Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
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Results section 8.4

Acetylsalicylic acid (ASA) versus placebo

From the HTA-report:
Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies

Ljungström E, Möller AC, Bergman L, Ekelund A-C, Hongslo Vala C, Jacobsson B, Kuusela P, Liljegren A, Petzold M, Sjögren P, Svensson M, Wennerholm U-B, Strandell A

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Abbreviations/Acronyms

17-OHPC 17-alpha-hydroxyprogesterone caproate
ART assisted reproductive technology
ASA acetylsalicylic acid
ASQ ages and stages questionnaire
BPD bronchopulmonary dysplasia
CDI child developmental inventory
CI confidence interval
CL cervical length
cm centimetre
d days
g gram
GDM gestational diabetes mellitus
HDP hypertensive disorders in pregnancy
HTA health technology assessment
ICP intrahepatic cholestasis in pregnancy
ICTRP International Clinical Trials Registry Platform
im intramuscular injection
IVF in vitro fertilization
IVH intraventricular haemorrhage
IQR interquartile range
LY life year
MD mean difference
mg milligram
mm millimetre
NEC necrotizing enterocolitis
NICU neonatal intensive care unit
PPROM preterm prelabour rupture of membranes
PROSPERO the international prospective register of systematic reviews
PTB preterm birth
RCT randomised controlled trial
RD risk difference
RDS respiratory distress syndrome
ROP retinopathy of prematurity
RR relative risk/risk ratio
SBU assessment of social service
SD standard deviation
SEK Swedish krona
SoF summary of findings
sPTB spontaneous preterm birth
SR systematic review
TVS transvaginal sonography
UK United Kingdom
US United States
VGR Region Västra Götaland
WHO World Health Organization

Results in singleton pregnancies

Included studies

One RCT with low risk of bias was included (Landman *et al.*, 2022) (Appendix 2).

Population

The trial included 387 women with a singleton pregnancy and a history of previous spontaneous preterm birth of a singleton between 22 and 37 gestational weeks.

Setting

The trial was conducted in 34 centres in the Netherlands.

Intervention

The intervention was a daily oral intake of 80 mg ASA or a matched placebo, starting between 8 and 16 gestational weeks. Good medication adherence was defined as tablet intake ≥80%. Medication adherence was calculated by dividing the number of used tablets by the expected number of doses per participant. Good adherence was reported by 63.3% of participants. Other interventions for preventing preterm birth, such as progesterone, cerclage, or pessary, could be used alongside the studied intervention if deemed appropriate by the physician.

Directness, study limitations, and precision

The trial had minor problems with directness because the number of eligible women approached to participate was not presented due to national regulations. There was no major study limitation, although there were some baseline differences. A greater proportion of participants in the intervention group had previously undergone cervical or uterine surgery, had a higher rate of previous second-trimester fetal loss, and a positive family history of preterm birth compared with the placebo group.

The precision of the trial was affected by a lower rate of preterm birth than assumed in the sample size calculation, thus underpowering the study. Typically, the certainty of evidence was downgraded two levels due to serious imprecision.

Results per outcome

Preterm birth in singletons across gestational weeks

Any preterm birth <37 weeks (Appendix 4.4.1.a)

The outcome occurred in 21.2% in the ASA group vs. 25.4% in the placebo group, resulting in RR 0.83 (95% CI 0.58 to 1.20) and RD -4.25 (95% CI -12.7 to 4.2). In a prespecified subgroup analysis including only women with good medication adherence (≥80%), (n=246), the rate of preterm birth <37 gestational weeks was lower in the ASA group (19.2%) but remained similar in the placebo group (24.8%), resulting in RR 0.77 (95% CI 0.48 to 1.25).

Conclusion: ASA compared with placebo may result in no difference in the risk of any preterm birth before 37 gestational weeks in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <37 weeks (Appendix 4.4.1.b)

The outcome occurred in 20.1% in the ASA group vs. 23.8% in the placebo group, resulting in RR 0.84 (95% CI 0.58 to 1.23) and RD -3.7 (95% CI -12.0 to 4.5).

