for measurement of several placental biomarkers were collected at the first trimester. Maternal demographic characteristics were recorded at the same time. Receiver operating characteristic curves and predictive values were used to analyze the predictive powers of the above parameters. Different combinations and their logistic regression predictive models were analyzed.

Results: Among 598 women, 20 developed preeclampsia (3.3%), 7 developed early-onset preeclampsia (1.2%), 52 developed gestational hypertension (8.7%), 10 developed gestational hypertension with delivery before 37 weeks (1.7%). Second trimester uterine artery pulsatility index was the best predictor with statistical significance for all the outcomes. In the multivariable logistic regression analysis, the best predictive value in the first and second trimester was obtained for the prediction of early onset preeclampsia. The combined screening showed significantly better results compared to either maternal parameters or Doppler alone.

Conclusion: As a single marker, second trimester Doppler has the highest predictive value for hypertensive disorders, preterm birth and SGA. Combination of the maternal demographic characteristics, maternal serum biomarker and uaD improves the screening efficacy, especially when this necessitates early delivery.

Key words: Hypertensive disorders of pregnancy, Doppler, Maternal serum biomarkers, Maternal demographic characteristics, Screening, Multivariable predictive model.

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ADAM12 : A disintegrin and metalloprotease 12

BMI : Body Mass Index (kg/m2)

CRL : Crown-rump length

DIAST : Diastolic flot (D)

FPV : False Positive value

FVW : Flow Velocity Waveform

GH : Gestational hypertension

β-HCG : Free human chorionic gonadotropin-β

LR : Likelihood ratio

MoM : Multiples of medians

NOTCH : Protodiastolic notch (a velocity range reserved for non-displayed clutter)

NT : Nuchal translucency thickness

OR : Odds ratio

PAPP-A : Pregnancy associated plasma protein A

PE : Preeclampsia

PI : Pulsatility index (PI=(S-D/Vm))

PP13 : Placental protein 13

RI : Resistance index (RI=(S-D/S))

SGA : Small for gestational age

SYST : Systolic flot (S)

VM : Average Speed

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Introduction

With the development of our medical technology and maternal/child care system, complications of illegal abortions, infections and death from postpartum haemorrhage are seldom seen in recent years. The maternal and perinatal mortality numbers have declined dramatically in many countries. However, hypertensive disorder of pregnancy and their complications, a major cause of maternal mortality, still complicate approximately 0.34-11.5% of pregnancies[1]. These variations depend on age distribution, ethnic differences, socioeconomic status, and number of previous deliveries. In addition, hypertensive disorders of pregnancy are also found to be strongly associated with fetal growth restriction and prematurity, contributing largely to perinatal morbidity and mortality. [2,3]

Hypertensive disorders of pregnancy is generally regarded as a multisystem disorder specific to pregnant women characterised by widespread endothelial damage which originates from the uteroplacental circulation but ultimately involves a variety of other organs such as the kidney, liver and brain. Its pathophysiology remains unclear, despite the progress made in the past decades[4]. Therefore, it is still a challenge to obtain an accurate prediction of women who are at risk of developing hypertensive disorders of pregnancy.

A theory regarding the etiology of hypertensive disorders of pregnancy has emerged in which maladaptation of the vasculature of the uteroplacental unit due to impaired trophoblast invasion has been implicated as the main causal factor[5]. Therefore, it should be possible to predict the risk by using Doppler ultrasonography to analyse the uteroplacental circulation in the pregnancy. This view is now widely accepted and many of these efforts have focused on biochemical markers, primarily those suggesting endothelial dysfunction and activation of coagulation[6,7].

1. Literature review

1.1. Hypertensive disorders in pregnancy

1.1.1. Classification of hypertensive disorders in pregnancy

Many classifications focus on diastolic blood pressure, or changes in diastolic blood pressure. Because of the great variation in clinical expression of the syndrome and the inability to distinguish symptoms induced by pregnancy from underlying (but often latent) maternal disorders, we have difficulty defining the symptoms, the various clinical forms, and the pathophysiology that becomes more complex every time new evidence is found. In fact, the criteria used to identify the disorder remain a subject of confusion and controversy. Obviously, a comprehensive and easily obtainable classification is needed to improve prognostics and decision making and to enable comparison of research work.

American College of Obstetricians and Gynecologists (ACOG) has recommended a classification to define hypertensive disorders of pregnancy. This classification is widely accepted and consists of four terms as follow:[8]

- Chronic hypertension
- Pre-eclampsia / Eclampsia
- Pre-eclampsia superimposed upon chronic hypertension
- Gestational hypertension: (1) transient hypertension of pregnancy if pre-eclampsia is not present at the time of delivery and blood pressure returns to normal by 12 weeks postpartum (a retrospective diagnosis) or (2) chronic hypertension if the elevation persists.

1.1.1.1. Definition of chronic hypertension

Chronic hypertension is defined as hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. Hypertension is defined as a blood pressure equal to or greater than 140 mm Hg systolic or 90 mm Hg diastolic. During pregnancy the hypertension remains, but proteinuria does not occur. Women who develop hypertension during pregnancy, without proteinuria or seizures, and whose blood

pressure remains elevated after pregnancy are also diagnosed with chronic hypertension. Hypertension that is diagnosed for the first time during pregnancy and that does not resolve postpartum is classified as chronic hypertension too.

1.1.1.2. Definition of pre-eclampsia/eclampsia

Pre-eclampsia is characterized by blood pressure greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic occurring after midpregnancy (20 weeks gestation), and accompanied by proteinuria. Preeclampsia may be further categorized as mild or severe. In the absence of proteinuria the disease is highly suspected when increased blood pressure appears accompanied by the symptoms of headache, blurred vision, and abdominal pain, or with abnormal laboratory tests, specifically, low platelet counts and abnormal liver enzymes. It is recommended that gestational blood pressure elevation be defined on the basis of at least two determinations. The repeat blood pressure should be performed in a manner that will reduce the likelihood of artifact and/or patient anxiety.

Proteinuria is defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen. This will usually correlate with 30 mg/dL ("1+ dipstick") or greater in a random urine determination with no evidence of urinary tract infection. However, because of the discrepancy between random protein determinations and 24-hour urine protein in pre-eclampsia (which may be either higher or lower), it is recommended that the diagnosis be based on a 24-hour urine if at all possible or a timed collection corrected for creatinine excretion if this is not feasible. Pre-eclampsia always presents potential danger to mother and baby. Other conditions may increase blood pressure and even result in proteinuria; thus, as the certainty of the diagnosis increases, the requirements for careful assessment and consideration for delivery also increase.

According to the severe of syndrome, ACOG made three categories for pre-eclampsia:

a. Mild preeclampsia
   BP 140/90
   300mg of proteinuria in 24hrs
b. Severe preeclampsia (any of these)
   BP 160/110

5g of proteinuria in 24hrs

Oliguria or <500 ml in 24hrs

Cerebral of visual disturbances

Pulmonary edema or cyanosis

Persistent pain of right-upper quadrant of abdomen

Fetal growth restriction

Thrombocytopenia (Platelet count is less than 100,000 cells/mm^3 and/or evidence of microangiopathic hemolytic anemia, with increased lactic acid dehydrogenase).

Impaired liver function (Elevated hepatic enzymes -alanine aminotransferase [ALT] or aspartate aminotransferase [AST]).

c. Eclampsia

Presence of new-onset seizures in a patient with preeclampsia

1.1.1.3. Definition of pre-eclampsia superimposed upon chronic hypertension

Lots of evidence indicates that pre-eclampsia may occur in women already hypertensive (i.e., who have chronic hypertension) and that the prognosis for mother and fetus is much worse than with either condition alone. Skills are needed to distinguish superimposed pre-eclampsia from worsening chronic hypertension. The principle of high sensitivity and unavoidable overdiagnosis is appropriate in order to facilitate clinical management. Close observation, with delivery indicated by the overall assessment of maternal-fetal well-being shall be provided at suspicion of superimposed pre-eclampsia. The diagnosis of superimposed pre-eclampsia is highly likely associated with the following findings:

- In women with hypertension and no proteinuria early in pregnancy (<20 weeks), new-onset proteinuria, defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen.
- In women with hypertension and proteinuria before 20 weeks' gestation.
- Sudden increase in proteinuria.

- A sudden increase in blood pressure in a woman whose hypertension has previously been well controlled.
- Thrombocytopenia (platelet count <100,000 cells/mm^3).
- An increase in ALT or AST to abnormal levels.

1.1.1.4. Definition of gestational hypertension (GH)

The woman who has blood pressure elevation detected for the first time after 20 weeks of gestation, without proteinuria, is classified as having gestational hypertension. This nonspecific term includes women with the pre-eclampsia syndrome who have not yet manifested proteinuria as well as women who do not have the syndrome. The hypertension may be accompanied by other signs of the syndrome, which will influence management. The final differentiation that the woman does not have the pre-eclampsia syndrome is made only postpartum. If pre-eclampsia has not developed and blood pressure has returned to normal by 12 weeks postpartum, the diagnosis of transient hypertension of pregnancy can be assigned. If blood pressure elevation persists, the woman is diagnosed as having chronic hypertension. Note that the diagnosis of gestational hypertension is used during pregnancy only until a more specific diagnosis can be assigned postpartum.

It is the elevation of blood pressure (>140/90mm Hg) during pregnancy or in the first 24 hours postpartum without other signs of preeclampsia or preexisting hypertension. The hypertension usually resolves in days to weeks after delivery. Rarely, women will become persistently hypertensive following a pregnancy complicated by transient hypertension. This condition is thought to foreshadow the development of essential hypertension later in life.

1.2. Measurement of blood pressure

For the purposes of accuracy and standardization, health professionals should take blood pressure measurements in pregnant women with the patient seated rather than lying on her side, because substantial differences exist between the blood pressures in the upper and lower arms when the patient is lying on her side. In addition, the National Institutes of Health (NIH) recommends that the diastolic pressure reading should be taken at

Korotkoff 5, with the disappearance of sound—not at Korotkoff 4, when sound becomes muffled. To meet strict criteria for hypertension, the patient's readings must be elevated on at least two separate occasions at least six hours apart.

a. Mercury manometer is still the gold standard.
b. Comfortable sitting position, patient seated with feet supported for 2-3 minutes, arm at the level of the heart.
c. Use appropriately sized cuff (large cuff if arm circumference > 33 cm).
d. Record systolic and diastolic pressures, the latter as Korotkoff Vth (disappearance). Only use Korotkoff IVth when Korotkoff Vth is absent.
e. If the Korotkoff Vth sound is not present, use the Korotkoff IVth but should note as such
f. In serial readings use the higher set of values
g. Relative BP change of 30mmHg/15mmHg is no longer used as hypertension

1.3. Epidemiology

1.3.1. Prevalence

The overall prevalence of hypertensive disorders of pregnancy was 7.5% in Brazilian women[9], 6.4% in African American, 4.8% in other American women[10], 3.7% in the United States[11], 3.3 % in southern Iran[12], 3% in northwest Saudi Arabia [13] and 2.6% in southwest Saudi Arabia[14]. These figures may not be accurate because the information is usually based on hospital populations and therefore biased, especially in countries where access to health care is low. The differences in classification and definitions also contribute to the variation of these figures, which may be different even among reports from the same region.

1.3.2. Impact on maternal and fetal mortality

Research shows that the occurrence of hypertensive disorders of pregnancy is inversely related to assess to health care of that region. In developed countries, hypertensive disorders of pregnancy were responsible for 16.1% (6.7-24.3%) of all maternal deaths.

The number was much higher (25.7%, 7.9-52.4%) in developing countries, especially in Latin America and the Caribbean. [15] (Fig. 1)

Fetal mortality from preeclampsia was usually caused by associated prematurity, IUGR, or hypermagnesemia. Hypertension and the poor placentation often seen with preeclampsia may result in placental insufficiency and eventually IUGR which is associated with several problems, including fetal and neonatal hypoxemia, acidosis and newborn resuscitation.

Svein Rasmussen and Lorentz M Irgens's study on 223541 single births in Norway from 1999 to 2002 showed that mothers with severe preeclampsia or preeclampsia superimposed on chronic hypertension gave birth earlier than those who had mild preeclampsia or transient hypertension. Median gestational age at birth in transient hypertension, mild-, and severe preeclampsia were 279, 277, and 259 days, respectively, against 280 days in normotensive pregnancies, while those with chronic hypertension with and without preeclampsia had median gestational age of 268 and 279 days, respectively. The rates of preterm birth (less than 37 weeks of gestation) in transient hypertension, mild-, and severe preeclampsia were 8.1, 9.7, and 48.2%, respectively, against 5.0% in normotensive women. The rates were also significantly higher in chronic hypertension with or without preeclampsia(34.5% and 8.9%).[16] (Fig. 2)

Victoria M Allen and their colleagues performed a study on all pregnant women and births in the Canadian province of Nova Scotia between 1988 and 2000, including 135,466 pregnancies. In their study, after controlling for potential confounders, women with any hypertensive disorder were 1.4 (95% CI 1.1, 1.8, $P = .02$) times more likely to have a stillbirth and 1.8 (95% CI 1.7, 1.9, $P < .001$) times more likely to have SGA as compared with normotensive women. Women with pre-existing hypertension were 3.2 (95% CI 1.9, 5.4, $P < .001$) times more likely to have a stillbirth and 2.5 (95% CI 2.1, 2.9, $P < .001$)times more likely to have SGA as compared with normotensive women.[17] (Table 1)

1.4. Risk factors of hypertensive disorders of pregnancy

Incidence of hypertensive disorders of pregnancy is associated with a number of risk factors (Table 2). Based on these factors, a comprehensive medical history and physical examination at the first antenatal visit can be used to estimate a mother's risk of developing the disorder.

Risk factors can be divided into four major groups as follows:

1.Pregnancy associated risk factors

2.Chronic risk factors

3.Hereditary risk factors

4.Other risk factors

Section 1.4.1.-1.4.4. provide detail descriptions of each of these risk factors.

1.4.1. Pregnancy associated risk factors

1.4.1.1. Nulliparity

Women in their first pregnancy are at an increased risk of hypertensive disorders of pregnancy. Previous pregnancies appear to have a protective effect, even if they ended early in abortion. In contrast, women with a history of hypertensive disorders in previous pregnancies are at an increased risk.[18] It is likely that women who have recurrent pre-eclampsia have an underlying pathological phenotype that puts them at risk of hypertension.[19]

1.4.1.2. High-risk pregnancy, abnormal pregnancy

Factors associated with the pregnant state itself that increase the risk of hypertensive disease are twin pregnancy[20], polyhydramnion[21], hydatidiform molar pregnancies and hydrops fetalis.[4] Extremely young (teenage) or relatively old (over 35) women are at an elevated risk too.[22]

1.4.1.3. Sperm exposure and time interval between deliveries

Normal pregnancy requires adaptation of the maternal immune response, so that the foetus and placenta, being partly allogenic, are not rejected. In pre-eclampsia, this adaptation may be inadequate in a first pregnancy with a new partner (and limited sperm exposure, primipaternity theory); while in subsequent pregnancies with the same partner the risk is lower.[23-25]

Although numerous studies have shown an increased risk of pre-eclampsia associated with a new partner[26], some investigators challenged this theory. In Trogstad's study on 547 238 women, time interval between pregnancies have shown a significant impact on the risk of pre-eclampsia. They also found that a change of paternity for the second pregnancy was associated with a reduced risk of pre-eclampsia after controlling for the time since first delivery, but the interaction between change in paternity and time between deliveries was significant only for women with no previous pre-eclampsia ($P = 0.04$) and the interaction between history of pre-eclampsia and time interval between the two deliveries was highly significant ($P < 0.001$). For women with no previous pre-eclampsia the risk of pre-eclampsia in second pregnancy increased with increasing time interval, whereas for women with previous pre-eclampsia the risk tended to decrease with increasing time interval between deliveries.[27]

The increased incidence of pre-eclampsia in donor insemination pregnancies indicates that prolonged exposure to paternal spermatozoa prior to conception, as in the partner insemination group, reduces the risk. Since recipients of donated spermatozoa are exposed to foreign fetal antigens encoded by the paternally derived genes, they are at higher risk. The finding of an increased incidence of gestational hypertension in ovum donation pregnancies provides further support to the hypothesis that the development of pre-eclampsia may be due to altered or inadequate immunoprotection of the fetoplacental unit in oocyte recipients due to short duration of exposure to non-maternal antigens.[28]

1.4.2. Chronic risk factors

Research indicates that some chronic diseases are associated with hypertensive disorders

of pregnancy, as detailed in the following paragraphs.

