International Blood Research & Reviews

Volume 15, Issue 1, Page 18-25, 2024; Article no.IBRR.110591
ISSN: 2321–7219

Evaluation of the Biological Response to Acetylsalicylic Acid by Platelet Occlusion Time in Pregnant Women in Brazzaville

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Authors' contributions

This work was carried out in collaboration among all authors. The authors would like to thank the managers of the obstetrics and gynecology departments of the six Brazzaville hospitals who made it possible to distribute the questionnaire, and all the obstetricians who agreed to answer it. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IBRR/2024/v15i1331

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/110591

Original Research Article

Received: 16/11/2023
Accepted: 21/01/2024
Published: 29/01/2024

ABSTRACT

Low-dose acetylsalicylic acid (ASA) has been recommended for pregnant women since 2011 by the OMS to prevent thrombotic phenomena. Despite the variability of its clinical efficacy (resistance phenomena), its non-standardized biological monitoring can be performed using platelet occlusion time (POT). The aim of this study was to assess the response to ASA using POT.

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A multicenter, cross-sectional, analytical study was conducted in the obstetrics and gynaecology departments of six Brazzaville hospitals over a period of 09 months and included pregnant women on ASA 100 mg daily for at least 7 days. POT was measured using the INNOVANCE® PFA®-200 system. The variables studied were clinical (age, medical and obstetrical history) and biological (blood count, POT). Non-response to ASA was defined by a POT of 150 seconds or less. Data analysis was performed using STATA 12 software. Logistic regression was used to assess the determinants associated with non-response. The incidence of obstetric complications according to ASA resistance was evaluated by the Kaplan-Meier method and the Log-Rank test. The significance threshold was p<0.005.

The study involved 39 pregnant women, mean age 33.9 ± 5.4 years, treated with ASA for hypertensive disorders of pregnancy n=19 (48.7%), chronic arterial hypertension n=7 (18%), diabetes n=3(7.7%) fetal death n=3(7.7%), unexplained miscarriage n=3(7.7%), advanced age n=2 (5.1%) and twin pregnancy n=2(5.1%). The median body index was 25.5 kg/m2 [23.7;29.4] with 35.9% women of normal weight, 48.7% overweight and 15.4% obese. Non-response to ASA was found in 12 pregnant women (30.7%). No statistically significant differences were observed between non-responders and responders with regard to epidemiological, clinical and haematological determinants (p>0.05). Non-response was more observed in women with complications 23.08% versus 7.7% (p=0,008).

Non-response to ASA, present in a third of hypertensive pregnant women, is associated with the occurrence of obstetrical complications in Brazzaville.

Keywords: pregnancy, acetylsalicylic acid, PFA-200, biological response.

1. INTRODUCTION

Low-dose acetylsalicylic acid (ASA) is recommended by the World Health Organization (WHO) for the prevention of thrombotic phenomena in gestational hypertensive disorders or antiphospholipid antibody syndrome [1]. Hypertensive disorders in pregnancy are a public health problem, as obstetric morbidity and maternal mortality due to hypertension are high in European and African studies, particularly in Congolese studies [1,2]. ASA, an antiplatelet agent, acts by irreversibly acetylating cyclooxygenase (COX-1) after a minimum of one week's daily administration [3]. However, ASA-based thrombosis prevention has shown some variability in its clinical and biological efficacy.

Indeed, the concept of "ASA resistance" has been introduced, defined as the inability of ASA to inhibit Thromboxane A2 formation or platelet aggregation. It has been reported to affect between 5% and 60% of the general population [4]. Its diagnosis can be made on the basis of methods for assessing the biological response to ASA. Among these, the measurement of platelet occlusion time (POT) simulates in vitro the hemodynamic conditions of platelet adhesion and aggregation. Furthermore, antiplatelet agents are generally prescribed blindly, unlike anticoagulants, which benefit from standardized biological monitoring to control their efficacy and safety [5]. Thus, with the aim of contributing to the management of hypertensive disorders in pregnancy, the objectives of this study were to assess the biological response to ASA by POT and to identify its involvement in adverse obstetric outcomes.