Conclusion: ASA compared with placebo may result in no difference in the risk of spontaneous preterm birth before 37 gestational weeks in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Any preterm birth <34 weeks (Appendix 4.4.2.a)
The outcome occurred in 9.3% in the ASA group vs. 8.8% in the placebo group, resulting in RR 1.05 (95% CI 0.56 to 1.98) and RD 0.5 (95% CI -5.2 to 6.2).
Conclusion: ASA compared with placebo may result in no difference in the risk of any preterm birth before 34 gestational weeks in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <34 weeks (Appendix 4.4.2.b)
The outcome occurred in 9.3% in the ASA group vs. 8.3% in the placebo group, resulting in RR 1.12 (95% CI 0.59 to 2.13) and RD 1.0 (95% CI -4.6 to 6.6).
Conclusion: ASA compared with placebo may result in no difference in the risk of spontaneous preterm birth before 34 gestational weeks in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Any preterm birth <28 weeks (Appendix 4.4.3.a)
The outcome occurred in 3.6% in the ASA group vs. 2.6% in the placebo group, resulting in RR 1.39 (95% CI 0.45 to 4.31) and RD 1.0 (95% CI -2.4 to 4.5).
Conclusion: ASA compared with placebo may result in no difference in the risk of any preterm birth before 28 gestational weeks in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <28 weeks (Appendix 4.4.3.b)
The outcome occurred in 3.6% in the ASA group vs. 2.6% in the placebo group, resulting in RR 1.39 (95% CI 0.45 to 4.31) and RD 1.0 (95% CI -2.4 to 4.5).
Conclusion: ASA compared with placebo may result in no difference in the risk of spontaneous preterm birth before 28 gestational weeks in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Gestational length (Appendix 4.4.4)
Median gestational length (Q1; Q2) was 38+1 weeks in both the ASA group (37+1; 39+1) and the placebo group (36+6; 39+2). The certainty of evidence was downgraded one level due to serious imprecision.
Conclusion: ASA compared with placebo probably results in no difference in gestational length in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕⊕◯).

Mortality and morbidity in neonates from singleton pregnancies

Perinatal mortality (Appendix 4.4.5)
The outcome occurred in six (3.1%) cases in the ASA group vs. two (1.0%) cases in the placebo group, resulting in RR 2.99 (95% CI 0.61 to 14.60) and RD 2.1 (95% CI -0.8 to 4.9).
Conclusion: It is uncertain if ASA compared with placebo results in any difference in the risk of perinatal death in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Composite adverse neonatal outcome (Appendix 4.4.6)
The outcome occurred in 4.6% in the ASA group vs. 2.6% in the placebo group, resulting in RR1.79 (95% CI 0.61 to 5.25) and RD 2.0 (95% CI -1.7 to 5.8). The composite adverse outcome included any intrauterine fetal death after 16 weeks of gestation, neonatal death, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotizing enterocolitis, confirmed sepsis, or retinopathy of prematurity.
Conclusion: It is uncertain if ASA compared with placebo results in any difference in the risk of composite adverse neonatal outcome in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Bronchopulmonary dysplasia (BPD) (Appendix 4.4.7)
The outcome occurred in one (0.5%) neonate in the ASA group vs. three (1.6%) neonates in the placebo group, resulting in RR 0.33 (95% CI 0.04 to 3.16) and RD -1.0 (95% CI -3.0 to 1.0).
Conclusion: It is uncertain if ASA compared with placebo results in any difference in BPD in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Intraventricular haemorrhage (IVH) (Appendix 4.4.8)
In the placebo group, the outcome occurred in one neonate in the ASA group vs. none in the placebo group.

Conclusion: It is uncertain if ASA compared with placebo results in any difference in IVH in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Necrotizing enterocolitis (NEC) (Appendix 4.4.9)
The outcome occurred in one neonate in the ASA group vs. none in the placebo group.
Conclusion: It is uncertain if ASA compared with placebo results in any difference in NEC in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Neonatal sepsis (Appendix 4.4.10)
The outcome occurred in four (2.1%) neonates in the ASA group vs. two (1.0%) neonates in the placebo group, resulting in RR 1.99 (95% CI 0.37 to 10.74) and RD 1.0 (95% CI -1.4 to 3.5).
Conclusion: It is uncertain if ASA compared with placebo results in any difference in neonatal sepsis in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Retinopathy of prematurity (ROP) (Appendix 4.4.11)

The outcome occurred in one (0.5%) neonate in the ASA group vs. two (1.0%) neonates in the placebo group, resulting in RR 0.50 (95% CI 0.05 to 5.44) and RD 0.5 (95% CI -2.3 to 1.2).
Conclusion: It is uncertain if ASA compared with placebo results in any difference in ROP in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Admittance to neonatal intensive care unit (Appendix 4.4.12)
The outcome occurred in 6.7% in the ASA group vs. 5.7% in the placebo group, resulting in RR 1.18 (95% CI 0.54 to 2.56) and RD 1.0 (95% CI -3.8 to 5.8). The median days admitted was twelve days in the ASA group vs. seven days in the placebo group.

