Continuing Medical Education

The Role of Acetylsalicylic Acid in the Prevention of Pre-Eclampsia, Fetal Growth Restriction, and Preterm Birth

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Summary

Background: Recent studies suggest that low-dose acetylsalicylic acid (ASA) can lower pregnancy-associated morbidity.

Methods: This review is based on pertinent publications that were retrieved by a selective search in PubMed, with special attention to systematic reviews, meta-analyses, and randomized controlled trials.

Results: Current meta-analyses document a reduction of the risk of the occurrence of pre-eclampsia (RR 0.85, NNT 50), as well as beneficial effects on the rates of preterm birth (RR 0.80, NNT 37), fetal growth restriction (RR 0.82, NNT 77), and perinatal death (RR 0.79, NNT 167). Moreover, there is evidence that ASA raises the rate of live births after a prior spontaneous abortion, while also lowering the rate of spontaneous preterm births (RR 0.89, NNT 67). The prerequisites for therapeutic success are an adequate ASA dose, early initiation of ASA, and the identification of women at risk of pregnancy-associated morbidity. Side effects of treatment with ASA in this patient group are rare and mainly involve bleeding in connection with the pregnancy (RR 0.87, NNH 200).

Conclusion: ASA use during pregnancy has benefits beyond reducing the risk of pre-eclampsia. The indications for taking ASA during pregnancy may be extended at some point in the future; at present, in view of the available evidence, it is still restricted to high-risk pregnancies.

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Acetylsalicylic acid (ASA) was originally used primarily for its analgesic and antipyretic effects, but it is increasingly being used prophylactically, mostly to prevent cardiovascular diseases (e1, e2).

Learning objectives

This article is intended to give the reader basic knowledge of:

- the pleiotropic effects of ASA that result from the inhibition of prostanoid synthesis, which help prevent pregnancy-specific diseases and improve obstetric outcomes;
- the current indications and pharmacological features of ASA use during pregnancy..

Methods

A selective search was carried out in PubMed for publications in English containing the following keywords: ("Aspirin"[Mesh]) AND (("Pre-Eclampsia"[Mesh]) OR ("Pregnancy"[Mesh]) OR ("Fetal Growth Retardation"[Mesh]) OR ("Abortion, Spontaneous"[Mesh]) OR ("Premature Birth"[Mesh]).

The search was limited to the article types "Clinical Trials," "Meta-Analysis," "Randomized Controlled Trial," and "Systematic Review."

The last date of searching was 5 December 2022; the search yielded a total of 337 with publication years going back to 1998. Older papers, papers that did not meet the search criteria, and guideline recommendations were also included if relevant.

Miscarriage risk and live birth rate

Spontaneous miscarriage occurs in almost 15% of ultrasonographically confirmed pregnancies (e3) and in 25% of pregnancies that are diagnosed at an earlier stage by the detection of human chorionic gonadotropin

Preventive aspects

Acetylsalicylic acid was originally used primarily for its analgesic and antipyretic effects, but it is increasingly being used prophylactically, mostly to prevent cardiovascular diseases

ASA in pregnancy

The findings of recent studies suggest that low-dose acetylsalicylic acid (ASA) lowers pregnancy-specific morbidity.

TABLE 1

The effect of acetylsalicylic acid on relevant endpoints in pregnancy

Endpoint	Inclusion criteria / reference	Design	N	Frequency of endpoint, ASA vs. placebo	Effect: (RR or OR) / 95% CI / p-value	Remarks
Live birth rate	1–2 spontaneous miscarriages (1)	RCT, 81 mg vs. placebo, starting before conception	1078	58% vs. 53%	RR 1.10; [0.98; 1.22]; p = 0.098	
	≥ 3 miscarriages (4)	RCT, 75 mg vs. placebo from pregnancy detection	400	83.0% vs. 85.5%	RR 0.97; [0.89; 1.06]; p = 0.58	
	≥ 2 miscarriages (5)	RCT, 80 mg ASA vs. placebo, < 6th WoG, 72.5% preconceptional	241	50.8% vs. 57.0%	RR 0.89; [0.71; 1.13]; p = 0.63	
	assisted reproduction (e83)	meta-analysis of RCTs, ASA vs. placebo	1468	not stated	OR 2.04; [0.65; 2.40]; p = 0.15	intention: endometrial preparation after ovarian stimulation
Miscarriage rate	recurrent miscarriages(6)	meta-analysis of RCTs, ASA+LMH vs. LMH	1849		RR 0.62; [0.30; 1.27]; p = 0.19	
Perinatal mortality	high-risk patients, preeclampsia risk ≥ 1:100 (12)	RCT, 150 mg vs. placebo, onset between 11th-14th WoG	1776	1.0% vs.1.7%	RR 0.59; 99% CI [0.19; 1.85]; no p-value given	
	risk for preeclampsia (19).	meta-analysis of RCTs, ASA vs. placebo	35 391	2.9% vs. 3.4%	RR 0.85; [0.76; 0.95]; p = 0.01	I^2 = 0 %, NNT 197
	high- and low-risk studies (32)	meta-analysis of RCTs, ASA vs. placebo with onset ≤ 16th WoG	2968	9.9‰ vs. 23.9‰	RR 0.47; [0.25; 0.88]; p = 0.02	I^2 = 0 %, NNT 92
	high- and low-risk studies (26)	meta-analysis of RCTs, ASA vs. placebo	13 860	2.1% vs. 2.7%	RR 0.79; [0.66; 0.96]; p = 0.02	I^2 = 0 %, NNT 167*
	low-risk, nulliparous (29)	RCT, 81 mg vs. placebo, onset between 6th and 13th WoG.	11 754	45. ‰ vs. 53.6‰	RR 0.86; [0.74; 1.00]; p = 0.048	
Premature placental abruption or bleeding during pregnancy	high-risk patients (33)	meta-analysis of RCTs for pre-eclampsia prevention, ASA ≥ 100 mg vs. placebo	3147	1.7% vs. 1.8%	RR 0.99; [0.57; 1.73]; p = 0.98	I^2 = 0 %
Vaginal bleeding	low-risk, nulliparity (29)	RCT, 81 mg vs. placebo, onset between 6th and 13th WoG	11 754	3.6% vs. 4.%	RR 0.87; [0.73; 1.04]; p = 0.125	NNH 200*

