Original paper

Does acetylsalicylic acid level the playing field? Low-dose aspirin and obstetric outcomes: a case-control study

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Abstract

Introduction: The administration of low-dose acetylsalicylic acid (ASA) during pregnancy has been advocated to enhance obstetric outcomes, particularly in high-risk cases. While ASA is known to reduce certain complications, its broader impact on pregnancy outcomes remains under scrutiny. This study explores the effects of ASA on key obstetric and neonatal parameters in a clinical setting.
Aim of the research: This research aims to evaluate the influence of ASA use during pregnancy on preterm birth rates, neonatal Apgar scores, and neonatal intensive care unit (NICU) admissions, assessing whether ASA improves outcomes in high-risk pregnancies.
Material and methods: A case-control study was conducted with 1644 pregnant individuals who underwent first-trimester screening and delivered at the Provincial Combined Hospital in Kielce. The case group comprised patients prescribed ASA, while the control group included those not using ASA. Outcomes such as preterm births (< 37 and < 35 weeks), Apgar scores at 1 and 10 minutes, and NICU admissions were compared. Statistical analyses, including odds ratios (ORs), assessed associations between ASA use and these outcomes.
Results: Out of the total cohort, 119 (10.22%) patients received low-dose acetylsalicylic acid (typically 150 mg). ASA users exhibited higher rates of preterm birth before 37 weeks of gestation (OR = 2.40), increased risk of neonatal intensive care unit (NICU) admission (OR = 2.23), and lower 1-minute Apgar scores (OR = 2.41); however, no significant differences were observed in Apgar scores at 10 minutes, and no differences were noted in the incidence of preterm birth before 35 weeks of gestation. Pre-existing conditions such as diabetes and hypertension were more prevalent among patients receiving ASA.
Conclusions: These findings suggest that while low-dose ASA is widely used, it does not fully offset the elevated risk associated with high-risk pregnancies.

Introduction

The use of acetylsalicylic acid (ASA) during pregnancy is increasingly common. Several reasons and varied indications support this trend. Firstly, high-quality data indicate a significant reduction in the risk of preterm preeclampsia when ASA is used prophylactically, as well as a decreased risk of foetal growth restriction (FGR) [1, 2]. Studies have also shown positive effects in cases of small-for-gestational-age (SGA) foetuses [2] and efficacy in cases of recurrent pregnancy loss (RPL) associated with antiphospholipid syndrome (APS) [3]. Some studies further support empirical use of ASA in RPL cases with unknown causes [4]. There is also evidence that low-dose aspirin (LDA) initiated in the first trimester may reduce the risk of preterm birth [5].

Safety data for ASA use in pregnancy have also expanded. Initially, concerns were raised regarding ASA use in the third trimester due to the potential risk of premature closure of the ductus arteriosus [6]. However, recent data have shown that its use is safe until the 36th week of gestation [7], now the standard recommendation [8].

The use of any pharmacological agent, regardless of its indication, involves a balance of potential benefits and associated risks. Based on current evidence, the reduction in the incidence of certain pregnancy-related complications through the administration of ASA is unequivocal. Any decrease in the occurrence of preeclampsia (PE) is expected to result in a corresponding reduction in preterm births and related complications of prematurity, including periventricular haemorrhage, necrotising enterocolitis, and respiratory distress syndrome. Nevertheless, this reduction does not signify the complete elimination of complications, despite the progressively refined criteria for selecting pregnant patients for such prophylactic therapy. Case-control studies allow for the comparison of overall pregnancy outcomes between

