Kliiniline küsimus nr 3

Kas ähvardava enneaegse sünnituse korral, kui laps on gestatsioonivanuselt eluvõimelisuse piiril (22+0...23+6), tuleb vastsündinu ravitulemi parandamiseks rakendada perinataalset proaktiivset ravi (transport keskusesse, kopsude ettevalmistus, keisrilõige lapsepoolsel näidustusel, neuroprotektsioon, tokolüüs, antibiootikumravi) võrreldes proaktiivse ravi mitterakendamisega?

Tulemusnäitajad: emade tervisetulem, suremus, lapse peamised tulemusnäitajad

Ravijuhendid

Kokkuvõte ravijuhenditest: 5 antud küsimust käsitlevat ravijuhendit.

Väga hea kvaliteediga NICE ravijuhend (nov 2015) soovitab raseduse kestuses 23+0 kuni 23+6 kortikosteroidide manustamise otsuse vastu võtta pärast vanemate nõustamist ja nendega arutlemist, arvesse võttes individuaalseid tegureid. Neuroprotektsiooni soovitatakse alates raseduse kestusest 24+0. Tokolüüsiks soovitatakse kasutada kaltsiumkanali blokaatoreid. Tokolüüsi soovitatakse alustada alates 24+1 raseduse kestusest, kuid tuleks silmas pidada, et tokolüütiliste ravimite kasutamise kohta enne 26+0 gestatsiooniaega puudub tõendusmaterjal. Sünnitusviisi osas soovitatakse vanemaid nõustada riskide osas ning sellest, et pole teada, kas keisrilõige tooks võrreldes vaginaalse sünnitusega rohkem kasu või kahju, kuna puudub piisav adekvaatne tõendusmaterjal. Keisrilõiget soovitatakse kaaluda alates 26+0 gestatsiooniajast loote tuharseisu korral.

Väga hea kvaliteediga Queenslandi ravijuhend (2014) soovitab eluvõimelisuse piiril oleva ähvardava enneaegse sünnituse korral antenataalset transporti kõrgema etapi haiglasse, kui plaanitakse elu toetavaid sekkumisi. In utero transporti ei soovitata, kui tegemist on ähvardava enneaegse sünnitusega enne 23. GN või kui plaanitakse vastsündinu palliatiivset ravi. Magneesiumsulfaadi kasutamist neuroprotektsiooni eesmärgil soovitatakse alates 23+0 raseduse kestusest. Kortikosteroide soovitatakse samuti kasutada alates 23+0 gestatsiooniajast. Samas rõhutatakse kõigi nende sekkumiste kohta, et kui elu toetavaid sekkumisi (elustamist) plaanitakse alates mingist kindlast gestatsiooniajast (nt 24+0), siis tasuks ema transportida/kortikosteroide või magneesiumi manustada paar päeva väiksema gestatsioonivanuse korral. Kuna keisrilõike kohta eluvõimelisuse piiril oleva sünnituse korral pole järelduste tegemiseks väga head tõendusmaterjali, siis ekspertide konsensus ei soovita lootepoolsetel näidustustel alla 24+0 gestatsiooniaja keisrilõike tegemist. Kõikide otsuste puhul peaks kasutama perekeskset lähenemist, arvestama peaks ema ja loote kasusid-kahjusid, vanemate soove ning individuaalseid faktoreid. Ühe sekkumise rakendamine ei tähenda automaatselt, et peaks rakendama kõiki sekkumisi (nt transport keskusesse ei pruugi tähendada, et vastsündinut elustama hakatakse). Sekkumise plaan on dünaamiline, vajab pidevalt üle vaatamist, kui sünnitus edasi lükkub ja gestatsioonivanus kasvab.

Hea kvaliteediga **Rootsi ravijuhend** (2014) soovitab eluvõimelisuse piiril oleva ähvardava enneaegse sünnituse korral ema antenataalset transporti kõrgema taseme haiglasse ning kõigile naistele soovitatakse manustada kortikosteroide.

Hea kvaliteediga **RCOG ACS ravijuhend** (2010) soovitab ettevaatusega ja kõrgema etapi otsusena kaaluda kortikosteroidide manustamist 23+0 kuni 23+6 gestatsiooniajas, kuid peab arvesse võtma kogu kliinilist informatsiooni ja individuaalseid tegureid.

Šveitsi riiklike soovituste dokument (2011) soovitab hiljemalt 23+0 raseduse kestuses emade transporti kõrgema etapi haiglasse. Kortikosteroide soovitatakse alates 24+0 GN. Keisrilõiget lootepoolsel näidustusel võiks kaaluda pärast 24+0 GN, kui on teostatud loote kopsude ettevalmistus kortikosteroididega. Eriolukordades, nt kui põhjalikult nõustatud vanemad seda siiski tungivalt soovivad, võib keisrilõiget kaaluda ka alates 23+0 GN.

RAVIJUHEND	VIIDE
Queenslandi 2014.a ilmunud väga hea kvaliteediga (AGREE hinne 91 p) ravijuhend eluvõimelisuse piiri kohta: - Use a family centred approach to the planning, delivery and evaluation of care. – Consensus - Using a multidisciplinary approach and in conjunction with the family, develop a plan of care at the earliest opportunity. Reassess the plan frequently with the family and document all decisions. – Consensus **In-utero transfer:** - Where preterm birth before 26+0 weeks gestation is considered very likely and where life sustaining interventions are planned or may be a possibility, recommend in-utero transfer to a level 6 facility.- III-2 In utero transfer not indicated if: - palliative care planned -birth certain or imminent at less than 23 weeks. If life sustaining interventions are to be initiated only if a specific gestational age achieved (e.g. interventions only if gestation reaches 24 weeks) then arrange transfer prior to the specified gestation (i.e. don't wait until 24 weeks+0 days). Inform the family that transfer does not oblige or necessarily equate to a final decision for life sustaining interventions. Survival rates are higher in centres that deliver a high volume of very low birth weight babies and provide the highest level of neonatal care. Inborn babies have a better prognosis than outborn babies. Aim to achieve in-utero transfer unless transfer puts the mother's life at risk—this may require a higher level of acceptance of the risk of birth en route. Consult with higher level clinical services as early as possible, preferably the neonatal unit where the baby will be cared for. If clinically appropriate, use tocolysis to allow in-utero transfer. *Tõendusmaterjal: FIGO, ACOG, Šveitsi ravijuhendid, Lasswell 2010 meta-analüüs* **Magnesium Sulfate for neuroprotection:** - Recommend Magnesium Sulfate to women at risk of preterm birth between 23+0 weeks and 30+0 weeks gestation where birth is imminent and life sustaining interventions are planned or may be a possibility. – I Magnesium Sulfate (MgSO4) given to mothers shortly before delivery reduces the risk of cerebral palsy and protects gross motor function in those infants born preterm. Number needed to treat (NNT): 63 babies for one baby to avoid cerebral palsy (95% CI 44-155). NNT to benefit (NNTB): 42 babies for combined death or cerebral palsy (95% CI 24-346). The effect may be greatest at early gestational ages and is not associated with adverse long-term fetal or maternal outcome. *Tõendusmaterjal: RCOG impact paper 2011, Doyle et al 2009 Cochrane ülevaade, Adelaide ülikooli juhend 2010* **Antenatal corticosteroids:** - Recommend corticosteroids to women who are at risk of preterm birth where life sustaining interventions are planned or may be a possibility. – I -Not indicated if birth is imminent at <23+0 weeks. If life sustaining interventions are to be initiated only if a specific	Queensland Clinical Guidelines. **Perinatal care at the threshold of viability.** Guideline No. MN 14.32-V1-R19. Queensland Health. **2014**. Available from: http://www.health.qld.gov.au/qcg/

gestational age achieved, (e.g. only if gestation reaches 24 weeks) then administer corticosteroids prior to the specified gestation (i.e. don't wait until 24 weeks+0 days). Inform the family that administration does not oblige or necessarily equate to a final decision for life sustaining interventions. Antenatal corticosteroids are associated with a significant reduction in rates of neonatal death, respiratory distress syndrome and intraventricular haemorrhage (IVH). Antenatal corticosteroid use is also associated with a reduction in necrotising enterocolitis, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life compared with no treatment or treatment with placebo. One study (n=10,541) reported a lower rate of death or neurodevelopmental impairment at 18–22 months for infants born at 23–25 weeks gestation who had antenatal exposure to corticosteroids compared with non-exposure. A single dose does not appear to be associated with significant maternal or fetal adverse effects.
Tõendusmaterjal: RCOG juhend, Roberts et al. 2006 Cochrane süst. ülevaade, Carlo et al. 2011 prospektiivne kohortuuring

Caesarean section for fetal indications:

There is insufficient evidence upon which to base firm recommendations regarding CS for fetal indications at extremely premature gestational ages. Consider individual circumstances including (but not limited to): Potential for fetal and maternal risk and benefit; Family preferences and wishes; Individual clinical circumstances (e.g. fetal presentation)

Consensus recommendations of the working party regarding CS for fetal indications:

- Not recommended at less than 24+0 weeks gestation
- Not usually recommended between 24+0 and 24+6 weeks gestation
- May be recommended from 25+0 weeks gestation depending on individual circumstances.

The optimal mode of birth for babies of very low gestational age is uncertain and controversial. There are very few randomised controlled trials— most studies are retrospective and are likely to be subject to selection bias and/or have other serious limitations (vt APPENDIX B allpool). Preterm caesarean section (CS) is usually technically more difficult to perform and is not without risk to the baby as lower segment is usually not well formed. A classical incision may be required with risks to future pregnancies including scar dehiscence, uterine rupture, placental adherence and maternal death. Discuss the implications of decision with the woman. Some studies suggest CS improves survival and/or morbidity of the extremely preterm neonate, while others have not demonstrated benefit. Similarly there are inconsistent results regarding CS for extremely preterm breech presentation with some studies reporting reduced morbidity and/or mortality and others reporting no difference.
Tõendusmaterjal: Alfirevic 2013 Cochrane ülevaade, retrospektiivsed uuringud (vt tabel allpool)

Resuscitation:

Less than 23 weeks:

• Life sustaining interventions are not recommended for babies of less than 23 weeks gestation
• Provide palliative care if live birth occurs

23 weeks and 0 days until 23 weeks and 6 days:

• Life sustaining interventions are not usually recommended • If after appropriate counselling the family make an informed decision for life sustaining interventions, then initiate resuscitation and intensive care • If parental wishes are unknown at the time of birth: o Consider the individual circumstances of the case o It may be appropriate to initiate life sustaining interventions and reassess the baby's condition when parental wishes can be ascertained <u>24 weeks and 0 days until 24 weeks and 6 days:</u> • Life sustaining interventions are usually recommended • If after appropriate counselling, the family make an informed decision for palliative care, family wishes should be supported 25 weeks and 0 days until 25 weeks and 6 days • Life sustaining interventions are recommended o It is unusual not to provide resuscitative interventions to babies born alive at <u>25 weeks gestation</u> • Where there are specific circumstances suggesting an intolerable burden or that intervention is likely to be futile, and if after appropriate counselling the family make an informed decision to choose palliative care, this should be supported • Where there is conflict in the decision-making process between parents and health care professionals take all possible steps to resolve the conflict **Withdrawal of life sustaining interventions** • Make decisions in consultation with the family and in accordance with principles outlined in preceding sections • Document decisions contemporaneously • Refer to Section 6 Palliative care - vt juhend lk 25 *Tõendusmaterjal: Queenslandi elustamise juhend 2011, prospektiivne kohortuuring Tyson et al, 2008*	

Appendix B: Evidence summary related to caesarean birth

All included studies are retrospective and all attempt to find independent predictors of outcomes by using regression analysis except Alfrevic (2013) which is a systematic review of randomised controlled trials. Full citation details of studies can be found in the guideline reference list.

Studies on the effect of delivery mode on SURVIVAL of severely preterm cephalic fetuses

Negative finding: No independent effect of CS on survival
Positive finding: An independent effect where CS is associated with an improved survival

First Author	Year	Number	Birth weight/Gestation	Findings
Alfrevic	2013	116	<37 weeks	Negative for all
Reddy	2012	2138	24–31 weeks	Negative for all
Ghi	2010	109	25+0–32+6 weeks	Negative for all
Vimercati	2009	84	<28 weeks	Negative for all
Malloy	2008	120,542	22–31 weeks	Positive for 22-25 weeks
Wylie	2008	2466	<1500 g	Negative for all
Lee	2006	54,695	<1500 g	Positive for all
Muhuri	2006	60,364	500–1500 g	Positive for 500-749 g and 1000-1249 g Negative for 750-999 g and 1250-1499 g
Riskin	2004	2955	<1500 g	Negative

Studies on the effect of delivery mode on the occurrence of IVH in severely preterm fetus

Negative finding: No independent effect of caesarean birth on the occurrence of IVH
Positive finding: An independent effect of caesarean birth on the occurrence of IVH

First Author	Year	Number	Birth weight/Gestation	Findings
Ghi	2010	109	25+0–32+6 weeks	Negative
Dani	2009	218	< 28 weeks	Positive for Grade 3 IVH Vaginal birth 18% vs CS 2%
Wylie	2008	2466	<1500 g	Positive for IVH, OR 0.73 (0.55–0.97)
Riskin	2008	5033	<1500 g	Negative for IVH, OR 0.98 (0.77–1.24)
Haque	2008	213	<1250 g	Negative for IVH Vaginal birth 47.7% vs CS 46.8%

Potential limitations of retrospective studies

- Selection biases (e.g. CS may be favoured if fetus presumed viable and vaginal birth favoured if fetal condition assessed as poor)
- Small sample size
- Range of gestations/birth weights beyond the threshold of viability included, limiting applicability
- Incomplete accounting for the small/large for gestational age fetus
- Failure to distinguish between elective and emergency CS and account for the possibility of increased availability of specialised care, resources for advanced resuscitation and/or opportunity to transfer to higher level facilities
- Inability to completely account (especially from retrospective data registers) for maternal comorbidities, complications of pregnancy, labour and birth, indication for CS and other clinical factors and practices
- Inability to account for the influence of parental wishes/preferences in the decision-making process
- Immediate advantage following CS may not necessarily equate with improved long-term survival or decreased long term impairment
- Limited ability to generalise from studies involving single sites

Table 7. Factors influencing viability

Aspects	Considerations
Gestational age	• At very low gestational ages survival rate increases as gestational age increases ○ Adding even a few additional intrauterine days may be of great benefit[32] • Even relatively small discrepancies in gestational age may have major implications for survival and long-term morbidity[5] • Base gestational age on ultrasound measurements of the crown-rump length at 8–12 weeks (accuracy +/- 4 days) and/or history of the last menstrual period (accuracy -6 to +14 days)[14] • Consider the possibility of growth restriction where later ultrasound measurements suggest a younger gestational age[5] • Gestational age by obstetric dating is more accurate than estimation from physical and neurological criteria • Where gestational age is uncertain—reassess in the immediate postnatal period [refer to Table 18. Birthweight percentile values (g) for live singleton females and males]