* Estimates of the number needed to treat (NNT) and number needed to harm (NNH) are based on the indicated absolute risk differences.
ASA: acetylsalicylic acid; CI: confidence interval; I^2: measure of heterogeneity; LMH: low-molecular-weight heparin; N: number of study participants; OR: odds ratio; RCT: randomized, controlled trial; RR: relative risk; WoG: week(s) of gestation

(e4). In the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, conducted in the USA, it was studied whether and to what extent ASA use that is started before conception affects the rate of live births (1) *(Table 1)*. Women who wished to conceive were randomly allotted to taking folic acid together with either 81 mg of ASA per day (n = 535) or placebo (n = 543). The treatment was continued for six menstrual cycles or for up to 36 weeks of gestation (SSW) in women who became pregnant. The ultrasonographic pregnancy rates were higher with ASA (70% vs. 64%; RR = 1.10; 95% confidence interval [1.01; 1.19]; p = 0.033), but the rates of live births, which were low overall, did not differ significantly (58% vs. 53%; RR = 1.10 [0.98; 1.22]; p = 0.098). In a per-protocol analysis taking account of treatment adherence, ASA use was associated with 15 additional live births per 100 study participants (2). The safety analysis of preconceptional ASA use in the EAGeR trial revealed no serious adverse events (3).

In women who had sustained three or more consecutive miscarriages of no identifiable cause, 75 mg ASA

ASA use before conception

In women who have previously hade a miscarriage, the preconceptional use of ASA can increase the rates of pregnancy and live birth.

ASA use after recurrent miscarriages

When ASA is taken after recurrent miscarriages, no reduction of the miscarriage rate is to be expected.

taken daily from the ultrasonic detection of fetal cardiac activity onward (n = 400) did not affect the rate of live births (83.0% vs. 85.5%; RR = 0.97 [0.89; 1.06]; p = 0.58) or that of miscarriages (16.5% vs. 14.0%; RR = 1.18 [0.74; 1.87]; p = 0.58) (4). Nor was the live birth rate in women with prior recurrent miscarriages improved in other trials in which ASA was initiated either (5, e5, e6). In the multicenter Anticoagulants for Living Fetuses (ALIFE) trial, the 72.5% of participants (n = 120) who took 80 mg/day of ASA starting before conception did not have a higher live birth rate than the placebo group (n = 121) (50.8% vs. 57.0%; RR = 0.89 [0.71; 1.13]; p = 0.63) (5). A meta-analysis has shown that the addition of ASA to low-molecular-weight heparin therapy does not lower the miscarriage rate either (RR = 0.62 [0.30; 1.27]; p = 0.19) (6).

An important risk factor for recurrent miscarriage is antiphospholipid syndrome (APLS), which, according to the Sidney criteria, can be associated both with thromboembolic events and with complications of pregnancy (e7). Low-dose ASA is an integral part of the treatment recommendations for APLS in pregnancy (e8-e11). A Cochrane meta-analysis concerned the effects of ASA use by women with persistent antiphospholipid (APL) antibodies and recurrent miscarriages (7). In summary, no robust data are available on the use of ASA alone, compared to either placebo or heparin, in this group. ASA combined with heparin (n = 640) was associated with a higher live birth rate than ASA alone (n = 655) (87.2% vs. 67.5%; RR = 1.27 [1.09; 1.49]; p = 0.002, heterogeneity measure I2 = 48%). The level of evidence for these statements was rated as very low because of the poor quality of the underlying studies. Further meta-analyses led to similar conclusions (e12e14), also among women with recurrent miscarriages (e15). In a number of well-designed trials, the live birth rates of women with a history of recurrent miscarriage (with or without APLS) were unexpectedly high (over 80%) regardless of the intervention (e16-e18).

