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Original Research Paper

Obstetrics & Gynaecology

BLEEDING RISK ASSOCIATION IN PATIENTS WITH ASPIRIN PROPHYLAXIS FOR PRE-ECLAMPSIA

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KEYWORDS :

INTRODUCTION

Preeclampsia is characterized by arterial hypertension in the pregnant patient that can condition the affection to a target organ. It is considered one of the main causes of morbi maternal-fetal mortality, affecting approximately between 3 to 8% of pregnancies at the world. Due to its relevance, there are currently screening and risk assessment methods to know if a patient can present this pathology. (1) Currently aspirin is a drug used worldwide for its anti-inflammatory and antiaggregant activity platelet, so since the 70's its consumption was proposed as a method of prevention for preeclampsia. (2).

Several systematic reviews associate preeclampsia with increased risk of cardiovascular events throughout life, and therefore greater morbidity and mortality of women in the medium and long term. Considering the most frequent perinatal repercussions of this pathology, the preterm birth in 19% and intrauterine growth restriction in 12%, both associated to increased neonatal mortality. (3)

Aspirin currently plays a fundamental role in the prevention of preeclampsia, so that most international guidelines recommend its use in patients with moderate risk or tall. Prophylactic use is recommended when one or more risk factors are present moderate with a dose of 75 to 150 mg daily from week 12 to week 36 to 37of gestation. (4). This drug has been considered safe during pregnancy, for this reason it has been proposed administer aspirin to all pregnant women since it is a cheap medicine, easily accessible for the population and in our country it does not require a prescription. Assuming they would decrease the costs in the care of the pregnant patient with the possible complication of preeclampsia, the cost-effect and cost-benefit of aspirin administration have been analyzed, evaluating the major side effects such as gastrointestinal bleeding and respiratory disease, without consider bleeding during pregnancy resolution. (5) However, there are reports in non-pregnant patients showing that chronic aspirin use increases the risk of gastrointestinal bleeding (6).

There are no studies to date that show that chronic aspirin use during pregnancy carries a higher risk of bleeding during the obstetric event.

THEORETICAL FRAMEWORK

PRE-ECLAMPSIA

Preeclampsia is defined as a multisystem disorder characterized by the presence of high blood pressure and proteinuria or target organ involvement with or without proteinuria establishment after 20 weeks of gestation and during the puerperium, caused by a placental dysfunction, with remission in most cases after resolution of the pregnancy. There are several mechanisms and theories proposed to know the pathophysiology by which it occurs. the disease, currently having greater evidence of placental ischemia and inadequate Vascular remodeling of the spiral arteries at the placental site. Other Mechanisms Described are immune maladaptation, very low-density lipoprotein toxicity, increased trophoblast apoptosis and exaggerated inflammatory response during trophoblast invasion.

Pathogenesis may involve these mechanisms together rather than any one of them in isolation.

Approximately 90% of cases occur after the 34th week of gestation, while that the remaining 10% that occur before said gestational age are associated with a worse prognosis both fetal and maternal. (9)

Diagnostic criteria

Hypertension is defined as systolic blood pressure above 140 mmHg and/or a pressure diastolic pressure above 90 mmHg, while severe hypertension is defined as pressure systolic greater than or equal to 160 mmHg or diastolic greater than or equal to 110 mmHg.

Preeclampsia is defined as new-onset hypertension and proteinuria after 1 week. 20 gestation or during the puerperium in previously normotensive patients.

Preeclampsia with severity criteria refers to a patient with severe hypertension (tension blood pressure greater than or equal to 160/110), in addition to signs and symptoms of alteration in the target organ.

Eclampsia occurs when a convulsive event occurs in a patient with preeclampsia in absence of previous neurological pathology.

HELLP syndrome is an entity characterized by hemolysis, increased enzymes hepatic and thrombocytopenia, and may or may not have criteria for the diagnosis of preeclampsia. (9)

PRE-ECLAMPSIA SCREENING

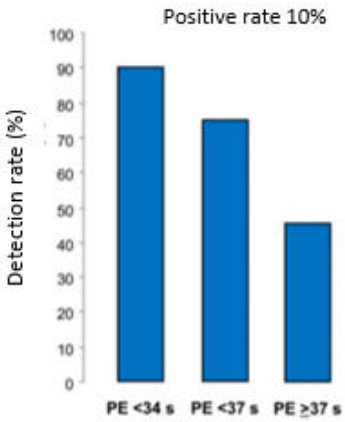
Over the years, studies of laboratory and office that have sensitivity and high specificity as predictors of preeclampsia.

The American College of Obstetrics and Gynecology recommends to take an adequate clinical history and advice on taking blood pressure. (9)

Biomarkers

- Angiogenic modulators: are important in the

pathogenesis of the disease, due to endothelial damage leading to increased capillary permeability. The main angiogenic agents studied include vascular endothelial growth factor (VEGF) and vascular endothelial growth factor placental (PlGF), as well as two antiangiogenic proteins, soluble endoglin (sEng) and full-length VEGF receptor type 1 (Flt-1) and its soluble tyrosine kinase form (sFlt-1).



Screening method	Tasa de detección		
	PE <34 s	PE <37 s	PE ≥37 s
Maternal factors	58%	50%	38%
PAM	65%	60%	43%
PAM, IPUT	80%	70%	44%
PAM, PLGF	85%	73%	47%
PAM, IPUT, PLGF	90%	75%	47%

The ischemic trophoblast increases the production of antiangiogenic proteins (sEng and sFlt-1) and decreases the production of angiogenic proteins (VEGF and PlGF).

