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# Epidemiology and prognosis of hypertension during pregnancy in French Guiana

Alexandra Mvogo

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UNIVERSITE DES ANTILLES  
ET DE LA GUYANE  
2019

FACULTE DE MEDECINE  
HYACINTHE BASTARAUD  
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**EPIDEMIOLOGY AND PROGNOSIS OF HYPERTENSION  
DURING PREGNANCY IN FRENCH GUIANA**

*Epidémiologie et pronostic de l'hypertension gravidique en  
Guyane Française*

**THESE**

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Et examinée par les Enseignants de la dite Faculté

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**DOCTEUR EN MEDECINE**

Par

**Alexandra MVOGO**

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# **Abstract**

## **Background**

Hypertensive diseases in pregnancy (HDP) are responsible for high maternal and fetal mortality and morbidity worldwide.

## **Objective**

Our objective was to report the epidemiological and clinical features of HDP in Cayenne General Hospital. Our secondary objectives were to search for factors associated to pre-eclampsia (PE) and to severe PE and factors associated to preterm birth in patients with PE.

## **Methods**

Our study is observational non-interventional. It is conducted over 4 month period (Jan to Apr 2019) in the Obstetrics and Gynaecology unit of the Cayenne General Hospital. We included all pregnant women after 20 weeks of gestation, who gave birth and who presented HDP and/or PE. The definitions used are in accordance with national and international recommendations.

## **Results**

One hundred fifty-three women were included. The median age was 33 (IQR 28 – 38) years. The rate of HDP was 12.6%. Eighty-five patients (55.6%) had at least one medical history. The most frequent medical histories were diabetes (27.5%) and chronic hypertension (23.5%). The socioeconomic status was low in 31% of patients.

Ninety-four patients (61.4%) developed PE with a severe form in 80.9% of cases. HELLP syndrome was diagnosed in 6.5% and nephropathy in 3.3% of cases. Delivery was by cesarean in 49.7% of cases. Gestational age at delivery was 37 weeks of gestation (IQR: 35 - 39).

Multivariable analysis showed no independent factors associated to the occurrence of PE, severe PE, or preterm birth.

## **Conclusion**

Our study shows a high prevalence of PE in patients with HDP. It failed to identify factors allowing a triage of patients at risk of PE, severe PE, or preterm birth. Hospitalization and repeated clinical evaluation are needed to screen for women exposed to develop such complications.

# Résumé

## Contexte

L'hypertension durant la grossesse (HDG) est responsable d'une mortalité et d'une morbidité maternelle et fœtale élevées dans le monde.

## Objectif

Notre objectif est de chercher les caractéristiques épidémiologiques et cliniques des HLG au Centre Hospitalier de Cayenne (CHC). Nos objectifs secondaires sont de rechercher les facteurs associés à la pré-eclampsie (PE) et à la PE sévère ainsi que les facteurs associés à la prématurité chez les patientes atteintes de PE.

## Méthodes

Notre étude est observationnelle non interventionnelle. Elle est menée sur une période de 4 mois (janvier à avril 2019) dans le service de Gynécologie-Obstétrique du CHC. Nous avons inclus toutes les femmes enceintes après 20 semaines d'aménorrhée, qui ont accouché et qui ont présenté une HDG et/ou une PE. Les définitions utilisées sont conformes aux recommandations nationales et internationales.

## Résultats

Cent cinquante-trois patientes ont été incluses. L'âge médian était de 33 ans (IQR 28 - 38). Le taux d'HDG était de 12,6%. Quarante-vingt-cinq patientes (55,6%) avaient au moins un antécédent médical. Les antécédents les plus retrouvés étaient le diabète (27,5%) et l'hypertension chronique (23,5%). Le niveau socioéconomique était bas chez 31% des patientes.

Quatre-vingt-quatorze patientes (61,4%) ont développé une PE avec une forme sévère dans 80,9% des cas. Un HELLP syndrome a été diagnostiqué dans 6,5% des cas et une néphropathie dans 3,3% des cas. L'accouchement était par césarienne dans 49,7% des cas. L'âge gestationnel à l'accouchement était de 37 semaines (IQR: 35 - 39).

L'analyse multivariée n'a montré aucun facteur indépendant associé à la survenue d'une PE, d'une PE sévère ou d'un accouchement prématuré.

## Conclusion

Notre étude montre une prévalence élevée de PE chez les patientes atteintes d'HDG. Elle n'a pas permis d'identifier les facteurs permettant un triage des patientes présentant un risque de PE, de PE sévère ou d'un accouchement prématuré. Une hospitalisation et une évaluation clinique répétée sont nécessaires pour dépister les patientes prédisposées à ces complications.

# Table of contents

<b>ABSTRACT</b> .....	<b>7</b>
<b>INTRODUCTION</b> .....	<b>ERREUR ! SIGNET NON DÉFINI.</b>
<b>MATÉRIELS ET MÉTHODES</b> .....	<b>ERREUR ! SIGNET NON DÉFINI.</b>
5-DÉFINITIONS.....	<b>ERREUR ! SIGNET NON DÉFINI.</b>
1 DATA COLLECTION .....	24
2 STATISTICAL ANALYSIS .....	24
<b>RESULTS</b> .....	<b>26</b>
1 EPIDEMIOLOGIC DATA OF ALL PATIENTS .....	26
1.1 <i>Distribution according to the month of the study</i> .....	26
1.2 <i>Geographic origin</i> .....	27
1.3 <i>Age</i> .....	27
1.4 <i>Medical history</i> .....	28
1.5 <i>Socioeconomic status</i> .....	29
2 CLINICAL DATA OF ALL PATIENTS.....	29
2.1 <i>The medical follow-up during pregnancy</i> .....	29
2.1.1 The clinical follow-up.....	29
2.1.2 The US examinations.....	31
2.2 <i>Clinical and biological data at admission</i> .....	31
2.2.1 Clinical data .....	31
2.2.2 Biological data .....	34
2.2.3 Proteinuria.....	34
2.2.4 Other biological parameters.....	38
2.2.5 Biological signs of severity in patients with pre-eclampsia.....	39
2.2.6 Therapeutic data at admission .....	40
2.3 <i>Classification of all patients</i> .....	40
2.4 <i>Delivery</i> .....	41
3 CHARACTERISTICS OF PATIENTS WITH PRE-ECLAMPSIA .....	45
3.1 <i>Associated factors to pre-eclampsia</i> .....	45
3.1.1 Maternal factors associated to pre-eclampsia .....	45
3.1.2 Foetal factors associated to pre-eclampsia .....	46
3.2 <i>Characteristics of patients with severe pre-eclampsia</i> .....	48
3.2.1 Maternal factors associated to severe pre-eclampsia .....	49
3.2.2 Foetal factors associated to severe pre-eclampsia.....	50
3.3 <i>Associated factors to preterm birth</i> .....	51
<b>DISCUSSION</b> .....	<b>56</b>
1 HISTORY.....	56
2 PHYSIOPATHOLOGY .....	56

3	EPIDEMIOLOGY .....	57
3.1	<i>Hypertensive disorders of pregnancy</i> .....	57
3.2	<i>Pre-eclampsia</i> .....	58
4	RISK FACTORS OF HYPERTENSIVE DISORDERS OF PREGNANCY .....	59
4.1	<i>Modifiable factors</i> .....	59
4.1.1	Body mass index .....	59
4.1.2	Anemia.....	60
4.1.3	Smoking.....	60
4.1.4	Alcohol intake .....	61
4.1.5	Education.....	61
4.2	<i>Non-modifiable factors</i> .....	61
4.2.1	Maternal age.....	61
4.2.2	Parity.....	62
4.2.3	History of complicated pregnancy .....	63
4.2.4	Gestational diabetes .....	63
4.2.5	Chronic hypertension.....	63
4.2.6	Other chronic diseases.....	63
4.2.7	Urinary tract infection.....	63
4.2.8	Family history.....	64
4.2.9	Genetic factors.....	64
5	THE DIAGNOSIS VALUE OF PROTEINURIA .....	64
6	COMPLICATIONS OF HYPERTENSIVE DISORDERS OF PREGNANCY.....	66
6.1	<i>Maternal complications</i> .....	66
6.1.1	Pre-eclampsia .....	66
6.1.2	Severe pre-eclampsia.....	66
6.1.3	HELLP syndrome.....	67
6.1.4	Renal impairment.....	68
6.1.5	Pulmonary edema .....	68
6.1.6	Eclampsia/cerebral hemorrhage.....	68
6.1.7	Acute fatty liver of pregnancy.....	69
6.1.8	Long term complications.....	69
6.2	<i>Foetal complications</i> .....	70
7	PREVENTION AND TREATMENT OF HDP AND PE.....	71
8	FOLLOW UP AND ORIENTATION OF PREGNANT WOMEN .....	73
	<b>CONCLUSION</b> .....	<b>74</b>
	<b>REFERENCES</b> .....	<b>75</b>

## Figures

Figure 1: Flow chart of hospitalized patients during the study period .....	26
Figure 2: Distribution of our patients according to the month of the study .....	27
Figure 3: Distribution of our patients according to age.....	27
Figure 4: Socioeconomic status of our patients. ....	29
Figure 5: Distribution of our patients according to the medical and/or midwife follow-up during pregnancy.....	30
Figure 6: Distribution of our patients according to the date of the diagnosis of hypertension.	32
Figure 7: Distribution of our patients according to the BMI. ....	33
Figure 8: The comparison of age between patients with and without chronic hypertension....	33
Figure 9: The comparison of BMI according to the presence of a history of chronic hypertension. ....	34
Figure 10: The results recorded on dipstick proteinuria at admission .....	35
Figure 11: Dipstick proteinuria results at admission in patients with PE.....	36
Figure 12: ROC curve showing the accuracy of the number of crosses on the urine dipstick in the diagnosis of PE (AUC:0.658).....	36
Figure 13: The correlation between spot urine protein to creatinine ratio and 24 hours urine protein dosage .....	37
Figure 14: Sensitivity, specificity, PPV and NPV of dipstick proteinuria in the diagnosis of PE, positive 24 hour proteinuria, and positive PCR.....	38
Figure 15: The antihypertensive drugs recorded at admission. ....	40
Figure 16: Maternal and foetal complications recorded in our patients.....	41
Figure 17: The frequency and type of delivery according to the gestational age (Weeks of Gestation). Dotted line indicates the median value. ....	42
Figure 18: The gestational age at delivery (Weeks of Gestation) according to the type of delivery ( $p < 0.001$ ).....	43
Figure 19: The frequency of the used antihypertensive drugs. ....	44

Figure 20: The distribution of our patients according to the occurrence of pre-eclampsia and of severe pre-eclampsia. ....	45
Figure 21: ROC curve showing the relationship between the apgar score at 10 min and the presence of pre-eclampsia (AUC :0.592) .....	47
Figure 22: Weight at birth according to the presence of pre-eclampsia.....	47
Figure 23: ROC curve showing the relationship between the weight at birth and the presence of pre-eclampsia (AUC :0.703).....	48
Figure 24: The distribution of patients with severe pre-eclampsia. ....	49
Figure 25: ROC curve showing the relationship between the systolic arterial pressure and the severity of pre-eclampsia (AUC :0.873).....	50
Figure 26: The accuracy of proteinuria in 24-hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with HDP. ....	52
Figure 27: The accuracy of proteinuria in 24-hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with pre-eclampsia. ....	53
Figure 28: The accuracy of proteinuria in 24 hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with HDP and without chronic hypertension. ...	53
Figure 29: The accuracy of proteinuria in 24 hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with pre-eclampsia and without chronic hypertension. ....	54
Figure 30: The distribution of our patients according to spot proteinuria (Panel A), 24 hour proteinuria (Panel B) and Spot protein to creatinineratio (Panel C) and the occurrence of preterm birth in patients with HDP. ....	55

## Tables

Table I: Medical histories recorded in our patients .....	28
Table II: The follow-up during pregnancy .....	30
Table III: The number of patients having ultrasound examination during pregnancy and abnormalities recorded on US exams. ....	31
Table IV: Clinical data recorded at admission.....	32
Table V: Biological parameters recorded at admission.....	35
Table VI: The diagnosis accuracy of dipstick proteinuria in the diagnosis of PE, positive 24 hour proteinuria, and positive PCR. ....	37
Table VII: Biological parameters recorded at admission. ....	39
Table VIII: Liver and kidney complications related to pre-eclampsia.....	39
Table IX: The distribution of our patients according to the presence of pre-eclampsia or chronic hypertension .....	41
Table X: The complications recorded at delivery and postpartum management.....	43
Table XI: Maternal variables associated to the occurrence of pre-eclampsia in our patients ..	46
Table XII: Foetal variables associated to the occurrence of pre-eclampsia in our patients .....	46
Table XIII: Variables associated to the severity of pre-eclampsia in our patients.....	49
Table XIV: Foetal variables associated with the severity of pre-eclampsia.....	50
Table XV: Variables associated with the occurrence of preterm birth in univariate analysis ..	51
Table XVI: Maternal complications of pre-eclampsia by organ system (from [30]).....	66



## Abbreviations

AGT	Angiotensinogen
AKI	Acute kidney injury
ALFP	Acute Fatty Liver of Pregnancy
AUC	Air Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CVD	Cardiovascular diseases
DIC	Disseminated IntraVascular Coagulation
DM	Diabetes Mellitus
DBP	Diastolic Blood Pressure
ESRD	End-stage renal disease
GDM	Gestational diabetes mellitus
GH	Gestational Hypertension
HELLP	Hemolysis, Elevated Liver enzymes Low Platelets
HDP	Hypertension During Pregnancy
ICU	Intensive Care Unit
IQR	Interquartile Range
MRI	Magnetic resonance imaging
NAMPT	Nicotinamide phosphoribosyl transferase
OR	Odd-Ratio
PCR	Protein creatinine ratio
PE	Pre-eclampsia
PRES	Posterior reversible leukoencephalopathy syndrome
ROC	Receiver operating characteristic
SBP	Systolic Blood Pressure
VDR	Vitamin D receptor
WHO	World Health Organization

## Introduction

According to the World Health Organization (WHO) data, pregnancy and child birth related complications are responsible of high mortality and morbidity in women and adolescent girls [1]. Among pregnancy related complications, hemorrhage, hypertensive disorders and sepsis are responsible for more than half of all maternal deaths worldwide. Thus, improving the quality of maternal healthcare for pregnant women is necessary to enable them to survive pregnancy and childbirth as part of their enjoyment of sexual and reproductive health and rights and living a life of dignity[2]. The main objective of the WHO is a world where “every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and the postnatal period”[3].

Hypertensive disorders of pregnancy can be divided into four groups: chronic hypertension, gestational hypertension, pre-eclampsia, and superimposed pre-eclampsia in the setting of chronic hypertension[4]. Although each condition increases the risk of maternal and neonatal morbidity, the greatest risks are associated with a diagnosis of pre-eclampsia, either de novo or superimposed[5,6]. According to the WHO data hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths[1,7].

Pre-eclampsia is a global health problem[7,8]. It is more common in Afro-Caribbean women, multifoetal gestation, and primigravidas[9]. It complicates 2%-8% of all pregnancies, and around 25%[10,11] of pregnant women with gestational or chronic hypertension. It contributes to 15% of preterm deliveries, and up to 26% of maternal deaths worldwide[12]. It is also a risk factor of cardiovascular disease throughout life[13–16]. The incidence of pre-eclampsia is increasing with the global increase in maternal age, obesity, assisted reproductive techniques, and medical predisposing comorbidities, such as diabetes, hypertension, and renal disease[17].

Pre-eclampsia is a multisystem disorder characterized by generalized endothelial damage, which can result in widespread end-organ damage like HELLP syndrome, renal impairment, pulmonary edema or eclampsia/cerebral hemorrhage. In addition it can be combined with

foetal growth restriction[17]. In addition, several studies showed that gravidic hypertension, and pre-eclampsia were associated with early preterm delivery[18–21].

French Guiana, a French territory in South America, has the highest fertility rate in Latin America (3.5%) and also has a high prematurity rate at 13.5% versus 7% in mainland France and 7.9% in South America. This prematurity rate is high despite efforts to improve care for pregnant women and to identify characteristics of women at risk for preterm delivery[22].

### **Objectives:**

Our primary objective was to report the epidemiological and clinical features of hypertension during pregnancy in Cayenne General Hospital

Our secondary objectives were to search for factors associated to pre-eclampsia and to severe pre-eclampsia and factors associated to preterm birth in patients with pre-eclampsia.

# Materials and methods

## 1 Setting and patients

Our study is an observational non-interventional work. It was conducted over 4-month period (January 2019 to April 2019) in the Obstetrics and Gynecology Unit of the Cayenne General Hospital. Our hospital is a 510-bed general center that serves as first-line medical center for an urban population of 150,000 inhabitants and as a referral center for a larger population coming from all French Guiana. Cayenne is the regional capital of French Guiana, which is a French territory located on the North Atlantic coast of South America. It has borders with Brazil and Suriname. Its area is 83,534 square kilometers, with an estimated population of 262,381 people in 2017 (<https://www.insee.fr/>). Migrant population are most of the time without documents. They contribute to the high level of poverty and to the precariousness rate. Indeed, in 2015, the national institute of statistics and economic studies (<https://www.insee.fr/>) had estimated the poverty rates at 44% in French Guiana.

The health care system in French Guiana is composed by 6 hospitals, three public hospitals in Cayenne, Saint Laurent du Maroni, and Kourou, and three private clinics in Cayenne. The Hospital of Cayenne manages 10 health centers and 11 health posts in isolated communities. The health posts are managed by paramedical nurses who can communicate with hospital doctors through telemedicine. In addition, twenty-three Mother and Child Health (MCH) centers cover the territory of Guiana but most of these prevention centers are chronically understaffed. In the report published in September 2017 by the departmental medical board in French Guiana, the density of active doctors in the territory is of 222 per 100,000 inhabitants, against 355.6 per 100,000 inhabitants in metropolitan France. This brings French Guiana to the 2nd rank of French departments where the medical density is the lowest. The density of general physicians is also weak, estimated at 39 per 100,000 inhabitants.

In French Guiana, there are 4 obstetrics centers. Two in Cayenne, one in Kourou and one in Saint Laurent du Maroni. All medical specialties dealing with mothers and newborns are connected by a local network called PERINAT GUYANE NETWORK. Its main objective is to improve care and follow-up for pregnant women and newborns, and to promote access to local health care through close medical coordination of perinatal professionals. It plays a major role in organizing the follow-up of pregnant women and the quality of care provided.

Our unit is a level III one performing 4300 deliveries per year. The team is composed of 12 doctors, 65 midwives, and 17 nurses.

## 2 Inclusion criteria

We included in our study all pregnant women after 20 weeks of gestation, hospitalized in our unit, who gave birth during the study period and who presented hypertension disease in pregnancy and/or pre-eclampsia.

## 3 Exclusion criteria

We excluded all patients without hypertension during pregnancy or pre-eclampsia, those who were pregnant before 20 weeks of gestation, and those who did not give birth during the study period.

## 4 Methods

Proteinuria was assessed by Urine Dipstick Test, Random Urine Protein Estimation, and Random Urinary Protein for Creatinine Ratio, and 24-Hour Urine Protein Estimation.

On admission, the patient is asked to submit a random urine sample in a urine container. The sample is then divided into two containers. The 1<sup>st</sup>, is sent to the biochemical laboratory for protein and creatinine dosage, and the second will serve to perform a Urine Dipstick Test.

*Urine Dipstick Test* is performed by the nurse in charge of the patient at admission. The dipstick analysis was done using URICHECK. The following are the grades of proteinuria as provided by the manufacturer:

- 0: absent
- Traces: 15 to 30mg/dL
- 1+: 30 to 100mg/dL
- 2+: 100 to 300mg/dL
- 3+: 300 to 1000mg/dL
- 4+: greater than 1000mg/dL.

