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Indication-based administration of low dose aspirin for the prevention of preeclampsia: A retrospective study in Northern Greece

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Abstract

Introduction: Preeclampsia is a multisystem progressive disorder characterized by vascular abnormalities and coagulation disorders. The administration of low-dose aspirin is recommended before 16 weeks to delay or even avoid the onset of preeclampsia, based on screening tests. This study aimed to investigate the targeted or non-targeted administration of low-dose aspirin in pregnancies, according to the indications for its administration.

Material and methods: This was a retrospective cohort study from the medical records of the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece, including pregnant women that were screened for preeclampsia. The parametric or non-parametric distribution of the data was examined using the Shapiro-Wilk test. The association between the intake and the indication for aspirin intake was examined by the x^2 independence test for each medical society's guidelines. The sensitivity, specificity, and positive and negative predictive values of the different criteria were calculated and compared by applying One-Way ANOVA. All results with a p-value < 0.05 were considered statistically significant.

Results: In total, 2,716 women were included in the study; a statistically significant relationship between patients' aspirin-taking behavior and the indication for aspirin according to the FMF, ACOG and NICE criteria was found. Sensitivity was the highest based on NICE criteria (78.6%), while specificity and positive predictive value (PPV) were the highest based on FMF criteria (89.9% and 61.1%, respectively).

Conclusion: Applying the FMF criteria for the use of aspirin results in its more targeted administration achieved high sensitivity, specificity and PPV. Examining the number of patients receiving low-dose aspirin in pregnancy without indication could have clinical implications, highlighting the need for better targeting of the population to which it is administered.

Key words: Preeclampsia, aspirin, targeted administration, adherence, screening, Greek

Introduction

Preeclampsia is a multisystem progressive disorder characterized by the new onset of hypertension and proteinuria or significant end-organ dysfunction or uteroplacental dysfunction, typically presenting after 20 weeks of gestation or postpartum and is considered to be a significant cause of maternal and fetal morbidity and mortality worldwide being the cause for 1 in 7 maternal deaths and 1 in 10 late fetal deaths globally.[1,2] Classification into mild or severe form is not recommended because preeclampsia may deteriorate rapidly, regardless of the timing of onset.[3] HELLP syndrome (Hemolysis, Elevated liver enzymes, Low platelets) constitutes a severe form of preeclampsia and not a separate entity.[3]

The use of low-dose aspirin to prevent preeclampsia was based on the hypothesis that preeclampsia may be related to vascular abnormalities and coagulation disorders resulting from disruption of prostacyclin and thromboxane A2.[4] Based on research data, low-dose aspirin administration is recommended mainly to avoid or at least delay the onset of preeclampsia.[5]

Administration of low-dose aspirin before 16 weeks of gestation significantly reduces the incidence of preeclampsia and its associated neonatal complications without increasing the risk of bleeding.[6] Moreover, daily low-dose aspirin is considered safe and not associated with serious maternal or fetal complications; its administration is recommended to start ideally before 16 weeks of gestation.[7] Prophylactic dosing should be considered in women at high risk for developing preeclampsia due to the presence of at least one severe factor such as the history of preeclampsia, multiple pregnancy, kidney disease, autoimmune disease, type 1 or type 2 diabetes, chronic hypertension, or more than one moderate risk factors such as first pregnancy, maternal age > 40 years, BMI > 35 kg/m^2, multiple pregnancy, family history of preeclampsia and demographic characteristics.[8]

Existing data do not support the prophylactic administration of aspirin, when there are no risk factors for preeclampsia, to prevent early pregnancy loss, fetal growth restriction, stillbirth, or preterm delivery.[9] The present research hypothesis is based on the clinical observation that an increasing number of pregnant women receive low-dose aspirin without necessarily fulfilling the criteria, as suggested by the relevant guidelines. Although the need for prophylactic low-dose aspirin in high-risk pregnancies is well established, its targeted or non-targeted use has not been examined.

The need to assess the risk that imposes the administration of aspirin with regards to the indications for its administration is widely discussed in the international literature; however, there are no relevant studies with a similar research purpose and methodological characteristics as with the current study. Therefore, this study aimed to investigate the targeted or non-targeted administration of low-dose aspirin in pregnancies, according to the indications for its administration.