The serum elevation and urine of such proteins precede the clinical form of preeclampsia by several weeks and even months, having a direct correlation with the severity of the disease and returning to serum levels normal during the puerperium. (22).

The sFlt/PlGF ratio is the best study for predicting preeclampsia with a 80% sensitivity and 92% specificity. (24)

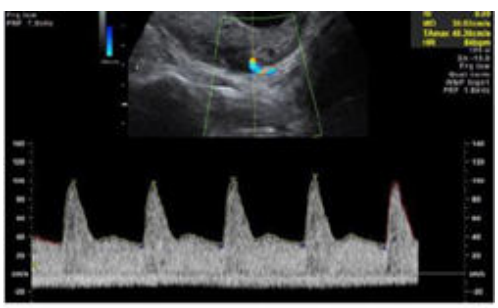


Fig. 1. Examen Doppler transabdominal de las arterias uterinas en el primer trimestre. En un corte para-cervical se localiza el cayado de la arteria uterina, y se registran al menos tres ondas idénticas, utilizando un ángulo de insonación lo más cercano posible a 0 grado.

Doppler of uterine arteries

It is recommended when patients have risk factors, since the rate of false positive is high and increases interventions that can increase costs and anxiety both at the doctor as well as the patient. This study is carried out between 11 and 13.6 weeks of gestation by transabdominal route or transvaginal. It is considered a predictive factor when a Pulsatility Index (PI) is obtained from the uterine arteries greater than the 90th percentile. Exclusively this marker can timely detect 48% of women who develop preeclampsia early and 26% of those who developed some type of hypertensive disorder during the remainder of pregnancy.(24) Normally the impedance of the uterine artery decreases as pregnancy progresses, so the stabilization or increase in it has been standardized as a screening method for preeclampsia and suggests impaired trophoblast differentiation, leading to remodeling Inadequate vascularization of the spiral arteries. The above described leads to the presence of vessels of high resistance and low capacitance, reflected clinically with arterial hypertension and Potential maternal and fetal complications. In a systematic review it was found that Doppler measurement of uterine arteries for prediction of preeclampsia has higher sensitivity during the second quarter with respect to that carried out in the first quarter. (23).

Maternal factors alone (age, weight, ethnicity, reproductive history, and smoking) can predict 49% of Preeclampsia before 37 weeks of gestation. By adding the PlGF concentration the prediction rate increases up to 60%. By combining the features mothers, mean uterine artery pulsatility index, mean arterial pressure, and PlGF within from weeks 11-13.6 the predicted rate of pre-eclampsia before weeks 37 is 75% and after week 37 it is 47%. (24)

ASPIRIN

A low dose of aspirin (75-150 mg) decreases the risk of preeclampsia, as well as complications associated with this entity such as preterm birth and restriction of fetal growth by 10 to 20%. It has been described that preeclampsia leads to an increase in levels of thromboxane, a stimulant of platelet aggregation, so aspirin therapy at low doses it confers benefit for the prevention of preeclampsia, especially in patients with risk factors for this disease.

This pathology is associated with a deficient intravascular production of prostacyclin, a vasodilator agent, and production excessive thromboxane, which has a vasoconstrictor effect. Thus, the use of aspirin would potentially help prevent or delay the development of pre-eclampsia. (7). The main benefit is directed at patients who have moderate or high-risk factors.

There is currently no consensus to define a high risk of preeclampsia, however, the American College of Obstetrics and Gynecology (8) estimates that any of the following factors can increase up to 8% the probability of presenting preeclampsia:

- Previous pregnancy with preeclampsia (higher risk if early onset)
- Twin pregnancy
- Diabetes Mellitus 1 or 2
- Autoimmune Disease (Systemic Lupus Erythematosus or Antiphospholipid Syndrome)
- Chronic kidney disease

In 2017, the American Heart Association along with the American College of Cardiology reviewed that patients with a previous pregnancy with preeclampsia or diabetes with high-grade arterial hypertension 1 (systolic blood pressure between 130 and 139 mmHg and/or diastolic between 80 and 89 mmHg) have a increased conferred risk of preeclampsia, which decreases with consumption of prophylactic dose of aspirin versus placebo (24 versus 39 percent) (10). The use of prophylaxis with aspirin in patients with grade I systemic arterial hypertension without additional risk factors. However, there is insufficient evidence to support this practice, so it is not recommended. Its routine use in this group. The incidence of

preeclampsia in a patient with only one risk factor is less than 8%. (10) It is important to emphasize that not all moderate risk factors have the same risk of preeclampsia and no study has currently evaluated each of these risk factors separately with the use of aspirin.

The US Preventive Services Task Force (USPSTF) states that low doses of aspirin for prevention of pre-eclampsia when they have two or more of the following factors moderate risks (11):

- Nulliparity
- Low socioeconomic status
- African American Race
- Maternal age greater than or equal to 35 years
- Family history of preeclampsia in mother or sister
- Body Mass Index greater than or equal to 30 kg/m2

Specific cases:

- Multiparous patients without a history of preeclampsia: low doses of aspirin even if there was no prophylaxis in previous pregnancies.
- Patients with an established diagnosis of preeclampsia: it is not recommended to give aspirin to because its use has been shown to prevent disease progression.