1.4.2.1. Cardiovascular disorders

Preeclampsia and cardiovascular disorders share similar risk factors like obesity, hyperlipidemia, increased insulin resistance, and analogous pathophysiology such as increased oxidative stress and vascular injury. [29] Cardiovascular disorders are risk factors for hypertensive disorders of pregnancy. Unfavourable cardiovascular and metabolic profiles may represent primary causes of pre-eclampsia, as well as subsequent cardiovascular disease.[19]

1.4.2.2. Chronic hypertension

Pregnancy has detrimental effects on chronic hypertension. The probability of exacerbating of hypertension and development of preeclampsia and eclampsia in patients with chronic hypertension is much higher than previously normotensive population.[30]

1.4.2.3. Renal diseases

Women suffering from renal disease have a high risk too, because hyperuricaemia precedes significant proteinuria in pre-eclampsia and is thought to result from either enhanced tubular reabsorption of uric acid, or breakdown of nuclear (or therefore purine) rich syncytiotrophoblast.[31]

1.4.2.4. Obesity

Obese women and those with hypercholesterolemia have an increased risk of developing or having preexisting manifestations of the metabolic syndrome. So, there are lots of potential risk factors to develop this disease.[32]

1.4.2.5. Diabetes

Diabetes is a condition in which the body cannot use the sugars and starches (carbohydrates) it takes in as food to make energy. The body either makes too little insulin in the pancreas or cannot use the insulin it makes to change those sugars and starches into energy. As a result, the body collects extra sugar in the blood and gets rid of some sugar in the urine. The extra sugar in the blood can damage organs of the body, such as the heart, eyes, and kidneys, if it is allowed to collect in the body too long. And,

insulin resistance might affect the pathogenesis of hypertensive disorders in pregnancy since mid-trimester. Women with hypertensive disorders in pregnancy were more likely to have gestational diabetes and pre-existing diabetes compared with normotensive women (2.3% and 0.3%, respectively). [17]

1.4.2.6. Smoking

An interesting observation is that smoking appears to have a protective effect. Women with a smoking history, even though they quit smoking in early pregnancy, still demonstrate lower probability of developing hypertensive disorders in pregnancy[33]

1.4.3. Hereditary risk factors

Research indicates that women with positive family history have a higher risk of developing preeclampsia. They may have inherent abnormalities, which predispose to vascular disease.[34] And, some ethnic groups, like African-American and Hispanic women in the US, have a higher incidence of hypertensive disorders of pregnancy compared to white women.[35] Some investigators believe that the hypothesis of a single gene whose expression is pregnancy-specific and which is alone responsible for the progression from preeclampsia to eclampsia. Various candidate genes have been proposed. Arngrimsson and colleagues have reported the highest lod score for a region on 2p13 without any obvious candidate genes, which seems has been confirmed.[36,37] But, in fact, no gene has gained common acceptance as the one that causes the hereditary component of preeclampsia.

1.4.4. Other risk factors

Stress and work related psychosocial strain increase the risk of developing hypertensive disorders of pregnancy. One possibility suggested that stress contributes to the etiology of preeclampsia via priming the immune system to produce inflammatory cytokines. [38] On the other hand, Annelies Rep's study mentioned that severe hypertensive disorders of pregnancy have a high psychological impact, especially when gestational age at onset of disease is below 30 weeks or if adverse infant outcome occurs.[39]

1.5. Doppler analysis and hypertensive disorders of pregnancy

1.5.1. Pathophysiology of hypertensive disorders of pregnancy

Blood supply to uterus is mainly provided by the left and right uterine arteries and to a less extent by the ovarian arteries. In the parametrium, the uterine arteries branches into the arcuate artery which in turn branch into the radial arteries. After crossing the myometrium, these radial arteries issued spiral arteries at the junction of the myometrial-endometrial and terminate in the basal endometrium. Radial artery also issue branches named basal arteries which do not pass endometrium.

1.5.1.1. Normal adaptation of the uteroplacental vasculature in pregnancy

In the first few weeks of pregnancy, conceptus cytotrophoblast cells invade the basal decidua and the decidual portion of the spiral arteries. Cytotrophoblast is divided into two different types at this stage. One is called endovascular trophoblast. The other is called interstitial trophoblast which penetrates the basal deciduas.

The interstitial trophoblast migrates retrogradely to colonise the myometrium at 10 to 12 weeks of pregnancy. Between 12 to 16 gestational weeks, endovascular trophoblast invades the myometrial portions of the spiral arteries, replaces the endothelium and disrupts the muscular vessel wall.

Finally, distended fibrinoid tubes incapable of vasoconstriction replace the spiral arteries from the myometrium to the intervillous space. This results in a low-resistance, high-capacity vascular circulatory system which facilities adequate maternal blood supply to the growing fetus.

1.5.1.2. Uterine vascular pathology in hypertensive disorders of pregnancy

Since the 1950s it has been acknowledged that hypertensive disorders of pregnancy were associated with extensive placental infarction. Thanks to increasing knowledge of the normal physiological adaptation of the arteries of the placental bed and more sophisticated microscopic techniques in recent days, people have better understanding of the pathogenesis of hypertensive disorders of pregnancy with two major distinct

abnormalities found in the uteroplacental circulation. First, normal physiological adaptation of pregnancy is impaired or absent in hypertensive disorders of pregnancy. Second, a distinctive vaso-occlusive lesion termed "acute atherosis" was found. These abnormalities impair maternal blood flow which results in placental insufficiency during pregnancy.

a. Impaired physiological adaptation:

Physiological changes of uterine artery only exist at the endometrial segments of the spiral arteries while the myometrial segments remain unchanged. Besides, trophoblast cells do not exist in the vessel wall of the spiral arteries that failed to undergo physiological changes. The extent of endovascular trophoblast invasion and physiological changes varies between spiral arteries. Some arteries do not show any physiological changes along their entire length.[40,41]

The association between impaired adaptation of spiral arteries, hypertensive disorders of pregnancy, and fetal growth restriction has been confirmed in recent studies.[42,43] The studies also show that endovascular trophoblast invasion is not an all-or-none phenomenon and that there is a gradient in the extent of trophoblast invasion of decidual and myometrial arteries in both normal pregnancy and pre-eclampsia. Uteroplacental vascular pathology, although being present in a percentage of normal pregnancies, has also been related to spontaneous prematurity and placental abruption. [44]

b. Acute atherosis:

Research shows that acute atherosis is related to pre-eclampsia and fetal growth restriction. An atheromatous infiltrate consisting of lipid-laden "foam cells" is a typical lesion characteristics, which originated from myocytes or macrophages, fibrin, and mononuclear cells. In addition, there is large amount of fibrin deposited in the vascular endothelium and the media. Cellulose necrosis and macrophage infiltration appeared at the earlier stages of the lesions.[45]

It was believed that acute atherosis only occurs in spiral arteries which fail to undergo physiological changes. Latest research showed that it can also occur in physiologically adapted spiral arteries.[45,46]

It is not clear what causes impaired trophoblast invasion and acute atherosis. The fact that trophoblast cells do not exist in the vessel wall of unchanged spiral arteries suggests a specific defect in the invasion of the endovascular type of trophoblast. The failure of endovascular trophoblast to express vascular adhesion phenotype molecules could play a role by impairing adhesion to the vessel wall. In recent studies, an increased number of activated macrophages were found in the placental bed of patients with pre-clampsia and widespread apoptosis of placental cytotrophoblast cells.[47,48] This phenomenon could be caused by a maternal immunological response against endovascular trophoblast, perhaps triggered by the deficiency in the expression of vascular adhesion molecules. In addition, recent reports indicate that a deficiency of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) is associated with pre-eclampsia.[49,50] Further investigation is required to understand the precise meaning of these findings.

1.5.2. Principles of Doppler analysis of ulteroplacental blood flow

Doppler signals from the maternal side of the uteroplacental circulation can be derived from the uterine artery, the arcuate arteries, or the spiral arteries (Fig. 3).
These vessels undergo profound changes in early pregnancy resulting in increased volume flow.
Cytotrophoblastic invasion of the maternal spiral arteries and replacement of their endothelium is central to the successful outcome of pregnancy, and results in the establishment of a low-resistance high-flow uteroplacental circulation. This process, known as physiologic transformation, begins as early as the 10th day after conception and continues throughout the pregnancy.
The noninvasive assessment of uterine artery resistance by means of Doppler ultrasound has demonstrated that a high-resistance blood flow pattern is invariably present at the beginning of the pregnancy. As a result of the physiological transformation of the spiral

arteries, a low-resistance pattern develops at varying gestational ages in different individual pregnancies.[42]

The mature placenta is a low resistance, high capacity system in which arteries have lost their elastic wall and drain directly into large venous pools without an interposed capillary bed. This results in low systolic maximum velocity and high forward diastolic flow. These changes are completed in normal pregnancy between 20 and 24 weeks (Fig.4)

1.5.3. The Doppler indices

Several indices have been described to quantify the information from the Doppler waveform. (Fig. 5)

The Resistance Index (RI) was introduced in 1974 by Planiol.[51] The Pulsatility Index (PI), a modified version of the resistance index, was introduced in 1971 by Gosling RG.[52]

The systolic/diastolic ratio is also used frequently in clinical practice. Several authors have noticed the presence of a diastolic "notch"(Fig.6) in waveforms from the uteroplacental circulation and used it in the prediction of pregnancy complications. This "notch" is present in most waveforms in nonpregnant women and early pregnancy but disappears in the second trimester in normal pregnancy. The presence of a diastolic notch beyond the 22nd week is generally considered to be abnormal. The physiological background of the changes in uteroplacental flow velocity waveform (FVW)s has been investigated using computer models to simulate the uteroplacental circulation.

To obtain reliable information about the uteroplacental circulation, the uterine artery is the best sample site; it is easy to locate on real time imaging, provides good reproducibility, and reflects the resistance in the entire distal placental bed. [53,54]

1.5.4. Prediction of hypertensive disorders of pregnancy by Doppler ultrasound

1.5.4.1. Doppler ultrasound as a diagnostic and prognostic tool in complicated pregnancies

Doppler ultrasound of the uteroplacental circulation could be used to predict poor pregnancy outcome in hypertensive pregnancies. In 1983, Campbell et al. used a pulsed

Doppler system to detect abnormal flow velocity waveforms (FVWs) in the arcuate arteries of 31 women with hypertension or suspected FGR, and found that abnormal FVWs were associated with a higher risk of proteinuric hypertension, premature delivery, and low birthweight. In addition, women with normal FVWs were likely to have a normal pregnancy outcome.[55]

1.5.4.2. Doppler analysis of the uteroplacental circulation as a screening test for pregnancy complications

The recognition of abnormal uteroplacental FVWs in patients with hypertensive disorders of pregnancy suggests the possibility of a screening test in early pregnancy. It is widely believed that in case of hypertensive disorders of pregnancy, uteroplacental resistance is increased already in the beginning of the second trimester, when normal adaptation of the spiral arteries has failed to occur. In 1986, Campbell and his colleagues performed the first screening study. In their study, a pulsed Doppler apparatus was used to assess the blood flow velocity profiles in uterine vessels (arcuate arteries) at 16 to 18 weeks' gestation. [56] Their purpose is to determine if complications associated with impaired trophoblastic invasion of the placental bed (ie, pregnancy-induced hypertension, intrauterine growth retardation, and fetal asphyxia) could be predicted by this measurement. Thirty-one of 126 consecutive pregnancies developed one or more of the above complications. The sensitivity was 68% and the specificity 69%; the predictive value of a positive test was 42% and that of a negative test 87%.

Presently, more and more investigators use Doppler as a screening test, and found that there are several points worth of attention.

a. The gestational age at the time of measurement

- First trimester

In normal pregnancy, uteroplacental resistance falls gradually between the late first trimester and mid second trimester. Screening before 20 weeks might result in a false-positive test result in subjects in which spiral artery adaptation is in normal progress but not yet completed. [57,58]

- Second trimester

Good predictive values are reported in studies where an initial scan at 18-20 weeks is followed –if abnormal- by a repeat scan at 24 weeks.[59] Two-stage screening (repeating an abnormal test after 4 weeks) have better predictive result in comparison with single sampling.[60]

b. Doppler screening is more accurate in predicting proteinuric pre-eclampsia compared to pregnancy-induced hypertension.

Some investigators found that abnormal uterine Dopplers have better predictive values for subgroups such as "severe" pre-eclampsia, in comparison to "uncomplicated" pregnancy-induced hypertension and pre-eclampsia.[7,61, 62] In their studies, "severe" pre-eclampsia includes the following symptoms: diastolic blood pressure over 90 mmHg, severe proteinuria, pre-eclampsia requiring delivery before 34 weeks, and pre-eclampsia combined with SGA ($\leq$ the 5th centile, $\leq$ the 10th centile).

c. The location of the placenta:

Lower PI and RI values are found in the uterine artery on the placental side at 16-20 weeks. In pregnancies with unilateral placental location, the uteroplacental Doppler flow measurements show significant side-to-side differences. In strictly unilateral placentas, there is a greater incidence of abnormal FVWs compared to central placentas and a greater incidence of pregnancy complications. Gonser's study suggests that a laterally located placenta is associated with a significantly increased incidence of preeclampsia, with a risk ratio of 3.1 when compared to pregnancies with centrally located placentas.[63]

d. The persistence of PI and Notch:

Gomez found that the persistence of an abnormal mean PI from the first to the second trimester identified the group with the greatest risk for adverse perinatal outcome (OR, 10.7; 95% CI, 3.7-30.9). In addition, women in whom the uterine artery mean PI shifted from abnormal to normal between the two trimesters and women in whom the reverse shift occurred showed a similar intermediate risk (OR, 5; 95% CI, 2.1-10.6), comparable to that in women with persistence of a bilateral notch (OR, 5.6; 95% CI, 2.9-10.7).[64] And, the high prevalence of notching indicates that the high mean uterine artery index is a more reproducible and objective basis for screening than using bilateral notches alone.[62]

1.6. Serum markers and hypertensive disorders of pregnancy

Early placental abnormalities were targeted by most current hypotheses regarding the pathophysiologic mechanisms of pregnancy-induced hypertention. Human placenta synthesizes steroid, protein, and glycoprotein hormones throughout gestation. A large number of serum markers that are measured in the maternal circulation have been evaluated in the prediction of hypertensive disorders of pregnancy. These include tests of fetal and placental endocrinology dysfunction, maternal renal dysfunction, endothelial dysfunction, and markers of abnormal oxidative stress. [65] It is becoming more and more evident that circulating factors in the maternal circulation may be associated with or cause defective trophoblastic invasion.

1.6.1. Human Chorionic Gonadotropin (hCG)

The hormone human chorionic gonadotropin (hCG) is a glycoprotein produced by syncytiotrophoblasts of the placenta. It is a peptide hormone produced in pregnancy, that is made by the embryo soon after conception and later by the syncytiotrophoblast. Its role is to prevent the disintegration of the corpus luteum of the ovary and thereby maintain progesterone production that is critical for a pregnancy in humans. The production of hCG by the placenta in early pregnancy is critical for implantation and maintanance of the blastocyst. hCG interacts with the LHCG receptor and promotes the maintenance of the corpus luteum during the beginning of pregnancy causing it to secrete the hormone progesterone.[66] Progesterone enriches the uterus with a thick lining of blood vessels and capillaries so that it can sustain the growing fetus. Due to its highly negative charge hCG may repel the immune cells of the mother, protecting the fetus during the first trimester. It has also been hypothesized that hCG may be a placental link for the development of local maternal immunotolerance.[67]

As preeclampsia is characterized by disturbed trophoblastic physiology, early placental dysfunction could be reflected by altered hCG concentrations.

Smith et al. reported increasing hCG Levels in severe preeclampsia for the first time in 1934[68]. Since then numerous studies have suggested that elevated maternal hCG serum levels may be associated with preeclampsia. [69-71]

1.6.2. Inhibin A

Inhibin is a peptide that is an inhibitor of Follicle-stimulating hormone (FSH) synthesis and secretion. Inhibin contains an alpha and beta subunit linked by disulfide bonds. Two forms of inhibin differ in their beta subunits (A or B), while their alpha subunits are identical. In women, FSH stimulates the secretion of inhibin from the granulosa cells of the ovarian follicles in ovary. In turn, inhibin suppresses FSH.

Inhibin A is glycoprotein hormone and member of the transforming growth factor b family. In pregnancy, it is predominantly secreted by the placenta. In normal pregnancies, its serum concentration rise during the third trimester. In vitro studies suggested that inhibin A increases human chorionic gonadotrophin (HCG) secretion,[72] whereas, in turn, HCG stimulates the production of inhibin A.[73] This causal chain might explain the generally observed simultaneous increase of inhibin A.

On the other hand, there is partial or complete failure of trophoblastic invasion of the myometrial segments of the spiral arteries for preeclampsia. The failure of trophoblastic invasion is associated with ischaemic damage to the syncytiotrophoblast causing functional alteration of the surface layer of the syncytiotrophoblast. This alteration in the surface layer of the syncytiotrophoblast has been postulated as a contributory factor for the increased 'leakage' of inhibin A into the maternal circulation, which might explain the increase in concentration of maternal serum inhibin A in preeclampsia.[74]

1.6.3. Pregnancy-associated plasma protein A (PAPP-A)

Pregnancy-associated plasma protein A (PAPP-A) is an important pregnancy protein. The main site of PAPP-A synthesis during pregnancy is the placenta. In the women the levels of PAPP-A are highest during pregnancy, when plasma levels increase by a factor of about 150 as compared to the nonpregnant state. PAPP-A is most abundant in the peripheral maternal circulation. It cleaves the insulin-like growth factor-dependent

binding protein-4 (IGFBP-4) and consequently modulates the amount of bioactive IGF-2, a factor known to promote trophoblast invasion.