Material and methods

This was a retrospective cohort study including data from the medical records of the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece. Data recording lasted 32 months and was carried out from 08/03/2019 to 03/17/2022. The following maternal and obstetrical characteristics were recorded: gestational age, body mass index (BMI), smoking, levels of free beta-chorionic gonadotropin (β-hCG) and pregnancy-associated Plasma Protein-A (PAPP-A), date of the examination, crown-rump length (CRL), exact gestational age at examination, comorbidities, conception with assisted reproduction, history of 1st trimester miscarriage risk. The risk for preeclampsia was calculated based on the Fetal Medicine Foundation (FMF) algorithm but, also, on the American College

of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE) criteria.[10-12] We then calculated the number of women that were either already or were advised to start on low-dose aspirin in order to identify the use of that preventive measure and we, finally, compared the 3 "groups" of criteria in order to identify the correct identification of preeclampsia risk.

All the data were tested for parametric or non-parametric distribution using the Kolmogorov-Smirnov test. The association between the intake and the indication for aspirin intake was examined by the x^2 independence test for each medical society's guidelines. The sensitivity, specificity and positive and negative predictive values of the different criteria were calculated and compared by applying One-Way ANOVA. All results with a p-value <0.05 were considered statistically significant.

Results

Demographics

In total, 2,716 pregnant women were included in the study. Regarding the somatometric characteristics, the BMI of the women ranged between 14.9 and 48.9 kg/m ^{2}. Moreover, 1,076 (62.8%) were nulliparous, 584 (21.5%) had a history of miscarriage, 302 (11.1%) were smokers and 171(6.3%) conceived via assisted reproduction.

Administration of aspirin based on the FMF algorithm

Aspirin adherence was examined based on the indications from the FMF algorithm and the data collected from ASTRAIA software. Out of 2,716 women, 555 (20.4%) were receiving aspirin and 2,162 (79.6%) were not. In total, 558 (20.5%) had an indication for receiving aspirin, whereas 2,158 (79.5%) did not. The percentage of pregnant women receiving aspirin with an indication in relation to the entire population with such an indication was 60.7%. However, the percentage of women receiving aspirin without any indication, and were therefore over-treated, was 10%. The percentage of patients who were not receiving aspirin, despite having an indication, and were therefore undertreated is 39.2% and those who did not receive aspirin and did not have any such indication was 89.9% (Table 1). According to the x^2 independence test, a statistically significant dependence of the patients' behavior regarding aspirin intake and the indication for aspirin intake was found (x^2: 702.15, p<0.001).

Administration of aspirin based on the ACOG criteria

We then examined the possible over- or under-treatment based on the ACOG criteria and only 110 (4.1%) out of 2,716 pregnant women had an indica-

Table 1. Number of patients who: (A) receive aspirin with an indication, (B) receive aspirin without indication, (C) do not receive aspirin and have an indication, and, (D) do not receive aspirin and have no indication. Data were analyzed according to the FMF criteria.

	INDICATION FOR ASPIRIN ADMINISTRATION		
ASPIRIN ADMINISTRATION	**YES**	**NO**	**TOTAL**
Yes	(A) 339 (60,7%)	(B) 216 (10%)	555 (20,4%)
No	(C) 219 (39,2%)	(D) 1,942 (89,9%)	2,161 (79,6%)
Total	558	2,158	2,716 (100%)

tion for receiving aspirin while the rest 2,606 (95.9%) did not. Data were analyzed according to the ACOG criteria and it was found that the percentage of women that were appropriately treated and were receiving aspirin was 9.4%, whereas 90.6% were over treated. The percentage of patients who were undertreated was 2.7%, and those who were treated correctly and did not receive aspirin since there was no indication was 97.3%. A statistically significant dependence of the patients' behavior regarding aspirin intake and the indication for aspirin intake according to the ACOG criteria was found (p<0.001) (Table 2).

Administration of aspirin based on the NICE criteria

We, finally, analyzed the same data according to the NICE criteria and we found that 14 (0.5%) women out of 2,716 had an indication for receiving aspirin whereas, the rest (2,702 / 99.5%) did not have such an indication. Aspirin was correctly administered, according to the NICE criteria, to 2.0% of our population but, 98% were deprived of its use. The percentage of patients who did not receive aspirin, despite having an indication was 0.1%, whereas those who did not receive it and did not have an indication was 99.9%. Based on the x^2 independence test, there is a statistically significant relationship between patients' aspirin-taking behavior and the indication for aspirin according to the NICE criteria (p<0.001) (Table 3).

