

Accepted Manuscript



Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit

David Wright, Ph.D., Daniel L. Rolnik, M.D., Argyro Syngelaki, Ph.D., Catalina de Paco Matallana, M.D., Mirian Machuca, M.D., Mercedes de Alvarado, M.D., Sofia Mastrodima, M.D., Min Yi Tan, M.D., Siobhan Shearing, R.M., Nicola Persico, M.D., Jacques C. Jani, M.D., Walter Plasencia, M.D., George Papaioannou, M.D., Francisca S. Molina, M.D., Liona C. Poon, M.D., Kypros H. Nicolaides, M.D.

PII: S0002-9378(18)30173-X

DOI: [10.1016/j.ajog.2018.02.014](https://doi.org/10.1016/j.ajog.2018.02.014)

Reference: YMOB 12087

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 2 January 2018

Revised Date: 14 February 2018

Accepted Date: 26 February 2018

Please cite this article as: Wright D, Rolnik DL, Syngelaki A, de Paco Matallana C, Machuca M, de Alvarado M, Mastrodima S, Yi Tan M, Shearing S, Persico N, Jani JC, Plasencia W, Papaioannou G, Molina FS, Poon LC, Nicolaides KH, Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit, *American Journal of Obstetrics and Gynecology* (2018), doi: 10.1016/j.ajog.2018.02.014.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit

David WRIGHT, Ph.D.,¹ Daniel L. ROLNIK, M.D.,² Argyro SYNGELAKI, Ph.D.,² Catalina de PACO MATALLANA, M.D.,³ Mirian MACHUCA, M.D.,^{2,4} Mercedes de ALVARADO, M.D.,^{2,5} Sofia MASTRODIMA, M.D.,^{2,6} Min Yi TAN, M.D.,^{2,7} Siobhan SHEARING, R.M.,⁸ Nicola PERSICO, M.D.,⁹ Jacques C. JANI, M.D.,¹⁰ Walter PLASENCIA, M.D.,¹¹ George PAPAIOANNOU, M.D.,¹² Francisca S. MOLINA, M.D.,¹³ Liona C. POON, M.D.,¹⁴ Kypros H. NICOLAIDES, M.D.²

1. University of Exeter, Exeter, UK.
2. King's College Hospital, London, UK.
3. Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain.
4. Medway Maritime Hospital, Gillingham, UK.
5. Homerton University Hospital, London, UK.
6. North Middlesex University Hospital, London, UK.
7. Lewisham University Hospital, London, UK
8. Southend University Hospital, Essex, UK.
9. Ospedale Maggiore Policlinico, Milan, Italy.
10. University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium.
11. Hospiten Group, Tenerife, Canary Islands, Spain.
12. Attikon University Hospital, Athens, Greece.
13. Hospital Universitario San Cecilio, Granada, Spain.
14. Kings' College, London, UK.

Conflict of interest statement: The authors report no conflict of interest.

Sources of Funding: The study was supported by grants from the Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme - FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852). These bodies had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Correspondence: Professor KH Nicolaidis, Fetal Medicine Research Institute, King's College Hospital, 16-20 Windsor Walk, Denmark Hill, London SE58BB
Telephone: +442032998256; email: kypros@fetalmedicine.com

Trial registration: ISRCTN13633058; <http://www.isrctn.com/ISRCTN13633058>.

Abstract word count: 650, Text word count: 2786

Condensation

Prophylactic use of aspirin in women at high-risk of preeclampsia reduces substantially the length of stay in the neonatal intensive care unit.

Short version of article title

Secondary analysis of ASPRE trial

Implications and Contributions

A. The study was conducted in women at high-risk of preeclampsia to examine the effect of prophylactic use of aspirin during pregnancy on length of stay in the neonatal intensive care unit.

B. Prophylactic use of aspirin reduces the length of stay in neonatal intensive care unit by about 70%, mainly due to a decrease in the rate of births at <32 weeks' gestation because of prevention of early-preeclampsia.

C. In women at high-risk of preeclampsia prophylactic use of aspirin reduces substantially both the risk of preterm-preeclampsia and length of stay in neonatal intensive care unit.

ABSTRACT

Background: Preeclampsia is a major pregnancy complication with adverse short- and long-term implications for both the mother and baby. Screening for preeclampsia at 11-13 weeks' gestation by a combination of maternal demographic characteristics and medical history with measurements of biomarkers can identify about 75% of women that develop preterm-preeclampsia with delivery at <37 weeks' gestation and 90% of those with early-preeclampsia at <32 weeks, at a screen positive rate of 10%. A recent trial (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) has reported that in women identified by first-trimester screening as being at high-risk for preeclampsia, use of aspirin (150 mg/day from the first to the third trimester), compared to placebo, reduced the incidence of preterm-preeclampsia, which was the primary outcome, by 62% (95% confidence interval, 26-80%) and the incidence of early-preeclampsia by 89% (95% confidence interval, 53-97%). The surprising finding of the trial was that despite the reduction in preeclampsia the incidence of admission to the neonatal intensive care unit, which was one of the secondary outcomes, was not significantly affected (odds ratio 0.93, 95% confidence interval, 0.62-1.40).

Objective: To examine the effect of prophylactic use of aspirin during pregnancy in women at high-risk of preeclampsia on length of stay in the neonatal intensive care unit.

