ORIGINAL ARTICLE

# Aspirin resistance may be associated with adverse pregnancy outcomes

**Anna Wójtowicz [1], Anetta Undas [2], Hubert Huras [1], Jacek Musiał [2], Krzysztof Rytlewski [1], Alfred Reroń [1], Maciej Wilczak [3], Robert Jach [4]**

1 Department of Obstetrics and Perinatology, Jagiellonian University, Cracow, Poland,
2 Institute of Cardiology, Jagiellonian University, Cracow, Poland
3 Department of Medical Education UM Poznań, Poland
4 Departament of Gynecological Oncology, Jagiellonian University Cracow, Poland

*Correspondence to:* Hubert Huras, MD., PhD.
Department of Obstetrics and Perinatology,
Jagiellonian University, Cracow, Poland
23 Kopernika Str., 31-501 Cracow, Poland.
tel: +48 4248412; e-mail: huberthuras@wp.pl

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**Abstract**

**OBJECTIVE:** Verify that resistance to aspirin may have an impact on pregnancy and neonatal outcome.

**METHODS:** We enrolled 43 pregnant women, aged 30.7 ± 4.0 years regularly taking 75 mg of aspirin daily and 32 (aged 30.8 ± 4 years) pregnant women not receiving aspirin who served as control group. Laboratory tests were performed at 18 to 22 weeks of gestation, 28 to 32 weeks of gestation and 16 to 32 weeks after delivery. Resistance to aspirin was defined as urinary 11-dehydrothromboxane $B_2$ (u11-$dTXB_2$) concentrations in the highest quartile and additionally, as the resistance index (RI) calculated for each woman, defined as the difference between u11-$dTXB_2$ concentration of each woman treated with aspirin and the median value at the same time point measured in the control group.

**RESULTS:** Women taking aspirin in the highest quartile of u11-$dTXB_2$ delivered prematurely (35.8±3.4 *vs* 38.1±1.7 weeks, $p$=0.02). Delivery of small for gestational age (SGA) newborns ($p$=0.003) as well as fetal distress ($p$=0.014) and preeclampsia ($p$=0.003) occured more frequently in aspirin-resistant women. Resistance to aspirin based on the RI value was also associated with higher prevalence of preeclampsia ($p$=0.02) and SGA newborns delivery ($p$=0.01). The two groups resistant to ASA designed on the basis of both (RI and u11—$dTXB_2$ urine levels) methods compared with ASA sensitive group differed in frequency of SLE prevalence.

**CONCLUSION:** Aspirin resistance may be associated with increased risk of adverse pregnancy outcomes including preeclampsia, premature delivery and delivery of SGA newborns.

## INTRODUCTION

Aspirin (ASA) reduces cardiovascular events risk by 25% in a broad spectrum of patients with cardiovascular diseases. Aspirin exerts its major antithrombotic effect by irreversibly acetylating platelet cyclooxygenase-1 (COX-1), thereby inhibiting thromboxane $A_2$ ($TXA_2$) synthesis (Antiplatelet Trialists' Collaboration 1994). A phenomenon termed aspirin resistance with a prevalence from below 1% to 45% of treated subjects has been postulated to be a potential cause of aspirin failure in the prevention of atherothrombosis (Pamukcu 2007). There is no widely accepted definition of aspirin resistance. It is most commonly based on results of laboratory assays showing an insufficient inhibition of platelet function. Recent meta-analyses showed an association between laboratory aspirin resistance and poor clinical outcomes (Snoep *et al.* 2007; Krasopoulos *et al.* 2008). Aspirin resistance has been reported in up to 60% of patients after stroke or peripheral arterial disease, up to 70% in stable coronary heart disease and even up to 80% in acute myocardial infarction (Zimmermann & Hohlfeld 2008). Low dose aspirin is also prescribed to pregnant women, who suffer from antiphospholipid syndrome (APS) (Lim *et al.* 2007), underwent in vitro fertilization (IVF) (Waldenstrom *et al.* 2004) or are at high risk of preeclampsia and intrauterine growth restriction (IUGR) (Fayyad & Harrington 2005). To our knowledge aspirin resistance has not been investigated in pregnant women taking this medication. Therefore, the aim of this study was to evaluate the impact of aspirin resistance on pregnancy outcomes and newborn state.

