Is the limit of viability shifting again?

A shift has been implied by the results of a recent cohort study in which **optimal antenatal corticosteroid (ACS) exposure** in 431 infants born between 22 0/7 and 23 6/7 weeks' gestation **was associated with increased survival to hospital discharge** and **increased survival without major morbidities.**

Chawla S, Wyckoff MH, Rysavy MA, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association of antenatal steroid exposure at 21 to 22 weeks of gestation with neonatal survival and survival without morbidities. JAMA Netw Open. 2022;5:e2233331. doi:10.1001/jamanetworkopen.2022.33331.

FAST TRACK

In infants not exposed to ACS compared with those who had partial exposure and those with complete exposure, complete ACS exposure was beneficial, increasing survival to discharge from 35.5% in the no-exposure group to 53.9%

EXPERT COMMENTARY

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The single most important intervention available in obstetrics to improve the health outcomes of preterm newborns is the maternal administration of corticosteroids. The 27 randomized controlled trials that formed the basis for this knowledge[1] did not include infants delivered at 24 weeks' gestation or less. This has not dissuaded us, over the last several decades, from using corticosteroids for impending delivery at 24 weeks' gestation; in the absence of randomized data, this has been based on observational evidence of benefit.

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Following the 2011 publication of a retrospective cohort study that analyzed data collected by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network between 1993 and 2009 (the Carlo study),[2] ACS started to be used widely even for impending delivery at 23 weeks' gestation. That study had found that the odds of death and neurodevelopmental impairment at 18 to 22 months of age were significantly lower in cases that received ACS and were born at 23 weeks (n = 1,978). The same benefit could not be verified for infants born at 22 weeks' gestational age (n = 402).

In a recent study conducted by the same NICHD Neonatal Research Network, antenatal steroid exposure at 21 to 22 weeks of gestation was examined.

Details of the study

Using prospectively collected data from 2016 to 2019, Chawla and colleagues conducted a retrospective cohort study that analyzed data from 431 infants who were born between 22 0/7 and 23 6/7 weeks' gestation and received neonatal intensive care (179 infants born at 22 weeks' gestation).[3] The infants not exposed to ACS were compared with those who had partial exposure (only 1 dose) and those with complete ACS exposure (2 doses).

Complete ACS exposure proved to be beneficial, increasing survival to discharge

from 35.5% in the no-exposure group to 53.9% (adjusted odds ratio [aOR], 1.95; 95% confidence interval [CI], 1.07–3.56). Of the survivors, 26.9% in the complete-exposure group had no major morbidities compared with 10% in the no-exposure group (aOR, 2.74; 95% CI, 1.19–6.30).

Study strengths and limitations

The strengths of this study include the use of a diverse, multicenter cohort, with contemporary delivery data, which increases the generalizability of the findings. The analysis included aspects often overlooked in other similar studies, such as the dose of ACS exposure and the gestational age at the time of exposure.

The observational study design, however, can suggest only associations rather than causal relationships. Observational studies also are apt to be affected by residual confounding. Such limitations can only be overcome by a randomized controlled trial, but such a trial of ACS at periviable gestational ages seems unfeasible due to limited ethical justification.

Another limitation is the reporting on outcomes as a collective group (22–23 weeks' gestation). It is important to consider each gestational age week separately due to differences in physiology and potential biological limitations. It cannot be assumed that 22 weeks behaves like 23 weeks, just as 21 weeks is not equivalent to 22 weeks.

The study results suggest that the protective effect of ACS was dose dependent. However, the interpretation that only a complete ACS exposure was beneficial should be viewed cautiously because the study had no power to assess the impact of a partial exposure.

