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Risk factors and outcomes associated with Preeclampsia: a retrospective study

Maria Francisca Silva de Matos

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Maria Francisca Silva de Matos

Aluna do 6º ano profissionalizante de Mestrado Integrado em Medicina no Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Número de aluno: 201405996

Endereço eletrónico: francisca.smatos@gmail.com

Orientador

Dr. António José Costa Lima da Cunha Braga

Médico assistente hospitalar do Serviço de Obstetrícia no Centro Materno Infantil do Norte Dr. Albino Aroso, Centro Hospitalar Universitário do Porto.

Co-orientador

Professor Doutor Hélder Bruno Carvalho Ferreira

Médico assistente hospitalar do Serviço de Ginecologia do Centro Materno Infantil do Norte Dr. Albino Aroso, Centro Hospitalar Universitário do Porto.

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RESUMO

Objetivo: Determinar os fatores de risco mais prevalentes em mulheres com pré-eclâmpsia e avaliar as complicações maternas e neonatais mais predominantes nesta população. Além disso, foi também objetivo deste estudo identificar o efeito benéfico, obstétrico e fetal, da profilaxia com aspirina. Foi também estabelecido como objetivo encontrar uma correlação entre a presença de fatores de risco e o desenvolvimento de pré-eclâmpsia grave e, ao mesmo tempo, avaliar a existência de associação entre a presença de critérios de severidade e determinados *outcomes* maternos e fetais.

Metodologia: Foram consideradas retrospetivamente 117 grávidas hospitalizadas com diagnóstico de pré-eclâmpsia entre janeiro de 2017 e dezembro de 2018. Foram recolhidos dados demográficos maternos, bem como dados clínicos obstétricos e fetais. Além disso, foi realizada uma análise descritiva. Adicionalmente, os testes qui-quadrado ou exato de Fisher, conforme apropriado, foram utilizados para comparar grupos de doentes.

Resultados: Nulíparas representam 65,1% (n=75) da população em estudo. 15,4% (n=18) apresentavam diagnóstico de hipertensão crónica e 4,3% (n=5) tinham diagnóstico prévio de proteinúria. Pré-eclâmpsia com critérios de severidade foi encontrada em 58,1% (n=68); dor epigástrica foi observada em 10,3% (n=12) das gravidezes; cefaleia em 11,1% (n=13) e distúrbios visuais em 5,1% (n=6) das pacientes. Apenas uma doente apresentou síndrome de HELLP, tendo sido a única a manifestar convulsões. Nasceram 122 nados vivos, incluindo 5 nascimentos de gémeos, com uma mediana de idade gestacional de 37 [27-40] semanas, sendo que ocorreram 47 (40,2%) nascimentos pré-termo. A ausência de fatores de severidade foi mais prevalente nas mulheres que realizaram terapia profilática com aspirina (p=0,022). A presença de pré-eclâmpsia severa foi associada a partos prematuros e a cesariana de emergência (p=0,003 e p=0,031, respetivamente). Registou-se agravamento clínico materno em 5 (4,3%) puérperas, tendo 3 delas sido transferidas para a unidade de cuidados intensivos.

Conclusão: A profilaxia com aspirina tem efeito protetor, sendo associada a menos complicações adversas. Foi encontrada uma correlação entre a presença de características graves da pré-eclâmpsia e piores consequências maternas e fetais.

Palavras chave: Gravidez, Pré-eclâmpsia, Pré-eclâmpsia Severa, Fatores de Risco

ABSTRACT

Aim: This study aimed to determine the most prevalent risk factors in women with preeclampsia and to establish the most predominant maternal and neonatal outcomes in this population. Furthermore, it was also a goal of this study to identify whether the aspirin prophylaxis has a significant benefit on the maternal and fetal outcomes. The study also intended to find the risk factors that promote the development of severe preeclampsia and to investigate the differences in outcomes on patients with and without severe features.

Statistical Analysis: This was a retrospective study that considered 117 pregnant women who were hospitalized with preeclampsia diagnosis between January 2017 and December 2018. Maternal and neonatal demographic data, as well as clinical data, were recorded. Moreover, a descriptive analysis was conducted and chi-square test and the Fisher's exact test, as appropriate, were used to compare groups.

