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ORIGINAL ARTICLE

# RETROSPECTIVE ANALYSIS ON THE USE OF ACETYLSALICYLIC ACID IN THE PREVENTION OF PREECLAMPSIA IN A MUNICIPALITY OF GOIÁS

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**ABSTRACT**

Objective: This study aims to analyze and quantify the use of ASA in pregnant women with a high risk of pre-eclampsia in a city of Goiás, a Brazilian state, between 2019 and 2020. Methodology: The study analyzed 400 prenatal records of the Health System of one city of Goiás and identified clinical criteria pre-defined by the International Federation of Gynecology and Obstetrics, which allowed to identify the indications and propaedeutics of the medication. Results: 147 pregnant women had an indication for use of prophylactic ASA and 92% of them did not receive the medication. Within the 8% medicated, there was no adequate prescription. In addition, among pregnant women with an indication, 85% started prenatal care on time for the introduction of the medication and, in the vast majority, it was not started. Conclusion: The dissemination of knowledge and the rate of prescription of acetylsalicylic acid are extremely low in the city of Goiás. Thus, the opportunity to prevent serious illness with a medication recommended by regulatory agencies is lost.

**KEYWORDS: PRE-ECLAMPSIA. PRENATAL. ASPIRIN. PREVALENCE. INFORMATION DISSEMINATION**

## INTRODUCTION

Preeclampsia (PE) is currently defined as hypertension (blood pressure ≥140x90 mmHg, on at least two occasions, measured four hours apart, in previously normotensive pregnant women), which normally occurs after 20 weeks of gestation, and is accompanied by one or more of these conditions: proteinuria (>300 mg/24 hours); evidence of other maternal organ dysfunction (acute kidney injury, liver involvement with or without right upper quadrant, epigastric abdominal pain, neurologic or hematologic complications); uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth), with resolution up to 12 weeks postpartum.[1]

The etiology of preeclampsia is not fully understood. However, many sources consider that an inadequate or deficient invasion of the trophoblast in the maternal spiral arteries occurs in early pregnancy. This invasion normally begins at the 8th week and is completed between the 16th and 22nd weeks of gestation.[2] This process triggers an imbalance between angiogenic and antiangiogenic factors.1 Thus, with abnormal placentation, there is a deficit in the intravascular production of prostacyclins (vasodilators) and excessive platelet production of thromboxane A2 (vasoconstrictor and platelet aggregation stimulant).[2]

Preeclampsia occurs in about 2 to 5% of pregnant women and is a major cause of maternal and fetal morbidity and mortality. This pathology annually causes the death of 76,000 women and 500,000 newborns worldwide.1

Risk factors have already been studied by numerous authors. However, when adopting the standards established by the International Federation of Gynecology and Obstetrics (FIGO), we find the following:

| Fatores de Alto Risco | Fatores de Médio Risco |
|---|---|
| História prévia de PE; | Nuliparas; |
| Doença renal; | Idade >35 anos; |
| Doença autoimune (Lúpus Eritematoso Sistêmico e Síndrome Antifosfolipídeo); | IMC >30 kg/m²; |
| | História familiar de PE; |
| Diabetes Mellitus 1 e 2; | Intervalo interpartal longo (>23 meses) e |
| Hipertensão Crônica. | curto (<12 meses); |
| | Reprodução assistida; |
| | Etnia afro-caribenha ou sul-asiática. |

**Chart 1 – Risk factors for preeclampsia.**
**Source: Own authorship based on FIGO manual [1]**

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These risk factors coincide, for the most part, with those defined by the World Health Organization (WHO), the National Institute Clinical Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG) and directly interfere with the prophylactic conduct with Acetylsalicylic acid (ASA).[3,1,4,5]

The risk factors (Chart 1), as determined by NICE and ACOG and endorsed by FIGO, are subdivided into medium and high risk, with pregnant women at high risk of developing PE having two medium risk factors or one high risk. With the objective of achieving a more effective screening and with fewer false-positive cases, FIGO proposes that the assessment with biomarkers, Mean Arterial Pressure (MAP) and uterine artery pulsatility index be added to the analysis of risk factors. However, the use of high risk factors, in places with low infrastructure and impossibility of performing other methods, may be sufficient to indicate prophylactic treatment. MAP must be measured using an appropriate technique and must be entered into specific calculators, together with the risk factors already mentioned in the table above.6 Biochemical markers: PLG-F (Placenta Growth Factor) and PAPP-A (Plasma Protein Associated with Pregnancy) and biophysical: measurement of uterine artery pulsatility, significantly increase the accuracy of screening, but because they are instruments of difficult access and high cost, they are rarely used.[1]