*Random Urinary Protein: Creatinine Ratio* (PCR) is calculated after obtaining the both random urine protein and creatinine concentrations in mg/L and mmol/L respectively. Ratio was calculated by the formula:  $PCR = \text{protein concentration (mg/L)} / \text{creatinine concentration (mmol/L)}$ .

*24-Hour Urine Protein Estimation* was carried out after admission. During 24 hours, patient was instructed to collect all the voided samples in a large container which was sent to

laboratory for further analysis. 24-hour urine protein was estimated by the formula: Total 24-hour urine protein excretion= Urine protein concentration (mg/L) × 24-hour urine volume in mL.

## 5 Definitions

The definition of hypertension in pregnancy is based only on office (or in-hospital) blood pressure (BP) values: systolic BP (SBP)  $\geq 140$  mmHg and/or diastolic BP (DBP)  $\geq 90$  mmHg[4,23,24]. Moderate arterial hypertension is considered with SBP = 140-159 mmHg / DBP = 90-109mmHg, and severe hypertension with SBP  $\geq 160$  or DBP  $\geq 110$ mmHg[25].

Hypertension disease in pregnancy (HDP) comprises[26]:

- Pre-existing or chronic hypertension precedes pregnancy or occur before 20 weeks of gestation. It usually persists for more than 42 days post-partum and may be associated with proteinuria.
- Gestational hypertension develops after 20 weeks of gestation and usually resolves within 42 days post-partum.
- Pre-eclampsia is defined by gestational hypertension with significant proteinuria [ $\geq 0.3$  g/24 hours or spot urine protein to creatinine ratio (PCR)  $\geq 30$  mg/mmol]. As proteinuria may be a late manifestation of pre-eclampsia, it should be suspected when de novo hypertension is accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelets and/or abnormal liver or renal function.
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.
- Antenatally unclassifiable hypertension: this term is used when BP is first recorded after 20 weeks of gestation and hypertension is diagnosed; re-assessment is necessary after 42 days post-partum.

Complications are defined as maternal and/or foetal complications.

Maternal complications are defined as renal injury, HELLP syndrome, acute fatty liver of pregnancy, pulmonary oedema, eclampsia, disseminated intravascular coagulation (DIC), and delivery haemorrhage.

Foetal complications are defined as prematurity, foetal death, foetal growth restriction, abnormal foetal rhythm or foetal distress.

Severe Features of Pre-eclampsia are defined by any of these findings[27]:

- ✓ Systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- ✓ Thrombocytopenia (platelet count less than 100,000/microliter)
- ✓ Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration)
- ✓ Severe persistent right upper quadrant and/or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses
- ✓ Progressive renal insufficiency (serum creatinine concentration greater than 135  $\mu\text{mol/L}$  without previous renal disease); or doubling of the serum creatinine concentration in the absence of other renal disease; or need for dialysis (without previous chronic renal failure)[28]
- ✓ Pulmonary edema
- ✓ New-onset cerebral or visual disturbances

*Eclampsia* refers to generalized tonic-clonic seizures in a pregnant or recently delivered woman with no other attributable cause[29,30].

HELLP syndrome is a complication of pregnancy characterized by Hemolysis (anemia with blood film evidence of hemolysis), Elevated Liver enzymes showing hepatic dysfunction (transaminitis greater than twice the normal range), and Low Platelets (platelet count of less than 150,000/dL) [12,31]

*Acute fatty liver of pregnancy* (AFLP) is characterized by unspecific symptoms starting during the third trimester such as nausea, vomiting, jaundice, malaise, and anorexia, with higher levels of transaminases and bilirubins in a short period of time, coagulopathies including disseminated intravascular coagulation(DIC) and hemolysis, with increased lactic dehydrogenase (LDH).Clinical evaluation with at least six Swansea criteria is considered sufficient to accurately diagnose the disease[31].The definite diagnosis is confirmed by anatomopathological exam on liver biopsy.

*Nephropathy* was defined as renal failure with serum creatinine level  $\geq 135 \mu\text{mol/L}$  [28] or proteinuria  $\geq 5 \text{ g/24 hours}$  [28].

*Early pre-eclampsia* is defined as pre-eclampsia occurring before 32 weeks of gestation.

*The follow-up during pregnancy* is defined by at least one consultation per month since the third month of gestation by a physician or a midwife. In our study we have divided the follow-up during pregnancy in three classes:

- Complete follow-up: are those patients who had at least 80% of the required consultations during pregnancy
- Incomplete follow-up: are those patients who had between 50 and 79% of the required consultations during pregnancy
- Poor follow-up: are those patients who had less than 50 % of the required consultations during pregnancy
- No follow-up: are those patients who had no consultation during pregnancy

*Body Mass Index (BMI)* is a person's weight in kilograms divided by the square of height in meters. Obese status is defined by a BMI greater than or equal to 30 kg/m<sup>2</sup>.

*Socioeconomic status* is defined in our study according to four indicators: educational level, occupation, income and housing.

*The educational level* is the highest level of education up to which the patient has arrived. Was considered as a low level of education a woman having completed her education until primary school or secondary school (between 8-12 years of study), and as a high level of study women who did graduate school after the bachelor's degree and corresponding to more than 12 years of study.

For the profession we determined whether the patient was unemployed or had a professional activity.

The incomes were defined from the social security status. To benefit from Universal Medical Coverage (CMU) or State Medical Aid (AME) patient must receive less than 734 euros per month which is a factor of disadvantage, the poverty line in France is either 855euros / month or 1026euros / month according to the definition of poverty used (respectively at 50% threshold and 60% of the median standard of living) (INSEE, 2016 data, available at <https://www.insee.fr/>). Patients with AME or CMU were therefore considered living below



the poverty line, and patients with social security associated with a mutual were considered living above the poverty line.

The housing was divided into two groups: Not precarious representative of proper premises (house, apartment) and precarious habitat that does not perform its functions energetic, insulating (wooden houses, squat ...)

A woman was considered having a low socioeconomic status when we found the presence of at least one of these four criteria, having a middle socio-economic level a woman with 2 of these criteria, and having a high socio-economic level those with more than 3 criteria.

*Preterm birth* is defined by birth before 37 completed weeks of amenorrhea.

## 6 Data collection

Data of all patients were collected and, a detailed clinical profile of each patient was established.

The following data were collected: demographic characteristics, which included age, socioeconomic level, presence of underlying diseases, clinical and biological profile at admission, maternal complications (pulmonary edema, HELLP syndrome, eclampsia, ....), foetal complications (in utero foetal death, acute foetal distress ...), length of hospital stay, and outcome at discharge from hospital.

Our database has been registered at the Commission National de l'Informatique et des Libertés (registration number 2214306 v 0), in compliance with French law on electronic data sources.

## 7 Statistical analysis

Results are reported as median and interquartile range (IQR: 25<sup>th</sup>–75<sup>th</sup>percentiles), or numbers with percentages.

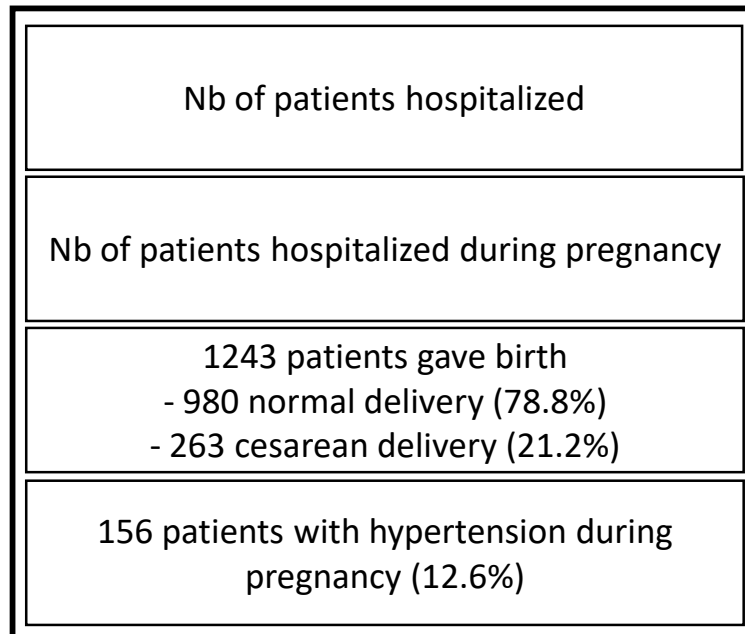
Initial bivariate statistical comparisons were conducted using the Chi-square or Fisher's exact test for categorical data and the Independent-Samples T test for continuous data. To identify patients' characteristics associated with pre-eclampsia, severe pre-eclampsia, and preterm birth we used multivariable logistic regression with a backward procedure. Non-redundant variables selected by bivariate analysis ( $p < 0.05$ ) and considered clinically relevant were entered into a logistic regression model. Results are expressed as odds ratios (OR) with their

95% confidence intervals (95%CI). A p value  $<0.05$  was considered statistically significant. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value of continuous variables in predicting severe outcome. The area under the curve was estimated by the method of Hanley and McNeill[32,33]. We calculated the sensibility, specificity, positive and negative predictive values, Youden test and the Q coefficient of Yule to assess the diagnosis value of a quantitative test.

All statistical analyses were carried out with Excel (2007) and Statistical Package for the Social Sciences (SPSS) program (Version 24).

## Results

During the study period 2446 patients were hospitalized in our unit. 2031 of them were hospitalized during pregnancy and 1243 gave birth. Among them, 156 were diagnosed with hypertensive disease in pregnancy (12.6%) (Figure 1)



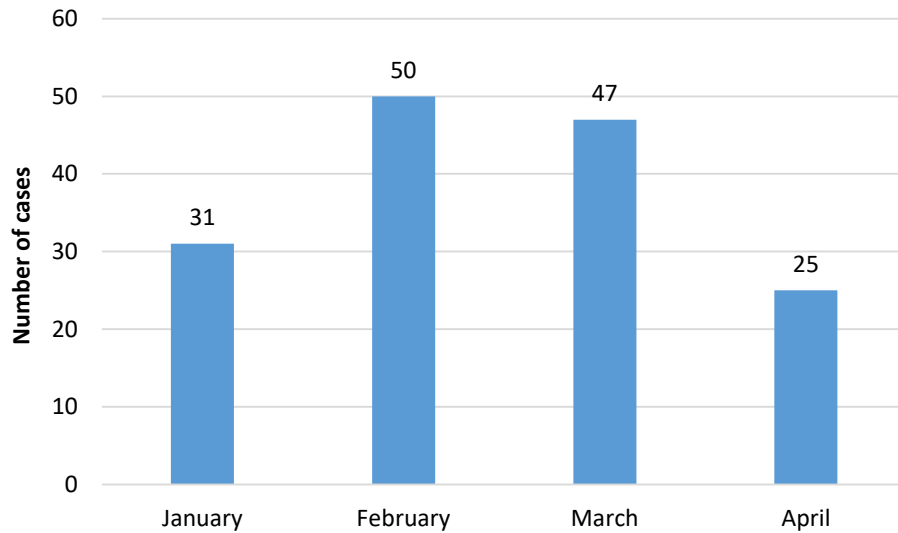
*Figure 1: Flow chart of hospitalized patients during the study period*

Three cases were excluded from our study because of incomplete data. Then, the total number of studied cases was 153 giving a rate of hypertensive disease in pregnancy of 12.6% out of the 1243 patients who have given birth during hospitalization.

### 1 Epidemiologic data of all patients

#### 1.1 Distribution according to the month of the study

The distribution of our patients according to the month of the study show an unequal spread varying from 25 cases to 50 cases per month (Figure 2).



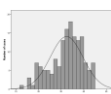
*Figure 2: Distribution of our patients according to the month of the study*

## 1.2 Geographic origin

Eighty-three patients (54.2%) were South American, 69 (45.1%) were from the Caribbean zone and one patient was African (0.7%).

## 1.3 Age

The median age of our patients was 33 (IQR 28 - 38) years. Ten patients (6.5%) were less than 20 years old. The distribution of our patients according to age is reported in figure 3.



*Figure 3: Distribution of our patients according to age*

## 1.4 Medical history

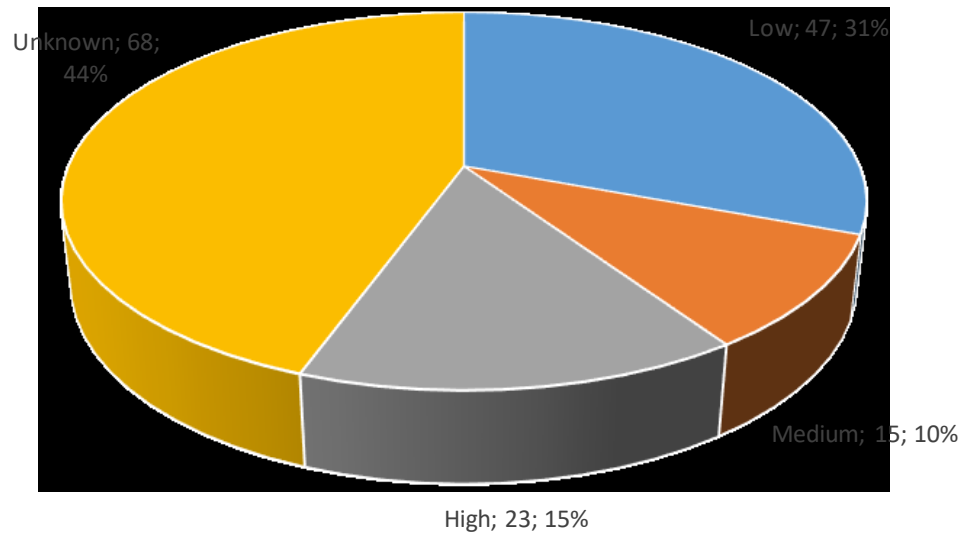
Eighty-five patients (55.6%) had at least one medical history. The most frequent medical histories were diabetes (27.5%) and chronic hypertension (23.5%). The diabetes was gestational in 78.6% of cases and type 2 diabetes in 21.4% of cases (Table I).

*Table I: Medical histories recorded in our patients*

<b>Medical history</b>	<b>Nb</b>	<b>nb(%) / Med(IQR)</b>
Chronic Hypertension	153	36 (23.5%)
Gestational hypertension	153	26 (17%)
Pre-eclampsia	153	30 (19.6%)
Eclampsia	153	1 (0.7)
Placental abruption	153	3 (2%)
Intrauterin foetal death	153	9 (5.9%)
Diabetes	153	42 (27.5%)
Gestational diabetes	42	33 (78.6%)
Type 2 diabetes	42	9 (21.4%)
Sicklecelldisease	153	19 (12.4%)
Haemoglobin gene		
AS	19	14 (73.7%)
AC		5 (26.3%)
Deep venous thrombosis	153	3 (2%)
Autoimmune disorder	153	2 (1.3%)
Gestation number	153	3 (2 - 5)
Parity number	153	2 (0 - 3)
Scarred uterus	153	31 (20.2%)
Myoma	153	11 (7.2%)
Anemia	153	10 (6.5%)
Asthma	153	7 (4.6%)
Social protection	150	131 (87.3%)

## 1.5 Socioeconomic status

The socioeconomic status was monitored in 85 patients (55.6%). It was low in 47 patients (31%). Figure 4 shows the socioeconomic status of our patients.



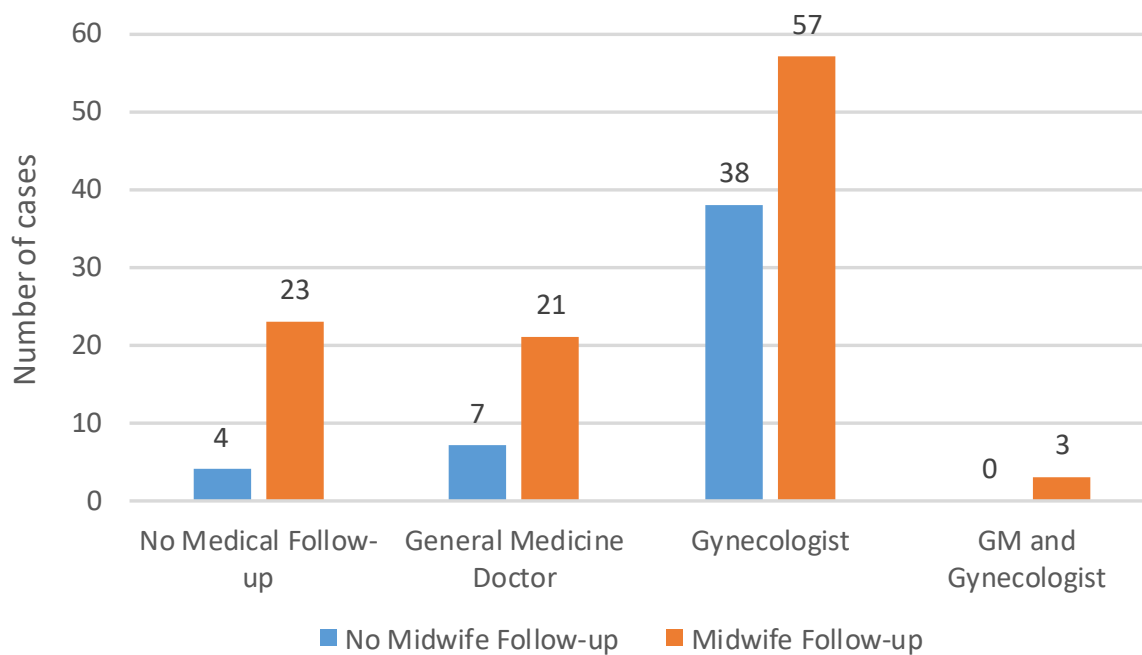
*Figure 4: Socioeconomic status of our patients.*

## 2 Clinical data of all patients

### 2.1 The medical follow-up during pregnancy

#### 2.1.1 The clinical follow-up

One hundred forty-three patients (93.5%) were examined at least three times during pregnancy by a doctor and/or a midwife and were considered as having a medical follow-up during pregnancy. Figure 5 and Table II shows the distribution of our patients according to the medical and/or midwife follow-up during pregnancy.



*Figure 5: Distribution of our patients according to the medical and/or midwife follow-up during pregnancy*

*Table II: The follow-up during pregnancy*

Variable	Nb	nb(%) / Med(IQR)
Medical follow-up (doctor and/or midwife)	153	149 (97.4%)
Follow-up by a doctor	153	126 (82.4%)
Follow-up by a midwife	153	104 (68.0%)
Nb of prenatal consultations	153	4 (2 - 6)
Nb of consultations in the emergency	153	1 (0 - 2)
Total Nb of consultations	153	5 (3 - 8)
Date of hypertension (Week of gestation)	117	37 (32 - 39)
Antihypertensive drug	153	70 (45.8%)
Sallicilicacid use	153	17 (11.1%)
Hospitalization during pregnancy	153	50 (32.7%)

## 2.1.2 The US examinations

Seventy-six patients (49.7%) had 3 ultrasound examinations (one in each quarter) during pregnancy. The number of patients having ultrasound examination per quarter is reported in Table III.

