Extremely preterm infants in Sweden study – a population-based registry study on short and long-term outcomes

Acronym
EXPRESS2

First responsible researcher
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Collaborating researchers
Please see attachment 1 in application to the regional ethical review board.

Ethical permit number(s)
Application submitted.

Background
Preterm birth is still a major cause of death worldwide. However, significant improvements in perinatal care in developed countries mean that preterm birth is no longer a fatal pregnancy complication. In fact, a steadily growing number of infants nowadays survive also after extremely short gestations. This development has contributed to an emerging interest in reducing short term complications and promoting long-term health in childhood and adult survivors of preterm birth.

In 2004, the extremely preterm infants in Sweden study (EXPRESS) started. The main objectives were to determine perinatal mortality and morbidity by each gestational week, identify perinatal risk factors for adverse outcome and to evaluate long-term health in infants born before 27 weeks of gestation. So far the EXPRESS-study has generated a large number of publications (the full publication list is given as attachment 12 in the ethics application) demonstrating a) high survival rates in an international comparison but at the same time b) worrying rates of severe neonatal morbidities and c) one out of four infants ending up with moderate to severe disability in early childhood. These results have called for action and several initiatives have recently been launched to improve quality of care such as national programs for optimized nutrition and growth, infection control and centralization of care. The results of the EXPRESS-study have also contributed to
altered governance of perinatal management at extremely short gestations with a new definitions, new legislations and new national as well as international guidelines.

Given the rapid development in perinatal medicine, we plan a national, population-based 10-year follow-up study with overall the same objectives as in the premier study (EXPRESS1) running in 2004-2007.

**Main hypotheses**
1. rates of extremely preterm births has increased, partly driven by larger proportions of pregnant women with advanced maternal age, with overweight or obesity and with pregnancies resulting from assisted reproduction (all significant risk factors for extremely preterm birth).
2. the perinatal management has become significantly more proactive in pregnancies with the shortest durations (gestational weeks 22-24).
3. the survival rates for extremely preterm infants have increased without parallel increases in severe neonatal morbidity or long-term disability.

**Primary objectives**
1. to determine delivery, stillbirth and liveborn rates for each gestational week
2. to determine perinatal, neonatal and infant mortality, and neonatal morbidity by gestational week
3. to assess long-term somatic and neuropsychological outcome for extremely preterm infants

**Secondary objectives**
1. to determine the clinical outcome in relation to mode of delivery
2. to determine the significance of the infants condition at birth and immediate actions for later health outcomes
3. to assess use of evidence-based practices in neonatal care and relation to outcome
4. to map the extent of postnatal transports and their significance for outcome
5. to evaluate use of and outcome after neonatal surgery
6. to assess perinatal and longer-term outcomes of multiple births
Study population (inclusion and exclusion criteria)

Inclusion criteria
All live-born infants born before 27 weeks of gestation and all stillbirths delivered at 22⁰ to 26⁰ weeks of gestation in Sweden between Jan 1 2014 and Dec 31 2016.

Exclusion criteria
Women delivering extremely preterm not residing in Sweden, and extremely preterm infants born outside Sweden during the study period.

Data extracts/registries
In contrast to EXPRESS1 in which data collection was performed using individual, paper protocols for each participating infant, EXPRESS2 will be based on population-based registries who have reached national coverage since the former study period.

We will use the Swedish Neonatal Quality (SNQ) registry and the Medical Birth Registry (MBR) to identify the participants. The causes of death registry will also be used for mortality outcomes. Patient IDs will be used for cross-links.

Main outcomes
Delivery rates, infant (perinatal and neonatal) mortality, severe neonatal morbidity (defined as intraventricular hemorrhage grade 3-4, cystic periventricular leucomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia or retinopathy of prematurity grades 3-5) and moderate to severe disability at 2 and 5-years of age (somatic and neurodevelopmental or psychological outcomes at 2 and 5 years-of-age as per national protocols, please see appendix in ethics application).

Exposures/risk factors and co-variates
Maternal: age, parity, diabetes (GDM, type 1 or II), smoking in pregnancy (any), nordic or non-nordic country of birth, assisted reproduction, BMI, pregnancy dating according to last menstrual date or ultrasonography
Obstetric: single-multiple pregnancy, preeclampsia/eclampsia, bleedings, chorioamnionitis, preterm prelabor rupture of membranes, preterm labor, antenatal steroids (any), tocolysis, antenatal transfer, born at regional (level III) center, onset of delivery, fetal presentation, mode of delivery, gestational age, neonatologist present at birth
Infant/neonatal data: birth weight, SGA/AGA/LGA, Apgar score at 1 and 5 min (including individual components), intubation at birth, admission for neonatal intensive care, surfactant administration within 2 hours after birth, IVH ≥3, cPVL, NEC (Bells stage 2 or more), malformations, mechanical ventilation (y/n), septicemia, PDA treatment, BPD (oxygen dependency@36wks), postnatal transfer between hospitals (y/n and numbers), neonatal surgery, weight, length and head circumference@36wks.

**Statistical analysis plan for primary objectives 1 and 2**

Associations between gestational age and various dichotomized variables will be analyzed using simple linear logistic regression. Overall survival will be determined by standard Kaplan-Meier survival analysis. Dichotomized risk factors for infant death will be evaluated using simple logistic regression analyses or, when specified, multiple logistic linear regression analyses adjusting for gestational age (entered as a continuous variable). The effect of selected perinatal interventions will analyzed in a multivariate model as specified. Goodness of fit will be evaluated with Hosmer-Lemeshow test. All will be 2-sided; P values of less than .05 will be considered statistically significant.

**Time plan**

Ethics application spring-summer 2016
Data acquisition and cleaning autumn-winter 2016
Writing and publishing of mortality paper 2017

**Key references**