## MATERIALS AND METHODS

*Patients*

The Ethics Committee of the Jagiellonian University approved this case-control study, and all patients gave informed written consent. We studied 75 pregnant women, aged 20 to 44 years. Forty-three women took 75 mg of aspirin daily because of primary APS (n=18), secondary APS in the course of systemic lupus erythematosus (SLE) (n=9), detected according to the American Rheumatism Association criteria (Tan *et al.* 1982), high risk of preeclampsia (n=8), documented cardiovascular disease (n=5) and after IVF (n=3). The remaining 32 women, who were not treated with ASA, represented 24 healthy women and 8 women with SLE. APS was detected before pregnancy as described (Miyakis *et al.* 2006). Preeclampsia and hypertensive disorders were diagnosed on the basis of the American College of Obstetricians and Gynecologists (ACOG) criteria (ACOG practice bulletin 2002). Exclusion criteria were as follows: multiple pregnancy, current smoking, acute and chronic infections, intake of NSAIDs other than aspirin, platelet count $< 100 \times 10^3$ /μl or $> 400 \times 10^3$/μl, gastric ulcer, low albumin levels, aspirin allergy, bleeding tendency, concomitant diseases such as cancer, diabetes mellitus, liver injury (alanine transaminase > 1.5 times higher than the upper normal limit), renal failure (serum creatinine > 120 μmol/l), severe fetal malformations detected by ultrasound examination. All women treated with 75 mg of aspirin per day, have been taking the medication for at least 2 weeks before the first blood and urine collection until the end of the study. Women with SLE were treated with 4 mg methylprednisolone before study enrollment. All patients were followed at 1 month intervals during pregnancy and 16 to 32 (on average 26) weeks after delivery. At each follow-up, clinical outcomes were recorded and medication use, including aspirin, was documented. Pregnancy outcome was recorded for each woman. We collected the following data: maternal age, maternal body mass index (BMI), gravidity, parity, gestational age at delivery, newborn birth weight, mode of delivery, occurrence of hypertension, preeclampsia, atherothrombotic events and postpartum complications, such as hemorrhage. IUGR and small for gestational age (SGA) newborns were defined basing on the ACOG criteria. Venous blood and urine samples were obtained 3 times: between 18 and 22 weeks of gestation (2nd trimester), between 28 and 32 weeks of gestation (3rd trimester) and 16 to 32 (on average 26) weeks after delivery. In the ASA group venous blood and urine samples were obtained 3 times in 26 (66.7%) women, 2 times in 12 (30.7%) women and one time in 1 (2.6%) woman. However, in the control group samples were obtained 3 times in 27 (87.1%) women, two times in 3 (9.7%) women and one time in 1 (3.2%) woman.

*Definition of aspirin resistance*

To identify patients resistant to aspirin we determined urinary 11-dehydrothromboxane $B_2$ (u11-$dTXB_2$) (Cayman Chemical, USA ) concentrations and defined aspirin resistance based on the quartile distribution (the highest quartile – women resistant to aspirin) as described (Eikelboom *et al.* 2002). Moreover, a new parameter, the resistance index (RI), namely, the difference between u11-$dTXB_2$ concentration of each woman treated with aspirin and the median value at the same time point measured in the control group.

*Statistical Analysis*

Results are expressed as mean value ± standard error of means (SEM) for continuous variables and as percentages for categorical variables. The W Shapiro-Wilk test was used to assess conformity with a normal distribution. When necessary, data were normalized using log transformation and were compared using Student's t-test. For categorical variables the $\chi^2$ test was used. A $p$-value < 0.05 was considered statistically significant.