Fournier's study suggested that PAPP-A, which can be localized in the trophoblast and in the deciduas, might be considered as an early marker of physiological trophoblast invasion.[75] Since trophoblast is a source of PAPP-A in vivo, PAPP-A has been used in prenatal genetic screening and studies of atherosclerosis.[76,77] Low blood levels of PAPP-A at first trimester of gestation suggest an increased risk of intrauterine growth restriction,[78] trisomy 21[79], premature delivery,[80] preeclampsia,[81] and stillbirth.[82]

1.6.4. A disintegrin and metalloprotease (ADAM12)

ADAM12 is a recently discovered pregnancy associated member of the ADAM family. ADAM12 is an IGFBP-3 and IGFBP-5 protease and is present in human pregnancy serum. The ADAMs constitute a multi-domain glycoprotein family with proteolytic and cell-adhesion activities. [83,84] Human ADAM12 exists in two forms, ADAM12-L (long) and ADAM12-S (short), the latter being the secreted form of ADAM12. ADAM12-S differs from ADAM12-L at the C-terminal end in that it does not contain the transmembrane and cytoplasmatic domains. The mRNA for ADAM12-S is particularly abundant in placenta.[85]

Laigaard's study indicates that serum ADAM12 levels in women who developed pre-eclampsia during pregnancy had a mean log MoM which was significantly lower than the mean log MoM for ADAM12 levels observed in serum samples from women with normal pregnancy ($P < .008$). They suggested that the IGF axis may play a role in preeclampsia. ADAM12 may be a useful early marker for preeclampsia.[86]

1.6.5. Maternal serum placental protein 13 (PP13)

First isolated from human placenta and characterized in 1983,[87] Placental protein 13 (PP13) is a 32-kd dimer protein that is produced only in the placenta and is thought to be involved in normal implantation and maternal artery remodeling. It is the member of the so-called 'pregnancy –related protein' family, which consists of 56 different proteins diverging either in their structure or function and grouped earlier on the basis of their

increased expression in placenta, in some maternal tissues, especially in the liver or in the fetus during pregnancy.[88]

As a potential marker for early detection of PE in low risk groups, PP13 has been designated galectin-13 because of its homology with members of the galectin family. There is a single conserved carbohydrate recognition domain and a strong binding affinity to sugar residues widely expressed in the placenta.[89] It was suggested that the unique dimerization via disulphide bonds might affect the activity of PP13upon the oxygenization changes in the placenta. As other galectins are involved in immunobiological functions, PP13 and its placental homologues might also have immune functions at feto-maternal interfaces. [89]

Recent tests of PP13 in pregnancy serum during the 1st and 2nd trimesters showed a decreased PP13 concentration in patients later developing pre-eclampsia , IUGR and PTD, [90-92] as well as a stably increased PP13 serum value during normal pregnancy period.

1.7. Screening test for hypertensive disorders of pregnancy

1.7.1. Serum Biomarkers screening test for hypertensive disorders of pregnancy

Risk prediction for pregnancy hypertensive disorders is of great value. Early tests focused on detecting early manifestations of disease, such as hypertension, proteinuria, edema, excessive weight gain, and increased vascular resistance. Based on the test result, clinicians identify women who require closer surveillance and permit early referral for their treatment when signs or symptoms occur. More recently, investigators are looking for changes closer to the period when the pathogenic events leading to preeclampsia occur, searching for measurable manifestations of the abnormal placentation and reduced placental perfusion that is said to initiate this disorder. Many of these efforts have focused on biochemical markers, primarily those suggesting endothelial dysfunction and activation of coagulation.

1.7.1.1. Single maternal biomarker screening test

There are differences in the metabolism of women who subsequently develop hypertensive disorders of pregnancy compared with women who remain normotensive during their pregnancy, as indicated by the serum biochemical assays.

Large amount of research has been done trying to identify a unique biomarker screening test that would predict the risk of developing hypertensive disorders of pregnancy before the classic symptoms appear. These include tests of the dysfunction of fetal and placental endocrinology, of maternal renal dysfunction, endothelial dysfunction, and markers of abnormal oxidative stress. [65] Only modest correlations were observed in most of these studies. The low predictive values could not justify any of them as a screening test alone for this condition.[93,94]

1.7.1.2. Combinations of maternal biochemical markers test

To be used in a screening program covering all pregnant women indiscriminately, the test should combine a high sensitivity to justify the cost. It should also have a high positive predictive value so as to avoid unnecessary interventions.[65] No a single biomarkers screening test available today can meet these requirements.

The use of more maternal biomarkers in screening program has much better predictive power.[95] It could be used to identify among high-risk pregnant women those with a very low probability of developing preeclampsia in their present pregnancy. In Floro's study, activin A, inhibin A, and a combination of activin A and inhibin A were tested respectively in a high risk population, and the test result showed that combining both hormones improved the predictive value of the test (positive predictive value of 86% as compared to 55% with activin A alone and 70% with inhibin A alone)[96] In this case, a multi-biomarkers test that achieves optimal negative predictor value could be used to reduce anxiety in the patient and to prevent unnecessary intervention and hospitalization.

1.7.2. Combinations of maternal factors, maternal biochemical markers and uterine artery Doppler test

It is widely accepted that the etiology of preeclampsia is multifactorial. They detect the early placental changes that are part of the evolving disease and only predict the imminent development of the preeclampsia syndrome. This explains why screening in the first trimester is unlikely to work as well as in the second or third trimester.
The use of multiple markers in the screening reflects different aspects of the disease process and increases the specificity and sensitivity of the screening. Combinations of maternal factors, maternal biochemical markers and uterine artery Doppler improve the screening efficacy for prediction of hypertensive disorders of pregnancy, especially for preeclampsia.

1.7.2.1. First trimester screening

One effective way of screening women in the second trimester is to use Doppler ultrasonography to assess increased impedance of blood flow in the maternal uterine arteries. However, the performance of this method became much poorer when investigated in the first trimester. In Martin's study, their Doppler index only showed 27% sensitivity for identifying pre-eclampsia in an unselected population at 11-14 weeks.[97]
One suggestion was to combine uterine artery Doppler with serum markers. This combination improves the effectiveness of the screening and has a relatively high detection rate. It also helps identify patients amenable to effective prevention early enough.[98]

Plasencia proposed a screening method in which maternal characteristics (such as maternal age, ethnic origin, BMI, smoking status and medical and obstetric history), free β-hCG and PAPP-A, as well as uterine artery Doppler were combined together. This screening method appeared to be particularly effective in identifying women who develop severe early onset PE (Pre-eclampsia/toxemia) rather than late-onset disease, GH or SGA. For a false-positive rate of 10%, the predicted detection rate of PE requiring delivery

before 34 weeks was 82%, compared to 31% for late PET, 12% for GH and 18% for SGA.[61]

1.7.2.2. Second trimester screening

Doppler is an effective method for screening early onset PE. Combining uterine artery Doppler velocimetry around 22 weeks' gestation with maternal biochemical markers further improves the sensitivity of the PE screening method.[99] As shown in Aquilina's study, for pre-eclampsia requiring delivery before 37 weeks, the sensitivity improved from 27% to 60% and the positive likelihood ratio improved from 9.2 to 20.8 at a false-positive rate of 3% when uterine artery notch data was combined with inhibin-A. The improvement in sensitivity was statistically significant for both preeclampsia ($P < 0.05$) and preterm pre-eclampsia ($P < 0.02$) when compared to either inhibin-A or uterine artery Dopplers alone.[100]

1.7.2.3. First trimester maternal serum markers in combination with second trimester uterine artery Doppler screening

The underlying pathology of hypertensive disorders of pregnancy is present at the early stages of pregnancy. There is evidence that it is associated with impaired placentation, which may produce unknown substance(s) leading to endothelial dysfunction. A variety of placental proteins and hormones have been studied as potential early markers of pre-eclampsia.

The use of Doppler ultrasonography to assess increased impedance to blood flow in the maternal uterine arteries is an effective method of screening women in the second trimester.

Therefore, the use of abnormal levels of first trimester biomarkers for selecting women for further follow-up with uterine artery Doppler may further improve the clinical discrimination.[101]

Spencer's study showed that both PP-13 and PAPP-A, when coupled with second-trimester mean PI as measured by Doppler velocimetry, provide better prediction over the use of Doppler ultrasonography alone. With a specificity set to 0.80, they got sensitivity for early onset preeclampsia and late onset preeclampsia 0.70 and 0.73 respectively. [81]

2. Thesis project

2.1. Viewpoints and objectives for the current study

Prevention of hypertensive disorders of pregnancy is a big challenge in clinic research. During the past 2 decades, numerous clinical studies and randomized trials were reported. These reports described the use of various methods to reduce the incidence and severity of preeclampsia. Prevention of any disease process requires knowledge of its etiology and pathogenesis, as well as the availability of methods for prediction of those at high risk for this disorder. Hypertensive disorders of pregnancy are disorders of unknown etiology. In addition, it is a clinical syndrome rather than a single disease. The possible causes of this disease include immunologic factors, genetic factors, dietary factors, preexisting medical conditions, or combination of these factors. Therefore it is very unlikely that any single intervention will be effective in preventing this syndrome.

The pathophysiological process of PE begins early in pregnancy; effective preventive strategies depend on early detection of risk, ideally in the first trimester. First trimester screening would clearly represent a major advantage over a second trimester approach because it opens prospects for early and more efficient interventions. In addition, first trimester screening followed by a second trimester screening may improve the prediction of PE by allowing concomitant (data from the same trimester) and/or sequential (data from 2 distinct trimesters) combinations between biological and biophysical data. The purpose of this study is to develop and validate a practical predictive model for PE, based on a combination of tests performed during the routine first and second trimester clinics, associating clinical (risk factors), biological (serum maternal biomarker levels) and velocimetric (UAD indices) data in high-risk pregnant women. An ideal model will offer a good sensitivity at a reasonably low false-positive rate which allows the estimation of a woman's individual risk for PE later in pregnancy and represents a valuable tool in clinical practice.

2.1.1. Study objectives

In this study , considering that the hypertensive disorders of pregnancy has multifactorial origins which involve fetoplacental and angiogenic factors, the combination of different tests represents a promising avenue for the early detection of these disorders. Based on the current knowledge, we propose to investigate combinations of uterine artery Doppler (uaD) analysis, biochemical tests (in early pregnancy, i.e. circulating maternal plasma levels of selected fetoplacental and endothelial biomarkers), socio-demographic and obstetrical characteristics as predictive indexes in our screening method.

2.1.2. Hypothesis:

The combination of uterine artery Doppler, biochemical tests, socio-demographic and obstetrical characteristics will provide a sensitive and specific strategy for an early prediction of the hypertensive disorders of pregnancy, leading to optimized management and prevention.

2.1.3. Objectives:

Primary **–** To elaborate a multivariable prediction model of hypertensive disorders of pregnancy based on the combination of selected maternal serum markers, uterine artery Doppler, socio-demographic and obstetrical characteristics during the 1st trimester.

Secondary –

1. To elaborate a multivariable prediction model of hypertensive disorders of pregnancy based on the combination of uterine artery Doppler, socio-demographic and obstetrical characteristics during the early 2st trimester (16 to 22 gestational weeks).

2. To elaborate a multivariable prediction model of SGA (small for gestational age) based on the combination of selected maternal serum markers, uterine artery Doppler, socio-demographic and obstetrical characteristics during the 1st trimester.

3. To determine if the evolution of velocimetric tests between the 1st and 2nd trimesters improve the prediction of hypertensive disorders of pregnancy.

2.2. Methods

2.2.1 Data sources

This was a prospective cohort screening study for hypertensive disorders of pregnancy in unselected low-risk women with singleton pregnancies. It was based on maternal and perinatal records of women who booked for maternity care and delivered at Saint-Justine hospital, Montreal, in the period between November 2005 and November 2007. Six hundreds and seventy healthy women were included in our study.

The study was approved by the Saint-Justine hospital Research Ethics Committee. Written informed consent was obtained from the women agreeing to participate in the study.

2.2.2. Study design

2.2.2.1. Population

Inclusion criteria:

- Singleton nulliparous pregnancy women
- More than 18 years old
- Followed their antenatal care at Saint-Justine hospital in their pregnancy period
- Expected delivery at Saint-Justine hospital

Exclusion criteria:

- Multiparous pregnant women
- Multiple gestations, e.g. twins, triplets, quadruplets
- Women who had suffered miscarriage or intrauterine death before 24 gestational weeks
- Foetal chromosomal or structural abnormalities

2.2.2.2. Definition:

Gestational hypertension was 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 was confirmed after either overnight rest in hospital or subsequent repeated BP measurements during the next few days visit. Early onset gestational hypertension was defined as gestational hypertension necessitating delivery before 37 week's gestation.

Preeclampsia was defined as two recordings of a systolic / diastolic blood pressure (at least one of which is ≥ 140 / 90 mmHg) measured at least 4 hours apart in previously normotensive women, and proteinuria ≥ 300 mg in a 24-hour, or two reading of at least 2+ on dipstick urinalysis of midstream or catheter urine specimens if 24 hour urine collection was unavailable. Eclampsia is diagnosed when convulsions occur in a woman with preeclampsia. Early on-set preeclampsia was defined as preeclampsia necessitating delivery before 37 week's gestation.

Small-for-gestational-age (SGA) was defined as a newborn's birth weight below the 10^{th} percentile for gestational age.

Preterm birth was defined as birth before 37 weeks' gestational age.

Gestational age was calculated from the last menstrual period, confirmed by ultrasound measurement of crown-rump length at first-trimester. If the date of the last menstrual period was not consistent, gestational age was estimated by ultrasound measurement of crown-rump length at first-trimester.

2.2.2.3 Measurement:

Doppler

For these women, two ultrasound examinations are routinely performed during

pregnancy. The first, at 11 to 14 weeks, is for pregnancy dating and assessment of risk for chromosomal abnormalities by measurement of fetal nuchal translucency thickness. The second, at 17 to 21 weeks, is for measurement of fetal growth and examination for fetal defects. In the cases where no major fetal defects were detected, women were offered the option of participating in the screening study for hypertensive disorder of pregnancy.

Uterine artery Doppler studies were performed by transabdominal sonography by certificated sonographers.

Women were placed in the semirecumbent position and transabdominal ultrasound was used to obtain a view of iliac arteries. Subsequently, color flow mapping was used to identify the uterine arteries as aliasing vessels. Pulsed wave Doppler was used to obtain flow velocity waveforms from the ascending branch of the uterine artery closest point closest. When three similar consecutive waveforms were obtained, the Pulsatility index (PI) and Resistance index (RI) were measured, and the mean PI of the left and right arteries was calculated. The presence or absence of an early diastolic notch in the waveform was recorded. Measurements were performed for both uterine arteries.

Socio-demographic and obstetrical characteristics:

At the first visit (11 to 14 gestational weeks), patients were asked to complete a questionnaire on maternal age, ethnicity, gravidity, parity, height, weight, smoking status, medical history (including chronic hypertension, renal disease, diabetes, cardiac disease, autoimmune disease, symptomatic hyperthyroidism thrombophilia, etc), obstetric history (previous pregnancy outcomes, including the presence of preeclampsia and whether the present pregnancy was from a new partner), and family history of preeclampsia (sister, mother, or both).

Biochemical markers:

Maternal blood samples were obtained by venipuncture. All the serum samples for measurement of pregnancy associated plasma protein A (PAPP-A), free human chorionic gonadotropin-β (β-hCG) , inhibin-A, placental protein 13 (PP13) and a disintegrin and

metalloprotease 12 (ADAM12) levels were collected between 11 to 13+6 gestational weeks. They were allowed to clot into a nonheparinized tube, and centrifuged.
Maternal serum free β-hCG , Inhibin-A and PAPP-A were measured over a period of 5 days on the Kryptor analyzer – a random access immunoassay analyzer using time-resolved amplified cryptate emission (TETHNICITY) technology – and the CIS automated immunofluorescent assays .
All the samples were shipped to Perkin-Elmer Life and Analytical Sciences (Turku, Finland) for analysis of PP13 and ADAM12 using solid-phase sandwich enzyme linked immunosorbent assay (ELISA).

All samples were analyzed by an examiner blinded to the clinical outcome.

Medical recorders, Doppler findings, Socio-demographic and obstetrical characteristics, and the results of biochemical testing were recorded in a computer database at the time of assessment.

Study quality control

Research nurses were trained for good clinical practice and Standard Operational Procedures. All biological tests were performed in the same laboratory under the responsibility of one of the co-investigators (ED). The laboratory of our hospital has been accredited following monitoring processes involving the assessment of the quality laboratory management and technical competence in accordance with the requirements of *the Société du Québec de Biologie Clinique (INTER n QUAL) and of the Ministère de la Santé Publique du Québec.*

2.2.3 Statistic analysis

2.2.3.1 Variables

Dependent variables

Dependent variables included early on-set preeclampsia, gestational hypertension with delivery before 37 gestational weeks, gestational hypertension, preeclampsia,

preterm birth and SGA. The factors that were potentially associated with these progressions were referred as independent or predictive variables. We assessed the sensitivity, specificity, screen-positive value and Likelihood ratios of these models.

Independent variables

Independent variables were Doppler indexes, maternal serum biochemical markers, sociodemographic and obstetrical characteristics. These included: PI, RI, bilateral notch, ethnicity, maternal age, smoking, body mass index (BMI), prior history of gestational hypertension, history of chronic disease, PAPP-A, β-hCG, inhibin-A, PP13 and ADAM12.

All results of maternal serum biochemical marker were expressed as a multiple of the median (MoM) in normal pregnancies and adjusted for gestational age.
SGA and Doppler indexes were expressed as percentiles in normal pregnancies and adjusted for gestational age.

Receiver-operating characteristics (ROC) curve analysis was used to define the appropriate cutoff point for the best combination of sensitivity and specificity as follows: *Mean Pulsatility index ≥ 90 percentiles at the second trimester and IMC =28*. (Table 3)
Because we do not have enough case information (early onset preeclampsia) for the first trimester, so we chose *"mean Pulsatility index ≥ 95 percentiles at the first trimester*", *"the presence of protodiastolic bilateral notch"*, "*free β-hCG ≤0.5MoM*", " *Inhibin-A ≥1.5 MoM*", " *PAPP-A ≤0.5MoM*", "*ADAM12 ≤0.5MoM*" *and* " *PP13≤0.5MoM*" as our study variable as most related studies suggested.

2.2.3.2 Statistic analysis

Differences between groups

The Student t-test was used for normally distributed continuous variables.
The Mann-Whitney test was used for non-normally distributed variables.
Chi -square test or Fisher's exact test was used for categorical variables.

Calculation of risk

Odds ratio (OR) was used as an approximation of the relative risk. An OR approximates how much more likely (or unlikely) the outcome is for those with the condition present (X=1) than among those with its absent (X=0).

Correlation

Spearman's rank correlation was used for a correlation assessment.

Logistic regression analysis

As a first step, univariable analysis was employed to evaluate individual variables (Doppler, biomarkers and maternal characteristics) as potentially significant predictors of pre-eclampsia or other outcomes.