Pre-eclampsia

The earliest description of a protective effect of ASA against pre-eclampsia dates back to the 1970s (e19, e20). In the first randomized trial (n=92), published in 1985, there were significantly fewer cases of pre-eclampsia (0 vs. 6, p < 0.005) in high-risk patients who took 150 mg of ASA daily from the first trimester onward (8). This finding could only be replicated in a small number of subsequent studies (9, e21), while many studies showed no effect or effects that failed to reach statistical significance (e22-e30) (10). There are three main reasons why it took some thirty years for ASA to become an established drug for the prevention of pre-eclampsia:

- ASA was given in too low a dose,
- ASA was started too late,
- and severe, clinically relevant early-onset pre-eclampsia (i.e., arising before week 34 of gestation) is a rare condition, affecting only 0.3–0.5% of pregnancies. Multiple meta-analyses shed further light on these facts (11, e31-e34)(11, e31–e34) *(Table 2)* and influenced the design of the Aspirin for Evidence-Based Pre-Eclampsia Prevention“ (ASPRE) trial (12, 13) . In this internationally conducted, placebo-controlled trial (n = 1776), the subjects were given 150 mg of ASA daily from the 11th –14th week of gestation onward (13). Before being included in the trial, prospective subjects were screened with a validated algorithm for the prediction of the risk of pre-eclampsia (14); only those with an estimated individual risk of 1% or higher were included in the trial. The primary endpoint was delivery with pre-eclampsia before the 37th week of gestation (early pre-eclampsia), an event that occurred in 0.7% of the screened study population (180/25 797) (15). The screening algorithm detected 77% of early cases of pre-eclampsia with a false-positive rate of 10%, making it clearly superior to the history alone *(Table 3)* (15–17).

Even though the rate of occurrence of the primary endpoint (pre-eclampsia before the 37th week of gestation) in the placebo group was lower, at 4.3% (35/806), than the expected rate of 7.6%, it was lower still in patients taking ASA, and this finding was statistically significant (1.6% [13/798], odds ratio [OR] = 0.38 [0.20; 0.74]; p = 0.004) (12). While there was a marked effect in the frequency of pre-eclampsia with delivery before the 34th week of gestation (1.8% vs. 0.4%; OR = 0.18 [0.03; 1.03]), no statistically significant differences were found from the 37th week of gestation onward (7.2% vs. 6.6%; OR = 0.95 [0.57; 1.57]). The latter finding probably reflects an ASA-induced shift in the timing of pre-eclampsia toward later times, rather than a lack of protective effect of ASA against late pre-eclampsia. When the presumed shifted cases are removed from the analysis, the estimated relative reduction in pre-eclampsia at term is 40% (18). The estimated shift toward later times of onset of pre-eclampsia is greatest, 4.4 weeks [1.4; 7.1], in the 24th week of gestation, decreases by 0.23 weeks [0.02; 0.40] for each subsequent week, and is 0.8 weeks [-0.03; 1.7] 40 SSW (18).

Pre-eclampsia and ASA use

ASA lowers the risk of pre-eclampsia with delivery before the 37th week of gestation by more than half.

Dose-response relationship

The preventive effect displays a clear dose-response relationship. In high-risk pregnancies, the administration of 150 mg ASA per day beginning before the 16th week of gestation is recommended.

TABLE 2

The effect of acetylsalicylic acid on the risk of pre-eclampsia, fetal growth restriction, and preterm birth