## RESULTS

The characteristics of the patient group and controls are given in Tables 1 and 2. Women treated with aspirin had similar u11-$dTXB_2$ during pregnancy

**Tab. 1.** Characteristics of women taking aspirin (ASA group) and controls.

| Variables | ASA group (n=43) | Control group (n=32) | *p*-value |
|---|---|---|---|
| Mean Maternal age (yr) | 30.7 ± 4.3 | 30.8 ± 4 | 0.86 |
| BMI (1), kg/m$^2$ | 26.1 ± 5.2 | 23.1 ± 3.3 | 0.01 |
| BMI (2), kg/m$^2$ | 28.7 ± 5 | 25.4 ± 3.4 | 0.007 |
| BMI (3), kg/m$^2$ | 26.1 ± 4.6 | 23 ± 3.3 | 0.006 |
| Primigravida, n (%) | 5 (11.6) | 18 (56.2) | < 0.000 |
| Primipara, n (%) | 17 (39.5) | 21 (65.6) | 0.025 |
| Among women who have been pregnant in the past | | | |
| Previous stillbirths, n (%) | 14 (32.6) | 4 (12.5) | 0.08 |
| Previous miscarriages, n (%) | 20 (46.5) | 7 (21.9) | 0.09 |
| Previous premature delivery, n (%) | 12 (27.9) | 5 (15.6) | 0.32 |
| Previous hypertension in pregnancy, n (%) | 15 (25.6) | 3 (3.1) | 0.02 |
| Previous preeclampsia, n (%) | 10 (23.3) | 2 (6.2) | 0.09 |

BMI-body mass index; (1) – second trimester; (2) – third trimester; (3) – after puerperium

**Tab. 2.** Pregnancy outcomes in the aspirin-treated and control groups.

| Variables | ASA group (n=43) | Control group (n=32) | *p*-value |
|---|---|---|---|
| Mean duration of pregnancy (weeks) | 34.8 ± 7.2 | 38.4 ± 2.4 | 0.004 |
| Stillbirths, n (%) | 4 (9.3) | 1 (3.1) | 0.55 |
| Miscarriages, n (%) | 4 (9.3) | 1 (3.1) | 0.55 |
| Hypertension in pregnancy, n (%) | 18 (41.9) | 3 (9.4) | 0.005 |
| Preeclampsia, n (%) | 11(25.6) | 4 (12.5) | 0.26 |
| Mode of delivery | | | |
| vaginal delivery n (%) | 12 (27.9) | 12 (37.5) | 0.378 |
| cesarean section n (%) | 27 (62.8) | 19 (59.4) | 0.763 |
| Atherothrombotic events during pregnancy, n (%) | 4 (9.3) | 0 (0) | 0.076 |
| Postpartum bleeding complications, n (%) | 5 (11.6) | 2 (6.2%) | 0.428 |
| Neonatal body weight at birth (gram) | 2798 ± 982 | 3093 ± 559 | 0.42 |
| Apgar score after 1 min ≤ 7, n (%) | 8 (18.6) | 7 (21.8) | 0. 726 |

and after puerperium (Figure 1). However, they had lower u11-dTXB$_2$ in comparison with the control group in the 2nd trimester (223.8 ± 257.1 pg/μmol creatinine *vs* 499.6 ± 182.1 pg/μmol creatinine, $p<0.0001$), the 3rd trimester (232.6 ± 235 pg/μmol creatinine *vs* 677.9 ± 336.8 pg/μmol creatinine, $p<0.0001$) and after puerperium (170 ± 154 pg/μmol creatinine *vs* 585.8 ± 186 pg/μmol creatinine; $p<0.0001$) (Figure 1).

*Quartile distribution*

In the second trimester women in the lowest quartile had u11-dTXB$_2$ below 49.5 pg/μmol creatinine, in the third trimester below 66 pg/μmol creatinine and after puerperium below 64.0 pg/μmol creatinine. Women in the highest quartile had u11-dTXB$_2$ in the second trimester above 393 pg/μmol creatinine, in the third trimester above 411 pg/μmol creatinine and after puerperium above 258 pg/μmol creatinine. The lowest and the highest quartile groups differ with regard to u11-dTXB$_2$ in the 2nd trimester (52.6 ± 36.4 pg/μmol creatinine *vs* 515 ± 241.2 pg/μmol creatinine; $p=0.0004$) as well as in the 3rd trimester (67 ± 26.1 pg/μmol creatinine *vs* 537.6 ± 190 pg/μmol creatinine; $p=0.0006$) and after puerperium (138 ± 94.4 pg/μmol creatinine *vs* 228.5 ± 104 pg/μmol creatinine; $p<0.0001$). In the second trimester the lowest quartile comprised 9 women but only 6 women stayed in this subgroup in the third trimester and only 4 women after puerperium. The lowest quartile comprised 9 women in the third trimester and 8 women after puerperium. The highest quartile consisted of 9 women, from whom 3 women delivered before the third trimester (33.3%), 5 women stayed in that quartile in the 3rd trimester and 2 women after puerperium. Using the range of values from the highest quartile in 2nd trimester women, there were 9 women in 3rd trimester and 3 women in puerperium who have also qualified to the highest quartile. Pregnancy outcomes were analyzed women, who in the 2nd and/or 3rd trimester were classified to the lowest quartile (women responsive to ASA, n=12) or to the highest quartile (women resistant to ASA n=13). There were significant differences with respect to SLE ($p=0.01$), the duration of the pregnancy ($p=0.05$), SGA newborn delivery ($p=0.003$) as well as preeclampsia and fetal distress occurrence ($p=0.014$) (Table 3).