2. PATIENTS AND METHODS

This was a multicenter, cross-sectional, analytical study conducted from March 1 to November 30, 2021, in the gynecology-obstetrics departments of six Brazzaville hospitals. It involved all pregnant women who had been taking ASA for at least seven days, or who had stopped taking it less than seven days previously. The ASA used was a soluble powder administered at a dose of one (1) 100 mg sachet per day. Pregnant women with a platelet count of less than 100 giga/l and/or a hematocrit of less than 10% were excluded. The selection of pregnant women was exhaustive.

Once selected, some gestational carriers were referred to the Centre National de Référence de la Drépanocytose for platelet occlusion time. Others were sampled at their follow-up centres. All patients rested for at least 10 minutes but did not have to fast before blood sampling. Blood was drawn by venipuncture at the elbow or at the non-perfused wrist for hospitalized patients. We collected five (05) ml of whole blood under

vacuum in tubes containing ethylene diamine tetra acetic acid (EDTA) or sodium citrate. Specimens were transported to room temperature within three hours and used for blood count and platelet occlusion time (POT). POT was determined using collagen kits combining epinephrine (COL/EPI INNOVANCE PFAP2Y®) and adenosine diphosphate (COL/ADP INNOVANCE PFAP2Y®) and the INNOVANCE® PFA®-200 system.

The variables studied were obstetric (gestational age, parity, spontaneous miscarriage, gravid hypertensive disorders, prematurity, fetal death in utero, intrauterine growth retardation), therapeutic (indication for ASA, duration of treatment) and platelet occlusion time. The reference values of the POT based on the collagen/epinephrine kit ranged from 80 to 150 seconds, so non-response to ASA was defined by a POT less than or equal to 150 seconds, and response to ASA by a lengthening of the POT greater than 150 seconds.

Data were analyzed using Stata 12® (College Station, Texas 77845, USA). Pregnant women's characteristics were presented for continuous variables as mean and 95% confidence interval when the distribution was normal, as median and interquartile range when it was abnormal; and for categorical variables as frequency. The logistic regression model was used to identify the determinants of ASA resistance. Variables with a value of $p<0.20$ in univariate analysis were retained for multivariate analysis. The results of the logistic regression model were presented as Odds Ratio (OR). For each of these factors, the proportional hazards hypothesis was tested using the Schönefeld residuals test. The incidence of obstetric complications according to ASA resistance was evaluated by the Kaplan-Meier method and the Log-Rank test. For all statistical analyses, the significance threshold was set at $p<0.05$.

3. RESULTS

Thirty-nine pregnant women aged average age of 33.9 ± 5.4 years with extremes of 22 and 42 years were treated with ASA for hypertensive disorders of pregnancy n=19 (48.7%), chronic arterial hypertension n=7 (18%), diabetes n=3(7.7%) fetal death n=3(7.7%), unexplained miscarriage n=3(7.7%), advanced age n=2 (5.1%) and twin pregnancy n=2(5.1%). The median body index was 25.5 kg/m^2 [23.7;29.4] with 35.9% women of normal weight, 48.7% overweight and 15.4% obese. Among them, non-response to ASA was found in 12 gestational carriers (30.7%). The mean gestational age at sampling was 26 amenorrhea weeks +2 days ± 7.9 amenorrhea weeks, and the median term of first prenatal contact was 13 amenorrhea weeks, with extremes of 7 amenorrhea weeks +2 days and 16 amenorrhea weeks +5 days. The median platelet occlusion time (POT) in our study was 180 seconds with extremes of 102 and 300 seconds. That of the 1st, 2nd and 3rd quarters was respectively 168 [150; 200], 170 [109; 239] and 158 [140; 170] seconds. The median POT in non-responders and responders to ASA was 121 seconds [101.5-141.5] and 200 seconds [168-239] respectively ($p<0.05$). No statistically significant differences ($p>0.05$) were observed between ASA non-responders and responders with regard to epidemiological, clinical and blood count determinants (Table 1). The age range of 30-39 years, and nonresponse to ASA were factors associated ($p<0,05$) with the occurrence of obstetric complications (Tables 2 and 3). The probability of complications in non-responders and responders was 72.2% (95% CI: 44.3-93.9%) and 23.4% (95% CI: 11.2-45.1) respectively, with $p=0.004$ (Fig. 1)