Study design: This was a secondary analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention trial to assess evidence of differences

in the effect of aspirin on length of stay in neonatal intensive care. Bootstrapping was used for the comparison of mean length of stay between the aspirin and placebo groups. Logistic-regression was used to assess treatment effects on stay in the neonatal intensive care unit.

Results: In the trial there were 1620 participants and 1571 neonates were liveborn. The total length of stay in neonatal intensive care was substantially longer in the placebo than aspirin group (1696 vs. 531 days). This is a reflection of significantly shorter mean lengths of stay in babies admitted to the neonatal intensive care unit from the aspirin than the placebo group (11.1 vs. 31.4 days; a reduction of 20.3 days (95% confidence interval, 7.0-38.6; $p=0.008$). Neonatal intensive care of babies born at <32 weeks' gestation contributed 1856 (83.3%) of the total of 2227 days in intensive care across both treatment arms. These occurred in 9 (1.2%) of the 777 livebirths in the aspirin group and in 23 (2.9%) of 794 in the placebo group (odds ratio 0.42; 95% confidence interval, 0.19-0.93; $p=0.033$). Overall, in the whole population, including zero lengths of stay for those that were not admitted to the neonatal intensive care unit, the mean length of stay was longer in the placebo than aspirin group (2.06 vs 0.66 days; reduction of 1.4 days (95% confidence interval, 0.45-2.81; $p=0.014$). This corresponds to a reduction in length of stay of 68% (95% confidence interval, 20-86%).

Conclusions: In pregnancies at high-risk of preeclampsia administration of aspirin reduces the length of stay in the neonatal intensive care unit by about 70%. This reduction could essentially be attributed to a decrease in the rate of births at <32 weeks' gestation, mainly because of prevention of early preeclampsia. The

findings have implications for both short- and long-term healthcare costs as well as infant survival and handicap.

Key words: First trimester screening, Aspirin, ASPRE trial, Preeclampsia, Neonatal intensive care, Health economics.

INTRODUCTION

Preeclampsia (PE), which affects 2-3% of pregnancies, is a major cause of death and morbidity for the mother and perinatal death and long-term handicap for the baby.¹⁻¹⁰ Additionally, the condition has important implications on healthcare cost;¹¹ in the USA it was estimated that in 2012 the cost of PE within the first 12 months of delivery was \$2.18 billion and was disproportionately borne by births of low gestational age.¹²

In the last decade extensive research has led to the development of a method of first-trimester screening for PE.¹³⁻¹⁶ A combination of maternal demographic characteristics and medical history with measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI) and serum placental growth factor (PLGF) at 11-13 weeks' gestation can identify about 75% of women that develop preterm-PE with delivery at <37 weeks' gestation and 90% of those with early-PE with delivery at <32 weeks, at a screen positive rate of 10%.¹⁶ Several randomized studies investigated the possibility of preventing PE by the prophylactic use of aspirin and reported contradictory results.¹⁷⁻²⁰ Recent meta-analyses reported that aspirin reduces the risk of PE by >60%, provided the daily dose of the drug is ≥ 100 mg, the gestational age at onset of therapy is <16 weeks and the outcome measure is preterm-PE rather than total PE.¹⁹⁻²⁰ A recent multicentre double-blind trial, Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPREE trial) has reported

that in women with singleton pregnancies identified by the first-trimester combined test as being at high-risk for PE, aspirin (150 mg/day) vs. placebo from 11 to 14 until 36 weeks' gestation was associated with a 62% reduction in the incidence of preterm-PE, which was the primary outcome (odds ratio 0.38; 95% confidence limits [CI], 0.20-0.74), and 89% reduction in early-PE (odds ratio 0.11, 95% CI 0.03-0.47).²¹ The surprising finding of the ASPRE trial was that despite the reduction in preterm-PE and early-PE the incidence of admission to the neonatal intensive care unit (NICU), which was one of the secondary outcomes, was not significantly affected (odds ratio 0.93; 95% CI, 0.62-1.40).

The objective of this study, which is a secondary analysis of data from the ASPRE trial, is first, to examine the effect of aspirin on length of stay in NICU and evaluate the potential impact on health care cost of screening for PE and treatment of the high-risk group by aspirin.

METHODS

Study design and population

The ASPRE trial was conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel.²¹ In the 13 participating hospitals routine screening for preterm-PE was carried out at 11-13 weeks' gestation by an algorithm combining maternal demographic characteristics and medical and

obstetrical history,¹⁵ and the measurements of MAP,²² UTPI²³ and serum pregnancy associated plasma protein-A and PLGF (PAPP-A and PIGF 1-2-3™ kits, DELFIA® Xpress random access platform; PerkinElmer Inc. Wallac Oy, P.O.Box 10, 20101 Turku, Finland).

The eligibility criteria for the trial were maternal age ≥ 18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus with no major abnormality demonstrated on the 11-13 weeks scan and estimated risk for preterm-PE of >1 in 100.²¹ Eligible women were randomly assigned, in a 1:1 ratio, with the use of a web-based system to receive either aspirin or placebo and in the random-sequence generation there was stratification according to participating center. After randomization, study participants were prescribed the investigational medicinal product, received instructions to take one tablet every night throughout the study and to stop taking tablets at 36 weeks' gestation or in the event of early delivery, at the onset of labor.