Results: Nulliparous represented 65.1% (n=75). A chronic hypertension was already diagnosed in 15.4% (n=18) and 4.3% (n=5) had a previous proteinuria diagnosis. Aspirin prophylaxis has been prescribed in 29.9% (n=35). Severe preeclampsia was found in 58.1% (n=68) and severe features like epigastric pain were observed in 10.3% (n=12) pregnancies, headache in 11.1% (n=13) and visual disturbances in 5.1% (n=6) patients. Criteria for HELLP syndrome were met in only one patient, who was the only one having convulsive manfestations. There were 122 live births, including 5 multigestational births, with a median term of 37 [27–40] gestational weeks, 47 (40.2%) births were pre-term. The absence of severe preeclampsia was more frequent in those who did aspirin prophylactic therapy (p=0.022). Preterm births and emergency c-section were more prevalent in patients with severe preeclampsia (p=0.003 and p=0.031, respectively). A maternal clinical worsening was recorded in 5 (4.3%) puerperal women, and 3 of them were transferred to the intensive care unit.

Conclusion: This study showed that prophylaxis with aspirin had a protective effect, being associated with fewer adverse complications. A correlation between the presence of severe features of preeclampsia and worse maternal and fetal outcomes was found.

Keywords: Pregnancy, Preeclampsia, Severe preeclampsia, Risk factors

ABBREVIATIONS

ACOG | American College of Obstetricians and Gynecologists

BMI | Body Mass Index

BP | Blood Pressure

CKD | Chronic Kidney Disease

ER | Emergency Room

FIGO | International Federation of Gynecology and Obstetrics

HDP | Hypertensive Disorders of Pregnancy

IUGR | Intrauterine Fetal Growth Restriction

LBW | Low Birth Weight

LDH | Lactate Dehydrogenase

MAP | Mean Arterial Pressure

PE | Preeclampsia

PIGF | Serum Placental Growth Factor

SPE | Severe Preeclampsia

UTPI | Uterine Artery Pulsatility Index

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INTRODUCTION

Hypertensive Disorders of Pregnancy (HDP) complicate nearly 10% of pregnancies.[1] The HDP spectrum includes gestational hypertension, chronic essential hypertension, preeclampsia (PE), superimposed preeclampsia and eclampsia.[2] In the developed countries, 16.1% of maternal death causes are associated with HDP.[3] Among the hypertensive disorders, PE and eclampsia stand out as main causes of perinatal and maternal morbidity and mortality.[4] In Portugal, the estimated prevalence of HDP is 6%, lower than that reported in most countries; PE represents only 1.4%, eclampsia 0.1%, and HELLP syndrome 0.1%.[5]

Gestational hypertension is defined as a systolic blood pressure (BP) greater than 140mmHg and/or a diastolic BP greater than 90mmHg after 20 weeks of gestation, in a woman without a previous diagnosis of arterial hypertension. The criteria for PE are met when, associated with arterial hypertension, the patient also has proteinuria.[6] Despite being a frequent finding, the new-onset of proteinuria is not mandatory for the diagnosis. In the case of the absence of proteinuria, it is important to investigate if the new-onset of hypertension was accompanied by analytical or clinical signs of maternal organ dysfunctions (e.g., thrombocytopenia, elevation of liver enzymes, the new development of kidney insufficiency, visual disturbances and severe headache) or signs of uteroplacental dysfunction (e.g. abnormal umbilical artery Doppler waveform analysis).[7] If PE develops in a patient with preexisting hypertension, a superimposed preeclampsia is diagnosed. PE complicates as eclampsia (occurrence of new-onset tonic-clonic, focal, or multifocal seizures that cannot be attributed to another etiology) or as HELLP syndrome (combination of hemolysis, elevated liver enzymes, and low platelet count).[6,8] Additionally, PE also predisposes potentially lethal complications involving disseminated intravascular coagulation, cardiovascular collapse, acute kidney failure, and hepatic failure.[9,10] Placental abruption, preterm birth, intrauterine fetal growth restriction (IUGR), low birth weight (LBW, ≤2500 grams) and intrauterine fetal demise are other adverse obstetric outcomes.[6,11] Risk factors for preeclampsia development are well established; hence, the classification of women with high and moderate risk is based on their personal and medical risk factors.[12] Patients with PE history, multifetal gestation, chronic hypertension, pregestational diabetes (diabetes mellitus type 1 or type 2), chronic kidney disease (CKD), or with autoimmune disease (systemic lupus erythematosus and antiphospholipid syndrome) are classified as high-risk patients. On the other hand, if the pregnant woman is nulliparous, 35 years old or older, African, has a body mass index (BMI) greater than 30mg/kg^2, family history of PE (mother or sister), or has an inter-gestational interval greater than 10 years, should be