Table 1. Distribution of epidemiological, clinical and blood count determinants accordingto biological response to ASA

	Pregnant women			
	Non-respondents n= 12	**Respondents *n*= 27**	**OR [IC95%]**	***p***
Epidemiological				
BMI (%)				
normal	5(12.8)	9(23.1)	Ref	
overweight	4(10.3)	15(38.5)	0.48[0.1-2.2]	0.3
obesity	3(7.7)	3(7.7)	1.8[0.2-2.5]	0.5
Clinics				
Comorbidities**** (%)	3(7.7)	10(25.6)	0.56[0.1-2.5]	0.4
	17(43.6)	9(23.1)	Ref	

	Pregnant women			
	Non-respondents n= 12	**Respondents *n*= 27**	**OR [IC95%]**	***p***
Prematurity (%)	2(5.1)	3(7.7)	1.6[0.2-11.08]	0.6
SM* (%)	6(15.4)	9(23.1)	2 [0.5-7.5]	0.3
	6(15.4)	18(46.1)		
FDIU** (%)	1(2.6)	7(18)	0.2 [0.2-2.3]	0.2
	20(51.28)	11(28.2)	Ref	
GHD*** (%)	8(20.5)	17(43.6)	1.17[0.7-8.8]	0.8
	4(10.3)	10(25.6)	Ref	
Blood count				
Anemia (%)				
slight	3(7.7)	12(30.8)	Ref	
moderate	6(15.4)	8(20.5)	2.9[0.5-15.6]	0.1
severe	3(18)	7(7.7)	1.7[0.2-10.9]	0.5
Hyperleukocytosis (%)	1(2.6)	2(5.1)	1.13[0.09-13.8]	0.9
	11(28.2)	25(64.1)	Ref	
Moderate thrombocytopenia (%)	3(7.7)	12(30.8)	0.41[0.9-1.8]	0.2
	9(23.1)	15(38.5)	Ref	

SM: Spontaneous miscarriage, FDIU**: Fetal death in utero, GHD***: gravid hypertensive disorders*
*BMI: body mass index, comorbidities****: diabetes and chronic arterial hypertension*

Table 2. Univariate analysis of clinical and biological factors in relation to obstetrical complications in pregnant women receiving ASA

	Pregnant women on ASA				
Features	**With obstetrical complications n (%)**	**Without obstetrical complications n (%)**	**Hazard Ratio**	**IC à 95%**	***p***
Clinics					
Age ranges (years)					
20 – 29	3 (7.69)	7 (17.95)	Ref		
30 – 39	4 (10.26)	5 (12.82)	2.32	[-]	
More Than 40	4 (10.26)	4 (10.26)	1.87	[-]	
BMI (kg/m^2)					
Normal	6 (15.38)	8 (20.51)	Ref		
Overweight	7 (17.95)	12 (30.77)	0.6		
Obesity	6 (15.38)	0 (0.0)	2.43	[-]	
Pregnancy number					
01	2 (5.13)	3 (7.69)	Ref		
2 - 3	10 (25.64)	8 (20.51)	1.51	[-]	
More than 3	7 (17.95)	9 (23.08)	1.11	[-]	
Parity					
Nulliparous	5 (12.82)	5 (12.82)	Ref		
Primiparous	5 (12.82)	4 (10.26)	0.99	[-]	
Pauciparous	6(15.38)	10(25.64)	0.29	[-]	
Multipara	3 (7.69)	1 (2.56)	0.88	[-]	
SM	8(20.51)	7(17,95)	1.005	[-]	
	11(28.21)	13(33.33)	Ref		
Premature delivery	3(7.69)	2(5.13)	1.21	[-]	
	16(41.03)	18(46.15)	Ref		
FDIU	3(7.69)	5(12.82)	0.77	[-]	
	16(41.03)	15(38.46)	Ref		