In 2019 a meta-analysis of 74 trials with more than 40,000 patients reported that aspirin reduces the incidence of proteinuria, stillbirth, preterm birth, intrauterine growth restriction and decreases the risk of suffering from preeclampsia with severity data. (7) The reason for starting aspirin prophylaxis at week 12 and not later than week 16 is that the pathophysiology of preeclampsia begins in early pregnancy, in the first wave of placentation. However, if the drug could not be started during that period can be used until before week 28, offering lesser results. (12) The adequate dose comprises between 81 to 150 mg daily. There is currently no established beneficial effect between some specific dose, however it is suggested that the dose is not greater than mentioned range. International guides recommend its consumption at night, although recent studies showed that it can cause gastric disease. (13). It is recommended continue aspirin until 36 weeks of gestation or discontinue 5 to 10 days before gestation estimated date for resolution of pregnancy.

A meta-analysis carried out by the team of K. Nicolaides in 2017, where patients were analyzed with preterm and term preeclampsia, showed that the use of prophylactic aspirin reduced the risk of preterm preeclampsia, but not term preeclampsia and only when it started before 16 weeks of gestation at doses of 100 mg daily or more. (14)

Aspirin Safety

Aspirin is listed by the Food & Drug Administration (FDA) as a prescription drug category D with doses of 500 mg daily, while doses between 75 to 150 mg daily have not demonstrated fetal alterations during the second and third trimesters. In a meta-analysis that reviewed 77 studies with 40,249 patients and their respective newborns with different doses of aspirin, from 50 mg to 150 mg daily, no significant risk of bleeding was found neonatal intraventricular (RR 0.90, 95% CI 0.75-1.08), although an increase in postpartum hemorrhage (greater than 500 ml) (RR 1.06, 95% CI 1.00-1.12) but these figures were minimized because the way of quantifying bleeding was heterogeneous. The risk of placental abruption is increased (RR 1.21, 95% CI 0.95 to 1.54), but they classify it as moderate risk of evidence. An 18% reduction in the incidence of proteinuria during preeclampsia. (7).

GUIDES

The American Heart Association recommends low-dose aspirin for patients with hypertension. primary or secondary chronic disease and in patients with a history of preeclampsia. (15)

The USPSTF recommends the use of 81 mg daily in patients at high risk of preeclampsia, with two moderate risk factors. (11) ACOG recommends starting doses of 81 mg daily in patients at high risk of preeclampsia between 12 to 28 weeks of gestation. (8)

The NICE Guideline and the World Health Organization recommend 75 mg per day for patients with a high risk factor. (16, 17)

FIGO recommends in patients with a risk factor a dose of 150 mg per day starting from 11 to 14.6 weeks of gestation taken overnight through 36 weeks. (18)

The Mexican clinical practice guideline recommends 100 mg of aspirin in patients with risk factors for preeclampsia. (19)

Cardiovascular implications continue in the long term as sequelae in patients who had preeclampsia. It has been described that at 10 years biventricular systolic function is altered, as well as endothelial function, which increases the risk of morbidity and mortality.

The risk of presenting a cardiovascular alteration increases up to 5.4 times in patients who presented preeclampsia with severity data compared to the general population. The above leads to these alterations persisting and making it more difficult for the mother to adapt to the following gestations. (24)

OBSTETRIC HEMORRHAGE

There are different definitions among the largest world institutions to define the obstetric hemorrhage. ACOG defines it as blood loss equal to or greater than 1,000 mL or blood loss accompanied by signs and symptoms of hypovolemia in the first 24 hours after delivery, regardless of the route of resolution. (27)

The Mexican Clinical Practice Guideline defined as bleeding greater than or equal to 500 ml at delivery and 1000 ml or more at cesarean section. (25).

According to the WHO (World Health Organization), postpartum hemorrhage is a loss greater than 500 ml in the first 24 hours after delivery regardless of the route of delivery birth and severe if there is loss of more than 1000 ml in the same period.

For the purposes of this writing, the definition of the Mexican Guide to Clinical Practice of Hemorrhage, since within the guidelines of Hospital Angeles Mexico for the protocol of hemorrhage will be considered these data.

In Mexico, the estimated incidence of obstetric hemorrhage is 16%, regardless of the route of delivery resolution.

During pregnancy, blood volume increases by 45%, resulting in approximately 1,200 to 1,600 additional ml to a non-pregnant patient, to cover the uteroplacental supply. Although this increase, the abrupt hemodynamic decompensation is what causes alterations in the general condition of the patient. During a full-term pregnancy, the uterus receives approximately 700 to 900 ml per minute. Due to this situation, the rapid action of the doctor and the knowledge of how to treat the disease are essential hemorrhage. Prior to attending the obstetric event, it is important to identify the risk factors and, in this way, way to prevent obstetric hemorrhage. The causes of hemorrhage are classified into four main causes that is uterine atony, retention of placental remains, cervical or vaginal injury during childbirth and coagulation disorders. Pregnant patients tolerate 15% loss of blood before they begin with alterations in vital signs or present low output symptomatology.

