

**Appendix A**

**Post delivery Survival of Fetuses at 20 weeks post fertilization (22 weeks LMP)**

**Selected publications 2015 to 2017**

1. N Engl J Med. 2017 Feb 16;376(7):617­628. doi: 10.1056/NEJMoa1605566. **Survival and Neurodevelopmental Outcomes among Periviable Infants**. Younge N , Goldstein RF , Bann CM , Hintz SR , Patel RM , Smith PB , Bell EF , Rysavy MA , Duncan AF , Vohr BR , Das A , Goldberg RN , Higgins RD , Cotten CM ; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.

“**Methods**:

We compared survival and neurodevelopmental outcomes among **infants born at 22 to 24 weeks** of gestation, as assessed at 18 to 22 months of corrected age, across three consecutive birth­year epochs (2000­2003 [epoch 1], 2004­2007 [epoch 2], and 2008­2011 [epoch 3]).

**Results**:

 Data on the primary outcome were available for 4274 of 4458 infants (96%) born at the 11 centers. The percentage of infants who survived increased from 30% (424 of 1391 infants) in epoch 1 to 36% (487 of 1348 infants) in epoch 3 (P<0.001). The percentage of infants who survived without neurodevelopmental impairment increased from 16% (217 of 1391) in epoch 1 to 20% (276 of 1348) in epoch 3 (P=0.001), whereas the percentage of infants who survived with neurodevelopmental impairment did not change significantly (15% [207 of 1391] in epoch 1 and 16% [211 of 1348] in epoch 3, P=0.29). After adjustment for changes in the baseline characteristics of the infants over time, both the rate of survival with neurodevelopmental impairment (as compared with death) and the rate of survival without neurodevelopmental impairment (as compared with death) increased over time (adjusted relative risks, 1.27 [95% confidence interval {CI}, 1.01 to 1.59] and 1.59 [95% CI, 1.28 to 1.99], respectively). Conclusions The rate of survival without neurodevelopmental impairment increased between 2000 and 2011 in this large cohort of periviable infants. (Funded by the National Institutes of Health and others; ClinicalTrials.gov numbers, NCT00063063 and NCT00009633 .).

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1. Robertson JE, Lisonkova S, Lee T, De Silva DA, von Dadelszen P, Synnes AR, et al. (2016) **Fetal, Infant and Maternal Outcomesamong Women with Prolapsed Membranes Admitted before 29 Weeks Gestation.** PLoS ONE 11(12): e0168285.doi:10.1371/journal.pone.0168285

**“Results :** 129 women at 22–25 weeks gestation and 65 women at 26–28 weeks gestation were admitted to hospital and the median time-to-delivery was 4 days in both groups. Stillbirth rates were 12.4% vs 4.6% among women admitted at earlier vs later gestation (AOR 2.8, 95% CI 0.5–14.8), while perinatal death rates were 38.0% vs 6.1% (AOR 14.1, 95% CI 3.5–59.0), respectively.”

Comment: 38% perinatal death rate means that 62% of the group between 22 and 25 weeks gestation by LMP (ie 20-23 weeks fertilization age) survived.

1. JAMA Pediatr. 2016 Jul 1;170(7):671­7. doi: 10.1001/jamapediatrics.2016.0207. **Survival Among Infants Born at 22 or 23 Weeks' Gestation Following Active Prenatal and Postnatal Care.** Mehler K , Oberthuer A , Keller T , Becker I , Valter M , Roth B , Kribs A

**“Results**: Of 106 liveborn infants (45 born at 22 weeks and 61 born at 23 weeks and 6 days), 20 (19%) received palliative care (17 born at 22 weeks and 3 born at 23 weeks), and 86 (81%) received active care (28 born at 22 weeks and 58 born at 23 weeks). Of the 86 infants who received active care (mean [SD] maternal age, 32 [6] years), 58 (67%) survived until hospital discharge (17 born at 22 weeks and 41 born at 23 weeks). Eighty­five infants survived without severe complications, with 1 infant born at 22 weeks excluded because of missing data (6 of 27 [22%] born at 22 weeks, and 16 of 58 [28%] born at 23 weeks). Survival was predicted by the Apgar score after 5 minutes (odds ratio, 0.62 [95% CI, 0.46­0.84]) and birth weight (odds ratio, 0.001 [95% CI, 0.00­0.40]).

**Conclusions and Relevance**: One in 4 infants born at the border of viability and offered active care survived without severe complications. …”

1. Neonatology. 2016 Nov 29;111(3):234­239. [Epub ahead of print] **End­of­Life Care and Survival without Major Brain Damage in Newborns at the Limit of Viability.** García­Muñoz Rodrigo F , Urquía Martí L, García Hernández JÁ, Figueras Aloy J, García­Alix Pérez A; SEN1500 Network of the Spanish Neonatal Society.