	Pregnant women on ASA				
Features	**With obstetrical complications n (%)**	**Without obstetrical complications n (%)**	**Hazard Ratio**	**IC à 95%**	***p***
GHD	12(30.77)	13(33.33)	1.14	[-]	
	7(17.95)	7(17.95)	Ref		
1st trimester	15(38.46)	18(46.15)	Ref		
	4(10.26)	2(5.13)	1.21	[-]	
Biological					
Anemia					
Slight	7(17.95)	8(20.51)	Ref		
Moderate	7(17.95)	7(17.95)	0.97	[-]	
Severe	5(12.82)	5(12.82)	1.91	[-]	
Leukocytes $\geq 10^4/mm^3$	2(5.13)	1(1.56)	1.76	[-]	
	17(43.59)	19(48.72)	Ref		
Thrombocytopenia	5(12.82)	11(28.21)	0.49	[-]	
	14(35.9)	9(22.07)	Ref		
No response to ASA	9 (23.08)	3 (7.69)	3.46	1.38 – 8.67	0.008
	10 (25.64)	17(43.59)	Ref		

SM: spontaneous miscarriage, FDIU**: fetal death in utero, GHG***: gravid Hypertensive Disorders, BMI: body mass index*

Table 3. Multivariate analysis of clinical and complications in ASA-selected women biological factors in relation to obstetrical

	Hazard ratio	**IC à 95%**	***p-value***
Age range 30 to 39 years	19.35	0.94-38.67	0.01
Overweight	0.66	0.10-4.06	0.6
Obesity	3.78	0.53-26.59	0.1
Nulliparous	0.25	0.42-1.49	0.1
Thrombocytopenia	0.62	0.95-4.75	0.6
No response to ASA	9.47	1.64-54.58	0.01

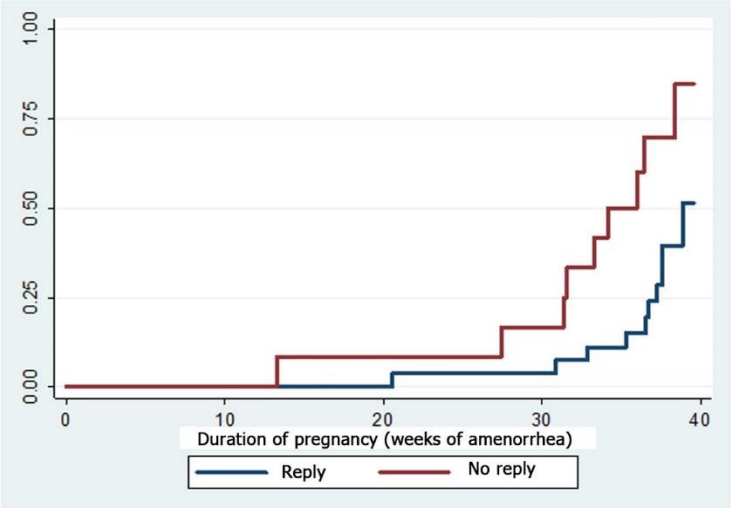

Fig. 1. Probability of obstetrical complications in newborns according to biological response to ASA

4. DISCUSSION

The biological response to acetylsalicylic acid (ASA), studied mainly in vascular pathologies (peripheral vascular disease, coronary artery disease or stroke), makes it possible to assess the efficacy of ASA-based thrombosis prevention. This study carried out in the gestational period, identified the phenomenon of nonresponse to ASA with PFA®-200 and assessed its epidemiological, clinical and haematological determinants.