The first to be affected is heart rate and filling retarded

capillary. (25). Signs of shock should be watched for at the time of active bleeding which include:

- Hypotension: Systolic blood pressure less than or equal to 90 mmHg
- Mean arterial pressure less than 60 mmHg
- Heart rate greater than 120 beats per minute
- Urinary volume less than 0.5 ml/kg/hr
- Capillary refill greater than 3 seconds

It is theorized that obstetric bleeding or hemorrhage in patients with prolonged use of aspirin is secondary to inhibition of thrombus formation in maternal vessels, which leads to a greater placental perfusion and therefore to an increase in bleeding even when aspirin is discontinued a week or more before the obstetric event. (26)

JUSTIFICATION

The prophylactic use of aspirin has been proposed for the prevention of preeclampsia in patients pregnant women with risk factors. There are studies in non-pregnant patients, where it is indicated aspirin as a preventive measure of cardiovascular events, observing an increase in the risk of bleeding; However, there are no conclusive studies to determine the risk of bleeding in the obstetric patient.

PROBLEM STATEMENT

Preeclampsia and obstetric hemorrhage are currently two of the main pathologies of maternal morbidity and mortality. The use of aspirin for the prevention of preeclampsia entails a great challenge, since we must select the candidate patient in an ideal way for receive this treatment without increasing the risk of another pathology such as hemorrhage obstetric.

RESEARCH QUESTION

Is there a relationship between aspirin prophylaxis for preeclampsia and bleeding in the event Obstetric?

HYPOTHESIS

The use of prophylactic aspirin increases the risk of bleeding in the obstetric event.

GENERAL OBJECTIVE

Relate the use of prophylactic aspirin for preeclampsia with bleeding in labor and cesarean section in Hospital Ángeles México in the period between April 2020 and January 2021.

MATERIALS AND METHODS

STUDY DESIGN:

- Cases and controls
- By the imposition or not of a maneuver by the investigator observational
- By monitoring the researcher over time Cross
- Due to the directionality in the data collection of the researcher Retrospective By the search for association or not between 2 variables by the researcher Descriptive

A review of 110 randomized clinical records of patients who had births in the period from April 2020 to January 2021 at Hospital Ángeles México.

For the statistical analysis, a database was created in Numbers 2021, means were established, standard deviation, interquantile range and percentages, with support from the SPSS Statistic program.

SAMPLE SELECTION

The selection of the sample will be probabilistic, based on availability.

INCLUSION CRITERIA

Pregnant patients who attended Hospital Angeles Mexico in the period from April 2020 to January 2021 for pregnancy resolution (vaginally or abdominally).

EXCLUSION CRITERIA

- Patients with preeclampsia.
- Patients using low molecular weight heparin
- Patients using serotonin reuptake inhibitors

VARIABLES

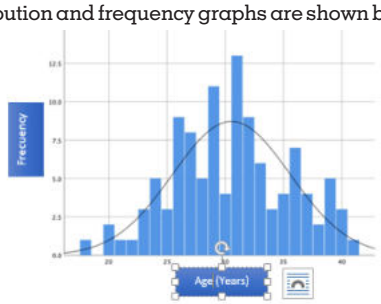
- AGE: Period of time that has elapsed since birth.Variable type Discrete quantitative Measurement scale: years
- BODY MASS INDEX: Ratio of weight to height squared. Type of variable: Continuous quantitative. Measurement scale: kg/m2
- SMOKING: Smoked cigarettes for 3 months prior to pregnancy Type of variable: Qualitative nominal dichotomous otherwise.
- ALCOHOL: Had at least one drink of alcohol during pregnancy. Type of variable: Qualitative nominal dichotomous otherwise.
- ASPIRIN USE: Used aspirin as prophylaxis for preeclampsia during pregnancy. Type of variable: Qualitative nominal dichotomous otherwise
- BLOOD LOSS: Amount of bleeding during the obstetric event. Type of variable: Quantitative Measurement Scale: Milliliters

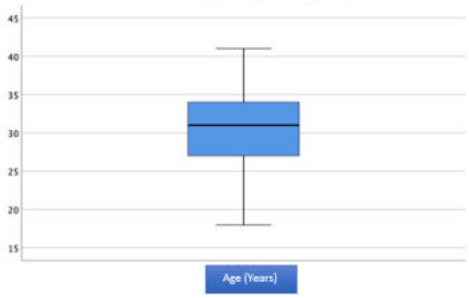
RESULTS

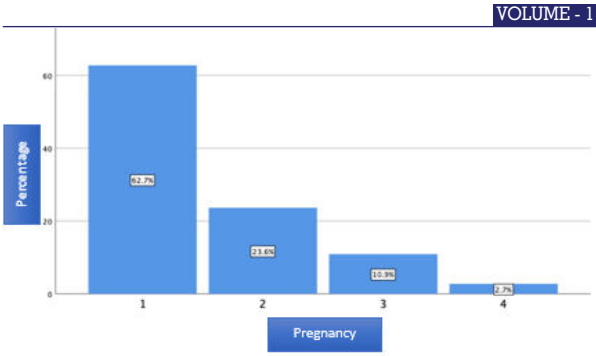
The clinical record of 110 female patients who completed their pregnancy in the period from April 2020 to January 2021 at Hospital Ángeles de México to evaluate the Association of aspirin use and obstetric bleeding.