classified as a moderate-risk patient. Moreover, the combination of multiple moderate-risk factors can identify the patients at high risk for PE.[6,13,14] Additionally, sleep obstructive apnea, assisted reproductive technology or ovulation induction, vitamin D deficiency, and family history of hypertension are also identified as risk factors.[15-18]

Antiplatelets agents are remarkably beneficial in preventing PE development in patients that present the aforementioned risk factors.[19,20] Therefore, a low-dose of aspirin prophylactic therapy is recommended in pregnant women with high-risk factors and also for women with more than one moderate-risk factor.[21] However, the International Federation of Gynecology and Obstetrics (FIGO) recently published new screening PE recommendations for first-trimester pregnancies. That screening test combines the risk factors, serum placental growth factor (PlGF), the uterine artery pulsatility index (UTPI) and, mean arterial pressure (MAP).[7] Women identified as being at high-risk by the FIGO's screening test or with high to moderate-risk factors should receive aspirin prophylaxis of 100-150 mg/day, commencing at 11-14^{+6} weeks, and that must be maintained up to the 36^{th} week of gestation or until the birth of the newborn.[7,12,20] This preventive therapy also decreases the adverse obstetric outcomes.[19,22] Nevertheless, despite the close maternal surveillance and the preventive measures, the delivery of the neonate remains the only definitive treatment.[23]

Data on pregnant women admitted in the emergency room (ER) of a university teaching hospital with preeclampsia were retrospectively collected and analyzed. Data included demographic and clinical parameters, as well as the presence of complications, both fetal and maternal. Thus, it was performed a retrospective analysis to investigate the most common risk factors, pregnancy outcomes, and complications in this particular population. Moreover, the study's goal was also to determine if the prophylaxis with aspirin concedes a significant protective effect for adverse complications and obstetric outcomes. Besides, it was also an aim to identify the risk factors that promote the development of severe preeclampsia (SPE) and the prevalence of complications associated with the presence of adverse features. According with the American College of Obstetricians and Gynecologists (ACOG)'s *Practice Bulletin for Gestational Hypertension and Preeclampsia*, severe features include: 1) Severe hypertension (systolic BP ≥ 160mmHg and/or diastolic BP ≥ 110mmHg); 2) thrombocytopenia; 3) impaired liver function indicated by elevation of liver enzymes, severe persistent right upper quadrant or epigastric pain; 4) renal insufficiency indicated by a serum creatinine concentration more than 1.1mg/dL; 5) Pulmonary edema; 6) new-onset headache and 7) Visual disturbances.[6]

MATERIALS AND METHODS

This retrospective study was conducted in the "Centro Materno Infantil do Norte" on Oporto, Portugal, in a group of 117 pregnant women, who were admitted to the ER in the period between January 2017 and December 2018. Two pregnant women that were admitted in 2018 but discharged in January 2019 were also included in the sample. Multifetal pregnancies were also included. Future mothers that were transferred before giving birth to another hospital were excluded from the study.

Data were retrieved from the hospital medical records electronic systems, namely SClínico®. PCE® and Alert®. Ethical approval for the conduction of this study was granted by the Ethics Committee of "Centro Hospitalar Universitário do Porto" [2020.013(010-DEFI/011-CE)].

Information related to maternal demographic data and risk factors were obtained from the case records, including age, ethnicity, parity, body mass index (BMI), conception method and personal history of chronic hypertension, diabetes, chronic kidney disease, and auto-immune disease. It was also collected information related to the presence of clinical severity criteria such as epigastric pain, headache, pulmonary edema, visual alterations, seizures, severe hypertension; as well as analytical criteria as thrombocytopenia, the value of the serum creatinine, elevation of lactate dehydrogenase (LDH) and the value of liver enzymes (AST and ALT) and 24h urinary protein. The presence of proteinuria was considered if one of the following situations occurred: 300 mg or more per 24-hour urine collection and/or Protein/creatinine ratio of 0.3 mg/dL or more and/or Dipstick reading of 2+.