The primary outcome measure was delivery with PE at <37 weeks' gestation. Preeclampsia was defined as per the International Society for the Study of Hypertension in Pregnancy.²⁴ Secondary outcomes were: adverse outcomes of pregnancy <34 , <37 and ≥ 37 weeks' gestation, stillbirth or neonatal death, neonatal morbidity, neonatal therapy, and low birth weight.

Quality control of screening and verification of adherence to protocol were

performed by the University College London Comprehensive Clinical Trials Unit (UCL-CCTU). Approval for the trial was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted.

Statistical analyses

Statistical analyses were performed on an intention-to-treat basis. The main analysis focuses on the assessment of the treatment effect on mean length of stay in NICU with zero values for babies who did not enter the unit. The rationale for this is that the expected total length of stay in a population is given by the population size multiplied by the mean length of stay. The data on length of stay contained very large numbers of zeros and the sample means were dominated by a relatively small number of babies with long lengths of stay. Rather than relying on the central limit theorem for inference, we therefore chose to use bootstrapping. The results presented were obtained from 100,000 bootstrap samples. We conducted the following additional analyses to examine the sensitivity of our conclusions: first, we applied t-tests to the difference in mean lengths of stay and Fiellers ratio of means and second, we examined the effect of truncating the extremely long lengths of stay. The results from these analyses did not alter materially the inferences regarding the effect of treatment on mean length of stay and are presented as supplementary information [Appendix 1].

Logistic-regression, with adjustment for the effect of the estimated risk of PE at screening and participating centers, was used to assess treatment effects on stay in the NICU. Separate analyses were conducted for admissions overall, for admissions with stays of ≥ 7 , ≥ 14 , ≥ 21 days and for admissions with gestational ages < 32 and < 37 weeks; overall, with PE and without PE. The treatment effect was quantified as odds ratio with 95% CI in the aspirin group. No corrections were made for multiple comparisons.

The statistical software package R was used for data analyses.²⁵ The R packages lme4²⁶ and boot²⁷ were used for mixed effects logistic regression and bootstrapping.

RESULTS

In the ASPRE trial there were 822 participants in the placebo group and 798 in the aspirin group.²¹ There were no significant differences between the aspirin and placebo groups in baseline characteristics.²¹ In the placebo group, there were 16 miscarriages or pregnancy terminations at ≤ 24 weeks' gestation, 12 stillbirths at ≥ 24 weeks and 794 live births. In the aspirin group, there were 14 miscarriages or pregnancy terminations, 7 stillbirths, and 777 live births.

Rates of admission to NICU and length of stay by treatment group are shown in Table 1 and Figure 1. There was no significant difference in rates of admission to

NICU between the aspirin and placebo groups (6.2% vs. 6.8%; odds ratio 0.94; 95% CI, 0.63-1.42). However, the total length of stay in NICU in the aspirin group was substantially shorter than in the placebo group (531 vs. 1696 days). This is a reflection of significantly shorter mean lengths of stay in babies admitted to NICU from the aspirin group than from the placebo group (11.1 days compared to 31.4 days); a reduction of 20.3 (95% CI, 7.0-38.6) days ($p=0.008$). In the whole population, including zero values for those that were not admitted to the NICU, the mean length of stay was 2.06 days in the placebo group and 0.66 days in the aspirin group; therefore, aspirin reduced the mean length of stay by an estimated 1.40 days (95% CI, 0.45 to 2.81 days; $p=0.014$).

The reduction in total length of stay in NICU in the aspirin group could essentially be attributed to a decrease in the rate of births at <32 weeks' gestation, mainly because of prevention of early-PE, and consequent decrease in number of babies with prolonged stays of ≥ 14 days (Table 1 and Figure 1). After 32 weeks' gestation there is flattening in the cumulative length of stay in NICU for both the aspirin and placebo groups (Figure1).

Babies born at <32 weeks' gestation contributed to 1856 (83.3%) of the total of 2227 days in NICU across both treatment arms; these occurred in 1.2% of livebirths in the aspirin group and in 2.9% in the placebo group (odds ratio 0.42; 95% CI, 0.19-0.93). Admission to NICU occurred in all 32 babies born at <32 weeks' gestation, in 23 (67.6%) of 34 born at 32-34 weeks, in 13 (12.5%) of 104

born at 35-36 weeks and in 34 (2.4%) of the 1401 born at 37-42 weeks.

Prolonged stay in NICU for ≥ 14 days contributed to 1914 (85.9%) of the total of 2227 days across both treatment arms; these occurred in 1.0% of livebirths in the aspirin group and in 3.0% in the placebo group (odds ratio 0.30; 95% CI, 0.11-0.81) and this is a reflection of the reduction in the number of babies born at < 32 weeks' gestation. The length of stay in NICU varied for individual babies from 1 to 230 days; it was 1-3 days in 39 (38.2%) of the 102 babies, 4-6 days in 11 (10.8%), ≥ 7 days in 52 (51.0%), ≥ 14 days in 32 (31.4%) and ≥ 21 in 23 (22.5%).

