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Impact of obstetric factors on outcome of extremely preterm births in Sweden: prospective population-based observational study (EXPRESS)

Running headline: Obstetric factors in extremely preterm births

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Conflicts of Interest

None of the authors has potential conflicts of interest to declare.

Abstract

Introduction. A population-based observational study investigated the contribution of obstetric factors to the survival and postnatal development of extremely preterm infants.

Material and Methods. Mortality up to one year and neurodevelopment at 2.5 years (Bayley-III test, cerebral palsy, vision, hearing) were evaluated in infants born <27 gestational weeks in Sweden 2004-2007 (n=1,011), using logistic regression analyses of risk factors.

Results: Of 844 fetuses alive at admission, 8.4% died *in utero* before labour, 7.8% died *intra partum*. Of 707 live-born infants, 15% died within 24 h, 70% survived ≥ 365 days, 64% were assessed at 2.5 years. The risk of death within 24h after birth decreased with gestational age (OR 0.3; 95%CI: 0.2-0.4), antenatal corticosteroids (OR 0.3; 95%CI: 0.1-0.6), and cesarean section (OR 0.4; 95%CI: 0.2-0.9); it increased with multiple birth (OR 3.0; 95%CI: 1.5-6.0), vaginal breech delivery (OR 2.3; 95%CI: 1.0-5.1), 5-minute Apgar score <4 (OR 50.4; 95%CI: 28.2-90.2), and birth at level II hospital (OR 2.6; 95%CI: 1.2-5.3). The decreased risk of death between 1 and 365 days remained significant for gestational age and corticosteroids. The risk of mental developmental delay decreased with gestational age, birth weight, and fetal growth; it increased with vaginal breech delivery (OR 2.0; 95%CI: 1.2-7.4), male gender, low Apgar score, and high CRIB-score.

Conclusion: Several obstetric factors, including abdominal delivery, influenced the risk of death within the first day of life, but not later. Antenatal corticosteroids and gestational age decreased the mortality up to 1 year. Mental developmental delay was related to vaginal breech delivery.

Keywords

Extremely preterm birth; mortality; risk factors; obstetric interventions; neurodevelopmental outcome; cesarean section; breech delivery

Abbreviations

BW: birth weight

CI: confidence interval

CP: cerebral palsy

CRIB: clinical risk index for babies

EDD: expected date of delivery

EFM: electronic fetal monitoring

EXPRESS: Extremely Preterm Infants in Sweden Study

GA: gestational age

LGA: large-for-gestational age

MDD: mental developmental delay

OR: odds ratio

PPROM: preterm prelabour rupture of membranes

SD: standard deviation

SDS: standard deviation score

SGA: small-for-gestational age

Key Message

The overall survival of extremely preterm infants was related to pro-active obstetric policy with use of tocolytics, antenatal corticosteroids, and cesarean section. Obstetric factors, except for vaginal breech delivery, were not associated with neurodevelopmental delay at 2.5 years of age.

Introduction

It is difficult to evaluate to which extent individual obstetric measures contribute to the substantially increased survival of extremely preterm born infants that was noted during recent two decades (1,2). The improved prognosis for these infants is mainly attributed to various improvements in neonatal care. The obstetric care differs between regions and between countries (3). This reflects the uncertainty of what is the optimal way of managing extremely preterm fetuses and how the management is influenced by medical care systems and funding in various societies. Finally, predominating attitudes among lay public generally favoring maintaining life under all circumstances may influence the obstetricians' opinion on these matters (4).

We have previously reported mortality, morbidity, one-year survival and neurodevelopmental outcome at 2.5 years of age in a population-based prospective observational study on all infants born before 27 weeks of gestation in Sweden during a three-year period ending 2007 (Extremely Preterm Infants in Sweden Study; EXPRESS) (2,5,6). The present study is an evaluation of how obstetric factors and management influenced the survival at various time-points and the neurodevelopmental outcome at 2.5 years of age.

Material and Methods

We collected perinatal data on all 1,011 infants born before 27 completed gestational weeks from April 1, 2004 to March 31, 2007 in Sweden. Data on both the live-born and stillborn infants were registered, from the latter at gestational age 22+0 to 26+6 weeks. The details of the study design and data collection have been reported previously (2); here only a short account is given.

The prospective collection of data was organized on a regional level (seven Health Care Regions with seven level III perinatal centers). The perinatal data comprised 220 items regarding the demographic information, medical and obstetric history, pregnancy course, labor and delivery, neonatal data, and data on the postnatal course during hospitalization until discharge home. Information on survival at one year was assessed through linkage with the Swedish Population Register. The gestational age (GA) was based on ultrasound dating performed before 20 postmenstrual weeks in 95% of pregnancies and in 16 pregnancies on the date of the last menstrual period. In 28 pregnancies the dating method was not specified. In 10% of live-born and in 13% of stillborn infants there was a difference of ≥ 14 days between the expected date of delivery (EDD) according to ultrasound and according to the last menstrual period. The birth weights (BW) were evaluated using the national intrauterine growth standard based on fetal weights (7). The deviation from the expected birth weight was expressed as a standard deviation score (SDS), small-for-gestational age (SGA) BW being more than two standard deviations (SD) below the mean.

Preeclampsia was defined as hypertension after 20 weeks of gestation (blood pressure $\geq 140/90$ mmHg and proteinuria ≥ 0.03 g/l). Preterm prelabour rupture of membranes (PPROM) was defined as spontaneous rupture of membranes $\geq$ one hour before the onset of contractions. The diagnosis of chorioamnionitis was made clinically. The following obstetric interventions were recorded per infant: antenatal use of tocolytics, antibiotics (any antibiotic drug administered to the mother during

hospitalization that resulted in delivery), and corticosteroids (at least one dose of betamethasone), electronic fetal heart rate monitoring (EFM), delivery at level III hospital, and delivery by cesarean section. Spontaneous preterm labour was defined as a labour beginning with spontaneous uterine contractions or contractions after PPROM. The delivery on maternal and/or fetal indication was described as iatrogenic vaginal or cesarean delivery, either after induced labor or as a prelabour cesarean section. The condition of infants at birth was evaluated with Apgar scores at 1 and 5 min and the neonatal illness severity was estimated using the clinical risk index for babies (CRIB score) (8).

At 2.5 years of corrected age, the children available for the follow-up were subjected to a clinical examination including vision and hearing. The motor, cognitive and language development of children was evaluated using the Bayley Scales of Infant and Toddler Development 3rd edition (Bayley-III) (9). In 41 cases the information about the children was obtained from their medical charts. Moderate or severe cerebral palsy (CP) and moderate or severe impairment regarding vision and hearing were characterized as neurosensory impairment. Mental developmental delay (MDD) was defined as the cognitive or language Bayley III scale $< \text{mean} - 2\text{SD}$ of the term control group, or moderate or severe developmental delay according to chart review. Moderate or severe neurodevelopmental disability was present if there was moderate or severe neurosensory impairment, Bayley III cognitive, language or motor scores $< \text{mean} - 2 \text{ SD}$ of the controls or moderate/severe developmental delay according to chart review. The methodological details of examinations have been described previously (6).

For analysis of the impact of obstetric factors, the study population ($n=1,011$) was divided into subgroups according to the outcome at given time-points: intrauterine death before admission to hospital ($n=167$), *ante* or *intra partum* death after admission ($n=137$), live-born infants that died within 24 h after birth ($n=106$), and infants that died between 1 and 365 days after birth ($n=104$),

infants who survived ≥ 365 days (n=497), and children that were examined at 2.5 years of corrected age (n=456).

The Regional Research Ethics Board at Lund University approved the study (Registration No. 42/2004).

Statistical methods

Risk factor analyses for stillbirth, postnatal death within 24 hours, death 1-364 days, and outcome at 2.5 years, were performed using logistic regression analyses. The details of each model are specified in the text and in table headings. For each outcome and evaluated potential risk factor, odds ratios (OR) with 95% confidence intervals (CI) were calculated: crude, adjusted for GA (entered as a linear continuous variable, and also as a second grade polynomial), and, for mortality, adjusted for GA (linear term) and for BW SDS (second grade polynomial). Variables with p-values < 0.2 after adjustments for GA and BW SDS, were entered into the final multiple models. When specifically studying the impact of BW SDS on survival, a cubic model of BW SDS was used in order to further improve the fit. The goodness of fit of each model was assessed by the Hosmer-Lemeshow test. For each model, the number of investigated factors never exceeded 1/10 of the number of cases. No adjustments were done for multiple comparisons. All statistical analyses were made using Gauss (Gauss, Aptech Systems Inc., Maple Valley, WA).