*Resistance index*

In the second trimester median u11-dTXB$_2$ concentration in the control group was 426 pg/μmol creatinine, in the third trimester 552 pg/μmol creatinine and after puerperium 343 pg/μmol creatinine. After deducting the 2nd and 3rd trimester u11-dTXB$_2$ values gathered from subjects in aspirin group from the median value in control group most women RI was below –200 (Figure 2). The aspirin group was divided into a group of women with a significant suppression of TXB$_2$ production (women with good response to aspirin, n=20) and a group where that supression has failed (women with

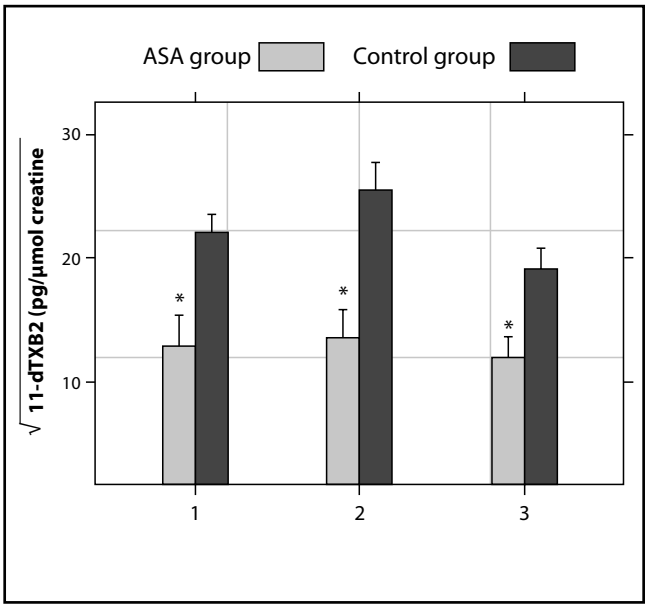


**Fig. 1.** Distribution of urinary 11-dehydrothromboxane $B_2$ (11-$dTXB_2$) concentrations in the aspirin (ASA) and control groups in the second (1) and third (2) trimester as well as after puerperium (3). *$p$<0.05 in comparison to the aspirin group

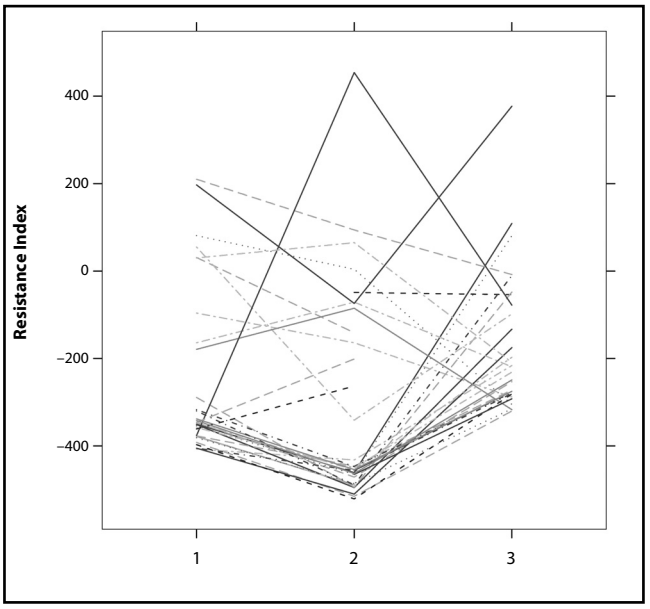


**Fig. 2.** Distribution of urinary 11-dehydrothromboxane $B_2$ concentrations in each subject in the aspirin group according to the resistance index in the second (1) and third (2) trimester as well as after puerperium (3).