Conclusion: ASA compared with placebo may result in no difference in admittance to neonatal intensive care unit in neonates from women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Mortality and morbidity in women with singleton pregnancies

Maternal mortality (Appendix 4.4.13)
No deaths were reported in this trial (GRADE ⊕◯◯◯).

Hypertensive disorders in pregnancy (HDP) (Appendix 4.4.14)
Gestational hypertension occurred in 2.1% in the ASA group vs. 2.6% in the placebo group, resulting in RR 0.80 (95% CI 0.22 to 2.92) and RD -0.5 (95% CI -3.5 to 2.5). Preeclampsia occurred in two cases each in the ASA and placebo groups, resulting in RR 1.00 (95% CI 0.14 to 6.99) and RD -0.0 (95% CI -2.0 to 2.0). Eclampsia did not occur in any of the groups.
Conclusion: It is uncertain if ASA compared with placebo results in any difference in gestational hypertension, preeclampsia, or eclampsia, in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Gestational diabetes mellitus (GDM) (Appendix 4.4.15)
The outcome occurred in 7.7% in the ASA group vs. 7.8% in the placebo group, resulting in RR 1.0 (95% CI 0.50 to 1.98) and RD -0.0 (95% CI -5.4 to 5.3).
Conclusion: ASA compared with placebo may result in no difference in GDM in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Infection (Appendix 4.4.16)
Urinary tract infection (UTI) or genital infection treated with antibiotics occurred in 3.1% in the ASA group vs. 7.8% in the placebo group, resulting in RR 0.40 (95% CI 0.16 to 1.00) and RD -4.7 (95% CI -9.2 to -0.2).
Conclusion: It is uncertain if ASA compared with placebo results in any difference in UTI or genital infections in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Bleeding (Appendix 4.4.17)
Vaginal bleeding occurred in 4.7% in the ASA group vs. 6.0% in the placebo group, resulting in RR 0.78 (95% CI 0.26 to 2.39) and RD -1.3(95% CI -7.2 to 4.6). Other bleedings (defined as anal bleeding, epistaxis, prolonged wound bleeding, gingival bleeding) occurred in 16.0% in the ASA group vs. 10.4% in the placebo group, resulting in RR 1.54 (95% CI 0.77 to 3.01) and RD 5.7 (95% CI -3.2 to 14.6).
Conclusion: It is uncertain if ASA compared with placebo results in any difference in bleeding in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕◯◯◯).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.4.18)
The outcome occurred in 4.6% in the ASA group vs. 9.3% in the placebo group, resulting in RR 0.50 (95% CI 0.23 to 1.08) and RD -4.7 (95% CI -9.8 to 0.4).
Conclusion: ASA compared with placebo may result in no difference in the risk of PPROM in women with a singleton pregnancy and a history of previous spontaneous preterm birth (GRADE ⊕⊕◯◯).

Project: Prevention of preterm birth
Appendix 4.4.1.a. Intervention acetylsalicylic acid (ASA)
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 41/194 (21.2%) RR 0.83 (95% CI 0.58-1.20) p=0.323 Compliance >80% 24/125 (19.2%) RR 0.77 (95% CI 0.48-1.25) p=0.291	Placebo 49/193 (25.4%) Compliance >80% 30/121 (24.8%)	PO Compliance in the whole randomised cohort 63.3%.	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.1.b. Intervention acetylsalicylic acid (ASA)
Outcome variable: Spontaneous preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 39/194 (20.1%) RR 0.84 (95% CI 0.58-1.23) p=0.376	Placebo 46/193 (23.8%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.2.a. Intervention acetylsalicylic acid (ASA)
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 18/194 (9.3%) RR 1.05 (95% CI 0.56-1.98) p=0.872	Placebo 17/193 (8.8%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.2.b. Intervention acetylsalicylic acid (ASA)
Outcome variable: Spontaneous preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 18/194 (9.3%) RR 1.12 (95% CI 0.59-2.13) p=0.732	Placebo 16/193 (8.3%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.3.a. Intervention acetylsalicylic acid (ASA)
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 7/194 (3.6%) RR 1.39 (95% CI 0.45-4.31) p=0.566	Placebo 5/193 (2.6%)	Not PO	+	+	-