The effect of aspirin in reducing the length of stay in NICU was partly mediated by a reduction in the rate of PE (Table 1). The incidence of babies admitted to the NICU after delivery because of PE was 2.3% (18 of 794) in the placebo group and 0.3% (2 of 777) in the aspirin group (odds ratio 0.11; 95% CI, 0.02-0.50). In the pregnancies delivering at < 37 and < 32 weeks' gestation the admission to NICU was 2.0% and 0.9%, respectively in the placebo group and 0.1% and 0% in the aspirin group (odds ratio 0.06; 95% CI, 0.01-0.50 and odds ratio 0.00; 95% CI, 0.00-0.56, respectively). Aspirin also had a non-significant effect in reducing the length of stay in NICU in pregnancies without PE with delivery at < 32 weeks' gestation (odds ratio 0.59; 95% CI, 0.26-1.36). There were 16 (2.0%) babies from the placebo group (8 after spontaneous birth, 7 after iatrogenic birth for fetal growth restriction and 1 for maternal indications) and 9 (1.2%) from the aspirin

group (6 after spontaneous birth, 2 after iatrogenic birth for fetal growth restriction and 1 for maternal indications).

Impact on cost

In a population of 10,000 pregnancies undergoing first-trimester screening for PE, at a screen positive rate of 10%, 1,000 pregnancies would be classified as high-risk. If these 1,000 pregnancies had not received aspirin and the mean length of stay in NICU was 2.06 days, the expected total length of stay would be 2,060 days. If they had received aspirin the expected total length of stay would be 660 days. It is difficult to attach specific costs to daily lengths of stay but, if we assume \$4,000, then the cost saving from such care by a policy of screening 10,000 pregnancies and treating the high-risk group with aspirin would be $\$4,000 \times (2,060 - 660) = \5.6m . This is equivalent to \$560 per patient screened, which is well in excess of the cost of screening.

COMMENT

Principal findings of this study

The ASPRE trial demonstrated that, in women with singleton pregnancies identified by means of first trimester screening as being at high-risk for PE, the prophylactic use of aspirin reduces the incidence of preterm-PE and early-PE by

approximately 60% and 90%, respectively.²¹ This secondary analysis demonstrated that use of aspirin reduces the length of stay in NICU by approximately 70%. This reduction could essentially be attributed to a decrease in the rate of births at <32 weeks' gestation, mainly because of prevention of early-PE.

The consequence of reduction in length of stay in NICU is substantial saving in healthcare cost which is well in excess of the cost of population screening and treatment of the high-risk group with aspirin. The study provides the basis for formal health economic studies.

Strengths and limitations of this study

ASPRE was a large multicentre trial that was powered for the primary outcome of preterm-PE and the statistical power for detecting less frequent outcomes is inevitably poor. This secondary analysis was triggered by the apparent contradiction that although aspirin use was associated with a major reduction in preterm- and early-PE there was no evidence of reduction in NICU admission. In this respect, the findings that first, babies born at <32 weeks' gestation contributed >80% of total length of stay in NICU, second, the incidence of birth at <32 weeks was lower in the aspirin group and third, in the aspirin group the total length of stay in NICU was substantially reduced, are not surprising.

However, it has to be recognised that this is an unplanned secondary analysis and, because of the small number babies with longer lengths of stay, there is considerable uncertainty in the estimation of the difference in mean length of stay between the aspirin and placebo groups. Including zero lengths of stay for those not admitted to the NICU, the 95% CI for the difference in mean length of stay ranged from 0.45 to 2.81 days. In a screened population of 10,000 pregnancies, treating 10% screened positive, this CI translates into an interval from 450 to 2,810 days. Assuming a cost of \$4,000 per day, the corresponding intervals for the cost saving would range from \$1.8m to \$11.2m which equate to between \$180 and \$1,120 per screening test.

Prediction and prevention of PE

The traditional approach of identifying women at high-risk of PE that could potentially benefit from the prophylactic use of aspirin is based on maternal characteristics and features of the medical and obstetrical histories.^{28,29} However, the performance of such screening is poor. With the method recommended by the National Institute for Health and Clinical Excellence (NICE) in the UK the detection rate of preterm-PE is about 40% at screen positive rate of 10% and with the method recommended by the American College of Obstetricians and Gynecologists in the USA the detection rate is 90% but at a screen positive rate of 67%.²⁸⁻³¹

Our approach to screening is to use Bayes' theorem to combine information from maternal factors with biophysical and biochemical measurements obtained at 11-13 weeks' gestation to derive the patient-specific risk. The method, which detects around 75% of cases of preterm-PE at FPR of 10%, was originally developed from a study of 58,884 pregnancies,^{13,14} updated with data from prospective screening in 35,948 pregnancies,^{15,16} and subsequently validated in two independent datasets derived from multicenter studies in 8,775 and 25,797 pregnancies, respectively.^{32,33}

Prophylactic use of aspirin was previously thought to reduce the risk of PE by only 10%.¹⁷ However, recent evidence suggests that the target for first-trimester screening should be severe PE leading to preterm birth, rather than all PE. In ASPRE, use of aspirin was associated with a 62% reduction in the rate of preterm-PE with no significant effect on rate of term-PE; a secondary analysis of the trial reported that the reduction of preterm-PE was even greater (75%) if the compliance was $\geq 90\%$.^{21,34} A recent systematic review and meta-analysis of 16 trials in a combined total of 18,907 participants, reported that aspirin (at a daily dose of ≥ 100 mg and gestational age at onset of therapy of ≤ 16 weeks) reduces the risk of preterm-PE by 67%; there was no significant benefit if the dose was < 100 mg/day and the onset of therapy was > 16 weeks.²⁰

Implications of prevention of early preterm birth

This secondary analysis of the ASPRE trial demonstrated that use of aspirin reduces the rate of early preterm birth and the potential consequence in healthcare cost from neonatal intensive care. In the ASPRE trial there was no long term follow up of the neonates. However, reduction in the risk of birth at <32 weeks' gestation is likely to be associated with reduction in risk of infant death, cerebral palsy and long term use of specialized health-care resources.