Table 1. Demographic characteristics of study groups

Parameter	ASA		*P*-value
	Yes	No	
Pre-pregnancy diabetes	3.36%	0.77%	0.00849
Pre-pregnancy hypertension	3.36%	0.29%	0.00004
In vitro fertilisation	5.80%	4.15%	0.64
Height	165 (8)	165 (7)	0.634785
Weight	70 (24)	63 (14)	< 0.001
BMI	25.89 (8.8)	23.04 (4.73)	< 0.001
BMI ≥ 25 kg/m^2	55.36%	30.78%	< 0.001
BMI ≥ 30 kg/m^2	27.68%	7.44%	< 0.001
BMI ≥ 35 kg/m^2	12.50%	2.01%	< 0.001
First pregnancy	30.25%	36.68%	0.07243
Multipara	69.75%	61.32%	0.73

women receiving ASA and those not considered eligible for this prophylactic intervention. Naturally, we acknowledge that this study design is inherently prone to indication bias. Women in the ASA group represent a population with a higher baseline risk of pregnancy complications. By analysing obstetric outcomes within this context and at the current stage of scientific understanding, we can identify whether there remain areas in clinical care that warrant further improvement.

Aim of the research

In this study, we aimed to assess whether nighttime low-dose ASA use during pregnancy, regardless of the indications, could be considered a risk factor for adverse obstetric outcomes such as preterm birth, low Apgar scores, and neonatal intensive care unit (NICU) admission.

Material and methods

This case-control study followed STROBE guidelines [9]. We included a cohort of patients who delivered at the Department of Obstetrics and Gynaecology at the Provincial Complex Hospital in Kielce and underwent first-trimester prenatal screening between 11 and 13+6 weeks of gestation. The "case" group comprised women who were taking ASA during pregnancy, while the control group included those who did not take ASA. We collected data on prenatal screening results and demographic characteristics of the enrolled patients. Women were assigned to the ASA group based on self-reported medication use; however, actual compliance was not assessed.

Follow-up included obstetric outcomes such as the rate of preterm births, newborn clinical status at birth, and NICU admission rates. ASA administration was based on prenatal screening results or risk factors, determined by the attending physician. Notably, during the study period (2020), our lab did not perform PE screening (based on PLGF, UtA PI, and sFLT-1); the only recommendation for ASA initiation was a PAPP-A protein concentration < 0.4 MoM, as per Polish Gynaecological Society guidelines.

Results

A total of 1644 patients were included in the study, of whom 119 (10.22%) received ASA therapy; ASA use data were unavailable for 11 patients. Among the ASA group, 112 patients received a 150-mg dose, while 7 received 100 mg. Pre-pregnancy medical history data for patients receiving ASA are presented in Table 1.

The overall rate of preterm birth in our cohort was 4.68%. Of these preterm births, 77% were spontaneous in onset, while the remaining cases were iatrogenic.

Patients on ASA more often had pre-pregnancy diabetes and hypertension and higher pre-pregnancy body weights, with a higher proportion of overweight and obese patients. However, the groups did not differ in the number of first-time pregnancies. We analysed biochemical and ultrasound results from first-trimester screening for both groups, presented in Table 2 (quantitative data) and Table 3 (qualitative data).

In women taking ASA during the first trimester, the median NT measurement of the foetus was statistically higher between 11 and 13 + 6 weeks, while non-normalised PAPP-A levels were lower. More women in the ASA group were classified as high-risk for Down syndrome. Table 4 presents perinatal outcomes for both groups, including the percentage of specific complications and odds ratios (OR) with 95% confidence intervals.

Table 2. Comparison of median values from first-trimester prenatal screening

Parameter	ASA – yes		ASA – no		
	Median	IQR	Median	IQR	*P*-value
NT	1.80000	0.40000	1.70000	0.47000	0.009765
fb-HCG	35.60000	26.63000	39.82000	31.89000	0.165943
PAPP-A	3.21000	2.86000	3.95000	3.17000	0.005789
fb-HCG MoM	1.12600	0.86200	1.10400	0.85600	0.798532
PAPP-A MoM	0.98500	0.70500	1.02300	0.68500	0.277032
DV PI	1.00000	0.24000	1.01000	0.23000	0.666593

NT – nuchal translucency, fb-HCG – free beta-HCG, PAPP-A – pregnancy-associated plasma protein A, MoM – multiple of median, IQR – interquartile range, DV PI – ductus venosus pulsation index.