Results

Overall, 1,011 infants were born to 887 mothers in 904 deliveries; 304 (30%) infants were stillborn and 707 (70%) live-born. 54% of all infants were males, 54% and 55% of the stillborns and the live-borns, respectively. There were 102 multiple births (11.3%); of these 7 were triplet births. In 22% of 540 mothers with available information on the country of origin, the women came from non-Nordic countries.

Mortality and survival

Of the stillborns, 55% died before the admission to hospital (Table 1). Of the 844 fetuses alive at admission, 8.4% died *in utero* before the onset of labour or before prelabour cesarean section, 7.8% died *intra partum* and 84% were born alive. Of all live-born infants, 70% survived ≥ 365 days after birth. Half of the postnatal deaths occurred during the first day of life. Of 497 survivors at one year of age, 6 children died before 2.5 years of corrected age.

The maternal chronic diseases, and pregnancy and labour complications are presented in Table S1. In the total of 1011 cases, frequencies of essential hypertension, preeclampsia and abruption of placenta including placenta praevia were 4.2%, 10.9% and 12.4%, respectively. The corresponding rates for PPRM and chorioamnionitis were 14.6% and 15.3%, respectively. Diabetes mellitus is not presented as it was reported only in 11 cases (1.1%). Abruptio of placenta and placenta praevia were most frequent in pregnancies with live-born infants and at higher GA (25-26 weeks).

Of all infants, 70% were born at level III hospitals, the corresponding figure for the live-born infants was 79% (Table 2). Antibiotics were given to mothers of 47% of infants, most often to the mothers of infants born alive (55%; in 89% of PPRM cases). In 74% of pregnancies with spontaneous preterm labour, tocolytic treatment was initiated; in 86% in the group of survivors without any differences

between the GA subgroups. Antenatal corticosteroids were given to 65% of all infants, to 84% of those born alive, and to 90% of survivors. In live-born infants, the use of EFM increased with increasing GA.

Of the 707 live-born infants, 50% were delivered by cesarean section (at 22-23 weeks 13%, at 24-26 weeks 61%) (Table 2). Cesarean section was performed in nine cases resulting in stillbirth, equally distributed among the gestational weeks. Of those, six were done on maternal indication (one severe preeclampsia, three placenta abruptions, two uterine pathology – multiple scars and large myoma, respectively), and one as a part of maternal resuscitation after cardiac arrest. Two cesarean sections were performed on fetal indication in twin pregnancies where one fetus had died *in utero*.

Table S2 presents the infant characteristics at birth according to outcome groups and gestational age. The BW ranged 100-1130g in the stillborns and 266-1500g in the live-born infants. The median BW of the 497 survivors was 770g (range 348-1315g). Of the stillborns, 39.5 % were SGA; of the infants born alive, 16% were SGA. Nine (1.3%) of the live-born infants were LGA (three with congenital anomalies, one hydrops, five with no concomitant diagnosis). Structural congenital anomalies were diagnosed in 4.6% of stillborns and in 11% of live-born infants. Apgar score <4 at 5 min was most common among 106 infants who died within the first day of life (79%), ranging from 92% at 22 weeks to 17% at 26 weeks. Among infants surviving the first 24 h, 7.5% had Apgar score at 5 min <4 with no significant differences between the gestational weeks or between the infants who died within one year and the survivors ≥ 365 days. The frequency of CRIB score >10 among infants who died between 1 and 365 days after birth (22%) was about twice that of the survivors (10%).

Of the children assessed at 2.5 years of corrected age, 34 of 456 (7.5%) had neurosensory impairment, 88 of 440 (20%) had MDD, and 124 of 456 (27.2%) had any moderate or severe disability.

Analyses of obstetric factors

Table 3 shows the associations between obstetric factors and stillbirth among fetuses admitted alive, neonatal death within 24 hours, and infant death between 1 and 365 days, respectively, as compared to infants born alive and surviving ≥ 365 days. The results shown are based on univariate analyses and on multiple models including the variables with p-values < 0.2 after adjustments for GA and BW SDS. The Supplementary tables S3-S5 present the complete results including the intermediate multiple models with GA, and GA and BW SDS, respectively.

The risk of *stillbirth* decreased with advancing GA, higher BW and increasing BW SD, whereas chorioamnionitis/PPROM, SGA, vaginal breech delivery, and birth at level II or level I hospital were associated with an increased risk in univariate analyses. In the multiple models, the associations remained significant.

In univariate analyses, the risk of *neonatal death within 24 hours* decreased with advancing GA, higher BW, preeclampsia/essential hypertension, tocolysis, antenatal corticosteroids and cesarean delivery. Multiple birth, vaginal breech delivery, birth at level II or I hospital, and Apgar score < 4 both at 1 and 5 min were adversely associated with outcome. In multiple models the associations remained significant with exception of preeclampsia and tocolysis. Administration of antenatal corticosteroids (risk decrease), Apgar score < 4 at 5 min and birth at level II or I hospital (risk increase) were the most significant predictors. Adjusting for all variables led to chorioamnionitis/PPROM becoming significantly associated with increased risk of death within 24 hours.

The risk of *infant death between 1 and 365 days* decreased with advancing GA, higher BW, antenatal antibiotics, and tocolysis, whereas vaginal breech delivery, Apgar score < 4 at 1 min, and high or increasing CRIB score were associated with an increased risk. The strongest associations between the

risk factors and death between 1 and 365 days of life were found for advancing GA and for antenatal corticosteroids (risk decrease), and for increasing CRIB score (risk increase). This did not change after adjusting for all variables in the multiple models.

Maternal demographic factors and fetal gender did not show any significant associations with the investigated outcomes, i.e., stillbirth, neonatal death within 24 hours, and infant death between 1 and 365 days.

Using a cubic model for BW SDS and a quadratic model for GA, very high goodness of fit for the logistic regression analyses was achieved (Hosmer and Lemeshow $p=0.72$ and $p=0.29$ for stillbirth and infant death, respectively). The results are presented in Figure 1. While the risk for stillbirth steadily decreased with increasing BW SDS, a U-shaped relation was found between BW SDS and infant death.

The results of analyses regarding the neurodevelopmental outcome at 2.5 years of corrected age are presented in Table 4. Of the obstetric factors, vaginal breech delivery was the only one significantly associated with the three categories of neurodevelopmental impairment. For the MDD, the increased risk remained significant after adjustment for GA ($p<0.05$). Male gender increased the risk for MDD and any moderate or severe disability; the increase remained significant after adjustment for GA ($p<0.01$ and $p<0.05$, respectively). Increase in the BW was associated with a risk decrease in all three categories of impairment. The strongest association with the neurodevelopmental outcome was found for neonatal condition, characterized by the Apgar score and CRIB score. Apgar score <4 at one minute and Apgar score <7 at five minutes were significantly related to an increased risk for MDD and any moderate or severe disability ($p<0.01$ in both cases after adjustment for GA). CRIB score >10 was significantly associated with an increase in the risk for all three neurodevelopmental categories ($p<0.001$).

Discussion

During 2004-2007, 70% of extremely preterm infants born alive before 27 gestational weeks in Sweden survived at least one year. Most obstetric interventions, including transport to level III perinatal centers, tocolysis, and cesarean section, decreased the risk of death within the first day of life, but not thereafter. Antenatal corticosteroids diminished the mortality risk both during the first 24 hours and up to the age of one year. Vaginal breech delivery was associated with both increased risk for mortality and for neurodevelopmental delay at 2.5 years of age.

Stillbirths after admission, but before the onset of labour (8.4%) were more common in association with chorioamnionitis/PPROM and at level II or I hospitals. It can be speculated that the obstetrician has refrained from actively delivering the mother in many of these cases due to anticipated poor survival. The number of *intra partum* deaths was rather low compared to other studies on extremely preterm deliveries (10,11). *Intra partum* EFM was applied often if the fetus was judged viable, however, the present material does not permit any conclusions regarding fetal monitoring during very preterm labour.