According to Antunes[2], the use of ASA in low doses has been suggested by several scholars and researches in the prevention of PE due to its ability to selectively inhibit the cyclooxygenase pathway in platelets, sparing the vascular endothelium.[7,8,9,10,11,1,12,5,3,4,13] Thus, ASA inhibits thromboxane synthesis without affecting the production of prostacyclins, protecting against vasoconstriction and abnormal placental clotting, that is, without altering uteroplacental blood flow.2

The ideal dose of ASA and its timely introduction are still being discussed by various literatures, as mentioned above. However, FIGO is the main reference, as it is an international body and has a recent guideline. The 2019 guideline recommends that patients weighing less than 40 kg should take 100 mg at night, while patients weighing more than 40 kg should take 150 mg. [1] It is recommended to start treatment before the 16th to 20th week of pregnancy, since it is in this fetal period that the development of the uterine spiral arteries ends and the placental invasion ends, places where ASA will act to prevent on foot. [12] The medication can be continued until 36 weeks of gestation or until delivery. [1]

ASA has been considered very effective in the prophylactic treatment of PE.[11,14,15] According to Gavillet[16], the prophylactic administration of ASA generates a 62% reduction in the risk of preeclampsia. Hoffman[17] observed in a randomized, double-blind study a reduction in the risk of preterm birth (less than 34 weeks), perinatal mortality, women who gave birth before 34 weeks with hypertensive disorders and fetal loss (infant death after 16 weeks of pregnancy and before seven days postpartum). Hoffman[17] also emphasizes that the medication is well tolerated and inexpensive, which favors the expansion of this propaedeutic.

According to FIGO, preeclampsia is responsible annually for about 10% of maternal deaths and 9 to 20% of perinatal deaths worldwide.[1] In addition, it is one of the four causes of maternal mortality and morbidity in countries with high, medium and low income. In Brazil, hypertensive events are among the three main causes of maternal mortality, along with sepsis and hemorrhage.[18]

In view of this perspective, this study aimed to analyze adherence to the use of prophylactic ASA in pregnant women at high risk of PE in a municipality in the State of Goiás, who underwent prenatal care between August 2019 and December 2020, since , despite the high level of scientific evidence, this approach is not frequently observed in daily medical practice. In addition, it was possible to observe the adequacy of the workup and dosage in line with current guidelines.

With the data obtained, this work will provide subsidies for the development of health policies aimed at the education and updating of health professionals and will bring benefits to future pregnant women, who, if they are at high risk of PE, will have greater chances of receiving prophylactic medication.

## METHODOLOGY

Retrospective observational study, carried out after approval by the Ethics and Research Committee (CEP), under opinion 4,529,556, through the review and analysis of 400 prenatal medical records from the public health network of a municipality in State of Goiás, which took place between August 2019 and December 2020. Data collection was authorized by the Municipal Health Department and the search was carried out between January and April 2021, through the municipality's Electronic Medical Records System, through reading, reviewing and identifying terms, data, signs and symptoms that included the pregnant woman in the high risk group for PE. After this analysis, the data were cataloged in Microsoft Excel tables and segmented into three comparative groups: patients who used the medication with adequate propaedeutics (dose recommended by FIGO and timely introduction), patients who used the medication with inadequate propaedeutics, and patients who did not use the medication. The tables obtained were converted into graphs to facilitate the understanding of the readers.

The population consisted of pregnant women who are considered by FIGO to be at high risk of preeclampsia, and who would have an indication for preventive treatment with ASA. Among them, those with one high risk factor or two or more medium risk factors, mentioned above, were counted. FIGO, in 2019, with the aim of increasing the reliability of the screening, recommended that these criteria be added to at least one of the following: MAP measurement, biochemical markers or Doppler ultrasound with measurement of the uterine artery pulsatility index.1 However, for this study, due

to its retrospective nature, limited access to information and the high cost of more accurate tools (specific markers and Doppler ultrasound) to the Unified Health System (SUS), screening was performed only with maternal risk factors . Despite being less accurate, isolated risk factors were used before the 2019 FIGO guideline.[3,5] Healthy pregnant women, or those who underwent prenatal care before August 2019 and after December 2020, or even inconsistent and incomplete medical records were excluded.