C; control, I; intervention, CI; confidence interval, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.3.b. Intervention acetylsalicylic acid (ASA)
Outcome variable: Spontaneous preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 7/194 (3.6%) RR 1.39 (95% CI 0.45-4.31) p=0.566	Placebo 5/193 (2.6%)	Not PO	+	+	-

C; control, I; intervention, CI; confidence interval, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.4. Intervention acetylsalicylic acid (ASA)
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d Median (Q1; Q2): 38+1 w (37+1; 39+1) (95% CI 37+6 to 38+3) p=0.964	Placebo Median (Q1; Q2): 38+1 (36+6; 39+2) (95% CI 37+6 to 38+4)	Not PO	+	+	?

C; control, CI; confidence interval, IQR; interquartile range, I; intervention, PO; primary outcome, sPTB; spontaneous preterm birth, w; weeks

Project: Prevention of preterm birth
Appendix 4.4.5. Intervention acetylsalicylic acid (ASA)
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d Fetal death 4/194 (2.1%) RR 1.99 (95% CI 0.37-10.74) p=0.685 Neonatal death 2/194 (1.0%) No statistics All mortality 6/194 (3.1%) RR 2.99 (95% CI 0.61-14.60) P=0.284	Placebo Fetal death 2/193 (1.0%) Neonatal death 0/193 (0%) All mortality 2/194 (1.0%)	Not PO. Fetal death is defined as death during pregnancy (≥16 weeks) or during labour. Neonatal death is defined as death occurring in the period after birth until discharge. All mortality is defined as death of a fetus or neonate at any time between a gestational age (≥16 weeks) and discharge.	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.6. Intervention acetylsalicylic acid (ASA)
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 9/194 (4.6%) RR 1.79 (95% CI 0.61-5.25) p=0.288	Placebo 5/193 (2.6%)	Not PO Composite adverse neonatal outcome includes all perinatal deaths recorded during the study period which includes two deaths in gestational week 16 and two deaths in midtrimester 18+6 and 21+4 and extreme premature births 24+2 and 25+2. In the intervention group and one death in midtrimester, 22+5, in the placebo group. Other adverse outcomes included were BPD, IVH, NEC, ROP, sepsis	+	+	-

BPD; bronchopulmonary dysplasia, C; control, CI; confidence interval, I; intervention, IVH; intraventricular haemorrhage, NEC; necrotising enterocolitis, PO; primary outcome, ROP; retinopathy of prematurity, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.7. Intervention acetylsalicylic acid (ASA)
Outcome variable: Bronchopulmonary dysplasia

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 1/194 (0.5%) RR 0.33 (95% CI 0.04-3.16) p=0.372	Placebo 3/193 (1.6%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.8. Intervention acetylsalicylic acid (ASA)
Outcome variable: Intraventricular haemorrhage

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 1/194 (0.5%) No statistics	Placebo 0/193 (0%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.9. Intervention acetylsalicylic acid (ASA)
Outcome variable: Necrotizing enterocolitis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 1/194 (0.5%) No statistics	Placebo 0/193 (0%)	Not PO	+	+	?

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.10. Intervention acetylsalicylic acid (ASA)
Outcome variable: Neonatal sepsis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 4/194 (2.1%) RR 1.99 (95% CI 0.37-10.74) p=0.424	Placebo 2/193 (1.0%)	Not PO Culture proven sepsis. Table S3 in the article states one more case of sepsis in the placebo group, no reason for exclusion is given.	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.11. Intervention acetylsalicylic acid (ASA)
Outcome variable: Retinopathy of prematurity

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 1/194 (0.5%) RR 0.50 (95% CI 0.05-5.44) p=0.623	Placebo 2/193 (1.0%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.12. Intervention acetylsalicylic acid (ASA)
Outcome variable: Admission to neonatal intensive care unit and median days spent at NICU