Calculation of Sensitivity, Specificity, Positive and Negative Predictive Value

The specificity and sensitivity of the three different guidelines (FMF, ACOG, NICE) were calculated, as well. The results showed the highest specificity

Table 2. Number and percentage of patients who: (A) receive aspirin and have an indication, (B) receive aspirin without an indication, (C) do not receive aspirin and have an indication, and (D) do not receive aspirin and have no indication. Data were analyzed according to ACOG criteria.

	INDICATION FOR ASPIRIN ADMINISTRATION		
ASPIRIN ADMINISTRATION	**YES**	**NO**	**TOTAL**
Yes	(A) 52 (9,4 %)	(B) 503 (90,6 %)	555
No	(C) 58 (2,7 %)	(D) 2,103 (97,3 %)	2,161
Total	110 (4,1%)	2,606 (95,9%)	2,716 (100%)

Table 3. Number and percentage of patients who: (A) receive aspirin with an indication, (B) receive aspirin without any indication, (C) do not receive aspirin and have an indication, and (D) do not receive aspirin and have no indication. Data were analyzed according to the NICE criteria.

	INDICATION FOR ASPIRIN ADMINISTRATION		
ASPIRIN ADMINISTRATION	**YES**	**NO**	**TOTAL**
Yes	(A) 11 (2 %)	(B) 544 (98 %)	555
No	(C) 3 (0,1 %)	(D) 2,158 (99,9 %)	2,161
Total	14	2,702	2,716 (100%)

for FMF which was 89.9% compared to ACOG and NICE, which was 79.9%. Regarding the sensitivity, it was 60.9% for FMF criteria, 47.2% for ACOG, and 78.6% for NICE. The positive (PPV) and the negative (NPV) predictive values were 61.1% and 89.9% for FMF, 9.3% and 99.8% for ACOG and 1.9% and 99.4% for NICE (Table 4).

Discussion

We examined the criteria for aspirin administration during pregnancy from three major scientific societies (FMF, ACOG, and NICE) and we found important differences between them when the adherence to aspirin intake was based on the indication examined in our sample (60.7% vs 9.4% vs 20%, respectively).

There is a need for evidence regarding the overall impact of risk prediction and subsequent clinical actions when identifying women at risk for preeclampsia; to comprehensively assess the influence of clinical risk prediction, it is crucial to consider the real effect.[13] When predicting preeclampsia risk, a high level of sensitivity might be more significant; outcomes, where the prediction fails to identify the risk (false negatives), could potentially be more harmful than cases where the risk is incorrectly identified (false positives).[14] It might be reasonable to contemplate a lower risk threshold and reduced PPV to implement measures like low-dose aspirin prophylaxis and increased monitoring.[15,16]

Highly sensitive tests will lead to positive findings for patients with a disease, whereas highly specific tests will show patients without a finding having no disease. Although, sensitivity and specificity should always merit consideration together to provide a holistic picture of a screening test; this should be highly sensitive, whereas a confirmatory test should be highly specific.[17] In contrast to sensitivity and specificity, predictive values exhibit variation based on the prevalence of a condition within a given population. Even if the screening test is highly specific, when the prevalence of a disease is low among the patients being tested, a significant portion of positive tests will be false positives, leading to a lower predictive value.[17]

Regarding the three major associations, significant adherence to aspirin intake was found in all cases. However, aspirin administration according to FMF criteria was found to be more targeted; 60.7% of the population received aspirin with an indication and only 10% received aspirin without having an indication, compared to ACOG (9.4% and 90.6%, respectively) and NICE (20% and 98%, respectively). As for the sensitivity of the criteria, NICE had the greatest sensitivity (78.6%), but with a considerably low PPV (1.9%); meaning that a higher portion of pregnant women received aspirin, potentially without needing it. Considering that the long-term risks of aspirin during pregnancy have not been fully investigated, its wide administration could not be justified. However, the usefulness of the administration of aspirin in cases of real risk for preeclampsia has been widely proven[4,5]; hence, a high sensitivity with a simultaneous high positive predictive value

Table 4. Sensitivity, specificity, positive (PPV), and negative (NPV) predictive value of criteria of three different international associations after analysis of the same data.