Sex
Birth weight
Plurality
	• Factors associated with improved survival and outcome include:
	  ○ Female sex[27,31]
	  ○ Singleton birth
	  ○ Appropriate higher birth weight at a given gestational age[5] [refer to Table 18]

Congenital anomaly	• The outcome or prognosis associated with a significant fetal anomaly may be worsened by extreme prematurity. Examples include (but are not limited to) complex heart disease, diaphragmatic hernia, significant bowel disease • In Queensland 2000–2008, 23.3% of perinatal deaths were attributed to congenital abnormalities. Of these, 60% of perinatal deaths occurred prior to 28 weeks gestation[4]

Antenatal pathology	• Presence and/or severity of pathology influences outcomes[24]:
	• Poor outcome associated with (but not limited to):
	  ○ Birth weight less than the 2nd centile[33]
	  ○ Prolonged rupture of membranes
	  ○ Severely abnormal fetal Doppler
	  ○ Chorioamnionitis
	  ○ Antepartum haemorrhage
	  ○ Twin to twin transfusion syndrome

Rootsi 2014.a. ravijuhend - hea kvaliteediga (Agree 70 p): **In-utero transfer:** - The obstetric care of a woman with threatened with an extremely premature birth and the immediate care of the infant who is born extremely prematurely ought as far as possible to take place at a hospital with substantial experience of such specialist care. Where a premature birth threatens to occur before 28 weeks, provided that the birth is not immediately imminent, the expectant mother should be transported to a hospital with access to specialist obstetrics and neonatal care. Transportation in plenty of time before the expected birth facilitates an obstetric assessment, discussions with neonatologists and the possibility of informing the expectant parents in plenty of time. The care of extremely premature infants requires special resources and competences and ought therefore, to the greatest possible extent, to be offered at hospitals that have substantial experience of specialist neonatal care. *Tõendusmaterjal: Rootsi EXPRESS prospektiivsed kohortuuringud* **Antenatal corticosteroids:** During the care, corticosteroids ought to be given to all women threatened with an extremely premature birth, the parents should if possible be informed of what an extremely premature birth means plenty of time before the child is born, the most important immediate measure is to attempt to lengthen the pregnancy on condition that there is no danger to the mother's or the child's life or future health. Corticosteroids for women threatened with premature birth reduce the risk of neonatal death and serious diseases in the child. Randomised studies of prenatal steroids include few children born before 28 weeks of pregnancy but analyses of substantial amounts of patient material	The Swedish National Board of Health and Welfare. Care of extremely premature infants. **A guideline for the care of children born before 28 full weeks of pregnancy have passed. 2014.**

indicate that steroids have an effect as early as 22 to 23 weeks of pregnancy. *Tõendusmaterjal: Roberts et al. 2006 süst. ülevaade, Mori et al 2011 retrospektiivne kohortuuring*	
Šveitsi madala kvaliteediga (Agree 66 p) 2011.a. ilmunud ravijuhend: **In utero transfer:** Criteria for timely transfer of mothers experiencing threatened preterm delivery must be defined clearly and should be evaluated on a regular basis. Transfer of mothers at risk to a perinatal centre should occur no later than at 23 0/7 weeks and possibly earlier if additional complications are present (e.g., premature rupture of membranes). Although no intensive care measures would be initiated at this age should delivery occur, transfer of the pregnant women allows for detailed counselling and preparation of the parents. Parents should be informed about the referral in such a way that their expectations are appropriate and remain realistic regarding their individual situation. In particular, parents must be told that the prognosis regarding mortality and morbidity of infants born at the limit of viability is better when the transfer to a level III perinatal centre occurs prior to delivery. *Tõendusmaterjal: põhineb kohort-uuringutel (Ritari et al, 2005, EPICure)* **Antenatal corticosteroids:** In the presence of threatened preterm delivery, foetal lung maturation should be accelerated as early as 24 0/7 weeks of gestation with a single course of 2 doses of betamethasone 12mg i.m. 24 hours apart. In certain situations, acceleration of foetal lung maturation can be started a few days earlier, but not before 23 0/7 weeks. As an exception, a second course can be administered if the first two doses of betamethasone have been given very early and the risk of preterm delivery has again increased. *Tõendusmaterjal: RCT (Crowther 2007, Murphy 2008, Garite 2009), retrospektiivne kohort-uuring (Hayes 2008)* **Delivery, delivery mode and placental period:** After 24 0/7 weeks of gestation, active interventions for foetal indications should be considered after completion of the acceleration of foetal lung maturation; in special situations, particularly at the explicit wish of the fully informed parents, it may also be considered prior to 24 0/7 weeks of gestation, but not before 23 0/7 weeks of gestation. Guidance regarding the impact of the mode of delivery, particularly Caesarean section, on the prognosis of preterm infants at the limit of viability can only be obtained from retrospective studies and international recommendations from experts. In general, a Caesarean section should not be performed routinely because of the gestational age alone, since rates of neurosensory impairment have not decreased despite increasing rates of Caesarean sections. If the infant is in cephalic position, intrapartum surveillance is possible and there are no maternal and/or foetal risk factors, a Caesarean section does not offer any benefit [46]. Caesarean section may reduce perinatal mortality of preterm infants with a gestational age <25 0/7 weeks, in multiples, in infants in breech presentation and in growth restricted preterm infants with a gestational age between 26 and 30 weeks. The foetus should be	Berger TM1, Bernet V, El Alama S, Fauchère JC, Hösli I, Irion O, Kind C, Latal B, Nelle M, Pfister RE, Surbek D, Truttmann AC, Wisser J, Zimmermann R. **Perinatal care at the limit of viability between 22 and 26 completed weeks of gestation in Switzerland. 2011 revision of the Swiss recommendations.** Swiss Med Wkly. 2011 Oct 18;141:w13280. doi: 10.4414/smw.2011.13280.

monitored with intrapartum cardiotocography (adapted to the gestational age) in order to be able to intervene when foetal well-being is threatened. Different surgical techniques (classical vertical uterotomy versus transverse uterotomy) have a significant influence on postpartal morbidity, the risk of preterm delivery and uterine rupture in subsequent pregnancies. *Tõendusmaterjal: ACOG juhend 2003, NICE juhend 2004, Cochrane süst. ülevaade (Grant 2000), retrospekt. kohort-uuringud (Lee 2006, Malloy 2008).*	

Table 5: Algorithm and classification of obstetrical interventions.

Gestational age (weeks)	In utero transfer to a perinatal centre	Antenatal corticosteroids	Caesarean section
<22 0/7	not indicated	not indicated	only for maternal indications
22 0/7 – 22 6/7	possibly indicated	not indicated	only for maternal indications
23 0/7 – 23 6/7	indicated	possibly indicated	rarely for foetal indications
24 0/7 – 24 6/7	indicated	indicated	to be considered for foetal indications
25 0/7 – 25 6/7	indicated	indicated	to be considered for foetal indications

Note: gestational age stratification of obstetrical and neonatal interventions is only a first step in the decision making process. Prenatally known prognostic factors (sex, estimated foetal weight, single or multiple birth and exposure or non-exposure to antenatal corticosteroids) can have a significant impact on mortality and morbidity rates (see table 1). *Inborns* have a better prognosis than *outborns*. The clinical condition of the infant immediately after birth and the response to resuscitative measures are not reliable prognostic factors.

Table 6: Algorithm and classification of neonatal interventions.

Gestational age (weeks)	Neonatal care	Classification of intensive care measures
<22 0/7	comfort care	not indicated (burden not acceptable)
22 0/7 – 22 6/7	comfort care	not indicated (burden not acceptable)
23 0/7 – 23 6/7	generally comfort care	not recommended, but acceptable in individual cases (burden likely not to be acceptable)
24 0/7 – 24 6/7	generally provisional intensive care	conditionally recommended, but non-institution acceptable in individual cases (burden likely to be acceptable)
25 0/7 – 25 6/7	provisional intensive care	recommended (burden acceptable)

Note: gestational age stratification of obstetrical and neonatal interventions is only a first step in the decision making process. Prenatally known prognostic factors (sex, estimated foetal weight, single or multiple birth and exposure or non-exposure to antenatal corticosteroids) can have a significant impact on mortality and morbidity rates (see table 1). *Inborns* have a better prognosis than *outborns*. The clinical condition of the infant immediately after birth and the response to resuscitative measures are not reliable prognostic factors.

NICE (ilmunud novembris 2015) ravijuhend: kõrge kvaliteediga ravijuhend **Kortikosteroidid:** -For women between **23+0 and 23+6** weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM, **discuss with the woman** (and her family members or carers as appropriate) **the use of maternal corticosteroids in the context of her individual circumstances.** *Tõendusmaterjal: Roberts et al 2006 süstem. ülevaade, Porto 2011 RCT, Onland 2011 süstem. ülevaade – tõendusmaterjal on madala kuni mõõduka tugevusega; tõendusmaterjal oli nii väikeste gestatsiooniaegade kohta on limiteeritud ja soovitused lähtuvad vanemate gestatsiooniaegade tõendusmaterjali ekstrapolatsioonil.* **Neuroprotektsioon:** -Offer intravenous magnesium sulfate for **neuroprotection** of the baby to women between **24+0** and 34+0 weeks of pregnancy who are: in established preterm labour or having a planned preterm birth within 24 hours. *Tõendusmaterjal: põhineb samadel RCT-tel, mis on kaasatud Doyle et al. 2009 Cochrane süstemaatilisse ülevaatesse. The use of magnesium sulfate for this indication has been studied in five randomized controlled trials, with enrollment started as early as 24 weeks of gestation* **Tokolüüs:** - Offer calcium channel blockers for tocolysis to women between **24+1** and 34+0 weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour.	National Institute for Health and Care Excellence. Preterm labour and birth. London, 2015.

-Be aware that there is an absence of evidence about all tocolytic medicines before 26+0 weeks of pregnancy. *The average gestational age profile of women included in the evidence for this section was 26 weeks but the range was wider and covered women between 24 and 36 weeks of gestation. The committee discussed the role of tocolytics by gestational age and recognised the lack of data for the effectiveness and/or harm of tocolytics on the fetus at a gestational age below 26 weeks.* **Delivery mode:**-Discuss the general benefits and risks of caesarean section and vaginal birth with women in suspected or diagnosed preterm labour and women with P-PROM (and their family members or carers as appropriate). -Explain to women in suspected or diagnosed preterm labour and women with P-PROM about the benefits and risks of caesarean section that are specific to gestational age. In particular, highlight the difficulties associated with performing a caesarean section for a preterm birth, especially the increased likelihood of a vertical uterine incision and the implications of this for future pregnancies. -Explain to women in suspected or diagnosed preterm labour that there are no known benefits or harms for the baby from caesarean section, but the evidence is very limited. -Consider caesarean section for women presenting in suspected or diagnosed preterm labour between **26+0** and 36+6 weeks of pregnancy **with breech presentation**, and explain to the woman that: □ caesarean section for breech presentation for preterm babies is common but not universal practice □ this practice is based on an extrapolation of evidence of best management for breech presentation for babies born at term □ there is some evidence that there may be a large reduction in perinatal mortality associated with caesarean section for preterm babies with breech presentation, but overall the evidence is inconclusive. *Tõendusmaterjal: Alfirevic 2013 Cochrane ülevaade – GA al 26 nädalat*	

Süstemaatilised ülevaated

Kokkuvõte: 4 mõõduka kuni hea kvaliteediga süstemaatilist analüüsi/meta-analüüsi.
Mõõduka kvaliteediga **meta-analüüs regionaliseerimise kohta (Lasswell et al. 2010)** leidis, et alla 1500 g või alla 32. GN vastsündinutel esineb madalama etapi haiglas sündides võrreldes III etapi haiglaga suurem risk neonataalseks surmaks.
Hea kvaliteediga **Jaapani süstemaatiline ülevaade (Ishii et al. 2013)** uuris 22-25. GN sündinud laste elulemust ja neuroloogilist tervisetulemit. Numbers and incidences (%) of infants with death or NDI (neurodevelopmental impairment) were 60 (80%) at 22 weeks and 156 (64%) at 23 weeks. Overall, 281 (26.6%) of the 1057 subjects were unimpaired or minimally impaired at 3 years of age: 9 (12.0%) of whom were born at 22 weeks' gestational age, 49 (20.0%) of whom were born at 23 weeks' gestational age.
Mõõduka kvaliteediga **USA süstemaatiline ülevaade ja meta-analüüs (Salihu et al. 2013)** käsitles eluvõimelisuse piiril sündinute elulemust ja tulemust parandavaid faktoreid (kaitsvaid faktoreid). Pooled survival to discharge (alla 24. GN) in the random-effects model was 45.9% (95% CI: 41.1-51.7) and 39.7% in the fixed-effect model (95% CI: 38.8-

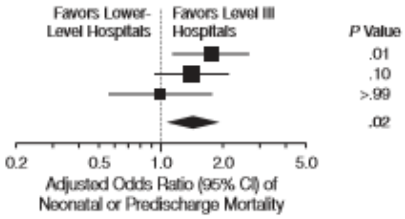
40.7). Kaitsvateks teguriteks osutusid antenataalsed kortikosteroidid, neonataalne elustamine ja intensiivravi.
Mõõduka kvaliteediga **Kanada meta-analüüs (Moore et al. 2013)** käsitles 22-25. GN sündinud laste neuroloogilist tulemit 4- ja 8-aastastel. All extremely preterm infant survivors have a substantial likelihood of developing moderate to severe impairment. Wide confidence intervals at the lower gestations (eg, at 22 weeks, 43% [95% CI, 21%-69%]; heterogeneity I2, 0%) and high heterogeneity at the higher gestations (eg, at 25 weeks, 24% [95% CI, 17%-32%]; I2, 66%) limit the results. Across these meta-analyses, the maximum mean weighted contribution of a study toward moderate to severe NDI rates was 52% at 22 weeks' GA, 21% at 23 weeks' GA,16% at 24 weeks' GA, and 15% at 25 weeks' GA.