When analyzing the possible risks, patients could have been subject to stigmatization, disclosure of information, invasion of privacy and risk of disclosure of confidential data. However, despite the severity of the risks, they were minimized by limiting access to medical records for the duration of the research. Confidentiality and privacy were ensured, since the patient's name was replaced by a numerical code, in order to protect individuals from exposure and stigmatization, ensuring that the information is not used to the physical, emotional and economic harm of people and/or the community. It is worth mentioning that there was no episode of violation of privacy.

It is also declared that there are no conflicts of interest between the researchers and the institution to be researched.

The research followed Resolution No. 466/2012 of the National Health Council (CNS), which regulates research involving human beings. There was no filing of data and/or medical records.

## RESULTS

The sample of the present study consisted of 395 pregnant women who underwent prenatal care between August 2019 and December 2020 in a municipality in the State of Goiás, with 5 pregnant women excluded from the population (400 pregnant women) for having performed a prenatal period in another location.

The age of the pregnant women ranged from 14 to 44 years, with a prevalence in the range of 21 to 25 years (Figure 1).

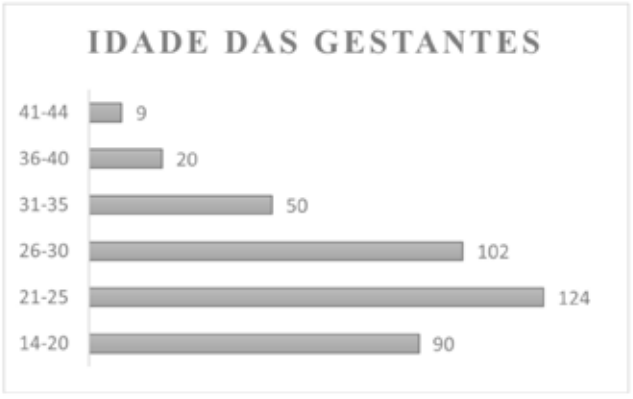


**FIGURE 1 - Segmentation by age of pregnant women**
**Caption: Pregnant women segmented by age. Source: Own authorship.**

Regarding the use of ASA, it was identified that 147 pregnant women (37.3%) had indication for prophylactic use (Figure 2). Of these, 92% did not use the medication and only 12 women (8%) used it, with [6] using the 100 mg dose, which is inadequate for the weight of these pregnant women (75 to 123 kg) and the other [6] did not have dosing information in the medical record. In addition, one of them made previous and constant use of medication for the treatment of Systemic Lupus Erythematosus.

Regarding the time of use and date of initiation of prophylaxis, all pregnant women who used ASA started the medication before the 16th week of pregnancy. However, there is only information about drug withdrawal in three medical records, in which the first kept the use of the medication until the eighth month of pregnancy, the second kept it until the 35th week and the third stopped using it on its own without a specified date. Thus, 8% of the pregnant women used the medication with inadequate propaedeutics and 0% used the medication properly (Figure 2). It was also concluded that of the 147 pregnant women who had an indication for the use of ASA, 15% started prenatal care late and there was no time to start the medication, since the Gestational Age (GA) at the first consultation exceeded 20 weeks. However, 85% of pregnant women started prenatal care in a timely manner and even so, ASA was not prescribed for them (Figure 2).


**Figure 2.A: Light pink: the use of ASA is not indicated; Gray: indicated the use of ASA; Figure 2.B: Light pink: pregnant women who did not use the medication; Gray: pregnant women who used the medication with inadequate propaedeutics; Light gray (no representation in the graph - 0%): pregnant women who used the medication with adequate propaedeutics; Figure 2.C: Light pink: not enough time to start using the medication; Gray: time to start using the medication. Source: Own authorship.**

Regarding high risk factors, the most common was Diabetes Mellitus [1] (DM1)/ Diabetes Mellitus [2] (DM2)/ Gestational Diabetes Mellitus (GDM) (Figure 3-A). As for the medium risk factors, nulliparity, BMI>30kg/m2 and intrapartum interval>23 months stood out (Figure 3-B). In addition, it is important to note that the patient's ethnicity was not reported in the medical records and in some of them (11.13%) the pregnant woman's intrapartum interval was also not mentioned.

