PERINATAL JOURNAL

Case(s) Report
Perinatal Journal 2024;32(1):66-69

Lifethreatennig upper gastrointestinal bleeding in a pregnant women under low-dose Aspirin – case report and literature review

Marta Plancha[1], Marta Espanhol Brito[2], Leonor Castro Ferreira[2], Natacha Oliveira[2]

[1]*São José Local Health Unit - Maternity Doctor Alfredo da Costa Gynecology and Obstetrics, Lisbon, Portugal*
[2]*São José Local Health Unit - Maternity Doctor Alfredo da Costa CRI - Fetal Medicine and Surgery & Maternal-Fetal Medicine Service, Lisbon, Portugal*

Abstract

Objective: Preeclampsia is a multisystem disorder that affects 2%-8% of pregnancies, is an important cause of maternal and perinatal morbidity and mortality, particularly in cases of early onset. Low-dose aspirin (75-150 mg) is commonly prescribed during pregnancy to prevent or delay the onset of preeclampsia, recommended for pregnant women at high risk by the most recent international obstetrics guidelines and societies. Contrary to evidence of aspirin´s efficacy in preventing cardiovascular events in the non-pregnant population, its use in pregnant women has not been associated with a significant increase of bleeding complications.

Case(s): We present a clinical case of a life-threatening upper gastrointestinal bleeding in a previous healthy pregnant woman using aspirin for prevention of preeclampsia.

Conclusion: Although rare, the risk of upper gastrointestinal bleeding should be considered when prescribing aspirin to pregnant women, particularly in low-risk pregnancies where the risks may outweigh the benefits.

Keywords: Preeclampsia, pregnancy, aspirin, digestive bleeding

Introduction

Preeclampsia is a multisystem disorder that complicates approximately 2% to 8% of pregnancies and remains a major cause of maternal and neonatal morbidity and mortality.[1] Pathogenesis of this disease is not fully understood, but there is a current theory that suggests a two-stage process.[2] The first one is caused by shallow invasion of the trophoblast which leads to inadequate and incomplete remodelling of the spiral arteries and consequently deficient placentation leading to a prostaglandin synthesis disturbance and an imbalance in prostacyclin and thromboxane metabolism.[1, 2] This may lead to the second stage involving maternal response to the endothelial dysfunction and imbalance between angiogenic and antiangiogenic factors, resulting in the clinical features of preeclampsia.[2, 12-15]

Aspirin has been known in the last decades, in general nonpregnant population, for its potential in the prevention of major cardiovascular events.[5, 7, 9, 10] Its use during pregnancy has also been studied during the past 30 years for the prevention of preterm preeclampsia, probably by its effects on inflammation, platelet aggregation and by inhibiting the biosynthesis of placental thromboxane A2 with minimal effects on vascular prostacyclin levels.[2, 3, 16-19] Aspirin benefit in preterm preeclampsia prevention is well established nowadays and international societies recommend its use in pregnant women at high risk for preeclampsia.[2-4, 20] Although not consensual between international societies, current literature tell us that the best method to predict the risk of preterm PE is FMF

Correspondence: Marta Plancha, São José Local Health Unit - Maternity Doctor Alfredo da Costa Gynecology and Obstetrics, Lisbon, Portugal, **e-mail:** martasantos92@gmail.com, **Received:** January 28, 2024 **Accepted:** March 18, 2024

How to cite this article: Plancha M, Brito ME, Ferreira LC, Oliveira N. Lifethreatennig upper gastrointestinal bleeding in a pregnant women under low-dose Aspirin – case report and literature review. Perinatal Journal 2024;32(1):66-69 DOI: 10.59215/prn.24.0321011

ORCID ID: M Plancha 0009-0007-4762-7678; ME Brito 0000-0001-8643-3779; LC Ferreira 0000-0002-4429-6646; N Oliveira 0000-0003-0992-8270

CETUS Publishing

triple test.[21] According to this screening, high risk pregnant woman should initiate aspirin 150 mg/night before 16 weeks of gestation.[2, 20]

Case(s)

The patient, a 39-year-old non-smoking black woman with a body mass index of 21.2 kg/m2, was identified as heterozygous for hemoglobin S. She had one previous uncomplicated term pregnancy 12 years prior and reported no other relevant medical or family history. She specifically denied having ever experienced dyspeptic symptoms. She was referred to our Prenatal Diagnosis Center for routine first trimester screening.