A study of 5567 neonates born alive at 22-34 weeks' gestation in 2011 in France, reported that at 2-years of age survival without neuromotor or sensory disabilities was 97.5% for those born at 32-34 weeks decreasing to 81.2% in those born at 22-31 weeks.³⁵ Similarly, a study of 2901 livebirths at 22-32 completed weeks' gestation in 1997 in France, reported that at 5-years of age 14% of the children had moderate to severe disability and 25% had minor disability. Specialized health-care resources were used by 34% of the children born prematurely, compared with only 16% in a reference group of children born at 39-40 weeks.³⁶

A study in Norway reported follow-up from birth to adulthood in 867,692 individuals who were born alive and without congenital anomalies between 1967 and 1983.³⁷ The rate of death within the first 5 years of life was 80% for those born at 23-27 weeks' gestation and this decreased to 40% for births at 28-30 weeks, 11.2% for births at 31-33 weeks, 2.3% for births at 34-36 and 0.6% for births at ≥ 37 weeks. In the survivors, the respective rates of cerebral palsy were 9.1%, 6.0%, 1.9%, 0.3% and 0.1%, the rates of mental retardation were 4.4%, 1.8%,

1.0%, 0.7% and 0.4% and the rates of medical disability severely affecting work capacity were 10.6%, 8.2%, 4.2%, 2.4% and 1.7%.

Conclusion

In pregnancies at high risk of PE identified by screening at 11-13 weeks' gestation administration of aspirin reduces the rate of birth at <32 weeks' gestation and length of stay in NICU. The findings have implications for both short- and long-term healthcare costs as well as infant survival and handicap.

References

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;376:631-44.
2. Mayama M, Uno K, Tano S, Yoshihara M, Ukai M, Kishigami Y, et al. Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms. *Am J Obstet Gynecol* 2016;215:239.e1-5.
3. Palatnik A, Grobman WA, Miller ES. Is a history of preeclampsia associated with an increased risk of a small for gestational age infant in a future pregnancy? *Am J Obstet Gynecol* 2016;215:355.e1-6.
4. White WM, Mielke MM, Araoz PA, Lahr BD, Bailey KR, Jayachandran M, et al. A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later. *Am J Obstet Gynecol* 2016;214:519.e1-519.e8.
5. Fields JA, Garovic VD, Mielke MM, Kantarci K, Jayachandran M, White WM, et al. Preeclampsia and cognitive impairment later in life. *Am J Obstet Gynecol* 2017;217:74.e1-74.e11.

6. Auger N, Rhéaume MA, Paradis G, Healy-Profitós J, Hsieh A, Fraser WD. Preeclampsia and the risk of cataract extraction in life. *Am J Obstet Gynecol* 2017;216:417.e1-417.e8.
7. Kajantie E, Osmond C, Eriksson JG. Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: the Helsinki Birth Cohort Study. *Am J Obstet Gynecol* 2017;216:281.e1-281.e7.
8. Saleem S, McClure EM, Goudar SS, et al, and the Global Network Maternal Newborn Health Registry Study Investigators. A prospective study of maternal, fetal and neonatal deaths in low- and middle-income countries. *Bull World Health Organ* 2014;92:605-12.
9. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013;209:544.e1-544.e12.
10. Irgens HU, Reisaeter L, Irgens LM, et al. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ* 2001;323:1213-7.

11. Li R, Tsigas EZ, Callaghan WM. Health and economic burden of preeclampsia: no time for complacency. *Am J Obstet Gynecol* 2017;217:235-6.
12. Stevens W, Shih T, Incerti D, Ton T, Lee H, Peneva D, et al. Short-term costs of preeclampsia to the United States health care system. *Am J Obstet Gynecol* 2017;217:237-48.
13. Wright D, Akolekar R, Syngelaki A, Poon L, Nicolaides KH. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther* 2012;32:171-8.
14. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013;33:8-15.
15. Wright D, Syngelaki A, Akolekar R, Poon L, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; 213: 62.e1-10.
16. O’Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon L, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks’ gestation. *Am J Obstet*

Gynecol 2016;214:103.e1-103.e12.

17. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007;369:1791-8.
18. Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. *Am J Obstet Gynecol* 2017;216(2):121-8 e122.
19. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. *Am J Obstet Gynecol* 2017;216:110-20 e116.
20. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2017 Nov 11. pii: S0002-9378(17)32326-8.
21. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;377:613-22.

22. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012;31:42-8.
23. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007;30:742-9.
24. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20: IX–XIV.
25. R Development Core Team. R. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2011;ISBN 3-900051-07-0, URL <http://www.R-project.org/>
26. Bates D, Maechler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software* 2015;67:1-48
27. Canty A, Ripley B. boot: Bootstrap R (S-Plus) Functions. R package 2017; version 1.3-20.

28. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. London: RCOG Press, 2010.
29. ACOG. First-trimester risk assessment for early-onset preeclampsia. Committee opinion No. 638. *Obstet Gynecol* 2015;126:e25-7.
30. Gallo DM, Wright D, Casanova C, Campanero M, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19-24 weeks' gestation. *Am J Obstet Gynecol* 2016;214:619.e1-619.e17.
31. O' Gorman N, Wright D, Poon LC, Rolnik D, Syngelaki A, de Alvarado M, et al. Multicenter screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison to NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol* 2017;49:756-60.
32. O'Gorman N, Wright D, Poon LC, Rolnik D, Syngelaki A, Wright A, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017;49:751-5.

33. Rolnik DL, Wright D, Poon LC, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2017;50:492-5.
34. Wright D, Poon LC, Rolnik DL, Syngelaki A, Delgado JL, Vojtassakova D, et al. Aspirin for evidence-based preeclampsia prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. *Am J Obstet Gynecol* 2017;217:685.e1–685.e5.
35. Pierrat V, Marchand-Martin L, Arnaud C, Kaminski M, Resche-Rigon M, Lebeaux C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ* 2017;358:j3448.
36. Larroque B, Ancel PY, Marret S, Marchand L, Andre M, Arnaud C, et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* 2008;371:813-20.
37. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008;359:262-73.