Additionally, it was also collected data related to the induction of the delivery, together with fetal and/or maternal reasons behind the decision, as well as the type of labor. Neonatal demographic data (e.g., birth weight, gestational age, APGAR score) were also collected.

Therefore, all the information was recorded using an extraction sheet. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25.0. Categorical variables were described with frequency and percentage and continuous variables were described as median. The chi-square test and the Fisher's exact test, as appropriate, were used to compare the risk factors, maternal complications and obstetric outcomes between patients who did aspirin prophylaxis from those who did not and between patients with and without SPE. Independent Samples T-test was applied for continuous variables and Mann-Whitney U-test for continuous non-normal distributed variables. A p-value of <0.05 was considered statistically significant.

RESULTS

The study analyzed 117 preeclamptic patients, including 5 multifetal pregnancies, that were admitted in the ER during the two-year period analyzed. The median of women age was 33 years old [19–48] with 40.2% of women being more than 35 years old. As shown in Table I, Caucasian ethnicity was prevalent (93.2%) although there were 8 (6.8%) African pregnant patients. Nulliparous represented 65.1% (n=75). From those, 35.9% multiparous, 28.9% had more than a 10-year pregnancy interval, 11.9% had a personal history pregnancy-induced hypertension and 9.5% had preeclampsia in a previous pregnancy. The median BMI at admission was 31.63 kg/m^2 [17.67-50.39], only 13.8% of the pregnancies were on the normal range of BMI, one patient was underweight, 26.7% had pre-obesity and 58.6% had a BMI greater than 30. From the 117 pregnant women, 15.4% (n=18) had a pre-existing hypertension, which classifies their PE as superimposed, and 4.3% had a previous proteinuria diagnosis. Pregestational diabetes was presented in 6.0% (n=7), autoimmune disease in 2.6% (n=3) patients and CKD in one patient.

At admission, proteinuria was diagnosed in 76.1% (n=89) of the patients. The evaluation of 24-hour protein was completed in 76 women, moderated proteinuria (0,300g to 2g) was diagnosed in 46.2%(n=54) of them, severe proteinuria (2g to <5g) was found in 10.5% (n=8) pregnancies and massive (≥5g) in only 1.7% (n=2) patients. Additionally, complications like epigastric pain were observed in 10.3% (n=12), headache in 11.1% (n=13) and visual disturbances in 5.1% (n=6) patients. Renal insufficiency was found in 5.1% (n=6) patients and severe hypertension in 29.9% (n=35). Thrombocytopenia was found in 5.1% (n=6) women, elevated liver enzymes (AST and/or ALT) in 27.4% (n=32) and elevation of LDH in 5.2% (n=6). Nonetheless, complete criteria for HELLP syndrome were met in only one patient and that same pregnant woman was the only one who had eclampsia. 122 live births happened at a median term of 37 [27–40] gestational weeks including 47 births before 37 weeks. Vaginal birth occurred in 43.6% of pregnancies (n=51) and elective cesarean where scheduled in 23.9% (n=28). There were performed 32.5% (n=38) emergency cesarean.

Regarding the neonatal outcomes, only the singleton pregnancies were analyzed. The APGAR score at the first minute inferior to 7 was present in 33 (39.5%) of the newborn; nonetheless, at minute five only 6 (5.4%) of them had an APGAR on that range. A diagnosis of IUGR was made in 31 (27.7%) of the pregnancies. One premature newborn (27 weeks gestation) died after his first day of life. The median birth weight for the singleton newborns was 2615 grams [470–4745], 47.9% (n=56) were born with LBW.

Regarding the maternal postpartum complications, hypertension was registered in 46.2% of the preeclamptic patients (n=54) and proteinuria after birth in only 4.3% (n=5). A maternal

clinical worsening was recorded in 5 (4.3%) puerperal women, and 3 of them were transferred to the intensive care unit.