Then, multivariable logistic regression analysis was employed to assess the contribution of each of these variables to our dichotomous outcomes. We used 'method: enter' 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 significant level for a variable to remain in the model.

Hosmer and Lemeshow Goodness-of-Fit test, chi-square goodness-of-fit test, Cox-Snell R^2 and Nagelkerke R^2 values were used to test whether the model's estimates fit the data at an acceptable level or not.

Receiver-operating characteristics (ROC) curve analysis was used to define the best predictors for the outcomes examined and to determine the optimal discriminatory point with the best combination of sensitivity and specificity.

A descriptive analysis was conducted for characteristics of study population and for certain clinical outcomes.

Statistical software

All calculations were performed with SPSS software (Statistical Package for theSocial

Sciences, SPSS Inc, Chicago, USA) version 15.0

Results were considered to be statistically significant when $p < 0.05$.

All tests presented are two-tailed.

2.3. Results

From November 2005 to November 2007, Six hundred and seventy singleton women were included in the study. According to our exclusion criteria, thirty five nulliparous women with missing data and all the thirty seven multiparous women were excluded. In total, the results of five hundred and ninety eight singleton nulliparous women were available for analysis.

2.3.1. General descriptions

Among 598 nulliparous, 20 women developed preeclampsia (3.3%), 7 women developed early onset preeclampsia (1.2%), 52 women developed gestational hypertension (8.7%), 10 women developed gestational hypertension with delivery before 37 weeks (1.7%), 37 women had a preterm birth (6.2%) and 54 women had a SGA newborn (9.0%).

2.3.1.1. Maternal demographic characteristics

Table 4 summarizes the maternal demographic characteristics and pregnancy outcomes of our study population. Mean maternal age was 29.5 years old and mean birth weight was 3400 grams. We had 20 pregnant women developed preeclampsia.

Table 5 shows the comparison results of maternal demographic characteristics between cases and no case groups.

For early onset preeclampsia, gestational hypertension with delivery before 37 weeks, and preterm birth (delivery before 37 weeks), the maternal demographic characteristics (maternal weight, BMI, ethnic African-Car and chronic disease history) are significantly different between cases and the no case groups.

For preeclampsia, the maternal demographic characteristics (maternal weight, BMI and ethnic African-Car) are significantly different between cases and no case groups.

For gestational hypertension, maternal weight, BMI and chronic disease history are significantly different between cases and no case groups.

For the prediction of SGA (birth weight less than the 10^{th} percentile), these maternal demographic characteristics do not differ significantly between cases and no case groups.

2.3.1.2. Maternal serum biochemical markers

Normal pregnancies (no case group)

Table 6 presents the mean and the median value of maternal serum biochemical markers (PAPP-A, free β-hCG, Inhibin-A, PP13 and ADAM12) by gestational age (weeks) in the first trimester in normal pregnancies.

Except for PP13, the mean values and (or) the median values of all the above mentioned biochemical markers show significant differences by the gestational age (weeks).

PAPP-A and ADAM12 are increasing, while free β-hCG and Inhibin-A are decreasing between the 11^{th} and the 13^{+6th} gestational weeks. (Figure 7)

Affected pregnancies (case group)

Table 7 presents the relationship between the serum biochemical markers and the outcomes studied.

Table 7 shows the median MoMs of biomarkers in the outcomes studied. The median MoMs were lower at certain degree depending on the biomarkers when compared with the median MoM of normal pregnancies, especially for PAPP-A.

In our study, *PAPP-A ≤ 0.5MoM* was statistically significantly associated with early onset preeclampsia, gestational hypertension with delivery before 37 gestational weeks, gestational hypertension and preterm birth.

PP13≤ 0.5MoM was statistically significantly associated with early onset preeclampsia, gestational hypertension and SGA.

ADAM12 ≤ 0.5MoM was statistically significantly associated with gestational hypertension, preterm birth and gestational hypertension with delivery before 37 gestational weeks.

Inhibin-A ≥ 1.5 MoM was statistically significantly associated with SGA.

free β-hCG ≤0.5MoM was statistically significantly associated with early onset preeclampsia and SGA.

2.3.1.3. Maternal Doppler results

Table 9 shows that "mean pulsatility index ≥ the 95th percentiles at the first trimester" has statistical significance with SGA, but not with other hypertensive disorders or preterm birth.

"Mean pulsatility index ≥ 90th percentiles at the second trimester" is a very sensitive Doppler index. It has statistical significance with all the diseases involved in our study.

As for normal pregnancies, study results show that mean PI has statistical significant differences between the gestational weeks with attenuating tendency in the first trimester. PI (11weeks) = 1.56, PI (12weeks) = 1.44, PI (13weeks) = 1.27, $p<0.001$. Mean PI shows no statistical difference between 17 and 21^{+6} gestational weeks (mean PI = 0.92, the difference between the gestational weeks p = 0.714) in this study. (Table 11, Figure 8)

Table 10 describes the presence of bilateral notch in the first and the second trimester and their statistical relationship with the diseases being studied. The presences of bilateral notch only in the first trimester or the presence of newly-present bilateral notch in the second trimester do not show any statistical significance with all the outcomes studied.

On the other hand, 'Have bilateral notch at second trimester' and 'bilateral notch with a persistent presence from first trimester to second trimester' shows statistical significance with most outcomes, including early onset preeclampsia, gestational hypertension with delivery before 37 gestational weeks, gestational hypertension and SGA.

2.3.2. Prediction of hypertensive disorders of pregnancy in the first trimester (11 to 13^{+6} gestational weeks)

2.3.2.1. Prediction of early onset preeclampsia

Univariable and multivariable logistic regression analysis showed that there are seven independent variables *(PAPP-A⩽0.5MoM, PP13 ⩽0.5MoM, free β-hCG⩽0.5MoM, BMI⩾28, ethnic African-Car, chronic disease history and maternal age*) which were

significantly associated with the developing of early onset preeclampsia.

Logistic regression model Formula: $e^z / 1+ e^z$

The formula suggested by this prediction model is:

(Pre36w) z = -10.519 + 0.404 (pappa0.5M) -0.100 (pp13_0.5M) +2.68 (hCG_0.5M) + 2.090 (IMC_28) + 0.851 (Eth_AfC) + 2.795 (Mala_pre) + 0.129 (Age)

Notes:
pappa0.5M (PAPP-A ≤ 0.5MoM =1, PAPP-A > 0.5MoM =0),
pp13_0.5M (PP13 ≤ 0.5MoM =1, PP13 > 0.5MoM =0)
hCG_0.5M (free β-hCG ≤ 0.5MoM =1, free β-hCG > 0.5MoM=0)
IMC_28 (BMI ≥28 =1, BMI < 28 =0)
Eth_AfC (ethnic African-Car =1, not ethnic African-Car =0)
Mala_pre (had chronic disease history =1, had not chronic disease history =0)

Example:

If a nulliparous singleton pregnant woman who had the following characteristics: PAPP-A ≤ 0.5MoM, PP13 ≤ 0.5MoM, free β-hCG ≤ 0.5MoM, BMI ≥28, was African-Car ethnic race, had chronic disease history and at 30 years old,

then:

(Pre36w) z = -10.519 + 0.404 (1) -0.100 (1) +2.68 (1) + 2.090 (1) + 0.851 (1) + 2.795 (1) + 0.129 (30)

z = 2.071

P (probability for developing early onset preeclampsia) = exp (2.071) / [1 + exp (2.071)], P = 88.8%

Therefore, this pregnant woman would be estimated to have 88.8% probability of developing preeclampsia.

Using the P = 0.50 as the cut-off point, its corresponding area under ROC curve was 94.9% (95%CI: 90.4% -- 99.5%)

In our study, we wanted a false positive value less than 10%. For this predictive model, according to ROC curve, we choose a false positive value = 3%, then the validity parameters of the model were as follow:

Sensitivity = 71.4%, specificity = 97% and a positive likelihood ratio = 23.8

2.3.2.2. Prediction of gestational hypertension with delivery before 37 weeks

Univariable and multivariable logistic regression analysis showed that there are six independent variables *(PAPP-A⩽0.5MoM, ADAM12 ⩽0.5MoM, BMI⩾28*, *ethnic African-Car, chronic disease history and maternal age*) which were significantly associated with the developing of gestational hypertension with delivery before 37 weeks.

The formula suggested by this prediction model is:

(Htag36w) z = -7.842 + 1.187 (pappa0.5M) + 0.963 (adam12_0.5M) + 1.198 (IMC_28)

+ 1.644 (Eth_AfC) + 1.698 (Mala_pre) + 0.086 (Age)

Notes:
pappa0.5M (PAPP-A ≤ 0.5MoM =1, PAPP-A > 0.5MoM =0),
adam12_0.5M (adam12 ≤ 0.5MoM =1, adam12 > 0.5MoM =0)
IMC_28 (BMI ≥28 =1, BMI < 28 =0)
Eth_AfC (ethnic African-Car =1, not ethnic African-Car =0)
Mala_pre (had chronic disease history =1, had not chronic disease history =0)

Example:

If a nulliparous singleton pregnant woman who had the following characteristics: PAPP-A ≤ 0.5MoM, ADAM12 ≤ 0.5MoM, BMI ≥28, was African-Car ethnic race, had chronic disease history and at 30 years old,

then:

(Htag36w) z = -7.842 + 1.187 (1) + 0.963 (1) + 1.198 (1) + 1.644 (1) + 1.698 (1)

+ 0.086 (30)

z = 1.43

P (probability for developing gestational hypertension with delivery before 37 weeks)

= exp (1,43) / [1 + exp (1,43)],

P = 80.7%

Therefore, this pregnant woman would be estimated to have 80.7% probability of

developing gestational hypertension with delivery before 37 weeks.

Using the P = 0.50 as the cut-off point, its corresponding area under ROC curve was 85.2% (95%CI: 71.9% -- 98.6%)

According to ROC curve, we choose a false positive value = 8.5%, then the validity parameters of the model were:

Sensitivity = 60.0%, specificity = 91.5% and a positive likelihood ratio = 7.1

2.3.2.3. Prediction of other hypertensive disorders of pregnancies, preterm birth and SGA

Table 12 part 1 shows that from 11 to 13^{+6} gestational weeks our predictive models of preeclampsia, gestational hypertension, preterm birth and SGA do not have an optimum area under the ROC curve (Less than 75%) or a good sensitivity when we choose a false positive value around 10%.

Therefore, our models do not provide good predictive value for the diseases mentioned above in the first trimester.

2.3.3. Prediction of hypertensive disorders of pregnancy in second trimester (17 to 21^{+6} gestational weeks)

2.3.3.1. Prediction of early onset preeclampsia

Univariable analysis showed that the independent variables *(PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history, maternal age, mean pulsatility index ≥ the 90 percentile and bilateral notch with a persistent presence from first trimester to second trimester*) were significantly associated with developing early onset preeclampsia.

In multivariable logistic regression analysis, *PAPP-A≤0.5MoM, PP13 ≤0.5MoM and maternal age* were removed in our model because their p value are higher than 0.100. In

our model, following parameters were significantly associated with developing of early onset preeclampsia: *free β-hCG≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history, mean pulsatility index ≥ 90 percentiles and bilateral notch with a persistent presence from the first trimester to second trimester.*

The formula suggested by this prediction model is:

(Pre36w) z = (Pre36w) z = -8.768 + 3.614 (hCG_0.5M) + 1.212 (IMC_28) + 0.326 (Eth_AfC) + 2.164 (Mala_Pre) + 3.539 (PI2_per90) + 1.693 (notchB_con)

Notes:
hCG_0.5M (free β-hCG ≤ 0.5MoM =1, free β-hCG > 0.5MoM=0)
IMC_28 (BMI ≥28 =1, BMI < 28 =0)
Eth_AfC (ethnic African-Car =1, not ethnic African-Car =0)
Mala_pre (had chronic disease history =1, had not chronic disease history =0)
PI2_per90 (mean pulsatility index ≥ 90 percentiles = 1, mean pulsatility index < 90 percentiles = 0)
notchB_con (bilateral notch with a persistent presence from first trimester to second trimester =1, otherwise =0)

Example:

If a nulliparous singleton pregnant woman who had the following characteristics: free β-hCG ≤ 0.5MoM, BMI ≥28, was African-Car ethnic race, had chronic disease history, mean pulsatility index ≥ 90 percentiles and bilateral notch with a persistent presence from first trimester to second trimester,

then:

(Pre36w) z = -8.768 + 3.614 (1) + 1.212 (1) + 0.326 (1) + 2.164 (1) + 3.539 (1) + 1.693 (1)

z = 3.78

P (probability for developing early onset preeclampsia) = exp (3.78) / [1 + exp (3.78)],

P = 97.8%

Therefore, this pregnant woman would be estimated to have 97.8% probability of developing preeclampsia.

Using the P = 0.50 as the cut-off point, its corresponding area under ROC curve was 97.5% (95%CI: 94.7% -- 100.0%)

For this predictive model, according to ROC curve, we choose a false positive value = 9.9%, then the validity parameters of the model were as follow:
Sensitivity = 100%, specificity = 90.1% and a positive likelihood ratio = 10.1

2.3.3.2. Prediction of gestational hypertension with delivery before 37 weeks

Univariable analysis showed that there are eight independent variables *(PAPP-A⩽0.5MoM, ADAM12 ⩽0.5MoM, BMI⩾28*, *ethnic African-Car, chronic disease history maternal age, mean pulsatility index ⩾ 90 percentiles and bilateral notch with a persistent presence from first trimester to second trimester*) which were significantly associated with developing gestational hypertension with delivery before 37 weeks.
In multivariable logistic regression analysis, *maternal age* was removed in our model because p value is higher than 0.100. In this model, parameters which were significantly associated with developing gestational hypertension with delivery before 37 weeks includes *PAPP-A⩽0.5MoM, ADAM12 ⩽0.5MoM, BMI⩾28*, *ethnic African-Car, chronic disease history, mean pulsatility index ⩾ 90 percentiles and bilateral notch with a persistent presence from the first trimester to second trimester.*

The formula suggested by this prediction model is:

(Htag36w) z = -5.970 + 0.273 (pappa0.5M) + 1.918 (adam12_0.5M) + 1.015 (IMC_28)

+ 1.206 (Eth_AfC) + 1.317 (Mala_Pre) + 2.692 (PI2_per90) + 0.742 (notchB_con)

Notes:
pappa0.5M (PAPP-A ≤ 0.5MoM =1, PAPP-A > 0.5MoM =0),
adam12_0.5M (adam12 ≤ 0.5MoM =1, adam12 > 0.5MoM =0)
IMC_28 (BMI ≥28 =1, BMI < 28 =0)
Eth_AfC (ethnic African-Car =1, not ethnic African-Car =0)
Mala_pre (had chronic disease history =1, had not chronic disease history =0)
PI2_per90 (mean pulsatility index ≥ 90 percentiles = 1, mean pulsatility index < 90 percentiles = 0)
notchB_con (bilateral notch with a persistent presence from first trimester to second trimester =1, otherwise =0)

Example:

If a nulliparous singleton pregnant woman who had the following characteristics:

PAPP-A ≤ 0.5MoM, ADAM12 ≤ 0.5MoM, BMI ≥28, was African-Car ethnic race, had chronic disease history, mean pulsatility index ≥ the 90 percentile and bilateral notch with a persistent presence from first trimester to second trimester,
then:

(Htag36w) z = -5.970 + 0.273 (1) + 1.918 (1) + 1.015 (1) + 1.206 (1) + 1.317 (1)

+ 2.692(1) + 0.742 (1)

z = 3.193

P (probability for developing gestational hypertension with delivery before 37 weeks)
= exp (3.193) / [1 + exp (3.193)],
P = 96.1%
Therefore, this pregnant woman would be estimated to have 96.1% probability of developing gestational hypertension with delivery before 37 weeks.

Using the P = 0.50 as the cut-off point, its corresponding area under ROC curve was 87.4% (95%CI: 71.7% -- 100.0%)
According to ROC curve, we choose a false positive value = 4.3%, then the validity parameters of the model were:
Sensitivity = 77.8%, specificity = 85.7% and a positive likelihood ratio = 8.1

2.3.3.3. Prediction of preeclampsia

Univariable and multivariable logistic regression analysis showed that there are five independent variables *(PAPP-A⩽0.5MoM, ethnic African-Car, BMI⩾28*, *maternal age and mean pulsatility index ≥ the 90 percentile)* which were significantly associated with developing preeclampsia.

The formula suggested by this prediction model is:

(Pre) z = -7.524 + 0.840 (pappa0.5M) + 0.830 (Eth_Afc) + 1.246 (IMC_28) + 0.098

(Age) + 1.461 (PI2_per90)

Notes:
pappa0.5M (PAPP-A ≤ 0.5MoM =1, PAPP-A > 0.5MoM =0),
IMC_28 (BMI ≥28 =1, BMI < 28 =0)
Eth_AfC (ethnic African-Car =1, not ethnic African-Car =0)
Mala_pre (had chronic disease history =1, had not chronic disease history =0)
PI2_per90 (mean pulsatility index ≥the 90 percentile = 1, mean pulsatility index < the 90 percentile = 0)

Example:

If a nulliparous singleton pregnant woman who had the following characteristics: PAPP-A ≤ 0.5MoM, was African-Car ethnic race, had chronic disease history, BMI ≥28 and mean pulsatility index ≥the 90 percentile,

then:

(Pre) z = -7.524 + 0.840 (1) + 0.830 (1) + 1.246 (1) + 0.098 (1) + 1.461 (1)

z = 3.049

P (probability for developing preeclampsia)
= exp (3.049) / [1 + exp (3.049)],
P = 95.5%
Therefore, this pregnant woman would be estimated to have 95.5% probability of developing preeclampsia.