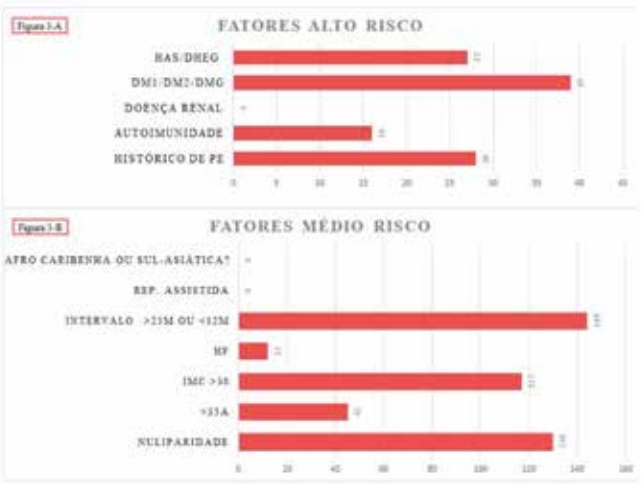


**FIGURE 3 - Frequency of high and medium risk factors**
**Caption: Frequency of risk factors found in pregnant women surveyed. Source: Own authorship.**

There were 18 reports of PE (4.5%), of which 17 (94.4%) had an indication for prophylactic ASA and the pregnant women did not receive the medication. There were also [8] cases of hypertensive/SHDP peaks, of which 7 (87.5%) were indicated for the use of ASA and only 28.6% had access to medication. Data related to pregnancy outcomes are shown in Figure 4-A and demonstrate that most pregnancies ended with cesarean delivery without complications (55%). However, among the high-risk pregnant women, there were 24 cases (16%) of hypertensive events or PE, of which only [2] used prophylactic ASA, however, with inadequate propaedeutics (Figure 4-B).

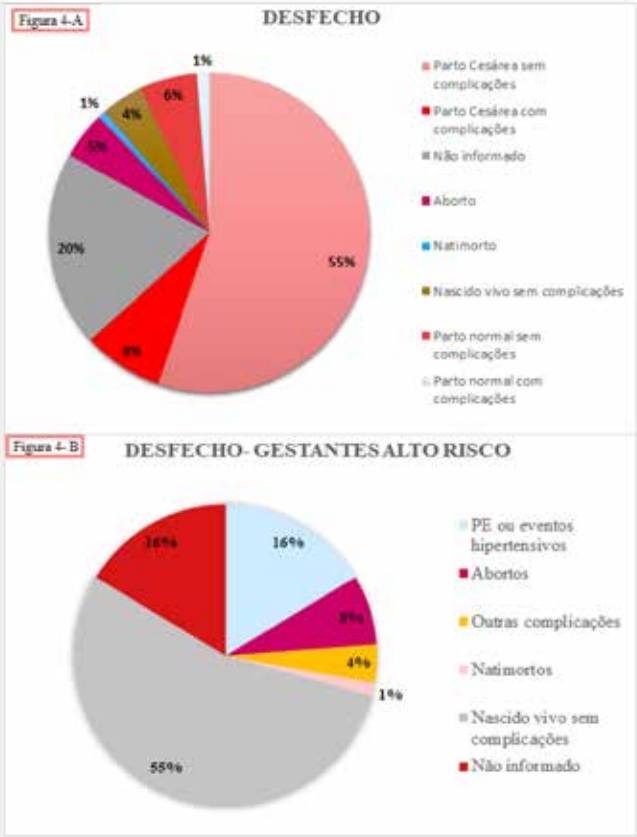


**FIGURE 4 - Outcomes of pregnancies**
**Caption: Figure 4-A: Light pink: cesarean delivery without complications; Red: cesarean delivery with complications; Gray: unreported outcome; Purple: miscarriages; Blue: stillbirths; Olive green: live births without complications (not differentiated between normal and cesarean delivery); Coral: normal delivery without complications; Light blue: normal delivery with complications. Figure 4-B: Gray: live birth without complications (not differentiated between normal and cesarean delivery); Red: unreported outcome; Baby blue: preeclampsia or hypertensive events; Purple: miscarriages; Yellow: other complications not related to PE; Light pink: stillbirths. Source: Own authorship.**

## DISCUSSION

It was identified in this study that about one third of the pregnant women were indicated for the use of low-dose ASA in the prophylaxis of preeclampsia. The fact that the minority used the medication and among these, none with the appropriate dosage, makes the situation more worrying. This makes us question the updating of doctors who work in prenatal care in the public network of a municipality in the State of Goiás. Although the FIGO guideline is from 2019 and has presented updates mainly regarding the indication of the use and dosage of ASA, the use of this medication has been established and recommended since 2013 by the WHO, that is, 6 years before the focus of this study. Thus, it was expected that a more significant portion of the pregnant women would have received the medication, even if in underdosage.