Table 3. Qualitative results from first-trimester prenatal screening

Variable	ASA – yes	ASA – no	*P*-value
PAPP-A < 0.4 MoM	4.2%	3.72%	0.820000
High risk T21	14.29%	7.35%	0.00851
Intermediate risk T21	19.33%	13.35%	0.07463
High risk T18	0%	0.77%	0.33561
Intermediate risk T18	4.20%	1.74%	0.06904
High risk T13	0%	0.64%	0.40596
Intermediate risk T13	0.93%	0.75%	0.40596

High risk > 1 : 300; Intermediate risk 1 : 300 – 1 : 1000; Low risk < 1 : 1000.

Table 4. Neonatal complication rates by patient group

Outcome	ASA – yes		ASA – no		*P*-value	OR	95% CI
	n	%	*n*	%			
Apgar < 8 (1st min)	8	11.11	37	4.93	0.032	2.41	1.0775 to 5.4000
Apgar < 4 (1st min)	2	2.78	4	0.53	0.0557	5.33	0.9602 to 29.6488
Apgar < 8 (10th min)	2	2.78	7	0.93	0.17	3.03	0.6190 to 14.8986
Apgar < 4 (10th min)	0	0.00	0	0.00	N/A		
PTL < 37 weeks	10	13.89	45	5.99	0.013	2.53	1.2161 to 5.2654
PTL < 35 weeks	4	5.56	18	2.40	0.12	2.39	0.7882 to 7.2799
NICU admission	8	11.11	37	4.93	0.049	2.23	1.0021 to 4.9952

PTL – preterm labour, NICU – neonatal intensive care unit.

Among pregnant women receiving ASA, we observed higher odds of moderate or poor neonatal condition, defined as an Apgar score < 8 at 1 minute of life. No statistically significant differences were found regarding poor neonatal condition (Apgar < 4) at either 1 or 10 minutes, nor for moderate or poor condition (Apgar < 8) at 10 minutes.

The difference in the proportion of neonates with an Apgar score < 4 at 1 minute was at the threshold of statistical significance. In this case, we cannot exclude the possibility of a Type II error, and a true difference may only become apparent in a larger patient cohort.

The rate of preterm birth before 37 weeks of gestation was higher in the ASA group (OR = 2.40), and the risk of NICU admission was also increased (OR = 2.23). However, no significant difference was observed in the rate of preterm birth before 35 weeks of gestation.

Discussion

Our study aimed to evaluate whether ASA use in the second and third trimesters could be considered a risk factor for adverse obstetric outcomes. This study is not intended to cast a negative light on low-dose

aspirin (LDA) use during pregnancy, as its cross-sectional design limits causal inferences. Our findings indicate that ASA use in a real-world cohort does not level the playing field for patients compared to those without LDA indications.

Several factors may contribute to this, although causation cannot be inferred from this study's design. One possible explanation is the incomplete reduction of preeclampsia risk with ASA use, which appears more effective in early-onset preeclampsia (< 37 weeks), with a 62% reduction in risk in the ASPRE study (OR = 0.38, 95% CI: 0.20–0.74), especially for younger pregnancies. However, no reduction in term preeclampsia (≥ 37 weeks) was observed (OR = 0.95, 95% CI: 0.57–1.57) [10]. Similar findings were reported in a 2018 meta-analysis, in which ASA did not affect term PE risk (RR = 0.92, 95% CI: 0.70–1.21) but significantly reduced PE risk before 37 weeks (RR = 0.62, 95% CI: 0.45–0.87) [11]. Although we did not directly evaluate this complication, PE may indirectly contribute to iatrogenic preterm births, observed more frequently in our ASA group.

Some studies in the literature have assessed which baseline characteristics may classify patients into groups unlikely to benefit from LDA and who may develop PE despite ASA use, such as chronic pre-pregnancy hypertension and extremely high-risk PE classifications based on FMF algorithm using PLGF (> 1 : 10) [12]. This incomplete ASA effectiveness in PE prevention may be a primary factor affecting our results and the lack of outcome equalisation between ASA and control groups.