Using the P = 0.50 as the cut-off point, its corresponding area under ROC curve was 75.0% (95%CI: 60.0% -- 90.0%)
According to ROC curve, we choose a false positive value = 9.1%, then the validity parameters of the model were:
Sensitivity = 60.0%, specificity = 90.9% and a positive likelihood ratio = 6.6

2.3.3.4. Prediction of other hypertensive disorders of pregnancies, preterm birth and SGA

Table 12 part 2 shows that between 17 and 21+6 gestational weeks our predictive models of gestational hypertension, preterm birth and SGA do not have a good area under the

ROC curve (Less than 75%) or a good sensitivity at the false positive value of around 10%.
Therefore, our models do not have good predictive value for the above mentioned diseases in the second trimester.

As a summary for our study results, mean PI at the 2nd trimester as a single marker had the highest sensitivity (83.3%) and specificity (88.5%) in the screening test of preeclampsia with a false positive value of 11.5%, LR = 7.2 (p=0.003). Compared with mean PI, the predictive value of "the presence of persistent bilateral notch" was lower (sensitivity 66.7%, specificity 83.9%, FPV 16.1%, LR 4.1, p=0.033). Analysis of different combinations revealed that the combination of maternal characteristics has higher predictive values (sensitivity 83.3%, specificity 91.0%, FPV 9.0%, LR 9.3, p=0.002) than the combination of maternal serum biomarkers (sensitivity 66.7%, specificity 88.5%, FPV 11.5%, LR 5.8, p=0.032). The combination of maternal characteristics, maternal serum and uterine artery Doppler has the best predictive values (sensitivity 100%, specificity 90.1%, FPV 9.9%, LR 10.1, p<0.001). (Table 12, Table 13, Figure 9)

After our multivariable logistic regression analysis, we got the good predictive models for early onset preeclampsia and gestational hypertension with delivery before 37 weeks in the second trimester. We got the moderate predictive models for preeclampsia in the second trimester, early onset preeclampsia and gestational hypertension with delivery before 37 weeks in the first trimester. (Table 12)

Conclusion

The purpose of this thesis is to improve our screening method for the prediction and risk estimation of hypertensive disorders of pregnancy, preterm birth and SGA in the first and second trimester in the antenatal health care unit.

The research was based on maternal characteristic information, biochemical analysis, Doppler results and statistical data from medical files, with the purpose of looking for an improved screening method which is simple, inexpensive, reproducible, widely and easily used, non-invasive and can be carried out in early pregnancy to allow for more efficient preventive or therapeutic intervention.

Maternal demographic characteristics

Comparing the results of maternal demographic characteristics between the case group and the no case group, our findings show that:

Increased maternal BMI (≥28) was the most popular and important factor leading to hypertensive disorders of pregnancy and preterm birth. This result agrees with the theory that obese and preeclamptic women share common features such as dyslipidemia, hyperinsulinemia, insulin resistance and impaired endothelial function, which are related to inflammation and altered vascular function. These shared features are consistent with the premise that obesity is a risk factor for preeclampsia due to preexisting inflammation and inflamed vasculature.[102]

"Ethnic African-Car" and "had a chronic disease history" were the second and the third major risk factors for developing these diseases. African Americans are known as one of the ethnic group that has the highest rate of hypertension and diabetes mellitus in the world[35,103]. The underlying genetic factors may have a strong relationship with developing hypertensive disorders of pregnancy, same as those observed in chronic disease conditions.

The last risk factor is the older maternal age. In our study, we excluded women less than 18 years old of age. So we could not find the contribution of teenage pregnancies.

But for SGA, these maternal demographic characteristics did not differ significantly between SGA and non-SGA groups.

Maternal serum biomarkers

The biochemical tests, which compared normal pregnant women with those who developed hypertensive disorders of pregnancy, show that:
"Maternal serum PAPP-A level ≤ 0.5 MoM" was the most sensitive biomarker for hypertensive disorders of pregnancy and preterm birth.
"ADAM12≤ 0.5 MoM, PP13≤ 0.5MoM" were good predictive biomarkers for the gestational hypertension.
"Inhibin-A ≥1.5 MoM" was found to have statistic significance with SGA, but not with hypertensive disorders of pregnancy and preterm birth. Note that our serum samples were collected in the first trimester (11 to 13^{+6} weeks). S.Mut. mentioned that inhibin A has better predictive value of hypertensive disorders at later gestational weeks.[104] Therefore, we need further studies to verify that.

Doppler results

Lots of researchers suggest that pregnancies with increased risk of developing hypertensive disorders and related complications already have abnormally increased uterine artery pulsatility index in early pregnancy. This provides a very useful predictive value for early onset preeclampsia. In our study, however, "mean pulsatility index ⩾ the 95 percentile at first trimester" only showed statistical significance with SGA, not with other hypertensive disorders or preterm birth. This could be due to the small sample size of our study -- only 7 cases of early onset preeclampsia with 2 of them not having complete Doppler information in the first visit. This affects the reliability of our study result.
As for normal pregnancies, our study results show that mean PI has statistical significant differences by gestational age with attenuating tendency in the first trimester.
This decrease in vascular resistance in fetoplacental circulation with advancing gestation could be the consequence of the increase in the number of vessels, and their relative

volume, within the chorionic villi and an expansion of the intervillous circulation as evidenced by the coinciding fall in uterine arterial resistance. This agrees with the findings in some previous studies which suggested that the fall in fetoplacental vascular resistance with increasing gestation could lead to a reduction in the fetal cardiac workload in normal pregnancies.[105]

"Mean pulsatility index $\geqslant$ the 90th percentile in the second trimester" is a very sensitive Doppler index. It showed statistical significance with all the outcomes in our study. This result indicates that in this gestational stage the abnormal uterine artery circulation developed more and more visibly. This is due to the fact that the process of physiological adaptation of the spiral arteries is usually completed around 22nd weeks of pregnancy. Therefore, Doppler assessment of the uterine arteries at second trimester is a useful tool in determining whether placentation has developed normally. Hence mean PI became one of the most reliable parameters in our screening program.
In normal pregnancies, mean PI showed no statistical difference between 17 and 21^{+6} gestational weeks in this study. This is different than that in the first trimester.

Studies showed that the persistence of an early diastolic "notch" in the flow velocity waveform indicates an insufficient physiological conversion of the spiral arteries and it depended mainly on vessel wall compliance. This is different than PI which is determined by vascular resistance distal to the uterine artery. [106]
Hence, "presence of bilateral notch" became another independent Doppler index which has also been extensively studied.
Our study analyzed the relationship between the diseases interested and the five notch conditions – **"**have bilateral notch at first trimester", "have bilateral notch at second trimester", "the presence of bilateral notch only at first trimester", "newly-present bilateral notch at second trimester", and "bilateral notch with a persistent presence from first trimester to second trimester".
Our results showed that "have bilateral notch at second trimester" and "bilateral notch with a persistent presence from first trimester to second trimester" has statistical significance with most of the outcomes studied, including early onset preeclampsia,

gestational hypertension, gestational hypertension with delivery before 37 weeks and SGA. Meanwhile, **"**have bilateral notch at first trimester" , "the presence of bilateral notch only at first trimester" or "newly-present bilateral notch at second trimester" failed to show any statistical significance with any of the diseases interested in our study. Hence, we chose "bilateral notch with a persistent presence from the first trimester to the second trimester" as a predictor in our logistic regression model.

Based on the previous study results, we decided to develop a combinative screening method which combines the advantages of each single screening method.

ROC analysis revealed that the combination of maternal characteristics, maternal serums and uterine artery Doppler in the second trimester have significant predictive values for hypertensive disorders, preterm birth and SGA in second trimester.

In our study, mean PI at the 2^{nd} trimester as a single marker had the highest sensitivity and specificity in the screening test of preeclampsia. Compared to mean PI, the predictive value of "the presence of persistent bilateral notch" was lower. Analysis of different combinations revealed that the combination of maternal characteristics has higher predictive values than the combination of maternal serum biomarkers. The combination of maternal characteristics, maternal serums and uterine artery Doppler has the best predictive values

In addition, screening with a combination of maternal characteristics, serum biomarkers and uterine artery Doppler was found to be particularly effective in identifying women who develop severe early onset preeclampsia rather than late onset disease, preterm birth or SGA. For a false-positive rate of 10%, the sensitivity for early onset preeclampsia was 71.4% compared to 57.9% for late preeclampsia in the first trimester, and 100% compared to 60% for late preeclampsia in the second trimester. This is particularly important because it is the early preeclampsia rather than the late preeclampsia that is associated with increased risks of perinatal mortality and morbidity as well as both short-term and long-term maternal complications.

No statistically significant relationship was found between the hypertensive disorders and Doppler indexes (mean PI, presence of bilateral notch) in the first trimester. After combining the maternal characteristics with serum biomarkers, some predictive values were obtained, but no as good as those in the second trimester.

Suggestions for future work

This study has the limitation of being a single-center study with small sample size and not having enough Doppler information in the first trimester. This limitation could be overcome in future studies with longer time period and increased number of participants.

Meanwhile, our studies have demonstrated the potential value of first-trimester screening for hypertensive disorders of pregnancy with a combination of maternal characteristics, maternal serum testing and sonographic assessment. Our models allow the identification of women requiring increased surveillance throughout pregnancy or preventive treatments such as low-dose aspirin or heparin. Moreover, it is a pragmatic approach: the predictive model was successful in identifying women at higher risk of early onset PE, the most clinically relevant form of the disease; it is quite easy to implement this new screening as an add-on procedure to the current Down's syndrome screening, taking advantage of an existing screening program at a relatively low cost. This integration in existing prenatal screening enables an easier transfer of new knowledge into clinical practice.

In conclusion, our study shows that the mean PI at 2^{nd} trimester has the highest predictive efficacy among the markers being analyzed. The results indicate that maternal characteristics are suffic effic important in screening for the preeclampsia. Serum biomarkers have modest efficacy in our predictive models. However, adding these maternal measurements to uterine artery Doppler velocimetry results in a clinically significant improvement in the prediction of hypertensive disorders of pregnancy.

The efficacy of this screening method is to be further verified in our ongoing study with increased sample sizes. Whether early therapeutic intervention in high-risk groups can

reduce the prevalence of the disease also remains to be determined. If a successful model is obtained, randomized controlled trials will become feasible in high-risk populations.

LIST OF TABLES

Table 1. Effect of hypertensive disorders in pregnancy on small for gestational age (< the 10th percentile) and stillbirth

	Odds ratio	Adjusted 95% CI	*P* value
Small for gestational age*			
Normotensive women	1.0	-	-
Hypertensive women (any type)	1.8	1.7,1.9	<0.001
Gestational hypertension without proteinuria	1.5	1.4,1.6	<0.001
Gestational hypertension withproteinuria	3.3	3.0,3.9	<0.001
Pre-existing hypertension	2.5	2.1,2.9	<0.001
Stillbirth**			
Normotensive women	1.0	-	-
Hypertensive women (any type)	1.4	1.1,1.8	0.02
Gestational hypertension without proteinuria	1.1	0.8,1.5	0.60
Gestational hypertension with proteinuria	1.6	0.9,2.9	0.08
Pre-existing hypertension	3.2	1.9,5.4	<0.001

CI denotes Confidence interval. * Adjusted for smoking, maternal age, gestational diabetes, pre-existing diabetes, maternal anemia, nulliparity, marital status, drug abuse, prepregnancy weight, weight gain, antenatal steroids, twins and infant sex. ** Adjusted for smoking, maternal autoantibodies, maternal age, pre-existing diabetes, maternal anemia,prepregnancy weight and twins.

(From: Allen, V.M et al. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. BMC Pregnancy Childbirth 4,2004)

Table 2. Risk factors of hypertensive disorders of pregnancy

Pregnancy associated risk factors • Nulliparity / Multiple / polyhydramnios /Primipaternity /Teenage pregnancy • Older age /Interval between pregnancies • Previous history of preeclampsia • Limited sperm exposure, Donor insemination, Oocyte donation • Partner who fathered a preeclamptic pregnancy • Hydrops fetalis • Hydatidiform moles
Chronic risk factors • Chronic hypertension, renal disease, cardiovascular disease • Obesity, insulin resistance • Gestational , type 1 and type 2 diabetes • Activated protein kinase C resistance • Protein S deficiency • Antiphospholipid antibodies • Hyperhomocysteinemia • Sick cell disease, sickle cell trait • Urinary infection
Hereditary risk factors • Family history of preeclampsia • Ethnicity (African-American and Hispanic women in the US) • Structural congenital anomalies • Chromosomal anomalies (trisomy 13, triploidy)
Other risk factors • Stress, work related psychosocial strain

Table 3. Receiver-operating characteristics (ROC) curve analysis for appropriate cutoff point of IMC and Mean Pulsatility index at the second trimester.

	Index	Chose value	Sensibility	1 - Specificity	percentiles	Area under curve (95%CI) (%)	p
Preterm+PE	IMC	28	0.778	0.130		79.3 (61.2-97.3)	0.008
	PI2	1.265	1.00	0.099	90	94.6 (91.1-98.1)	0.000

Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia

Table 4. Demographic characteristics and pregnancy outcomes of the study population (n = 598)

Maternal variables	N	Mean	Median	Minimum	Maximum	Range
Maternal age (years)	598	29.5	29.0	18.0	43.0	25.0
Weight (kg)	598	64.3	61.5	41.8	148.4	106.6
BMI	594	23.8	22.5	17.0	50.0	33.0
Height (m)	594	1.6	1.65	1.2	1.9	.6
Birth weight (g)	598	3339.5	3400.0	645.0	4850.0	4205.0
Gestational age (weeks)	595	39.1	39.0	24.0	42.0	18.0
	N				**Frequency**	**Percent**
Ethnic group	598		Caucasian		486	81.3
			African-American		37	6.2
			Mid-Eastern		27	4.5
			Hispanic		17	2.8
			Asian		9	1.5
			Mixed/others		22	3.7
Have chronic diseases before this pregnancy	598		No chronic disease		566	94.6
			diabetics		4	.7
			Chronic hypertension		7	1.2
			Renal disease		3	.5
			Cardiac disease		7	1.2
			Autoimmune disease		4	.7
			Symptomatic hyperthyroid		1	.2
			Thrombophilia		6	1.0
Partner information	597	New father			582	97.3
		Not a new father			15	2.5
				Has a preeclampsia history wife	1	6.7
Smoking status	598		Nonsmoker		563	94.1
			Smoker		35	5.9
Baby sex	598		Male		301	50.3
			Female		297	49.7
Delivery mode	594		vaginal		451	75.9
			Caesarean		143	24.1
Hypertensive disorders of pregnancies	598		Eclampsia		0	00.0
			Preeclampsia		20	3.3
			Gestational hypertension		52	8.7
			Early-onset preeclampsia		7	1.2
			Gestational hypertension with delivery before 37 weeks		10	1.7
Preterm birth	598				37	6.2
SGA (≤10 percentiles)	598				54	9.0

Table 5. Prescriptive demographic characteristics stratified by selected outcomes

	N		Mean (95%CI) years		p
Age	yes	no	yes	no	
Preterm+PE	7	585	32.4(28.6—36.3)	29.5(29.2—29.9)	.107
Preterm+GH	10	582	32.0 (29.1—35.0)	29.5 (29.2—29.9)	.088
Preterm	36	556	29.8 (28.2—31.3)	29.5 (29.2—29.9)	.413
PE	20	572	31.5 (29.6—33.4)	29.5 (29.1—29.9)	.066
GH	52	540	29.9 (28.6—31.2)	29.5 (29.1—29.9)	.689
SGA	54	538	29.2 (28.0—30.5)	29.6 (29.2—29.9)	.716
BMI	N		Mean (95%CI)		p
	yes	no	yes	no	
Preterm+PE	7	581	30.5 (23.7—37.3)	23.7 (23.4—24.1)	.008
Preterm+GH	10	578	30.2 (25.0—35.4)	23.7 (23.4—24.1)	.001
Preterm	36	552	26.5 (24.3—28.7)	23.7 (23.3—24.0)	.010
PE	20	568	27.6 (25.1—30.2)	23.7 (23.3—24.1)	.001
GH	52	536	27.5 (25.8—29.2)	23.5 (23.1—23.8)	.001
SGA	54	534	24.4 (22.9—25.9)	23.8 (23.4—24.2)	.921
Weight	N		Mean (95%CI) kg		p
	yes	no	yes	no	
Preterm+PE	7	585	81.8 (62.8—101.0)	64.1 (63.0—65.1)	.021
Preterm+GH	10	582	80.8(66.3—95.3)	64.1 (63.0—65.0)	.009
Preterm	36	556	71.2(65.3—77.1)	63.8 (62.8—64.9)	.021
PE	20	572	74.5(67.3—81.8)	63.9 (62.9—64.9)	.001
GH	52	540	73.8(69.0—78.5)	63.4 (62.3—64.4)	.001
SGA	54	538	64.4(60.3—68.5)	64.3 (63.2—65.3)	.361
Gestational weeks	N		Mean (95%CI) weeks		p
	yes	no	yes	no	
Preterm+PE	7	585	35.0(34.1—36.0)	39.1 (39.0—39.3)	.001
Preterm+GH	10	582	35.2(34.5—35.9)	39.1 (39.0—39.3)	.001
Preterm	36	556	34.4(33.5—35.3)	39.4 (39.3—39.5)	.001
PE	20	572	37.6(36.5—38.6)	39.1 (39.0—39.3)	.001
GH	52	540	38.2(37.7—38.7)	39.1 (39.0—39.3)	.001
SGA	54	538	39.1(38.9—39.2)	39.1 (38.4—39.3)	.323
Birth weight	N		Mean (95%CI) grams		p
	yes	no	yes	no	
Preterm+PE	7	585	1914.6(1491.6—2337.5)	3357.2(3317.9—3396.4)	.001
Preterm+GH	10	582	2126.2(1763.6—2488.8)	3361.0(3321.8—3400.1)	.001
Preterm	36	556	2311.9(2109.0—2515.0)	3406.7(3371.5—3441.8)	.001
PE	20	572	2819.5(2411.4—3227.6)	3358.3(3318.9—3397.8)	.002
GH	52	540	3057.5(2866.2—3248.8)	3367.3(3326.9—3407.7)	.001
SGA	54	538	2652.5(2547.9—2757.1)	3409.1(3369.8—3448.5)	.001

Ethnic African-Car	N		Percentage (%)		Chi-Square		Odds Ratio
	yes	no	yes	no	Pearson	Fisher's	(95% CI)
Preterm+PE	2 /7	35/588	28.6	6.0		.065	6.3(1.2—33.7)
Preterm+GH	3 /10	34/585	30.0	5.8		.020	6.9(1.8—28.1)
Preterm	8 /37	29/558	21.6	5.2	.001		5.0(2.1—12.0)
PE	5 /20	32/578	25.0	5.5		.005	5.7(1.9—16.6)
GH	6 /52	31/546	11.5	5.7	.094		2.2(0.9—5.5)
SGA	6 /54	31/538	11.1	5.8	.122		2.0(0.8—5.1)

Chronic disease history*	N		Percentage (%)		Chi-Square		Odds Ratio
	yes	no	yes	no	Pearson	Fisher's	(95% CI)
Preterm+PE	3 /7	29/588	42.9	4.9		.004	14.5(3.1—67.6)
Preterm+GH	4 /10	28/585	40.0	4.8		.001	13.3(3.5—49.7)

Preterm	6 /37	26/558	16.2	4.7	.003		4.0(1.5—10.3)
PE	3 /20	29/578	15.0	5.0		.085	3.3(0.9—12.1)
GH	6 /52	26/546	11.5	4.8	.050		2.6(1.02—6.7)
SGA	5 /54	27/538	9.3	5.0		.200	1.9(0.7—5.2)

BMI= weight / height^2
Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia
Preterm+GH : Delivery before 37 gestational weeks + Gestational hypertension
Preterm : Preterm birth, delivery before 37 gestational weeks
PE : Preeclampsia
GH : Gestational hypertension
SGA: birth weight less than the 10th percentile
*Chronic disease history (at least has one of them): diabetes, chronic hypertension, thrombophilie, symptomatic hyperthyroid, autoimmune, renal and cardiac disease.