*Table III: The number of patients having ultrasound examination during pregnancy and abnormalities recorded on US exams.*

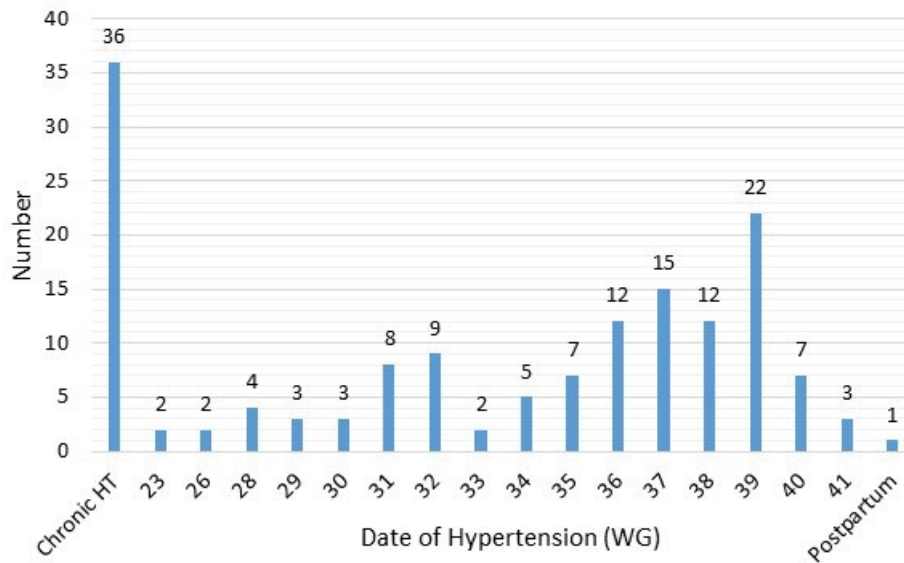
<b>Variable</b>	<b>Nb</b>	<b>nb(%) / Med(IQR)</b>
US examination in the 1st quarter	153	97 (63.4%)
US examination in the 2nd quarter	153	128 (83.7%)
US examination in the 3rd quarter	153	121 (79.1%)
<b>Ultrasound signs</b>		
Intra uterine growth restriction	153	22 (14.4%)
Oligohydramnios	153	10 (6.5%)
Small for gestational age	153	14 (9.2%)
Umbilical artery doppler abnormality	153	16 (10.5%)

## 2.2 Clinical and biological data at admission

### 2.2.1 Clinical data

The gestational age at admission was recorded in 152 patients. It was 37 weeks of gestation (IQR: 34 - 39). One patient was hospitalized at day 8 postpartum because of new onset hypertension on the postpartum period. In patients without chronic hypertension, the date of the diagnosis of hypertension was 37 weeks of gestation (IQR: 32-39) (Figure 6). Clinical data recorded at admission to our unit are reported in Table IV.



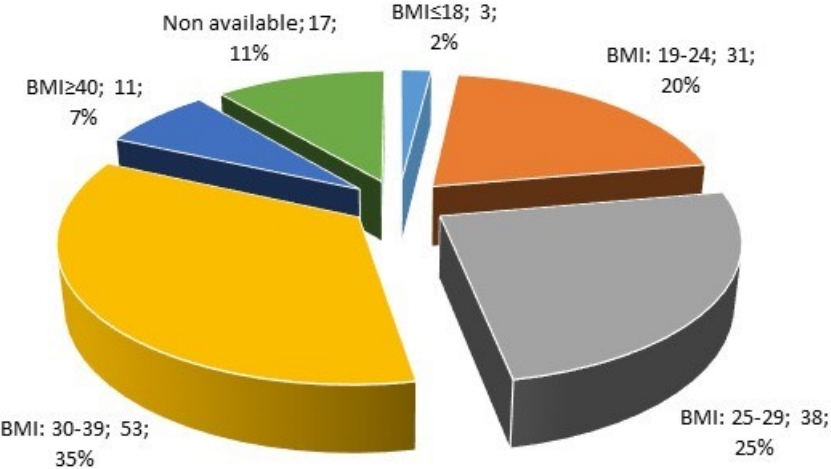


*Figure 6: Distribution of our patients according to the date of the diagnosis of hypertension*

*Table IV: Clinical data recorded at admission*

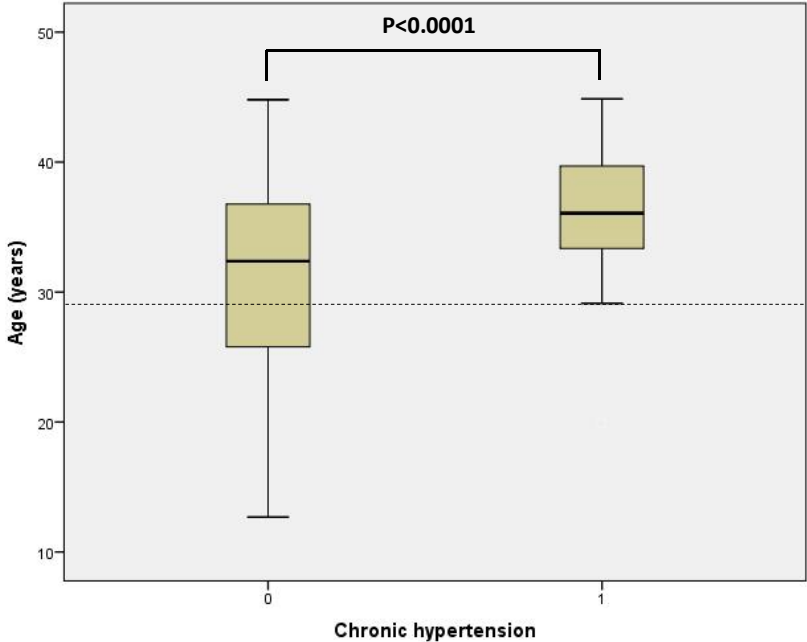
Variable	Nb	nb(%) / Med(IQR)
Body Mass Index	136	29 (25 - 34)
Systolic arterial pressure, mmHg	153	157 (147 - 172)
Diastolic arterial pressure, mmHg	153	96 (89 - 101)
Head ache	153	55 (35.9%)
Akufen	153	9 (5.9%)
Abdominal pain	153	19 (12.4%)
Vision disorder	153	18 (11.8%)
Hyperreflexia	153	3 (2%)
Seizures	153	6 (3.9%)
Edema	152	75 (49.3%)
Pulmonary edema	153	1 (0.7%)

The distribution of our patients according to the BMI shows that 64 patients (42%) were obese (Figure 7).



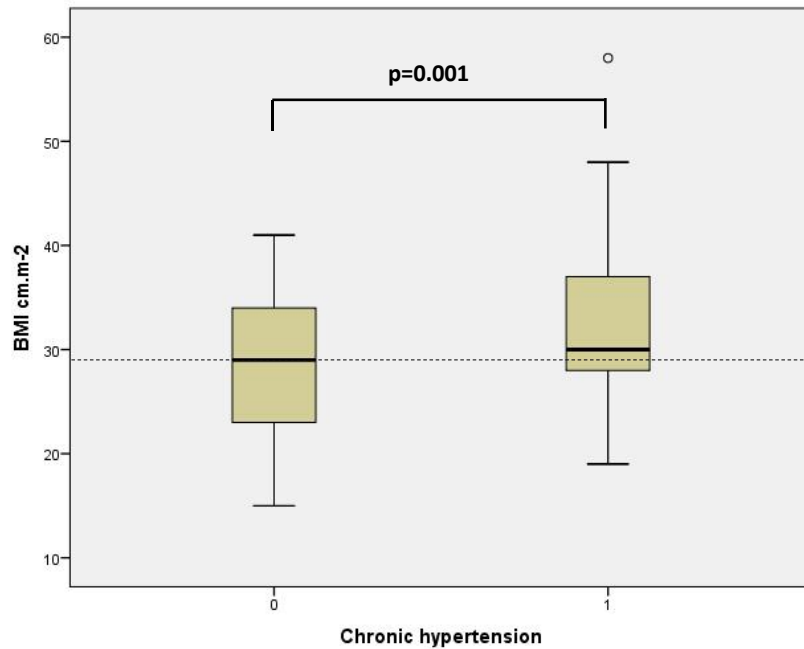
*Figure 7: Distribution of our patients according to the BMI.*

Age was higher in patients with chronic hypertension [36 (IQR: 33-39) vs 32 (IQR: 25-36);  $p < 0.001$ ] (Figure 8).



*Figure 8: The comparison of age between patients with and without chronic hypertension*

The comparison of clinical data according to the presence of a medical history of hypertension showed no difference between subgroups except for BMI which was higher in patients with medical history of hypertension [30 (IQR: 27.7-37.5) vs 29 (23-34);  $p=0.001$ ] (Figure 9).

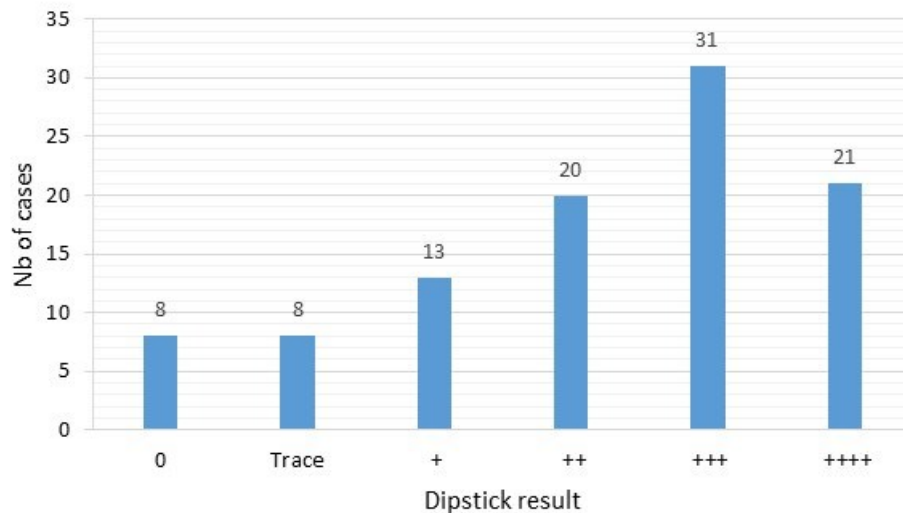


*Figure 9: The comparison of BMI according to the presence of a history of chronic hypertension.*

## 2.2.2 Biological data

### 2.2.3 Proteinuria

In our study, 101 patients (66%) had dipstick proteinuria at admission. It was positive ( $\geq 2+$ ) in 72 patients (71.3%). Figure 10 shows the results recorded on dipstick at admission.



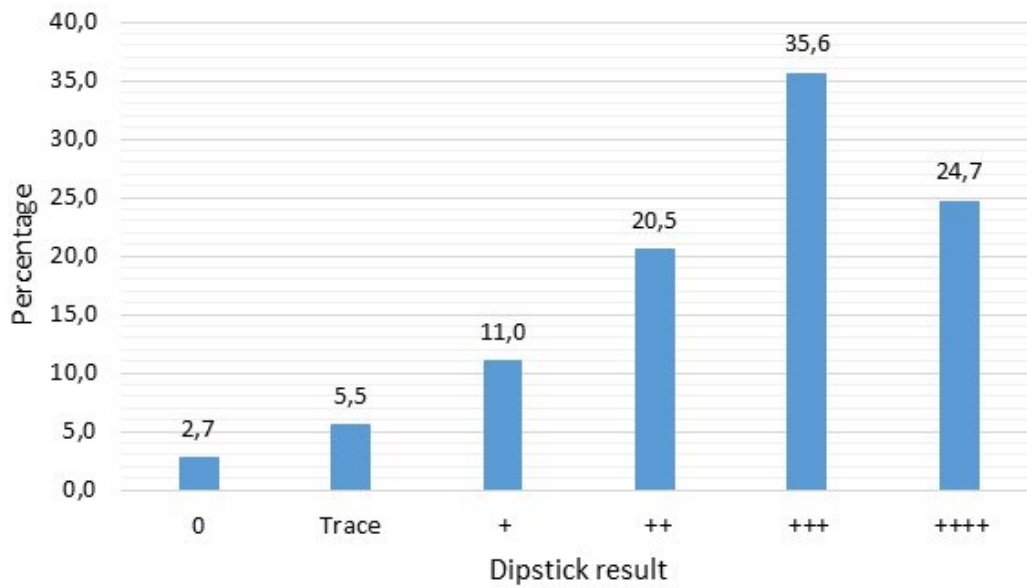
*Figure 10: The results recorded on dipstick proteinuria at admission*

Proteinuria (g/L) dosage was available in 119 patients (77.8%). It was over 0.3 g/24hours in 71 cases (59.6%). Spot urine protein/creatinine ratio was available in 105 patients (68.7%). It was over 30 in 69 cases (65.7%). Urine output monitoring during 24 hours was available in 92 cases (60.1%). It was below 500 ml in only one case.

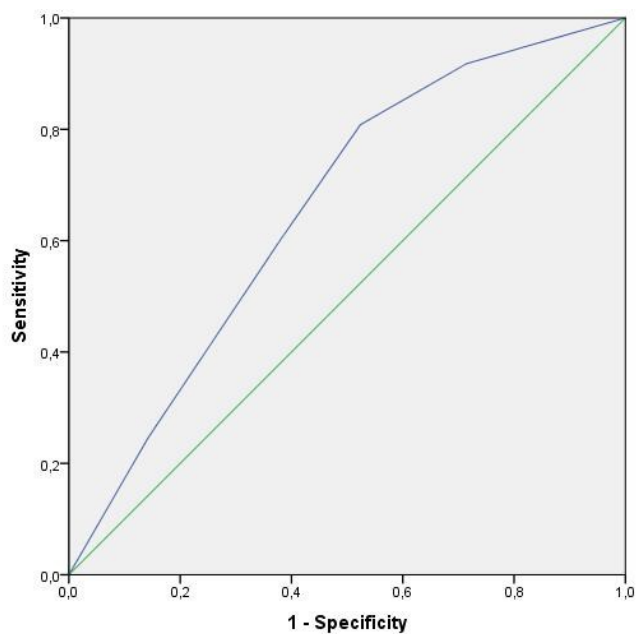
Overall, 133 patients (86.9%) had proteinuria and/or spot PCR dosage. Among them, 94 (70.7%) had proteinuria  $\geq$  0.3 g/24 hours or spot PCR  $\geq$ 30 mg/mmol and then, they were diagnosed with pre-eclampsia. The results of dipstick proteinuria at admission in patients with pre-eclampsia is reported in figure 11. In preeclamptic patients, 19.2% of dipstick proteinuria were <2+ (false negative). In non preeclamptic patients, 12.9% of dipstick proteinuria were  $\geq$ 2+ (false positive). Figure 12 shows the accuracy of the number of crosses on the urine dipstick in the diagnosis of PE.

*Table V: Biological parameters recorded at admission.*

	<b>Nb</b>	<b>nb(%) / Med(IQR)</b>
Spot proteinuria, g/L (on urine sample)	119	0.41 (0.14 - 1.3)
Urine creatinine, mmol/L	105	8 (4.5 - 14.5)
Spot urine protein to creatinine ratio	105	45 (25 - 166)
Proteinuria, g/24-hour	97	0.54 (0.28 - 2.5)
Duresis, ml/24hour	92	2000 (1500 - 2500)

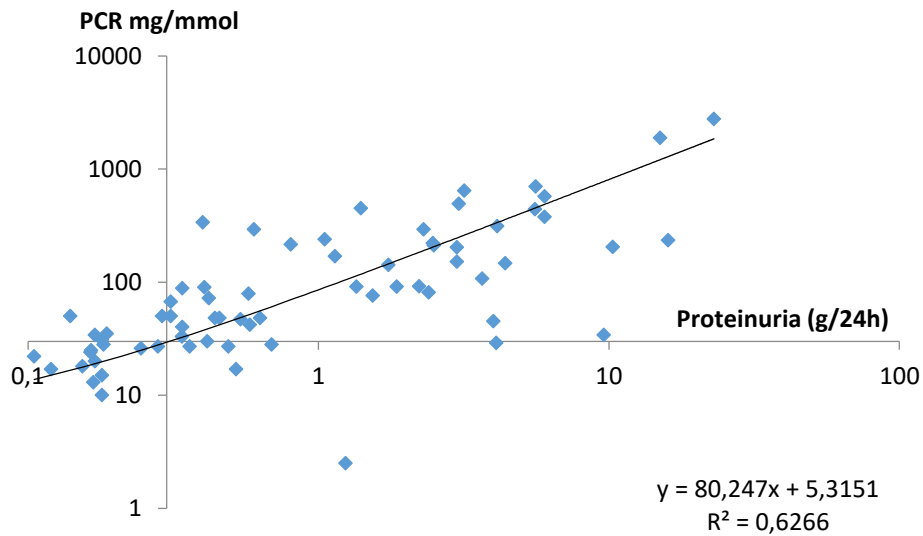


*Figure 11: Dipstick proteinuria results at admission in patients with PE.*



*Figure 12: ROC curve showing the accuracy of the number of crosses on the urine dipstick in the diagnosis of PE (AUC:0.658)*

Figure 13 shows the correlation between spot urine protein to creatinine ratio and 24 hours urine protein dosage.



*Figure 13: The correlation between spot urine protein to creatinine ratio and 24 hours urine protein dosage*

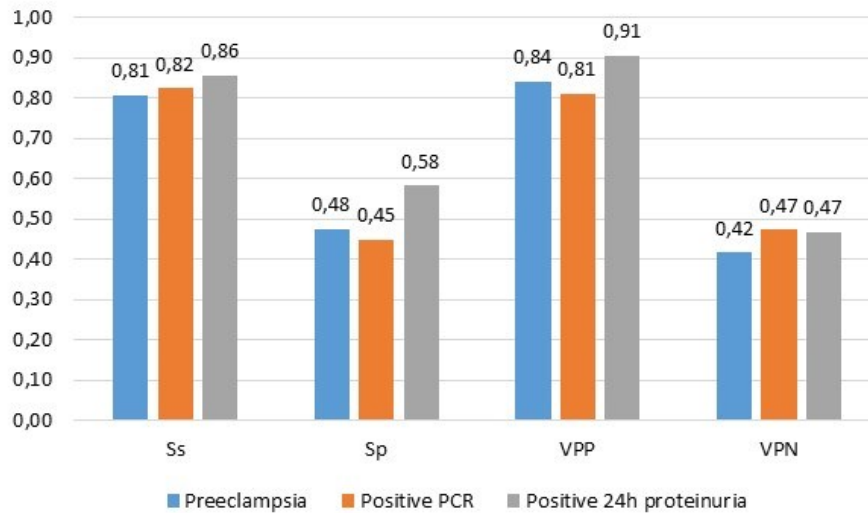
The comparison of proteinuria (g/Lon urine sample), spot protein to creatinine ratio and 24 hour urine protein according to the presence of chronic hypertension showed no difference between subgroups ( $p= 0.420, 0.208$  and  $0.829$  respectively).

Table VI and figure 14 shows the diagnosis accuracy of dipstick proteinuria in the diagnosis of PE, positive 24 hour proteinuria, and positive PCR.

*Table VI: The diagnosis accuracy of dipstick proteinuria in the diagnosis of PE, positive 24 hour proteinuria, and positive PCR.*

Comparison variable	Nb	Ss	Sp	PPV	NPV	Q	Youden
Pre-eclampsia	94	0.81	0.48	0.84	0.417	0.59	0.28
Positive PCR	77	0.82	0.45	0.810	0.47	0.59	0.28
Positive 24h proteinuria	68	0.86	0.58	0.906	0.47	0.79	0.44

Ss: sensitivity. Sp: Sensibility, PPV: Positive predictive value, NPV: Negative predictive value, Q: Coefficient of Yule



*Figure 14: Sensitivity, specificity, PPV and NPV of dipstick proteinuria in the diagnosis of PE, positive 24 hour proteinuria, and positive PCR.*

#### 2.2.4 Other biological parameters

Table VII shows the biological parameters recorded at admission. Biological renal function was monitored in 146 cases (95.4%). It showed renal impairment in 14 cases (9.6%). Liver enzymes dosage was performed in 146 cases (95.4%). They were elevated in 10 cases (6.8%). Platelet count was available in all patients. It was below 150 G/L in 20 cases (13.1%). Haptoglobin dosage was available in 116 cases (75.8%). It was not dosable in 15 cases (12.9%).

*Table VII: Biological parameters recorded at admission.*

	<b>Nb</b>	<b>nb(%) / Med(IQR)</b>
Ureanitrogen, mmol/L	143	2.6 (1.9 - 3.7)
Uricacid, $\mu\text{mol/L}$	141	306 (257 - 363)
Blood creatinine, $\mu\text{mol/L}$	146	55 (48.3 - 65)
ASAT, UI/L	146	17 (13 - 22)
ALAT, UI/L	146	11 (8 - 19)
Plateled count, Giga/L	153	232 (187 - 285.5)
Hemoglobin, g/dL	153	11 (10.3 - 11.8)
Haptoglobin, g/L	101	1 (1 - 1)
Non dosable haptoglobin	116	15 (12.9%)
Schizocyte	2	<1%

### 2.2.5 Biological signs of severity in patients with pre-eclampsia

In our patients, 94 (61.4%) had a proteuniria level  $\geq 0.3$  g/24 hours or a PCR ratio  $\geq 30$  mg/mmol, and consequently they were diagnosed as having pre-eclampsia. Liver and kidney complications related to pre-eclampsia are reported in table VIII.