In our study, we observed an increased risk of poorer neonatal condition and higher rates of NICU admission, probably influenced by prematurity, but potentially also associated with a greater risk of foetal hypoxia in the ASA group. Existing literature supports the beneficial role of ASA in reducing the risk of FGR, which may indirectly decrease the long-term risk of cerebral palsy [13].

In our cohort, no significant differences were observed in the rate of preterm birth before 35 weeks of gestation. This finding may support the hypothesis that ASA is more effective in preventing early-onset preeclampsia than its late-onset form. However, given the relatively low prevalence of very early preterm births in our study population, we cannot exclude the possibility of a Type II error in relation to this particular complication.

The study results may also be affected by potential adverse effects of ASA treatment, as antiplatelet agents, due to their primary function, can cause bleeding-related complications [14]. However, ASA studies are typically conducted in older patients with cardiovascular risks, not younger pregnant populations. Some studies suggest an increased risk of placental abruption with ASA use [15, 16], while others report protective or no effects [17]. Studies in pregnant populations have not indicated an increased risk of complications such as epistaxis, rectal bleeding, haematemesis, and ecchymoses [17].

One important factor that may influence pregnancy outcomes is patient adherence to medical recommendations. Evidence indicates that compliance with prophylactic treatment plays a critical role in the prevention of complications, and non-adherence may be a key contributor to treatment failure [18]. Some studies report that non-compliance with prescribed therapy affects over 20% of patients, with only 5.9% of women choosing to discuss their decision to discontinue treatment with a healthcare provider [19].

Adherence is influenced by several factors, including the requirement for daily medication intake, initiation of treatment before the 16th week of gestation, and the necessity of administration at a specific time of day. Chronotherapeutic studies suggest that the greatest reductions in the incidence of preeclampsia, gestational hypertension, preterm delivery, and intrauterine growth restriction (IUGR) are observed when ASA is taken at bedtime [20].

In our study, this variable was not assessed. Women were included in the ASA group based solely on the recommendation to take the medication; no data were collected regarding actual adherence.

Given current scientific evidence, we recognize the positive impact of ASA on obstetric outcomes in high-risk PE women, along with a reduction in neonatal complications, such as perinatal death (RR = 0.47; 95% CI: 0.25–0.88), significant reduction in 5-min Apgar score < 7 (RR = 0.75; 95% CI: 0.58–0.96), and periventricular haemorrhage (RR = 0.68; 95% CI: 0.47–0.99) [16].

Our study suggests that low-dose ASA use could be considered a risk factor for adverse obstetric and neonatal outcomes, as ASA does not equalise the risk between groups.

A key limitation of this study is the inability to establish causal relationships – an inherent constraint of all case-control designs – along with potential biases such as indication bias. Another limitation was the lack of assessment of preeclampsia severity; ASA may influence not only the occurrence but also the clinical course of the condition. We also did not evaluate patient adherence to ASA therapy, which could significantly impact outcomes. Furthermore, pregnancy complications related to bleeding – potentially associated with ASA use – were not assessed in our study.

Additionally, patients who delivered at our facility and were taking ASA but did not undergo prenatal screening at our centre were excluded from the analysis. This may have resulted in a narrower, more selective study population and limited the generalisability of our findings.

Future research should focus on improving the criteria for patient selection for ASA administration, as

well as investigating interventions aimed at reducing complications that are only marginally mitigated by ASA use, such as late-onset preeclampsia. Another important research direction involves evaluating educational strategies that enhance patient adherence to prescribed treatment, ensuring the highest possible compliance rates. Additionally, further studies should assess potential complications associated with ASA use in pregnant women to optimise its safety and efficacy.

Conclusions

From the perspective of the second and third trimesters, ASA use can be considered a risk factor for adverse obstetric events, including preterm birth, lower Apgar scores, and NICU admissions.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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