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# Mini-commentary on BJOG-23-0402.R1 Improving motor function in fetal surgery for open spina bifida.

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Since publication of the Management of Myelomeningocele Study (MOMS) clinical trial in 2011, prenatal surgery for myelomeningocele (MMC) has widely become the standard of care globally (Sacco et al, Prenatal Diagnosis 2018;38:1020-1027) and an increasingly acceptable alternative to conventional postnatal repair in selected patients. Although prenatal surgery improves brain and motor function compared with postnatal repair, nevertheless a high proportion of children have movement difficulties (Howtrow et al, JAMA Pediatrics 2021;175:e205674), and require daily urinary catheterization that reduces their quality of life. Spinal cord tethering is also a problem. Fibrosis and inflammation at the site of the MMC repair are thought to be responsible, so teams are exploring adjuvant neuroprotective and immunomodulatory strategies to improve surgical outcomes.

In this pre-clinical study in pregnant sheep with surgically created fetal MMC, Yoann et al report that application of a cellular patch containing term sheep umbilical cord mesenchymal stem cells (MSC) improves short-term motor and sphincter function, and reduces fibrosis compared with the use of acellular patch. The patch was applied just prior to skin closure, and a variety of clinical neurological assessments, electrophysical examinations, spine imaging and histological examinations were used to assess efficacy.

Conducting research in animal models of MMC has challenges. Firstly they can never completely capture all the features of the spontaneously occurring fetal congenital defect. Research teams commonly use a modified approach to create an MMC defect at mid-gestation (75 days in sheep pregnancy) with removal of the skin, paraspinal muscles, L1–L6

vertebral laminae, and the dorsal dura matter overlying the exposed spinal cord without myelotomy. Although spontaneous spinal cord closure has been reported, reassuringly Yoann et al did not observe this in their control group. Secondly, fetal loss is common due to the requirement for two surgeries; one to create the defect and a second to repair it. The number of animals reaching the primary endpoint at 24 hours (9 out of 14 operated animals) was small. Nevertheless, the authors did reach their prespecified sample size providing confidence that a real improvement in outcomes if present, could be demonstrated. Lastly, long-term follow up is not possible when animals, especially those in a control group, may experience significant harm. Follow up of patients in the eventual clinical studies through to child and adulthood is therefore vital to understand the true benefit of an intervention.

Adding fetal stem cells to fetal MMC repair improves treatment efficacy in a variety of preclinical models (Kunpalin et al Prenatal Diagnosis 2021;41:283-300). In particular a patch containing early gestation human placental MSCs seeded on a porcine matrix improved hindlimb function short-term and increased neuron density in fetal sheep with MMC (Kabagambe et al Journal of Pediatric Surgery 2017;53:178-182). This is now subject to a safety and efficacy clinical trial: “Cellular Therapy for In Utero Repair of Myelomeningocele: CuRE trial” (ClinicalTrials.gov ID NCT04652908) combining surgical fetal MMC repair with placement of a commercially available dural graft seeded with placental MSCs, to compare outcomes with a contemporaneous control group receiving no placental MSC graft.