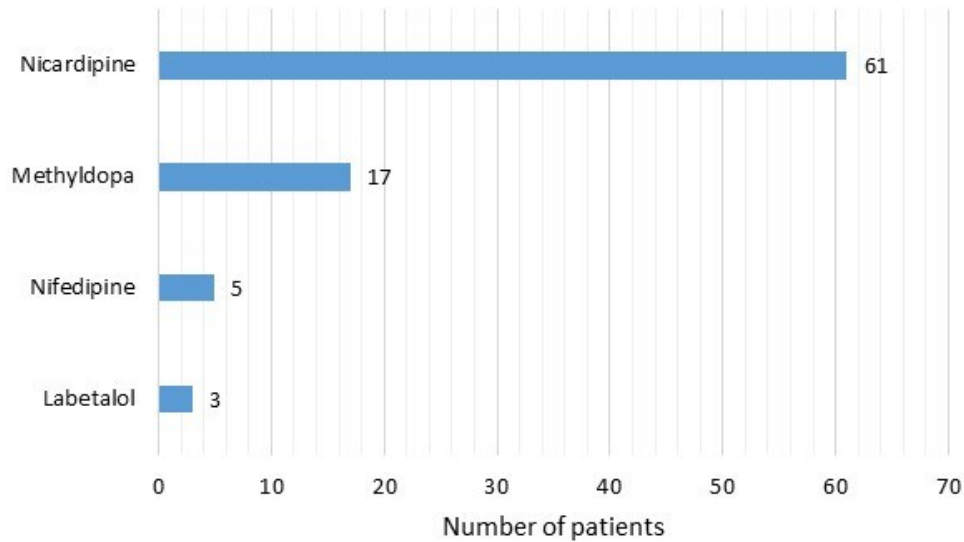
*Table VIII: Liver and kidney complications related to pre-eclampsia*

	<b>Nb</b>	<b>nb(%) / Med(IQR)</b>
HELLP syndrome	153	10 (6.5%)
Acute fatty liver of pregnancy	153	0 (0%)
Nephropathy	153	5 (3.3%)



### 2.2.6 Therapeutic data at admission

Seventy patients (45.8%) received antihypertensive therapy at admission. Of them, 54 patients received one molecule and 16 received Two molecules. The molecules used are represented in Figure 15.



*Figure 15: The antihypertensive drugs recorded at admission.*

17 patients (11.1%) received salicylate at admission. Of them, 11 patients (64.7%) had a history of HDP ( $p < 0.0001$ ).

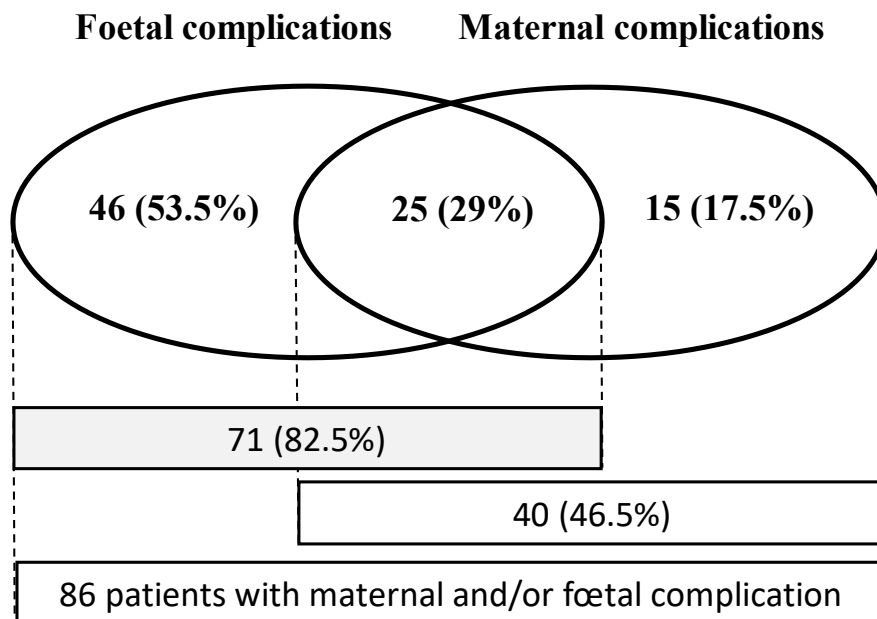
### 2.3 Classification of all patients

Pre-eclampsia was diagnosed in 94 patients (61,4%). The distribution of our patients according to the presence of pre-eclampsia and chronic hypertension is reported in table IX.

History of chronic Hypertension		Total patients n=153
Yes n=36	No n=117	
Chronic Hypertension n=7	Gestational Hypertension n=32	Total Hypertension without preeclampsia n=39
Superimposed Preeclampsia n=21	Preeclampsia n=73	Total Preeclampsia n=94
Chronic Hypertension without available Proteinuria n=8	Gestational Hypertension without available Proteinuria n=12	Not available Proteinuria n=20

*Table IX: The distribution of our patients according to the presence of pre-eclampsia or chronic hypertension*

In patients with pre-eclampsia, maternal complications were found in 40 cases (26.1% of all patients and 46.5% of complicated patients) and foetal complications were found in 71 cases (46.4% of all patients and 82.5% of complicated patients) (Figure 16).

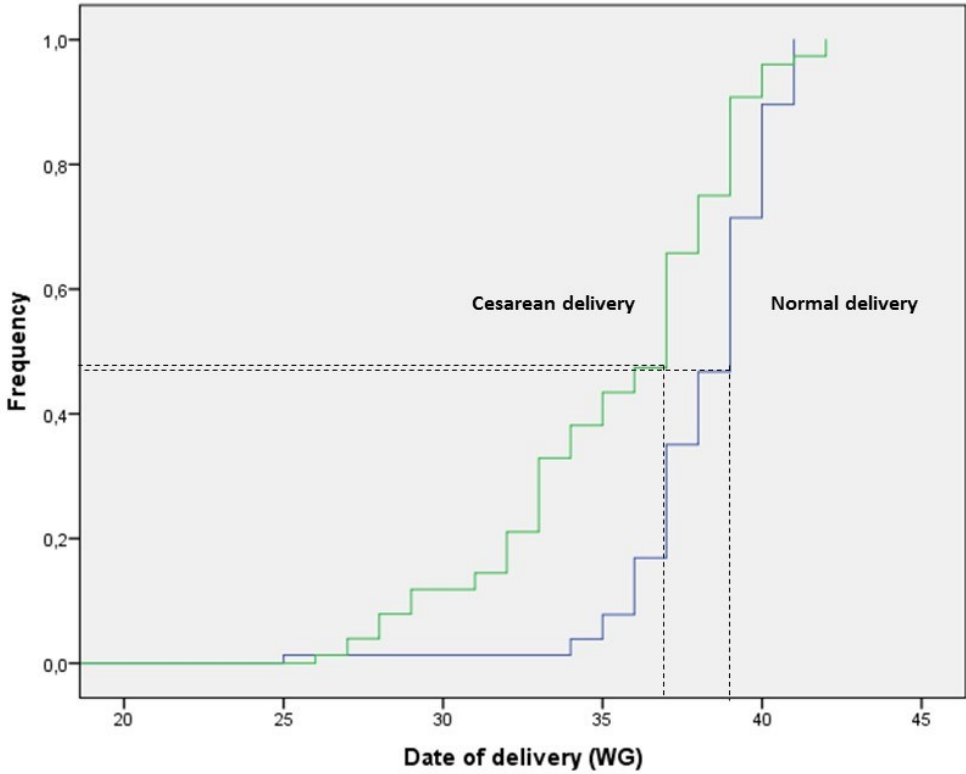


*Figure 16: Maternal and foetal complications recorded in our patients.*

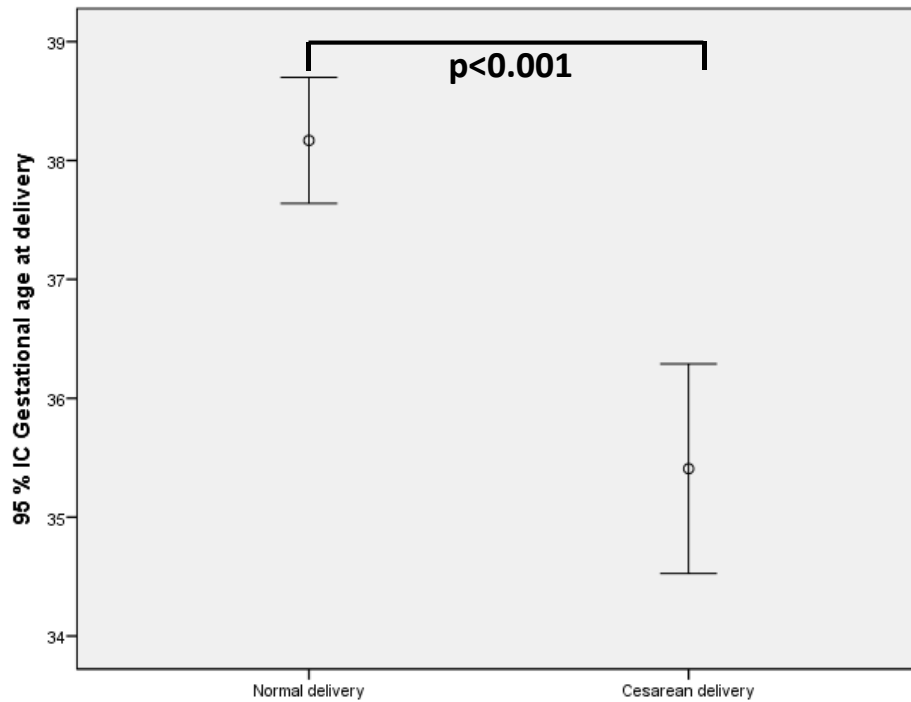
## 2.4 Delivery

Delivery was normal in 77 cases (50.3%) and by cesarean in 76 cases (49.7%). Cesarean was emergent in 50 cases (65.8%) and scheduled in 26 cases (34.2%). Gestational age at

delivery was 37 weeks of gestation (IQR: 35 - 39). Figure 12 shows the frequency and type of delivery according to the gestational age. Figure 17 and 18 shows the gestational age at delivery according to the type of delivery ( $p < 0.001$ ). Table X shows the complications recorded at delivery and postpartum management.



*Figure 17: The frequency and type of delivery according to the gestational age (Weeks of Gestation). Dotted line indicates the median value.*

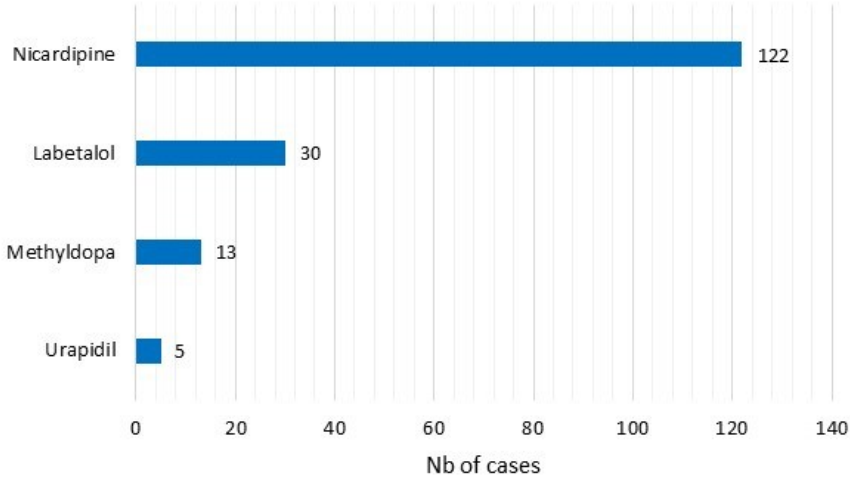


*Figure 18: The gestational age at delivery (Weeks of Gestation) according to the type of delivery ( $p < 0.001$ )*

*Table X: The complications recorded at delivery and postpartum management.*

	<b>Nb</b>	<b>nb(%) / Med(IQR)</b>
Placental abruption	76	5 (6.6%)
Postpartum hemorrhage	153	23 (15%)
Transfusion	153	16 (10.5%)
Red bloodcell transfusion	153	16 (10.5%)
Frozen plasma transfusion	153	2 (1.3%)
Platelet transfusion	153	0 (0%)
Fibrinogen administration	153	1 (0.6%)
Antihypertensive drug	153	125 (81.7%)
Magnesium sulfate administration	153	13 (8.5%)
Maternal hospitalization in ICU	153	7 (4.6%)

During hospitalization, 125 patients (81.7%) received antihypertensive drug for a median duration of 2 days (IQR: 2-3, extremes: 1-15 days). Thirty-nine patients (25.5%) received 2 drugs and 5 patients (3.3%) received 3 antihypertensive drugs. The most prescribed antihypertensive drug was nifedipine (122 patients; 97.6%). The distribution of antihypertensive drug used is reported in Figure 19.

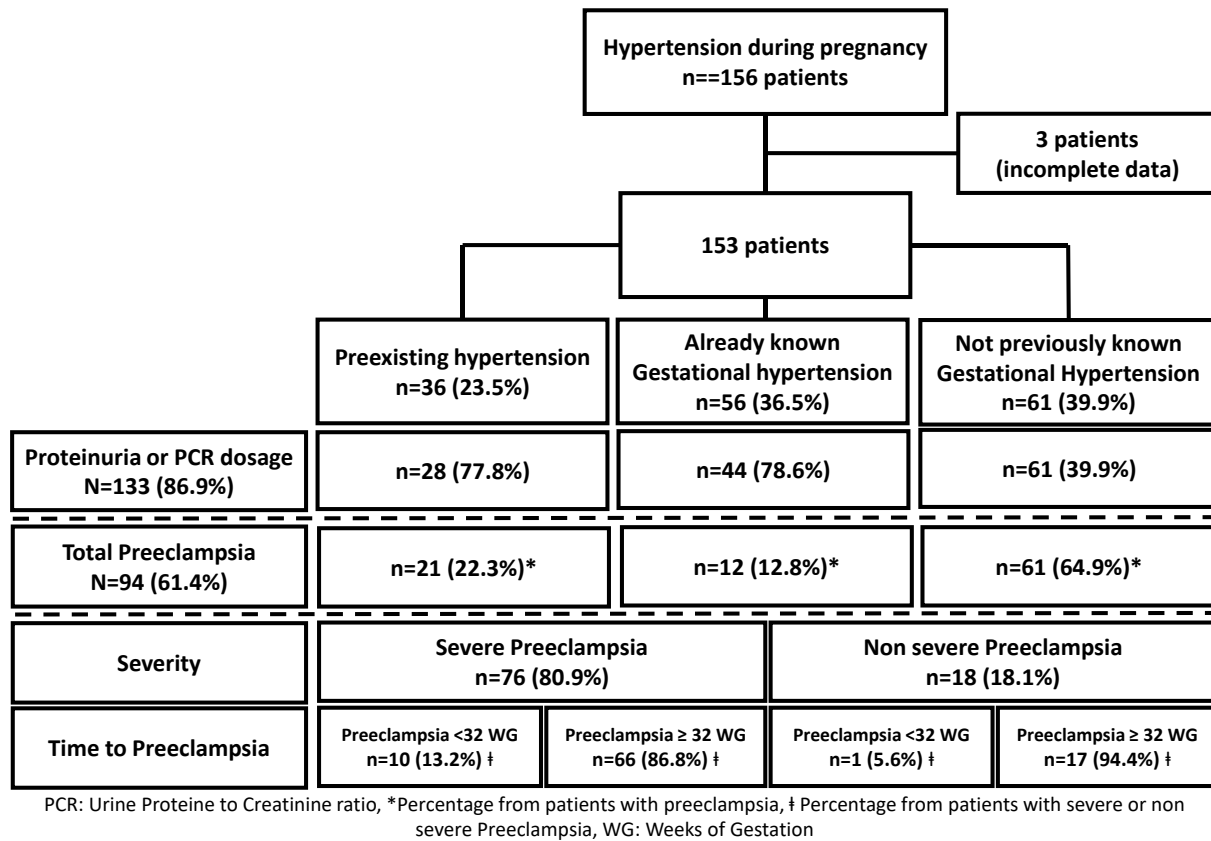


*Figure 19: The frequency of the used antihypertensive drugs.*

Thirteen patients (8.5%) received Magnesium sulfate. In patients with pre-eclampsia and patients with severe pre-eclampsia, 12 (12.7%) and 10 (13.2%) received Magnesium sulfate respectively.

### 3 Characteristics of patients with pre-eclampsia

Figure 20 shows the distribution of our patients according to the occurrence of pre-eclampsia and to the severity of pre-eclampsia.



*Figure 20: The distribution of our patients according to the occurrence of pre-eclampsia and of severe pre-eclampsia.*

#### 3.1 Associated factors to pre-eclampsia

The comparison of epidemiological and clinical variables according to the occurrence of pre-eclampsia is reported in Annex1.

##### 3.1.1 Maternal factors associated to pre-eclampsia

Maternal variables associated with the occurrence of pre-eclampsia are reported in table XI.

*Table XI: Maternal variables associated to the occurrence of pre-eclampsia in our patients*

Variable	Pre-eclampsia		No Pre-eclampsia		p
	Nb	Nb (%) / Med(IQR)	Nb	Nb (%) / Med(IQR)	
Age <20 years	94	9(9.6%)	39	0	0.045
Gestational age at admission, WG	93	36 (32 -38)	39	38 (36 -39)	0.001
Systolic arterial pressure, mmHg	94	162 (150 -175)	39	151 (145 -160)	0.001
Diastolic arterial pressure, mmHg	94	99 (90 -104)	39	94 (87 -100)	0.007
Headache	94	43 (45.7%)	39	9 (23.1%)	0.015
Edema	93	57 (61.3%)	39	13 (33.3%)	0.003
Spot Proteinuria, g/L	85	0.67 (0.3 -2.03)	34	0.14 (0.08 -0.23)	0.004
Spot urine protein to creatinine ratio, mg/mmol	75	81 (41 -226)	30	19 (13 -24)	0.011
Proteinuria in the 24-hour collection, mg	76	1.10 (0.41 -3.01)	21	0.17 (0.14 -0.18)	0.005
HELLP syndrome	94	10 (10.6%)	39	0 (0%)	0.034
Maternal complications	94	30 (31.9%)	39	5 (12.8%)	0.023
Gestational age at delivery, WG	94	37 (33 -39)	39	39 (37 -39)	0.002
Preterm birth	94	38 (40.4%)	39	8 (20.5%)	0.028
Frozen plasma transfusion	12	0 (0%)	3	1 (33.3%)	0.038
Medical follow-up	94	80 (85.1%)	39	20 (51.3%)	0.000

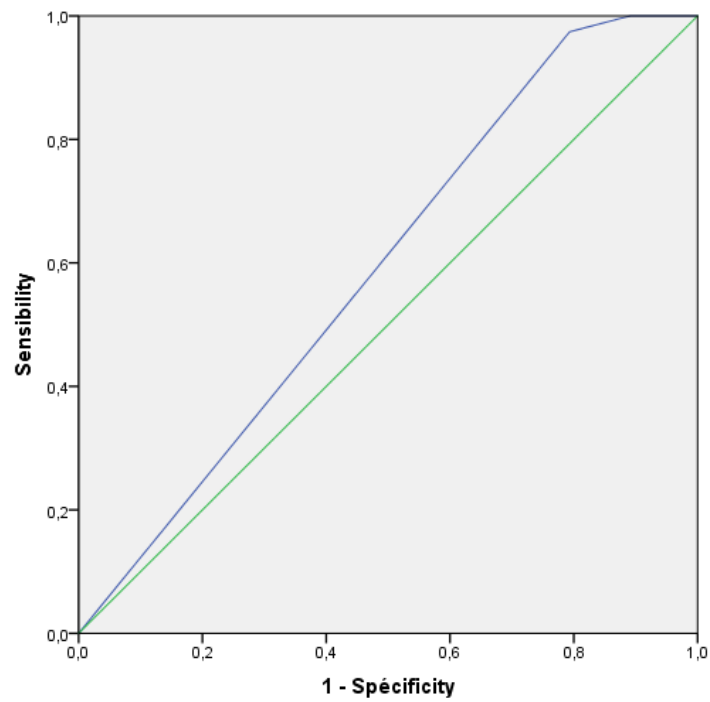
Multivariable analysis showed no relationship between any of the significantly associated factors to pre-eclampsia in univariable analysis and the occurrence of pre-eclampsia.