Several classical obstetric complications associated with preterm delivery, e.g. multiple pregnancy, PPRM, related to infection and inflammation (12), or vaginal breech delivery, were associated with an increased risk for neonatal deaths within the first 24 hours. It has been claimed that the neonatal deaths occurring during the first 12 hours after birth do reflect the obstetric management and the degree of activity at primary resuscitation (13). Later deaths probably reflect more the standard of neonatal care. Our results show that if the child survived the first 24 hours, continuing survival was likely.

The cesarean section rate was 50%, comparable to that in the Finnish population-based study (58%) (14), but much higher than reported from the EPICure study for infants born before 26 gestational weeks (15.6%) (15). The optimal mode of delivery for extremely preterm infants is not established. Retrospective register-based studies reported that a liberal use of cesarean section on fetal indication in very preterm deliveries is associated with increased survival rate also when controlling for birth weight (16). Data from prospective studies are very limited and inconclusive due to methodological difficulties (3,17). There are some observational and registry studies (18,19) indicating that cesarean delivery is preferable for preterm fetuses in breech presentation. For vertex presentation in very preterm deliveries there are no conclusive data supporting routine use of cesarean section (19). In the present study, cesarean section was associated with increased survival within the first 24 hours after birth, but not thereafter.

Delivery at a level II or I hospital was associated with higher rates of stillbirth and death within 24h after birth. This relationship concurs with the previous observational study in Sweden (20). An important goal of centralization is to provide the level III units with a higher number of cases, thus improving the skills and experience of the specialized perinatal teams.

The antenatal treatment with tocolytics and corticosteroids was more frequent than reported in the literature (10,14,15) and the results indicated a high efficacy with decreased mortality. In contrast to tocolytics, the significant effect of corticosteroids remained after adjustment for other variables. A plausible explanation of the beneficial effect of tocolysis might be the time gain enabling corticosteroid treatment and transport to the level III hospital. Another possibility might be that our finding just reflects selection of a group of mothers at best health. In agreement with many other studies the present study confirmed the strong association between antenatal corticosteroids and the improved neonatal outcome (21). We did not find any difference in the steroid effect when comparing the estimates for 23 wks with those for 24-26 wks ($p=0.75$), thus suggesting that the antenatal steroids

are efficient already at that early GA. There were too few cases at 22+0 to 22+6 weeks to allow corresponding comparison.

At 2.5 years of corrected age, low 1-minute and 5-minute Apgar scores, and high CRIB scores were strongly associated with neurodevelopmental disability after adjustment for GA. These indicators, besides acute and chronic fetal conditions, reflect *intra partum* obstetric management, resuscitation and initial stabilization after birth. Previously, CRIB score was shown to have little value for predicting neurodevelopmental outcome (22). In our study CRIB score >10 was a better predictor than birth weight or gestational age. Although Apgar scores are associated with outcome at group level, it must be emphasized that individual Apgar scores cannot discriminate between infants who eventually survive unimpaired or who survive with impairment (23).

In contrast to several studies, male gender was not associated with higher mortality. At follow-up, however, the neurodevelopmental outcome of boys was poorer than that of girls which is also reported by others (24). We were not able to show an association between 2.5-year outcome and SGA, which might be due to the early age at follow-up. However, a recent large study from the National Institute of Child Health and Human Development reported significantly increased risks for low Bayley-III cognitive and language scores at 18-24 months in SGA infants born at 23-26 weeks (25). Severe intrauterine growth restriction has been also associated with greater risk for cognitive impairment at 5-8 years in boys born at median 26.9 weeks (26).

In this study, among obstetric factors, only vaginal breech delivery was significantly associated with adverse outcome (MDD) at 2.5 years corrected age – the unadjusted OR for neurosensory impairment (moderate and severe cerebral palsy, moderate or severe impairment regarding vision and hearing) was significantly increased. In the EPICure study, breech delivery was associated with increased risk for cerebral palsy at 30 months of age in infants born at <26 weeks (27) and a recent Norwegian

registry study, reported an increased risk for cerebral palsy at 4 years in preterm children after breech delivery (28). The fact that term infants with breech presentation exhibit greater risk for cerebral palsy than those with cephalic presentation regardless of mode of delivery (28) indicates that underlying conditions causing breech presentation contribute to the outcome. The previously not reported finding of the association with MDD might reflect a pathophysiology different from that associated with CP. This merits further exploration in our cohort at later follow-up at 6.5 and 11 years.

Proper counseling of the parents and the obstetric decision making require access to accurate and up-to-date information not only on mortality, but also on morbidity. Considering the rather high long-term morbidity of extremely preterm infants (29), it should go without saying that institutions providing care for these mothers and infants should continuously perform long-term follow-up into childhood and beyond.

In the EXPRESS study the one-year survival was high as compared with other national figures (10,14,30). When evaluating the impact of obstetric factors and interventions, several possibly contributing circumstances specific for the Swedish health care system should be considered. A standardized antenatal and perinatal care is free of charge for all inhabitants. Almost all pregnancies are dated with ultrasound in the first or early second trimester. Generally, the ultrasound pick-up rate of severe malformations is high. Hence pregnancies with severe malformations are frequently terminated which is the most likely explanation for the low rate of severe malformations in the present material. Teenage pregnancies are very few (<4%) depending on liberal use of contraception and a rather high rate of terminations of pregnancy among young women. Single embryo transfer is generally implemented in all in-vitro fertilization programs since 2003, which significantly decreased the proportion of preterm deliveries due to multiple pregnancies.

To provide evidence for obstetric management of extremely preterm births, randomized controlled trials would be desirable. Unfortunately, to perform randomized trials in this group of patients is very difficult. In this perspective, the strength of the prospective observational EXPRESS study is that it is truly population-based and that it includes antenatal deaths and early delivery room deaths. The weakness of this type of study is the difficulty or even impossibility to distinguish the effect on survival of the underlying pathology from the effects of preterm labour and delivery *per se*.

Furthermore, the ultrasound dating of some of these pregnancies in the second trimester can be misleading because of early growth restriction and possibility of systematic GA underestimation. The resulting p-values should be interpreted with caution as some might be due to multiple comparisons. The found beneficial effect of cesarean section on short-term survival might include a risk of selection bias – it cannot be excluded that mothers with more favorable prospects for infant survival were those most often selected for cesarean section.

In conclusion, pro-active obstetric policy with antenatal use of tocolytics and corticosteroids, transport to level III perinatal centers and liberal use of cesarean section, is associated with improved survival in extremely preterm infants. Vaginal breech delivery increases risk for mortality and for neurodevelopmental delay at 2.5 years of age, thus supporting the view that cesarean section in these cases should be the method of choice.

Supporting Information published online

Table S1. Maternal chronic diseases, and pregnancy and labour complications according to outcome groups and gestational age.

Table S2. Infant characteristics according to outcome groups and gestational age.

Table S3. Factors associated with stillbirth among fetuses admitted to hospital alive versus infants born alive and surviving at least 365 days.

Table S4. Factors associated with neonatal death within 24 hours after birth compared to infants alive at one year of age.

Table S5. Factors associated with infant death between 1 and 365 days after birth compared to infants alive at one year of age.

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Figure legends and Table captions

Figure 1. Risk for stillbirth and infant death in relation to fetal growth. The fetal growth is expressed as birth weight standard deviation scores according to the Swedish intrauterine growth standard (7). Only fetuses alive at admission to the delivery unit were included. Odds ratios (with 95% confidence intervals as vertical bars) were obtained from multiple logistic regression analyses using a cubic model for birth weight standard deviation scores and a quadratic model for gestational age.

Table 1. Mortality and survival according to gestational age of all infants born before 27 weeks of gestation in Sweden during three years (2004-2007). Number (percent).

Table 2. Obstetric interventions according to outcome groups and gestational age. Number (percent).

Table 3. Factors associated with stillbirth among fetuses admitted to hospital alive, with neonatal death within 24 hours and with infant death between 1 and 365 days, respectively, versus infants born alive and surviving at least 365 days. Results from univariate analyses and multiple logistic regression analyses. The multiple models include all variables with p-value <0.2 after adjustment for gestational age and fetal growth (data not shown), with exception of Apgar score and CRIB score that were considered to be intermediate variables .