Among the 39 pregnant women in our study, biological non-response to ASA was found in almost a third (30.7%) of the population studied. This phenomenon is often unrecognized in our daily practice and under-diagnosed due to insufficient technical resources. This frequency is within the range of those (5 and 60%) reported in the general population [4]. It is comparable to those found by the teams of Caron et al in Canada [6] and Jeske M. et al in the Netherlands [7], which are respectively 28.7% (assessed using PFA®-100 in 87 gestations in 2007) and 30.4% (assessed using PFA®-200 in 23 gestations in 2020). However, this figure is significantly lower than that found in the 2012 study by Leila Abid et al in Tunisia, in which resistance to ASA was found in 54.4% of patients [8]. These results may be explained by the difference between the populations in their studies, which consisted of patients with coronary artery disease of both sexes. In two more recent studies conducted in the UK, the prevalences of ASA non-response reported in the second trimester of pregnancy were 14.7% and 36% respectively. Their results differ from ours due to the methods used to measure ASA non-response, which were serum thromboxane B2 assay for Vinogradov et al in 2021 [9] and urinary 11- dehydrothromboxane B2 assay for Navaratnam et al in 2017 in the second study [10]. Indeed, the assay methods used by the latter in the detection of non-response to ASA more specifically identify the phase of primary hemostasis not inhibited by ASA, notably that of platelet activation [11,12].

With regard to the determinants of non-response, no statistically significant differences ($p>0.05$) were observed between non-responders and responders to ASA in terms of epidemiological, clinical and haematological factors (Table 1). The mean age of pregnant women in our study was 33.9 ± 5.4 years [22y-42y]. This is similar to that reported by Caron et al in 2007 and Rey et al in 2012 in Montreal, where it was 33.6 ± 5.4 and 32.3 ± 5.0 respectively. These similarities may be explained by the fact that the latter also worked on obstetric populations taking ASA for an obstetric indication like ours [13,14]. The majority of our pregnant women were overweight or obese (48.7% and 35.9% respectively). Their median body mass index was comparable to that found by Rey et al in Canada, which was 28.3 kg/m2. However, the proportion of obese subjects (49.5% versus 35.9%) was higher than ours [14]. These differences may be explained by lifestyle, and in particular by poorer eating habits in countries where 26.8% of the adult population is obese [15].

The mean gestational age at initiation of ASA treatment was higher in our series (14.3 SA±4.6) than those reported by Caron et al (10.0±4.4SA) and Rey et al (9.9±3.7SA) [6,14]. This is because prenatal contacts in developed countries start earlier, and in their studies, high-risk gestational carriers, once identified, could benefit directly from ASA treatment at a date imposed by the study methodology, which in this case was earlier than ours. The majority of patients were recruited in the second trimester of pregnancy, with a mean age at the time of platelet occlusion time (POT) of 26 weeks' amenorrhea and 2 days ± 7.9. This age is considerably higher than that reported in the Canadian series [13,14]. In fact, the methodologies used in the latter series required that pregnant women be recruited at the first prenatal contact (which was earlier than for our participants), and a first POT was performed on this occasion. The Caron et al study was interventional, with a POT performed on the day of inclusion, 15 days later and between 24 and 32 weeks of amenorrhea, in order to study variations in POT as a function of gestational age. When a patient unresponsive to 81 mg ASA was identified, the dose of ASA was increased and a sample was taken 15 days later. The same pattern was followed by Jeske M. et al. in Amsterdam, who also performed POT in the 1st, 2nd and 3rd trimesters of pregnancy and at three months postpartum [7].