### 3.1.2 Foetal factors associated to pre-eclampsia

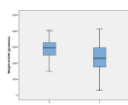
Foetal variables associated with the occurrence of pre-eclampsia are reported in table IX.

*Table XII: Foetal variables associated to the occurrence of pre-eclampsia in our patients*

Variable	Pre-eclampsia		No Pre-eclampsia		p
	Nb	Nb (%) / Med(IQR)	Nb	Nb (%) / Med(IQR)	
Umbilical artery doppler abnormality	94	16 (17%)	39	0 (0%)	0.006
Apgar score at 10 minutes	92	10 (10 -10)	39	10 (10 -10)	0.040
Preterm birth	43	41 (95.3%)	13	7 (53.8%)	0.000
Other causes of Hospitalization in neonatology	0	0	13	4 (30.8%)	0.000
Mechanical ventilation	94	19 (20.2%)	39	2 (5.1%)	0.030

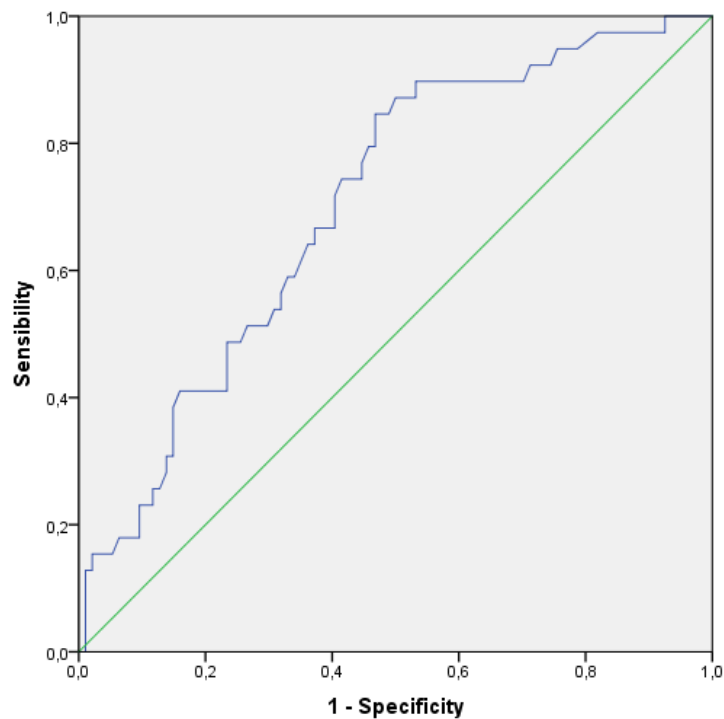


*Figure 21: ROC curve showing the relationship between the apgar score at 10 min and the presence of pre-eclampsia (AUC :0.592)*



*Figure 22: Weight at birth according to the presence of pre-eclampsia*



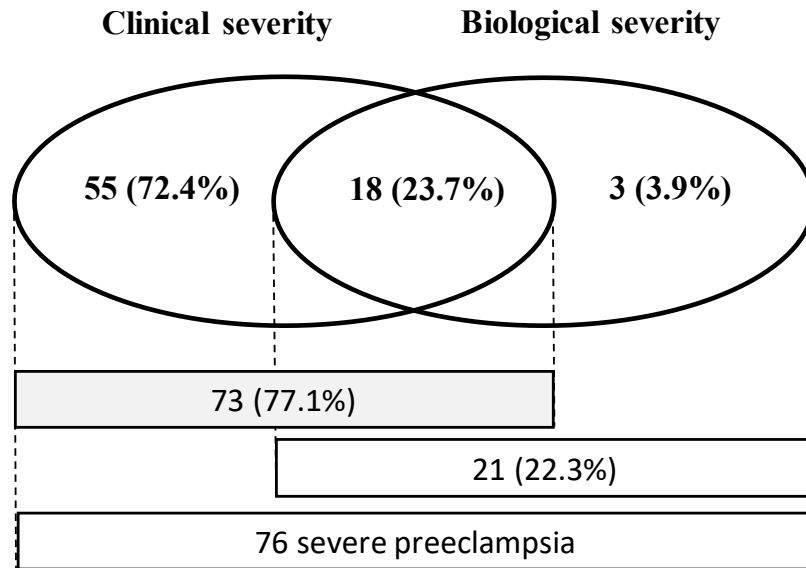


*Figure 23: ROC curve showing the relationship between the weight at birth and the presence of pre-eclampsia (AUC :0.703)*

Multivariable analysis showed no relationship between any of the significantly associated factors to pre-eclampsia in univariable analysis and the occurrence of pre-eclampsia.

### 3.2 Characteristics of patients with severe pre-eclampsia

In our patients, 76 presented severity signs of pre-eclampsia (80.9% of patients with pre-eclampsia). Clinical severity was recorded in 73 cases (77.7%) and biological severity was recorded in 21 cases (22.3%). Figure 18 shows the distribution of patients with severe pre-eclampsia.



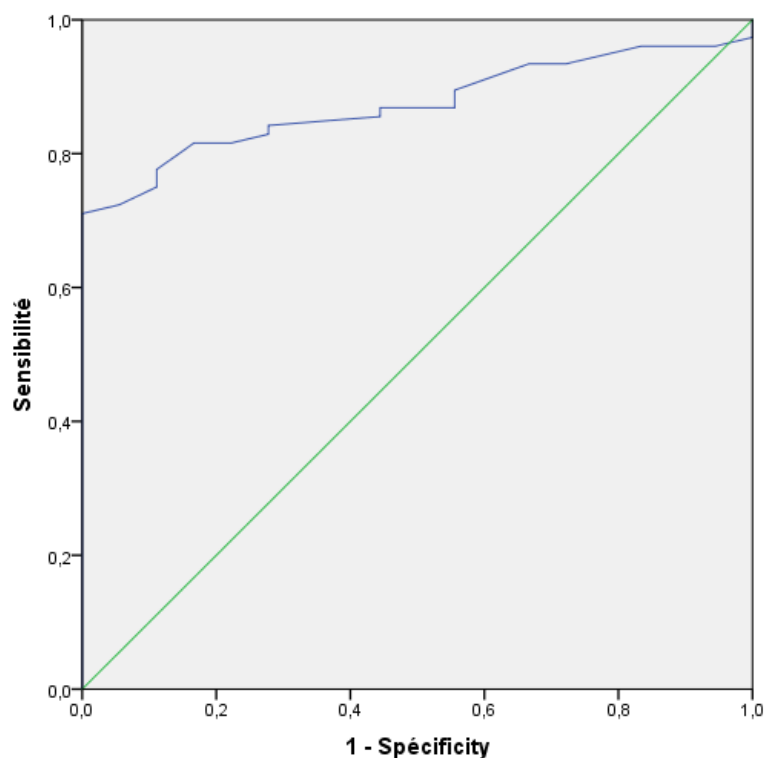
*Figure 24: The distribution of patients with severe pre-eclampsia.*

### 3.2.1 Maternal factors associated to severe pre-eclampsia

Maternal variables associated to severe pre-eclampsia are reported in table X.

*Table XIII: Variables associated to the severity of pre-eclampsia in our patients*

Variable	Severe pre-eclampsia		Non severe pre-eclampsia		p
	Nb	Nb (%) / Med(IQR)	Nb	Nb (%) / Med(IQR)	
Age, years	76	34 (28 -37)	18	30 (23 -33)	0.030
Age <20 years	76	5 (6.6%)	18	4 (22.2%)	0.043
Gestation number	76	4 (2 -5)	18	2 (1 -3)	0.025
Parity number	76	2 (1 -4)	18	1 (0 -2)	0.030
Follow-up by a midwife	76	48 (63.2%)	18	16 (88.9%)	0.035
Systolic arterial pressure, mmHg	76	167 (157 -178)	18	148 (143 -152)	0.000
Head ache	76	43 (56.6%)	18	0 (0%)	0.000
Abdominal pain	76	15 (19.7%)	18	0 (0%)	0.040
Urine creatinine, mmol/L	62	7.3 (4.1 -12.5)	13	12.6 (8.4 -17.5)	0.046
Platelet count, Giga/L	76	226 (166 -269)	18	284 (215 -326)	0.009
Complications	76	50 (65.8%)	18	5 (27.8%)	0.003
Maternal complications	76	30 (39.5%)	18	0 (0%)	0.001
Normal delivery	76	29 (38.2%)	18	14 (77.8%)	0.002
Cesarean delivery	76	47 (61.8%)	18	4 (22.2%)	0.002
Antihypertensive drug	76	70 (92.1%)	18	12 (66.7%)	0.004
Length of antihypertensive drug administration	45	2 (2 -3)	6	2 (2 -2)	0.025



*Figure 25: ROC curve showing the relationship between the systolic arterial pressure and the severity of pre-eclampsia (AUC :0.873)*

Multivariable analysis showed no relationship between any of the significantly associated factors to severe pre-eclampsia in univariable analysis and the occurrence of severe pre-eclampsia.

### 3.2.2 Foetal factors associated to severe pre-eclampsia

Foetal variables associated with the severity of pre-eclampsia are reported in table XI.

*Table XIV: Foetal variables associated with the severity of pre-eclampsia*

Variable	Severe pre-eclampsia		Non severe pre-eclampsia		p
	NB	Nb (%)	NB	Nb (%)	
Small for gestational age	76	3 (3.9%)	18	5 (27.8%)	0.001
Foetal complications	76	43 (56.6%)	18	5 (27.8%)	0.028
Foetal distress	76	41 (53.9%)	18	5 (27.8%)	0.046

### 3.3 Associated factors to preterm birth

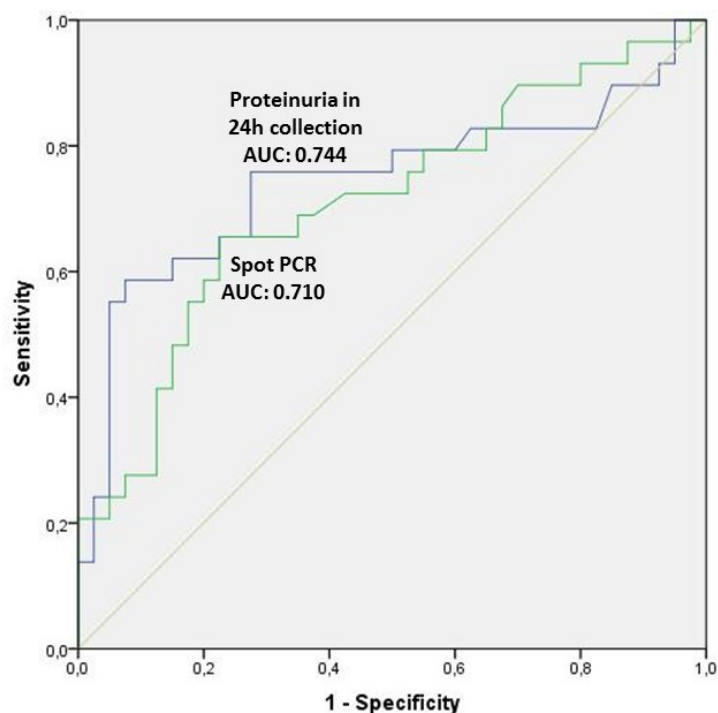
The comparison of epidemiological and clinical variables according to the occurrence of preterm birth is reported in Annex 3. Variables associated with the occurrence of preterm birth in univariate analysis are reported in table XII.

*Table XV: Variables associated with the occurrence of preterm birth in univariate analysis*

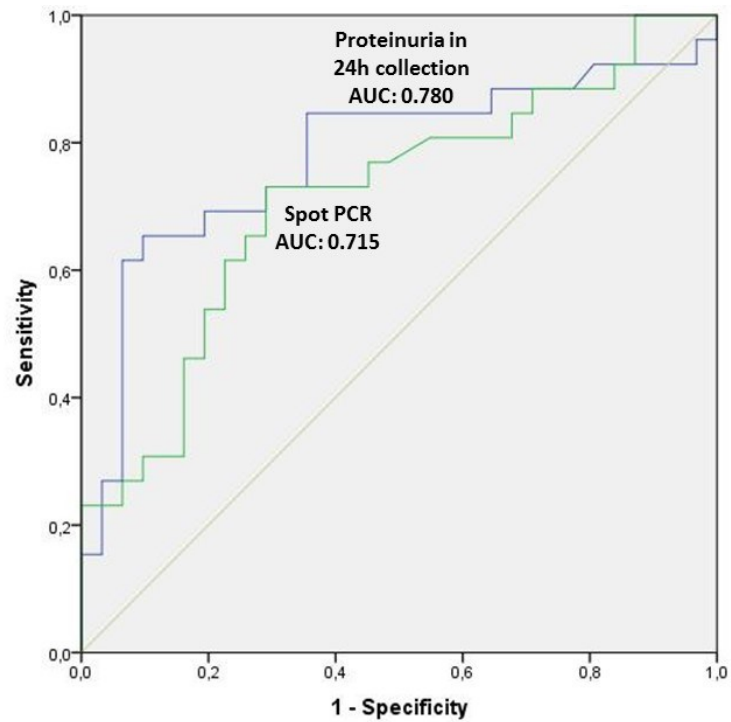
Variable	Preterm birth (+)		Preterm birth (-)		p
	Nb	Nb (%) / Med(IQR)	Nb	Nb (%) / Med(IQR)	
History of Pre-eclampsia	49	16 (32.7%)	104	14 (13.5%)	0.005
Nb of prenatal consultations	49	3 (2 - 5)	104	5 (3 - 6)	0.005
Intra uterine growth restriction	49	14 (28.6%)	104	8 (7.7%)	0.001
Umbilical artery doppler abnormality	49	11 (22.4%)	104	5 (4.8%)	0.001
Gestational age at admission	49	32 (30 - 34)	103	39 (37 - 39)	0.000
Systolic arterial pressure, mmHg	49	164 (151 - 178)	104	154.5 (145 - 164)	0.002
Diastolic arterial pressure, mmHg	49	100 (90 - 105)	104	95 (89 - 100)	0.005
Hypertension	49	47 (95.9%)	104	98 (94.2%)	0.003
Severe hypertension	47	31 (66%)	98	40 (40.8%)	0.005
Abdominal pain	49	11 (22.4%)	104	8 (7.7%)	0.010
Hyperreflexia	49	3 (6.1%)	104	0 (0%)	0.011
Pre-eclampsia	46	38 (82.6%)	87	56 (64.4%)	0.028
Spot urine proteine creatinine ratio, mg/ $\mu$ mol	33	147 (40 - 312)	72	35 (22 - 76.75)	0.011
Proteinuria in the 24 hour collection, mg	42	1.60 (0.33 - 4.07)	55	0.40 (0.22 - 1.19)	0.002
Uric acid, $\mu$ mol/L	45	328 (275 - 405)	96	292 (247 - 358)	0.014
Haptoglobin, g/L	33	0.81 (0.51 - 1.30)	68	1.11 (0.79 - 1.43)	0.032
Non dosable haptoglobin	44	11 (25%)	72	4 (5.6%)	0.002
HELLP syndrome	49	8 (16.3%)	104	2 (1.9%)	0.001
Nephropathy	49	4 (8.2%)	104	1 (1%)	0.019
Pre-eclampsia	46	38 (82.6%)	87	56 (64.4%)	0.028
Biological severity	38	16 (42.1%)	56	5 (8.9%)	0.000
Complications	49	49 (100%)	104	37 (35.6%)	0.000
Maternal complications	49	19 (38.8%)	104	21 (20.2%)	0.015
Weight at birth	49	1750 (1300 - 2080)	104	2950 (2575 - 3312)	0.000
Length of stay (postpartum)	49	8 (6 - 11)	104	5.5 (4 - 6.25)	0.000

Multivariate analysis did not show any association between variables significantly associated to preterm birth in univariate analysis and preterm birth (in patients with HDP, in non-chronic hypertensive patients with HDP, and in non-chronic hypertensive patients with pre-eclampsia).

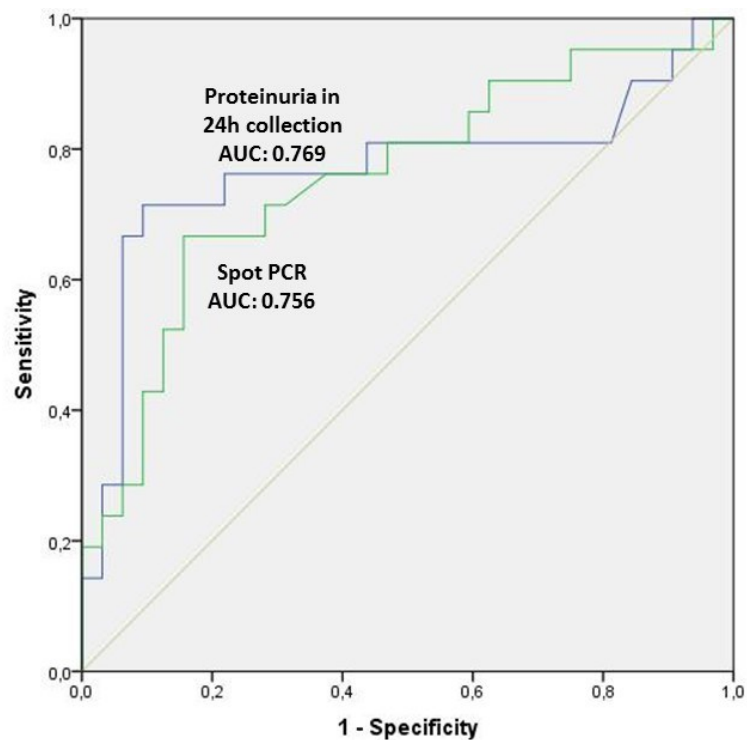
Proteinuria was correlated to preterm birth in patients with HDP or pre-eclampsia in univariable analysis. We studied the accuracy of spot proteinuria (g/L), 24-hour proteinuria (g/24h) and Spot protein to creatinine ratio (mg/mmol) to predict the occurrence of preterm birth (in patients with HDP or PE, in non-chronic hypertensive patients and in patients with chronic hypertension). Spot PCR and 24 hour proteinuria showed an acceptable accuracy to predict preterm birth in patients with HDP (Figure 20 – AUC: 0.710 and 0.744) and in patients with pre-eclampsia (Figure 21 – AUC: 0.715 and 0.780). They showed also an acceptable accuracy to predict preterm birth in patients with HDP without chronic hypertension (Figure 26- AUC: 0.756 and 0.769) and in patients with pre-eclampsia without chronic hypertension (Figure 27- AUC: 0.751 and 0.796). However, they were not discriminative to predict preterm birth (Figure 28).