Table 4. Factors associated with outcome at 2.5 years of corrected age. Results from univariate analyses and multiple logistic regression analyses adjusting for gestational age. Children who were not evaluated at 2.5 years were excluded.

Supplementary material

Table S1. Maternal chronic diseases, and pregnancy and labour complications according to outcome groups and gestational age. Number (percent).

Table S2. Infant characteristics according to outcome groups and gestational age.

Table S3. Factors associated with stillbirth among fetuses admitted to hospital alive versus infants born alive and surviving at least 365 days. Results from univariate analyses and multiple logistic regression analyses including gestational age alone or gestational age and fetal growth expressed as standard deviation of birth weight according to the Swedish standard curve for intrauterine growth. For each column, the ‘base-adjustment-variable-set’ is indicated with grey colour; the unmarked variables were added separately one at a time. The results of grey-marked variables were derived from models in which no other variables than those grey-marked (gestational age alone or gestational age and SD of birth weight) were entered.

Table S4. Factors associated with neonatal death within 24 hours after birth compared to infants alive at one year of age. Results from univariate analyses and multiple logistic regression analyses including gestational age alone or gestational age and fetal growth expressed as standard deviation of birth weight according to the Swedish standard curve for intrauterine growth. For each column, the ‘base-adjustment-variable-set’ is indicated with grey colour; the unmarked variables were added separately one at a time. The results of grey-marked variables were derived from models in which no other variables than those grey-marked (gestational age alone or gestational age and SD of birth weight) were entered.

Table S5. Factors associated with infant death between 1 and 364 days after birth compared to infants alive at one year of age. Results from univariate analyses and multiple logistic regression analyses including gestational age alone or gestational age and fetal growth expressed as standard deviation of birth weight according to the Swedish standard curve for intrauterine growth. For each column, the ‘base-adjustment-variable-set’ is indicated with grey colour; the unmarked variables were added separately one at a time. The results of grey-marked variables were derived from models in which no other variables than those grey-marked (gestational age alone or gestational age and SD of birth weight) were entered.

Table 1. Mortality and survival according to gestational age of all infants born before 27 weeks of gestation in Sweden during three years (2004-2007).

Number (percent).

	Gestational age (completed weeks)					
	22*	23	24	25	26	Total <27 weeks
All infants	n=142	n=183	n=191	n=250	n=245	n=1011
Death before admission	39 (27.5)	43 (23.5)	30 (15.7)	25 (10.0)	30 (12.2)	167 (16.5)
Alive at admission	n=103	n=140	n=161	n=225	n=215	n=844
Death before onset of labour or before elective cesarean section	12 (11.7)	20 (14.3)	15 (9.3)	17 (7.6)	7 (3.3)	71 (8.4)
Intrapartum death	40 (38.8)	19 (13.6)	2 (1.2)	3 (1.3)	2 (0.9)	66 (7.8)
Live-born	n=51	n=101	n=144	n=205	n=206	n=707
Death <24h after birth	39 (76.5)	30 (29.7)	21 (14.6)	10 (4.9)	6 (2.9)	106 (15.0)
Death 1-6 days	2 (3.9)	9 (8.9)	9 (6.2)	13 (6.3)	13 (6.3)	46 (6.5)
Death 7-27 days	4 (7.8)	7 (6.9)	11 (7.6)	6 (2.9)	7 (3.4)	35 (5.0)
Death 28-364 days	1 (2.0)	2 (2.0)	7 (4.9)	9 (4.4)	4 (1.9)	23 (3.3)
Alive at 365 days	5 (9.8)	53 (52.5)	96 (66.7)	167 (81.5)	176 (85.4)	497 (70.3)
Alive at 2.5 years corrected age	5 (9.8)	52 (51.5)	95 (66.0)	166 (81.0)	173 (84.0)	491 (69.4)
Assessed at 2.5 years**	5 (9.8)	47 (46.5)	86 (59.7)	151 (73.7)	167 (81.1)	456 (64.5)

*Includes 2 infants born alive at 21+5 and 21+6 (weeks+days), respectively; **Includes 41 children evaluated according to patient charts.

Table 2. Obstetric interventions according to outcome groups and gestational age. Number (percent).

	Gestational age (weeks)					
	22	23	24	25	26	Total <27 weeks
Alive at admission, stillbirths	n=52	n=39	n=17	n=20	n=9	n=137
Antibiotics	22 (42.3)	20 (51.3)	11 (64.7)	6 (30.0)	2 (22.2)	61 (44.5)
Tocolysis, n/N [§]	19/43 (44.2)	15/32 (46.9)	8/13 (61.5)	5/9 (55.6)	2/5 (40.0)	49/102 (48.0)
Corticosteroids	7 (13.4)	29 (74.4)	17 (100)	9 (45.0)	2 (22.2)	64 (46.7)
Electronic FHR monitoring (EFM)	7 (13.5)	4 (10.3)	4 (23.5)	10 (50.0)	2 (22.2)	27 (19.7)
No information on EFM	8 (15.4)	16 (41.0)	6 (35.3)	3 (15.0)	2 (22.2)	35 (25.5)
Cesarean section	1 (1.9)	1 (2.6)	1 (5.9)	1 (5.0)	1 (11.1)	5 (3.6)
Delivery at level III hospital	24 (46.2)	30 (76.9)	15 (88.2)	12 (60.0)	4 (44.4)	85 (62.0)
Live-born, death <24 h after birth	n=39	n=30	n=21	n=10	n=6	n=106
Antibiotics	23 (59.0)	19 (63.3)	14 (66.7)	4 (40.0)	4 (66.7)	64 (60.4)
Tocolysis, n/N [§]	19/33 (57.6)	17/27 (63.0)	16/18 (88.9)	4/7 (57.1)	3/4 (75.0)	59/89 (66.3)
Corticosteroids	10 (25.7)	21 (70.0)	19 (90.4)	7 (70.0)	0 (0.0)	62 (58.5)
Electronic FHR monitoring (EFM)	0 (0.0)	8 (26.7)	11 (52.4)	4 (40.0)	4 (66.7)	27 (25.5)
No information on EFM	6 (15.4)	10 (33.3)	1 (4.8)	0 (0.0)	1 (16.7)	18 (17.0)
Cesarean section	3 (7.7)	1 (3.3)	6 (28.6)	6 (60.0)	4 (66.7)	20 (18.9)
Delivery at level III hospital	14 (35.9)	18 (60.0)	21 (100)	6 (60.0)	4 (66.7)	63 (59.4)

Table 2 (continued).

Live-born, death 1 - 364 days	n=7	n=18	n=27	n=28	n=24	n=104
Antibiotics	4 (57.1)	8 (44.4)	11 (40.7)	13 (46.4)	10 (41.7)	46 (44.2)
Tocolysis, n/N [§]	5/7 (71.4)	14/17 (82.4)	14/18 (77.8)	10/17 (58.8)	8/11 (72.7)	51/70 (72.9)
Corticosteroids	5 (71.4)	16 (88.9)	24 (88.9)	20 (71.4)	17 (70.8)	82 (78.8)
Electronic FHR monitoring (EFM)	0 (0.0)	4 (22.2)	16 (59.3)	18 (64.3)	16 (66.7)	54 (51.9)
No information on EFM	1 (14.3)	5 (27.8)	5 (18.5)	5 (17.9)	0 (0.0)	16 (15.4)
Cesarean section	0 (0.0)	3 (16.7)	15 (55.6)	19 (67.9)	18 (75.0)	55 (52.9)
Delivery at level III hospital	5 (71.4)	14 (77.8)	25 (92.6)	19 (67.9)	19 (79.2)	82 (78.8)
Survivors, alive at 365 days	n=5	n=53	n=96	n=167	n=176	n=497
Antibiotics	5 (100)	35 (66.0)	56 (58.3)	94 (56.3)	88 (50.0)	278 (55.9)
Tocolysis, n/N [§]	4/5 (80.0)	40/47 (85.1)	63/74 (85.1)	103/118 (87.3)	93/107 (86.9)	303/351 (86.3)
Corticosteroids	5 (100)	48 (90.6)	87 (90.6)	149 (89.3)	158 (89.8)	447 (89.9)
Electronic FHR monitoring	2 (40.0)	18 (34.0)	54 (56.2)	122 (73.1)	149 (84.7)	345 (69.4)
No information on EFM	1 (20.0)	10 (18.9)	12 (12.5)	17 (10.2)	16 (9.1)	56 (11.3)
Cesarean section	0 (0.0)	13 (24.5)	46 (47.9)	103 (61.7)	119 (67.6)	281 (56.5)
Delivery at level III hospital	5 (100)	47 (88.7)	83 (86.5)	141 (84.4)	137 (77.8)	413 (83.1)

FHR = fetal heart rate; EFM = electronic FHR monitoring; [§]calculated for cases of spontaneous preterm labour only (N).