First trimester combined screening performed at twelve weeks and three days revealed a low risk for trisomies 21, 18 and 13 and a high risk for preterm preeclampsia (1/41) and fetal growth restriction (1/18), according to Fetal Medicine Foundation Algorithm.[11] This increased risk was mainly due to biochemical measurements (PAPP-A 0.3 multiples of median) and median uterine artery pulsatility index above the 95th percentile.

For prevention of preterm preeclampsia, the patient initiated a regimen of 150 mg of aspirin daily at night. She showed no additional analytical anomalies and a hemoglobin level of 12.4 g/dL on first trimester blood test. During follow-up appointments the patient never complained about epigastric pain, dyspepsia or reflux symptoms. Her pregnancy progressed normally until 29 weeks, at which point she was found unconscious after several episodes of severe hematemesis. When the emergency team arrived, she was hypotensive (90/60 mmHg) and with tachycardia (120 bpm). Nasogastric tube was inserted draining a great amount of blood, intravenous fluids were started for resuscitation and pantoprazole 80 mg was given in bolus followed by a perfusion of 8 mg/h was started. In the emergency room she was managed by a multidisciplinary team with gastroenterologists and obstetrics. Her hemoglobin was 6.8 g/dL, platelets 130000 and INR 1,1. After fluid resuscitation she was transfused with three units of blood and three units of fresh frozen plasma. After hemodynamic stabilization, an upper endoscopy was performed which showed a 8 mm bleeding ulcer Forrest IB in the greater curvature of the stomach. After trying to use hemoclip without success, BICAP endoscopic coagulation was performed to achieve hemostatic control with success. Due to pathological cardiotocography record (persistent fetal tachycardia with reduced variability and recurrent late decelerations) an emergent caesarean was performed at 29 weeks of gestation and a female infant with 1250 grams was born with Apgar Scores of 4, 8 and 10 after 1, 5 and 10 minutes, respectively. Abdominal computerized tomography angiography was also done and there were no signs of active bleeding. Two days later a new endoscopy was done, only showing an irregularity on the previous treated area without any bleeding point. Oral intake was started after 24 hrs, pantoprazole perfusion was maintained for 72 hrs and changed for oral 40 mg bid. Patient remained in the hospital for seven days and no recurrence was observed.

She was discharged home with a hemoglobin level of 9,7 g/dL and medicated with proton pump inhibitors (PPI) (omeprazole 40 mg), keeping ambulatory surveillance with the gastroenterology team. Newborn was admitted to the neonatal intensive care unit, where he stayed hospitalized for 53 days.

A follow-up endoscopy was performed six months later, and no abnormalities were detected. Gastric biopsies showed a mild chronic gastritis, negative for helicobater pylori, with no atrophy and/or intestinal metaplasia. By then, she was discharged for her general medical doctor and two years after the previous described event she remains asymptomatic. She was advised not to use anti-inflammatory drugs again or, if needed, to use PPI concomitantly.

Discussion

Studies on aspirin in non-pregnant population have demonstrated a consistent association between aspirin chronic administration and an increased risk of major gastrointestinal and cerebral bleeding complications.[5, 7, 9, 10] Revisions on aspirin-users for prevention of preterm preeclampsia during the pregnancy do not show a higher risk of antepartum bleeding episodes. This may be explained by the fact that this population is younger, in most cases healthier and uses aspirin for a limited period of time, when comparing with non-pregnant aspirin-users.[8]

The observational cohort study by Hastie et al in 2021 investigated whether aspirin use during pregnancy was associated with an increased risk of bleeding complications.[8] Aspirin was prescribed to 4088 pregnant women at high risk for preeclampsia according to their medical and obstetric history. Bleeding complications were analysed and compared between aspirin users vs. non-users. The authors concluded that using aspirin was not related to antepartum bleeding events but although rare, it was associated with increased postpartum bleeding (10.2% vs. 7.8%, adjusted OR 1.23 – 95% CI 1.08 – 1.39) as well as postpartum hematoma (0.4% vs. 0.1%, adjusted OR 2.1 – 95% CI 1.13 – 4.34). They also reported an increased risk of fetal intracranial haemorrhage but the numbers were too small to draw any consistent conclusions.[8]

The low risk on bleeding complications with the use

of aspirin in the pregnancy was also documented by the revision of Cochrane in 2019 on antiplatelet agents for preventing preterm preeclampsia and its complications.[6] The authors observed that low-dose aspirin led to small-to-moderate benefits, including reduction on preterm preeclampsia, preterm birth, small for-gestational age fetus, fetal or neonatal death, with a slightly increased risk of postpartum haemorrhage of more than 500 ml.[6]