Endpoint	Inclusion criteria / reference	Design	N	Frequency of endpoint, ASA vs. placebo	Effect: (RR or OR) / 95% CI / p-value	Remarks
Pre-eclampsia < 37th WoG	high-risk patients, pre-eclampsia risk ≥ 1:100 (12)	RCT, 150 mg vs. placebo, start between 11th-14th WoG	1776	1.6 % vs. 4.3 %	OR 0.38; [0.20; 0.74]; p = 0.004	
Pre-eclampsia < 34th WoG	high-risk patients, pre-eclampsia risk ≥ 1:100 (12)	RCT, 150 mg vs. placebo, start between 11th-14th WoG	1777	0.4 % vs. 1.8 %	OR 0.18; 99% CI [0.03; 1.03]; no p-value	
Pre-eclampsia	preeclampsia risk (19)	meta-analysis of RCTs, ASA vs. placebo	36 716	9.3 % vs. 7.7 %	RR 0.82; [0.77; 0.88]; p = < 0.0001	I^2 = 18.47%, NNT 61
	chronic hypertension (23)	meta-analysis of RCTs, ASA vs. placebo			OR 0.83; [0.55; 1.25]; no p-value	
	high- and low-risk studies (26)	meta-analysis of RCTs, ASA vs. placebo	14 093	9.3 % vs. 11.3 %	RR 0.85; [0.75; 0.95]; p = 0.01	I^2 = 0%, NNT 50*
	chronic hypertension (19)	meta-analysis of RCTs, ASA vs. placebo	1813	15.2 % vs. 20.4 %	RR 0.67; [0.47; 0.95]; p = 0.03	I^2 = 44.77%
	multiple pregnancy (20)	RCT, 60 mg vs. placebo, subgroup analysis	225	6 % vs. 16 %	OR 0.32; [0.12; 0.82]; p = 0.014	
	multiple pregnancy (21)	meta-analysis of RCTs, ASA vs. placebo	898	10.9 % vs. 16.4 %	RR 0.67; [0.48; 0.94]; p = 0.02	I^2 = 0%
SGA	high-risk patients, preeclampsia risk ≥ 1:100 (24)	RCT, 150 mg vs. placebo, start between 11th-14th WoG	1776	0.8 % vs. 2.9 %	RR 0.27; [0.11; 0.64]; p = 0.0035	
	preeclampsia risk (11)	meta-analysis of RCTs, ASA vs. placebo	2939	not reported	RR 0.56; [0.44; 0.70]; no p-value	dose-dependent effect when ASA is started before the 16th WoG
	preeclampsia risk (19)	meta-analysis of RCTs, ASA vs. placebo	35 761	4.1 % vs. 4.8 %	RR 0.84; [0.76; 0.92]; p = < 0.001	I^2 = 10.15 %
	high- and low-risk studies (26)	meta-analysis of RCTs, ASA vs. placebo	14 385	9.1 % vs. 10.4 %	RR 0.82; [0.68; 0.99]; p = 0.04	I^2 = 41.24%, NNT 77*
Preterm birth (all)	pre-eclampsia risk (19)	meta-analysis of RCTs, ASA vs. placebo	35 212	16.0 % vs. 17.6 %	RR 0.91; [0.87; 0.95]; p = < 0.0001	I^2 = 28.52%, NNT 61
	high- and low-risk studies (26)	meta-analysis of RCTs, ASA vs. placebo	13 619	19.7 % vs. 22.4 %	RR 0.80; [0.67; 0.95]; p = 0.02	I^2 = 48.7 %, NNT 37*
	prior spontaneous preterm birth (30)	RCT, 80 mg ASA vs. placebo, start between 8th and 16th WoG	406	21.2 % vs. 25.4 %	RR 0.83; [0.58; 1.20]; p = 0.32	underpowered study
Preterm birth < 34th WoG (all)	low-risk, nulliparity (27)	meta-analysis of RCTs, ASA vs. placebo	14 731	2.9 % vs. 4.0 %	RR 0.50; [0.26; 0.96]; p = 0.04	I^2 = 68%
Spontaneous preterm birth < 34th WoG	low-risk, nulliparity (28)	RCT, 60 mg ASA, start between 13th and 25th WoG	2543	not reported	RR 0.46; [0.23; 0.89]; p = 0.01	
	low-risk, nulliparity (29)	RCT, 81mg vs. placebo, start between 6th and 13th WoG	11 754	3.3 % vs. 4.0 %	RR 0.75; [0.61; 0.93]; p = 0.039	
Spontaneous preterm birth < 37th WoG	low-risk, nulliparity (29)	RCT, 81 mg vs. placebo, start between 6thand 13th WoG	11 754	11.6 % vs. 13.1 %	RR 0.89; [0.81; 0.98]; p = 0.012	NNT 67*
	previous spontaneous delivery (31)	registry-based cohort study, ASA low-dose vs. nothing	22 127	5.5 % vs. 12.9 %	RR 0.70; [0.57; 0.86]; no p-value	3057 women taking aspirin; RR adjusted according to risk factors

* Estimates of the number needed to treat (NNT) and number needed to harm (NNH) are based on the indicated absolute risk differences.
ASA: acetylsalicylic acid; CI: confidence interval; I^2: measure of heterogeneity; LMH: low-molecular-weight heparin; N: number of study participants; OR: odds ratio;
RCT: randomized, controlled trial; RR: relative risk; SGA: small for gestational age; WoG: week(s) of gestation

In a recent Cochrane meta-analysis of 77 randomized trials that included a total of 36 716 women at increased risk of pre-eclampsia, it was concluded that ASA lowers the overall risk of pre-eclampsia among all study participants from 9.3% to 7.7% (RR = 0.82 [0.77; 0.88]; p < 0.0001) (19).

The quality of the evidence supporting this conclusion was rated as high. ASA also lowered the frequency of preterm birth (16.0% vs. 17.6%, RR = 0.91 [0.87; 0.95]) and perinatal death (2.9% vs. 3.4%, RR = 0.85 [0.76; 0.95]). These effects occurred when ASA treatment was started before the 20th week of gestation at a dose above 75 mg/day. ASA also appears to reduce the risk of pre-eclampsia in twin pregnancies (20, 21). Dose-related effects (50–150 mg daily) on the prevention of pre-eclampsia, severe pre-eclampsia, and fetal growth restriction were estimated in a meta-analysis of 45 randomized trials with a total of 20 909 patients (11). It was found that ASA treatment initiated up to the 16th week of gestation lowered the frequency of these three endpoints in a dose-dependent manner, while starting ASA after the 16th week had little or no effect. The dose-response relation was confirmed in further studies (e35, e36).

There is other evidence in favor of a secondary protective effect of ASA against pre-eclampsia in women with chronic arterial hypertension (9, 19), but no such effect was found in a subgroup analysis of the ASPRE study (110 patients) (22). A meta-analysis specifically concerning this question revealed no more than a trend toward a reduction of the frequency of pre-eclampsia in chronically hypertensive women (OR = 0.83 [0.55; 1.25]) (23). Pregravid hypertension can thus be considered a risk factor for the development of pre-eclampsia that is not preventable with ASA, and the severity of the hypertension seems to play an important role (e37, e38). The published study findings suggest that ASA use may, in fact, lower the risk of pre-eclampsia in women with grade 1 chronic hypertension (130–139/80–89 mmHg) to that of normotensive women, but that the preventive effect diminishes at higher blood pressures because of irreversible vascular changes (e38-e41).