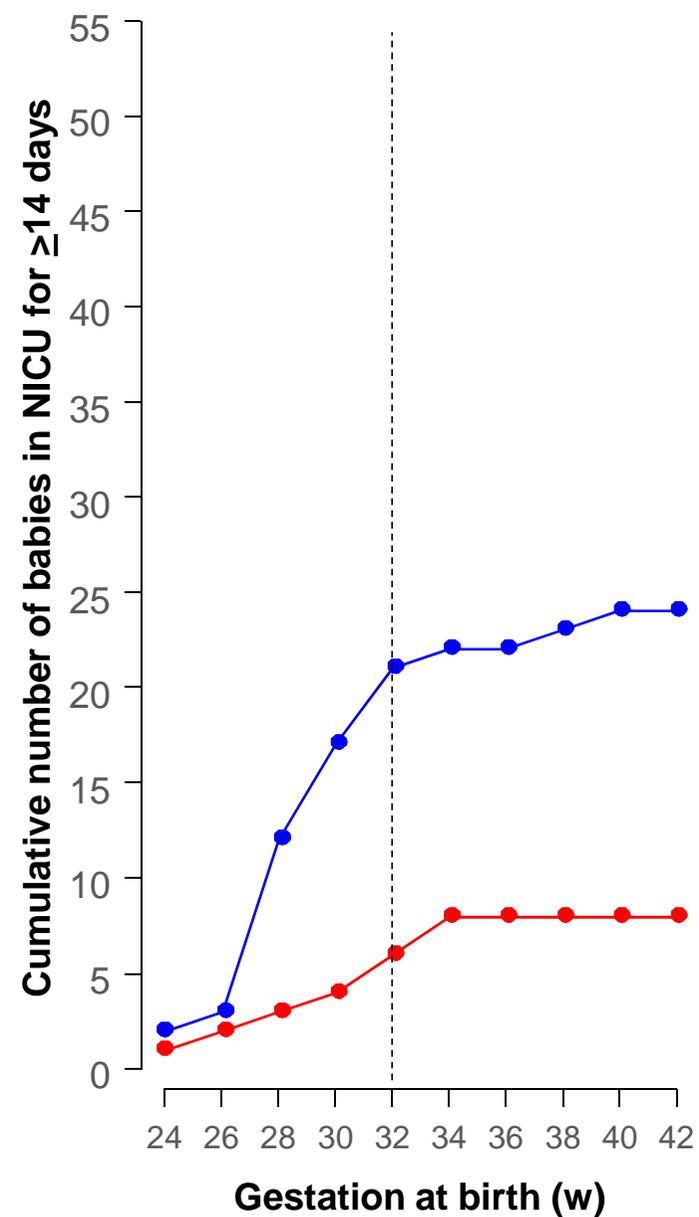
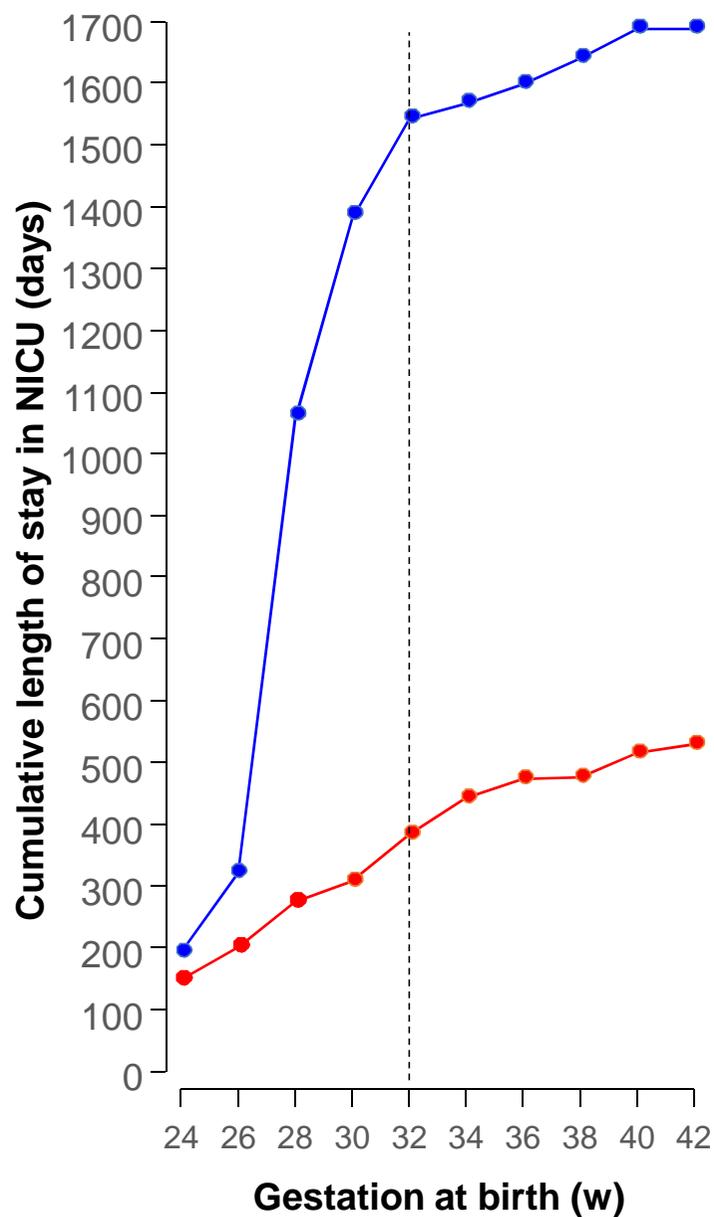
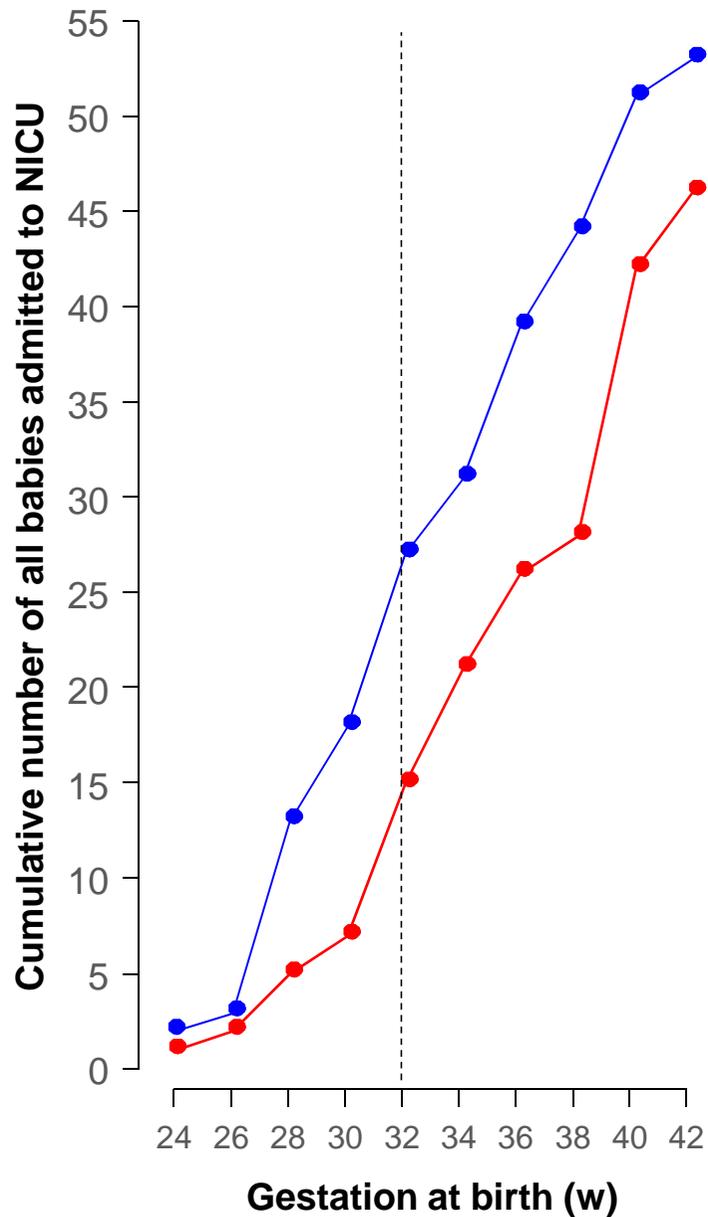
Figure legends

Figure 1. Cumulative number babies admitted to the neonatal intensive care unit (NICU) according to gestational age at birth for the placebo (blue circles) and aspirin group (red circles). In the left panel is the cumulative number of all babies admitted to NICU, in the centre panel is the cumulative length of stay in NICU and in the right panel is the cumulative number of babies with intensive care for >14 days.

Table 1. Admission to neonatal intensive care unit in livebirths from the aspirin and placebo groups according to length of stay and gestational age at birth.