Aspirin Prophylaxis

Aspirin prophylaxis was prescribed in 29.9% (n=35) patients. Patients exposed to prophylactic aspirin had less severe criteria (54.3% did not display SPE and 11.4% expressed one severe feature) in comparison with the group without treatment (p=0.022). In the group without aspirin treatment, 36.6% (n=30) did not present SPE, and the same percentage presented only one severe feature (Table II). Nonetheless, when analyzed each severe feature with aspirin prophylactic therapy, no statistically significant differences from the no prophylactic group were found. However, a mean value of AST and ALT were both lower in those patients who took aspirin (18.25±8.2 and 16.94±12.47, respectively) comparing with patients who did not take it (34,00±55.38 for AST and 35.12±78.41 for ALT) with a p=0.033 and p=0.352, respectively. Regarding obstetric and fetal outcomes, no statistically significant associations were found between the two groups (Table III and IV).

Severe Preeclampsia

The presence of at least one of the severe features of PE was found in 58.1% (n=68); 29.1% (n=34) with one criteria, 21.4% (n=25) with two features and 7.7% (n=9) with three or more. There were no statistically significant differences between groups with and without SPE for the well-known risk factors such as maternal age, parity, BMI, preexisting hypertension, and diabetes mellitus (Table I). Notwithstanding, when analyzed the risk factors for each severe feature independently, some correlations were detected. Epigastric pain seems to be more frequent in multiparous women with a p=0.008 (Figure 1). Secondly, elevated liver enzymes (AST and/or ALT) were more prevalent in preeclamptic patients without obesity, with a p=0.002 (Figure 2); this severe feature was also predominant in the multifetal pregnancies with a p=0.019 (Figure 3). Additionally, a correlation between the BMI ≥ 30kg/m2 and the presence of headache was found with a p=0.043 (Figure 4). Finally, a previous diagnosis of chronic hypertension was associated with a higher risk of developing severe hypertension with a p<0.001 (Figure 5). Analyzing visual disturbances, thrombocytopenia, pulmonary edema, convulsions, right upper quadrant pain, and kidney insufficiency no statistically significant differences, related to risk factors, were observed.

Concerning the presence of SPE and the obstetric and fetal outcomes some correlations were identified. Comparing the types of birth, an urgent cesarean section was performed in 43.6% of the pregnancies with SPE, in contrast with 18.4% from those patients without severe criteria (p=0.031). A vaginal birth occurred in 34.7% and an elective cesarean in 30.6% of preeclamptic patients without PE, being these types of delivery more prevalent in

this group (Table III). Regarding the maternal causes of birth, the severe laboratory abnormalities, the sudden uncontrolled hypertension, and the worsening of symptoms were more prevalent designated as maternal reasons for the delivery (p<0.001, Table III). The presence of SPE was associated with a higher prevalence (51.5%) of preterm birth (p=0.003), with an average birth age of 35.59±2.59 weeks, slightly low comparing with pregnancies without severe features (36.53±2.67 weeks), with a p=0.012. Fetal outcomes of singleton pregnancies, such as APGAR score, IUGR diagnosis, and LBW, were not statistically significant different from groups with and without SPE (Table IV). Even though there was no statistically significant association with the birth weight, the mean birth weight for SPE was 2350±773 grams, inferior than those for pregnancies without severe features, which presented a mean of 2645±743 grams (p=0.055). Nevertheless, when analyzed the severe features individually for each fetal outcome, it was found that all the five singleton pregnancies with kidney insufficiency were also diagnosed with IUGR (p=0.001). These same five patients gave birth to a newborn with a birth weight ≤2.500 grams (p=0.018). Thrombocytopenia occurred in five singleton pregnancies, and all resulted in newborns with LBW (p=0.018). For the other analyzed parameters, the differences were not statistically significant.

DISCUSSION

Aspirin is an important prophylactic therapy in women with risk factors for PE.[19,22] We found that the absence of SPE criteria was more prevalent in the group of patients previously treated with aspirin prophylactic therapy, in spite of the fact that these patients had an increased risk for the development of PE. Nonetheless, in our study the scarcity of other significant findings can be justified by the small sample size as well as the existing bias related to the fact that the therapy is commonly prescribed to patients with risk factors for PE and with a high risk of maternal complications and adverse obstetric outcomes.[24,25]