Table 3. Factors associated with stillbirth among fetuses admitted to hospital alive, with neonatal death within 24 hours and with infant death between 1 and 365 days, respectively, versus infants born alive and surviving at least 365 days. Results from univariate analyses and multiple logistic regression analyses. The multiple models include all variables with p-value <0.2 after adjustment for gestational age and fetal growth (data not shown), with exception of Apgar score and CRIB score that were considered to be intermediate variables .

	Stillbirth among fetuses admitted alive				Neonatal death within 24 hours				Infant death between 1 and 365 days			
	Univariate analysis		Multiple model		Univariate analysis		Multiple model		Univariate analysis		Multiple model	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Gestational age and intrauterine growth												
GA, one-week increment	0.4	0.4-0.5***	0.4	0.3-0.5***	0.3	0.2-0.3***	0.3	0.2-0.4***	0.7	0.6-0.8***	0.6	0.5-0.8***
SD (birth weight), one-step increment	0.7	0.6-0.8***	-	-	1.3	1.1-1.6**	-	-	0.8	0.7-0.9**	0.8	0.6-1.0*
SD (birth weight), second grade model												
Linear model	0.8	} Simultaneous p<0.001	0.6	} Simultaneous p<0.001	1.6	} Simultaneous p<0.001	1.5	} Simultaneous p<0.001	-	-	-	-
Quadratic term	1.1		1.0		1.1		1.3		-	-	-	-
Pregnancy and delivery												
Preeclampsia/Essential hypertension	1.2	0.7-2.1	-	-	0.4	0.1-0.9*	0.7	0.1-2.8	1.2	0.7-2.3	-	-
Chorioamnionitis/PPROM	1.7	1.1-2.6*	1.9	1.2-3.0**	1.3	0.8-2.0	2.5	1.3-4.8**	0.9	0.5-1.6	-	-
Multiple birth	-	-	-	-	1.9	1.2-3.0*	3.0	1.5-6.0**	1.5	0.9-2.5	1.4	0.8-2.4
Abruption of placenta	0.8	0.4-1.6	-	-	0.8	0.4-1.7	-	-	0.9	0.5-1.9	-	-
Breech, vaginal delivery	4.0	2.5-6.4***	3.0	1.7-5.2***	4.4	2.4-7.8***	2.3	1.0-5.1*	2.5	1.2-5.1*	1.7	0.8-3.9
Birth at level II or level I hospital	2.3	1.6-3.4***	1.8	1.1-2.9*	3.4	2.1-5.3***	2.6	1.2-5.3*	1.3	0.8-2.2	1.2	0.6-2.3
Cesarean section	-	-	-	-	0.2	0.1-0.3***	0.4	0.2-0.9*	0.9	0.6-1.3	-	-
Antenatal antibiotics	-	-	-	-	1.2	0.8-2.0	-	-	0.6	0.4-0.9*	0.8	0.5-1.3
Antenatal corticosteroids	-	-	-	-	0.1	0.1-0.2***	0.3	0.1-0.6**	0.3	0.2-0.6***	0.3	0.2-0.8**
Tocolysis§	-	-	-	-	0.3	0.2-0.5***	0.8	0.3-1.9	0.4	0.2-0.8*	0.6	0.3-1.2
Newborn characteristics												
Male gender (vs. female)	1.0	0.7-1.5	-	-	1.0	0.6-1.5	-	-	1.1	0.7-1.7	-	-
Birth weight (100 g increment)	0.4	0.4-0.5***	Not included		0.6	0.5-0.6***	Not included		0.7	0.6-0.8***	Not included	
SGA	2.1	1.4-3.3***	Not included		0.5	0.3-1.1	Not included		1.6	0.9-2.6	Not included	
Apgar score <4 at one minute	-	-	-	-	13.2	7.8-22.3***	Not included		1.6	1.0-2.6*	Not included	
Apgar score <4 at five minute	-	-	-	-	50.4	28.2-90.2***	Not included		1.4	0.7-2.9	Not included	

Table 3 (continued).

CRIB score >10	-	-	-	-	-	-	-	-	2.6	1.5-4.5***	Not included
CRIB score (continuous), one-step increment	-	-	-	-	-	-	-	-	1.2	1.1-1.3***	Not included

OR: Odds ratio; 95%CI: 95% confidence interval; GA: gestational age; SD: standard deviation of birth weight according to the Swedish standard curve for intrauterine growth;⁷ PPRM: preterm prelabour rupture of membranes; SGA: small-for-gestational age, i.e. birth weight below the mean -2SD of the standard⁷. ***: p<0.001; **: p<0.01; *: p<0.05. §Only cases with spontaneous preterm labour.

Table 4. Factors associated with outcome at 2.5 years of corrected age. Results from univariate analyses and multiple logistic regression analyses adjusting for gestational age. Children who were not evaluated at 2.5 years were excluded.

	N	Neuro-sensory impairment ^A				Mental developmental delay ^B				Any moderate or severe disability ^C			
		N = 34/456 (7.5%)				N = 88/440 (20%)				N = 124/456 (27.2%)			
		%	OR crude	OR adjusted ^D	95% CI	%	OR crude	OR adjusted ^D	95% CI	%	OR crude	OR adjusted ^D	95% CI
GA, one-week increment			0.6**				0.6***				0.6***		
SD (birth weight), one-step increment			1.0	0.9	0.7-1.3		0.8	0.8**	0.6-0.9		1.0	0.9	0.7-1.0
Preeclampsia / Essential hypertension	62	6.5	0.8	1.0	0.3-3.0	16.7	0.8	1.0	0.5-2.0	25.8	0.9	1.1	0.6-2.1
Chorioamnionitis / PPRM	112	6.2	0.7	0.8	0.3-2.0	18.3	0.8	0.9	0.5-1.7	25.0	0.7	0.8	0.5-1.5
Abruption of placenta	67	4.5	0.5	0.6	0.2-1.9	15.4	0.7	0.7	0.4-1.5	23.9	0.8	0.9	0.5-1.6
Multiple birth	86	5.8	0.7	0.8	0.3-2.1	24.7	1.4	1.5	0.8-2.7	31.4	1.3	1.4	0.8-2.4
Breech / vaginal delivery	29 / 202	17.2	3.5*	2.4	0.7-8.7	46.4	4.5***	2.0*	1.2-7.4	55.2	3.6**	2.1	0.9-5.1
Birth at level II or level I hospital	77	6.9	1.6	1.9	0.8-4.4	18.6	0.9	1.1	0.5-2.1	27.4	0.9	1.1	0.6-1.9
Cesarean section	254	7.5	1.0	1.5	0.7-3.2	19.4	0.9	1.3	0.8-2.2	25.2	0.8	1.1	0.7-1.8
Antenatal antibiotics	252	7.9	1.1	1.0	0.5-2.1	19.4	0.9	0.8	0.5-1.3	28.6	1.1	1.0	0.6-1.6
Antenatal corticosteroids	411	7.5	1.0	1.1	0.3-4.8	20.0	0.7	0.7	0.3-1.9	27.7	1.1	1.2	0.5-2.9
Tocolysis ^S	256 / 325	8.2	1.0	1.0	0.3-2.7	20.5	0.9	0.9	0.4-1.8	29.3	1.0	0.9	0.5-1.8

Table 4 (continued).