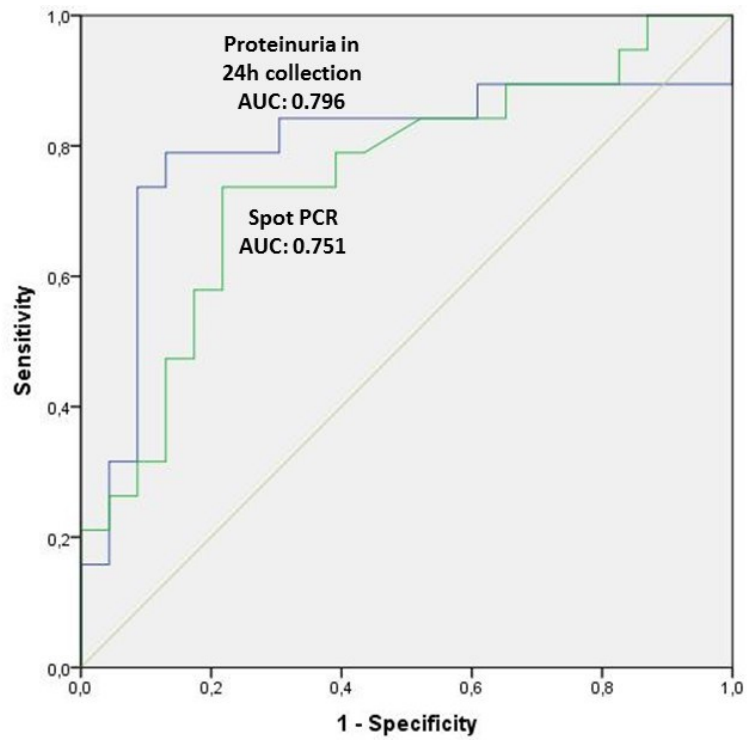
*Figure 26: The accuracy of proteinuria in 24-hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with HDP.*



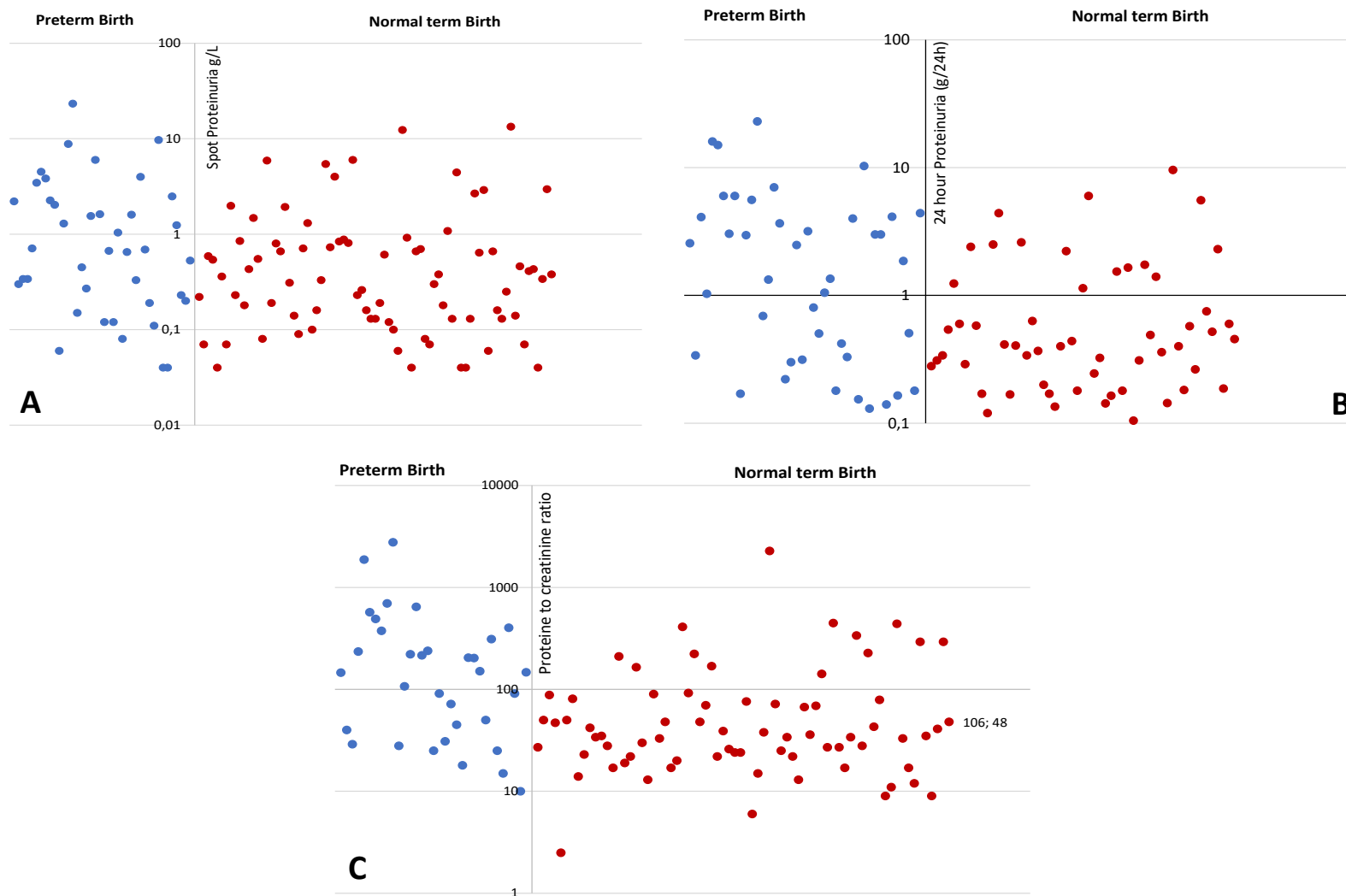
*Figure 27: The accuracy of proteinuria in 24-hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with pre-eclampsia.*



*Figure 28: The accuracy of proteinuria in 24 hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with HDP and without chronic hypertension.*



*Figure 29: The accuracy of proteinuria in 24 hour collection and spot urine to creatinine ratio in the prediction of preterm birth in patients with pre-eclampsia and without chronic hypertension.*



*Figure 30: The distribution of our patients according to spot proteinuria (Panel A), 24 hour proteinuria (Panel B) and Spot protein to creatinineratio (Panel C) and the occurrence of preterm birth in patients with HDP.*



# Discussion

## 1 History

One of the earliest descriptions of pre-eclampsia was published in 1637 by Francois Mauriceau [34]. He noted the high risk of seizures in pre-eclampsia as well as the increased risk of this condition in primigravidas. Mauriceau attributed the development of eclamptic seizures to either abnormal lochial blood flow or intrauterine foetal death. In the 1700s, Boissier de Sauvages theorized that eclamptic seizures were nature's attempt to rid itself of a "morbid element". He made the important distinction between epilepsy and eclampsia on the basis of the resolution of symptoms postpartum in the latter. Pre-eclampsia was further defined in 1843 by John Lever, who found that the urine of women with pre-eclampsia contained albumin, and by Robert Johns, who noted the characteristic symptoms of headache, vision changes and oedema in affected patients [34]. In the 1960s, researchers discovered the involvement of impaired placental implantation in pre-eclampsia, and in 1989 Roberts and al. hypothesized that the impaired placental perfusion seen in pre-eclampsia led to widespread maternal endothelial dysfunction [35].

## 2 Physiopathology

In a normal pregnancy, there is a considerable increase in uterine blood flow in order to ensure adequate supplementation for the intervillous space and, by extension, adequate fetal development. In order to achieve this result, spiral arteries undergo a process of remodeling promoted by a trophoblastic invasion of their walls. This process is known as placentation.

Any hypertensive disorder of pregnancy can result in pre-eclampsia which is multisystemic disorder with a poorly understood pathogenesis. It is likely to be the result of two interrelated stages with abnormal placentation and maternal inflammatory response. Abnormal placentation is associated to defective spiral artery remodelling, leading to reduced blood flow to the placenta. This, result on cellular ischaemia, and placental hypoxia which induce an inflammatory response with an imbalance between angiogenic (such as the vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)) and anti-angiogenic factors (the placental soluble fms-like tyrosine kinase 1 (sFlt-1) in favour of anti-angiogenic factors[36].The consequence is a widespread endothelial dysfunction, affecting all the

maternal organ systems. Indeed, the ischaemia-reperfusion damage of the placenta leads to the stress of the syncytio trophoblast (STB) which causes necrosis, apoptosis and release of excess placental debris (STB microparticles and vesicles) into the maternal circulation. This mechanism increases inflammatory responses.

STB microparticles and pro-inflammatory cytokines are responsible of a widespread endothelial dysfunction and lead to the clinical signs of PE, such as hypertension, thrombotic micro-angiopathy, presenting as proteinuria, hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, pulmonary or cerebral edema and seizure. It causes also foetal impacts such as fetal growth restriction and oligohydramnios. It is therefore believed that placental ischaemia-reperfusion injury is central to the development of PE[36].

### 3 Epidemiology

#### 3.1 Hypertensive disorders of pregnancy

The incidence of the hypertensive disorders of pregnancy varies from country to country and according to the used classification. Indeed, in low- and middle-income countries (LMICs), incidence estimates are restricted to hospital surveys which can overestimates the rate because of the high proportion of births occurring in the home.

In a multinational Survey on maternal and newborn health in 29 countries across Africa, Asia, Latin America and the Middle East (2010–2012), 313.030 women were included who were admitted to 357 health facilities. The prevalence of chronic hypertension, pre-eclampsia, or eclampsia was 2.7% of the total number of women included in the study [37]. This prevalence estimate ranged between 1.8% in the Middle East and 4.5% in the Americas region. In contrast, smaller single hospital-based surveys have reported higher hypertensive disorder of pregnancy rates, ranging from 4.0% to 12.3% [38–41]. However, in high-income countries, several large national cohorts report a hypertensive disorder of pregnancy incidence of 4.6–9.2% [42–45]. In addition, The diagnostic criteria used in these studies vary among published international guidelines, particularly between the research and clinical setting, and in the discrimination between gestational hypertension, pre-eclampsia, and severe pre-eclampsia[4,10,17,23]. In one of the biggest survey in the USA which monitored ~39 million births over a 10-year period, the incidence of hypertensive disorders in pregnancy (pre-

eclampsia, eclampsia, gestational hypertension and chronic hypertension) is estimated to be 5.9% [46,47].

Our study is a single hospital-based survey. It was conducted in Cayenne obstetric center, the only tertiary obstetrics center of the department (60% of births in FG) and the referral one for at-risk pregnancies and deliveries coming from all the department and from the border's countries. Patients coming from the border's countries are most of the time without documents. They contribute to the high level of poverty (above 44%) and to the precariousness rate. Our hospital works according to international, European and French standards. It is the illustration of the paradox, hospital in high-income country dealing with low-income and precarious population.

The rate of HDP in our center was about 7.4% and the rate of PE was about 4.6% in 2018 (*Perinat Guyane Network data*). In our study, it was 12.6% of patients who gave birth during the study period. Further studies in collaboration with the *Perinat Guyane Network* will allow us to calculate this rate in all French Guiana.

## 3.2 Pre-eclampsia

Pre-eclampsia is defined as significant proteinuria ( $\geq 0.3$  g/24 h or spot urine PCR  $\geq 30$  mg/mmol) in the setting of new-onset hypertension occurring after 20 WG or pre-existing hypertension (superimposed pre-eclampsia) [4,46]. It can be inaugural in patients without diagnosed hypertension [46]. It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or in patients with pre-existing hypertension, renal disease, or diabetes. It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity. The only cure is delivery [48]. It should be suspected when de novo hypertension is accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelets and/or abnormal liver function. Pre-eclampsia is a leading complication of pregnancy affecting 4–5% of pregnancies worldwide [8,49–51] and incurring a large burden of maternal and foetal morbidity and mortality [52].

Pre-eclampsia and eclampsia are estimated to cause over 50,000 maternal deaths worldwide per year [53], with substantial variance in frequency by geographical region. It is

worth noting that rates of hypertensive disorders of pregnancy have risen in industrialized countries in relation to African- American women at higher risk of associated mortality than Hispanic, American- Indian, white and Asian or Pacific- Islander women [54].

The rate of PE in our center was about 4.6% in 2018 (*Perinat Guyane Network data*). In our study, pre-eclampsia was diagnosed in 70.7% of patients with HDP and 7.5% of patients who gave birth during the study period. It was severe in 80.9% of cases and was responsible of higher rate of cesarean delivery and preterm birth. Multivariable analysis failed to find any factor which can predict the occurrence of pre-eclampsia or severe pre-eclampsia. For this reason, we believe that women with HDP and pre-eclampsia or organ dysfunction should be hospitalized and closely monitored to detect the occurrence of complication. Further studies are needed to estimate the epidemiology of HDP and pre-eclampsia in French Guiana and to search for the characteristics of predisposed patients and risk factors for maternal and foetal complications.

## 4 Risk factors of hypertensive disorders of pregnancy

Risk factors of hypertension disease in pregnancy can be divided in modifiable and non-modifiable factors[17].

### 4.1 Modifiable factors

#### 4.1.1 Body mass index

Body mass index was found to be associated to the risk of HDP [55–58]. Ye and al.[55] found that subjects with a BMI of 24.0–27.9 and  $\geq 28.0$  kg/m<sup>2</sup> showed a 1.79- and 3.11-fold higher prevalence of HDP, respectively compared with subjects with a BMI of 24.0 kg/m<sup>2</sup>. Bryant and al.[56] showed that a 5 kg/m<sup>2</sup> increase in BMI is associated with a 1.60-fold higher prevalence of HDP.

Lee and al.[58] found that subjects with a BMI  $> 24.2$  and  $< 19.8$  kg/m<sup>2</sup> were at a 2.4 and 0.6 fold higher risk of PE compared with subjects with a BMI of 19.8–24.2 kg/m<sup>2</sup>.

Wang and al.[57] in a meta-analysis has reported that subjects with a BMI of  $< 20.0$ , 25.0–29.9, 30.0–34.9 and  $\geq 35.0$  kg/m<sup>2</sup> had a 0.77-, 1.70-, 2.93- and 4.14 fold higher risk of PE compared with subjects with a BMI of 20.0–24.9 kg/m<sup>2</sup>, respectively.

In all these studies, an elevated BMI but also a low BMI were associated to a higher risk of HDP. In our study, BMI was available in 136 women. The median value was 29 Kg/m<sup>2</sup> (IQR: 25-34). It was  $\leq 18$  Kg/m<sup>2</sup> in 2% of cases, between 19 and 24 Kg/m<sup>2</sup> in 20% of cases and  $\geq 30$  Kg/m<sup>2</sup> in 41.8% of cases. Since all our patients presented HDP, the design of our study did not allow us to evaluate the association between BMI and the occurrence of HDP. In addition, we did not find any relationship between BMI, or obesity (BMI  $\geq 30$  Kg/m<sup>2</sup>) and the occurrence of pre-eclampsia.

#### 4.1.2 Anemia

Abalos and al. [37] found that subjects with anemia had a 4.06 fold times higher risk of PE than subjects who were not anemic. In our work, haemoglobin concentration was not associated to the occurrence of PE or severe PE.

#### 4.1.3 Smoking

In some studies, smoking appear as a protective factor against gestational hypertension and PE[59–61]. Ros and al.[59] found that the odds ratios of subjects who smoked 1-9 and  $\geq 10$  cigarettes per day were 0.86 and 0.48 for gestational hypertension and 0.64 and 0.55 for PE, respectively, compared with subjects who did not. Conde-Agudelo and al.[60] and Wei and al.[61] showed an inverse association between cigarette smoking and the risk of PE. Subjects who habitually smoked during pregnancy showed a 0.67-fold lower risk of PE compared with subjects who were not habitual smokers [60].

However, in other studies, smoking was an associated factor to gestational hypertension and PE[62–64]. Jacobs and al.[62] found a 1.57 fold higher risk of GH among subjects with habitual smoking compared with subjects who were not habitual smokers. Hayashi and al.[63] found that subjects who smoked during pregnancy had a 1.20-fold higher risk for PIH compared with subjects who did not smoke during pregnancy. In addition, Kobashi and al.[64] has also shown that the frequency of smoking before pregnancy was significantly higher in women with BMI of  $\geq 24.0$  kg/m<sup>2</sup> and PE.

In our work, we have not studied the smoking behavior of our patients. So, we cannot evaluate this association. However, an advice is regularly given to our patients against smoking.

#### 4.1.4 Alcohol intake

A positive association between alcohol intake and the risk of gestational hypertension and PE is reported [55,65]. Subjects with alcohol intake showed a 1.75-fold higher risk of HDP compared with subjects without alcohol intake [55]. However, a prospective study of Americans has shown that subjects who were habitual drinkers had a 0.55-fold lower risk of PE compared with subjects who did not drink habitually [65].

In our work, we have not studied the alcohol intake in our patients. So, we cannot evaluate this association. However, an advice is regularly given to our patients against alcohol drinking.

#### 4.1.5 Education

In some studies, patients with high education level showed a lower risk of gestational hypertension and PE[37,66]. This association was not found in other studies [58,67]. A cross-sectional study has shown that those who graduated from university or college had  $\approx 35\%$  lower pregnancy induced hypertension (PIH) prevalence compared with subjects who completed elementary school [66]. The study based on the WHOMCS database has shown that subjects who went to school for 0 years and 5-8 years has shown 1.20- and 1.21-fold higher risk of PE than subjects who went to school for  $\geq 11$  years[37]; however, in this study, the risk of PE among subjects who went to school for 1-4 years, 9-11 years and  $\geq 11$  years was not significantly different[37]. Notably, studies of Latin Americans and Taiwanese subjects have shown no association between educational status and the risk of PE [58,67].

In our study 20.5% of women were graduated from university and had high level education. This parameter was not associated to pre-eclampsia, severe pre-eclampsia or preterm birth.

### 4.2 Non-modifiable factors

#### 4.2.1 Maternal age

A higher maternal age was also positively associated with the risk of PE[37,55,58,62,66–68]. Indeed, in a Chinese study[55], subjects aged 35–39 and  $\geq 40$  years had a 1.84- and 2.39-fold higher risk of HDP than subjects aged 25–29 years. In another Chinese study[66], subjects aged  $\geq 35$  years had  $\approx 60\%$  higher prevalence of PIH than those aged 20-34 years. In

an Australian study [62], subjects aged  $\geq 40$  years had a 1.45-fold higher risk of HDP compared with subjects aged 30-34 years. In other studies from Latin America and Taiwan, women aged  $\geq 35$  years had 1.67- and 1.8-fold higher risks of PE compared with similar subjects aged 20-34 years [58,67]. The study based on the WHOMCS database has shown that subjects aged  $>35$  years had a 1.78-fold higher risk of PE compared with subjects aged 20–35 years [37]. A cross-sectional study of Americans has examined the association between age groups of mothers and the risk of PE [68]. Subjects aged  $\geq 35$  years showed a 1.7-fold higher risk of PE than those aged 30-34 years. However, this association was not observed among White subjects [68].

However, other epidemiological studies has shown no association [55,58,62,66,67,69] or an inverse relationship [37,68] between higher maternal age and the prevalence of HDP, gestational hypertension (GH) or PE. Indeed, a positive association between lower maternal age and the prevalence of PE has been shown in both White and non-White American subjects [68]. White subjects aged 20-24, 18-19 and 15-17 years had a 1.4-, 1.8- and 2.6-fold higher risk of PE compared with those aged 30-34 years, respectively. Subjects aged 18–19 and 15–17 years had a 2.0- and 2.4-fold higher risk of PE, respectively, compared with subjects aged 30–34 years [68]. The study based on WHOMCS database has shown an inverse association between lower maternal age and the risk of PE [37]. Subjects aged 17-19 years had a 0.72-fold lower risk of PE compared with subjects aged 20-35 years [37].

In our study, the median age was 33 (IQR 28 - 38) years. Six patients (3.9%) were less than 18 years old. Age was higher in patients with chronic hypertension. However, age was not associated to pre-eclampsia, severe pre-eclampsia or preterm birth in multivariate analysis.

#### 4.2.2 Parity

Primiparity and multiparity were found to be associated with a higher risk of GH and PE [37,55,58,62,65,67,69]. In our study, primipara was found in 28.8% and multiple pregnancy was recorded in 53.5% of women. No association between parity and pre-eclampsia or severe pre-eclampsia was found in multivariable analysis.