Table 6. Maternal serum biochemical markers in *normal pregnancies from 11 to 13^{+6} gestational weeks

	n	mean (95%CI)	Std.deviation	median	n		p
					> median	≤ median	
PAPP-A (IU/L)							
11w	107	1.70 (1.51—1.88)	.96	1.45	25	82	.001
12w	315	2.89 (2.68—3.11)	1.95	2.39	149	166	
13w	165	4.44 (3.95—4.93)	3.49	3.77	115	50	
Free β-hCG (µg/L)							
11w	100	59.79 (52.82—66.75)	35.10	54.45	58	42	.034
12w	286	59.52 (54.68—64.36)	41.60	48.15	143	143	
13w	151	50.18 (45.29—55.07)	30.40	40.80	67	84	
Inhibin-A (ng/L)							
11w	86	315.17 (285.20—345.15)	139.82	281.20	49	37	.004
12w	241	288.75 (271.38—306.13)	136.94	254.20	122	119	
13w	123	251.62 (231.14—272.11)	114.75	238.30	55	68	
PP13 (pg/ml)							
11w	78	81.99 (74.86—89.11)	31.61	77.39	41	37	.867
12w	211	79.92 (75.95—83.89)	29.25	75.77	105	106	
13w	109	81.66 (72.76—90.57)	46.91	73.65	53	56	
ADAM12 (ng/ml)							
11w	78	494.68 (453.66—529.70)	168.65	474.00	24	54	.001
12w	211	575.69 (549.58—601.80)	192.41	534.00	99	112	
13w	109	663.12 (623.30—702.94)	209.76	658.00	76	33	

*Normal pregnancies: pregnancies without adverse outcomes

Table 7. The relationship between serum biochemical markers and diseases studied

	N			Percentage (%)		Odds Ratio (95% CI)	P
	total	yes	no	yes	no		
PAPP-A (≤ 0.5MoM)							
Preterm+PE	585	4 / 7	125 / 578	57.14	21.63	4.83 (1.07—21.87)	0.05
Preterm+GH	585	6 / 10	123 / 575	60.00	21.39	5.51 (1.53—19.84)	0.01
Preterm	585	13 / 37	116 / 548	35.14	21.17	2.02 (1.00—4.08)	0.05
PE	587	9 / 19	121 / 568	47.37	21.30	3.33 (1.32—8.37)	0.01
GH	587	24 / 51	106 / 536	47.06	19.78	3.61 (2.00—6.50)	0.001
SGA	582	15 / 53	113 / 529	28.30	21.36	1.45 (0.77—2.74)	0.25
Free β-hCG (≤ 0.5MoM)							
Preterm+PE	585	3 / 7	60 / 578	42.86	10.38	6.48 (1.42—29.62)	0.03
Preterm+GH	585	3 / 10	60 / 575	30.00	10.43	3.68 (0.93—14.60)	0.08
Preterm	585	4 / 37	59 / 548	10.81	10.77	1.00 (0.34—2.94)	1.00
PE	587	3 / 19	61 / 568	15.79	10.74	1.56 (0.44—5.50)	0.45
GH	587	7 / 51	57 / 536	13.73	10.63	1.34 (0.58—3.11)	0.50
SGA	582	11 / 53	52 / 529	20.75	9.83	2.40 (1.17—4.95)	0.02
Inhibin-A (≥ 1.5MoM)							
Preterm+PE	493	1 / 7	96 / 486	14.29	19.75	0.68 (0.08—5.69)	1.00
Preterm+GH	493	1 / 10	96 / 483	10.00	19.88	0.45 (0.06—3.58)	0.70
Preterm	493	7 / 33	90 / 460	21.21	19.57	1.11 (0.47—2.63)	0.82
PE	494	4 / 15	93 / 479	26.67	19.42	1.51 (0.47—4.85)	0.51
GH	494	6 / 44	91 / 450	13.64	20.22	0.62 (0.25—1.52)	0.30
SGA	492	4 / 49	93 / 443	8.16	20.99	0.34 (0.12—0.95)	0.04
ADAM12 (≤ 0.5MoM)							
Preterm+PE	438	1 / 7	11 / 431	14.29	2.55	6.36 (0.71—57.43)	0.18
Preterm+GH	438	2 / 10	10 / 428	20.00	2.34	10.45 (1.96—55.60)	0.03
Preterm	438	3 / 32	9 / 406	9.38	2.22	4.56 (1.17—17.78)	0.05
PE	438	1 / 14	11 / 424	7.14	2.59	2.89 (0.35—24.07)	0.33
GH	438	4 / 41	8 / 397	9.76	2.02	5.26 (1.51—18.29)	0.02
SGA	437	3 / 42	9 / 395	7.14	2.28	3.30 (0.86—12.69)	0.10
PP13 (≤ 0.5MoM)							
Preterm+PE	438	2 / 7	25 / 431	28.57	5.80	6.50 (1.20—35.16)	0.06
Preterm+GH	438	2 / 10	25 / 428	20.00	5.84	4.03 (0.81—19.99)	0.12
Preterm	438	3 / 32	24 / 406	9.38	5.91	1.65 (0.47—5.79)	0.44
PE	438	2 / 14	25 / 424	14.29	5.90	2.66 (0.56—12.54)	0.21
GH	438	7 / 41	20 / 397	17.07	5.04	3.88 (1.53—9.83)	0.002
SGA	437	7 / 42	20 / 395	16.67	5.06	3.75 (1.48—9.48)	0.003

Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia
Preterm+GH : Delivery before 37 gestational weeks + Gestational hypertension
Preterm : Preterm birth, delivery before 37 gestational weeks
PE : Preeclampsia
GH : Gestational hypertension
SGA: birth weight less than the 10^{th} percentile

Table 8. The median MoMs for biomarkers in the outcome groups

	PAPP-A	hCG	Inhibine-A	ADAM12	PP13
Preterm+PE	0.33	0.57	0.73	0.89	0.65
Preterm+GH	0.36	0.64	0.94	0.82	0.65
Preterm	0.76	1.08	1.07	0.77	0.85
PE	0.53	0.70	0.80	0.91	0.79
GH	0.52	0.79	0.96	0.89	0.79
SGA	0.62	0.85	0.88	1.03	0.83

Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia
Preterm+GH : Delivery before 37 gestational weeks + Gestational hypertension
Preterm : Preterm birth, delivery before 37 gestational weeks
PE : Preeclampsia
GH : Gestational hypertension
SGA: birth weight less than the 10^{th} percentiles

Table 9. Abnormal doppler pulsatility index in the 1st and 2nd trimester outcomes

PI1_Per95	N			Percentage (%)		Odds Ratio (95% CI)	p
	total	yes	no	yes	no		
Preterm+PE	552	1 / 5	27 / 547	20.0	4.9	4.8 (0.5—44.6)	0.23
Preterm+GH	552	1 / 8	27 / 544	12.5	5.0	2.7 (0.3—23.0)	0.34
Preterm	552	1 / 33	27 / 519	3.0	5.2	0.6 (0.1—4.3)	1.00
PE	553	1 / 16	27 / 537	6.3	5.0	1.3 (0.2—9.9)	0.57
GH	553	4 / 46	24 / 507	8.7	4.7	1.9 (0.6—5.8)	0.28
SGA	550	6 / 46	22 / 504	13.0	4.4	3.3 (1.3—8.6)	0.01
PI2_Per90							
Preterm+PE	487	5 / 6	51 / 481	83.3	10.6	42.2(4.8—367.9)	0.001
Preterm+GH	487	7 / 9	49 / 478	77.8	10.3	30.6(6.2—151.6)	0.001
Preterm	487	8 / 29	48 / 458	27.6	10.5	3.3 (1.4—7.7)	0.005
PE	489	7 / 16	50 / 473	43.8	10.6	6.6 (2.3—18.4)	0.001
GH	489	14 / 44	43 / 445	31.8	9.7	4.4 (2.1—8.9)	0.001
SGA	486	11 / 42	45 / 444	26.2	10.1	3.1 (1.5—6.7)	0.002

Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia
Preterm+GH : Delivery before 37 gestational weeks + Gestational hypertension
Preterm : Preterm birth, delivery before 37 gestational weeks
PE : Preeclampsia
GH : Gestational hypertension
SGA: birth weight less than the 10th percentiles
PI1_per95 : mean pulsatility index ≥ 95th percentile in the first trimester
PI2_per90 : mean pulsatility index ≥ 90th percentile in the second trimester

Table 10. Bilateral notch and diseases studied

1.	**Have bilateral notch at first trimester**						
		N		Percentage (%)		Odds Ratio (95% CI)	p
	total	yes	no	yes	no		
Preterm+PE	580	4 / 6	226 / 574	66.70	39.40	3.08 (0.56—16.95)	0.221
Preterm+GH	580	6 / 9	224 / 571	66.70	39.20	3.10 (0.77—12.51)	0.166
Preterm	580	16 / 36	214 / 544	44.40	39.30	1.23 (0.63—2.43)	0.544
PE	581	7 / 18	223 / 563	38.90	39.60	0.97 (0.37—2.54)	0.951
GH	581	21/ 50	209 / 531	42.00	39.40	1.12 (0.62—2.01)	0.715
SGA	578	26 / 53	204 / 525	49.10	38.90	1.52 (0.86—2.67)	0.148
2.	**Have bilateral notch at second trimester**						
Preterm+PE	522	5 / 6	127 / 516	83.30	24.60	15.32 (1.77—132.32)	0.005
Preterm+GH	522	6 / 9	126 / 513	66.70	24.60	6.14 (1.51—24.92)	0.010
Preterm	522	11 / 31	121 / 491	35.50	24.60	1.68 (0.78—3.61)	0.178
PE	525	8 / 18	125 / 507	44.40	24.70	2.45 (0.94—6.33)	0.058
GH	525	21 / 49	112 / 476	42.90	23.50	2.44 (1.33—4.46)	0.003
SGA	521	18 / 47	114 / 474	38.30	24.10	1.96 (1.05—3.66)	0.032
3.	**No bilateral notch at first trimester and have bilateral notch at second trimester**						
Preterm+PE	515	1 / 6	52 / 509	16.67	10.22	1.76 (0.20—15.34)	0.48
Preterm+GH	515	1 / 9	52 / 506	11.11	10.28	1.09 (0.13—8.90)	1.00
Preterm	515	3 / 31	50 / 484	9.68	10.33	0.93 (0.27—3.17)	1.00
PE	516	3 / 17	50 / 499	17.65	10.02	1.92 (0.54—6.93)	0.40
GH	516	7 / 48	46 / 468	14.58	9.83	1.57 (0.67—3.69)	0.30
SGA	514	5 / 46	48 / 468	10.87	10.26	1.07 (0.40—2.83)	0.90
4.	**Have bilateral notch at first trimester and no bilateral notch at second trimester**						
Preterm+PE	515	0 / 6	120 / 509	0	23.58	0.99 (0.97—0.99)	0.34
Preterm+GH	515	1 / 9	119 / 506	11.11	23.52	0.41 (0.05—3.28)	0.69
Preterm	515	5 / 31	115 / 484	16.13	23.76	0.62 (0.23—1.64)	0.39
PE	516	2 / 17	118 / 499	11.76	23.65	0.43 (0.10—1.91)	0.38
GH	516	7 / 48	113 / 468	14.58	24.15	0.54 (0.23—1.23)	0.14
SGA	514	10 / 46	110 / 468	21.74	23.50	0.90 (0.44—1.88)	0.78
5.	**Have bilateral notch at first trimester and second trimester**						
Preterm+PE	515	4 / 6	73 / 509	66.67	14.34	11.95(2.15—66.40)	0.005
Preterm+GH	515	5 / 9	72 / 506	55.56	14.23	7.54 (1.98—28.73)	0.005
Preterm	515	8 / 31	69 / 484	25.80	14.26	2.09 (0.90—4.87)	0.08
PE	516	5 / 17	72 / 499	29.41	14.43	2.47 (0.85—7.22)	0.155
GH	516	14 / 48	63 / 468	29.17	13.46	2.65 (1.35—5.21)	0.004
SGA	514	13 / 46	64 / 468	28.26	13.68	2.49 (1.24—4.98)	0.008

Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia
Preterm+GH : Delivery before 37 gestational weeks + Gestational hypertension
Preterm : Preterm birth, delivery before 37 gestational weeks
PE : Preeclampsia
GH : Gestational hypertension
SGA: birth weight less than the 10^{th} percentile

Table 11. Mean *PI and the prevalence of the 95th percentile PI, the 90th percentile PI and Bilateral Notch in *normal pregnancies

Gestational weeks	Mean PI			Bilateral Notch		*95th PI		*90th PI	
	n	Mean PI (95% CI)	p	n	Percentage(%)	n	Percentage(%)	n	Percentage (%)
11 —11^{+6}	95	1.56 (1.45 – 1.67)	< 0.001	47	48	4	4.2		
12 —12^{+6}	268	1.44 (1.38 – 1.51)		116	70	13	4.9		
13 —13^{+6}	144	1.27 (1.20 – 1.35)		44	43	7	4.9		
Total	507			209		24			
17 —17^{+6}	17	0.92 (0.80 – 1.04)	= 0.714	7	41			1	5.9
18 —18^{+6}	84	0.95 (0.88 – 1.00)		25	30			8	9.5
19 —19^{+6}	180	0.91 (0.88 – 0.95)		42	22			18	10.2
20 —20^{+6}	134	0.90 (0.85 – 0.95)		29	21			13	9.9
21 — 21^{+6}	30	0.85 (0.79 – 0.92)		6	20			3	10.0
Total	325			109					43

*PI: mean pulsatility index
*Normal pregnancies: pregnancies without adverse outcomes
*95^{th} PI: The 95^{th} percentile PI in first trimester
*90^{th} PI : The 90^{th} percentile PI in second trimester

Table 12 . Area under ROC curve and the validity parameters of the predictive model

	Area under curve (95%CI) (%)	False Positive Value (%)	Sensitivity (%)	Specificity (%)	LR(+)	p
11 – 13+6 Gestational weeks						
Preterm+PE	94.9 (90.4—99.5)	3.0	71.4	97.0	23.8	.001
Preterm+GH	85.2 (71.9—98.6)	8.3	60.0	91.7	7.2	.001
Preterm	71.9 (61.3—82.6)	11.9	46.9	88.1	3.9	.001
PE	73.0 (59.5—86.5)	9.0	57.9	91.0	6.4	.001
GH	68.6 (59.5—86.5)	12.5	46.3	87.5	3.7	.001
SGA	59.4 (48.9—70.0)	8.5	27.0	91.5	3.1	.058
17 – 21+6 Gestational weeks						
Preterm+PE	97.5 (94.7—100.0)	9.9	100.0	90.1	10.1	.001
Preterm+GH	87.4 (71.7—100.0)	4.3	77.8	95.7	18.1	.001
Preterm	63.6 (51.4—75.9)	12.1	41.1	87.9	3.4	.001
PE	75.0 (60.0—90.0)	9.1	60.0	90.9	6.6	.001
GH	73.6 (63.7—83.4)	11.4	48.6	88.6	4.3	.001
SGA	68.9 (59.4—78.4)	7.3	28.1	71.9	3.8	.001