Viited

SÜSTEM. ÜLEVAADE/META-ANALÜÜS	VIIDE
Regionaliseerimine. Mõõduka kvaliteediga meta-analüüs 2010.a.: CONTEXT: For more than 30 years, guidelines for perinatal regionalization have recommended that very low-birth-weight (VLBW) infants be born at highly specialized hospitals, most commonly designated as level III hospitals. Despite these recommendations, some regions continue to have large percentages of VLBW infants born in lower-level hospitals. OBJECTIVE: To evaluate published data on **associations between hospital level at birth and neonatal or** predischarge **mortality for VLBW and very preterm (VPT) infants.** DATA SOURCES: Systematic search of published literature (**1976-May 2010**) in MEDLINE, CINAHL, EMBASE, and PubMed databases and manual searches of reference lists. STUDY SELECTION AND DATA EXTRACTION: Forty-one publications met a priori inclusion criteria (randomized controlled trial, cohort, and case-control studies measuring neonatal or predischarge mortality among live-born infants **< or = 1500 g or < or = 32 weeks' gestation** delivered at a level III vs lower-level facility). Paired reviewers independently assessed publications for inclusion and extracted data using standardized forms. Discrepancies were decided by a third reviewer. Publications were reviewed for quality by 3 authors based on 2 content areas: adjustment for confounding and description of hospital levels. We calculated weighted, combined odds ratios (ORs) using a random-effects model and comparative unadjusted pooled mortality rates. DATA SYNTHESIS: We observed **increased odds of death for VLBW infants (38% vs 23%; adjusted OR, 1.62; 95% confidence interval [CI], 1.44-1.83) and VPT infants (15% vs 17%; adjusted OR, 1.55; 95% CI, 1.21-1.98) born outside of level III hospitals.** Consistent results were obtained when restricted to higher-quality evidence (mortality in VLBW infants, 36% vs 21%; adjusted OR, 1.60; 95% CI, 1.33-1.92 and in VPT infants, 7% vs 12%; adjusted OR, 1.42; 95% CI, 1.06-1.88) and infants weighing less than 1000 g (59% vs 32%; adjusted OR, 1.80; 95% CI, 1.31-2.46). No significant differences were found through subgroup analysis of study characteristics. **Meta-regression by year of publication did not reveal a change over time** (slope, 0.00; P = .87). **CONCLUSION:** For VLBW and VPT infants, birth outside of a level III hospital is significantly associated with increased likelihood of neonatal or predischarge death.	Lasswell, S.M., Barfield, W.D., Rochat, R.W., Blackmon, L., **2010. Perinatal regionalization for very low-birth-weight and very preterm infants: a meta-analysis.** JAMA 304, 992–1000. doi:10.1001/jama.2010.1226

Figure 5. Meta-analysis Results of Adequate- and High-Quality Publications on Very Preterm Infants

Source	Level Comparison	Deaths/Live Births, No. Lower Levels	Level III	Adjusted Odds Ratio (95% CI)	Z value	P Value
Lee et al,[24] 2003[a]	Outborn vs inborn	89/508	274/2454	1.75 (1.14-2.68)	2.56	.01
Johansson et al,[56] 2004	II vs III	136/1320	131/924	1.41 (0.98-2.13)	1.63	.10
Palmer et al,[58] 2005	Outborn vs inborn	15/148	88/746	1.00 (0.56-1.78)	0.00	>.99
Overall Test for heterogeneity: $Q=2.31$; $P=.31$		240/1976	493/4124	1.42 (1.06-1.88)	2.38	.02



CI indicates confidence interval. Size of data markers indicates size of study population. Inborn infants are those born in a level III hospital; outborn infants are those born in a lower-level hospital then transferred to a level III hospital.
[a] Included data combine reported gestational age strata (<26 weeks, 27-29 weeks, and 30-31 weeks).

Laste tervisetulem. Jaapani hea kvaliteediga süstemaatiline ülevaade, 2013.a.: OBJECTIVE: To provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age. METHODS: The study cohort consisted of **1057 infants born at 22 to 25 weeks in the Neonatal Research Network, Japan.** Neurodevelopmental impairment (NDI) at 36 to 42 months' chronological age was defined as any of the following: cerebral palsy, hearing impairment, visual impairment, and a developmental quotient <70. A systematic review was performed by using databases of publications of **cohort studies with neonatal and neurodevelopmental outcomes at 22 and 23 weeks**. RESULTS: Numbers and incidences (%) of infants with **death or NDI were 60 (80%) at 22 weeks and 156 (64%) at 23 weeks.** In logistic regression analysis, gestational ages of 22 weeks (odds ratio [OR]: 5.40; 95% confidence interval [CI]: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) were associated with increased risk of death or NDI compared with 24 weeks, but a gestational age of 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) was associated with decreased risk of death or NDI. In the systematic review, the medians (range) of the incidence of death or NDI in 8 cohorts were 99% (90%–100%) at 22 weeks and 98% (67%–100%) at 23 weeks. Overall, 281 (26.6%) of the 1057 subjects were **unimpaired or minimally impaired at 3 years of age: 9 (12.0%) of whom were born at 22 weeks' gestational age, 49 (20.0%) of whom were born at 23 weeks' gestational age**, 89 (26.8%) of whom were born at 24 weeks' gestational age, and 134 (33.1%) of whom were born at 25 weeks' gestational age.
CONCLUSIONS: Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants at born at 24 weeks. However, outcomes were improved compared with those in previous studies. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation.

Ishii, N., Kono, Y., Yonemoto, N., Kusuda, S., Fujimura, M., Neonatal Research Network, Japan, **2013. Outcomes of infants born at 22 and 23 weeks' gestation.** Pediatrics 132, 62–71. doi:10.1542/peds.2012-2857

TABLE 1 Characteristics of Study Cohort

	Gestational Age		
	22 Weeks ($n=75$)	23 Weeks ($n=245$)	24 Weeks ($n=332$)
Demographic and perinatal characteristics			
BW, mean ± SD, g	488 ± 72	575 ± 80	634 ± 103
BW <400 g, *n/N* (%)	7/75 (9.3)	3/245(1.2)	7/332(2.1)
Male, *n/N* (%)	32/75 (42.7)	133/244[a] (54.5)	163/332 (49.1)
Multiple birth, *n/N* (%)	16/75 (21.3)	60/245 (24.5)	61/332 (18.4)
Preterm rupture of membranes, *n/N* (%)	36/75 (48.0)	96/245 (39.2)	140/332 (42.2)
Antenatal steroid use, *n/N* (%)	16/75 (21.3)	79/245 (32.2)	137/332 (41.3)
Maternal transport, *n/N* (%)	38/75 (50.7)	151/245 (61.6)	207/331[a] (62.5)
Outborn, *n/N* (%)	6/75 (8.0)	20/245 (8.2)	31/332 (9.3)
Cesarean delivery, *n/N* (%)	18/75 (24.0)	104/245 (42.4)	218/332 (65.7)
In-hospital morbidities and interventions, *n/N* (%)			
RDS diagnosed	60/74[a] (81.1)	191/245 (78.0)	251/332 (75.6)
CLD at 36 weeks[b]	15/71[a] (21.1)	71/236[a] (30.1)	121/319[a] (37.9)
PDA ligation	4/72[a] (5.6)	34/238[a] (14.3)	50/316[a] (15.8)
Neonatal seizure	11/74[a] (14.9)	28/245 (11.4)	40/331[a] (12.1)
IVH grade 3–4	18/74[a] (24.3)	52/241[a] (21.6)	48/328[a] (14.6)
Cystic PVL	2/74[a] (2.7)	10/244[a] (4.1)	13/331[a] (3.9)
Sepsis	17/74[a] (23.0)	58/244[a] (23.8)	73/331[a] (22.1)
Necrotizing enterocolitis	1/74[a] (1.4)	16/245 (6.5)	10/331[a] (3.0)
ROP requiring treatment	15/75[a] (20.0)	73/245 (29.8)	102/331[a] (30.8)

BW, birth weight; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.
[a] There were cases without data on this characteristic.
[b] CLD at 36 weeks was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks.

TABLE 2 Neurodevelopmental Outcomes at 3 Years of Age According to Gestational Age

	Gestational Age		
	22 Weeks	23 Weeks	24 Weeks
Evaluated at 3 years, *n*	23	119	180
CP, *n/N* (%)[a]	5/23 (21.7)	21/118[b] (17.8)	14/173[b] (8.1)
Profound CP	4/23 (17.4)	12/118[b] (10.2)	9/173[b] (5.2)
Hearing impairment, *n/N* (%)[a]	0/23 (0.0)	4/119 (3.4)	2/168[b] (1.2)
Visual impairment, *n/N* (%)[a]	2/23 (8.7)	12/118[b] (10.2)	6/175[b] (3.4)
Cognitive delay, *n/N* (%)[a]	12/21[b] (57.1)	55/110[b] (50.0)	49/152[b] (32.2)
KSPD DQ of 50–69	5/11 (45.5)	12/58 (20.7)	27/104 (26.0)
KSPD DQ of <50	0/11 (0.0)	7/58 (12.1)	11/104 (10.6)
Judgment of delay by pediatrician	7/10 (70.0)	36/52 (69.2)	11/48 (22.9)
NDI, *n/N* (%)[a]	12/23 (52.2)	65/114[b] (57.0)	53/142[b] (37.3)
Profound NDI	7/23 (30.4)	45/114[b] (39.5)	23/142[b] (16.2)
Death or NDI, *n/N* (%)[c]	60/75 (80.0)	156/245 (63.7)	129/332 (38.9)
Death or Profound NDI	55/75 (73.3)	136/245 (55.5)	99/332 (29.8)
Unimpaired/minimally impaired, *n/N* (%)[c]	9/75 (12.0)	49/245 (20.0)	89/332 (26.8)

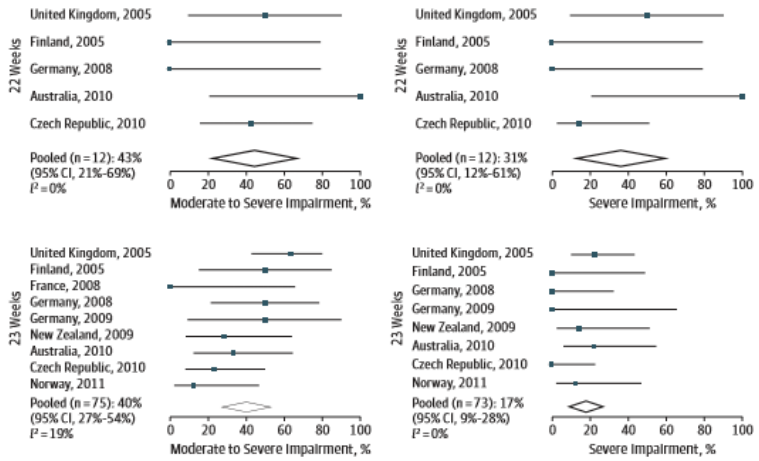
Eluvõimelisuse piiril sündinute elulemus, kaitsvad faktorid. USA

Salihu, H.M., Salinas-Miranda,

süstemaatiline ülevaade ja meta-analüüs, 2013.a: The objective of this paper is to review observational studies that addressed the survival of pre-viable gestations in the United States. We searched PubMed, Ovid, CINAHL, and Web of Knowledge for studies reporting survival of infants born at <24 gestational weeks and/or <500g in the United States and published between January 2003 and January 2013. The full texts of 70 articles were examined and a total of **15 studies (3 prospektiivset ja 12 retrospektiivset heakvaliteedilist kohortuuringut)** qualified and were selected. **8 uuringut kaasati meta-analüüsi.** We analyzed fixed-effect and random-effects models for eight studies on survival to discharge. Pooled survival to discharge in the random-effects model was 45.9% (95% CI: 41.1-51.7) and 39.7% in the fixed-effect model (95% CI: 38.8-40.7). Studies differed by pre-viable survival measures and epochs (1985-2009). **Protective factors included antenatal corticosteroids, neonatal resuscitation, and intensive care**. The current survival threshold for pre-viable infants warrants reconsideration of the limits of viability. Protective factors that enhance survival should be considered in the management of these infants.	A.A., Hill, L., Chandler, K., **2013. Survival of pre-viable preterm infants in the United States: a systematic review and meta-analysis.** Semin. Perinatol. 37, 389–400. doi:10.1053/j.semperi.2013.06.021
Neuroloogiline tulem 4- ja 8-aastastel. Kanada meta-analüüs, 2013: IMPORTANCE: Many centers delivering infants at 22 to 25 weeks' gestation have limited data regarding their outcomes. **A meta-analysis of the 4- to 8-year neurodevelopmental outcomes** and exploration of the limitations of meta-analysis would aid physicians and parents to plan care for these infants. OBJECTIVES: To determine the rate of moderate to severe and severe neurodevelopmental impairment by gestational age in extremely preterm survivors followed up between ages 4 and 8 years, as well as to determine whether there is a significant difference in impairment rates between the successive weeks of gestation of survivors. EVIDENCE REVIEW: A peer-reviewed search strategy obtained English-language publications from MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, and EMBASE. Personal files and reference lists from identified articles were searched. Contemporary cohorts were obtained by restriction to those published after 2004. Inclusion criteria were prospective cohort studies, follow-up rate of 65% or more, use of standardized testing or classification for impairment, reporting by gestation, and meeting prespecified definitions of impairment. We excluded randomized clinical trials, highly selective cohorts, consensus statements, and reviews. Of 1771 identified records, 89 full-text publications were assessed for eligibility. Using the full text of each publication, 2 authors independently followed a 2-step procedure. First, they determined that **9 studies** met inclusion criteria. Next, they extracted data using a structured data collection form. Investigators were contacted for data clarification. RESULTS: All extremely preterm infant survivors have a substantial likelihood of developing moderate to severe impairment. **Wide confidence intervals at the lower gestations (eg, at 22 weeks, 43% [95% CI, 21%-69%]; heterogeneity I2, 0%) and high heterogeneity at the higher gestations (eg, at 25 weeks, 24% [95% CI, 17%-32%]; I2,**	Moore, G.P., Lemyre, B., Barrowman, N., Daboval, T., **2013. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: a meta-analysis.** JAMA Pediatr 167, 967–974. doi:10.1001/jamapediatrics.2013.2395

66%) limit the results. There was a statistically significant absolute decrease in moderate to severe impairment between each week of gestation (6.5% [95% CI, 2%-11%]). Moderate to severe NDI rates demonstrated increasing heterogeneity as the GA increased, and small sample sizes for the lowest GAs resulted in wide confidence intervals around the estimates. **Across these meta-analyses, the maximum mean weighted contribution of a study toward moderate to severe NDI rates was 52% at 22 weeks' GA, 21% at 23 weeks' GA,16% at 24 weeks' GA, and 15% at 25 weeks' GA.** CONCLUSIONS AND RELEVANCE: Knowledge of these data, including the limitations, should facilitate discussion during the shared decision-making process about care plans for these infants, particularly in centers without their own data. More prospective, high-quality, complete cohorts are needed.	

Figure 2. Random-Effects Meta-analysis of Moderate to Severe and Severe Neurodevelopmental Impairment Rates



Üksikuuringud

Kokkuvõte: Leidsin mitu prospektiivset kohortuuringut, mis käsitlevad eluvõimelisuse piiril olevate vastsündinute tervisetulemeid (Prantsusmaa EPIPAGE-2, Rootsi EXPRESS, Inglismaa EPICURE-2 uuringud).

EXPRESS uuring leidis, et tokolüüsi, antenataalsete kortikosteroidide kasutamise ja ema transpordi korral III etapi haiglasse esineb imikueas väiksem risk surmaks. Samuti leiti, et proaktiivne perinataalne käsitlus vähendab suremust 2,5 aasta vanustel (korrigeeritud vanus) ilma et tõuseks mõõduka/raske arenguhäire risk.

Inglismaa prospektiivne kohortuuring EPICURE-2 leidis, et kolmanda taseme tervishoiuasutuses oli risk neonataalseks surmaks vähenenud, kuid nende osakaal, kes jäid ellu ilma neonataalse haigestumiseta, oli sarnane. Pärast transporti III etapi haiglasse oli vähem sünnitusaegseid ja sünnitusosakonnas aset leidvaid surmasid ning üldine suremus oli 2. etapi haiglasse jäänud vastsündinutel kõrgem.