### 4.2.3 History of complicated pregnancy

Studies of Americans have shown a positive association between hypertensive disorders in the first pregnancy and the risk of hypertensive disorders in the second pregnancy [70,71]. Subjects with GH and PE/eclampsia in the first pregnancy had a 3.0 to 6.3-fold higher risk of hypertension in the second pregnancy[70,71]. Duckitt and al. [72] in a systematic review found that subjects with PE in a previous pregnancy had a 7.19 to 7.6-fold higher risk of PE compared to those who did not[72].

In our study, a history HDP was found in 19.5% of cases. This parameter was not associated to pre-eclampsia or to severe pre-eclampsia in multivariable analysis.

### 4.2.4 Gestational diabetes

Gestational diabetes (GD) often occurs together with HDP. It can be associated with a 1.87 to 3.11-fold higher risk of HDP [55,59,62,67]. In our study, 33 patients (21.6%) had GD. The design of our study did not allow to search for a relationship between GD and HDP.

### 4.2.5 Chronic hypertension

Subjects with a history of chronic hypertension had a 1.99- to 8.32-fold higher risk of PE compared with subjects who did not [37,67,73]. In our patients, chronic hypertension was recorded in 23.5% of cases. Of them, 58.3% had superimposed PE. Chronic hypertension was not associated to a greater risk of PE or severe PE.

### 4.2.6 Other chronic diseases

The study based on the WHOMCS database has shown that histories of heart disease, renal disease and hepatic disease are positively associated with the risk of PE [37]. The odds ratios of the history of these diseases are 2.12, 4.52 and 4.07, respectively[37]. No chronic diseases were diagnosed in our patients.

### 4.2.7 Urinary tract infection

Urinary tract infection has been reported to be a risk factor of HDP [37,58]. Urinary tractinfection during pregnancy has been associated with a 1.6 to 4.8-fold higher risk of PE [37,58].However,another study has shown noassociation between urinary tract infection and the risk of GH [62].



#### 4.2.8 Family history

A family history of hypertension and type 2 diabetes are reported to be a risk factors of HDP (OR: 3.17- 2.67)[55].A family history of PE has also been reported to be a risk factor of PE. A systematic review has shown that subjects with a family history of PE had a 2.9-fold higher risk of PE [72].

#### 4.2.9 Genetic factors

Many studies have investigated the association between genetic variants and HDP. An association with the M235T variant of the angiotensinogen (AGT) gene has been shown. However, there are racial differences among these associations. In Caucasian subjects, Ward and al.[74] have shown that the frequency of the TT genotype of AGT is significantly higher in primigravid PE (65%) than in primigravid controls (40%). In Japanese subjects, the frequency of the TT genotype is significantly higher in primigravid HDP(93% in PE and 94% in GH) than in primigravid controls (77%) [75]. Zafarmand and al.[76]found that the M235T polymorphism was associated with a history of elevated blood pressure during pregnancy [76].

In a Brazilian study, the T allele of the rs1319501 of the nicotinamide phosphoribosyl transferase (NAMPT) gene was found in 82% of patients with PE vs. 73% in controls (OR=1.626, CI95% : 1.170–2.257) [77]. In a Chinese study, the G allele of rs 2228570 of the Vitamin D receptor (VDR) gene was found to be associated to the risk of PE (62% in PE vs. 55% in controls, OR=1.137, CI95% : 1.111–1.610) [78].

In our center, we did not perform genetic investigations in patients with HDP. Given the high prevalence of HDP in our region, a project of a research program will be designed to investigate genetic variants of our patients.

### 5 The diagnosis value of proteinuria

The diagnosis of pre-eclampsia is based on the presence of HDP after 20 WG with significant proteinuria [26]. Proteinuria is best measured using a 24-hour urine collection [79] and significant level is defined as total protein $\geq$ 300 mg/day. However, this test needs a delay of more than 24 hours to collect urines and to dose proteins. For this, it did not allow rapid decision making about the need for delivery or admission in women with suspected pre-eclampsia.

A spot protein creatinine ratio (PCR) is used to indicate significant proteinuria when  $\geq 30$  mg/mmol [79]. It can be performed quickly on a single urine sample and provides a rapid result that can facilitate efficient clinical management with a high negative predictive value. However, a positive test should always be followed up by a 24-hour urine collection and proteinuria dosage [79]. Ramos and al. [80] found that the PCR measured in a single urine sample taken from hypertensive pregnant women showed good sensitivity and specificity for the diagnosis of 24-h proteinuria  $\geq 300$  mg. In a meta-analysis, Morris and al. [81] found that the maternal spot urine PCR shows promising diagnostic value for significant proteinuria in suspected PE. The existing evidence is not, however, sufficient to determine how PCR should be used in clinical practice. Insufficient evidence exists to predict adverse pregnancy outcome.

In practice, clinical management is often based on dipstick assessment for proteinuria. Thus, the management of PE is initiated based on significant proteinuria on dipstick  $\geq 2+$  in presence of strong clinical suspicion. However, practitioners should be aware from the poor sensitivity of dipstick testing (NPV: 0.6) [79] especially in women where PE is strongly suspected with a negative urine dip. This can be responsible of many missed cases of PE when relying on dipstick testing alone. A false positive value of dipstick can also be induced by urine infection.

In case of proteinuria without hypertension, women should be monitored for development of PE or other renal disease, but not treated as preeclamptic. Indeed, as many as 51% of women presenting with proteinuria without hypertension will go on to develop PE in the remainder of pregnancy [82]. Baba and al. [83] showed that normotensive pregnant women had a significant correlation between the PCR and 24-hour urine protein level. All normotensive pregnant women with a PCR  $> 85$  mg/mmol had significant proteinuria, suggesting that a PCR  $> 85$  mg/mmol may be the 'rule-in' threshold of significant proteinuria in this population.

In our study spot PCR was strongly correlated to 24-hour collection proteinuria. It did not differ between patients with and without chronic hypertension. After multivariable analysis, spot PCR and 24-hour collection proteinuria levels were not associated to the risk of severe PE nor to the risk of preterm birth in the general population and in the subgroups with and without history of chronic hypertension. Indeed, in patients with history of chronic hypertension, a preexisting glomerular injury can cause protein leakage in the urines

independently of pre-eclampsia. For this, we analyzed patients with and without chronic hypertension separately to avoid this potential confounder factor.

## 6 Complications of hypertensive disorders of pregnancy

HDP is predisposing factor to maternal and foetal complications.

### 6.1 Maternal complications

Women with HDP can develop complications during pregnancy (Table XIII) and are at risk of late complications during their life[30,84,85].

*Table XVI: Maternal complications of pre-eclampsia by organ system (from [30])*

Cardiorespiratory	Neurological	Renal	Hepatic	Hematological
ARDS	Eclampsia	Acute tubular necrosis	Periportal inflammation	Thrombocytopenia
Pulmonary edema	Cerebral thrombosis or hemorrhage	Acute kidney injury	Hepatic dysfunction	DIC
Cardiomyopathy	PRES	Glomerular endotheliosis	Hepatic hematoma/rupture	Microangiopathic hemolysis
Generalized edema	Altered mental status		Acute fatty liver of pregnancy	Venous thromboembolism

**Abbreviations:** ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulopathy; PRES, posterior reversible leukoencephalopathy syndrome.

#### 6.1.1 Pre-eclampsia

Pre-eclampsia is the main complication of HDP. It can complicate chronic hypertension or, it can occur without any tensional manifestation. It is characterized by generalized endothelial damage, which can result in multisystem disorder and in widespread end-organ damage. Maternal deaths attributable to pre-eclampsia are mainly related to cerebral or hepatic complications [86].

#### 6.1.2 Severe pre-eclampsia

Severe Features of Pre-eclampsia are defined by SBP $\geq$  160 mmHg or DBP $\geq$ 110 mmHg, thrombocytopenia, impaired liver function, severe persistent right upper quadrant and/or epigastric pain, progressive renal insufficiency, pulmonary edema or new-onset cerebral or

visual disturbances[27]. The debate between setting the systolic blood pressure definition of severe hypertension at either 160 mm Hg or 170 mm Hg needs to be resolved because of rising concerns about lethal maternal stroke risks at the lower threshold for blood pressure[87]. None of the classification systems seemsto have been independently assessed for the ability to identify women and fetuses at heightened risk of the adverse events that make pre-eclampsia so important[12].

Our study, failed to identify factors allowing a triage of patients at risk of severe pre-eclampsia. Probably because of the small sample of our patients. However, other studies failed also to find such association. Our explanation is that severe pre-eclampsia depends on the severity of the immune reaction. For this, epidemiological studies are not sufficient to detect those patients. Currently, we are planning a longitudinal observational study in our unit on a largest sample of patients and we are working on a project of a Hospital Program of clinical Research to perform a deeper analyze of our patient's characteristics allowing probably a more precise screening of women exposed to develop severe pre-eclampsia.

### 6.1.3 HELLP syndrome

HELLP syndrome is characterized by Hemolysis (anemia with blood film evidence of hemolysis), Elevated Liver enzymes showing hepatic dysfunction (transaminitis greater than twice the normal range), and Low Platelets (platelet count of less than 150,000/dL) [12,31]. It occurs in around 5% of pre-eclampsia cases [88]and 10%–20% of severe pre-eclampsia. It is associated with 1.1% maternal mortality and severe morbidity including disseminated intravascular coagulopathy, liver hematoma, liver failure, and renal failure [89].The reported perinatal mortality rate in case of HELLP is at 6%-17%[90,91].An initial minor derangement in transaminases and platelets can deteriorate rapidly. Blood tests should be repeated every 6-12 hours if the trend is worsening and the decision has been made to prolong pregnancy to allow administration of corticosteroids for foetal lung maturity. HELLP requires multidisciplinary care and should be managed in intensive care unit.

In our study, HELLP was diagnosed in 6.5% of patients. It was a strong conductor to a prompt delivery and to hospitalization in intensive care unit. Maternal and foetal outcomes were favorable in all cases.

#### 6.1.4 Renal impairment

Renal perfusion and filtration increase in normal pregnancy, and creatinine levels should therefore be lower than normal [92]. Creatinine level over 90  $\mu\text{mol/L}$  can be sufficient to diagnose pre-eclampsia in the presence of hypertension even without proteinuria [10]. Acute kidney injury (AKI) as a complication of pre-eclampsia affects only about 1% of cases [52]. However, when it is associated with HELLP, AKI is much more common, occurring in 7-15% of cases [89,93]. During pre-eclampsia, renal impairment is due to glomerular endothelium damages (glomerular endotheliosis) worsened by the state of relative intravascular volume constriction. Renal impairment usually resolves with treatment of the pre-eclampsia. However, it may be worsened by the practice of fluid restriction or diuretics in management of severe pre-eclampsia, which make difficult the management of coexisting renal injury and pulmonary edema. It is worth noting that the diagnosis of AKI in pregnancy has not been standardized either in practice or research[94].

In our study, a renal injury was diagnosed in 3.3% of cases. All patients recovered well and none of them presented a progression to chronic kidney disease.

#### 6.1.5 Pulmonary edema

In normal conditions, the endothelium plays the function of a selective permeable barrier to regulate plasma fluids exchanges, and molecules and cells trafficking. Pre-eclampsia, is a multisystem disorder characterized by generalized endothelial damage. This can lead to an increased permeability of the endothelial cell. In addition, hypoalbuminemia leads to reduced oncotic pressure favoring the leak of fluid from the intravascular to the interstitial space according to Frank–Starling law. This result on edema both on the lungs and in the peripheral tissues leading to a relative intravascular volume depletion. For this reason, careful fluid management is critical in all women with pre-eclampsia especially in the setting of concomitant renal injury. Accordingly, hospitalization and monitoring in the setting of an intensive care unit is most appropriate for women with signs of pulmonary edema in pre-eclampsia.

#### 6.1.6 Eclampsia/cerebral hemorrhage

Eclampsia literally means lightning, and it is the rapidity of the onset that is so concerning. Eclampsia refers to generalized tonic-clonic seizures in a pregnant or recently delivered

woman with no other attributable cause. It complicates 1%-2% of severe pre-eclampsia and account for 10% of severe maternal morbidity [29]. The management of eclampsia should include prompt treatment of seizures and search for another underlying cause. Generally, all generalized seizures in pregnancy after 20 weeks should be managed as eclampsia unless a clear alternate cause (hypoglycemia, head trauma or known epilepsy) is identified. Seizures can arise with no or minimal preceding symptoms and signs, or in a woman who has had stable “mild” disease for several weeks. The most common preceding symptoms are severe headache, visual disturbance, and nausea, and may be present in 79% of cases. Eclampsia is about 10-30 times more common in developing countries, largely because of differences in the quality of antenatal monitoring [8].

Cerebral injury is caused by a failure of autoregulation related to endothelial damage, exacerbated by acute or large changes in the blood pressure. A common finding in eclampsia is posterior reversible leukoencephalopathy syndrome (PRES) [95], vasogenic edema in the posterior cerebral circulation, a finding also seen in hypertensive encephalopathy. The hypertension associated with eclampsia and PRES is often less severe than in nonpregnant hypertensive encephalopathy, and it is possible that the endothelial damage associated with pre-eclampsia predisposes to this syndrome even at lower blood pressure.

In our study, 3.9% of patients presented eclampsia. Management consisted on immediate benzodiazepine administration, emergent cesarean and hospitalization in intensive care unit. All of these patients developed PRES syndrome documented on the cerebral MRI.

### 6.1.7 Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is characterized by unspecific symptoms starting during the third trimester such as nausea, vomiting, jaundice, malaise, and anorexia, with higher levels of transaminases and bilirubin in a short period of time. Coagulopathies, including disseminated intravascular coagulation (DIC) and hemolysis, with increased lactic dehydrogenase (LDH). Clinical evaluation with at least six Swansea criteria is considered sufficient to accurately diagnose the disease [31]. The definite diagnosis is confirmed by anatomopathological exam on liver biopsy.

### 6.1.8 Long term complications

- Cardiovascular diseases

Patients with pre-eclampsia are at increased risk of long-term adverse health outcomes and cardiovascular diseases (CVD)[84,85]. For this, the American Heart Association now recommends a pregnancy history as part of the cardiovascular risk evaluation of women [96]. Indeed, women with pre-eclampsia are at greater risk of hypertension, ischaemic heart disease, peripartum cardiomyopathy and stroke [16,97–99]. Pre-eclampsia and CVD share many common risk factors, such as chronic hypertension and obesity. Whether the long-term CVD risks that are associated with pre-eclampsia result from persistent vascular damage that is induced during the affected pregnancy or simply reflect common pre-existing risk factors that are shared by pre-eclampsia and CVD is unknown.

- Metabolic syndrome

Women with pre-eclampsia are also at greater risk of metabolic syndrome, including increased levels of fasting blood glucose, insulin, triglycerides and total cholesterol [98,100]. For this, a periodic assessment of blood pressure, lipids, fasting blood glucose and body mass index are recommended in women who have a history of preterm or recurrent pre-eclampsia[4].

- Renal disease

The incidence of end-stage renal disease (ESRD) is also increased in women with a history of pre-eclampsia[101,102]. Conversely, the risks of adverse pregnancy outcomes and pre-eclampsia are increased in women with chronic kidney disease or a history of acute kidney injury, even after a return to apparently normal renal function [103,104].

## 6.2 Foetal complications

Pre-eclampsia incurs a large burden of foetal morbidity and mortality, with substantial contribution to prematurity of the fetus [21,46,52,105]. It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity since the only cure is delivery [48]. In French Guiana, Leneuve-Dorilas and col. [21] found that gravidic hypertension and pre-eclampsia were a major contributor to induced early preterm delivery. Indeed, gravidic hypertension was associated to 66.7% of very preterm delivery (95% CI=8.2 (2.8–24.2); adjusted OR: 8.4 (1.5–45.5); p=0.01) and pre-eclampsia was associated to 94.1% of very preterm delivery (95% CI=75.7 (16.8–340.3); adjusted OR: 121.7 (21.6–684.7); p=0.0001). They found also that gravidic hypertension and pre-eclampsia were

predictors of spontaneous and induced preterm birth delivery in French Guiana with an adjusted OR: 22.9 (1.8– 299) ; p=0.02; and 746.3 (127.3–4373.6) ; p=0.0001 respectively.

Koike and al.[105] showed that The risk of pre-eclampsia-related preterm delivery was 54.4 times (17.2 to 172.5) higher in women with a previous pre-eclampsia-related preterm delivery than in women with a previous term delivery (5/19 vs. 5/1034). Women who had a history of pre-eclampsia-related preterm birth had a greater risk of pre-eclampsia-related preterm birth in a subsequent pregnancy as compared with women with a previous term birth.

Thangaratinam et al. [106] conducted a review to determine the accuracy with which the amount of proteinuria predicts maternal and foetal complications in women with pre-eclampsia. They found that for prediction of adverse foetal outcomes, the only statistically significant results in the prediction of stillbirths were observed for cut-off levels of 5 g/24 h, 1+ and 3+ proteinuria with Likelihood ratios ranging from 1.3 to 2.3 [106–110].

Ryu A and col. [111] in a prospective observational study, found that in women with pre-eclampsia, maternal serum uric acid level is an important parameter for predicting low birth weight. Additionally, the combination of uric acid, hemoglobin, and bilirubin levels appear to be optimal for predicting low birth weight in women with pre-eclampsia.

Pre-eclampsia is also an important risk factor for neonatal respiratory distress syndrome and bronchopulmonary dysplasia [112,113]; however, the mechanisms that underlie these associations are unclear. Studies have suggested that bronchopulmonary dysplasia is characterized by impaired angiogenesis in the foetal lung [114].

## 7 Prevention and treatment of HDP and PE

According to the WHO recommendations[115]:

- Women at high or moderate risk of pre-eclampsia should be advised to take aspirin (100-150 mg daily from week 12 to weeks 36-37) and calcium supplementation (1.5– 2.0 g elemental calcium/day during pregnancy in areas where dietary calcium intake is low).
- Vitamin C and E do not decrease pre-eclampsia risk; on the contrary, they are more frequently associated with a birth weight < 2.5kg and adverse perinatal outcomes.



- Magnesium sulfate is recommended for the prevention of eclampsia in women with severe PE in preference to other anticonvulsants and can be used for the treatment of eclampsia with women on crisis. Administered before 32 weeks of amenorrhoea, magnesium sulfate acts as foetal brain's protector.
- In women with gestational hypertension and/or PE, initiation of drug therapy is recommended when PAS > 140mmHg or PAD > 90mmHg.
- A systolic blood pressure  $\geq$  170mmHg or PAD  $\geq$  110mmHg in pregnant women represents an emergency requiring hospitalization.
- The first-line molecules for the management of hypertension in pregnant women are Methyldopa, Labetolol, Nicardipine and Nifedipine.
- In women with gestational hypertension or moderate pre-eclampsia, delivery is recommended in pre-eclampsia with visual disturbances or haemostatic disorders, and at 37 weeks of amenorrhoea in asymptomatic women.
- ACE inhibitors, angiotensin II antagonists should not be used, regardless of the term of pregnancy and are contraindicated in the 2nd and 3rd trimesters. Subsequently, women with gestational hypertension or pre-eclampsia increase their chances of developing long-term high blood pressure, stroke, and myocardial infarction.

According to the European Guidelines[116]:

- The initiation of drug treatment in all women with persistent elevation of BP =150/95 mmHg and at values >140/90 mmHg
- In women with: Methyldopa, beta-blockers (most data available for labetalol), and calcium antagonists (most data available for nifedipine) are the drugs of choice.
- Beta-blockers appear to be less effective than calcium antagonists and may induce foetal bradycardia, growth retardation, and hypoglycaemia; consequently, their type and dose should be carefully selected, with atenolol best avoided.
- Women with pre-existing hypertension may continue their current antihypertensive medication unless on ACE inhibitors, ARBs, and direct renin inhibitors, which are contraindicated due to adverse foetal and neonatal outcomes.
- The plasma volume is reduced in pre-eclampsia, therefore diuretic therapy is best avoided unless in the context of oliguria, when low-dose furosemide may be considered.
- Delivery of intravenous magnesium sulfate is recommended for the prevention of

eclampsia and treatment of seizures, but should not be given concomitantly with CCBs (there is a risk of hypotension due to potential synergism).