Chronic placental insufficiency and fetal growth restriction

More than 80% of mothers with early-onset pre-eclampsia are carrying growth-restricted fetuses (e42, e43), and 40% of mothers of hypotrophic preterm infants (i.e., infants delivered before the 32nd week of gestation with a birth weight below the 10th percentile) have accompanying pre-eclampsia (24). Maternal endothelial dysfunction may be a pathophysiologic factor that underlies both of these entities and thereby accounts for their association (e44). In the ASPRE trial, the rate of hypotrophic neonates born before 32nd week of gestation was significantly lower with 150 mg ASA than in the placebo group (0.8% vs. 2.9%; RR = 0.27 [0.11; 0.64], p = 0.0035) (24). This effect was particularly pronounced in the presence of concomitant pre-eclampsia (0.1% vs. 1.1%, RR = 0.11 [0.02; 0.70], p = 0.0295) but was also seen in its absence (0.6% vs. 1.7%, RR = 0.37 [0.14; 0.97], p = 0.0741). A meta-analysis of 17 randomized trials with a total of 2939 patients, taking the heterogeneous design of these trials into account, revealed a slightly smaller preventive effect of ASA against fetal growth restriction; no distinction was drawn between patients with and without concomitant pre-eclampsia (RR = 0.56 [0.44; 0.70], p < 0.001) (11). The best effect was achieved when ASA was started before the 16th week of gestation and given at a dose of 150 mg/d up to the 36th week (25, e36).

Preterm birth

Low-dose ASA has been shown to reduce the complications of pre-eclampsia (19, 26). This includes preterm delivery (19.7% vs. 22.4%; RR = 0.80 [0.67; 0.95]; p = 0.02), which usually occurs because of medical indications involving maternal or fetal risk (26). Yet a meta-analysis including a low-risk cohort revealed a protective effect of ASA against birth before the 34th week of gestation that was independent of pre-eclampsia (2.9% vs. 4.0%; RR = 0.50 [0.26; 0.96]; p = 0.04) (27). Further secondary analyses of randomized trials indicated that low-dose ASA may lessen the rate of spontaneous preterm birth (28, e45, e46). In a multicenter trial (2543 patients) of the effect of ASA at a dose of 60 mg/d on the rate of pre-eclampsia in healthy primiparous women, ASA was found to lessen the rate of spontaneous preterm birth before the 34th week of gestation by more than half (1.0% vs. 2.3%; RR = 0.46 [0.23; 0.89]; p = 0.01) (28, e47).

The Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas (ASPIRIN) trial, a randomized, double-blinded, placebo-controlled multicenter trial (e48), points in the same direction. After gestational age was determined by ultrasound, 11 976 otherwise healthy first-time mothers of gestational age (GA) 6 0/7 to 36 6/7 weeks were included in the trial (29). Women in the intervention group were given 81 mg of ASA per day until GA 36 6/7 or

Reduced risk of fetal growth restriction

ASA lowers the risk of fetal growth restriction, particularly in the setting of hypertension during pregnancy.

Evidence for prevention of spontaneous preterm births

There is mounting evidence that ASA can lessen the frequency of spontaneous preterm birth.

TABLE 3

Test characteristics of various first-trimester screening methods for predicting pre-eclampsia in the course of pregnancy

Screening method	N	Rate of pre-eclampsia	Detection rate [95% CI]	False positive rate [95% CI]
History (USPSTF*[1])	4 524	4.89%	14.0% [10.1; 19.2]	4.2% [3.6; 4.8]
History (NICE*[2])	4 524	4.89%	13.1% [9.3; 18;2]	4.0% [3.5; 4.7]

Screening method	N	Rate of pre-eclampsia	Detection rate [95% CI]	Positive screening rate
History (NICE*[2])	16 747	2.8%	30.4% [26.3; 34.6]	10.3%
Combined screening (FMF) with history, mean arterial blood pressure, PAPP-A	16 747	2.8%	42.5% [38.0; 46.9]	10.0% (fixed)

Screening method	N	Pre-eclampsia rate < 37th WoG	Detection rate [95% CI]	Positive screening rate
History (NICE*[2])	16 747	0.8%	40.8% [32.8; 48.9]	10.0% (fixed)
Combined screening (FMF) with history, mean arterial blood pressure, PAPP-A PAPP-A PAPP-A	16 747	0.8%	53.5% [45.3; 61.7]	10.0% (fixed)
Combined screening (FMF) with history, mean arterial blood pressure, PLGF	16 747	0.8%	69.0% [61.4; 76.6]	10.0% (fixed)
Combined screening (FMF) with history, mean arterial blood pressure, mean uterine artery pulsatility index	16 747	0.8%	73.9% [65.9; 80.9]	10.0% (fixed)
Combined screening (FMF) with history, mean arterial blood pressure, mean uterine artery pulsatility index, PLGF	16 747	0.8%	82.4% [76.1; 88.7]	10.0% (fixed)