Preterm+PE : Delivery before 37 gestational weeks + Preeclampsia.
(Predictors in the model:
First trimester: PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history and maternal age
Second trimester: PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history, maternal age, mean pulsatility index ≥ the 90th percentile and bilateral notch with a persistent presence from first trimester to second trimester)
Preterm+GH : Delivery before 37 gestational weeks + Gestational hypertension.
(Predictors in the model:
First trimester: PAPP-A≤0.5MoM, ADAM12 ≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history and maternal age
Second trimester: PAPP-A≤0.5MoM, ADAM12 ≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history maternal age, mean pulsatility index ≥ 90 percentiles and bilateral notch with a persistent presence from first trimester to second trimester
PE : Preeclampsia.
(Predictors in the model:
Second trimester: PAPP-A≤0.5MoM, ethnic African-Car, BMI≥28, maternal age and mean pulsatility index ≥ the 90 percentile
Preterm : Preterm birth, delivery before 37 gestational weeks.
GH : Gestational hypertension.
SGA: birth weight less than the 10th percentile

Table 13. Predictive values of different combinations for early on-set preeclampsia (2nd trimester)

	Area under curve (95%CI) (%)	False Positive Value (%)	Sensitivity (%)	Specificity (%)	LR(+)	p
*A total combination	97.5 (94.6 –100.0)	9.9	100	90.1	10.0	.001
*Biomarkers combination	75.5 (50.7—100.0)	11.5	66.7	88.5	5.8	.032
*Maternal characteristics combination	86.5 (69.5 –100.0)	9.0	83.3	91.0	9.3	.002
Mean *PI at 17 to 21+6 weeks	85.9 (68.5 –100.0)	11.5	83.3	88.5	7.2	.003
Persistent bilateral notch	75.3 (53.0 –97.6)	16.1	66.7	83.9	4.1	.033

*A total combination: PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history, maternal age, mean pulsatility index ≥ the 90th percentile and bilateral notch with a persistent presence from first trimester to second trimester

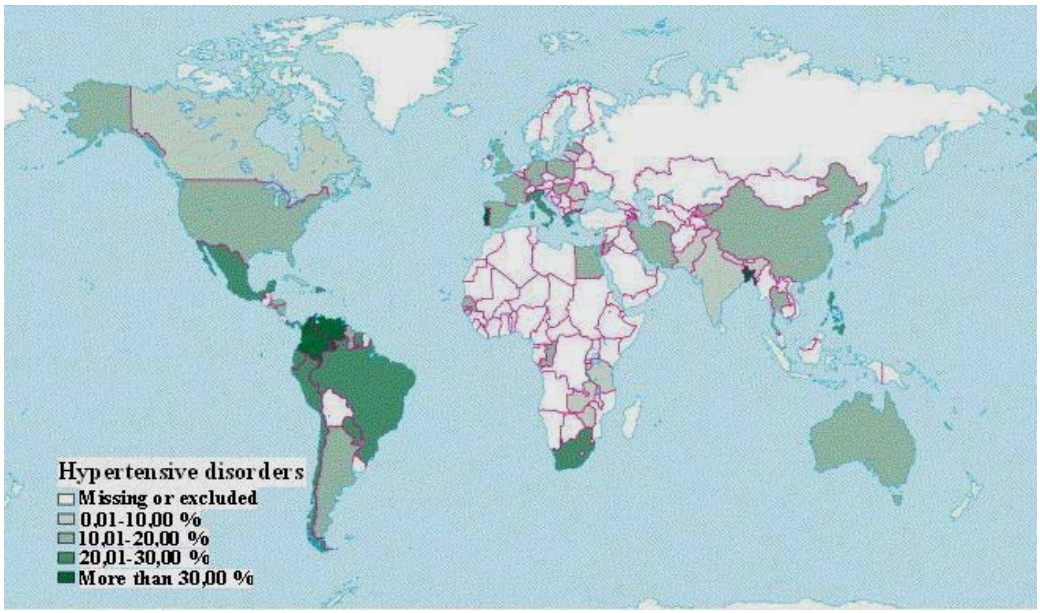
*Biomarkers combination: PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM

*Maternal characteristics combination: BMI≥28, ethnic African-Car, chronic disease history, maternal age

*PI: mean pulsatility index

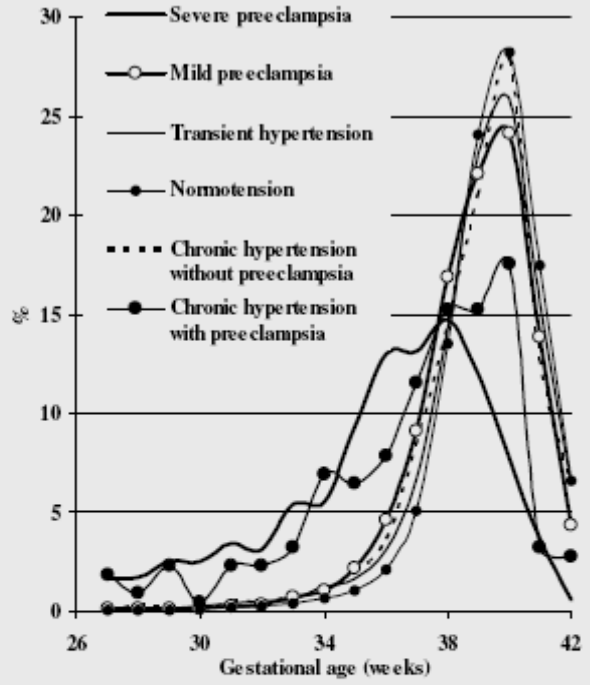
LIST OF FIGURES

Figure 1. Country distribution of hypertensive disorders of pregnancy as cause of maternal deaths



(From: Khan, K.S., Wojdyla, D., Say, L., Gulmezoglu, A.M. & Van Look, P.F. WHO analysis of causes of maternal death: a systematic review. Lancet 367,2006)

Figure 2. Different hypertensions and their preterm birth rates.



	Preterm (n)	%	95% CI	Median gestational age (days)
Normotension	10237	5.0	4.9–5.1	280
Transient hypertension	260	8.1	7.3–9.1	279
Mild preeclampsia	544	9.7	8.9–10.5	277
Severe preeclampsia	1048	48.2	46.1–50.3	259
Chronic hypertension without preeclampsia	80	8.9	7.2–10.9	279
Chronic hypertension with preeclampsia	75	34.6	28.6–41.1	268

(From: Rasmussen, S. & Irgens, L.M. The effects of smoking and hypertensive disorders on fetal growth. BMC Pregnancy Childbirth 6, 2006))

Figure 3. The uteroplacental blood supply

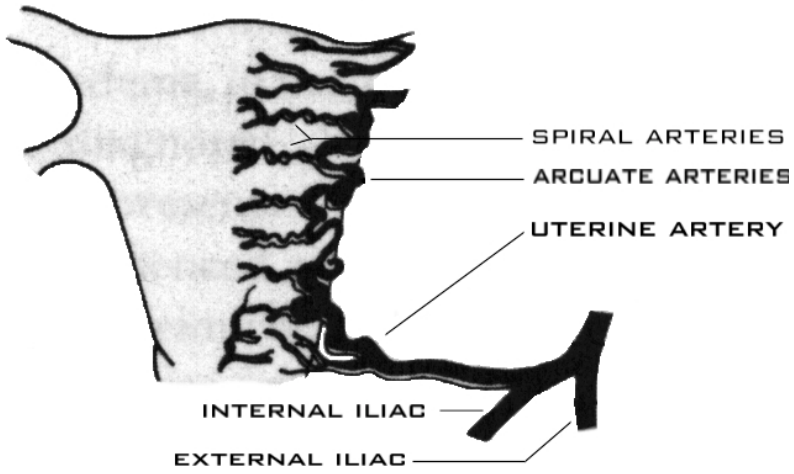


Figure 4. Normal third trimester uteroplacental flow velocity waveform with high diastolic flow.

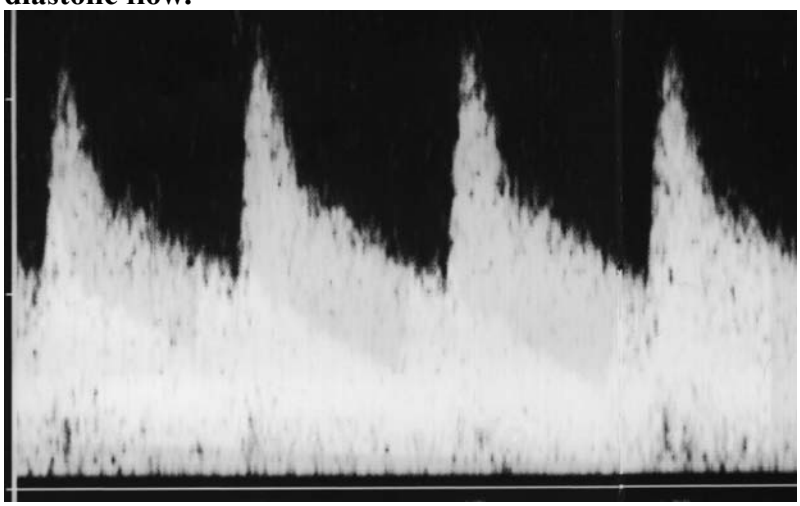


Figure 5. Diagrammatic representation of the Doppler indices and diastolic notch

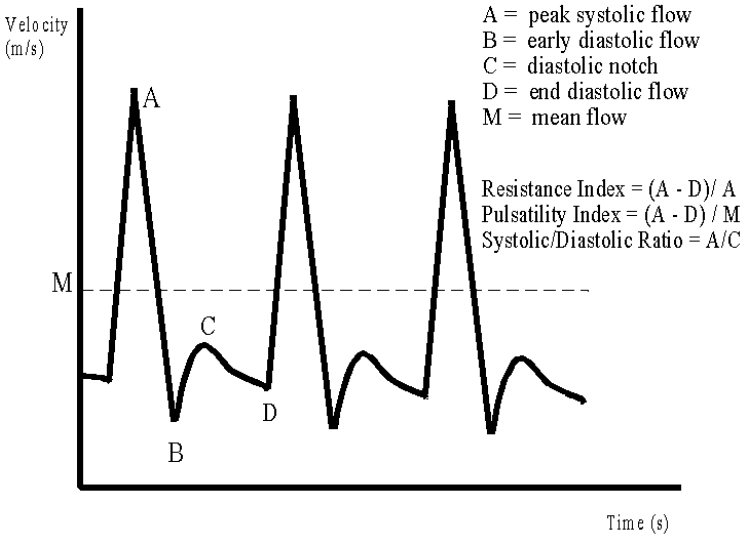


Figure 6. Abnormal FVW with decreased diastolic flow and pronounced diastolic notch.

