OBSTETRICS

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

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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 who 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/d 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: We sought 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; $P = .008$). 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; $P = .033$). Overall, in the whole population, including 0 lengths of stay for those 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; $P = .014$). This corresponds to a reduction in length of stay of 68% (95% confidence interval, 20−86%).

CONCLUSION: 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 health care costs as well as infant survival and handicap.

Key words: aspirin, Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial, first-trimester screening, health economics, neonatal intensive care, preeclampsia

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 health care cost[11]; in the United States 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, uterine artery pulsatility index, and serum placental growth factor at 11−13 weeks' gestation can identify about 75% of women who 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

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AJOG at a Glance

Why was this study conducted?

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 (NICU).

Key findings

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

What does this add to what is known?

In women at high risk of preeclampsia, prophylactic use of aspirin reduces substantially both the risk of preterm preeclampsia and length of stay in NICU.

PE.[19-20] A recent multicenter double-blind trial, Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) 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/d) vs placebo from 11−14 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 interval [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.

Materials and 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 mean arterial pressure,[22] uterine artery pulsatility index,[23] and serum pregnancy-associated plasma protein-A and placental growth factor (1-2-3 kits, DELFIA Xpress random access platform; PerkinElmer Inc, Wallac Oy, 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 1 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. PE 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 birthweight.

Quality control of screening and verification of adherence to protocol were performed by the University College London Comprehensive Clinical Trials Unit. Approval for the trial was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted (trial registration: ISRCTN13633058; http://www.isrctn.com/ISRCTN13633058).

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 0 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 0s 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 Fieller 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).

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, and ≥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 lme4[26] and boot[27] 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 livebirths. In the aspirin group, there were 14 miscarriages or pregnancy terminations, 7 stillbirths, and 777 livebirths.

Rates of admission to NICU and length of stay by treatment group are shown in the Figure and Table. 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 vs 31.4 days), a reduction of 20.3 (95% CI, 7.0−38.6) days ($P = .008$). In the whole population, including 0 values for those 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, 0.45−2.81 days; $P = .014$).

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 (Figure and Table). After 32 weeks' gestation there is flattening in the cumulative length of stay in NICU for both the aspirin and placebo groups (Figure).

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 1-230 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). 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 nonsignificant 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%, 1000 pregnancies would be classified as high risk. If these 1000 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 2060 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 $4000, 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 $4000 × (2060 − 660) = $5.6 million. This is equivalent to $560 per patient screened, which is well in excess of the cost of screening.