Aa.: arteries; FMF: Fetal Medicine Foundation; PAPP-A: pregnancy-associated plasma protein A; PLGF: placental growth factor; NICE: National Institute for Health and Care Excellence; USPSTF: United States Preventive Services Task Force

References: (16, e84)

*[1] US Preventive Services Task Force: high risk is present with at least one high-risk factor (previous pre-eclampsia, multiple pregnancy, chronic hypertension, type 1/2 diabetes mellitus, chronic kidney disease) or at least 2 moderate-risk factors (primigravidity, age ≥ 35 years, previous SGA situation or perinatal death

*[2] National Institute for Health and Care Excellence: high risk is present with at least one high-risk factor (previous hypertension in pregnancy, chronic hypertension, diabetes mellitus type 1/2, chronic kidney disease) or at least 2 moderate-risk factors (primigravidity, age ≥ 40 years, multiple pregnancy)

delivery. The primary endpoint, the rate of preterm birth before GA 37 weeks, was decreased by ASA (11.6% vs. 13.1%; RR = 0.89 [0.81; 0.98], p = 0.012). Decreases were also seen in perinatal mortality (45.7 ‰ vs. 53.6 ‰, RR = 0.86 [0.74; 1.00], p = 0.048), early preterm birth before the 34th week of gestation (3.3% vs. 4.0%; RR = 0.75 [0.61; 0.93], p = 0.039), and hypertensive pregnancy disorders or pre-eclampsia with delivery before the 34th week of gestation (0.1% vs. 0.4%; RR = 0.38 [0.17; 0.85], p = 0.015) (29). Although no distinction was drawn between spontaneous and iatrogenic preterm birth, one may assume it was mainly the rate of spontaneous preterm birth that was lowered (29). This trial was carried out in six developing countries and the rate of perinatal mortality, approximately 5%, was markedly higher than that in Germany (29).

In the Aspirin for the Prevention of Recurrent Spontaneous Preterm Labor (APRIL) trial, carried out in the Netherlands, 406 women with spontaneous preterm labor in a prior pregnancy were randomized to receive either 80 mg of ASA daily or placebo (30), starting in the 8th to 16th week of gestation and ending in the 36th week. Preterm delivery occurred in 41 (21.2%) women receiving ASA and 49 (25.4%) receiving placebo (RR = 0.83 [0.58; 1;20], p = 0.32). Adherence was over 80%. 24 women on ASA (19.2%) and 30 on placebo (24.8%) had a preterm birth (RR = 0.77 [0.48; 1.25], p = 0.29). The combined neonatal morbidity was 4.6% (n = 9) in the ASA arm and 2.6% (n = 5) in the placebo arm (RR 1.79 [0.61; 5.25], p = 0.29) (30). This trial was, unfortunately, underpowered because of an overestimation of the preterm birth rate in the case-fatality calculation (e49). In a Swedish registry-based cohort study of

Reduced perinatal mortality

ASA lowers perinatal mortality independently of pre-eclampsia and prematurity.

No increased rate of serious adverse events

Serious adverse events such as premature placental abruption or massive bleeding are not any more frequent under treatment with ASA.

women with a prior preterm birth (n = 22 127), low-dose ASA was associated with a lower risk of spontaneous preterm birth (5.5% vs. 12.9%; adjusted RR = 0.70 [0.57; 0.86]) (31).

Perinatal mortality, premature placental abruption, and bleeding risk

A meta-analysis of 40 randomized trials (n = 34 807) found that prophylactically administered ASA lowered perinatal mortality independently of pre-eclampsia and preterm delivery (9.9 ‰ vs. 23.9 ‰; RR = 0.47 [0.25; 0.88]; p = 0.02) (32). The effect was seen only when ASA was begun no later than the 16th week of gestation and given at a dose of at least 100 mg/day. There was no association between ASA use and premature placental abruption (2.0 vs. 2.8%; RR = 0.68 [0.40; 1.15]; p = 0.15). Another meta-analysis of studies on women at low obstetric risk (10 studies, 23 162 patients) likewise showed no effect of ASA at a dose of 100 mg/d or less on the risk of antepartum or postpartum hemorrhage (RR = 1.06 [0.66; 1.70]; p = 0.81 and RR = 1.24 [0.90; 1.71]; p = 0.19, respectively) (27). Nor was there any increased risk of antepartum hemorrhage or premature placental abruption for ASA doses of 100 mg or above, regardless of whether ASA was started in or before the 16th week of gestation (1.0% vs. 1.9%; RR = 0.62 [0.31; 1.26]; p = 0.19; I2 = 0%) or at a later time (3.6% vs. 1.7%; RR = 2.08 [0.86; 5.06]; p = 0.11; I2 = 0%) (33).

Fetal and neonatal safety

Large-scale cohort and case-control studies of ASA in pregnancy have not revealed any link to an increased risk of congenital anomalies (34, 35). Nor is the cardiac function of fetuses and neonates harmed by prenatal exposure to low-dose ASA (e50). In large randomized trials, the frequencies of fetal and neonatal adverse drug events did not differ (10, 12). One review summarized animal studies documenting a role of cyclooxygenase (COX)-2/prostaglandin E_2 in both pre- and postnatal neuronal development (e51). The clinical relevance of these data was debated, because COX-2-deficient rodents were used as animal models, while ASA has a COX-unselective effect that is dose-dependent and possibly also tissue-dependent (e52).