A study conducted in 2017 retrospectively evaluated

pregnant women who gave birth at Thomas Jefferson University Hospital before and after the publication of the 2016 ACOG guideline, which determined the use of ASA 80 mg for PE prophylaxis, and it was noticed that the percentage of use increased from 7% to 70%.19 This proportion was not found in the present study, since, even after numerous guidelines, the number of indications in the studied municipality is not similar to what was found by Banala, in the United States of America ( USA).

It is impossible, with the present study, to state the reasons for not performing prophylactic treatment. However, we raise the possibility of medical negligence, medical choice or non-adherence to prophylaxis on behalf of the patient. In this case, this last reason tends to be discarded, since the prescription or any information about the patient's refusal is not included in the medical records. Even so, this possibility should be considered in the future, since, in a 2020 multicenter study, with the objective of identifying the adherence of pregnant women at high risk of PE to prophylactic treatment with ASA, it was identified that 79% of pregnant women were instructed to undergo treatment with low-dose ASA and only 21.5% actually used it. Of the women who used it, the vast majority used the medication according to the protocol. Among the women who did not use the medication, the majority stated that they believed they were not included in the profile of prophylactic indication. The second reason for not using the medication was the lack of recommendation by the professional who accompanied the prenatal care.[10] Thus, it is essential to promote in Brazil, a broader discussion about the benefits of this prophylaxis with all medical professionals. In addition, full and effective communication between pregnant women and health professionals should be encouraged, in order to ensure the use of medication and achieve an adequate prophylactic level.

Regarding diagnostic screening, it is known that the accuracy becomes greater as the specificity and technology used in the tests increases – biomarkers and Doppler ultrasound.[20] However, in a deficient socioeconomic context, where these resources are not widely available, as in SUS - Brazil, it is known that it is better to opt for screening based on risk factors and start therapy based on these criteria. In addition, in this study, there was a perception of the effectiveness of the analysis of risk factors, since within the medical records analyzed, practically all the patients who progressed to outcomes related to hypertensive problems had an indication of the prophylactic use of ASA, and only 2 women who had this outcome did not meet the criteria for the use of prophylactic medication. Thus, even if there are no tools available to investigate the risk of PE according to FIGO's gold standard indications, a careful analysis of the risk factors and possible indication of ASA is worth, since the benefit is gigantic, in addition to the medication being safe, as long as it is in a low dose (150 mg), with medical indication and monitoring. Furthermore, it is a cheap and widely accessible medication.[21]

The basic health unit (UBS) is the gateway for pregnant women to the prenatal service. Thus, it is necessary to focus and disseminate knowledge about this prophylaxis to physicians responsible for primary care. Since, in most cases, they will be responsible for monitoring the pregnant woman during the gestational interval of 16-22 weeks, in which there will be an indication to institute the medication.[22] It should also be noted that the indicated dose, 150 mg, can be administered with one and a half tablets of infant ASA (100 mg/tablet). ASA protect, coated tablet, cannot be broken.[23]

Despite the positive results, it is necessary that new studies be carried out in the area and with periodic intervals, aiming to increase the prescription of medication and, consequently, reduce the incidence of preeclampsia, maternal and fetal deaths. However, even with significant results, the retrospective work limited the research and the search for data, since, as researchers, we depend on the information questioned and collected at the time of prenatal care and recorded in medical records. Thus, it would be interesting for a new study to be carried out in a prospective format.

## CONCLUSION

From this study, it was possible to prove the hypothesis generated based on the observation of daily medical practice that, despite ASA being extremely effective in the prophylactic treatment of preeclampsia, it was not offered to patients who underwent prenatal care in a municipality of the State of Goiás, in the period 2019-2020.

Thus, the need to update general practitioners, family doctors and obstetrician-gynecologists is clear, so that the medication is offered to pregnant women whenever there is an indication. With such an attitude, given the effectiveness of the medication, we will reduce the chances of hypertensive events and possible maternal and fetal deaths. Continuous updating is extremely important in medicine, as well as affecting the doctor and the patient himself. A study carried out in Hong Kong identified that more than 90% of physicians understand the need for continuous updating[24], associated with this, Robertson and Long[25], highlighted the consequences of error or negligence for the physician himself, which can generate demotivation, feelings of guilt, shame or depression. Therefore, this work can be used as a subsidy for the dissemination of knowledge and awareness of physicians.

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