**“Results**: A total of 3,371 patients were born alive, 3,236 of whom were admitted to the neonatal intensive care unit (NICU). Survival without MBD was 44.4% among patients admitted to the NICU, increasing from 12.5% at 22 weeks to 57.9% at 26 weeks' GA. The proportion of survivors without MBD relative to the total number of survivors was 81.1%

**Conclusions**: The proportion of survivors without MBD, when referred to the total number of survivors, is relatively high and is independent of GA. EoL decisions after the occurrence of MBD seem to play an important role in this respect. These results support the attitude of "giving an opportunity" even to the most immature patients, if this is in accordance with the parents' wishes.”

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1. JAMA Pediatr . 2016 December 01; 170(12): 1164–1172.

**Association of Neurodevelopmental Outcomes and Neonatal Morbidities of Extremely Premature Infants With Differential Exposure to Antenatal Steroids**

Sanjay Chawla, MD, Girija Natarajan, MD, Seetha Shankaran, MD, Athina Pappas, MD, Barbara J. Stoll, MD, Waldemar A. Carlo, MD, Shampa Saha, PhD, Abhik Das, PhD, Abbot R. Laptook, MD, and Rosemary D. Higgins, MD for the National Institute of Child Health and Human Development Neonatal Research Network

“All neonates born with a birth weight of 401 to 1000 g and/or a GA of 22 to 27 weeks as determined by early ultrasonography or last menstrual period…. Of 6121 eligible infants, 4284 (70.0%) survived to 18- to 22-month follow-up.”

1. N Engl J Med. 2015 May 7; 372(19): 1801–1811. doi:10.1056/NEJMoa1410689

**Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants**

Matthew A. Rysavy, B.S., Lei Li, Ph.D., Edward F. Bell, M.D., Abhik Das, Ph.D., Susan R. Hintz, M.D., Barbara J. Stoll, M.D., Betty R. Vohr, M.D., Waldemar A. Carlo, M.D., Seetha Shankaran, M.D., Michele C. Walsh, M.D., Jon E. Tyson, M.D., M.P.H., C. Michael Cotten, M.D., M.H.S., P. Brian Smith, M.D., M.P.H., M.H.S., Jeffrey C. Murray, M.D., Tarah T. Colaizy, M.D., M.P.H., Jane E. Brumbaugh, M.D., Rosemary D. Higgins, M.D., and for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

“Overall rates of survival, survival without severe impairment, and survival without moderate or severe impairment were 5.1% (interquartile range, 0 to 10.6), 3.4% (interquartile range, 0 to 6.9), and 2.0% (interquartile range, 0 to 0.7), respectively, among children born at 22 weeks of gestation and were 23.1% (interquartile range, 0 to 50.0), 15.4% (interquartile range, 0 to 33.3), and 9.0% (interquartile range, 0 to 14.6), respectively, among those born at 22 weeks of gestation who received active treatment.” [underline mine]

“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. (Funded by the National Institutes of Health.)”

1. Obstet Gynecol. 2012 Apr;119(4):795­800. doi: 10.1097/AOG.0b013e31824b1a03. **Improving survival of extremely preterm infants born between 22 and 25 weeks of gestation**.

Kyser KL , Morriss FH Jr, Bell EF, Klein JM, Dagle JM

“**Results**: Survival rates for the decade by gestational age (compared with predicted rates) were: 22 weeks, 33% (compared with 19%); 23 weeks, 58% (compared with 38%); 24 weeks, 87% (compared with 58%); and 25 weeks, 85% (compared with 70%). Antenatal corticosteroids were administered in 96% of pregnancies. Variables that significantly predicted survival and their odds ratios (OR) with 95% confidence intervals (CI) are: antenatal corticosteroid administration (OR 5.27, CI 1.26­22.08); female sex (OR 3.21, CI 1.42­7.26); gestational age (OR 1.89, CI 1.27­2.81); 1minute Apgar score (OR 1.39, CI 1.15­1.69); and birth year (OR 1.17, CI 1.02­1.34). The number needed to treat with any antenatal corticosteroid therapy to prevent one death was 2.4.

**Conclusion:** In this single­institution cohort treated aggressively (antenatal corticosteroid administration [even if less than 24 weeks], tocolysis until steroid course complete, cesarean for fetal distress) by perinatologists and neonatologists, survival rates at 22­25 weeks of gestation age for inborn infants during the 2000s exceeded predicted rates, with increasing odds of survival during the decade. Antenatal corticosteroid administration had a significant effect on survival.

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