Even though no statistically significant differences were found when analyzed the risk factors and presence of SPE, when investigated each severe feature, described by ACOG, some associations were observed. Patients with chronic hypertension were more likely to present superimposed preeclampsia with severe hypertension. Epigastric pain seems to be more frequent in the multiparous women group. Increased levels of liver enzymes were more prevalent in preeclamptic patients with a BMI lower than 30 kg/m^2 (without obesity). Previous studies have identified many risk factors for PE, and these factors are recognized for obstetric societies worldwide.[6,7] Some studies have investigated risk factors for adverse outcomes in preeclamptic patients.[26,27] Nevertheless, to our knowledge, few articles focused on the development of severe features and risk factors - severe obesity, history of preeclampsia, chronic hypertension, primiparous pregnancy - have been shown as a maternal risk factors for the development of SPE, but none of them specifies individually the severe features that a certain risk factor predisposes. [28,29]

This study also showed that the cesarean delivery rate was significantly higher in patients with severe preeclampsia, and patients without SPE were more likely to have a vaginal birth or an elective c-section. This result matches those of previous studies, which have documented an increased rate of operative delivery in women with severe preeclampsia.[30] This increased rate for operative delivery is not unexpected when severe features are found, given that their presence jeopardizes the maternal and/or fetal health, and urgent abdominal delivery is often the route to diminish adverse outcomes. Furthermore, preterm delivery is associated with severe features of PE. That happens given that the risk to mother and fetus of continuing the pregnancy before 37 weeks of gestation outweighs the benefit. In this study, patients with SPE were more likely to give birth to a premature neonate than those without severity criteria. This is also in line with previously published studies.[31,32] According to the literature, a low birth weight is also expected to be more prevalent in pregnancies with severe features of PE.[31] In this study, a high rate of newborns with LBW occurred in pregnancies with SPE, although no statistically significant differences were observed (p=0.063, which could be justified by the small sample of the study). Nonetheless, the

presence of kidney insufficiency was significatively associated with IUGR and LBW. Therefore, appropriate assessment of SPE and identification of pregnancies at a greater risk of developing adverse complications and unfavorable obstetric outcomes are essential to prevent worse outcomes and to be prepared if they emerge.

There are some drawbacks to this study. We relied on medical records, some of which did not contain all the data inquired that led to a considerable number of cases with incomplete data. Another limitation is the single-center experience and the relatively small sample size, which makes it difficult to draw conclusions on rare outcomes such as right upper quadrant pain, pulmonary edema, HELLP syndrome, and eclampsia. Thirdly, the absence of a control group of healthy pregnant women prevents a rigorous estimation of the different frequencies of adverse fetal and obstetrical events. Furthermore, multicenter observational cohort studies and with a larger number of patients are indispensable for more precise results.

In conclusion, our data demonstrated that some risk factors are associated with severe features of PE and that aspirin has a protective effect in the presence of those features. It was also showed that the presence of SPE is correlated with more critical maternal and fetal outcomes. Thus, physicians should be extremely cautious and attentive in the prenatal evaluation of the pregnant woman to obtain a complete medical history and to well establish the risk factors, which would allow them to provide the best medical care.

APPENDIX

TABLES

Table I. Characteristics of the pregnant women

	Total (n=117)		Aspirin prophylaxis					Severe preeclampsia				
			Yes (n=35)		No (n=82)			Yes (n=68)		No (n=49)		
	n	%	n	%	n	%	*P*	n	%	n	%	*P*
Socio-demographic factors												
African Ethnicity	8	6.8	4	11.4	4	4.9	0.237*	4	5.9	4	91.8	0.718*
Nulliparous	75	64.1	17	48.6	58	70.7	0.022	43	63.2	32	65.3	0.818
Assisted conception[1]	7	6.0	2	5.7	5	6.1	1.000*	2	4.1	5	7.4	0.697*
Maternal age ≥35 years	47	40.2	17	48.6	30	36.6	0.226	29	42.6	18	36.7	0.520
BMI (kg/m^2) [2]							0.971*					0.959*
18.5-24.9	16	13.8	5	14.3	11	13.6		10	14.9	6	12.2	
25.0-29.9	31	26.7	10	28.6	21	25.9		18	26.9	13	26.5	
≥ 30 (obesity)	68	58.6	20	57.1	48	59.3		38	56.7	30	61.2	
Medical history												
Chronic hypertension	18	15.4	13	37.1	5	6.1	<0.001	13	19.1	5	10.2	0.187
Previous proteinuria	5	4.3	5	14.3	-	-	0.002*	4	5.9	1	2.0	0.398*
Diabetes mellitus	7	6.0	6	17.1	1	1.2	0.003*	3	4.4	4	8.2	0.450
Spontaneous abortion	27	23.1	9	25.7	18	21.6	0.658	13	19.1	14	28.6	0.231
Induced abortion	14	12	3	8.6	11	13.4	0.550*	8	11.8	6	12.2	0.937
Multiple pregnancy	5	4.3	2	5.7	3	3.7	0.635*	4	5.9	1	2.0	0.398
Apirinin prophylaxix	35	29.9						16	23.5	19	38.8	0.076
Others[3]	5	4.3	4	11.4	1	1.2	0.028	3	4.4	2	4.1	1.000

