OBSTETRICS

Long-term neurologic outcomes after common fetal interventions

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OBJECTIVE: Fetal interventions have clearly decreased mortality, but the neurological outcomes of survivors are of critical concern. Here we consolidated available data on long-term neurological outcomes after common fetal interventions to guide counseling, management, and future research.

STUDY DESIGN: Published studies assessing long-term neurological outcomes after common fetal interventions from 1990 through 2014 were collected. We included all studies with a cohort of more than 5 patients and with follow-up of 1 year or longer. We divided procedures into those performed for singletons and for multiples. Singleton procedures included amnioinfusion for preterm premature rupture of membranes, intrauterine transfusion for red cell alloimmunization—associated anemia, intrauterine transfusion for parvovirus-associated anemia, vesicoamniotic shunts, thoracoamniotic shunts, ventriculoamniotic shunts, fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia, and open fetal cases by myelomeningocele and others. Multiple procedures included those done for monochorionic twins including serial amnioreduction, selective fetoscopic laser photocoagulation, and selective termination.

RESULTS: Of 1341 studies identified, 28 met the inclusion criteria. We combined available literature for all procedures. Studies varied in their length of follow-up and method of assessing neurological status. Neurological outcome after intervention varied by procedure but was normal in 40-93%, mildly impaired in 3-33%, and severely impaired in 1-40%. Follow-up to school age was rare with the exception of procedures for monochorionic twins.

CONCLUSION: Fetal treatments have been successful in achieving survival in previously hopeless cases, but success should also be determined by the outcomes of survivors. Except for monochorionic twins, there is a dearth of reported long-term outcomes. Standardized reporting of long-term neurological sequelae is imperative so that meaningful analysis and study comparisons can be made.

Key words: congenital anomalies, fetal therapy, long-term morbidity

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Initially, fetal therapy was reserved for conditions deemed otherwise lethal or severely disabling without intervention. The early outcomes for interventions such as those for congenital diaphragmatic hernia, obstructive uropathy, and hydrocephaly varied from very successful to near catastrophic.[1,2] Cephaloamniotic shunts, for example, often allowed infants who would otherwise have died to survive but at the cost of significant impairment. Not surprisingly, fetuses with porencephalic cysts or trisomy 13 or 18 would not do well, even with shunting.

Advancements in both fetal medicine and neonatal care now allow survival in many previously hopeless cases. After successes in life-or-death situations, evolving to quality of life situations became reasonable. Thus, we hypothesized that vesicoamniotic shunts might improve renal function, even when unnecessary to prevent pulmonary hypoplasia, and that meningomyelocele repairs might improve the functional status of children with spina bifida. This change in mentality eventually led to the Management of Myelomeningocele trial, which represents the first randomized clinical trial promoting a fetal surgical intervention focused principally on morbidity.[3]

Neurological morbidity is undoubtedly one of the most significant outcome sequelae that can affect management plans, and it is clearly associated with multiple perinatal factors. When attempting to ascertain the impact of any treatment, it is crucial to know the natural history of the condition against which to compare. Additionally, there is an increased risk of poor neurological outcome not only with particular anomalies but also with decreasing gestational age at delivery, chorioamnionitis, multiple gestations, and intrauterine growth restriction.[4,5]

Recent studies have met with varying success in attempting to identify new risk factors for poor outcome.[6,7] Because

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associated risks are common cofactors in the arena of fetal intervention, we must now address whether interventions promote survival at the expense of long-term, serious morbidity. The aim of this study therefore was to consolidate the available data on long-term neurological outcomes after common fetal interventions in an effort to guide counseling and future research.

Materials and Methods

We compiled available literature including all studies reporting long-term (longer than 1 year) neurological outcome after common fetal interventions from 1990 through 2014. Institutional review board approval was not obtained because this study was a review of previously published data.

Procedures were divided by singletons or multiples. Singleton procedures included amnioinfusion for preterm premature rupture of membranes, intrauterine transfusion for red cell alloimmunization—associated anemia, intrauterine transfusion for parvovirus-associated anemia, vesicoamniotic shunts, thoracoamniotic shunts, ventriculoamniotic shunts, fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia, and open fetal cases for myelomeningocele (MMC) and others, such as fetal lung lesions with hydrops. Procedures done on multiples included those done for complicated monochorionic pregnancies: serial amnioreduction, selective fetoscopic laser photocoagulation of anastamotic vessels, and selective termination.

Both PubMed and Cochrane databases were searched for articles published in English from January 1990 through April 2014 using the search terms listed in Table 1. Additionally, citations were reviewed from all included papers, and relevant studies were also included. Because available data are limited, we included all published studies if they had neurological outcome information for a cohort of more than 5 patients and if the follow-up period was 1 year or longer. In studies that combined patients from multiple cohorts, we attempted to include all patients who were not included from other reports.[8-10] We excluded studies with fewer than 5 patients, those in which the neurological outcome was unclear, and those in which it was impossible to discern which of a cohort had been previously included.

Study results were combined to give an overall impression of outcome over multiple experiences and centers.

Results

Of 1341 studies identified by the search engines, 54 potentially relevant publications were reviewed, and 28 met our inclusion criteria (Table 1). The length of follow-up in each category and methods

TABLE 1
Search terms and results for studies reporting long-term neurological outcome after common fetal interventions

Variable	Key words used in search	Studies identified, n	Potentially relevant studies, n	Studies used, n
Singleton procedures				
Amnioinfusion for PPROM	Amnioinfusion and outcome	153	7	3
Intrauterine transfusion for alloimmunization	Intrauterine transfusion and outcome	454	6	4
Intrauterine transfusion for parvovirus	Intrauterine transfusion and outcome	454	6	2
Vesicoamniotic shunts	Vesicoamniotic shunt or vesicoamniotic shunting and outcome	32	2	2
Thoracoamniotic shunts	Thoracoamniotic shunt or thoracoamniotic shunting and outcome	30	3	1
Ventriculoamniotic shunts	Ventriculoamniotic shunt or ventriculoamniotic shunting and outcome	3	2	1
Fetal endoscopic tracheal occlusion	Tracheal occlusion and diaphragmatic hernia and outcome	83	1	1
Open fetal surgery (MMC)	Fetal surgery and myelomeningocele and outcome	119	4	2
Open fetal surgery (others)	Fetal surgery and open and outcome	257	2	1
Multiples (MC/DA)				
Amniodrainage	Amnioreduction and long term and outcome	21	9	3
Selective fetoscopic laser photocoagulation	Laser and TTTS and outcome	150	8	7
Selective termination	Selective reduction and monochorionic and twins and outcome	39	4	1

DA, diamniotic; *MC*, monochorionic; *MMC*, myelomeningocele; *PPROM*, preterm premature rupture of membranes; *TTTS*, twin-twin transfusion syndrome.

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