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Opinion

Call to action: long-term neurodevelopment in monochorionic twins

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Introduction

There is much to celebrate in the increasingly successful management of complicated monochorionic (MC) multiple pregnancy over the last three decades. Advances in our understanding of the unique placental architecture and physiology of MC pregnancies[1] has been translated into improved clinical management and ever-increasing survival, even in complicated MC pregnancies[2]. Fetoscopic laser treatment has become standard in the management of twin–twin transfusion syndrome (TTTS)[3], the distinct pathological condition of twin anemia–polycythemia sequence (TAPS) has been described and management reported[4] and the classification of selective fetal growth restriction (sFGR)[5] has facilitated improved counseling and directed intervention towards the highest risk cases.

Even so, there persists a glaring research gap that is of increasing concern to clinicians and families. Beyond survival, what matters most to parents is the health and quality of life that their child or children will have[6], and yet there is significant under-reporting of long-term outcomes in studies of multiple pregnancies[7]. In clinical decision-making during the care of a complicated MC pregnancy, the interests of multiple fetuses and their mother are not necessarily aligned, and parents want to know how to give their children the best chance at not only life, but life in all its fullness. As multiple pregnancy continues to increase in frequency[8], its impact on neonatal and infant health outcomes and resource use will increase in tandem. As yet, we are poorly equipped to counsel families on the best way to optimize long-term life and health for families after a multiple pregnancy, especially a MC pregnancy.

What do we know already and where are there gaps in the literature?

We know that children born after a multiple pregnancy exhibit differences in neurodevelopment compared to their singleton counterparts and that these differences can be related to chorionicity, complications during pregnancy and fetal number[5]. Large cohort studies have demonstrated that MC multiples are at greater risk of cerebral palsy and neurodevelopmental impairment (NDI) (Figure S1) than are dichorionic multiples[9,10], although both are at greater risk than singletons[11]. Higher order multiples are at increased risk compared to age- and gestational-age-at-delivery-matched twins, although the data are even more limited[12,13].

Neurodevelopmental impairment in uncomplicated monochorionic pregnancy

The prevailing assumption is that the majority of cases of NDI observed in multiple pregnancies are due to increased iatrogenic and spontaneous preterm birth, with the additional contribution of monochorionicity-specific complications in MC pregnancies. Around 70% of MC pregnancies do not exhibit TTTS, sFGR, TAPS, twin reversed arterial perfusion sequence or monoamnionicity (Figure S2)[14]. These babies are usually given a good prognosis. There is, however, evidence that even uncomplicated MC pregnancy is associated with an increase in long-term NDI. Using a stricter definition of NDI, NDI was identified in 7% of children after uncomplicated MC pregnancy[14], half of whom were born > 32 weeks' gestation, including one child with cerebral palsy. While long-term pediatric follow-up of extremely preterm infants is common, MC babies delivered at or close to term are unlikely to receive specialist follow-up in many healthcare systems, and the incidence of milder impairments may be under-reported.

Long-term outcome after complicated monochorionic pregnancy

The most significant predictor of NDI in MC pregnancy remains the occurrence of monochorionicity-specific complications including TTTS, sFGR, TAPS and monoamniotic pregnancy. Complications of monochorionicity increase the risk of NDI to variable degrees, with the highest risk being associated with acute perimortem TTTS (Figure 1)[8]. Of note, more data are needed to establish whether this risk varies with gestational age, which would determine the optimal timing of delivery in complicated MC twin pregnancies.

In the era of fetoscopic selective laser coagulation (FSLC), long-term outcomes, after TTTS in particular,

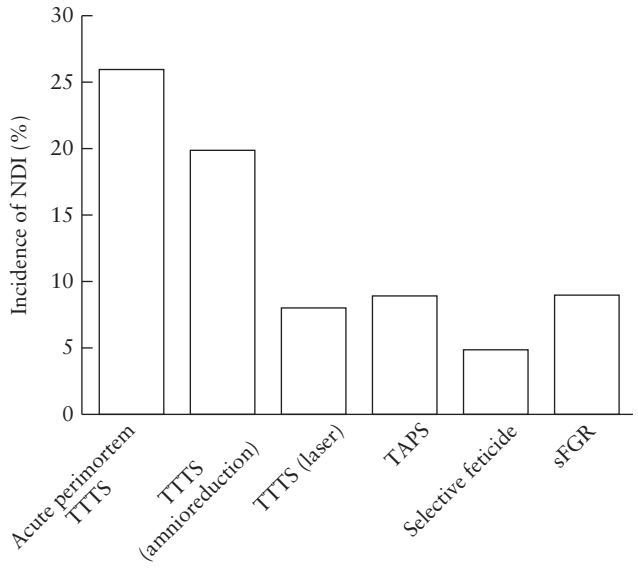

Figure 1 Incidence of neurodevelopmental impairment (NDI) in twins after complicated monochorionic pregnancy[8]. sFGR, selective fetal growth restriction; TAPS, twin anemia–polycythemia sequence; TTTS, twin–twin transfusion syndrome.