The pharmacodynamics and pharmacokinetics of ASA in pregnancy

ASA inhibits COX isoforms by irreversible acetylation. Its analgesic, antipyretic, and anti-inflammatory effects are mediated by the reduced formation of COX-2-dependent prostaglandins, and its antiplatelet effect by the reduced formation of COX-1-dependent thromboxanes (e53, e54). Low-dose ASA (100–300 mg/d) suffices to obtain the clinical effect of inhibiting COX-1, but not COX-2. COX-independent mechanisms may also play a role in the obstetrically relevant preventive effects of ASA (36, 37) (e55).

The postulated mechanisms of pre-eclampsia prevention by ASA are based primarily on in vitro studies and presumably work by improving placentation (38, 39). The functional systems modulated by ASA involve cytokine release as well as anti-apoptotic and vasoprotective mechanisms (e56-e58). The thromboxane/prostacyclin ratio, which is altered in pre-eclampsia, can be normalized by ASA-induced inhibition of thromboxane synthesis (e59, e60). Dysregulation of angiogenic growth factors also plays a role in the pathogenesis of pre-eclampsia and can be positively influenced by ASA (e61-e65). No effect of ASA on the trophoblast-induced transformation of spiral arteries was demonstrated in the relevant studies (e27, e66-e68). In a chronotherapy study, the preventive effects of ASA were found to be strongest when the drug was taken in the evening (e69).

The onset of birth was found to be delayed in COX-1-deficient mice (e70), suggesting a mechanism by which ASA can prevent preterm birth (e70). In a murine model of preterm birth with an inflammatory trigger, the pharmacological inhibition of COX-1 prolonged gestation (e70, e71).

Studies on the pharmacokinetics of ASA in the form of its major metabolite, salicylic acid, have shown that, in pregnant (compared to non-pregnant) women, both the area under the curve (AUC) and the maximum plasma concentration are approximately one-third lower, with accompanying increased clearance (e72). 150 mg/d of ASA in pregnant women yielded AUC values near those of non-pregnant women taking 100 mg/d of ASA. An enteric-coated formulation was absorbed with a delay in comparison with non-enteric-coated ASA, with a peak plasma concentration that was 47% lower ($p < 0.01$).

Pre-eclampsia that arises despite ASA prophylaxis may be due to so-called aspirin resistance of various possible causes, including pharmacokinetics (e73). In a cohort study, 28.7% of 87 pregnant women taking 81 mg/d of enteric-coated ASA were non-responders with respect to inhibition of platelet aggregation (e74). Non-response was more common with advancing gestational age. In most cases, adequate platelet inhibition was achievable at a higher dose (162 mg/d).

Unclear mechanisms

It is unclear how ASA lowers these risks.

Altered pharmacokinetics

The pharmacokinetics of ASA are different in pregnancy, with increased clearance and a lower plasma concentration of metabolites.

In a pre-eclampsia prevention study with 496 participants, median serum thromboxane B2 levels in women between the 24th and 28th weeks of gestation taking 60 mg/d of ASA were higher in obese women than in women of normal weight (1.0 ng/mL vs. 0.21 ng/mL; p = 0.03), and undetectable thromboxane levels were less common in grade III obese women than in women of normal weight (20% vs. 46%; adjusted OR = 0.33 [0.15; 0.72]) (e75).

A common cause of aspirin resistance is inadequate adherence, with a reported non-adherence rate of 46.3% in pregnant women at high risk of pre-eclampsia (e76). In the ASPRE trial, ASA significantly lowered the risk of pre-eclampsia when the adherence was 90% or higher (0.9% vs. 3.7%; OR = 0.24 [0.09; 0.65]) but did not do so when it was under 90% (3.3% vs. 5.6%; OR = 0.59 [0.23; 1.53]) (e77). The importance of adherence in preventing pre-eclampsia was confirmed by measurements of platelet aggregation and ASA metabolites (e78).

There is no consensus on the optimal prophylactic ASA dose in women who are at increased risk of pre-eclampsia. The findings of a meta-analysis suggest that there is a dose-response effect up to a dose of 150 mg/d (e79). This dose is recommended in the German guideline (40).

Overview

A large body of evidence now suggests that ASA can prevent a number of pregnancy-related conditions. In the at-risk population, it can be considered certain that the early administration in ASA in an appropriate dose lowers the risk of pre-eclampsia and its associated morbidity. Extensive patient education is required to ensure adherence, which is essential for the therapeutic effect. There is also evidence that ASA may improve pregnancy outcomes after prior spontaneous abortion and reduce the risk of fetal growth restriction and spontaneous preterm birth. If future studies confirm these findings, more pregnant women will be given ASA prophylactically. The German guideline contains a recommendation for ASA prophylaxis in all pregnant women with a pre-gravid BMI ≥ 35 kg/m2, which goes far beyond the usual indications *(Tables 1 and 2)* in the absence of other risk factors (e80). A general recommendation for prophylactic ASA in all pregnant women is under consideration in the English-speaking countries, not least because of cost-benefit analyses (e81, e82). Given the current state of the evidence, however, ASA should only be given prophylactically in pregnancy after an analysis of the risks facing the individual patient.