A further limitation is the lack of consideration in analysis for maternal comorbidities and fetal growth restriction. In the

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Illustration: Kimberly Martens for OBG Management

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In 2001, the Institute of Medicine of the National Academies introduced the concept of shared decision-making as a key component of quality care. In very few other clinical situations is shared decision-making as critical as in the context of planning intervention when delivery is anticipated at 22 weeks' gestation. The truth remains that even with the coordinated provision of ACS and active postnatal care, survival at this gestational age is still a toss-up, and survivors face a high probability of neurodevelopmental impairment and other long-term adverse health outcomes. In this setting, decision-making is complex, with the need to balance patient autonomy and nonmaleficence. On the other hand, the concept of patient autonomy is blurred because the patient (fetus) is incompetent and the negotiation is conducted between physicians and parents. However, no intervention should be undertaken unless the parents so desire. Since parental wishes are frequently emotional, overwhelmingly driving intervention, thorough and timely interdisciplinary counseling is needed. Evidence indicates that both obstetricians and neonatologists may, at times, underestimate the chance of a favorable health outcome for infants born extremely preterm.[8,9] Early involvement of the neonatal and obstetric team is pivotal to put forward a coherent, nonconfusing, nonpaternalistic, balanced message. When outcomes information is shared during prenatal counseling, it should be based on local, not only national, data. Following appropriate consultation with the parents, the physicians will adjust the expectations to the local standards, outcomes data, and availability regarding periviable neonatal support.

Recent data suggest that the rate of cesarean delivery (CD) in the periviable period is increasing.[10] There is no clear evidence in favor of CD to improve neonatal outcomes, whereas there is concern that periviable CD is associated with significantly increased maternal risks. Regardless of uterine incision type, periviable CD results in an increased risk of uterine rupture in a subsequent pregnancy.[11] Consistent with the principle of nonmaleficence, a discussion of these risks should be included in shared decision-making.

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Carlo study, the beneficial effect of corticosteroids in 23-week gestational age deliveries was not demonstrable in pregnancies affected by fetal growth restriction or maternal hypertension.

Other studies considered

Given all its limitations, can we assume that the study by Chawla and colleagues has reliably refuted the Carlo study's suggestion of lack of ACS efficacy in infants born at 22 weeks' gestation? Taken by itself, probably not. In the context of other recent investigations, yes.

A retrospective registry study that used data from the Vermont Oxford Network for the period 2012–2016 on 1,058 infants born at 22 weeks' gestation found that infants who were exposed to ACS and received postnatal life support were more likely to survive to hospital discharge without major morbidity compared with infants who received postnatal life support alone.[4] Overall survival was 38.5% versus 17.7% (adjusted risk ratio [aRR], 2.11; 95% CI, 1.68–2.65), and survival without major morbidity was 4.4% versus 1.0% (aRR, 4.35; 95% CI, 1.84–10.28).

An even larger cohort study that used data from the National Center for Health Statistics concluded that survival at age 1 year for infants born at 22 weeks (n = 2,635) during 2009–2014 was improved in those exposed to ACS followed by postnatal life support compared with postnatal life support alone (45.2% vs 27.8%; aRR, 1.6; 95% CI, 1.2–2.1).[5]

A meta-analysis of observational studies that reported on infants born between 22 0/7 and 22 6/7 weeks' gestation (n = 2,226) who received proactive neonatal treatment found that administration of ACS doubled the rate of survival when compared with no ACS administration (39% vs 19.5%; $P<.01$).[6]

In September 2021, the recommendations from the American College of Obstetricians and Gynecologists changed, stating that ACS can be considered at 22 weeks' gestation when active postnatal management is desired.[7] This recommendation is largely congruent with those from several other national and international medical organizations, including the World Association of Perinatal Medicine, the Royal College

of Obstetricians and Gynaecologists, and the German, Austrian and Swiss societies of gynecology and obstetrics. The implication is that the limit of viability may have shifted again, from 23 to 22 weeks' gestation, and considering the importance of adequate timing in ACS administration (within 1 week from delivery), Chawla and colleagues posited that ACS administration can be considered as early as 21 weeks' gestation when birth is anticipated at 22 weeks and active postnatal management is planned (notably, this should be the correct interpretation of the article title, not that ACS may be beneficial in 21-weeks' gestational age births). ●

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