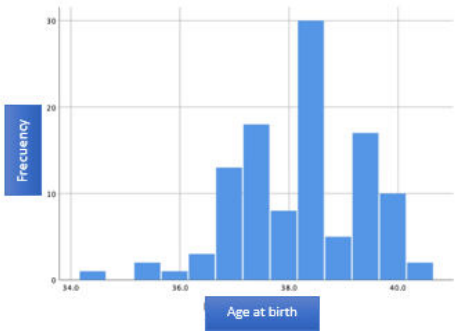
The average age observed was 30.5 years (SD 5.0) with a minimum and maximum value of 18 and 41 years of age, respectively; 23.6% (n=26) was classified as advanced maternal age, which was defined with the criteria of the Clinical Practice Guideline as being greater than or equal to 35 years of age. It was recorded that in 62.7% (n=69) it was the first pregnancy; 23.6% (n=26) of the second; 10.9% (n= 12) of the third; and 2.7% (n=3) of the fourth. The average age of birth was 38.2 weeks of gestation (SD 1.2), with a minimum and maximum value of 34.4 and 38.3 weeks, respectively. In relation to fetal weight, an average of 2,923.32 grams (SD 338.4) was observed, with a minimum and maximum value of 1,790 grams and 4,020 grams, respectively. It was observed a Mean BMI prior to pregnancy of 24.6 kg/m2 (SD 3.3), with a minimum and maximum value of 17.7 kg/m2 and 35.7 kg/m2 . While the current average BMI was 28.0 kg/m2 (SD 3.3), with a minimum and maximum value of 21.4 kg/m2 and 36.5 kg/m2 ; with an average weight difference estimated 9kg.

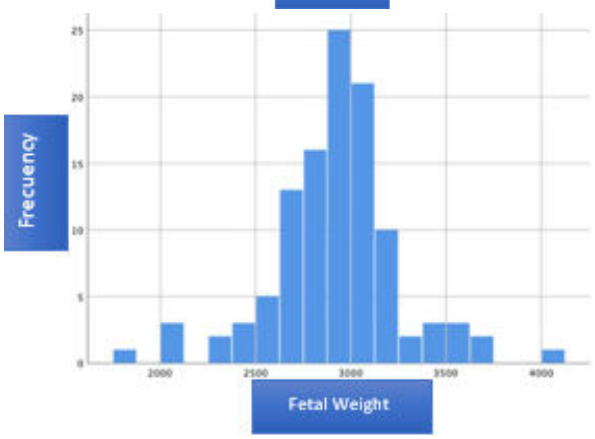
The distribution and frequency graphs are shown below.

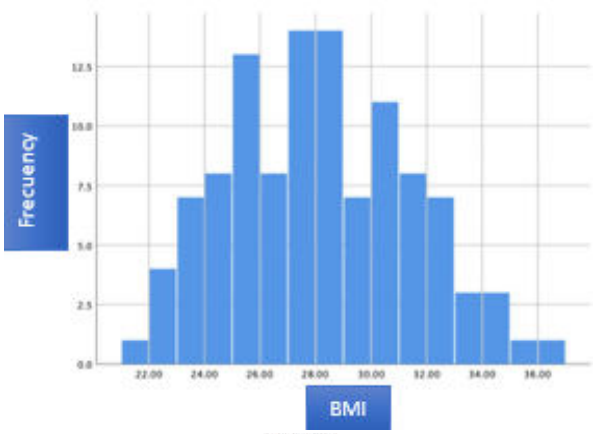


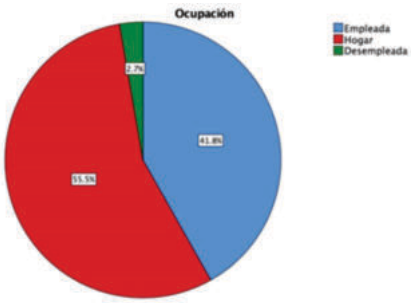










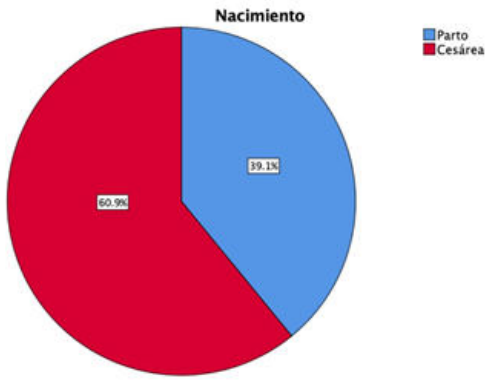


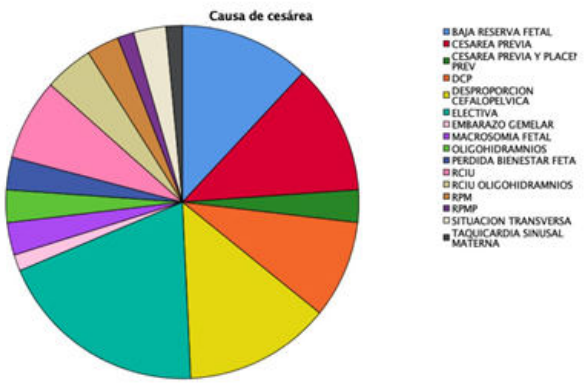
Of the total number of women, 41.8% (n= 46) reported themselves as employees, 55.5% (n= 61) as housewives, home and 2.7% (n=3) as unemployed. 4.5% (n= 5) had a history of smoking, 2.7% (n=3) of alcohol consumption and 11.8% (n=13) had had a previous caesarean section.

Assisted reproduction was performed in 2.7% (n= 3) of the patients and only one multiple pregnancy (0.9%).