Aspirin resistance

A common cause of aspirin resistance is inadequate adherence, with a reported non-adherence rate of 46.3% in pregnant women at high risk of pre-eclampsia

Conflict of interest statement
The authors state that they have no conflict of interest.

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▶ **Supplementary material**

eReferences:
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- Participation in the CME certification program is possible only via the Internet: cme.aerzteblatt.de. The submission deadline is 14 September 2024. Submissions by letter, email, or fax cannot be considered.
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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the percentage of spontaneous abortion in ultrasonographically monitored pregnancies?

a)0%; b)5%; c)15%; d)20% ; e)30%

Question 2

In a 36-year-old primigravida at 13 weeks of gestation, first-trimester screening revealed an estimated pre-eclampsia risk of 1:71. For which of the following putative measures to prevent pre-eclampsia is the evidence strongest?

a) ASA, 50 mg/d, starting before the 16th week of gestation
b) ASA, 50 mg/d, starting after the 20th week of gestation
c) ASA, 150 mg/d, starting before the 20th week of gestation
d) ASA, 150 mg/d, starting after the 20th week of gestation
e) ASA, 150 mg/d, and folic acid, 80 mg/d, starting after the 20th week of gestation

Question 3

A 25-year-old woman needed premature delivery of her infant two years ago because of early-onset pre-eclampsia at 31 weeks of gestation. You recommend that she should take low-dose ASA if she becomes pregnant again. She is unsure whether she should follow this recommendation and asks you about the risks. Which answer is correct?

a) A slightly higher rate of bleeding complications cannot be ruled out, but the potential benefits clearly outweigh the risks.
b) The risk of causing neurodevelopmental delay is minimal because of the infant's gestational age when ASA is started.
c) Because of the increased risk of premature placental abruption due to ASA use, ASA should be stopped at 32 weeks of gestation.
d) There is no evidence of ASA-related fetal or maternal adverse effects at the low dosage used.
e) The lower risk of fetal growth restriction outweighs the higher risk of prenatal death.

Question 4

Which of the following statements about the preventive effect of ASA is false, according to a meta-analysis involving over 34 000 patients?

a) Perinatal mortality was reduced independently of pre-eclampsia and preterm birth.
b) ASA administration should start at or before 16 weeks of gestation.
c) The ASA dose was at least 100 mg/day.
d) Perinatal mortality was reduced by a factor of 3 with 300 mg/day of ASA.
e) There was no association between ASA intake and premature placental abruption.

Question 5

Which statement about the pharmacodynamics of ASA for the prevention of pregnancy-related diseases is correct?

a) The preventive effects are mainly due to an anti-inflammatory effect.
b) Effective inhibition of platelet function requires a daily dose of more than 300 mg.
c) Taking ASA in the evening is more effective than taking it in the morning.
d) ASA stimulates spiral artery transformation and thereby lowers the risk of pre-eclampsia.
e) Pre-eclampsia despite prophylactic ASA can only happen if thromboxane synthesis has not been completely inhibited.

Question 6

Which of the following is an important feature of the pharmacokinetics of ASA during pregnancy?

a) The maximum plasma concentration of ASA is about one-third lower in pregnant women than in non-pregnant women.
b) The clearance of ASA is the same in pregnant and non-pregnant women.
c) Enteric-coated ASA is absorbed more rapidly than non-enteric-coated ASA.
d) The dose-dependent inhibition of platelet function is independent of the body weight of the pregnant woman.
e) The dose-dependent inhibition of platelet function is stronger with increasing gestational age.

Question 7

Which of the following can cause so-called aspirin resistance?

a) the use of a generic drug
b) constipation during pregnancy
c) combining ASA with vitamin D
d) less than 90% adherence
e) a body-mass index under 20 kg/m^2

Question 8

Obesity is an important risk factor for pre-eclampsia. From which pregravid body mass index does the German-language guideline recommend the prophylactic administration of ASA?

a) 28 kg/m^2; b) 30 kg/m^2; c) 32 kg/m^2; d) 35 kg/m^2; e) 40 kg/m^2

Question 9

What is the effect of 75 mg/d of ASA in pregnant women who have had recurrent miscarriages with no identifiable cause?

a) doubles the live birth rate
b) does not alter the live birth rate or the miscarriage rate
c) increases the miscarriage rate
d) decreases the miscarriage rate
e) lowers the live birth rate

Question 10

According to the findings of the recent ASPIRIN trial, how many women need to be treated with ASA to prevent one preterm delivery before the gestational age of 37 weeks?

a) 27; b) 47; c) 67; d) 87; e) 107

► **Participation is only possible online: cme.aerzteblatt.de**

Supplementary material to:

The Role of Acetylsalicylic Acid in the Prevention of Pre-Eclampsia, Fetal Growth Restriction, and Preterm Birth

by Johannes Stubert, Burkhard Hinz, and Richard Berger

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