	FMF	ACOG	NICE
Sensitivity	60.9%	47.2%	78.6%
Specificity	89.9%	79.9%	79.9%
PPV	61.1%	9.3%	1.9%
NPV	89.9%	99.8%	99.4%

could lead to a more targeted manner of administration of aspirin.

Overall, when a screening test is administered in a more targeted manner, such that the proportion of tested individuals with the actual risk for disease is higher, the test's predictive value is enhanced. Large longitudinal studies are needed to investigate the real prevalence of preeclampsia in the Greek population. This could lead to a more targeted administration of aspirin; with a higher proportion of pregnant women receiving aspirin because they need it and a lower proportion receiving aspirin without needing it.

The existing evidence to determine whether model-based risk prediction would enhance outcomes for preeclampsia beyond the risk assessment methods currently utilized by healthcare practitioners is insufficient. The effectiveness of multivariable risk assessment models in terms of their performance and impact on health outcomes necessitates thorough validation and well-designed studies that assess their clinical implications. To our knowledge, this is the first study regarding the adherence to aspirin intake in the Greek pregnant population, based on criteria from three major associations. The main limitation of this cohort is its retrospective nature, including the potential information bias. However, the existing electronic databases (ASTRAIA software) may eliminate the risk of missing data due to poor registration.

FMF was found to have a more targeted administration of aspirin, with a high sensitivity, specificity, and PPV simultaneously. Finding the number of patients receiving off-label low-dose aspirin in pregnancy could also have clinical implications, highlighting the need for better targeting of the population to which it is administered, and opening the field for discussion about the outcomes of pregnancies receiving low-dose aspirin off-label. The relatively short time frame of pregnancy, along with the rarity and unpredictability of severe preeclampsia and maternal and fetal risks pose challenges to straightforward estimation of screening performance, benefits, and harms. The absence of information on the potential harms of risk prediction, considering the high false-positive rates, is a notable shortcoming of the risk prediction literature. Without comparisons of proposed models to current clinical practices, the potential benefits and harms of risk prediction cannot be determined.

References

1. Hodgins S. Pre-eclampsia as Underlying Cause for Perinatal Deaths: Time for Action. Glob Health Sci Pract. 2015;3:525-7.
2. Tsakiridis I, Giouleka S, Arvanitaki A, et al. Gestational Hypertension and Preeclampsia: An Overview of National and International Guidelines. Obstet Gynecol Surv. 2021;76:613-33.
3. Brown MA, Magee LA, Kenny LC, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018;72:24-43.
4. Espinoza J. Low-Dose Aspirin for the Prevention of Preeclampsia. JAMA. 2021;326:1153-5.
5. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018;218:287-93 e1.
6. Choi YJ, Shin S. Aspirin Prophylaxis During Pregnancy: A Systematic Review and Meta-Analysis. Am J Prev Med. 2021;61:e31-e45.
7. ACOG Committee Opinion No. 743 Summary: Low-Dose Aspirin Use During Pregnancy. Obstet Gynecol. 2018;132:254-6.
8. Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. National Institute for Health and Clinical Excellence: Guidance. London2010.
9. Green M, Shennan A. Aspirin should be targeted

to those who need it. BJOG. 2021;128:157.
10. NICE. Hypertension in pregnancy: diagnosis and management. 2019.
11. American College of O, Gynecologists' Committee on Practice B-O. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135:e237-e60.
12. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017;377:613-22.
13. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. Ann Intern Med. 2006;144:201-9.
14. Cnossen JS, ter Riet G, Mol BW, et al. Are tests for predicting pre-eclampsia good enough to make screening viable? A review of reviews and critical appraisal. Acta Obstet Gynecol Scand. 2009;88:758-65.
15. Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification G. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753.
16. Bartsch E, Park AL, Kingdom JC, Ray JG. Risk threshold for starting low dose aspirin in pregnancy to prevent preeclampsia: an opportunity at a low cost. PLoS One. 2015;10:e0116296.
17. Lucy A. McNamara SWM. Principles of Epidemiology and Public Health. 2018.

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