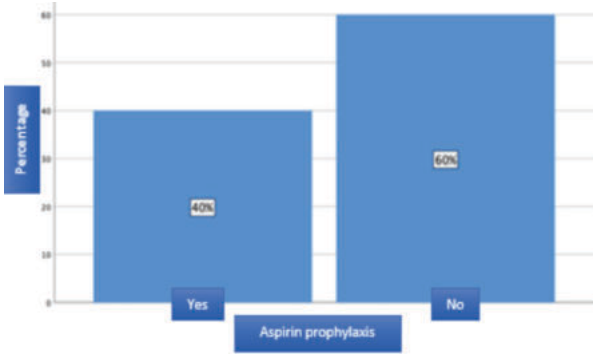
During pregnancy, it was observed that 5.5% (n= 6) presented gestational diabetes, 1.8% (n= 2) placenta previa and no cases of placental abruption with normal insertion (DPPNI). 39.1% (n= 43) of births were by delivery, while 60.9% (n= 67) were by cesarean section; being the main cause the elective with 19.4% (n=13) followed by disproportion cephalopelvic in 13.4% (n=9). Within deliveries, instrumentation was required in 7% (n=3).

Lung maturation was performed in 34.5% (n=38) of births.





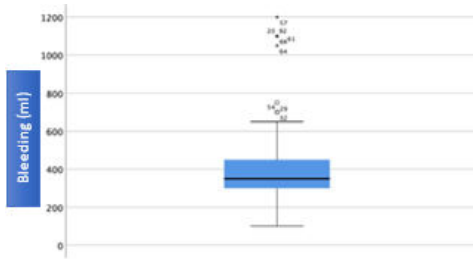
Prophylactic treatment with Aspirin was used in 40% (n= 44) of the pregnant patients, with an average of initiation and suspension of treatment at 12.4 and 35 weeks of gestation, respectively.

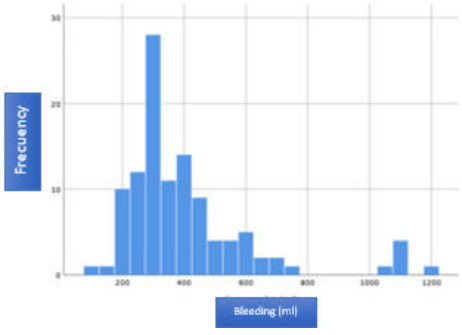


In relation to the variables of obstetric bleeding, an average of 404.1 bleeding was recorded ml (DE 212.4), with a minimum and maximum value of 100 ml and 1,200 ml, respectively. 13.6% (n= 15) had obstetric hemorrhage (delivery >500ml,

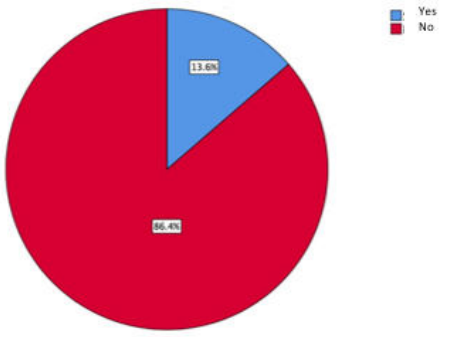
caesarean section >1000ml), of which 7 (6.4%) was classified as intrapartum and 8 (7.3%) postpartum.

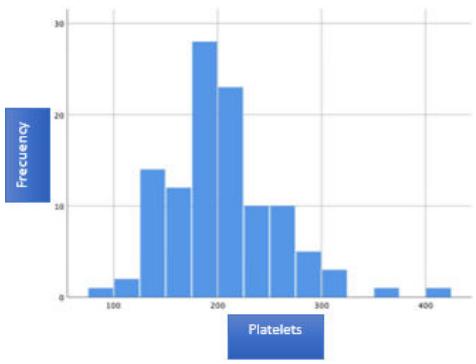
Only one patient (0.9%) presented hematoma postpartum mean prepartum platelets were 202.85 per microliter (SD 52.6) with a minimum and maximum value of 97 per microliter and 400 per microliter, respectively.





Obstetric Hemorrhage





The following tables show the comparison of obstetric bleeding and platelets prior to delivery. delivery in different comparison groups, including the use of prophylactic Aspirin.

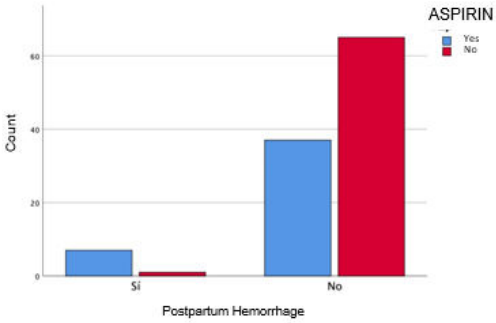
There is an increase in the average bleeding associated with diabetes gestational (198ml, CI95% 25 – 372) and the use of aspirin (197.7 ml, CI95% 125 – 271).

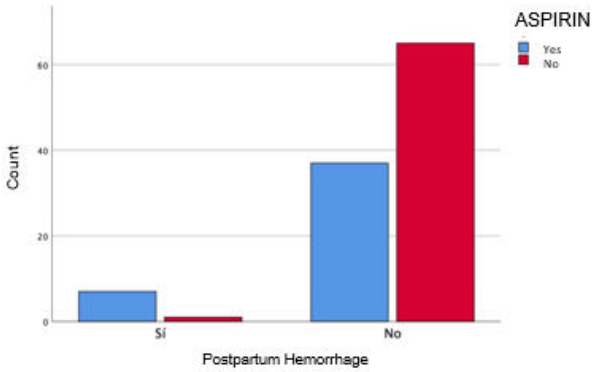
In relationship with platelets, no association was observed.