Male gender	248	8.9	1.6	1.7	0.8-3.5	24.2	1.8*	2.0**	1.2-3.3	31.0	1.6*	1.7*	1.1-2.6
Birth weight, 100g increment			0.8*	1.0	0.7-1.3		0.7***	0.8**	0.6-0.9		0.7***	0.9	0.7-1.0
SGA	73	6.8	0.9	1.1	0.4-3.0	22.2	1.2	1.5	0.8-2.8	27.4	1.0	1.3	0.7-2.3
Apgar score <4 at one minute	109	7.3	1.0	0.9	0.4-2.0	28.6	1.9*	1.7*	1.0-2.8	36.7	1.8*	1.6*	1.0-2.6
Apgar score <4 at five minutes	33	3.0	0.4	0.3	0.0-2.7	30.3	1.8	1.8	0.8-3.9	36.4	1.6	1.5	0.7-3.3
Apgar score <7 at five minutes	149	6.7	0.8	0.8	0.3-1.6	29.5	2.3***	2.1**	1.3-3.5	36.9	2.0**	1.9**	1.2-2.9
CRIB score >10	42	23.8	5.1***	3.7**	1.6-8.9	50.0	4.8***	3.5***	1.7-7.2	61.9	5.2***	3.7***	1.8-7.3
CRIB score (continuous), one-step increment			1.2***	1.2*	1.0-1.3		1.2***	1.2***	1.1-1.3		1.2***	1.1***	1.1-1.2

^AModerate or severe impairment regarding vision, hearing, or cerebral palsy (CP); ^BMDD: mental developmental delay = cognitive or language Bayley III scale < mean-2SD, or moderate/severe developmental delay according to chart review; ^Cvisual or hearing impairment, CP, low Bayley-III composite cognitive, language or motor score or moderate/severe developmental delay according to chart review; ^DAdjusted for gestational age (continuous, linear). OR: Odds ratio; 95% CI: 95% confidence interval; GA: gestational age; SD (birth weight): standard deviation of birth weight according to the Swedish standard curve for intrauterine growth⁷; PPRM: preterm prelabour rupture of membranes; SGA: small-for-gestational age (birthweight below the mean -2SD of the standard); CRIB: clinical risk index for babies. ***: p<0.001; **: p<0.01; *: p<0.05. §Only cases with spontaneous preterm labour.

Table S1. Maternal chronic diseases, and pregnancy and labour complications according to outcome groups and gestational age. Number (percent).

	Gestational age (weeks)					
	≤22*	23	24	25	26	Total <27 weeks
Death before admission, stillbirths	n=39	n=43	n=30	n=25	n=30	n=167
Essential hypertension	3 (7.7)	1 (2.3)	2 (6.7)	0 (0.0)	2 (6.7)	8 (4.8)
Preeclampsia	1 (2.6)	1 (2.3)	1 (3.3)	1 (4.0)	3 (10.0)	7 (4.2)
Abruption of placenta or placenta praevia	5 (12.9)	2 (4.7)	2 (6.7)	1 (4.0)	5 (16.7)	15 (9.0)
PPROM	8 (20.5)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	9 (5.4)
Chorioamnionitis	5 (12.8)	8 (18.6)	1 (3.3)	1 (4.0)	1 (3.3)	16 (9.6)
Twins or triplets	7 (17.9)	9 (20.9)	2 (6.7)	0 (0.0)	2 (6.7)	20 (12.0)
Alive at admission, stillbirths	n=52	n=39	n=17	n=20	n=9	n=137
Essential hypertension	0 (0.0)	2 (5.1)	4 (23.5)	3 (15.0)	1 (11.1)	10 (7.3)
Preeclampsia	2 (3.8)	6 (15.4)	4 (23.5)	6 (30.0)	0 (0.0)	18 (13.1)
Abruption of placenta or placenta praevia	4 (7.7)	5 (12.8)	3 (17.6)	1 (5.0)	1 (11.1)	14 (10.2)
PPROM	16 (30.8)	14 (35.9)	3 (17.6)	3 (15.0)	0 (0.0)	36 (26.3)
Chorioamnionitis	12 (23.1)	5 (12.8)	5 (29.4)	1 (5.0)	2 (22.2)	25 (18.2)
Twins or triplets	16 (30.8)	9 (23.1)	4 (23.5)	1 (5.0)	1 (11.1)	31 (22.6)

Table S1 (continued)

Live-born, death <24 h after birth	n=39	n=30	n=21	n=10	n=6	n=106
Essential hypertension	1 (2.6)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	2 (1.9)
Preeclampsia	2 (5.1)	1 (3.3)	1 (4.8)	1 (10.0)	0 (0.0)	5 (4.7)
Abruption of placenta or placenta praevia	5 (12.3)	2 (6.7)	1 (4.8)	2 (20.0)	1 (16.7)	11 (10.4)
PPROM	9 (23.1)	11 (36.7)	4 (19.0)	1 (10.0)	1 (16.7)	26 (24.5)
Chorioamnionitis	7 (17.9)	4 (13.3)	4 (19.0)	3 (30.0)	2 (33.3)	20 (18.9)
Twins or triplets	13 (33.3)	7 (23.3)	7 (33.3)	3 (30.0)	3 (50.0)	33 (31.1)
Live-born, death 1 - 364 days	n=7	n=18	n=27	n=28	n=24	n=104
Essential hypertension	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	1 (1.0)
Preeclampsia	0 (0.0)	0 (0.0)	4 (14.8)	6 (21.4)	6 (25.0)	16 (15.4)
Abruption of placenta or placenta praevia	0 (0.0)	4 (22.2)	1 (3.7)	6 (21.4)	3 (12.5)	14 (13.4)
PPROM	0 (0.0)	4 (22.2)	3 (11.1)	5 (17.9)	2 (8.3)	14 (13.5)
Chorioamnionitis	2 (28.6)	0 (0.0)	4 (14.8)	2 (7.1)	6 (25.0)	14 (13.5)
Twins or triplets	6 (85.7)	3 (16.7)	5 (18.5)	6 (21.4)	8 (33.3)	28 (26.9)
Survivors, alive at 365 days	n=5	n=53	n=96	n=167	n=176	n=497

Table S1 (continued)

Essential hypertension	0 (0.0)	0 (0.0)	5 (5.2)	10 (6.0)	6 (3.4)	21 (4.2)
Preeclampsia	0 (0.0)	4 (7.5)	7 (7.3)	23 (13.8)	30 (17.0)	64 (12.9)
Abruption of placenta or placenta praevia	0 (0.0)	5 (9.5)	11 (11.5)	24 (14.4)	31 (27.5)	71 (13.3)
PPROM	0 (0.0)	7 (13.2)	8 (8.3)	25 (15.0)	23 (13.1)	63 (12.7)
Chorioamnionitis	1 (20.0)	7 (13.2)	17 (17.7)	33 (19.8)	22 (12.5)	80 (16.1)
Other specified diseases and complications	0 (0.0)	3 (5.7)	3 (3.1)	6 (3.6)	10 (5.7)	22 (4.4)
Twins or triplets	2 (40.0)	6 (11.3)	20 (20.8)	29 (17.4)	40 (22.7)	97 (19.5)

*Includes 2 infants born alive at 21+5 and 21+6 (weeks+days), respectively; PPRM: preterm prelabour rupture of membranes.

Table S2. Infant characteristics according to outcome groups and gestational age.

