EDITORIAL

Long-term Outcomes of Children After Fetal Surgery for Spina Bifida—Toward Sustainability

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The study by Houtrow et al[1] is an eagerly awaited new chapter of an intriguing story that began almost 70 years ago.

In 1956, Cameron published a *Lancet* article to describe allegedly secondary tissue damage of the openly exposed spinal cord tissue of fetuses and newborn babies with spina bifida (SB) aperta (ie, myelomeningocele or myeloschisis).[2] The lesion was characterized by neural tissue damage that was apparently acquired in utero or during birth. This observation did not yet elicit in-depth interpretations regarding the prenatal natural history of SB and possible therapeutic implications.

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After a decade-long phase of hibernation, analogous descriptions by Jordan et al[3] and Meuli et al[4] of spinal cord damage acquired in utero generated the 2-hit hypothesis for the pathogenesis of SB, which was revolutionary at the time. The first hit is a segmental, usually lumbosacral, failure of neurulation, and the second hit is the progressive destruction of the unprotected cord tissue within the lesion. With the availability of improved prenatal diagnostic tools and with prenatal surgery being a reality for conditions other than SB,[5] clinicians began investigating whether the neurologic sequelae often present in patients with SB were the result of the second hit, and if so, whether prenatal protective coverage of the SB lesion would reduce postnatal devastation.

An avant-garde series of fetal sheep experiments, published in 1995 by Meuli et al[6] in *Nature Medicine*, produced compelling evidence that the extremely frail spinal cord is progressively destroyed during gestation when exposed to the amniotic cavity, and that timely in utero lesion repair spares neurologic function at birth. This article paved the way for the first open human fetal SB repair by Adzick.

That *Lancet* report[7] triggered a number of larger series that altogether produced evidence confirming the potential benefit of SB surgery before birth.[8,9]

The most powerful product of clinical research was the National Institutes of Health–sponsored Management of Myelomeningocele Study (MOMS), orchestrated and published by Adzick et al[10] in the *New England Journal of Medicine* in 2011. This prospective, randomized, controlled study (prematurely stopped for better results of the prenatal surgery arm) showed that for children aged 30 months, outcomes were significantly superior in the fetal surgery group than in the postnatal surgery group (although, as to be expected, prenatal intervention was not free of risks). In the *New England Journal of Medicine* editorial,[11] Simpson and Greene hinted at critical issues including whether beneficial results could also be attained outside the rigors of a MOMS-like study (the answer is given as yes by Möhrlen et al[12]) and, even more importantly, whether they would be consistent over time—here, definitive answers are pending (U. Moehrlen, MD, written communication, 2020).

The work published here by Houtrow and colleagues[1] is one of the National Institutes of Health–sponsored follow-up studies after the original MOMS trial (MOMS2). It presents worldwide, first-time evidence that motor spinal levels and, consequently, functional mobility are better in school-aged patients with a history of prenatal rather than postnatal SB surgery. Of note, these clinically essential results, durable over a period of 5 to 10 years and thereby persisting into school age, were identified in the very same patients who were, as fetuses, included in the test and control arms of the MOMS trial. This carefully crafted and scientifically sound long-term "offspring study" is the most valid research pathway to seek out the best of clinical truth, in that the highest level of evidence possible—ie, that derived from an originally prospective, randomized, and controlled study—remains, basically, unchanged.

Because this consideration theoretically holds true for all MOMS2 follow-up studies, the original cohorts of the study and the control patients are a scientific gold mine. An already significant number of such studies published demonstrates that fetal surgery rather than postnatal surgery is associated with more favorable outcomes.[13-17]

Of course, a rigorous lifelong follow-up of the original MOMS cohorts is obligatory. All pertinent somatic, cognitive, and psychosocial functional capabilities deserve longitudinal observation and, eventually, medical care.

Hydrocephalus formation is a prominent issue. Current data indicate that fetal surgery cuts the shunt rate in half, and patients who reach the age of 1 year are very unlikely to develop shunt-dependent hydrocephalus thereafter.[17] The question remains: is this true over an individual's life span?

Bladder and bowel control are key indicators of normal voiding functions and good quality of life. What is the fate of continence over time? Can it be improved when patients are able to understand and to cooperate in training programs? What is the effect of prostate growth during puberty? Does sphincter control fade in the long run when compared with healthy, especially female, individuals? What is the impact of eventual new therapeutic strategies (artificial sphincters, electrostimulation, stem cell injections, specific drugs, etc) to enhance continence?

Ambulation, if present, may worsen with time because of, eg, malformation-inherent degeneration of the spinal-peripheral neural-muscular axis. Ambulation may also worsen because of limited capacity, ie, the neural-muscular axis performs well up to a certain body weight, but not beyond

(patients with SB have a propensity to become obese). What is the role of standard comprehensive gait analysis regarding optimization of conservative and operative orthopedic management?

In addition, cognition and psychosocial performance are paramount. How do these abilities develop over time? Do already-documented disparities between normal individuals and patients with or without fetal surgery for SB persist into adulthood? What are the effects of puberty, especially given the fact that patients with SB have a predisposition for pubertas praecox, or abnormally early sexual maturity? To what extent can special educational, coaching, and training programs corroborate nonsomatic functions? What about the effect of SB on school and profession, private life, partnership, sexuality, and having children?

Taken together, there is a sheer endless list of clinical research issues to be addressed sequentially and, ideally, over the life spans of the original MOMS patients. This means that more than 1 generation of physicians, scientists, therapists, and caregivers will have to work on this multifaceted, long-term project.

The authors of the article under consideration here[1] have to be commended on delivering essential new information on long-term outcomes that will affect the prenatal and postnatal management of patients with SB. This work contributes to a unique scientific masterpiece in modern spinabifidology.

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