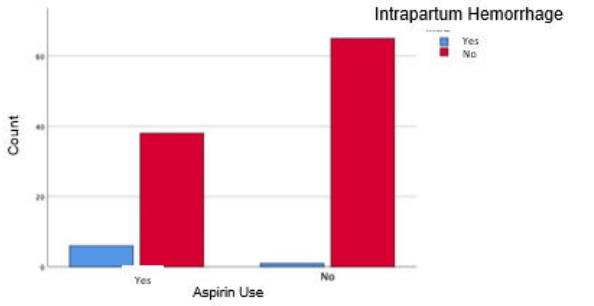
Obstetric Bleeding Comparisson Chart				
Cluster	**n**	**Mean (ml) (DE)**	**Difference IC95%**	**P value**
Advanced maternal age	26	485.4 (301)	106.5 (-19 – 232)	0.13
Normal Age	84	378.9 (171)		
Smoking	5	450 (141)	48.1 (-145 – 241)	0.26
Non smoking	105	401.9 (215.5)		
Gestational Diabetes	6	591.7 (273)	198.4 (25 – 372)	0.02*
Non gestational diabetes	104	393.3 (205)		
Pulmonary Maturation	38	458.4 (269)	83 (-13 – 179)	0.28
Non pulmonary maturation	72	375.4 (171)		
Birth	43	416.7 (225)	20.7 (-62 – 103)	0.50
Cesarea section	67	396 (205)		
Aspirin	44	533.7 (249)	197.7 (125 – 271)	0.001*
Non Aspirin	66	325 (137)		
*p<0.05; a U of Mann-Whitney Test.				

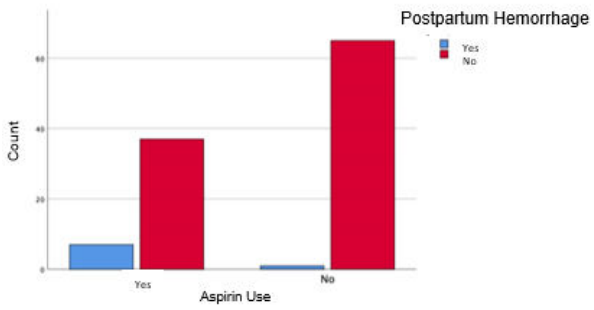
The following are the tables of proportion of variables of obstetric hemorrhage and use of aspirin. No significant difference was observed in the use of aspirin between the different risk factors for obstetric hemorrhage. However, when assessing the risk of bleeding, observed a significant increase with obstetric, intrapartum and postpartum hemorrhage, with an OR of 13.4, 10.2 and 12.3, respectively.

Aspirin Usage Rate Comparison Table				
Cluster	**Aspirin n = 44 n (%)**	**Non Aspirin n = 66 n (%)**	**OR Ic95%**	**P value**
Advanced maternal age	14 (31.8)	12 (18.2)	2.1 (0.86 – 5.1)	0.10b
Smoking	3 (6.8)	2 (3)	2.3 (0.4 – 14.6)	0.39c
Gestational Diabetes	2 (4.5)	4 (6.1)	0.74 (0.13 – 4.2)	0.99c
Pulmonary Maturation	18 (40.9)	20 (30.3)	1.6 (0.72 – 3.5)	0.25b
Birth	20 (45.5)	23 (34.8)	1.6 (0.71 – 3.4)	0.26b
Obstetric Hemorrhage	13 (29.5)	2 (3)	13.4 (2.9 – 63.2)	0.001*b
Intrapartum Hemorrhage	6 (13.6)	1 (1.5)	10.2 (1.2 – 88.5)	0.02*c
Postpartum Hemorrhage	7 (15.9)	1 (1.5)	12.3 (1.5 – 103.9)	0.007*c
*p<0.05; b Pearson X2, c Fisher Exact Test.				



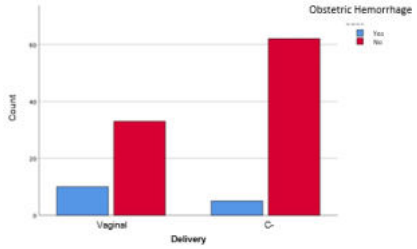






Below are different variables that could participate as risk factors for obstetric hemorrhage. The 34th was identified with a higher risk of obstetric hemorrhage. delivery, with an OR of 3.76 compared to patients who underwent Caesarean section.

Aspirin Usage Rate Comparison Table				
Cluster	**Obstetric hemorrhage n = 15 n (%)**	**Non hemorrhage n = 95 n (%)**	**OR IC95%**	**P value**
Advanced Maternal Age	4 (26.7)	22 (23.2)	1.2 (0.4 – 4.2)	0.75c
Smoking	2 (13.3)	3 (3.2)	4.7 (0.7 – 30.9)	0.14c
Gestational Diabetes	2 (13.3)	4 (4.2)	3.5 (0.6 – 21.1)	0.19b
Pulmonary Maturation	7 (46.7)	31 (32.6)	1.8 (0.60 – 5.4)	0.28b
Birth	10 (66.7)	33 (34.7)	3.76 (1.2 – 11.9)	0.02*b
***p<0.05; b Pearson X2, c Fisher Exact Test.**				



The table below shows the regression model that best explains the risk of Aspirin-associated obstetric hemorrhage, adjusting for type of birth and gestational diabetes.