BMI - Body mass index

[1]Assisted conception includes ovulation drugs and *in vitro* fertilization.

[2]One missing value was found in BMI variable and one patient was underweight at admission.

[3]One patient had a personal medical history of fetal death, one had a previous diagnosis of Chronic Kidney Disease and three pregnant women had an autoimmune disease (two Lupus and one Antiphospholipid Syndrome).

**P*-value calculated with Fisher's exact Test.

Table II. Maternal complications

	Total (n=117)		Aspirin prophylaxis				
			Yes (n=35)		No (n=82)		
	n	%	n	%	n	%	*P*
Proteinuria	89	76.1	29	82.9	60	73.2	0.375
Severe Hypertension (BP ≥ 160/110 mmHg)	35	29.9	11	31.4	24	29.3	0.989
Epigastric pain	12	10.3	5	14.3	7	8.5	0.340*
Visual disturbances	6	5.1	1	2.9	5	6.1	0.667*
Headache	13	11.1	2	5.7	11	11.3	0.339
Renal insufficiency (S. creatinine > 1.1 mg/dL)	6	5,1	1	2.9	5	6.1	0.667*
Transaminases elevation (AST and/or ALT)	32	27.4	9	25.7	23	28.0	0.795
Thrombocytopenia (platelets <100x10^9/L)	6	5.1	1	2.9	5	6.1	0.667*
Severe PE	68	58.1	16	45.7	52	63.4	0.076
Absence of severe features	49	41.9	19	54.3	30	36.6	
Only one severe feature	34	29.1	4	11.4	30	36.6	0.022
≥ 2 severe features	34	29.1	12	34.3	22	26.8	
Other complications[1]	3	2.6	1	2.9	2	2.4	1.000

BP - Blood Pressure; PE - Preeeclampsia

[1]There was one patient that had HELLP syndrome and was also the only one that presented convulsive manifestations. One patient had right upper quadrant pain and another one presented pulmonary edema.

**P*-value calculated with Fisher's exact Test.

Table III. Obstetric outcomes

	Total (n=117)		Aspirin prophylaxis					Severe Preeclampsia				
			Yes (n=35)		No n=82)			Yes (n=64)		No (n=48)		
	n	%	n	%	n	%	*P*		%	n	%	*P*
Type of birth							0.712					0.031
Vaginal birth												
Normal	31	26.5	8	22.9	23	28.0		14	20.6	17	34.7	
Assisted	20	17.1	5	14.3	15	18.3		12	17.6	8	16.3	
Cesarean section												
Elective	28	23.9	8	22.9	20	24.4		13	19.1	15	30.6	
Emergency	38	32.5	14	40.0	24	29.3		29	42.6	9	18.4	
Onset of labor							0.443					0.286
Spontaneous[1]	19	16.2	8	22.9	11	13.4		13	19.1	6	12.2	
Induced[2]	70	59.8	19	54.3	52	62.2		42	61.8	29	57.1	
Elective cesarean section	28	23.9	8	22.9	20	24.4		13	19.1	15	30.6	
Maternal causes of birth							0.279					<0.001*
37 weeks of gestation	54	46.2	13	37.1	41	50.0		23	33.8	31	63.3	
Severe laboratory abnormalities	22	18.8	6	17.1	16	19.5		21	30.9	1	2.0	
Sudden uncontrolled severe hypertension	8	6.8	3	8.6	5	6.1		6	8.8	2	4.1	
Worsening of symptoms	8	6.8	1	2.9	7	8.5		6	8.8	2	4.1	
Spontaneous onset of labor	6	5.1	3	8.6	3	3.7		3	4.4	3	6.1	
Other or fetal cause	19	16.2	9	25.7	10	12.2		10	20.4	9	13.2	
Fetal causes of birth							0.084*					0.650*
Pathologic cardiotocography	9	7.7	2	5.7	7	8.5		5	7.4	4	8.2	
Altered doppler fluxometry	8	6.8	4	11.4	4	4.9		3	4.4	5	10.2	
Severe IUGR	4	3.4	2	5.7	2	2.4		2	2.9	2	4.1	
Placental abrution	2	1.7	2	5.7	-	-		2	2.9	-	-	
Other or maternal cause	94	80.3	25	71.4	69	84.1		56	82,4	38	77,6	
Pre-term birth	47	40.2	16	45.7	31	37.8	0.424	35	51.5	12	24.5	0.003