poor response to aspirin, n=16). Women from the highest quartile of u11-$dTXB_2$ represented a group of poor response to aspirin, while those from the lowest quartile constituted a group of good response to aspirin, defined with the resistance index. In good responders the effect of aspirin seen as a reduction in u11-$dTXB_2$ concentrations during the second trimester was more profound during the third trimester and weaker after puerperium (Figure 2). In women who poorly responded to aspirin, u11-$dTXB_2$ concentrations increased during the third trimester, decreased after puerperium and then were similar to those in women responsive to aspirin (Figure 2). Furthermore, SLE (37.5% *vs* 5%, $p$=0.04), preeclampsia (50% *vs* 10%, $p$=0.02) and SGA newborns delivery (43.7% *vs* 5%, $p$=0.01) occurred more frequently in women with poor response to ASA than in good responders to ASA.

## DISCUSSION

To our knowledge this study is the first to evaluate aspirin resistance in pregnant women. Importantly, aspirin resistance in pregnant women was associated with a higher risk of complications during pregnancy such as preeclampsia, preterm delivery and delivery of the SGA newborns. We also showed that pregnancy by itself favours this phenomenon. We also noted that ASA resistance occurs more frequently in pregnant women with SLE.

In our study a mean concentration of u11-$dTXB_2$ was about 10 times higher than that observed by Eikelboom *et al.* (2002), in which elderly patients with cardiovascular diseases were enrolled, and several times higher than that in a study of Vainio *et al.* (2004), where a radioimmunoassay was used to measure thromboxane derivatives. However, current values were similar to those published by Qayyum *et al.* (2008), where non-pregnant women were enrolled.

Several studies showed that patients with aspirin resistance are at increased risk of cardiovascular disorders and that the prevalence of this phenomenon is higher in women than in men (Chen *et al.* 2007; Lee *et al.* 2005). It might be speculated that aspirin resistance contributed to adverse pregnancy outcomes reported in the presented study.

During pregnancy, puerperium and breast feeding eicosanoids metabolism appears to be altered. There is evidence for increased expression of COX-1 and COX-2 in pregnancy, and major production of thromboxane by trophoblast (Slater *et al.* 1994; Hirst *et al.* 1995; Luppi & Deloia 2006; Nelson & Walsh 1989).

In our study women resistant to aspirin did not differ from good responders to aspirin with regard to age and BMI, i.e. the factors which may increase the risk of pregnancy complications (Duckitt & Harrington 2005). SLE occurred more frequently in poor responders to aspirin. Systemic lupus erythematosus is a known risk factor of poor obstetrical outcomes (Clowse *et al.* 2006).

It is unclear which mechanisms underlie the associations between adverse pregnancy outcomes and aspirin resistance. It has been shown that some environmental and genetic factors contribute to low platelet response

**Tab. 3.** Maternal characteristics in relation to quartile distribution based on urinary thromboxane $B_2$ levels at the 2nd and 3rd trimester.

| Variables | I quartile (n=12) | III quartile (n=13) | *p*-value |
|---|---|---|---|
| Mean Maternal age (yr) | 30.2 ± 4.2 | 30 ± 4.5 | 0.85 |
| BMI (1), kg/m$^2$ | 27.3 ± 6.9 | 25.9 ± 3.8 | 0.5 |
| BMI (2), kg/m$^2$ | 30.2 ± 6.3 | 21.9 ± 13 | 0.06 |
| BMI (3), kg/m$^2$ | 27.2 ± 7 | 26.4 ± 3.3 | 0.72 |
| Primigravida, n (%) | 1 (8.3) | 6 (46.1) | 0.035 |
| Primipara, n (%) | 6 (50.0) | 7 (53.8) | 0.847 |
| APS, n (%) | 7(58.4) | 8(61.5) | 0.87 |
| SLE, n (%) | 0 (0) | 5(38.4) | 0.016 |
| Hypertension in pregnancy, n (%) | 4(33.3) | 7(53.8) | 0.3 |
| Preeclampsia, n (%) | 0(0) | 7(53.8) | 0.003 |
| Gestational diabetes, n (%) | 1(8.3) | 4(30.7) | 0.35 |
| Mean duration of pregnancy (weeks) | 38.1±1.7 | 35.8±3.4 | 0.05 |
| Mode of delivery | | | |
| Cesarean section, n (%)<br>Vaginal delivery, n (%) | 7(58.4)<br>5(41.6) | 11(84.7)<br>2(15.3) | 0.14 |
| Neonatal body weight at birth (grams) | 3145 ± 355 | 2467 ± 1180 | 0.06 |
| SGA newborn delivery, n (%) | 0(0.0) | 7(53.8) | 0.003 |
| Apgar score after 1 min ≤ 7, n (%) | 1 (8.3) | 7 (53.8) | 0.014 |