The POT averages observed in the first two trimesters in our work were respectively close to and slightly higher than those observed in the third trimester. Studies have shown that pregnancy induces shortening of the POT determined on the basis of the collagen-epinephrine kit by PFA®-100 [16] and, more specifically, from the 2nd trimester onwards in medication-free pregnant women. Caron et al

found similar results in pregnant women on ASA, with a shortening of POT from the 2nd trimester onwards [6]. Jeske et al observed a greater decrease in the 3rd trimester, with a mean of 207.87±15.4 seconds using the PFA-200 [7]. POT values corresponding to the diagnosis of ASA resistance may fluctuate during pregnancy due to the expansion of plasma volume, changes in blood cell counts, coagulation factors and steroid hormones during pregnancy.

This resistance to ASA may be due to several factors. A normal erythrocyte count facilitates platelet aggregation by stimulating prostaglandin formation by the platelet, and by recruiting neighbouring platelets, despite the intake of ASA. In addition, a normal monocyte or macrophage count capable of expressing COX-2 provides the platelet, whose COX 1 is effectively inhibited by ASA, with the PGG2 and PGH2 required for thromboxane formation. Thus, despite the effectiveness of ASA in inhibiting COX-1, inhibition of platelet aggregation is reduced. These cells induce platelet aggregation by supplying thromboxane substrates, promoting degranulation or producing thromboxane A2 via COX-2, which is insensitive to inhibition by low doses of ASA [2]. Then, in the event of endothelial dysfunction (atherosclerosis, hypercholesterolemia, diabetes, smoking and arterial hypertension), nitric oxide production is reduced and its inactivation is accentuated [17]. The resulting nitric oxide deficiency could translate into a state of platelet hyperactivity, which could explain aspirin's inability to inhibit platelet activity in some individuals. These abnormalities responsible for endothelial dysfunction may also contribute to the production of isoprostanes at high levels, as a result of the imbalance between oxidants and antioxidants [17, 18, 19, 20]. Among the isoprostanes formed, 8-iso- PGF2a binds to the thromboxane platelet receptor and activates platelet aggregation. Thus, it could bypass aspirin's inhibition of thromboxane formation and result in sustained platelet activation, explaining apparent resistance to ASA. Finally, genetic variability generated by single nucleotide polymorphism can explain variation in a drug's effect [21]. This polymorphism is observed in receptors such as GPIIb-IIIa, collagen and thromboxane A2 receptors, and in enzymes (COX-1, COX-2, thromboxane A2 synthetase). Differences in the gene coding for platelet COX, the ADP receptor P2Y1 or GPIIb/IIIa may also explain the variability in platelet response to ASA [2].

5. CONCLUSION

Acetylsalicylic acid is one of the most widely used prophylactics for thrombotic complications in pregnant women in our practice. Non-response to this prophylaxis accounts for almost a third of pregnant women seen in obstetrical settings in Brazzaville. However, there is no national guide including a precise therapeutic algorithm with options for screening tests, ASA dosage and complementary tests. The absence of epidemiological, clinical or haematological determinants associated with this condition opens the door to molecular and genetic studies to elucidate its mechanisms.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was conducted anonymously and an ethical opinion was obtained (369/MERSIT/IRSSA6CERSA).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia: Background [Enligne].Switzerland: WHO; 2011.
2. Bileckot R. Programme biennal de développement sanitaire 2015-2016: Mortalité maternelle. Brazzaville. Disponible programme biennal 2015-2016_final_03_sept14_pro.pdf (who.int) Consulté le 13/04/20; 2014.
3. Lordkipanidze M. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. European Heart Journal. 2007; 28(14):1702-1708.
4. Fontana P, Boehlen F, De Moerloose P. Résistance à l'aspirine: Etat des lieux. RMS[En ligne]. 2004 ;0(23554). Available:https://www.revmed.ch/RMS/2004/RMS-2466/23554