MOSAIC uuring vaatles Euroopa riikides esinevat varieeruvust väga enneaegsete vastsündinute elulemuse osas. Vt tulemusi lähemalt allpool.

Rahuldava kvaliteediga retrospektiivne kohortuuring (Smith et al., 2012) leidis, et keskustes, kus kasutatakse enam kortikosteroide 22-24. GN-s, on ka 25-27. GN-l sündinute tervisetulemid paremad. Autorid seostavad seda sellega, et kui arstidel on hea valmidus proaktiivset ravi kasutada eluvõimelisuse piiril oleva ähvardava enneaegse sünnituse korral,

siis kasutatakse rohkem kortikosteroide ka hilisemates gestatsiooninädalates.
Leidsin 2 uuemat retrospektiivset kohortuuringut sünnitusviisi valiku kohta. Deutsch et al. (2011) leidsid, et keisrilõige eluvõimelisuse piiril loote tuharseisu korral seostub suurenenud elulemusega kõigi sünnikaalude korral raseduse kestuses 23+0 kuni 24+6. Laste haigestumus oli aga keisrilõike korral võrreldes vaginaalse sünnitusega suurem. Lannon et al. (2015) leidsid, et naistel, kel on enneaegse sünnituse korral eluvõimelisuse piiril teostatud keirilõige, on võrreldes naistega, kel on ajalise sünnituse korral keisrilõige tehtud, on järgmise raseduse korral suurem risk emaka ruptuuriks. Sama seos leiti ka sel juhul, kui oli teostatud ristilõige emaka alumises segmendis.

EPIPAGE-2 (Prantsusmaa prospektiivne kohortuuring), 2015: **Objectives** To determine **survival and neonatal morbidity of infants born from 22 through 34 completed weeks' gestation** in **France in 2011** and **compare these outcomes with a comparable cohort in 1997.** **Design, Setting, and Participants** The EPIPAGE-2 study is a **national, prospective, population-based cohort study** conducted in all maternity and neonatal units in France in 2011. A total of **2205 births** (stillbirths and live births) and terminations of pregnancy at 22 through 26 weeks' gestation, 3257 at 27 through 31 weeks, and 1234 at 32 through 34 weeks were studied. Cohort data were collected from January 1 through December 31, 1997, and from March 28 through December 31, 2011. Analyses for 1997 were run for the entire year and then separately for April to December; the rates for survival and morbidities did not differ. Data are therefore presented for the whole year in 1997 and the 8-month and 6-month periods in 2011. **Main Outcomes and Measures** Survival to discharge and survival without any of the following adverse outcomes: grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, severe bronchopulmonary dysplasia, retinopathy of prematurity (stage 3 or higher), or necrotizing enterocolitis (stages 2-3). **Results A total of 0.7% of infants born before 24 weeks' gestation survived to discharge**: 31.2% of those born at 24 weeks, 59.1% at 25 weeks, and 75.3% at 26 weeks. Survival rates were 93.6% at 27 through 31 weeks and 98.9% at 32 through 34 weeks. **Infants discharged home without severe neonatal morbidity represented 0% at 23 weeks**, 11.6% at 24 weeks, 30.0% at 25 weeks, 47.5% at 26 weeks, 81.3% at 27 through 31 weeks, and 96.8% at 32 through 34 weeks. **Compared with 1997, the proportion of infants surviving without severe morbidity in 2011 increased by 14.4%** ($P < .001$) at 25 through 29 weeks and 6% ($P < .001$) at 30 through 31 weeks but **did not change appreciably for those born at less than 25 weeks**. **The rates of antenatal corticosteroid use, induced preterm deliveries, cesarean deliveries, and surfactant use increased significantly in all gestational-age groups, except at 22 through 23 weeks.** **Conclusions and Relevance** The substantial improvement in survival in France for newborns born at 25 through 31 weeks'	Ancel, P.-Y., Goffinet, F., EPIPAGE-2 Writing Group, et al., **2015. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study.** JAMA Pediatr 169, 230–238. doi:10.1001/jamapediatrics.2014.3351

gestation was accompanied by an important reduction in severe morbidity, but **survival remained rare before 25 weeks.** Although improvement in survival at extremely low gestational age may be possible, its effect on long-term outcomes requires further studies. The long-term results of the EPIPAGE-2 study will be informative in this regard.

The proportion of live-born infants increased with gestational age from 13.5% at 22 weeks to 98.5% at 34weeks. **Only one infant born at 22 through 23 weeks (ie, 0.1% of all births and 0.7% of live births) survived to discharge.**
Among infants who died, the proportion whose deaths followed a decision to limit intensive care varied from 80.9% at 22 through 24 weeks and 70.3% at 25 through 26 weeks to 57.0% at 27 through 31 weeks. The median age at death was the day of birth for infants born at 22 through 24 weeks.
Among the live-born infants at 22 weeks, 36.2% were born in **level III hospitals** compared with 61.8% at 23 weeks, 77.4% at 24 weeks, 85.0% at 25 through 26 weeks, 84.8% at 27 through 31 weeks, and 50.1% at 32 through 34 weeks.
The percentage of infants exposed to antenatal corticosteroids was very low at 22 (1.8%) and 23 (12.3%) weeks but increased to 56.7% at 24 weeks and 78.4% at 25 through 26 weeks. **Cesarean rates** were 6.3% at 22 through 23 weeks and 13.5% at 24 weeks compared with 34.0% at 25 weeks and 59.9% at 26 weeks; this rate reached 69.8% at 27 through 31 weeks. Few of the infants born at 22 through 23 weeks were **admitted to NICUs** (6.1%); this percentage increased to 60.8% at 24 weeks, 91.9% at 25 weeks, 95.6% at 26 weeks, and 98.9% at 27 through 31 weeks.
Among infants born alive at 22 through 23 weeks in the 9 regions studied in 1997, none survived in 1997 or 2011, and the chance of survival at 24 weeks did not change between the studies.
The general policy in France is not to intervene before 24 weeks' gestation; infants born earlier receive palliative but not intensive care.

Table 1. Vital Status at Birth, Deaths, and Survival by Gestational Age in 2011

	No. (%) of Events						
Gestational Age, wk	All Infants (N = 6696)	TOP[a] (n = 214)	Stillbirths[a] (n = 1313)	Live Births[a] (n = 5169)	Deaths in Maternity Ward[b] (n = 289)	Deaths in NICU[b] (n = 413)	Survival to Discharge[b,c] (n = 4467)
22	430	53 (12.3)	319 (74.2)	58 (13.5)	56 (96.6)	2 (3.4)	0
23	414	43 (10.4)	282 (68.1)	89 (21.5)	82 (92.1)	6 (6.7)	1 (1.1) [0-3.3]
24	404	40 (9.9)	178 (44.1)	186 (46.0)	73 (39.2)	55 (29.6)	58 (31.2) [24.5-37.8]
25	435	28 (6.4)	99 (22.8)	308 (70.8)	25 (8.1)	101 (32.8)	182 (59.1) [53.6-64.6]
26	522	24 (4.6)	85 (16.3)	413 (79.1)	18 (4.4)	84 (20.3)	311 (75.3) [71.1-79.5]

Table 2. Perinatal Characteristics and Obstetric and Neonatal Interventions by Gestational Age in 2011[a]

Gestational Age, wk	Multiple Birth[b]	Birth Weight, Median (IQR), g[c]	Birth in Level III Maternity[b]	Antenatal Corticosteroid Use[b]	Indicated Preterm Delivery[b,d]	Cesarean Delivery[b]	Surfactant Use[e]	Postnatal Corticosteroid Use[f]	Length of Hospital Stay, Median (IQR), wk[e]
22	20/58 (34.5)	490 (438-523)	21/58 (36.2)	1/57 (1.8)	8/57 (14.0)	5/57 (8.8)	1/2 (50.0)	0/2 (0)	0
23	31/89 (34.8)	570 (510-620)	55/89 (61.8)	10/81 (12.3)	8/88 (9.1)	4/87 (4.6)	5/7 (71.4)	0/7 (0)	147
24	52/186 (28.0)	680 (618-730)	144/186 (77.4)	101/178 (56.7)	20/182 (11.0)	24/178 (13.5)	108/112 (96.4)	30/109 (27.5)	119 (109-141)
25	121/308 (39.3)	760 (700-830)	258/308 (83.8)	225/298 (75.5)	71/303 (23.4)	103/303 (34.0)	270/278 (97.1)	75/273 (27.5)	104 (90-123)
26	114/413 (27.6)	860 (750-940)	355/413 (86.0)	328/407 (80.6)	153/400 (38.3)	246/411 (59.9)	375/389 (96.4)	78/379 (20.6)	92 (82-105)

EXPRESS study (Rootsi prostpektiivne kohortuuring) 2010 (haigestumus 1-aastaselt):

AIMS: The aim of this study was to determine the **incidence of neonatal morbidity in extremely preterm infants** and to **identify associated risk factors.**

METHODS: Population based study of infants born **before 27 gestational weeks and admitted for neonatal intensive care** in **Sweden** during **2004-2007.**

RESULTS: Of **638 admitted infants**, 141 died. Among these, life support was withdrawn in 55 infants because of anticipation of poor long-term outcome. Of **497 surviving infants**, 10% developed severe intraventricular haemorrhage (IVH), 5.7% cystic periventricular leucomalacia (cPVL), 41% septicaemia and 5.8% necrotizing enterocolitis (NEC); 61% had patent ductus arteriosus (PDA) and 34% developed retinopathy of prematurity (ROP) stage > or =3. Eighty-five per cent needed mechanical ventilation and 25% developed severe bronchopulmonary dysplasia (BPD). **Forty-seven per cent (47%) survived to one year of age without any severe IVH, cPVL, severe ROP, severe BPD or NEC. Tocolysis increased** and prolonged mechanical ventilation decreased **the chances of survival without these morbidities.** Maternal smoking and higher gestational duration were associated with lower risk of severe ROP, whereas PDA and poor growth increased this risk.

Keisrilõike osas ei leitud, et see seostuks haigustumuse vähenemisega.

CONCLUSION: **Half of the infants surviving extremely preterm birth suffered from severe neonatal morbidities. Studies on how to reduce these morbidities and on the long-term health of survivors are warranted.**

EXPRESS Group, **2010. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS).** Acta Paediatr. 99, 978–992. doi:10.1111/j.1651-2227.2010.01846.x

Table 3 Infants who survived without neonatal morbidity or with one, two or three morbidities by gestational age at birth

	Gestational age											
	22 weeks		23 weeks		24 weeks		25 weeks		26 weeks		Total <27 weeks	
	N = 5		N = 53		N = 96		N = 167		N = 176		N = 497	
	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Morbidity												
Severe BPD[A], ROP stage ≥3 and/or severe brain injury[B]												
No morbidity	1	(20)	9	(17)	32	(33)	79	(47)	114	(65)	235	(47)
One morbidity	2	(40)	30	(57)	44	(45)	56	(34)	52	(30)	184	(37)
Two morbidities	1	(20)	14	(26)	19	(19)	26	(16)	8	(4.5)	68	(14)
Three morbidities	1	(20)	0	(0)	1	(1.0)	6	(3.6)	2	(1.1)	10	(2.0)
Any degree of BPD[C], ROP≥ stage 3 and/or severe brain injury[B]												
No morbidity	0	(0)	0	(0)	16	(17)	31	(19)	67	(38)	114	(23)
One morbidity	1	(20)	20	(38)	37	(39)	80	(48)	81	(46)	219	(44)
Two morbidities	3	(60)	29	(55)	37	(39)	45	(27)	22	(13)	136	(27)
Three morbidities	1	(20)	4	(7.6)	6	(6.3)	11	(6.6)	6	(3.4)	28	(5.6)

EXPRESS study 2009 (1-aasta elulemus):
Objective: To determine **the 1-year survival in all infants born before 27 gestational weeks** in **Sweden** during **2004-2007**.
Design, Setting, and Patients: Population-based prospective observational study of extremely preterm infants (**707 live-born and 304 stillbirths**) born to 887 mothers in 904 deliveries (102 multiple births) in all obstetric and neonatal units in Sweden from April 1, 2004, to March 31, 2007.
Main Outcome Measures: Infant survival to 365 days and survival without major neonatal morbidity (intraventricular hemorrhage grade >2, retinopathy of prematurity stage >2, periventricular leukomalacia, necrotizing enterocolitis, severe bronchopulmonary dysplasia). Associations between perinatal interventions and survival.
Results: The incidence of extreme prematurity was 3.3 per 1000 infants. Overall **perinatal mortality** was 45% (from **93% at 22 weeks** to 24% at 26 weeks), with 30% stillbirths, including 6.5% intrapartum deaths. Of live-born infants, 91% were admitted to neonatal intensive care and 70% survived to 1 year of age (95% confidence interval [CI], 67%-73%). The Kaplan-Meier survival estimates for 22, 23, 24, 25, and 26 weeks were 9.8% (95% CI, 4%-23%), 53% (95% CI, 44%-63%), 67% (95% CI, 59%-75%), 82% (95% CI, 76%-87%), and 85% (95% CI, 81%-90%), respectively. **Lower risk of infant death was associated with tocolytic treatment (adjusted for gestational age odds ratio [OR], 0.43; 95% CI, 0.36-0.52), antenatal corticosteroids (OR, 0.44; 95% CI, 0.24-0.81), surfactant treatment within 2 hours after birth (OR, 0.47; 95% CI, 0.32-0.71), and birth at a level III hospital (OR, 0.49; 95% CI, 0.320.75). However, when adjusted for the use of perinatal interventions, birth at a level III hospital was no longer associated with a reduced risk, implying that the survival advantage of birth at a level III hospital was related to the use of interventions.**
Keisrilõike puhul ei leitud, et see oleks seotud kuni 1 aasta vanuseks saamiseni vähenenud riskiga suremiseks.
Among 1-year survivors, 45% had no major neonatal morbidity. **Overall survival at 1 year of age for infants born alive was**

EXPRESS Group, Fellman, V., Hellström-Westas, L., Norman, M., Westgren, M., Källén, K., Lagercrantz, H., Marsál, K., Serenius, F., Wennergren, M., **2009. One-year survival of extremely preterm infants after active perinatal care in Sweden.** JAMA 301, 2225–2233. doi:10.1001/jama.2009.771

70%: for those born at 22 weeks it was 9.8%; at 23 weeks 53%; at 24 weeks 67%; at 25 weeks 82%; and at 26 weeks 85%.
Conclusion: During 2004 to 2007, 1-year survival of infants born alive at 22 to 26 weeks of gestation in Sweden was 70% and ranged from 9.8% at 22 weeks to 85% at 26 weeks.