Multivariate logistic regression for the risk of obstetric hemorrhage associated with aspirin use.			
Variable	**OR**	**IC (95%)**	**P value**
Aspirin	14.76	2.9 a 76.4	0.001*
Birth	4.17	1.1 a 15.7	0.034*
Gestational diabetes	10.85	0.84 a 140.1	0.07
Constant	0.01	0.002 a 0.07	0.001*
PsR2 = 0.27, p 0.001*; * p<0.05			

Statistic analysis

Descriptive statistics were used for the presentation of data with measures of central tendency and dispersion. The Kolmogorov-Smirnov test was performed to determine the distribution of the data.

An inferential analysis of comparison of means was performed using the t-test of Student for the variables with normal distribution and with non-parametric tests (U test of Mann-Whitney) for those with non-normal distribution. An analysis of proportions was performed using Pearson's X2 test and for cases where expected values were found by box <5 observations Fisher's exact test was used.

A regression analysis was performed multivariate logistics to identify the best model to explain the risk of bleeding obstetric associated with the use of prophylactic aspirin.

The results were summarized as OR and their respective 95% confidence intervals (CI). In all cases, a value of p<0.05 was considered statistically significant, respectively. For data processing, Stata/MP 16.0 statistical package and IBM SPSS Statistics 25.0 statistical package were used.

DISCUSSION

The use of aspirin as prophylaxis was indicated in 40% of the study population, compared to the average reported in the world literature (11). A possible explanation would be that being a private environment, patients have greater adherence during prenatal control; Also, during the ultrasound screening 11-14 uterine artery pulsatility index measurement with or without the presence of risk factors, which leads to starting treatment without indication standardized.

The start of treatment was at 12.4 weeks and suspension at 35 weeks, unlike the recommendation provided by the international guidelines for suspension at 36 weeks of gestation. According to the definitions of obstetric hemorrhage of 500 milliliters in resolution vaginally and of 1000 milliliters in resolution abdominally, in the population studied 13.6% (15 patients) presented this complication, of which 6.4% (7 patients) occurred in the intrapartum period and 7.3% (8 patients) in the postpartum period. Mean blood loss, regardless of resolution pathway, was 401 milliliters.

Gestational diabetes was found in 5.5% of the patients, it is already established that this pathology increases the risk of bleeding during the obstetric event, in this study found a significant p of 0.02 in the 6 cases that were obtained, these presented a mean of bleeding of 591.7 milliliters, which was 197.7 milliliters higher than that of the general population, in this specific case it is a modifiable factor that must be addressed correctly from diagnosis in order to prevent this outcome.

The literature stipulates that it mainly increases the risk of bleeding in vaginal delivery due to uterine atony.

Platelets were taken prior to delivery in all patients, and no association was found between bleeding with respect to this variable, the average was 202,850 per microliter with a value minimum of 97,000 per microliter and maximum of 400,000 per

microliter.

In the proportion of obstetric hemorrhage and the use of aspirin, no difference was found significant difference in the use of aspirin among the different risk factors for obstetric hemorrhage. When evaluating the risk of bleeding, a significant increase was found with an OR of 13.4, with a significant p of 0.001, this would have as an explanation that a large part of the patients (40%) received prophylactic aspirin and that in the Hospital there is no standardized method for the quantification of blood loss and is assessed subjectively on some occasions.

Regarding the moment in which the hemorrhage occurs, it was practically the same during the moment delivery or postpartum with an OR of 10.2 and 12.3 respectively.

A higher risk of obstetric hemorrhage was observed in delivery than in caesarean section, contrary to what discussed in the literature, this may be due to the cut-off point in which the obstetric hemorrhage cataloging it as 500 ml in childbirth and 1000 ml in caesarean section.

In another study, (26) the use of prophylactic aspirin had been associated with an increased risk of hematoma, however in this study only one patient with this outcome was found, which was not statistically significant.

CONCLUSIONS

The use of prophylaxis for preeclampsia with aspirin should be taken with caution since it is not an innocuous medication, the established criteria for starting prophylaxis must be clear. In this group of patients, aspirin prophylaxis was 40%, which is well above reported in the global literature therefore the increased risk of bleeding.

International guidelines recommend administration in those patients with risk factors and not universally.

In reports of non-pregnant patients, it has been associated with an increased risk of hemorrhage. gastrointestinal. There is only one published study where an increased risk of postpartum bleeding and hematoma.

In this group of patients, there is an increase in the average bleeding associated with diabetes pregnancy and the use of aspirin, both statistically significant.

Until now, the physiopathogenic mechanism by which aspirin is a factor is unknown. risk of increased bleeding even if suspended more than a week prior to obstetric resolution. However, recent studies have proposed a hypothesis of placental changes from the third wave of placentation that can be reflected in the long term. (26)

A higher risk of obstetric hemorrhage was observed in delivery than in caesarean section, contrary to what discussed in the literature, this may be due to the cut-off point in which the obstetric hemorrhage cataloging it as 500 ml in childbirth and 1000 ml in caesarean section.
It is proposed to carry out a prospective study to standardize the measurement of bleeding as well as use the different hemorrhage guidelines using hemodynamic factors.

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