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 13/194 (6.7%) RR 1.18 (95% CI 0.54-2.56) p=0.683 Median (IQR)days 12 (4-46) (95% CI 2-54) n=13 Median diff. 5 days p=0.560	Placebo 11/193 (5.7%) Median days spent (IQR) 7 (2-58) (95% CI 2-82) n=11	Not PO Days spent at NICU calculated of those neonates with an admission until 3 months corrected age.	+	+	-

C; control, CI; confidence interval, I; intervention, IQR; interquartile range, NICU; neonatal intensive care unit, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.13. Intervention acetylsalicylic acid (ASA)
Outcome variable: Maternal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 0/194 (0%) No statistics	Placebo 0/193 (0%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.14. Intervention acetylsalicylic acid (ASA)
Outcome variable: Maternal morbidity, hypertensive disorders in pregnancy (gestational hypertension, preeclampsia/HELLP syndrome, eclampsia)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d GH 4/194 (2.1%) RR 0.80 (95% CI 0.22-2.92) p=0.751 PE/HELLP 2/194 (1.0%) RR 1.00 (95% CI 0.14-6.99) p=1.00 Eclampsia 0/194 (0%) No statistics	Placebo GH 5/193 (2.6%) PE/HELLP 2/193 (1.0%) Eclampsia 0/193 (0%)	Not PO	+	+	?

C; control, CI; confidence interval, GH; gestational hypertension, HELLP; haemolysis, elevated liver enzymes, low platelets, I; intervention, PE; preeclampsia, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.15. Intervention acetylsalicylic acid (ASA)
Outcome variable: Maternal morbidity, Gestational diabetes

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 15/194 (7.7%) RR 1.00 (95% CI 0.50-1.98) p=0.988	Placebo 15/193 (7.8%)	Not PO	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.16. Intervention acetylsalicylic acid (ASA)
Outcome variable: Maternal morbidity, infections treated with antibiotics (urinary tract infections/genital infections, Bacterial vaginosis)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d UTI/GI 6/194 (3.1%) RR 0.40 (95% CI 0.16-1.00) p=0.051 BV 12/194 (6.2%) RR 0.57 (95% CI 0.29-1.12) p=0.104	Placebo UTI/GI 15/193 (7.8%) BV 21/193 (10.9%)	Not PO	+	+	-

BV; bacterial vaginosis, C; control, CI; confidence interval, GI; genital infection, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth, UTI; urinary tract infection

Project: Prevention of preterm birth
Appendix 4.4.17. Intervention acetylsalicylic acid (ASA)
Outcome variable: Maternal morbidity, bleeding during pregnancy (placental abruption, vaginal bleeding, other bleedings, admission to hospital)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d Placental abruption 0/194 (0%) No statistics	Placebo Placental abruption 2/193 (1.0%)	Not PO Vaginal bleeding and other bleeding are self-reported, thus altering the denominator due to response rates.	+	+	-
			I: 106 C:116	Vaginal bleeding 5/106 (4.7%) RR 0.78 (95% CI 0.26-2.39) p=0.666	Vaginal bleeding 7/116 (6.0%)	Types of other bleeding: anal bleeding, epitaxis, prolonged wound bleeding, gingival bleeding. Admission to hospital due to vaginal bleeding during pregnancy.			
			I: 106 C:115	Other bleedings 17/106 (16.0%) RR 1.54 (95% CI 0.77-3.01) p=0.222	Other bleedings 12/115 (10.4%)	Postpartum haemorrhage not reported			
			I: 194 C: 193	Hospital admission 10/194 (5.2%) RR 1.11 (95% CI 0.46-2.66) p=0.823	Hospital admission 9/193 (4.7%)				

C; control, CI; confidence interval, I; intervention, PO; primary outcome, RR; risk ratio, sPTB; spontaneous preterm birth

Project: Prevention of preterm birth
Appendix 4.4.18. Intervention acetylsalicylic acid (ASA)
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Landman 2022 The Netherlands (34 centres)	Singletons	History of sPTB	I: 194 C: 193	80 mg oral ASA/d 9/194 (4.6%) RR 0.50 (95% CI 0.23-1.08) p=0.077	Placebo 18/193 (9.3%)	Not PO Defined as PPROM <37 weeks of gestation.	+	+	-

C; control, CI; confidence interval, I; intervention, PO; primary outcome, PPROM; preterm prelabour rupture of membranes, RR; risk ratio, sPTB; spontaneous preterm birth