Perinataalne suremus:
22 GN – 93%
23 GN – 66%
24 GN – 40%

1 a elulemus elusalt sündinud lastel
22 GN – 9,8%
23 GN – 53%
24 GN – 67%

1 a elulemus ilma raskete haigusteta (IVH, ROP, raske BPD, PVL, NEC)
22 GN – 2%
23 GN – 8,9%
24 GN – 21%

Table 2. Mortality by Gestational Age for All Infants and Live-Born Infants

	No. (%) of Infants by Gestational Age, wk					
	≤22[a]	23	24	25	26[b]	Total <27 wk
All infants	(n=142)	(n=183)	(n=191)	(n=250)	(n=245)	**(N=1011)**
Perinatal death	132 (93)	121 (66)	77 (40)	68 (27)	58 (24)	456 (45)
Stillbirth	91 (64)	82 (45)	47 (25)	45 (18)	39 (16)	304 (30)
Intrapartum death	40 (28)	19 (10)	2 (1)	3 (1.2)	2 (0.8)	66 (6.5)
Live-born infants	(n=51)	(n=101)	(n=144)	(n=205)	(n=206)	**(N=707)**
Neonatal death	45 (88)	46 (46)	41 (29)	29 (14)	26 (13)	187 (26)
Early neonatal death, 0-6 days	41 (80)	39 (39)	30 (21)	23 (11)	19 (9.2)	152 (22)
Delivery room death	28 (55)	16 (16)	10 (6.9)	4 (2)	0	58 (8.2)
Late neonatal death, 7-27 days	4 (7.8)	7 (6.9)	11 (7.6)	6 (2.9)	7 (3.4)	35 (5)
Infant death, 0-365 days	46 (90)	48 (48)	48 (33)	38 (19)	30 (15)	210 (30)

[a]Category denotes gestational age of 22 weeks 0 days to 22 weeks 6 days but also includes 1 infant born at 21 weeks 5 days and 1 infant born at 21 weeks 6 days.
[b]Category denotes gestational age of 26 weeks 0 days to 26 weeks 6 days.

Table 3. One-Year Survival, Major Neonatal Morbidity Among Survivors, and Survival Without Major Neonatal Morbidity

	No. With Event/No. in Group (%)					
	Gestational Age, wk					
	≤22[a]	23	24	25	26[b]	Total <27 wk
Survival 365 days						
All infants including stillbirths	5/142 (3.5)	53/183 (29)	96/191 (50)	167/250 (67)	176/245 (72)	497/1011 (49)
Live-born infants	5/51 (9.8)	53/101 (53)	96/144 (67)	167/205 (82)	176/206 (85)	497/707 (70)
Infants admitted to neonatal intensive care unit	5/19 (26)	53/81 (65)	96/132 (73)	167/200 (84)	176/204 (86)	497/636 (78)
Survival 365 days with major neonatal morbidity[c]						
Intraventricular hemorrhage grade >2	1/5 (20)	10/53 (19)	10/96 (10)	20/166 (12)	9/173 (5.2)	50/493 (10)
Retinopathy of prematurity stage >2	4/5 (80)	33/53 (62)	45/94 (48)	54/167 (32)	33/174 (19)	169/493 (34)
Severe bronchopulmonary dysplasia	2/5 (40)	13/49 (26)	27/87 (31)	45/153 (29)	26/158 (17)	113/452 (25)
Periventricular leukomalacia	0/5 (0)	5/53 (9.4)	6/96 (6.2)	9/167 (5.4)	8/176 (4.5)	28/497 (5.6)
Necrotizing enterocolitis	0/5 (0)	1/53 (1.9)	9/96 (9.4)	10/167 (6.0)	9/176 (5.1)	29/497 (5.8)
Survival 365 days without major neonatal morbidity[d]						
Live-born infants	1/51 (2)	9/101 (8.9)	30/144 (21)	75/205 (37)	111/206 (54)	226/707 (32)
Survivors at 1 year	1/5 (20)	9/53 (17)	30/96 (31)	75/167 (45)	111/176 (63)	226/497 (45)

[a]Category denotes gestational age of 22 weeks 0 days to 22 weeks 6 days but also includes 1 infant born at 21 weeks 5 days and 1 infant born at 21 weeks 6 days.
[b]Category denotes gestational age of 26 weeks 0 days to 26 weeks 6 days.
[c]Infants with known information in denominator.
[d]Survival without any of the major neonatal morbidities (intraventricular hemorrhage, retinopathy of prematurity, severe bronchopulmonary dysplasia, periventricular leukomalacia, or necrotizing enterocolitis) as described. Denominators are for all infants, including 21 infants without reported morbidity but with some information missing.

Table 4. Association Between Perinatal Interventions and Risk of Death to Age 1 Year Among Live-Born Infants

	Live-Born Infants		Odds Ratio (95% Confidence Interval)[a]		
	All (n = 707), No.[b]	Dead at 0-364 d (n = 210), No. (%)	Crude	Adjusted[c]	Multivariate Model[d]
Tocolytic treatment					
Yes	413	110 (27)	0.36 (0.23-0.57)	0.43 (0.36-0.52)	0.60 (0.39-0.94)
No	96	48 (50)	1 [Reference]	1 [Reference]	1 [Reference]
Antenatal corticosteroids					
Yes	591	144 (24)	0.31 (0.18-0.54)	0.44 (0.24-0.81)	0.41 (0.20-0.81)
No	85	55 (65)	1 [Reference]	1 [Reference]	1 [Reference]
Cesarean delivery					
Yes	356	75 (21)	0.43 (0.31-0.60)	0.89 (0.60-1.32)	0.98 (0.62-1.52)
No	351	135 (39)	1 [Reference]	1 [Reference]	1 [Reference]
Surfactant administered within 2 hours after birth					
Yes	497	116 (23)	0.47 (0.33-0.68)	0.47 (0.32-0.71)	0.48 (0.31-0.74)
No	189	74 (39)	1 [Reference]	1 [Reference]	1 [Reference]
Born at level III hospital					
Yes	558	145 (26)	0.45 (0.31-0.66)	0.49 (0.32-0.75)	0.78 (0.45-1.35)
No	149	65 (44)	1 [Reference]	1 [Reference]	1 [Reference]

[a] Odds ratios were obtained from logistic regression analysis (simple and adjusted for gestational age) and from a multivariate model including gestational age and all evaluated interventions listed in the table.
[b] All live-born infants with available information.
[c] Adjusted for gestational age at birth.
[d] Only 659 infants with all available information were included in the model (of these, 185 [28%] died at 0-364 days); evaluated with Hosmer-Lemeshow goodness of fit test ($P = .27$).

EXPRESS study 2015 (Tervisetulem 2,5 aasta vanuselt)

OBJECTIVE: To examine the **association between intensity of perinatal care and outcome at 2.5 years' corrected age** (CA) in extremely preterm (EPT) infants **(<27 weeks**) born in **Sweden** during **2004-2007.**

METHODS: A national **prospective study in 844 fetuses** who were alive at the mother's admission for delivery: **707 were live born, 137 were stillborn**. **Infants were assigned a perinatal activity score on the basis of the intensity of care (rates of key perinatal interventions) in the infant's region of birth**. Obstetric and neonatal activity scores reflecting the intensity of care in each region were calculated on the basis of the rates of **4 key obstetric indicators** (delivery at level III hospitals, complete course of antenatal steroids, cesarean delivery, tocolytic treatment) and **4 key neonatal indicators** (surfactant within 2 hours after birth, delivery attended by a neonatologist, intubation immediately after birth, infants admitted for intensive care [out of infants alive at 30 minutes after birth]). ***Ei hinnatud indviduaalsete sekkumiste efekti (nt eraldi keisrilõiget)***. Scores were calculated separately for each gestational week (gestational age [GA]-specific scores) and for the aggregated cohort (aggregated activity scores). Primary outcomes were 1-year mortality and death or neurodevelopmental disability (NDI) at 2.5 years' CA in fetuses who were alive at the mother's admission.

RESULTS: Among fetuses alive at the mother's admission for delivery, higher activity scores were associated with a reduced risk of stillbirth (adjusted odds ratio [aOR]: 0.90; 95% confidence interval [CI]: 0.83–0**.97) and death before 1 year** (aOR: 0.84; 95% CI: 0.78–0.91). **Among infants born alive, higher scores were associated with a reduced risk of death within 12 hours** (aOR: 0.79; 95% CI: 0.71–0.88) and 1 year (aOR: 0.86; 95% CI: 0.79–0.93). **When analyzed by GA groups, the risk reductions were confined to the 22- to 24-week group. After exclusion of infants who died before 12 hours, no significant effect remained. Among children assessed at 2.5 years' CA, the rates of NDI were similar in both high-activity (27%) and low activity (30%) regions, and after adjustment there were no intensity related differences in NDI risk between high- and low-activity regions.**

Serenius, F., Blennow, M., Maršál, K., Sjörs, G., Källen, K., EXPRESS Study Group, **2015. Intensity of perinatal care for extremely preterm infants: outcomes at 2.5 years.** Pediatrics 135, e1163–1172. doi:10.1542/peds. 2014-2988

CONCLUSIONS: Proactive perinatal care decreased mortality without increasing the risk of NDI at 2.5 years' CA in EPT infants. A proactive approach based on optimistic expectations of a favorable outcome is justified.	
EXPRESS study shows significant regional differences in 1-year outcome of extremely preterm infants in Sweden: Aim: The aim of this study **was to investigate differences in mortality up to 1 year of age in extremely preterm infants (before 27 weeks) born in seven Swedish healthcare regions.** Methods: National prospective observational study of consecutively born, extremely preterm infants in Sweden 2004–2007. Mortality was compared between regions. Crude and adjusted odds ratios and 95% CI were calculated. Results: **Among 844 foetuses alive at mother's admission for delivery, regional differences were identified in perinatal mortality for the total group (22–26 weeks) and in the stillbirth and perinatal and 365-day mortality rates for the subgroup born at 22–24 weeks. Among 707 infants born alive, regional differences were found both in mortality before 12 h and in the 365-day mortality rate for the subgroup (22–24 weeks) and for the total group (22–26 weeks). The mortality rates were consistently lower in two healthcare regions. There were no differences in the 365-day mortality rate for infants alive at 12 h or for infants born at 25 weeks. Neonatal morbidity rates among survivors were not higher in regions with better survival rates. Perinatal practices varied between regions.** Conclusion: Mortality rates in extremely preterm infants varied considerably between Swedish healthcare regions in the first year after birth, particularly between the most immature infants.	Acta Paediatr. 2014 Jan;103(1):27-37. doi: 10.1111/apa.12421. Epub 2013 Oct 30. RESS study shows significant regional differences in 1-year outcome of extremely preterm infants in Sweden. ius F1, Sjörs G, Blennow M, Fellman V, Holmström G, Maršál K, Lindberg E, Olhager E, Stigson L, Westgren M, Källen K; EXPRESS study group.

Table 3 Frequency of obstetric and neonatal interventions between healthcare regions

	Region						
	Stockholm n (%)	Uppsala n (%)	Linköping n (%)	Lund n (%)	Göteborg n (%)	Örebro n (%)	Umeå n (%)
Obstetric interventions							
*Foetuses alive at admission**	213	147	69	142	161	26	86
Birth at level III hospital	164 (77)	103 (70)	47 (68)	109 (77)	138 (86)	18 (69)	64 (74)
Antenatal steroids, 2 doses	85 (40)	91 (62)	36 (52)	87 (61)	98 (61)	9 (35)	62 (72)
Caesarean section	61 (29)	79 (54)	27 (39)	85 (60)	48 (30)	12 (46)	49 (57)
Tocolytic treatment†	108 (68)	70 (70)	47 (89)	81 (79)	92 (75)	18 (81)	45 (70)
Neonatal interventions							
Infants born alive	177	135	59	117	126	21	72
Surfactant within 2 h after birth	65 (37)	99 (73)	21 (36)	78 (67)	44 (35)	10 (24)	50 (69)
Neonatologist present at birth	130 (73)	108 (80)	48 (81)	106 (91)	109 (87)	20 (90)	66 (92)
Intubation at birth	53 (48)	101 (75)	21 (36)	79 (68)	53 (42)	8 (38)	54 (75)
Admitted to NICU§	150 (92)	132 (99)	50 (89)	111 (98)	124 (98)	18 (90)	69 (100)

*Foetus alive at mother's admission for delivery.
†For the subgroup with spontaneous preterm labour only (denominator N values: 158, 101, 53, 103, 122, 22 and 64 for the seven regions, respectively).
§For infants alive 30 min after birth (denominator N values: 163, 133, 56, 113, 126, 20 and 69 for the seven regions, respectively).
Tocolysis $p = 0.06$; all other obstetric and neonatal interventions $p < 0.05$.

	Stockholm n/N (%)	Uppsala n/N (%)	Linköping n/N (%)	Lund n/N (%)	Göteborg n/N (%)	Örebro n/N (%)	Umeå n/N (%)	p-Value
Foetus alive at mothers admission for delivery (n = 844)								
Stillbirth								
22–24 weeks	30/110 (27)	4 /57 (7.0)	9/33 (27)	22/72 (30)	29/78 (37)	4/15 (27)	10/39 (26)	<0.001
25–26 weeks	6/103 (5.8)	8/90 (8.8)	1/36 (2.7)	3/70 (4.3)	6/83 (3.6)	1/11 (9)	4/47 (8.5)	0.81
22–26 weeks	36/213 (17)	12/147 (8.2)	10/69 (15)	25/142 (18)	35/161 (22)	5/26 (19)	14/86 (16)	0.06
Perinatal death								
22–24 weeks	70/110 (64)	12/57 (21)	23/33 (70)	38/72 (53)	49/78 (63)	10/15 (67)	16/39 (41)	<0.001
25–26 weeks	14/103 (14)	20/90 (22)	6/36 (17)	9/70 (13)	13/83 (16)	2/11 (18)	7/47 (15)	0.74
22–26 weeks	84/213 (39)	32/147 (22)	29/69 (42)	47/142 (33)	62/161 (39)	12/26 (46)	23/86 (27)	<0.01
Died before 365 days								
22–24 weeks	78/110 (71)	22/57 (43)	25/33 (75)	41/72 (60)	54/78 (69)	11/15 (73)	19/39 (49)	<0.001
25–26 weeks	21/103 (20)	24/90 (27)	9/36 (25)	16/70 (23)	16/83 (19)	3/11 (27)	8/47 (17)	0.84
22–26 weeks	99/213 (46)	46/147 (31)	34/69 (49)	57/142 (40)	70/161 (43)	14/26 (54)	27/86 (31)	0.12
Infant born alive (n = 707)								
Died before 12 h								
22–24 weeks	37/80 (46)	6/53 (11)	11/24 (46)	11/50 (22)	16/49 (33)	4/11 (36)	5/29 (17)	<0.001
25–26 weeks	3/97 (3.1)	3/82 (3.7)	2/35 (5.7)	2/67 (3.0)	3/77 (3.9)	1/10 (10)	2/43 (4.7)	0.60
22–26 weeks	40/177 (23)	9/135 (6.7)	13/59 (22)	13/117 (11)	19/126 (15)	5/21 (24)	7/72 (9.7)	<0.01
Died before 365 days								
22–24 weeks	48/80 (60)	18/53 (34)	16/24 (67)	19/50 (38)	25/49 (51)	7/11 (64)	9/29 (31)	<0.001
25–26 weeks	15/97 (15)	16/82 (20)	8/35 (23)	13/67 (19)	10/77 (13)	2/10 (20)	4/43 (9.3)	0.60
22–26 weeks	63/177 (36)	34/135 (25)	24/59 (41)	32/117 (27)	35/126 (28)	9/21 (43)	13/72 (18)	0.02
Infant alive at 12 h (n = 608)								
Died before 365 days								
22–24 weeks	11/43 (26)	14/49 (29)	5/13 (38)	11/42 (26)	9/33 (27)	3/7 (43)	5/25 (20)	0.88
25–26 weeks	12/94 (13)	13/79 (16)	7/34 (21)	11/65 (17)	7/74 (9.4)	1/9 (11)	2/41 (4.8)	0.32
22–26 weeks	23/137 (17)	27/128 (21)	12/47 (26)	22/107 (21)	16/107 (15)	4/16 (25)	7/66 (11)	0.32
Infant alive at 365 days (n = 497)								
Major neonatal morbidity*								
22–24 weeks	26/32 (81)	27/35 (77)	7/8 (88)	22/31 (71)	19/24 (79)	2/4 (50)	11/20 (55)	0.33
25–26 weeks	38/82 (46)	27/66 (41)	13/27 (48)	26/54 (48)	32/67 (48)	3/8 (38)	18/39 (46)	0.98

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

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 1 year and neurodevelopment at 2.5 years (Bayley-III test, cerebral palsy, vision, hearing) were evaluated in infants born before 27 weeks of gestation in Sweden 2004–2007 (n = 1011)**, using logistic regression analyses of risk factors.