BMI – body mass index; APS – antiphospholipid syndrome; SLE – systemic lupus erythematosus; SGA – small for gestational age

to aspirin. What is important is that even women who do not take ASA tend to have greater platelet activation, compared with men, in response to multiple agonists. Moreover, after low-dose aspirin therapy women continue to have higher platelet aggregation compared to men, suggesting that women may benefit less from protective actions of aspirin (Becker *et al.* 2006). Undas *et al.* reported that aspirin resistance is associated with lack of aspirin-induced reduction in thrombin generation in response to vascular injury (Undas *et al.* 2007). It is tempting to speculate that heightened thrombin formation together with enhanced platelet reactivity present during pregnancy predispose to thrombosis in the placental vessels which might contribute to disturbed intrauterine growth or preeclampsia (Sheu *et al.* 2002).

Several limitations of the current study should be acknowledged. First, the number of women studied was limited and the women enrolled initially had high risk of obstetrical complications. A prospective trial involving a large number of women in reproductive age taking aspirin with the evaluation of resistance to the medication before conception and during pregnancy would allow to reliably assess the prevalence of this phenomenon in pregnant women. It should be emphasized that despite the fact that in this study the measures of aspirin resistance were not compared with those obtained for age-matched healthy non-pregnant women, but only with the data determined on average 26 weeks after delivery, it seems that aspirin resistance is more pronounced during pregnancy than in the first year after delivery. Secondly, we cannot exclude that irregular aspirin intake could contribute to increased u11-dTXB$_2$ concentration. Only witnessed intake of the drug or sample collection a few hours after aspirin administration is thought to ensure that non-adherence is not a reason for apparent aspirin resistance. We used a new approach to define aspirin resistance called the resistance index, which is aimed to objectively estimate aspirin's effect in each subject referring to the concentration of u11-dTXB$_2$ in a group of women who were not treated with aspirin or other drugs.

Third, the optical aggregometry is nowadays considered to be the gold standard for determining aspirin's effect on platelet reactivity. We started our study in 2004 and decided to use the method introduced by Eikelboom *et al.* in 2002 to identify aspirin-resistant women. However, uncertain sensitivity and specificity, low reproducibility are the major disadvantages of the currently used assays. Moreover, the correlations between results of different tests of aspirin responsiveness are poor (Santilli *et al.* 2009). Given the fact that aspirin inhibits mainly platelet TXA$_2$ production, which can be determined by measuring urinary stable metabolites of TXA$_2$ as in the present study, Eikelboom *et al.* reported that higher concentration of 11-dTXB$_2$ is associated with 1.8 fold higher risk of cardiovascular event despite aspirin treatment. However, the study of Santili *et al.* showed that among the biochemical and functional assays, serum TXB$_2$ had the highest signal-to-noise ratio and the lowest interindividual and intra-individual variabilities.

In conclusion, we addressed an intriguing issue of aspirin resistance in pregnant women for the first time. Our findings indicate that insufficient inhibition of COX-1 by aspirin in this group of patients might be clinically relevant and shows associations with adverse pregnancy outcomes. Furthermore, aspirin resistance was shown to be more frequent in women with SLE. Further studies in a larger group of pregnant women are needed to validate our results. Given increasing age of

pregnant women and higher prevalence of cardiovascular disorders in this population, the actual role of poor response to aspirin in pregnancy outcomes appears of vital clinical importance.

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