IUGR - Intrauterine Growth Restriction

[1]Spontaneous onset of labor resulted in 4 normal births, 2 dystocic births and 13 emergency c-sections.

[2]Labor induction resulted in 27 eutocic vaginal birth, 18 assisted births and 25 emergency cesareans.

**P*-value calculated with Fisher's exact Test.

Table IV. Fetal outcomes for singleton pregnancies

	Total (n=117)		Aspirin prophylaxis					Severe Preeclampsia				
			Yes (n=33)		No (n=79)			Yes (n=64)		No (n=48)		
	n	%	n	%	n	%	*P*	n	%	n	%	*P*
Birth weight ≤2500g	51	45.5	16	48.5	35	44.3	0.735	34	53.1	17	35.4	0.063
APGAR score ≤7												
1st minute	33	29.5	11	33.3	22	27.8	0.724	23	35.9	10	20.8	0.083
5th minute	6	5.4	1	3.0	5	6.3	0.805	5	7.8	1	2.1	0.235
IUGR	31	27.7	13	39.4	18	22.8	0.119	16	25.0	15	31.3	0.464

IUGR - Intrauterine Growth Restriction

FIGURES

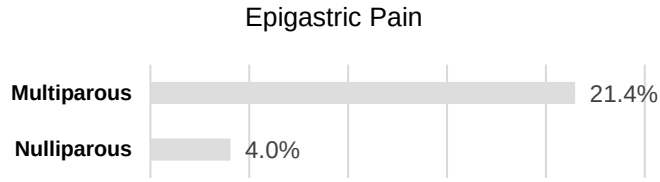

Figure 1. Epigastric pain and parity

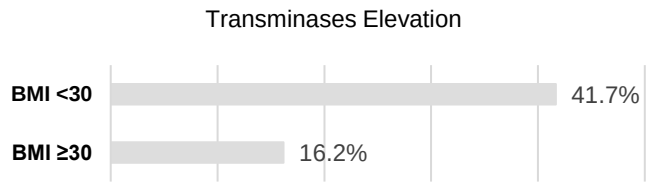

Figure 2. Elevated concentrations of liver enzymes and body mass index

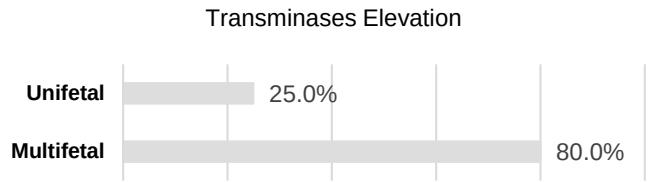

Figure 3. Elevated concentrations of liver enzymes and multifetal pregnancy

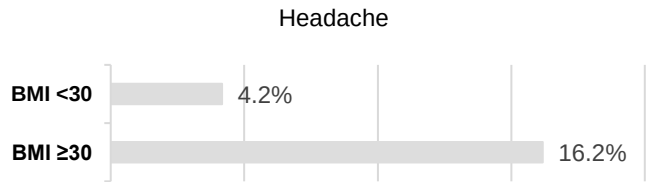

Figure 4. Headache and body mass index

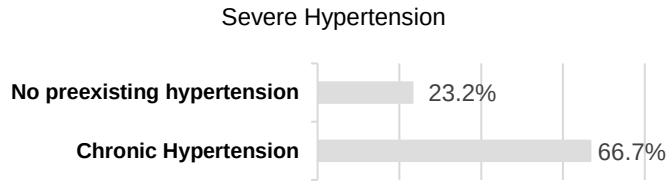

Figure 5. Severe hypertension and preexisting hypertension

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