Outcome measure	Aspirin	Placebo	
Length of stay in NICU (d)			Differences in means (95% CI)
Study population: admissions to NICU	n=48	n=54	
Mean (standard deviation)	11.1 (23.4)	31.4 (53.0)	20.3 (7.0 – 38.6)
Study population: all cases in the trial	n=798	n=822	
Mean (standard deviation)	0.66 (6.3)	2.06 (15.5)	1.40 (0.45 - 2.81)
Number of babies in NICU			Odds Ratio (95% CI)
Study population: livebirths*	n=777	n=794	
<i>Number by gestational age at birth</i>			
Any, n (%)	48 (6.2)	54 (6.8)	0.94 (0.63 - 1.42)
Preeclampsia	2 (0.3)	18 (2.3)	0.11 (0.02 - 0.50)
No preeclampsia	46 (5.9)	36 (4.5)	1.38 (0.88 – 2.15)
<37 w, n (%)	28 (3.6)	40 (5.0)	0.75 (0.54 - 1.04)
Preeclampsia	1 (0.1)	16 (2.0)	0.06 (0.01 - 0.50)
No preeclampsia	27 (3.5)	24 (3.0)	0.96 (0.66 - 1.38)
- Spontaneous	17 (2.2)	14 (1.8)	1.27 (0.62 - 2.60)
- Medically indicated	10 (1.3)	10 (1.3)	1.01 (0.38 - 2.73)
<32 w, n (%)	9 (1.2)	23 (2.9)	0.42 (0.19 - 0.93)
Preeclampsia	0	7 (0.9)	0.00 (0.00 - 0.56)
No preeclampsia	9 (1.2)	16 (2.0)	0.59 (0.26 - 1.36)
- Spontaneous	6 (0.8)	8 (1.0)	0.79 (0.27 - 2.28)
- Medically indicated	3 (0.4)	8 (1.0)	0.41 (0.11 - 1.54)
<i>Number by length of stay</i>			
≥ 7 days, n (%)	18 (2.3)	34 (4.3)	0.57 (0.32 - 1.04)
≥ 14 days, n (%)	8 (1.0)	24 (3.0)	0.36 (0.16 - 0.83)
≥ 21 days, n (%)	5 (0.6)	18 (2.3)	0.30 (0.11 - 0.81)

*These estimates relate to the population of livebirths as distinct from the previous publication²¹ where study population comprised all pregnancies.



Appendix 1: Supplementary Information

In evaluation of interventions applied to large populations, by virtue of the central limit theorem, totals can be assumed to follow a Gaussian distribution regardless of the distribution of individual observations. The mean of the distribution of the total is $N\mu$ where N is the population size and μ the mean of the distribution for individuals. This relationship between the mean of the total and the mean of the individuals does not apply to other measures of location such as the median. In this context, the mean of the distribution is therefore an appropriate measure of location, even in situations where it would not be considered as appropriate as a measure of central tendency for the distribution of individuals, as might be the case for a highly skewed distribution.

In this paper we focus on the effect of aspirin on mean length of stay (LOS) in the Neonatal Intensive Care Unit. These data have a very highly skewed distribution as do most data on LOS. A technique whose validity does not depend on any specific form of underlying distribution is the bootstrap. However, even with bootstrapping there are concerns that extremes will impact on the inferences concerning means. See O'Hagan A, Stevens JW. Assessing and comparing costs: how robust are the bootstrap and methods based on asymptotic normality? *Health Econ* 2003;12:33-49.

In the Table below we present the results of a sensitivity analysis looking at the effect of truncating extremely large lengths of stay. We compare the results of bootstrapping with those obtained from applying t-tests that rely on the central limit theorem. Further support for the robustness of our conclusion regarding the effect of aspirin on LOS is provided by the effect of aspirin on the number of stays for ≥ 7 , ≥ 14 and ≥ 21 days given in Table 1 of the paper.

Estimates and 95% confidence intervals for differences in mean length of stay (LOS)

Truncation		Difference in mean LOS (P-A)	Ratio of mean LOS (A/P)
None	Bootstrap	1.40 (0.54 to 2.81)	0.32 (0.14 to 0.80)
	t test	1.40 (0.25 to 2.55)	0.32 (0.10 to 0.77)
180 days	Bootstrap	1.30 (0.45 to 2.83)	0.34 (0.15 to 0.83)
	t test	1.30 (0.23 to 2.37)	0.34 (0.11 to 0.79)
90 days	Bootstrap	0.90 (0.27 to 1.68)	0.40 (0.20 to 0.83)
	t test	0.90 (0.20 to 1.60)	0.40 (0.17 to 0.79)

Bootstrapping

Bootstrap confidence intervals results were obtained using the bootstrap with a log transformation for the ratio of mean LOS. 100,000 replicates were used as shown in the Figure below. Results were obtained using the package boot in R. The intervals are BCa intervals. Angelo Canty and Brian Ripley (2017). boot: Bootstrap R (S-Plus) Functions. R package version 1.3-20.

t-test

Confidence intervals for ratios of means were obtained from Fieller's theorem implemented using the mratios package in R. Gemechis Dilba Djira, Mario Hasler, Daniel Gerhard and Frank Schaarschmidt (2012). mratios: Inferences for ratios of coefficients in the general linear model. R package version 1.3.17. <https://CRAN.R-project.org/package=mratios>.

Bootstrap Samples