Results. Of 844 fetuses alive at admission, 8.4% died in utero before labor, 7.8% died intrapartum. 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 24 h after birth decreased with gestational age** [odds ratio (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-min Apgar score <4** (OR 50.4; 95% CI 28.2–90.2**), and birth at a level II hospital** (OR 2.6; 95% CI 1.2–5.3). **The risk of death between 1 and 365 days remained significantly decreased for gestational age and corticosteroids.** The **risk of mental developmental delay at 2.5 years** decreased with gestational age, birthweight 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 Clinical Risk Index for Babies 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.**

Acta Obstet Gynecol Scand. 2015 Nov;94(11):1203-14. doi: 10.1111/aogs.12726. Epub 2015 Sep 7.
Impact of obstetric factors on outcome of extremely preterm births in Sweden: prospective population-based observational study (EXPRESS).
Källén K1, Serenius F2,3, Westgren M4, Maršál K5; EXPRESS Group.

EPICURE-2 study, 2014. Inglismaa prospektiivne kohortuuring. Perinataalsed tervisetulemid sõltuvalt sünni kohast ja perinataalsest transpordist:

BACKGROUND: Expertise and resources may be important determinants of outcome for extremely preterm babies. **We evaluated the effect of place of birth and perinatal transfer on survival and neonatal morbidity within a prospective cohort of births between 22 and 26 weeks of gestation in England during 2006.**

METHODS: We studied the whole population of **2460 births where the fetus was alive at the admission of the mother to hospital for delivery.** Outcomes to discharge were compared between level 3 (most intensive) and level 2 maternity services, with and without transfers, and by activity level of level 3 neonatal unit; ORs were adjusted for gestation at birth and birthweight for gestation (adjusted ORs (aOR)).

FINDINGS: Of this national birth cohort, **56% were born in maternity services with level 3 and 34% with level 2 neonatal units; 10% were born in a setting without ongoing intensive care facilities (level 1).** When compared with level 2 settings, **risk of death in level 3 services was reduced (aOR 0.73 (95% CI 0.59 to 0.90)), but the proportion surviving without neonatal morbidity was similar (aOR 1.27 (0.93 to 1.74)).** Analysis by intended hospital of birth confirmed reduced mortality in level 3 services. **Following antenatal transfer into a level 3 setting, there were fewer intrapartum or labour ward deaths, and overall mortality was higher for those remaining in level 2 services (aOR 1.44 (1.09 to 1.90)). Among level 3 services, those with higher activity had fewer deaths overall (aOR 0.68 (0.52 to 0.89)).**

INTERPRETATION: Despite national policy, only 56% of births between 22 and 26 weeks of gestation occurred in maternity services with a level 3 neonatal facility. Survival was significantly enhanced following birth in level 3 services, particularly those with high activity; this was not at the cost of increased neonatal morbidity.

Marlow, N., Bennett, C., Draper, E.S., Hennessy, E.M., Morgan, A.S., Costeloe, K.L., **2014. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study.** Arch. Dis. Child. Fetal Neonatal Ed. 99, F181–188. doi:10.1136/archdischild-2013-305555

Table 2 Mortality and morbidity to discharge for babies of women transferred antenatally and for those who delivered in level 2 and level 3 services without transfer for births in England in 2006 between 22 and 26 weeks of gestation

Outcome	Level 2 (n=829)		Antenatal transfer (n=440)		Level 3 (n=947)		p Value*	aOR L3 vs L2	aOR Level 2 v ANT	aOR Level 3 vs ANT
Antenatal death	174	21%	45	10%	163	17%	0.104	0.86 (0.66 to 1.13)	1.52 (1.03 to 2.26)	1.31 (0.89 to 1.93)
Delivery room deaths†	143	17%	30	7%	118	12%	0.002	0.53 (0.37 to 0.77)	1.67 (1.02 to 2.72)	0.89 (0.54 to 1.46)
Neonatal unit deaths <7 days	116	14%	50	11%	118	12%	0.005	0.69 (0.51 to 0.94)	1.80 (1.23 to 2.63)	1.25 (0.86 to 1.81)
All early neonatal deaths	259	31%	80	18%	236	25%	0.0001	0.61 (0.47 to 0.79)	1.85 (1.33 to 2.57)	1.12 (0.81 to 1.56)
Late neonatal death (7–28 days)†	56	7%	43	10%	79	8%	0.932	0.94 (0.64 to 1.38)	1.08 (0.69 to 1.68)	1.01 (0.67 to 1.53)
Death 29 days to discharge	35	4%	32	7%	54	6%	0.853	1.08 (0.68 to 1.73)	0.86 (0.50 to 1.46)	0.93 (0.57 to 1.51)
All deaths	524	63%	200	45%	532	56%	0.014	0.75 (0.59 to 0.95)	1.44 (1.09 to 1.90)	1.08 (0.83 to 1.41)
Survival without morbidity	70	8%	65	15%	92	10%	0.086	1.14 (0.80 to 1.61)	0.65 (0.44 to 0.96)	0.74 (0.51 to 1.06)
Survivors only										
No morbidity	70	23%	65	27%	92	22%	0.166	0.99 (0.69 to 1.43)	0.72 (0.48 to 1.08)	0.71 (0.49 to 1.04)
Perinatal factors										
Antenatal steroid (any)	531/824	64%	412/436	95%	656/936	70%	<0.0001	1.15 (0.90 to 1.47)	0.20 (0.12 to 0.31)	0.23 (0.14 to 0.36)
Resuscitation withheld	89/653	14%	12/395	3%	61/784	8%	0.002	0.41 (0.25 to 0.66)	1.25 (0.62 to 2.55)	0.51 (0.24 to 1.09)
Alive with HR>100 at 5 m	463/551	84%	342/379	90%	610/710	86%	0.243	1.16 (0.84 to 1.60)	0.70 (0.46 to 1.06)	0.81 (0.53 to 1.22)
Admitted to NNU	511/829	62%	365/440	83%	664/947	70%	0.014	1.41 (1.09 to 1.81)	0.69 (0.50 to 0.96)	0.98 (0.70 to 1.35)

*p Value for overall significance of transfer adjusted for gestational age and birthweight for gestation.
†Heterogeneity of effect of antenatal transfer across gestational age for two outcomes (p=0.048 for delivery room and p=0.039 for late neonatal deaths).
ANT, antenatal transfer; aOR, OR adjusted for gestational age and birthweight for gestation based on population alive at start of time period.

EPICURE uuringud: Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006.

OBJECTIVE: **To determine survival and neonatal morbidity for babies born between 22 and 26 weeks' gestation in England during 2006**, and to evaluate changes in outcome since 1995 for babies born between 22 and 25 weeks' gestation.

DESIGN: **Prospective national cohort studies**.

SETTING: Maternity and neonatal units in **England.**

PARTICIPANTS: **3133 births** between 22 and 26 weeks' gestation in 2006; 666 admissions to neonatal units in 1995 and 1115 in 2006 of babies born between 22 and 25 weeks' gestation.

MAIN OUTCOME MEASURES: Survival to discharge from hospital, pregnancy and delivery outcomes, infant morbidity until discharge.

RESULTS: **In 2006, survival of live born babies was 2% (n=3) for those born at 22 weeks' gestation, 19% (n=66) at 23 weeks**, 40% (n=178) at 24 weeks, 66% (n=346) at 25 weeks, and 77% (n=448) at 26 weeks (P<0.001). At discharge from hospital, 68% (n=705) of survivors had bronchopulmonary dysplasia (receiving supplemental oxygen at 36 weeks postmenstrual age), 13% (n=135) had evidence of serious abnormality on cerebral ultrasonography, and 16% (n=166) had laser treatment for retinopathy of prematurity. For babies born between 22 and 25 weeks' gestation from March to December, the number of admissions for neonatal care increased by 44%, from 666 in 1995 to 959 in 2006. By 2006 adherence to evidence based practice associated with improved outcome had significantly increased. Survival increased from 40% to 53% (P<0.001) overall and at each week of gestation: **by 9.5% (confidence interval -0.1% to 19%) at 23 weeks**, 12% (4% to 20%) at 24 weeks, and 16% (9% to 23%) at 25 weeks. **The proportions of babies surviving in 2006 with bronchopulmonary dysplasia, major cerebral scan abnormality, or weight and/or head circumference <-2 SD were similar to those in 1995, but the proportion treated for retinopathy of prematurity had increased from 13% to 22% (P=0.006).** Predictors of mortality and morbidity were similar in both cohorts.

CONCLUSION: Survival of babies born between 22 and 25 weeks' gestation has increased since 1995 but the pattern of major neonatal morbidity and the proportion of survivors affected are unchanged. These observations reflect an important increase in the number of preterm survivors at risk of later health problems.

Survival to discharge
22 GN – 2% (n=3)
23 GN – 19% (n=66)
24 GN – 40% (n=178)

Costeloe, K.L., Hennessy, E.M., Haider, S., Stacey, F., Marlow, N., Draper, E.S., **2012. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies).** BMJ 345, e7976.

EPICURE uuringud: Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006 (kaugtulem 3-aastaselt): **OBJECTIVE:** To determine outcomes at **age 3 years** in babies born **before 27 completed weeks'** gestation in **2006,** and to **evaluate changes in outcome since 1995** for babies born between 22 and 25 weeks' gestation. **DESIGN: Prospective national cohort studies, EPICure and EPICure 2.** **SETTING:** Hospital and home based evaluations, **England.** **PARTICIPANTS: 1031** surviving babies born in 2006 before 27 completed weeks' gestation. Outcomes for **584 babies** born at **22-25 weeks'** gestation were compared with those of **260 surviving babies of the same gestational age born in 1995.** **MAIN OUTCOME MEASURES: Survival to age 3 years, impairment (2008 consensus definitions), and developmental scores**. Multiple imputation was used to account for the high proportion of missing data in the 2006 cohort. **RESULTS:** Of the 576 babies evaluated after birth in 2006, **13.4% (n=77) were categorised as having severe impairment and 11.8% (n=68) moderate impairment.** The **prevalence of neurodevelopmental impairment** was significantly associated with length of gestation, with greater impairment as gestational age decreased: **45% at 22-23 weeks**, 30% at 24 weeks, 25% at 25 weeks, and 20% at 26 weeks (P<0.001). Cerebral palsy was present in 83 (14%) survivors. Mean developmental quotients were lower than those of the general population (normal values 100 (SD 15)) and showed a direct relation with gestational age: 80 (SD 21) at 22-23 weeks, 87 (19) at 24 weeks, 88 (19) at 25 weeks, and 91 (18) at 26 weeks. These results did not differ significantly after imputation. **Comparing imputed outcomes between the 2006 and 1995 cohorts, the proportion of survivors born between 22 and 25 weeks' gestation with severe disability, using 1995 definitions, was 18% (95% confidence interval 14% to 24%) in 1995 and 19% (14% to 23%) in 2006.** Fewer survivors had shunted hydrocephalus or seizures. **Survival of babies admitted for neonatal care increased from 39% (35% to 43%) in 1995 to 52% (49% to 55%) in 2006, an increase of 13% (8% to 18%), and survival without disability increased from 23% (20% to 26%) in 1995 to 34% (31% to 37%) in 2006, an increase of 11% (6% to 16%).** **CONCLUSION:** Survival and impairment in early childhood are both closely related to gestational age for babies born at less than 27 weeks' gestation. Using multiple imputation to account for the high proportion of missing values, **a higher proportion of babies admitted for neonatal care now survive without disability, particularly those born at gestational ages 24 and 25 weeks.** 3 a vanuselt oli 22-23 GN sündinutest 45%-l mõõdukas või raske NDI.	Moore, T., Hennessy, E.M., Myles, J., Johnson, S.J., Draper, E.S., Costeloe, K.L., Marlow, N., **2012. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies.** BMJ 345, e7961.

MOSAIC uuring (prospektiivne kohortuuring). Investigating the variations in survival rates for very preterm infants in 10 European regions:

OBJECTIVE: To investigate the variation in the survival rate and the mortality rates for very preterm infants across Europe.
DESIGN: A **prospective birth cohort** of very preterm infants for **10 geographically defined European regions during 2003**, followed to discharge home from hospital.
PARTICIPANTS: All deliveries **from 22 + 0 to 31 + 6 weeks'** gestation.
MAIN OUTCOME MEASURE: All outcomes of pregnancy by gestational age group, including termination of pregnancy for congenital anomalies and other reasons, antepartum stillbirth, intrapartum stillbirth, labour ward death, death after admission to a neonatal intensive care unit (NICU) and survival to discharge.
RESULTS: Overall the proportion of this very preterm cohort who survived to discharge from neonatal care was 89.5%, varying from 93.2% to 74.8% across the regions. **Less than 2% of infants <24 weeks' gestation and approximately half of the infants from 24 to 27 weeks' gestation survived to discharge home from the NICU.** However **large variations** were seen in the timing of the deaths by region. Among all fetuses alive at onset of labour of 24-27 weeks' gestation, between 84.0% and 98.9% were born alive and between 64.6% and 97.8% were admitted to the NICU. **For babies <24 weeks' gestation, between 0% and 79.6% of babies alive at onset of labour were admitted to neonatal intensive care.**
CONCLUSIONS: There are wide variations in the survival rates to discharge from neonatal intensive care for very preterm deliveries and in the timing of death across the MOSAIC regions. **In order to directly compare international statistics for mortality in very preterm infants, data collection needs to be standardised. We believe that the standard point of comparison should be using all those infants alive at the onset of labour as the denominator for comparisons of mortality rates for very preterm infants analysing the cohort by gestational age band.**

Draper, E.S., Zeitlin, J., Fenton, A.C., Weber, T., Gerrits, J., Martens, G., Misselwitz, B., Breart, G., MOSAIC research group, **2009. Investigating the variations in survival rates for very preterm infants in 10 European regions: the MOSAIC birth cohort.** Arch. Dis. Child. Fetal Neonatal Ed. 94, F158–163. doi:10.1136/adc.2008.141531

Table 2 Outcomes of pregnancy, models of organising access to intensive care cohort by gestational age group for infants known to be alive at the onset of labour, excluding terminations of pregnancy for congenital anomalies but not for other reasons

Country, region		Alive at onset of labour	% Born alive (95% CI)	% Admitted for NIC (95% CI)	% Live discharge (95% CI)
	<24 weeks' gestation	N			
BE	Flanders	44	43.2 (28.4 to 59.0)	11.4 (3.8 to 24.6)	4.5 (0.6 to 15.5)
DE	Hesse	31	64.5 (45.4 to 80.8)	35.5 (19.2 to 54.6)	9.7 (2.0 to 25.8)
DK	Eastern	15	46.7 (21.3 to 73.4)	13.3 (1.7 to 40.5)	0.0 (0.0 to 20.0)
FR	Ile-de-France	102	26.5 (18.2 to 36.1)†	2.9 (0.6 to 8.4)†	1.0 (0.0 to 5.4)
IT	Lazio	27	55.6 (35.3 to 74.5)	48.1 (28.7 to 68.1)	3.7 (0.1 to 19.0)
NL	Eastern & Central	43	62.8 (46.7 to 77.0)	0.0 (0.0 to 8.2)†	0.0 (0.0 to 6.98)
PL	Wielkopolksa/Lubuskie	49	89.8 (77.8 to 96.6)*	79.6 (65.7 to 89.8)*	2.0 (0.1 to 10.9)
PO	Northern	14	64.3 (35.1 to 87.2)	57.1 (28.9 to 82.3)	7.1 (0.2 to 33.9)
UK	Northern	24	54.2 (32.8 to 74.5)	33.3 (15.6 to 55.3)	8.3 (1.0 to 27.0)
UK	Trent	39	64.1 (47.2 to 78.8)	28.2 (15.0 to 44.9)	2.6 (0.1 to 13.5)
All	Regions	388	53.1 (48.0 to 58.2)	25.8 (21.6 to 30.5)	3.1 (1.6 to 5.4)

Neonatal Research Network. Prospektiivne kohortuuring.