	Gestational age (weeks)					
	22	23	24	25	26	Total <27 weeks
Death before admission, stillbirths	n=39	n=43	n=30	n=25	n=30	n=167
Birth weight, g, median (range)	460 (102-750)	405 (132-850)	444 (195-950)	477.5 (100-804)	732.5 (205-1130)	470 (100-1130)
Birth weight SDS, median (range)	-0.6 (-6.7 – 5.0)	-3.0 (-6.5-2.2)	-3.1 (-6.3-3.1)	-3.6 (-7.4 - -0.2)	-2.4 (-6.7-0.9)	-2.5 (-7.4-5.0)
SGA, n (%)	9 (23.1)	24 (55.8)	16 (53.3)	14 (56.0)	17 (56.7)	80 (47.9)
LGA, n (%)	1 (2.6)	1 (2.3)	1 (3.3)	0 (0.0)	0 (0.0)	3 (1.8)
Congenital anomalies, n (%)	1 (2.6)	4 (9.3)	2 (6.7)	1 (4.0)	3 (10.0)	11 (6.6)
Alive at admission, stillbirths	n=52	n=39	n=17	n=20	n=9	n=137
Birth weight, g, median (range)	470 (160-660)	500 (200-655)	534 (290-790)	557 (370-965)	640 (290-988)	492.5 (160-988)
Birth weight SDS, median (range)	-0.6 (-5.9-1.5)	-1.4 (-5.7-0.7)	-2.2 (-5.2-0.7)	-3.0 (-4.7-0.2)	-3.2 (-3.7- -0.1)	-1.1 (-5.9-1.5)
SGA, n (%)	8 (15.4)	8 (20.5)	8 (47.1)	10 (50.0)	6 (66.7)	40 (29.2)
LGA, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomalies, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	1 (11.1)	3 (2.2)
Live-born, death <24 h after birth	n=39	n=30	n=21	n=10	n=6	n=106
Birth weight, g, median (range)	500 (280-730)	550 (320-740)	659 (474-930)	847.5 (266-1235)	986.5 (703-1500)	571.5 (266-1500)

Table S2 (continued)

Birth weight SDS, median (range)	0.0 (-3.2-3.9)	-0.6 (-3.8-1.4)	-0.3 (-2.7-2.9)	0.0 (-5.8-4.0)	-0.1 (-2.5-3.5)	-0.2 (-5.8-4.0)
SGA, n (%)	3 (7.7)	3 (10.0)	1 (4.8)	2 (20.0)	1 (16.7)	10 (9.4)
LGA, n (%)	2 (5.1)	0 (0.0)	2 (9.5)	1 (10.0)	1 (16.7)	6 (5.7)
Congenital anomalies, n (%)	0 (0.0)	1 (3.3)	1 (4.8)	3 (30.0)	1 (16.7)	6 (5.7)
Apgar score 1 min <4	32 (82.1)	28 (93.3)	18 (85.7)	7 (70.0)	1 (16.7)	86 (81.1)
Apgar score 5 min <4	36 (92.3)	26 (86.7)	16 (76.2)	5 (50.0)	1 (16.7)	84 (79.2)
Live-born, death 1 - 364 days	n=7	n=18	n=27	n=28	n=24	n=104
Birth weight, g, median (range)	498 (440-645)	590.5 (463-808)	620 (374-1070)	723 (435-1060)	765.5 (510-1161)	657.5 (374-1161)
Birth weight SDS, median (range)	-0.7 (-1.6-1.3)	-0.3 (-2.0-3.1)	-1.1 (-3.8-3.1)	-1.3 (-4.4-1.1)	-1.8 (-3.8-1.8)	-1.1 (-4.4-3.1)
SGA, n (%)	0 (0.0)	0 (0.0)	6 (22.2)	8 (28.6)	10 (41.7)	24 (23.1)
LGA, n (%)	0 (0.0)	1 (5.6)	1 (3.7)	0 (0.0)	0 (0.0)	2 (1.9)
Congenital anomalies, n (%)	0 (0.0)	2 (11.1)	5 (18.5)	6 (21.4)	4 (16.7)	17 (16.3)
Apgar score 1 min <4	2 (28.6)	12 (66.7)	10 (37.0)	7 (25.0)	5 (20.8)	36 (34.6)
Apgar score 5 min <4	0 (0.0)	3 (16.7)	2 (7.4)	2 (7.1)	3 (12.5)	10 (9.6)
CRIB-score >10, n/N [§] (%)	1/7 (14.3)	6/16 (33.3)	6/27 (22.2)	5/27 (17.9)	5/24 (20.8)	23/101 (22.1)

Table S2 (continued)

Survivors, alive at 365 days	n=5	n=53	n=96	n=167	n=176	n=497
Birth weight, g, median (range)	554 (361-581)	600 (423-770)	690 (375-835)	790 (348-1114)	924 (430-1315)	770 (348-1315)
Birth weight SDS, median (range)	0.3 (-2.8-1.2)	-0.4 (-3.1-1.6)	-0.5 (-3.9-1.1)	-0.7 (-4.8-1.8)	-0.8 (-5.0-2.2)	-0.7 (-5.0-2.2)
SGA, n (%)	1 (20.0)	4 (7.5)	9 (9.4)	29 (17.4)	37 (21.0)	80 (16.1)
LGA, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Table S2 (continued).						
Congenital anomalies, n (%)	0 (0.0)	6 (11.3)	9 (9.4)	20 (12.0)	19 (10.8)	54 (10.9)
Apgar score 1 min <4	1 (20.0)	13 (24.5)	35 (36.5)	45 (26.9)	28 (15.9)	122 (24.5)
Apgar score 5 min <4	0 (0.0)	2 (3.8)	12 (12.5)	11 (6.6)	10 (5.7)	35 (7.0)
CRIB-score >10, n/N [§] (%)	0/5 (0.0)	17/52 (32.7)	16/96 (16.7)	12/164 (7.2)	5/171 (2.8)	50/488 (10.2)

SDS: standard deviation score of birth weight according to the Swedish standard curve for intrauterine growth⁷; SGA: small-for-gestational age; LGA: large-for-gestational age; CRIB: Clinical risk index for babies; [§]calculated only for cases with CRIB-score available.

Table S3. Factors associated with stillbirth among fetuses admitted to hospital alive versus infants born alive and surviving at least 365 days. Results from univariate analyses and multiple logistic regression analyses including gestational age alone or gestational age and fetal growth expressed as standard deviation of birth weight according to the Swedish standard curve for intrauterine growth. For each column, the ‘base-adjustment-variable-set’ is indicated with grey colour; the unmarked variables were added separately one at a time. The results of grey-marked variables were derived from models in which no other variables than those grey-marked (gestational age alone or gestational age and SD of birth weight) were entered.

	Univariate analysis		Multiple models with gestational age		Multiple models with gestational age and fetal growth		Multiple model ^A including all listed variables in the column	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Gestational age and intrauterine growth								
GA, one-week increment	0.4	0.4-0.5***	0.4	0.4-0.5***	0.4	0.3-0.6***	0.4	0.3-0.5***
SD (birth weight), one-step increment	0.7	0.6-0.8***	0.5	0.4-0.6***	-	-	-	-
SD (birth weight), second grade model								
Linear term	0.8	} Simultaneous p=1.9*10 ⁻⁸	0.7	} Simultaneous p=2.1*10 ⁻¹³	0.7	} Simultaneous p=2.1*10 ⁻¹³	0.6	} Simultaneous p=3.5*10 ⁻¹⁴
Quadratic term	1.1		1.1		1.1		1.0	
Pregnancy and delivery								
Preeclampsia / Essential hypertension	1.2	0.7-2.1	2.2	1.2-4.0*	0.8	0.4-1.7	-	-

Table S3 (continued)

Chorioamnionitis / PPROM	1.7	1.1-2.6*	1.9	1.2-3.1**	1.8	1.0-3.1*	1.9	1.2-3.0**
Abruption of placenta	0.8	0.4-1.6	1.0	0.5-2.0	1.4	0.6-3.1	-	-
Breech, vaginal delivery	4.0	2.5-6.4***	3.0	1.8-5.0***	2.4	1.4-4.4**	3.0	1.7-5.2***
Birth at level II hospital	2.3	1.6-3.4***	1.6	1.0-2.5*	1.8	1.1-2.9*	1.8	1.1-2.9*
Newborn characteristics								
Male gender (vs. female)	1.0	0.7-1.5	1.0	0.7-1.5	1.0	0.6-1.5	.-	-
Birth weight (100g increment)	0.4	0.4-0.5***	0.5	0.4-0.6***	-	-	-	-
SGA	2.1	1.4-3.3***	4.4	2.6-7.4***	-	-	-	-

OR: Odds ratio; 95%CI: 95% confidence interval; GA: gestational age; SD: standard deviation of birth weight according to the Swedish standard curve for intrauterine growth;⁷ PPROM: preterm prelabour rupture of membranes; SGA: small-for-gestational age (birth weight below the mean -2SD of the standard).