5. Bonello L, Camion-Jau P, Barragan, Paganeli F, Interet des tests biologiques plaquettaires avant angioplastie coronaire. Revue La Lettre du cardiologue. 2009; 3(424):4-5.
6. Caron N, Rivard G, Michon N, Morin F, Pilon D, Moutquin J-M, et al. Low-dose ASA response using the PFA-100 in women with high-risk pregnancy. J Obstet Gynaecol Canada. 2009; 31(11):1022–7.
7. Bij de Weg, JM, Abheiden CNH, Fuijkschot, WW, Harmsze AM, de Boer. Resistance of aspirin during and after pregnancy: A longitudinal cohort study. Pregnancy Hypertension. 2020;19(6): 25–30.
DOI:10.1016/j.preghy.2019.11.008
8. Leila Abid, Zied Frikha, Ikram Ben Amor, Najla Hentai , Jalel Gargouri , Samir Kammoun. Comparison of different methods to evaluate the effect of aspirin on platelet function in patients with coronary artery disease.ELSEVIER. 2012;4(0):124-125.
9. Vinogradov R, Boag C, Murphy P, McGeeney D, Kunadian V, et Robson SC. Aspirin non-response in pregnant women at increased risk of preeclampsia. ELSEVIER. 2020;254:292-297.
10. Navaratnam K, Alfirevic A, Jorgensen A, Alfirevic Z. Aspirin non-responsiveness in pregnant women at high-risk of pre-eclampsia. Eur J Obstet Gynecol Reprod Biol. 2018;221:144–50.
11. Fay RA, Hughes AO, Farron NT. Platelets in pregnancy: Hyperdestruction in pregnancy.
Obstet Gynecol. 1983;61(2):238–40.
12. Harrison P, Briggs C, Machin S. Advances in platelet counting. Hematology. 2001; 5(6):421-427.
DOI: 10.1080/10245332.2001.11746538
13. Frelinger AL, Furman MI, Linden MD, Li Y, Fox ML, Barnard MR. Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cyclooxygenase-1- and cyclooxygenase-2- independent pathway: A 700-patient study of aspirin resistance. Circulation. 2006;113(25):2888–96.
14. Rey E, Rivard G-E. Is testing for aspirin response worthwhile in high-risk pregnancy? Eur J Obstet Gynecol Reprod Biol. 2011;157(1):38–42.
15. Embonpoint et obésité chez les adultes. 2018. Statistique Canada 2019;82:1-8.
Available:https://www150.statcan.gc.ca/n1/pub/82-625-x/2019001/article/00005-fra.htm
16. Gum PA, Marchant-Kottke K, Poggio ED, Gurm H, Welsh PA, Brooks L, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol. 2001; 88(3):230-5.
17. Russo G, Leopold lA, Loscaizo J. Vasoactive substances: Nitric oxide and endothelial dysfunction in atherosclerosis. Vascul Phannacol. 2002;3(8):259-269.
18. Rosado JA, Saavedra FR, Redondo PC, Hernandez-Cruz JM, Salido GM,Pariente JA. Reduced plasma membrane ca2+-atpase function in platelets from patients with non- insulin-dependent diabetes mellitus. Haematologica. 2004;89(9):1142–1144.
19. Davi G, Catalano I, Averna M, Notarbartolo A, Strano A, Ciabattoni G, et al. Thromboxane biosynthesis and platelet function in type II diabetesmellitus. N Engl J Med. 1990;322:1769–74.
20. Favaloro E. Clinical utility of closure times using the platelet function analyzer-100/200. Am J Hematol. 2017;92(4):398-404.
21. Dreyfus M, Veyradier A, Lambert T, Blot I, Tchernia G. Hématologie et grossesse. Traité d'obstétrique. Paris: Médecine-Sciences Flammarion. 2003:617-34.

Peer-review history:
The peer review history for this paper can be accessed here:
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