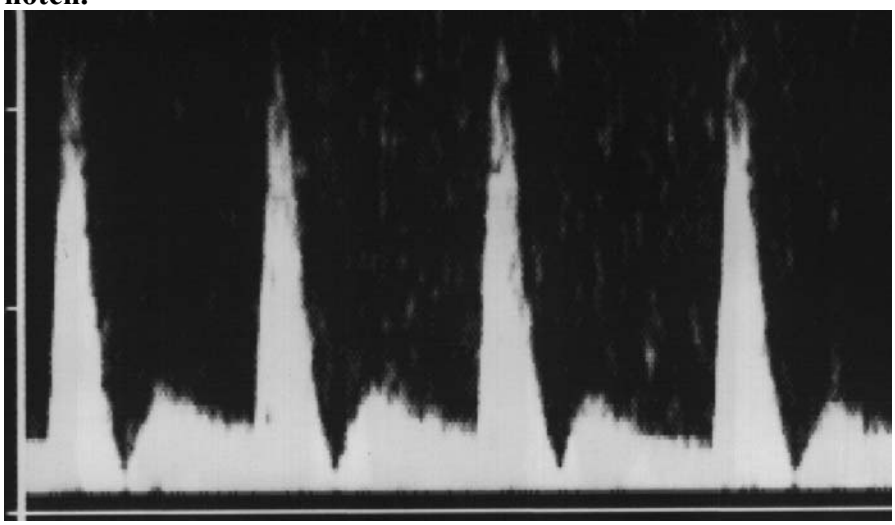


Figure 7. Maternal biochemical markers median tendency in first trimester

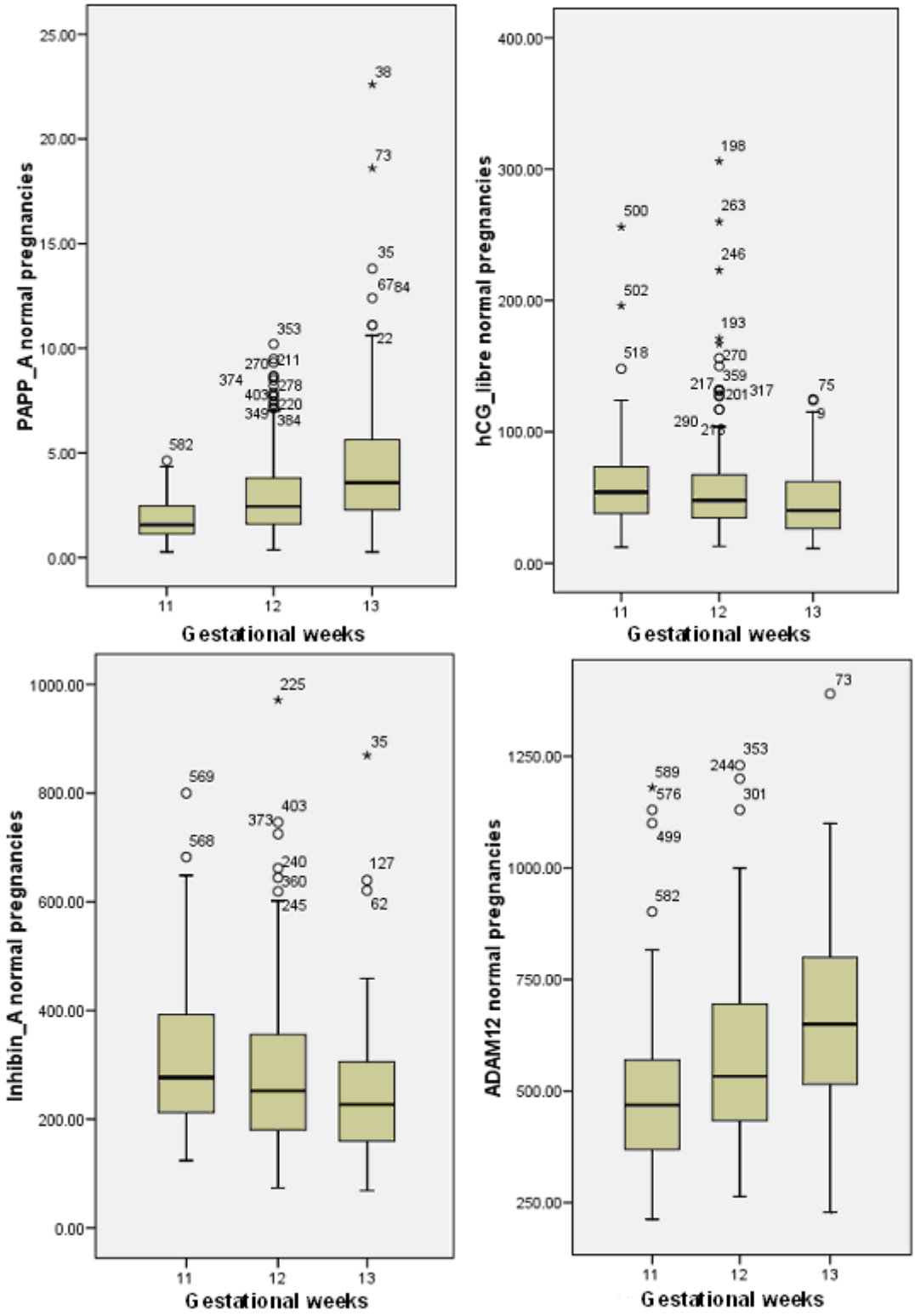


Figure 8. Mean PI in different gestational weeks in normal pregnancy

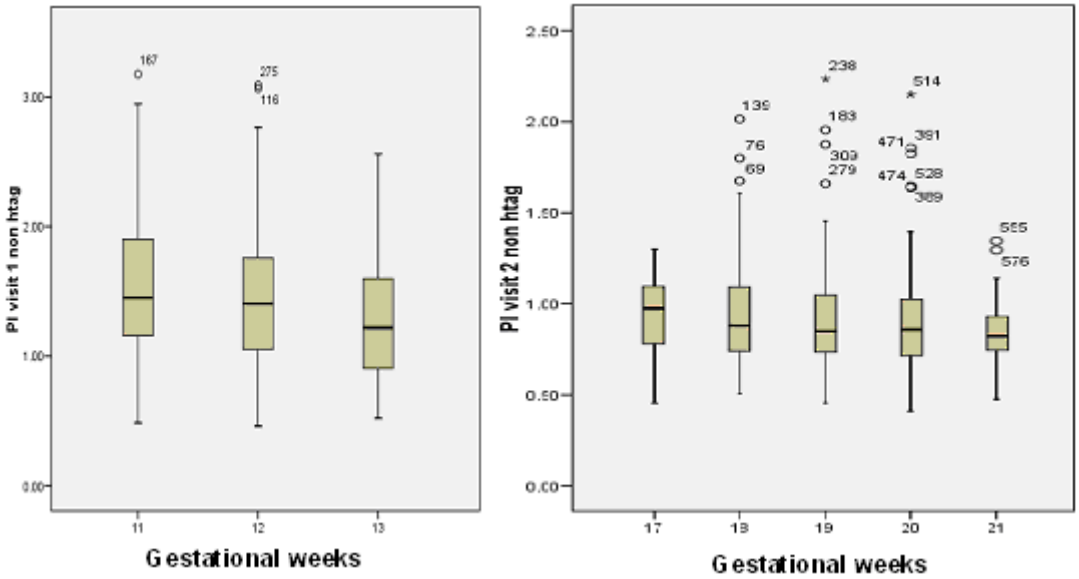
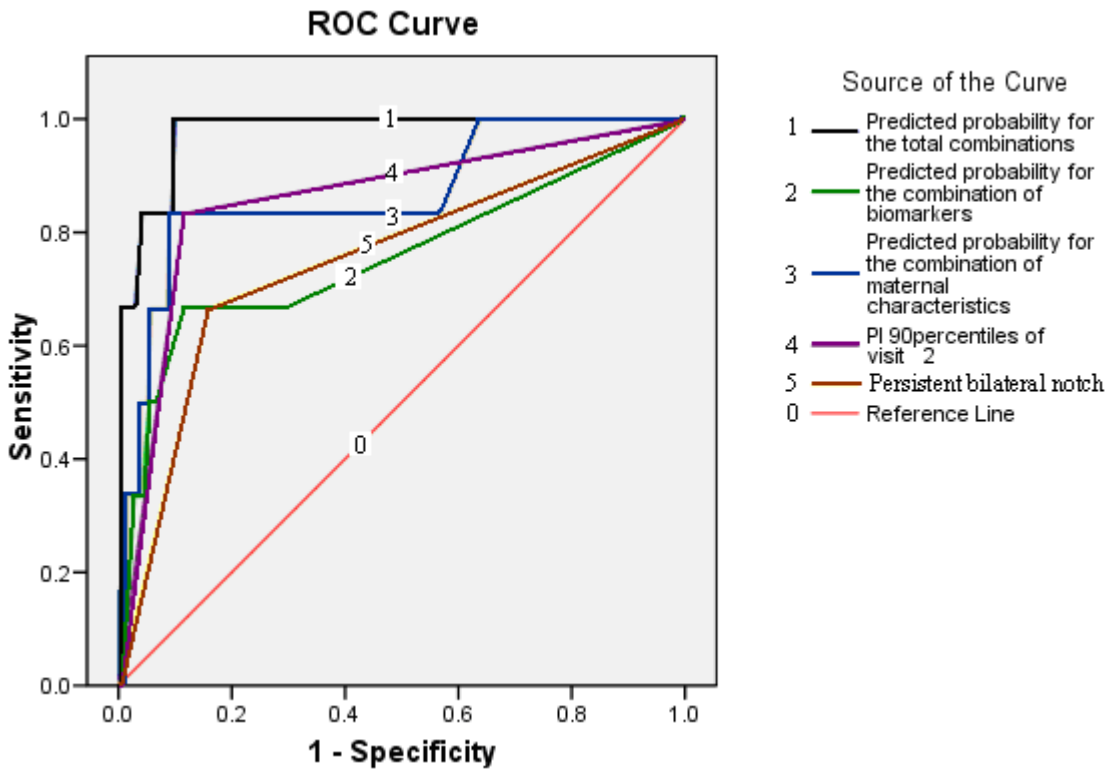


Figure 9.Combination and predictive values for early onset preeclampsia



1*A total combination: PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM, BMI≥28, ethnic African-Car, chronic disease history, maternal age, mean pulsatility index ≥ the 90th percentile and bilateral notch with a persistent presence from first trimester to second trimester
2*Biomarkers combination: PAPP-A≤0.5MoM, PP13 ≤0.5MoM, free β-hCG≤0.5MoM
3*Maternal characteristics combination: BMI≥28, ethnic African-Car, chronic disease history, maternal age

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Formulaires d’information et de consentement

1. FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

TITRE DE L'ÉTUDE : Stratégie de dépistage précoce du risque de prééclampsie par marqueurs sériques maternels et Doppler des artères utérines: Étude pilote à l'Hôpital Sainte-Justine

Chercheur principal (Hôpital Sainte-Justine): François Audibert, MD

Collaborateurs de l'Hôpital Sainte-Justine: Edgard Delvin, MD
William Fraser, MD
Zhong-Cheng Luo, PhD
Lucie Morin, MD
Evelyne Rey, MD
Lise Tremblay, PhD
Françoise Rypens, MD

Nous vous invitons à participer à une étude ayant pour but d'étudier des tests de dépistage précoce de la prééclampsie, une maladie de la grossesse caractérisée par l'apparition d'une hypertension artérielle et de protéines dans l'urine.

Cette étude est financée par le Centre de Recherche de l'Hôpital Sainte-Justine et les Instituts de Recherche en Santé du Canada (IRSC).

Prenez tout le temps nécessaire pour lire les lignes qui suivent. Pour plus d'informations, n'hésitez pas à poser des questions au personnel de l'étude.

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1. Pourquoi mener une telle étude?

Les médecins responsables de cette enquête souhaiteraient vérifier la faisabilité de cette étude au sein de notre établissement hospitalier avant de mettre en place une étude clinique de grande envergure qui aura lieu dans plusieurs centres hospitaliers. L'étude a pour objectif général d'élaborer un test de prédiction de la prééclampsie qui reposera sur la combinaison de certains tests sanguins et échographiques (Doppler utérin) au cours de la grossesse. Environ 2000 femmes enceintes seront recrutées pour participer à cette étude.

2. En quoi consiste ma participation à l'étude?

Avec votre permission, le personnel de recherche pourra avoir accès à votre dossier médical et saisir les données cliniques concernant votre statut de grossesse, les traitements que vous aurez reçu et les événements qui auront eu lieu du début de votre grossesse jusqu'à votre accouchement. L'infirmière de recherche vous posera également quelques questions afin d'évaluer votre risque de prééclampsie. Votre participation à cette enquête implique un test sans risques pour vous ou votre bébé (doppler) effectué en même temps que l'échographie du 1er trimestre qui consiste à mesurer le flot sanguin des artères utérines. Cette mesure sera effectuée une deuxième fois au 2ième trimestre de la grossesse lors de votre échographie de routine. Ces tests seront combinés à une prise de sang qui déterminera le niveau dans votre sang de certaines protéines associées au fonctionnement placentaire. La prise de sang du premier trimestre sera faite en même temps que les prélèvements pour le dépistage de la trisomie 21 et nécessitera de prendre 4ml de sang supplémentaire (soit moins d'une cuillère à thé). La deuxième prise de sang ne sera pas combinée à des tests de routine, nous devrons prélever 8 ml de sang soit environ 2 cuillères à thé. Ce projet représente la première étape d'une étude de plus grande envergure. Cependant, dans l'éventualité qu'aucun support financier ne soit obtenu pour poursuivre cette étude, et qu'une partie des tests biochimiques ne puissent être complétés, l'investigateur s'engage à détruire les échantillons sanguins prélevés.

3. Quels sont les bénéfices reliés à ma participation?

Les résultats de ces tests ne seront pas utilisés avant d'avoir obtenu les conclusions de l'étude. En conséquence, votre participation ne modifiera pas la prise en charge de votre grossesse, ni la surveillance ni les traitements qui vous seront proposés, mais conduira à une meilleure compréhension et un meilleur dépistage de la prééclampsie.

4. Quels sont les risques potentiels reliés à ma participation?

Il n'y a aucun risque pour vous ou votre bébé lors de l'échographie et du Doppler. L'étude pourrait allonger la durée de votre échographie d'une durée de 5 à 10 minutes. Les réactions reliées aux prélèvements sanguins sont, le plus souvent, une irritation locale et une douleur légère. Un petit saignement et/ou une petite contusion momentanée (un bleu) pourraient survenir.

5. Y a-t-il d'autres options possibles?

Si vous refusez de participer à cette étude, le dépistage du premier trimestre pour la trisomie 21 sera effectué comme convenu sans ajouter le doppler pour le dépistage de la préeclampsie.

6. Comment la confidentialité est-elle assurée?

Toutes les informations recueillies dans le cadre de ce projet de recherche seront traitées de façon confidentielle. Pour ce faire, les renseignements pouvant vous identifier seront codés et gardés sous clés pour une période de 5 ans suivant la fin de l'étude. À moins qu'il n'en soit autrement exigé par la loi, les seules personnes qui auront accès directement à votre dossier médical dans le cadre de l'étude sont les responsables de l'étude, les membres du Comité d'éthique de la recherche de l'Hôpital Sainte-Justine et les inspecteurs des organismes de réglementation gouvernementale.

Par ailleurs, les résultats de cette étude pourront être publiés ou communiqués dans un congrès scientifique mais aucune information pouvant vous identifier ne sera alors dévoilée.

7. Pouvez-vous refuser de faire partie de cette étude?
Votre participation à cette étude se fait sur une base entièrement volontaire. Vous pouvez choisir de ne pas participer à l'étude ou vous en retirer à tout moment sans justification de votre part. Votre refus de participer ou votre décision de vous retirer n'affectera d'aucune façon la qualité des soins que vous recevrez au cours de votre grossesse ou durant et après votre accouchement.

8. Communication des résultats

Aucun résultats personnel des tests de recherche ne vous sera communiqué mis à part les résultats lié au dépistage de la trisomie 21.

9. Responsabilité des chercheur(e)s
En signant ce formulaire de consentement, vous ne renoncez à aucun de vos droits prévus par la loi. De plus, vous ne libérez pas les investigateurs de leur responsabilité légale et professionnelle advenant une situation qui vous causerait préjudice.

10. Qui devez-vous contacter si vous avez des questions?
Pour toute question concernant l'étude ou pour tout dommage que vous subiriez en lien avec l'enquête, veuillez contacter le médecin, Dr François Audibert qui est responsable de cette étude à l'hôpital Sainte-Justine, en lui téléphonant au (514) 345-4706.

En tout temps vous pouvez contacter l'infirmière de recherche : Valérie Tremblay au (514) 345-4931 poste 6827.

Pour toute question concernant vos droits en tant que participante à une étude, vous pouvez contacter la conseillière à la clientèle de l'Hôpital Sainte-Justine au (514) 345-4749.

Il est important de bien comprendre ce qui suit avant de signer ce document. Vous recevrez une copie signée de ce formulaire de consentement .

Consentement

Participante
J'ai lu et compris ce formulaire de consentement. J'ai pu discuter avec le(la) professionnel(le) de la santé qui m'a expliqué le but de l'étude ainsi que les risques et bénéfices qui lui sont associés. On a répondu à toutes mes questions. J'accepte de participer volontairement et librement à cette étude et j'autorise l'accès à mon dossier médical.

_____
Nom de la participante (lettres moulées)

_____ _____
Signature de la participante **Date**

Investigateur (ou personne déléguée)
Le projet de recherche a été décrit à la participante ainsi que les modalités de la participation. Un membre de l'équipe de recherche (chercheur ou infirmière de recherche) a répondu ses questions et lui a expliqué que la participation au projet de recherche est libre et volontaire. L'équipe de recherche s'engage à respecter ce qui a été convenu dans le formulaire de consentement.

_____
Nom de l'investigateur (lettres moulées)

_____ _____
Signature **Date**

FORMULAIRE D'EXPOSÉ DE CAS

Visite 1

VÉRIFICATION DE L'ÉLIGIBILITÉ

CRITÈRES D'INCLUSION
La patiente peut être ELIGIBLE à l'enquête si elle a répondu « OUI » à tous les critères d'inclusion suivants :

La patiente est enceinte entre 11 et 14 semaines	NON ☐	OUI ☐
A au moins 18 ans	NON ☐	OUI ☐
Parle une langue connue du personnel médical	NON ☐	OUI ☐
Accouchement prévu à l'hôpital Sainte-Justine	NON ☐	OUI ☐

CRITÈRES D'EXCLUSION
Indiquer si la patiente présente l'une des conditions médicales suivantes en cochant la case appropriée.

Grossesse multiple	NON ☐	OUI ☐
Âge gestationnel >14 semaines à la première visite	NON ☐	OUI ☐

Date à laquelle la patiente a signé le consentement dans le cadre de cette étude
(jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐

ÉVALUATION INITIALE DU RISQUE DE PRÉÉCLAMPSIE

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	

FORMULAIRE D'EXPOSÉ DE CAS

HISTOIRE MÉDICALE

a. **Date de naissance** (jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐

b. **Ethnie** Caucasienne ☐ Afro-américaine ☐ Asiatique ☐
Hispanique ☐ Autre/mixte ☐

c. **Histoire médicale obstétricale** :

Gravida ☐ Para ☐

Grossesses antérieures

Année	Issue grossesse	Age gestationnel	Prééclampsie	Autres pathologies / remarques

d. **Condition médicale préexistante** :

Diabète type I	NON ☐	OUI ☐
Diabète type II	NON ☐	OUI ☐
Hypertension chronique	NON ☐	OUI ☐
Maladie rénale	NON ☐	OUI ☐
Maladie cardiaque	NON ☐	OUI ☐
Maladie autoimmune	NON ☐	OUI ☐
Hyperthyroïdie symptomatique	NON ☐	OUI ☐
Thrombophilie	NON ☐	OUI ☐

Autre (préciser)

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	

FORMULAIRE D'EXPOSÉ DE CAS

ÉVALUATION INITIALE DU RISQUE DE PRÉÉCLAMPSIE (SUITE)

INDICE DE MASSE CORPORELLE (IMC)

Poids (Kg) ☐ Taille (m) ☐

RISQUE DE PRÉÉCLAMPSIE ASSOCIÉ AU PARTENAIRE

Nouveau père NON ☐ OUI ☐

Si vous avez sélectionné NON ci-haut, sélectionner OUI ou NON aux choix suivants :

Partenaire ayant déjà eu un enfant avec une femme prééclamptique NON ☐ OUI ☐

Même partenaire que la grossesse précédente NON ☐ OUI ☐

USAGE DU TABAC

Généralement, fumez-vous des cigarettes ? NON ☐ OUI ☐

Présentement la participante :

1 Fume la cigarette tous les jours Si oui : Nombre/jour = ☐☐
2 Fume la cigarette à l'occasion (pas tous les jours)
3 N'a jamais fumé
4 A cessé de fumer en début de grossesse
5 A cessé de fumer avant la grossesse

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	

FORMULAIRE D'EXPOSÉ DE CAS

Visite 1

1er DOPPLER utérin

Âge gestationnel estimé selon la dernière période menstruelle : ☐☐ semaines ☐☐ jours /7

Dernière Période Menstruelle (jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐

Âge gestationnel à l'admission estimé par l'échographie : ☐☐ semaines ☐☐ jours /7

Date de l'échographie précoce (jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐

Longueur cranio-caudale ☐☐ mm

Diamètre biparietal ☐☐ mm

Date d'accouchement prévue (jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐

Résultats du Doppler utérin	**Droite**		**Gauche**
Index de pulsatilité (PI= (S-D) /Vm)			
Index de résistance (RI= (S-D) /S)			
Flot Systolique (S)		(cm/s)	
Flot Diastolique (D)		(cm/s)	
Vitesse moyenne (Vm)		(cm/s)	

Notch protodiastolique :

Aucun ☐ Unilatéral Droit ☐ Gauche ☐ Bilatéral ☐

Date de la 1e prise de sang (si différente écho) ☐☐ ☐☐☐ ☐☐☐☐

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	

FORMULAIRE D'EXPOSÉ DE CAS

Visite 2

2ième DOPPLER utérin

Âge gestationnel à la visite 2 estimé selon la dernière période menstruelle :	☐	semaines	☐	jours /7
Âge gestationnel à la visite 2 estimé par l'échographie précoce :	☐	semaines	☐	jours /7

Résultats du 2e Doppler utérin	**Droite**		**Gauche**
Index de pulsatilité (PI= (S-D) /Vm)	☐		☐
Index de résistance (RI= (S-D) /S)	☐		☐
Flot Systolique (S)	☐	(cm/s)	☐
Flot Diastolique (D)	☐	(cm/s)	☐
Vitesse moyenne (Vm)	☐	(cm/s)	☐

Notch protodiastolique :

Aucun ☐ Unilatéral Droit ☐ Gauche ☐ Bilatéral ☐

Date du Doppler (jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐
Date de la 2e prise de sang (si différente) ☐☐ ☐☐☐ ☐☐☐☐

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	

FORMULAIRE D'EXPOSÉ DE CAS

ISSUE de la GROSSESSE

Indiquer si la patiente présente l'une des conditions médicales suivantes en cochant la case appropriée

CONDITIONS MÉDICALES	NON	OUI	Non disponible
Mortalité maternelle			
Mortalité fœtale			
Mortalité néonatale			
Prééclampsie Si oui age gestationnel au diagnostic : ☐☐ semaines ☐ jours			
Hypertension gestationnelle			
Éclampsie			
HELLP syndrome			
Hématome rétroplacentaire			
Restriction sévère de croissance fœtale (<5ième percentile)			
RCIU modérée (5ième-10ième percentile)			

Date d'accouchement (jj mmm aaaa) ☐☐ ☐☐☐ ☐☐☐☐

Age gestationnel à l'accouchement ☐☐ semaines ☐ jours

Poids de naissance ☐☐☐☐ grammes

Sexe Masculin ☐ Féminin ☐

Mode d'accouchement
- Accouchement vaginal spontané ☐
- Césarienne avant travail ☐
- Césarienne en travail ☐

Mode de début de travail
- Spontané ☐
- Induction pour raison médicale ☐
- Induction « sociale » ☐

MÉDICAMENTS

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	

FORMULAIRE D'EXPOSÉ DE CAS

Si applicable, inscrire dans le tableau ci-dessous les médicaments que la participante a reçu au cours de sa grossesse et indiquer la posologie, la date du début et de la fin du traitement.

Médicaments	**Posologie**	**Début** (jj mmm aaaa)	**Fin** (jj mmm aaaa)

INTERVENTIONS OU AUTRES ÉVÈNEMENTS

Si applicable, inscrire dans le tableau ci-dessous les interventions médicales que la participante a subi au cours de sa grossesse et indiquer la date.

Interventions / Évènements	**Date** (jj mmm aaaa)

Signature de l'infirmière de recherche ou investigateur qui a complété cette page du questionnaire	
Date (jj-mmm-aaaa)	
Numéro patiente	