Roberge et al in 2017 studied the effect of aspirin on the risk of placental abruption or antepartum hemorrhage, in correlation with gestational age at onset of therapy and with drug dosage, through a systematic review and meta-analysis of randomized controlled trials. They observed a low prevalence of bleeding complications (1.5%) and that daily aspirin < 100 mg for prevention of preeclampsia did not influence the risk of placental abruption or antepartum haemorrhage irrespective of the gestational age at the beginning of the therapy. On the other hand, aspirin dosage 9100 mg when initiated before 16 weeks of gestation, instead of later, may decrease the risk of bleeding complications.[22]

In the ASPRE study, the most recent randomized trial on use of aspirin to prevent preeclampsia, it was demonstrated that with a daily dose of 150 mg of aspirin in women at high risk for preeclampsia, the risk of preterm PE was reduced in more than 60%, and that there were no significant differences between-groups in adverse bleeding events.[17]

Most guidelines do not specify the recommended dose of aspirin, suggesting a range between 75-150 mg. However, there aren't randomized trails comparing pregnancy outcomes and the risk of bleeding complications with different dosages of aspirin. The physiological changes in pregnancy alters the pharmacokinetic of medication in pregnancy.[23] A study from 2019 studying aspirin pharmacokinetics through its major active metabolite, salicylic acid, demonstrated a consistent reduction in total drug metabolite concentration of aspirin in pregnancy. It was suggested that use of 150 mg dose of aspirin should be done in pregnant women in order to achieve drug metabolite concentration similar to that from 100 mg of aspirin in nonpregnant women.[23] Whether higher dosages of aspirin may increase the risk of bleeding events has not been studied but in the randomized ASPRE study, where an aspirin daily dose of 150 mg was prescribed, the risk of bleeding events was not increased when compared with pregnant aspirin non-users' population.

Conclusion

Use of aspirin universally in all pregnant women has been a question of debate in recent studies, defending the idea that this could lead to fewer cases of preeclampsia and fewer costs, without increasing the risk of bleeding complications.[24-27] In fact, low-dose aspirin during pregnancy has already proven its efficacy in the prevention of preterm preeclampsia and the truth is that majority of systematic reviews of randomized controlled trials have not reported an increased risk of important haemorrhagic events both for the mother and for the fetus.[28] When analysing the patient reported in our clinical case, there is no doubt that she would benefit from taking aspirin during pregnancy. However, it's important to remember that aspirin is not free of possible risks and this should be taken into account when prescribing it to pregnant women, especially when considering prescribing universal aspirin, as the its benefits may not outweigh its risks in pregnant women whose risk for developing preeclampsia is low.[29] It's also important to actively inquire pregnant woman on daily aspirin during routine appointments about gastric complaints such as epigastric pain and dyspepsia and to inform them about possible signals or symptoms they should pay attention to. Possibly, the risk of postpartum hemorrhage should also be taken into account.[30] We can also speculate on the benefit of using concomitant PPI in women with previous dyspepsia aiming at decreasing complicated ulcers.

References

1. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol, 2019. 133(1): p. 1.
2. Poon, L.C., et al., The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet, 2019. 145 Suppl 1(Suppl 1): p. 1-33. [PubMed][CrossRef]
3. ACOG Committee Opinion No. 743: Low-Dose Aspirin Use During Pregnancy. Obstet Gynecol, 2018. 132(1): p. e44-e52. [PubMed][CrossRef]
4. National Guideline, A., National Institute for Health and Care Excellence: Clinical Guidelines, in Hypertension in pregnancy: diagnosis and management. 2019, National Institute for Health and Care Excellence (UK) Copyright © NICE 2019.: London.
5. Bowman, L., et al., Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med, 2018. 379(16): p. 1529-1539. [PubMed][CrossRef]
6. Duley, L., et al., Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev, 2019. 2019(10). [PubMed][CrossRef]
7. Gaziano, J.M., et al., Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-