Comment

Principal findings of this study

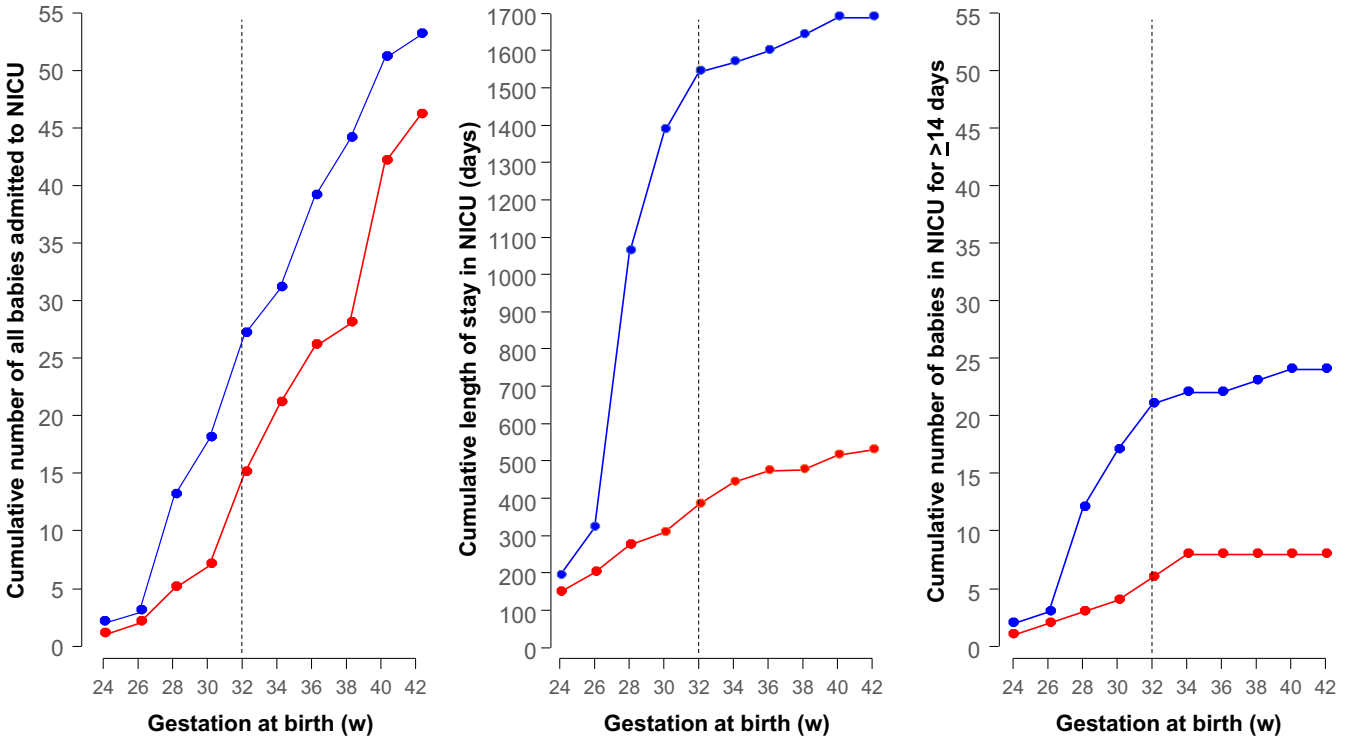
The ASPRE trial demonstrated that, in women with singleton pregnancies identified by means of first-trimester screening as being at high risk for PE, the prophylactic use of aspirin reduces the incidence of preterm PE and early PE by approximately 60% and 90%, respectively.[21] This secondary analysis 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 health care 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 multicenter 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

FIGURE
Admission to neonatal intensive care unit in the trial groups



Cumulative number of babies admitted to neonatal intensive care unit (NICU) according to gestational age at birth for placebo (blue circles) and aspirin (red circles) groups. Cumulative NICU: number of all babies admitted (left), length of stay (center), and number of babies with length of stay >14 days.

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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 recognized 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 0 lengths of stay for those not admitted to the NICU, the 95% CI for the difference in mean length of stay ranged from 0.45−2.81 days. In a screened population of 10,000 pregnancies, treating 10% screened positive, this CI translates into an interval from 450−2810 days. Assuming a cost of $4000 per day, the corresponding intervals for the cost saving would range from $1.8-11.2 million, which equate to between $180-1120 per screening test.

Prediction and prevention of PE

The traditional approach of identifying women at high risk of PE who 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 Care Excellence in the United Kingdom, the detection rate of preterm PE is about 40% at screen-positive rate of 10% and with the method recommended by the American Congress of Obstetricians and Gynecologists in the United States 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 false positive rate 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 2 independent data sets derived from multicenter studies in 8775 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

TABLE
Admission to neonatal intensive care unit in livebirths from 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 (SD)	11.1 (23.4)	31.4 (53.0)	20.3 (7.0–38.6)
Study population: all cases in trial	n = 798	n = 822	
Mean (SD)	0.66 (6.3)	2.06 (15.5)	1.40 (0.45–2.81)
Babies in NICU, n			Odds ratio (95% CI)
Study population: livebirths[a]	n = 777	n = 794	
Gestational age at birth, n (%)			
Any	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 wk	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 wk	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)
Length of stay, n (%)			
≥7 d	18 (2.3)	34 (4.3)	0.57 (0.32–1.04)
≥14 d	8 (1.0)	24 (3.0)	0.36 (0.16–0.83)
≥21 d	5 (0.6)	18 (2.3)	0.30 (0.11–0.81)

CI, confidence interval; *NICU*, neonatal intensive care unit.

[a] These estimates relate to population of livebirths as distinct from previous publication[21] where study population comprised all pregnancies.

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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 ≥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/d 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 health care 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 from 1967 through 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 weeks, 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 health care costs as well as infant survival and handicap. ■

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