Stoll, B.J., Hansen, N.I.,

TRENDS IN CARE PRACTICES:
OBJECTIVE: **To review** 20-year trends **in maternal/neonatal care, complications, and mortality among extremely preterm infants born at Neonatal Research Network centers.**
DESIGN, SETTING, PARTICIPANTS: Prospective registry of 34,636 infants, 22 to 28 weeks' gestation, birth weight of 401 to 1500 g, and **born at 26 network centers between 1993 and 2012.**
EXPOSURES: Extremely preterm birth.
MAIN OUTCOMES AND MEASURES: Maternal/neonatal care, morbidities, and survival. Major morbidities, reported for infants who survived more than 12 hours, were severe necrotizing enterocolitis, infection, bronchopulmonary dysplasia, severe intracranial hemorrhage, cystic periventricular leukomalacia, and/or severe retinopathy of prematurity. Regression models assessed yearly changes and were adjusted for study center, race/ethnicity, gestational age, birth weight for gestational age, and sex.
RESULTS: Use of antenatal corticosteroids increased from 1993 to 2012 (**24%** [348 of 1431 infants]) **to 87%** (1674 of 1919 infants]; P < .001), **as did cesarean delivery** (44% [625 of 1431 births] **to 64%** [1227 of 1921]; P < .001). **Delivery room intubation decreased from 80%** (1144 of 1433 infants) in 1993 **to 65%** (1253 of 1922) in 2012 (P < .001). After increasing in the 1990s, postnatal steroid use declined to 8% (141 of 1757 infants) in 2004 (P < .001), with no significant change thereafter. Although most infants were ventilated, continuous positive airway pressure without ventilation increased from 7% (120 of 1666 infants) in 2002 to 11% (190 of 1756 infants) in 2012 (P < .001). **Despite no improvement from 1993 to 2004, rates of late-onset sepsis declined between 2005 and 2012 for infants of each gestational age** (median, 26 weeks [37% {109 of 296} to 27% {85 of 320}]; adjusted relative risk [RR], 0.93 [95% CI, 0.92-0.94]). **Rates of other morbidities declined, but bronchopulmonary dysplasia increased between 2009 and 2012 for infants at 26 to 27 weeks' gestation** (26 weeks, 50% [130 of 258] to 55% [164 of 297]; P < .001). **Survival increased between 2009 and 2012 for infants at 23 weeks' gestation** (27% [41 of 152] to 33% [50 of 150]; adjusted RR, 1.09 [95% CI, 1.05-1.14]) and 24 weeks (63% [156 of 248] to 65% [174 of 269]; adjusted RR, 1.05 [95% CI, 1.03-1.07]), with smaller relative increases for infants at 25 and 27 weeks' gestation, and **no change for infants at 22, 26, and 28 weeks' gestation. Survival without major morbidity increased approximately 2% per year for infants at 25 to 28 weeks' gestation, with no change for infants at 22 to 24 weeks' gestation.**
CONCLUSIONS AND RELEVANCE: Among extremely preterm infants born at US academic centers over the last 20 years, changes in maternal and infant care practices and modest reductions in several morbidities were observed, although bronchopulmonary dysplasia increased. Survival increased most markedly for infants born at 23 and 24 weeks' gestation and survival without major morbidity increased for infants aged 25 to 28 weeks. These findings may be valuable in counseling families and

Bell, E.F., Walsh, M.C., Carlo, W.A., Shankaran, S., Laptook, A.R., Sánchez, P.J., Van Meurs, K.P., Wyckoff, M., Das, A., Hale, E.C., Ball, M.B., Newman, N.S., Schibler, K., Poindexter, B.B., Kennedy, K.A., Cotten, C.M., Watterberg, K.L., D'Angio, C.T., DeMauro, S.B., Truog, W.E., Devaskar, U., Higgins, R.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, **2015. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates**, 1993-2012. JAMA 314, 1039–1051. doi:10.1001/jama.2015.10244

developing novel interventions.	

Table 3. Survival to Discharge for Infants Born at Gestational Ages 22 Through 28 Weeks in NRN Centers[a]

	Study Year, No. of Infants/Total No. (%)					
	1993	2012	1993-1997	1998-2002	2003-2007	2008-2012
All infants (N = 34 636)	1433	1922	7027	9132	9600	8877
Died	426/1433 (30)	409/1922 (21)	1992/7027 (28)	2489/9132 (27)	2725/9600 (28)	2131/8877 (24)
Died within 12 h	193/1433 (13)	166/1922 (9)	909/7027 (13)	1025/9132 (11)	1054/9600 (11)	843/8877 (9)
Survived to Discharge Among All Infants						
All infants	1007/1433 (70)	1513/1922 (79)	5035/7027 (72)	6643/9132 (73)	6875/9600 (72)	6746/8877 (76)
By gestational age, wk						
22	5/79 (6)	7/75 (9)	25/358 (7)	27/437 (6)	25/421 (6)	22/334 (7)
23	34/122 (28)	50/150 (33)	184/660 (28)	215/821 (26)	226/873 (26)	252/779 (32)
24	85/163 (52)	174/269 (65)	465/871 (53)	715/1273 (56)	752/1377 (55)	774/1241 (62)
25	153/225 (68)	249/308 (81)	784/1070 (73)	1065/1397 (76)	1081/1503 (72)	1077/1391 (77)
26	208/250 (83)	291/333 (87)	980/1194 (82)	1317/1542 (85)	1322/1580 (84)	1281/1513 (85)
27	238/283 (84)	337/357 (94)	1183/1337 (88)	1536/1720 (89)	1615/1837 (88)	1568/1733 (90)
28	284/311 (91)	405/430 (94)	1414/1537 (92)	1768/1942 (91)	1854/2009 (92)	1772/1886 (94)
Survived to Discharge Without Major Morbidity Among All Infants[b]						
All infants evaluated[c]	256/1256 (20)	559/1895 (29)	1096/6100 (18)	2119/8869 (24)	2318/9368 (25)	2493/8723 (29)
By gestational age, wk						
22	0/79	0/75	2/355 (<1)	3/437 (<1)	0/421	0/334
23	2/120 (2)	1/150 (<1)	12/650 (2)	9/820 (1)	16/871 (2)	13/779 (2)
24	12/160 (8)	15/268 (6)	60/850 (7)	77/1269 (6)	65/1377 (5)	87/1238 (7)
25	33/208 (16)	61/306 (20)	128/1001 (13)	198/1384 (14)	212/1493 (14)	237/1383 (17)
26	52/213 (24)	85/331 (26)	199/1028 (19)	371/1516 (24)	433/1555 (28)	413/1505 (27)
27	69/242 (29)	167/353 (47)	305/1090 (28)	628/1650 (38)	669/1785 (37)	735/1693 (43)
28	88/234 (38)	230/412 (56)	390/1126 (35)	833/1793 (46)	923/1866 (49)	1008/1791 (56)
Survived to Discharge Without Major Morbidity Among Infants Who Survived to Discharge						
All survivors to discharge (n = 25 299)	1007	1513	5035	6643	6875	6746
All survivors evaluated[d]	256/830 (31)	559/1486 (38)	1096/4108 (27)	2119/6380 (33)	2318/6643 (35)	2493/6592 (38)
By gestational age, wk						
22	0/5	0/7	2/22 (9)	3/27 (11)	0/25	0/22
23	2/32 (6)	1/50 (2)	12/174 (7)	9/214 (4)	16/224 (7)	13/252 (5)
24	12/82 (15)	15/173 (9)	60/444 (14)	77/711 (11)	65/752 (9)	87/771 (11)
25	33/136 (24)	61/247 (25)	128/715 (18)	198/1052 (19)	212/1071 (20)	237/1069 (22)
26	52/171 (30)	85/289 (29)	199/814 (24)	371/1291 (29)	433/1297 (33)	413/1273 (32)
27	69/197 (35)	167/333 (50)	305/936 (33)	628/1466 (43)	669/1563 (43)	735/1528 (48)
28	88/207 (43)	230/387 (59)	390/1003 (39)	833/1619 (51)	923/1711 (54)	1008/1677 (60)

Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants: **BACKGROUND** Between-hospital variation in outcomes among extremely preterm infants is largely unexplained and may reflect differences in hospital practices regarding the initiation of active lifesaving treatment as compared with comfort care after birth. **METHODS** We studied infants born between April 2006 and March 2011 at 24 hospitals included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Data were collected for **4987 infants born before 27 weeks** of gestation without congenital anomalies. **Active treatment was defined as any potentially lifesaving intervention administered after birth. Infants were considered to have received active treatment if they received any of the following interventions: surfactant therapy, tracheal intubation, ventilatory support (including continuous positive airway pressure, bag–valve–mask ventilation, or mechanical ventilation), parenteral nutrition, epinephrine, or chest compressions.** Survival and neurodevelopmental impairment at 18 to 22 months of corrected age were assessed in 4704 children (94.3%). **RESULTS Overall**	N Engl J Med. 2015 May 7;372(19):1801-11. doi: 10.1056/NEJMoa1410689. Between-hospital variation in treatment and outcomes in extremely preterm infants. Rysavy MA1, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, Vohr BR, Carlo WA, Shankaran S, Walsh MC, Tyson JE, Cotten CM, Smith PB, Murray JC, Colaizy TT,Brumbaugh JE, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.

rates of active treatment ranged from 22.1% (interquartile range [IQR], 7.7 to 100) among infants born at 22 weeks of gestation to 99.8% (IQR, 100 to 100) among those born at 26 weeks of gestation. **Overall rates of survival and survival without severe impairment ranged from 5.1% (IQR, 0 to 10.6) and 3.4% (IQR, 0 to 6.9), respectively, among children born at 22 weeks of gestation** to 81.4% (IQR, 78.2 to 84.0) and 75.6% (IQR, 69.5 to 80.0), respectively, among those born at 26 weeks of gestation. **Hospital rates of active treatment accounted for 78% and 75% of the between-hospital variation in survival and survival without severe impairment, respectively, among children born at 22 or 23 weeks of gestation,** and accounted for 22% and 16%, respectively, among those born at 24 weeks of gestation, but the rates did not account for any of the variation in outcomes among those born at 25 or 26 weeks of gestation. **CONCLUSIONS** Differences in hospital practices regarding the initiation of active treatment in infants born at 22, 23, or 24 weeks of gestation explain some of the between-hospital variation in survival and survival without impairment among such patients.	

Approach to infants born at 22 to 24 weeks' gestation: relationship to outcomes of more-mature infants (<u>retrospektiivne kohortuuring</u>): **APPROACH TO INFANTS. OBJECTIVE:** We sought to determine if a center's approach to care of premature infants at the youngest gestational ages (22-24 weeks' gestation) is associated with clinical outcomes among infants of older gestational ages (25-27 weeks' gestation). **METHODS: Retrospektiivne kohortuuring.** Inborn infants (n=8858 ELBW; 3631 – 41% 22-24 GN) of 401 to 1000 g birth weight and **22 0/7 to 27 6/7 weeks' gestation** at birth from **2002 to 2008** were enrolled into a **prospectively collected database at 20 centers** participating in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. **Markers of an aggressive approach to care for 22- to 24-week infants included use of antenatal corticosteroids, cesarean delivery, and resuscitation.** The primary outcome was death before postnatal day 120 for infants of 25 to 27 weeks' gestation. Secondary outcomes were the combined outcomes of death or a number of morbidities associated with prematurity. **RESULTS:** Our study included 3631 infants 22 to 24 weeks' gestation and 5227 infants 25 to 27 weeks' gestation. **Among the 22- to 24-week infants, use of antenatal corticosteroids ranged from 28% to 100%, cesarean delivery from 13% to 65%, and resuscitation from 30% to 100% by center.** **Few infants born at 22 weeks received antenatal corticosteroids (12%), were delivered via cesarean delivery (7%), or were resuscitated at birth (20%).** **Centers with higher rates of antenatal corticosteroid use in 22- to**	Smith, P.B., Ambalavanan, N., Li, L., Cotten, C.M., Laughon, M., Walsh, M.C., Das, A., Bell, E.F., Carlo, W.A., Stoll, B.J., Shankaran, S., Laptook, A.R., Higgins, R.D., Goldberg, R.N., Generic Database Subcommittee, Eunice Kennedy Shriver National Institute of Child Health Human Development Neonatal Research Network, **2012. Approach to infants born at 22 to 24 weeks' gestation: relationship to outcomes of more-mature infants.** Pediatrics 129, e1508–1516. doi:10.1542/peds.2011-2216