## 8 Follow up and orientation of pregnant women

Recently, the French National Authority of Health (Haute Autorité de Santé - HAS) published recommendations about the follow up and orientation of pregnant women according to identified risk situations and depending on their chronological occurrence during pregnancy[117]. According to these recommendations:

- During the first pregnancy consultation, women with BMI  $\leq 17.5\text{kg} / \text{m}^2$  or  $\geq 40\text{kg} / \text{m}^2$  (morbid obesity) should obtain the opinion of a gynecologist-obstetrician but can be followed by a general doctor.
- Women with a history of chronic hypertension, type 1 or 2 diabetes, homozygous sickle cell disease or other hemoglobinopathy, a systemic disease such as lupus, Multiple Sclerosis, Antiphospholipid syndrom or rheumatoid arthritis, should have regular follow-up by a gynecologist-obstetrician.
- A pregnant women with heterozygous sickle cell disease can be referred to a midwife or general doctor but with a specialist's advice asked beforehand.
- In cases of women with an obstetrical history of pregnancy-induced hypertension, pre-eclampsia, HE
- LLP syndrome, premature labor, retroplacental hematoma, severe intrauterine growth restriction ( $<3\text{rd}$  percentile), fetal death in utero of vascular origin should be followed only by a specialist gynecologist-obstetrician.

## **Conclusion**

Our study, shows a high prevalence of PE in patients with HDP. It failed to identify factors allowing a triage of patients at risk of PE or severe PE.

Given the findings of our study, factors to screen and prevent PE and severe PE remains unclear. We believe hospitalization and repeated clinical evaluation are needed to screen for women exposed to develop such complications. Moreover, future cohort studies are needed to provide robust evidence concerning the association clinical and biological alterations with maternal outcomes. Ideally, these studies should stratify pregnant women according to the severity of their hypertensive disorder (chronic hypertension with superimposed PE, gestational hypertension, early onset PE, and late onset PE).

## References

1. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2015.
2. Office of the United Nations High Commissioner for Human Rights. Technical guidance on the application of a human rights-based approach to the implementation of policies and programmes to reduce preventable maternal morbidity and mortality. Human Rights Council, twentieth session. New York: United Nations General Assembly. 2012.
3. Tunçalp Ö, Were WM, MacLennan C, Oladapo OT, Gülmezoglu AM, Bahl R, et al. Quality of care for pregnant women and newborns-the WHO vision. *BJOG*. 2015;122:1045–9.
4. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122–31.
5. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2014;348:g2301.
6. Chappell LC, Enye S, Seed P, Briley AL, Poston L, Shennan AH. Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study. *Hypertension*. 2008;51:1002–9.
7. World Health Organisation. The World Health Report 2005: Make Every Mother and Child Count. Geneva, Switzerland: World Health Organization; 2005. 2005.
8. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130–7.
9. Vergheze L, Alam S, Beski S, Thuraisingham R, Barnes I, MacCallum P. Antenatal screening for pre-eclampsia: evaluation of the NICE and pre-eclampsia community guidelines. *J Obstet Gynaecol*. 2012;32:128–31.
10. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;4:97–104.
11. Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. *BJOG*. 2005;112:601–6.
12. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376:631–44.
13. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213–7.
14. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet*. 2001;357:2002–6.
15. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797–803.

16. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.
17. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. *Hypertens Res*. 2017;40:213–20.
18. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. *Semin Fetal Neonatal Med*. 2004;9:429–35.
19. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. *Semin Fetal Neonatal Med*. 2016;21:68–73.
20. Passini R, Cecatti JG, Lajos GJ, Tedesco RP, Nomura ML, Dias TZ, et al. Brazilian multicentre study on preterm birth (EMIP): prevalence and factors associated with spontaneous preterm birth. *PLoS ONE*. 2014;9:e109069.
21. Leneuve-Dorilas M, Favre A, Louis A, Bernard S, Carles G, Nacher M. Risk Factors for Very Preterm Births in French Guiana: The Burden of Induced Preterm Birth. *AJP Rep*. 2019;9:e44–53.
22. Leneuve-Dorilas M, Buekens P, Favre A, Carles G, Louis A, Breart G, et al. Predictive factors of preterm delivery in French Guiana for singleton pregnancies: definition and validation of a predictive score. *J Matern Fetal Neonatal Med*. 2018;1–8.
23. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens*. 2014;4:105–45.
24. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ Guidelines for the Management of Hypertensive Disorders of Pregnancy 2014. *Aust N Z J Obstet Gynaecol*. 2015;55:11–6.
25. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–357.
26. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:3147–97.
27. Ramos JGL, Sass N, Costa SHM. Preeclampsia. *Rev Bras Ginecol Obstet*. 2017;39:496–512.
28. Hennessy A, Makris A. Preeclamptic nephropathy. *Nephrology (Carlton)*. 2011;16:134–43.
29. Knight M, UKOSS. Eclampsia in the United Kingdom 2005. *BJOG*. 2007;114:1072–8.
30. Townsend R, O'Brien P, Khalil A. Current best practice in the management of hypertensive disorders in pregnancy. *Integr Blood Press Control*. 2016;9:79–94.
31. García-Romero CS, Guzman C, Cervantes A, Cerbón M. Liver disease in pregnancy: Medical aspects and their implications for mother and child. *Ann Hepatol*. 2019;

32. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
33. Zou Kelly H., O'Malley A. James, Mauri Laura. Receiver-Operating Characteristic Analysis for Evaluating Diagnostic Tests and Predictive Models. *Circulation*. 2007;115:654–7.
34. Bell MJ. A historical overview of preeclampsia-eclampsia. *J Obstet Gynecol Neonatal Nurs*. 2010;39:510–8.
35. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol*. 1989;161:1200–4.
36. Mayrink J, Costa ML, Cecatti JG. Preeclampsia in 2018: Revisiting Concepts, Physiopathology, and Prediction. *ScientificWorldJournal*. 2018;2018:6268276.
37. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*. 2014;121 Suppl 1:14–24.
38. Sebastian T, Yadav B, Jeyaseelan L, Vijayaselvi R, Jose R. Small for gestational age births among South Indian women: temporal trend and risk factors from 1996 to 2010. *BMC Pregnancy Childbirth*. 2015;15:7.
39. Adane AA, Ayele TA, Ararsa LG, Bitew BD, Zeleke BM. Adverse birth outcomes among deliveries at Gondar University Hospital, Northwest Ethiopia. *BMC Pregnancy Childbirth*. 2014;14:90.
40. Baragou S, Goeh-Akue E, Pio M, Afassinou YM, Atta B. [Hypertension and pregnancy in Lome (sub-Saharan Africa): epidemiology, diagnosis and risk factors]. *Ann Cardiol Angeiol (Paris)*. 2014;63:145–50.
41. Olusanya BO, Solanke OA. Perinatal outcomes associated with maternal hypertensive disorders of pregnancy in a developing country. *Hypertens Pregnancy*. 2012;31:120–30.
42. Verburg PE, Tucker G, Scheil W, Erwich JJHM, Dekker GA, Roberts CT. Seasonality of gestational diabetes mellitus: a South Australian population study. *BMJ Open Diabetes Research and Care*. 2016;4:e000286.
43. Morikawa M, Yamada T, Yamada T, Cho K, Sato S, Minakami H. Seasonal variation in the prevalence of pregnancy-induced hypertension in Japanese women. *J Obstet Gynaecol Res*. 2014;40:926–31.
44. Hayes DK, Feigal DW, Smith RA, Fuddy LJ. Maternal asthma, diabetes, and high blood pressure are associated with low birth weight and increased hospital birth and delivery charges; Hawai'i hospital discharge data 2003-2008. *Hawaii J Med Public Health*. 2014;73:49–57.
45. Mehrabadi A, Liu S, Bartholomew S, Hutcheon JA, Magee LA, Kramer MS, et al. Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study. *BMJ*. 2014;349:g4731.
46. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol*. 2019;15:275–89.

47. Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiology. *Cardiovasc J Afr.* 2016;27:71–8.
48. Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ.* 2016;353:i1753.
49. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. *Am J Hypertens.* 2008;21:521–6.
50. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ.* 2013;347:f6564.
51. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2013;170:1–7.
52. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol.* 2009;113:1299–306.
53. Quinn MJ. Pre-eclampsia - The “uterine reinnervation” view. *Med Hypotheses.* 2014;83:575–9.
54. Abou El Hassan M, Diamandis EP, Karumanchi SA, Shennan AH, Taylor RN. Preeclampsia: an old disease with new tools for better diagnosis and risk management. *Clin Chem.* 2015;61:694–8.
55. Ye C, Ruan Y, Zou L, Li G, Li C, Chen Y, et al. The 2011 survey on hypertensive disorders of pregnancy (HDP) in China: prevalence, risk factors, complications, pregnancy and perinatal outcomes. *PLoS ONE.* 2014;9:e100180.
56. Bryant M, Santorelli G, Lawlor DA, Farrar D, Tuffnell D, Bhopal R, et al. A comparison of South Asian specific and established BMI thresholds for determining obesity prevalence in pregnancy and predicting pregnancy complications: findings from the Born in Bradford cohort. *Int J Obes (Lond).* 2014;38:444–50.
57. Wang Z, Wang P, Liu H, He X, Zhang J, Yan H, et al. Maternal adiposity as an independent risk factor for pre-eclampsia: a meta-analysis of prospective cohort studies. *Obes Rev.* 2013;14:508–21.
58. Lee CJ, Hsieh TT, Chiu TH, Chen KC, Lo LM, Hung TH. Risk factors for pre-eclampsia in an Asian population. *Int J Gynaecol Obstet.* 2000;70:327–33.
59. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *Am J Epidemiol.* 1998;147:1062–70.
60. Conde-Agudelo A, Althabe F, Belizán JM, Kafury-Goeta AC. Cigarette smoking during pregnancy and risk of preeclampsia: a systematic review. *Am J Obstet Gynecol.* 1999;181:1026–35.
61. Wei J, Liu C-X, Gong T-T, Wu Q-J, Wu L. Cigarette smoking during pregnancy and preeclampsia risk: a systematic review and meta-analysis of prospective studies. *Oncotarget.* 2015;6:43667–78.

62. Jacobs DJ, Vreeburg SA, Dekker GA, Heard AR, Priest KR, Chan A. Risk factors for hypertension during pregnancy in South Australia. *Aust N Z J Obstet Gynaecol.* 2003;43:421–8.
63. Hayashi K, Matsuda Y, Kawamichi Y, Shiozaki A, Saito S. Smoking during pregnancy increases risks of various obstetric complications: a case-cohort study of the Japan Perinatal Registry Network database. *J Epidemiol.* 2011;21:61–6.
64. Kobashi G, Ohta K, Hata A, Shido K, Yamada H, Fujimoto S, et al. An association between maternal smoking and preeclampsia in Japanese women. *Semin Thromb Hemost.* 2002;28:507–10.
65. Eskenazi B, Fenster L, Sidney S. A multivariate analysis of risk factors for preeclampsia. *JAMA.* 1991;266:237–41.
66. Ma R, Liu J-M, Li S, Ye R-W, Chen H, Xue M-J, et al. [Study on the descriptive epidemiology of pregnancy-induced hypertension from 1995 - 2000 in Jiaxing of Zhejiang province, China]. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2005;26:960–3.
67. Conde-Agudelo A, Belizán JM. Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. *BJOG.* 2000;107:75–83.
68. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. *Am J Obstet Gynecol.* 1990;163:460–5.
69. Coonrod DV, Hickok DE, Zhu K, Easterling TR, Daling JR. Risk factors for preeclampsia in twin pregnancies: a population-based cohort study. *Obstet Gynecol.* 1995;85:645–50.
70. Zhang J, Troendle JF, Levine RJ. Risks of hypertensive disorders in the second pregnancy. *Paediatr Perinat Epidemiol.* 2001;15:226–31.
71. Boghossian NS, Albert PS, Mendola P, Grantz KL, Yeung E. Delivery Blood Pressure and Other First Pregnancy Risk Factors in Relation to Hypertensive Disorders in Second Pregnancies. *Am J Hypertens.* 2015;28:1172–9.
72. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ.* 2005;330:565.
73. Catov JM, Ness RB, Kip KE, Olsen J. Risk of early or severe pre-eclampsia related to pre-existing conditions. *Int J Epidemiol.* 2007;36:412–9.
74. Ward K, Hata A, Jeunemaitre X, Helin C, Nelson L, Namikawa C, et al. A molecular variant of angiotensinogen associated with preeclampsia. *Nat Genet.* 1993;4:59–61.
75. Kobashi G, Hata A, Shido K, Kato EH, Yamada H, Fujimoto S, et al. Association of a variant of the angiotensinogen gene with pure type of hypertension in pregnancy in the Japanese: implication of a racial difference and significance of an age factor. *Am J Med Genet.* 1999;86:232–6.
76. Zafarmand MH, Franx A, Sabour S, van der Schouw YT, Grobbee DE, de Leeuw PW, et al. The M235T variant of the angiotensinogen gene is related to development of self-reported hypertension during pregnancy: the Prospect-EPIC cohort study. *Hypertens Res.* 2008;31:1299–305.



77. Luizon MR, Belo VA, Palei AC, Amaral LM, Lacchini R, Sandrim VC, et al. Effects of NAMPT polymorphisms and haplotypes on circulating visfatin/NAMPT levels in hypertensive disorders of pregnancy. *Hypertens Res.* 2015;38:361–6.
78. Zhan Y, Liu M, You Y, Zhang Y, Wang J, Wang X, et al. Genetic variations in the vitamin-D receptor (VDR) gene in preeclampsia patients in the Chinese Han population. *Hypertens Res.* 2015;38:513–7.
79. Chappell LC, Shennan AH. Assessment of proteinuria in pregnancy. *BMJ.* 2008;336:968–9.
80. Ramos JG, Martins-Costa SH, Mathias MM, Guerin YL, Barros EG. Urinary protein/creatinine ratio in hypertensive pregnant women. *Hypertens Pregnancy.* 1999;18:209–18.
81. Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. *BMJ.* 2012;345:e4342.
82. Morikawa M, Yamada T, Yamada T, Cho K, Yamada H, Sakuragi N, et al. Pregnancy outcome of women who developed proteinuria in the absence of hypertension after mid-gestation. *J Perinat Med.* 2008;36:419–24.
83. Baba Y, Ohkuchi A, Usui R, Takahashi H, Matsubara S. Urinary protein-to-creatinine ratio indicative of significant proteinuria in normotensive pregnant women. *J Obstet Gynaecol Res.* 2016;42:784–8.
84. Chen CW, Jaffe IZ, Karumanchi SA. Pre-eclampsia and cardiovascular disease. *Cardiovasc Res.* 2014;101:579–86.
85. Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women: a review. *J Am Coll Cardiol.* 2014;63:1815–22.
86. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG.* 2011;118 Suppl 1:1–203.
87. Martin JN, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol.* 2005;105:246–54.
88. Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in pregnancy. *J Am Soc Hypertens.* 2008;2:484–94.
89. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol.* 1993;169:1000–6.
90. Haddad B, Barton JR, Livingston JC, Chahine R, Sibai BM. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome versus severe preeclampsia: onset at < or =28.0 weeks' gestation. *Am J Obstet Gynecol.* 2000;183:1475–9.
91. Malvino E, Muñoz M, Ceccotti C, Janello G, Mc Loughlin D, Pawlak A, et al. [Maternal morbidity and perinatal mortality in HELLP syndrome. Multicentric studies in intensive care units in Buenos Aires area]. *Medicina (B Aires).* 2005;65:17–23.

92. Larsson A, Palm M, Hansson L-O, Axelsson O. Reference values for clinical chemistry tests during normal pregnancy. *BJOG*. 2008;115:874–81.
93. Gul A, Aslan H, Cebeci A, Polat I, Ulusoy S, Ceylan Y. Maternal and fetal outcomes in HELLP syndrome complicated with acute renal failure. *Ren Fail*. 2004;26:557–62.
94. Jim B, Garovic VD. Acute Kidney Injury in Pregnancy. *Semin Nephrol*. 2017;37:378–85.
95. Wagner SJ, Acquah LA, Lindell EP, Craici IM, Wingo MT, Rose CH, et al. Posterior reversible encephalopathy syndrome and eclampsia: pressing the case for more aggressive blood pressure control. *Mayo Clin Proc*. 2011;86:851–6.
96. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011;57:1404–23.
97. Leslie MS, Briggs LA. Preeclampsia and the Risk of Future Vascular Disease and Mortality: A Review. *J Midwifery Womens Health*. 2016;61:315–24.
98. Veerbeek JHW, Hermes W, Breimer AY, van Rijn BB, Koenen SV, Mol BW, et al. Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension. *Hypertension*. 2015;65:600–6.
99. Bello N, Rendon ISH, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2013;62:1715–23.
100. Al-Nasiry S, Ghossein-Doha C, Polman SEJ, Lemmens S, Scholten RR, Heidema WM, et al. Metabolic syndrome after pregnancies complicated by pre-eclampsia or small-for-gestational-age: a retrospective cohort. *BJOG*. 2015;122:1818–23.
101. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med*. 2008;359:800–9.
102. McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: a systematic review and meta-analysis. *Am J Kidney Dis*. 2010;55:1026–39.
103. Tangren JS, Powe CE, Ankers E, Ecker J, Bramham K, Hladunewich MA, et al. Pregnancy Outcomes after Clinical Recovery from AKI. *J Am Soc Nephrol*. 2017;28:1566–74.
104. Piccoli GB, Cabiddu G, Attini R, Vigotti FN, Maxia S, Lepori N, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *J Am Soc Nephrol*. 2015;26:2011–22.
105. Koike T, Minakami H, Izumi A, Watanabe T, Matsubara S, Sato I. Recurrence risk of preterm birth due to preeclampsia. *Gynecol Obstet Invest*. 2002;53:22–7.
106. Thangaratinam S, Coomarasamy A, O'Mahony F, Sharp S, Zamora J, Khan KS, et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. *BMC Med*. 2009;7:10.
107. Buchbinder A, Sibai BM, Caritis S, Macpherson C, Hauth J, Lindheimer MD, et al. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. *Am J Obstet Gynecol*. 2002;186:66–71.
108. Fliegner JR. Placental function and renal tract studies in pre-eclampsia with proteinuria and long-term maternal consequences. *Am J Obstet Gynecol*. 1976;126:211–7.

109. Hall DR, Odendaal HJ, Steyn DW, Grové D. Urinary protein excretion and expectant management of early onset, severe pre-eclampsia. *Int J Gynaecol Obstet*. 2002;77:1–6.
110. Taylor HC, Tillman AJ, Blanchard J. Fetal losses in hypertension and preeclampsia. I. An analysis of 4432 cases. *Obstet Gynecol*. 1954;3:225–39.
111. Ryu A, Cho NJ, Kim YS, Lee EY. Predictive value of serum uric acid levels for adverse perinatal outcomes in preeclampsia. *Medicine (Baltimore)*. 2019;98:e15462.
112. Wang A, Holston AM, Yu KF, Zhang J, Toporsian M, Karumanchi SA, et al. Circulating anti-angiogenic factors during hypertensive pregnancy and increased risk of respiratory distress syndrome in preterm neonates. *J Matern Fetal Neonatal Med*. 2012;25:1447–52.
113. Hansen AR, Barnés CM, Folkman J, McElrath TF. Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. *J Pediatr*. 2010;156:532–6.
114. Thébaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med*. 2007;175:978–85.
115. WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
116. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018;36:1953–2041.
117. Haute Autorité De santé. Suivi et orientation des femmes enceintes en fonction des situations à risque identifiées. 2016.