controlled trial. Lancet, 2018. 392(10152): p. 1036-1046. [PubMed][CrossRef]
8. Hastie, R., et al., Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. Am J Obstet Gynecol, 2021. 224(1): p. 95.e1-95.e12. [PubMed][CrossRef]
9. Li, L., et al., Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet, 2017. 390(10093): p. 490-499. [PubMed][CrossRef]
10. Mahmoud, A.N., et al., Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. Eur Heart J, 2019. 40(7): p. 607-617. [PubMed][CrossRef]
11. Akolekar, R., et al., Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn, 2011. 31(1): p. 66-74. [PubMed][CrossRef]
12. Staff, A.C., et al., Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. Am J Obstet Gynecol, 2022. 226(2s): p. S895-s906. [PubMed][CrossRef]
13. Robillard, P.Y., et al., Progress in the understanding of the pathophysiology of immunologic maladaptation related to early-onset preeclampsia and metabolic syndrome related to late-onset preeclampsia. Am J Obstet Gynecol, 2022. 226(2s): p. S867-s875. [PubMed][CrossRef]
14. Stepan, H., et al., Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction. Ultrasound Obstet Gynecol, 2023. 61(2): p. 168-180. [PubMed][CrossRef]
15. Rana, S., S.D. Burke, and S.A. Karumanchi, Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. Am J Obstet Gynecol, 2022. 226(2s): p. S1019-s1034. [PubMed][CrossRef]
16. Roberge, S., et al., The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol, 2017. 216(2): p. 110-120.e6. [PubMed][CrossRef]
17. Rolnik, D., Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med, 2017. 377(24): p. 2400. [CrossRef]
18. Wang, Y., et al., Aspirin for the prevention of preeclampsia: A systematic review and meta-analysis of randomized controlled studies. Front Cardiovasc Med, 2022. 9: p. 936560. [PubMed][CrossRef]
19. Dutta, S., et al., Molecular Targets of Aspirin and Prevention of Preeclampsia and Their Potential Association with Circulating Extracellular Vesicles during Pregnancy. Int J Mol Sci, 2019. 20(18).[PubMed][CrossRef]
20. Chaemsaithong, P., D.S. Sahota, and L.C. Poon, First trimester preeclampsia screening and prediction. Am J Obstet Gynecol, 2022. 226(2s): p. S1071-S1097.e2. [PubMed][CrossRef]
21. Piya Chaemsaithong, MD, PhD., et al., First trimester preeclampsia screening and prediction, 2020. American Journal of Obstetrics and Gynecology, Expert Review, Volume 226, Issue 2. [PubMed][CrossRef]
22. Roberge, S., E. Bujold, and K.H. Nicolaides, Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol, 2018. 218(5): p. 483-489. [PubMed][CrossRef]
23. Shanmugalingam, R., et al., A pharmacokinetic assessment of optimal dosing, preparation, and chronotherapy of aspirin in pregnancy. Am J Obstet Gynecol, 2019. 221(3): p. 255.e1-255.e9. [PubMed][CrossRef]
24. Mone, F., et al., Preeclampsia Prevention Using Routine Versus Screening Test-Indicated Aspirin in Low-Risk Women. Hypertension, 2018. 72(6): p. 1391-1396. [PubMed][CrossRef]
25. Mone, F., et al., Should we recommend universal aspirin for all pregnant women? Am J Obstet Gynecol, 2017. 216(2): p. 141.e1-141.e5. [PubMed][CrossRef]
26. Mone, F., et al., Trial of feasibility and acceptability of routine low-dose aspirin versus Early Screening Test indicated aspirin for pre-eclampsia prevention (TEST study): a multicentre randomised controlled trial. BMJ Open, 2018. 8(7): p. e022056. [PubMed][CrossRef]
27. Mallampati, D., et al., Strategies for Prescribing Aspirin to Prevent Preeclampsia: A Cost-Effectiveness Analysis. Obstet Gynecol, 2019. 134(3): p. 537-544. [PubMed][CrossRef]
28. Joudi, N., et al., Aspirin in pregnancy: a review of indications, timing, dosing and efficacy, 2023. Current Opinion in Obstetrics and Gynecology, Volume 35, Number 2, pp. 94-100. [PubMed][CrossRef]
29. Wright, D., et al., When to give aspirin to prevent preeclampsia: application of Bayesian decision theory. Am J Obstet Gynecol, 2022. 226(2s): p. S1120-s1125. [PubMed][CrossRef]
30. Yi Jiang, MD, et al., Low-dose asprin use during pregnancy may be a potential risk for pospartum hemorrhage and increased blood loss: a systematic review and meta-analysis. American Journal of Obstetrics and Gynecology MFM, Volume 5, Issue 4. [PubMed][CrossRef]