24-week infants had reduced rates of death, death or retinopathy of prematurity, death or late-onset sepsis, death or necrotizing enterocolitis, and death or neurodevelopmental impairment in 25- to 27-week infants. **CONCLUSIONS: This study suggests that physicians' willingness to provide care to extremely low gestation infants as measured by frequency of use of antenatal corticosteroids is associated with improved outcomes for more-mature infants.**	
Cesarean delivery versus vaginal delivery: impact on survival and morbidity for the breech fetus at the threshold of viability. 2010. **<u>Retrospektiivne kohortuuring:</u>** Objective. To determine **if cesarean delivery is associated with improved survival and morbidity** in the **breech fetus at the threshold of viability**. Study design. The **Missouri** maternally linked cohort data files covering the period **1989 through 2005** were utilized for analysis. All pregnancies with singleton fetuses in the breech presentation delivered between **23+0 and 24+6** weeks gestation and birth weights between 400 and 750 g were included. Logistic regression was used to compare cesarean to vaginal delivery after controlling for maternal demographics and pregnancy complications. Results. A total of **325 breech singletons were analyzed; cesarean deliveries accounted for 46.1% (150) and vaginal deliveries accounted for 53.9% (175). Cesarean delivery was associated with a survival benefit across all birth weights. Morbidity was higher in cesarean compared to vaginal delivery.** Morbidity was defined as a composite of the following abnormal conditions: birth injury, hyaline membrane disease, meconium aspiration syndrome, assisted ventilation 30 min, and seizures. Conclusion. **Although cesarean delivery appears to be associated with an increase in survival at the threshold of viability for the breech fetus, there is a concomitant increase in morbidity. Any benefit that cesarean delivery conveys on survival at the threshold of viability should be weighed against the increased maternal morbidity and high overall neonatal morbidity.**	Deutsch, A., Salihu, H.M., Lynch, O., Marty, P.J., Belogolovkin, V., **2011. Cesarean delivery versus vaginal delivery: impact on survival and morbidity for the breech fetus at the threshold of viability.** J. Matern. Fetal. Neonatal. Med. 24, 713–717. doi:10.3109/14767058.2010.516287
Uterine Rupture Risk After Periviable Cesarean Delivery. 2015. **<u>Retrospektiivne kohortuuring.</u>** OBJECTIVE: **To investigate the risk of uterine rupture in women with prior periviable cesarean delivery and prior term cesarean delivery independent of initial incision type.** METHODS: We conducted a **retrospective longitudinal cohort study** using Washington state birth certificate data and hospital discharge records, identifying primary cesarean deliveries performed at **20–26 weeks and 37– 41 weeks** of gestation **with subsequent delivery between 1989 and 2008. We compared subsequent uterine rupture risk in the two groups considering both primary incision type and subsequent labor induction and augmentation.** RESULTS: We identified **456 women with index periviable cesarean delivery** and 10,505 women with index term cesarean delivery. Women with index periviable	Lannon, S.M.R., Guthrie, K.A., Vanderhoeven, J.P., Gammill, H.S., **2015. Uterine rupture risk after periviable cesarean delivery.** Obstet Gynecol 125, 1095–1100. doi:10.1097/AOG.0000000000000832

cesarean delivery were younger, more frequently of nonwhite race, more likely to smoke, and more likely to have hypertension. **Women in the periviable group had more index classical incisions (42% compared with 1%, P,.001) and fewer subsequent inductions and augmentations (8% compared with 16%, P,.001). Uterine rupture in the subsequent pregnancy occurred more frequently among women in the index periviable group than those in the index term group (8/456 [1.8%] compared with 38/10,505 [0.4%], odds ratio [OR] 4.9, 95% confidence interval [CI] 2.3–10.6). This relationship persisted among women with a low transverse incision** (4/ 228 [1.8%] compared with 36/9,558 [0.4%], OR 4.7, 95% CI 1.7–13.4). CONCLUSION: Cesarean delivery at periviability compared with term is associated with an **increased risk for uterine rupture in a subsequent pregnancy, even after low transverse incision.** These data support judicious use of cesarean delivery at periviable gestational ages and inform subsequent counseling.

Table 2. Risk of Uterine Rupture by Gestational Age Group of the Index Cesarean Delivery

Risk Category	Periviable (20–26 Weeks of Gestation)	Term (37–41 Weeks of Gestation)	Unadjusted	
			OR (95% CI)	*P*
All patients	8/456 (1.8)	38/10,505 (0.4)	4.9 (2.3–10.6)	<.001
By incision type				
Classical	4/163 (2.5)	0/61 (0)	—*	—
Low transverse	4/228 (1.8)	36/9,558 (0.4)	4.7 (1.7–13.4)	.004
Other†	0/1 (0)	0/11 (0)	—*	—
Missing	0/64 (0)	2/875 (<0.1)	—*	—
By induction or augmentation				
No	8/420 (1.9)	23/8,824 (0.3)	7.4 (3.3–16.7)	<.001
Yes	0/36 (0)	15/1,681 (0.9)	—*	—

OR, odds ratio; CI, confidence interval.
Data are n/N (%) unless otherwise specified.
* OR could not be estimated for classical, other, and missing incision types or for women with induction or augmentation owing lack of events.
† Other incision types as determined by International Classification of Diseases, 9th Revision, Clinical Modification procedure code 74.4 or 74.9.

KONSENSUSLIKUD DOKUMENDID:

RCOG 2014 scientific impact paper elulemuse piiri kohta:
Maternal and Fetal Antenatal Interventions:
Although tocolysis at the threshold of viability does not appear to confer a short or long term benefit on neonatal outcome, it may be useful for those women who require transfer for neonatal care or time to complete a course of corticosteroids. As most babies delivering at 23 weeks of gestation are likely to receive active stabilisation at birth, **antenatal steroids should be given after 22+6 weeks of gestation unless a policy decision has been taken not to offer active intervention after delivery.**
Peripartum magnesium infusion is recommended once 24 weeks of gestation is reached. Before that, it would seem sensible to consider its use if a decision has been made for active intervention.
If the mother is a carrier of GBS, intrapartum intravenous Penicillin should be given.
Mode of Delivery:
Obstetric management, in particular a decision for caesarean section,

Royal College of Obstetricians & Gynaecologists. **Perinatal Management of Pregnant Women at the Threshold of Infant Viability (The Obstetric Perspective). Scientific Impact Paper** No. 41. **2014.**

due to fetal indication must be individualised taking into account the wishes of the parents, and making it clear that a classical caesarean section may be required**. It is unusual to deliver by caesarean section before 24 weeks of gestation. However each decision should be on a case–by–case basis** on the understanding that if the pregnancy continues, the decision on mode of delivery will need to be reassessed, possibly even on a daily basis. **The surgical complications of Caesarean delivery** to mother and baby at such extremes of gestation must be explicit, and even the rarity of hysterectomy and infertility should be mentioned but placed in context. When this information has been given, the couple's views must be added and a final decision on how to proceed is made. **At 25+0 weeks of gestation, newborn survival should be given priority. Although clear evidence for the optimum mode of delivery is unavailable, in cases of spontaneous labour with a single and cephalic fetus, vaginal delivery should be attempted**. However if continuous CTG monitoring reveals features of suspected acute fetal compromise/distress, a caesarean section should be performed without delay. Caesarean delivery at an extreme preterm gestation can be complex and a senior obstetrician should be present. As there is a significant risk of cord prolapse during labour with transverse lie or footling breech presentation at extremely preterm gestations, emergency caesarean section should be discussed with the parents if the decision is taken to opt for active obstetric intervention. Keeping the amniotic membranes intact may reduce the risk of trauma to the fetus during labour and delivery. If labour is induced, there is no requirement to rupture the membranes. Intravenous oxytocin can be used should labour not progress, without the need for amniotomy. Ultrasound during labour can be useful to monitor fetal viability and descent of the presenting part through the vagina when the membranes are kept intact. Episiotomy may be useful to widen the introitus and aid delivery of the presenting part in non–cephalic presentations. In flexed or extended breech deliveries complications such as an entrapped fetal head may arise, therefore an attendant with suitable experience should be present at delivery. The risks and benefits of delayed cord clamping should be considered prior to delivery and discussed with the parents and with the neonatal team who will manage neonatal resuscitation to derive a clear plan of management at birth.	

Raju et al. 2014. **Periviable birth: executive summary of a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists.** J Perinatol. 2014 May;34(5):333-42. doi: 10.1038/jp.2014.70. Epub 2014 Apr 10.

Table 3. General guidance regarding obstetric interventions for threatened and imminent periviable birth, according to whether the fetus is considered potentially viable, and the parents' wishes for aggressive intervention[a]

	Weeks of gestation[b]		
	< 22 0/7 Weeks	*22 0/7 Weeks to 22 6/7 Weeks*	*23 0/7 Weeks or more*
Antenatal corticosteroids	Not recommended	Consider if delivery at or later than 23 0/7 weeks is anticipated	Recommended
Tocolytics to enhance latency for potential steroid benefit	Not recommended	Not recommended unless concurrent with antenatal steroids	Consider
Magnesium sulfate for neuroprotection	Not recommended	Not recommended	Recommended
Antibiotics for PROM to enhance latency	Consider if delivery is not imminent	Consider if delivery is not imminent	Recommended if delivery is not imminent
Intrapartum antibiotics for GBS prophylaxis[c]	Not recommended	Not recommended	Recommended
Continuous intrapartum electronic fetal monitoring	Not recommended	Not recommended	Recommended
Cesarean delivery for fetal indication[d]	Not recommended	Not recommended	Recommended
Aggressive newborn resuscitation	Not recommended, comfort care only	Not recommended unless considered potentially viable based on individual circumstances	Recommended unless considered nonviable based on individual circumstances

Abbreviations: PROM, preterm rupture of membranes; GBS, group B streptococcus.
[a]Survival of infants born in the periviable period is dependent on resuscitation and support. Between 22 and 25 weeks of gestation, there may be mitigating factors (for example, intrauterine growth restriction, small fetal size, the presence of fetal malformations or aneuploidy and pulmonary hypoplasia due to prolonged membrane rupture) that will affect the potential for survival and the determination of viability (Table 2). The majority of survivors born at 25 6/7 weeks of gestation or less will incur major morbidities, regardless of gestational age at birth. [b]Infants born before 22 0/7 weeks of gestation are generally considered nonviable. Data from recent large studies suggest survival with delivery at 22 0/7 weeks through 22 6/7 weeks to be 5–6%.[25,27] With survival rates of ~26–28% and higher, infants born at 23 0/7 weeks through 25 6/7 weeks of gestation are generally considered potentially viable (Tables 1 and 2). [c]GBS carrier or carrier status is unknown. [d]For example, persistently abnormal fetal heart rate patterns or biophysical testing (category II–III).

American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine. ***2015. Periviable birth. Obstetric care consensus. http://www.acog.org/Resources-And-Publications/Obstetric-Care-Consensus-Series/Periviable-Birth***

Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes (34–37). Specific data on the use of steroids in the periviable period are supported by a combination of laboratory data on the response of lung tissue and clinical observational studies (34, 38, 39). Data from a Eunice Kennedy Shriver NICHD Neonatal Research Network observational cohort revealed a significant reduction in death and neurodevelopmental impairment at 18–22 months for infants who had been exposed to antenatal corticosteroids and born at 23 weeks of gestation (83.4% versus 90.5%), 24 weeks of gestation (68.4% versus 80.3%), and 25 weeks of gestation (52.7% versus 67.9%) (34). At 22 weeks of gestation, no significant difference in these outcomes was noted (90.2% versus 93.1%) (34). In this study, antenatal corticosteroid exposure also decreased incidence of death, intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis in infants born between 23 weeks and 25 weeks of gestation.

Magneesiumsulfaat: Maternal treatment with magnesium sulfate has been shown to improve neurologic outcomes when administered before anticipated early preterm birth. The use of magnesium sulfate for this indication has been studied in five randomized controlled trials, with enrollment started as early as 24 weeks of gestation (18, 40). Although data specific to the periviable period are not available, antenatal magnesium sulfate treatment has been shown to reduce the incidence of any cerebral palsy (relative risk, 0.68; 95% confidence interval, 0.54–0.87) without increasing mortality (relative risk, 1.04; 95% confidence interval, 0.92–1.17) when administered before 30 weeks of gestation (18). Given these findings, magnesium sulfate prophylaxis is recommended if periviable delivery of a potentially viable infant is anticipated.

Tokolüüs: Studies suggest that nifedipine and indomethacin tocolysis of women in preterm labor with intact membranes may delay delivery between 48 hours and 72 hours after 26 weeks of gestation, but specific data for pregnancies treated before 26 weeks of gestation are lacking (43, 44). Theoretically, a brief delay of delivery with tocolytic therapy for preterm labor could reduce neonatal morbidity and mortality in the periviable period, particularly if antenatal steroids can be administered. However, although some studies have found that tocolytics delay delivery for a short time, improvements in actual neonatal outcomes have not

been consistently demonstrated (45). Because there is some evidence of brief pregnancy prolongation but no consistent data suggesting improved newborn outcomes at any gestational age, a specific and strong recommendation in favor of or against tocolytic therapy for preterm labor cannot be made.

AB ja PPROM: Administration of broad-spectrum antibiotics during expectant management of preterm PROM has been shown to prolong pregnancy and reduce newborn infections (41). Alternatively, antibiotic treatment of women with preterm labor and intact membranes has been shown to have no effect on pregnancy prolongation or on the improvement of newborn outcomes; indeed, the combination of amoxicillin–clavulanic acid in the setting of preterm labor may worsen long-term outcomes for the offspring (42). Thus, although data specific to the periviable period are not available, broad-spectrum antibiotic treatment to prolong pregnancy during expectant management of periviable preterm PROM generally is recommended at 24 weeks of gestation and beyond. Conversely, there are inadequate data to help obstetrician–gynecologists and other obstetric providers balance any potential efficacy at earlier gestational ages against potential risks. In the setting of preterm labor with intact membranes, because of the lack of evidence of benefit and the potential risks, such treatment is not recommended.

Keisrilõige: Routine cesarean delivery is not recommended for the indication of periviable delivery alone because it has not been shown to decrease mortality or intraventricular hemorrhage after early preterm birth (51). Randomized controlled trials comparing cesarean delivery with vaginal delivery have not been done in the periviable period. Although limited retrospective data provide some support for cesarean delivery in the presence of malpresentation, delivery for women in the periviable period should be individualized, recognizing increased maternal morbidity associated with cesarean delivery, particularly if the need for classical cesarean delivery is anticipated (7, 52–54). Cesarean delivery before 22 weeks of gestation is appropriate only for maternal indications (eg, placenta previa or uterine rupture).

Otsingustrateegia:

Otsingusõnad: periviability, periviable birth, extremely preterm infant, extremely premature infant, threshold of viability

Otsingud:

25.09.15 Pubmed Search: ((((periviability) OR periviable birth) OR extremely preterm infant) OR extremely premature infant) OR threshold of viability Filters: Guideline, Practice Guideline, Meta-Analysis, Systematic Reviews, 10 years, Humans, English n=124 - neist asjakohaseid 18

27.09.15 National Guideline Clearinghouse. Otsingusõnad „periviable birth“ ja „threshold of viability“- vasteid 0

27.09.15 Trip database: „periviable birth“ – n=13- neist 2 sobilikku

03.10.15 Pubmed Search: ((((periviability) OR periviable birth) OR extremely preterm infant) OR extremely premature infant) OR threshold of viability Filters: Comparative Study, Clinical Trial, Controlled Clinical Trial, Multicenter Study, Observational Study, Randomized Controlled Trial, Full text, 5 years, Humans, English n=298 –neist sobilikke 5

Lisaks kontrollitud oluliste allikate viiteid.