***: p<0.001; **: p<0.01; *: p<0.05. ^AThe multiple model includes all variables with p-value below 0.2 in model 3.

Table S4. Factors associated with neonatal death within 24 hours after birth compared to infants alive at one year of age. Results from univariate analyses and multiple logistic regression analyses including gestational age alone or gestational age and fetal growth expressed as standard deviation of birth weight according to the Swedish standard curve for intrauterine growth. For each column, the ‘base-adjustment-variable-set’ is indicated with grey colour; the unmarked variables were added separately one at a time. The results of grey-marked variables were derived from models in which no other variables than those grey-marked (gestational age alone or gestational age and SD of birth weight) were entered.

	Univariate analysis		Multiple models		Multiple models with		Multiple model ^A	
			with gestational age		gestational age		including all listed	
					and fetal growth		variables in the column	
	OR	95% CI	OR	OR	OR	95% CI	OR	95% CI
Gestational age and intrauterine growth								
GA, one-week increment	0.3	0.2-0.3***	0.3	0.2-0.3***	0.3	0.2-0.3***	0.3	0.2-0.4***
SD (birth weight), one-step increment	1.3	1.1-1.6**	1.1	0.9-1.4	1.1	0.9-1.4	-	-
SD (birth weight), second grade model								
Linear term	1.6	} Simultaneous p=9.6*10 ⁻⁵	1.5	} Simultaneous p=1.0*10 ⁻⁴	1.5	} Simultaneous p=1.0*10 ⁻⁴	1.5	} Simultaneous p=5.4*10 ⁻⁶
Quadratic term	1.1		1.2		1.2		1.3	
Pregnancy and delivery								
Preeclampsia / Essential hypertension	0.4	0.1-0.9*	0.5	0.2-1.6	0.3	0.1-1.0 n.s	0.7	0.1-2.8

Table S4 (continued).

Chorioamnionitis / PPROM	1.3	0.8-2.0	2.1	1.1-3.9*	1.8	1.0-3.5 n.s.	2.5	1.3-4.8**
Multiple birth	1.9	1.2-3.0*	2.1	1.2-3.9*	2.3	1.2-4.3**	3.0	1.5-6.0**
Abruption of placenta	0.8	0.4-1.7	1.4	0.6-3.3	1.6	0.6-3.9	-	-
Breech, vaginal delivery	4.4	2.4-7.8***	2.2	1.1-4.4*	2.1	1.0-4.2*	2.3	1.0-5.1*
Birth at level II hospital	3.4	2.1-5.3***	2.9	1.6-5.2**	3.2	1.7-6.0***	2.6	1.2-5.3*
Cesarean section	0.2	0.1-0.3***	0.5	0.3-1.0*	0.4	0.2-0.8*	0.4	0.2-0.9*
Antenatal antibiotics	1.2	0.8-2.0	1.0	0.6-1.6	1.1	0.6-1.9	-	-
Antenatal corticosteroids	0.1	0.1-0.2***	0.2	0.1-0.5***	0.2	0.1-0.5***	0.3	0.1-0.6**
Tocolysis [§]	0.3	0.2-0.5***	0.4	0.2-0.8**	0.4	0.2-0.7**	0.8	0.3-1.9
Newborn characteristics								
Male gender (vs. female)	1.0	0.6-1.5	1.0	0.6-1.7	1.1	0.7-1.9	-	-
Birth weight (100g increment)	0.6	0.5-0.6***	1.2	0.9-1.5	Not included		Not included	
SGA	0.5	0.3-1.1	0.9	0.4-2.1	Not included		Not included	
Apgar score <4 at one minute	13.2	7.8-22.3***	8.6	4.7-15.6***	9.3	4.8-17.8***	Not included	
Apgar score <4 at five minutes	50.4	28.2-90.2***	28.1	14.7-53.8***	36.0	17.2-75.2***	Not included	

Table S4 (continued)

[§]Only cases with spontaneous preterm labour. OR: Odds ratio; 95%CI: 95% confidence interval; GA: gestational age; SD: standard deviation of birth weight according to the Swedish standard curve for intrauterine growth;⁷ PPRM: preterm prelabour rupture of membranes; SGA: small-for-gestational age (birthweight below the mean -2SD of the standard). ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$; n.s.: non-significant. ^AThe multiple model includes all variables with p-value below 0.2 in model 3 (with exception of Apgar score which was considered to be an intermediate variable).

Table S5. Factors associated with infant death between 1 and 364 days after birth compared to infants alive at one year of age. Results from univariate analyses and multiple logistic regression analyses including gestational age alone or gestational age and fetal growth expressed as standard deviation of birth weight according to the Swedish standard curve for intrauterine growth. For each column, the ‘base-adjustment-variable-set’ is indicated with grey colour; the unmarked variables were added separately one at a time. The results of grey-marked variables were derived from models in which no other variables than those grey-marked (gestational age alone or gestational age and SD of birth weight) were entered.

	Univariate analysis		Multiple models with gestational age		Multiple models with gestational age and fetal growth		Multiple model ^A including all listed variables in the column	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gestational age and intrauterine growth								
GA, one-week increment	0.7	0.6-0.8***	0.7	0.6-0.8***	0.6	0.5-0.8***	0.6	0.5-0.8***
SD (birth weight), one-step increment	0.8	0.7-1.0*	0.8	0.7-0.9**	0.8	0.7-0.9**	0.8	0.6-1.0*
Pregnancy and delivery								
Preeclampsia / Essential hypertension	1.2	0.7-2.3	1.5	0.8-2.8	1.0	0.5-2.1	-	-
Chorioamnionitis / PPROM	0.9	0.5-1.6	1.0	0.6-1.8	1.0	0.6-1.7	-	-
Abruption of placenta	0.9	0.5-1.9	1.1	0.5-2.2	1.2	0.6-2.4	-	-
Multiple birth	1.5	0.9-2.5	1.5	0.9-2.5	1.4	0.9-2.4	1.4	0.8-2.4

Table S5 (continued).

Breech, vaginal delivery	2.5	1.2-5.1*	1.7	0.8-3.6	1.9	0.9-4.1	1.7	0.8-3.9
Birth at level II hospital	1.3	0.8-2.2	1.5	0.9-2.5	1.7	1.0-2.9 n.s.	1.2	0.6-2.3
Cesarean section	0.9	0.6-1.3	1.2	0.7-1.9	1.0	0.6-1.6	-	-
Antenatal antibiotics	0.6	0.4-0.9*	0.6	0.4-0.9*	0.6	0.4-1.0	0.8	0.5-1.3
Antenatal corticosteroids	0.3	0.2-0.6***	0.3	0.2-0.6***	0.3	0.1-0.6***	0.3	0.2-0.8**
Tocolysis [§]	0.4	0.2-0.8*	0.4	0.2-0.8*	0.5	0.2-0.9*	0.6	0.3-1.2
Newborn characteristics								
Male gender (vs. female)	1.1	0.7-1.7	1.2	0.8-1.8	1.2	0.8-1.9	-	-
Birth weight, 100g increment	0.7	0.6-0.8***	0.8	0.7-0.9**	-	-	-	-
SGA	1.6	0.9-2.6	2.0	1.2-3.4*	-	-	-	-
Apgar score <4 at one minute	1.6	1.0-2.6*	1.4	0.9-2.3	1.5	0.9-2.3	Not included	
Apgar score <4 at five minutes	1.4	0.7-2.9	1.4	0.7-3.0	1.4	0.7-3.0	-	-
CRIB score >10	2.6	1.5-4.5***	2.0	1.1-3.6*	1.7	1.0-3.1 n.s.	-	-
CRIB score (continuous), one-step increment	1.2	1.1-1.3***	1.2	1.1-1.3***	1.2	1.1-1.3 ***	Not included	

Table S5 (continued)

§Only cases with spontaneous preterm labour. OR: Odds ratio; 95%CI: 95% confidence interval; GA: gestational age; SD: standard deviation of birth weight according to the Swedish standard curve for intrauterine growth;⁷ PPROM: preterm prelabour rupture of membranes; SGA: small-for-gestational age (birth weight below the mean -2SD of the standard); CRIB: clinical risk index for babies. ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$; n.s.: non-significant. . ^The multiple model includes all variables with p-value below 0.2 in model 3 (with exception of Apgar score or CRIB score which were considered to be intermediate variables).