are continuing to improve[2]. Increasing survival has been linked to improvements in surgical technique and instruments, advances in the learning curve as more fetal surgeons acquire significant experience of fetoscopic interventions, enhanced detection and referral of high-risk pregnancies, and improvements in neonatal unit care[15]. After laser treatment for TTTS, the risk of severe NDI is decreased to 3–6% of surviving children, while mild NDI occurred in up to 23%[2]. Of children with NDI after TTTS treated by FSLC, 35% are delivered at > 32 weeks without evidence of cerebral injury on perinatal imaging[2], highlighting the key importance of longer term follow-up, even for lower risk babies. The most significant contributors to adverse outcome in pregnancies with TTTS remain intrauterine demise (IUD) and spontaneous preterm birth after FSLC. Despite the several large clinical trials of FSLC in TTTS and many large observational cohorts reported, long-term outcomes are rarely reported in the literature[16]; yet, when key stakeholders worked to agree on the core outcomes of the highest priority for investigators working on improving treatment of TTTS, neurological development at 18–24 months was prioritized[17]. Importantly, long-term follow-up should not stop at 2 years of age, but should ideally continue until at least school age, as some impairments (mainly mental and behavioral) cannot always be detected at a younger age and often become more apparent only later in life.

In TAPS, the long-term outcomes include NDI in 30% of survivors, with the donor affected more frequently than the recipient[18]. The treatment of TAPS varies widely between fetal therapy centers[19], with the role of FSLC not yet demonstrated in clinical trials. The development and validation of intervention protocols for TAPS is likely to lead to improvement in perinatal and long-term outcomes, but this cannot be demonstrated if they are not measured. Importantly, one in eight TAPS donors has bilateral deafness. Early detection and prompt intervention with hearing amplification devices is of paramount importance to stimulate language development and reduce the risk of speech delay[18].

sFGR appears to occur at a similar rate, of 11–12%, in both MC and DC pregnancies[20], although neurological complications are more common in affected MC than DC pregnancies[21]. The pathology of sFGR brings together the effects of unequal placental sharing, impaired placental function and the paradoxical effects of placental anastomoses on cerebral perfusion and development. The incidence of severe NDI in MC twins with birth-weight discordance is reported to be as high as 42%[22], compared with 13% in DC twins with birth-weight discordance and 8% in concordant MC twins. In comparison to TTTS or TAPS, however, the literature on sFGR is extremely limited. The most recent systematic review of NDI in sFGR identified only five studies, with such heterogeneous outcomes that meta-analysis was precluded. When managed expectantly, neurologically intact survival of both twins at 6 months was reported in 96% of cases with Type-I sFGR but in only 33% of Type-II cases[23]. In Type-III sFGR, 62% of cases managed expectantly had intact neurology[24]. NDI appears to be more common in the smaller twin, presumably as the smaller twin is more likely to have experienced placental insufficiency and undernutrition[25]. However, the possible confounding effect of prematurity and its associated complications should be taken into account. Fetal therapy, either by selective reduction or FSLC, may be offered for sFGR, especially in early-onset cases, but the relative effect on NDI and long-term outcome is under-reported. Only six out of 39 studies evaluating treatment for sFGR reported any long-term infant outcomes[26]. Although fetoscopic intervention in sFGR is more technically challenging, it is of particular interest because, even though it is associated with a high risk of IUD of the smaller twin, it may protect the larger twin from the consequences of cotwin demise without requiring cord occlusion and still afford the smaller twin a chance of survival[24]. Consistent reporting of neurological morbidity is clearly essential to determining the clinical utility of interventions for sFGR.

The perinatal event associated most strongly with NDI in MC twins is IUD of one twin, which is followed by death of the cotwin in 15% of cases and severe NDI in 26%[27]. A key benefit of fetal intervention for sFGR, TAPS and TTTS is separation of the fetal circulations prior to IUD of a twin, thereby preventing subsequent cerebral injury of the cotwin. Even in uncomplicated MC diamniotic (DA) pregnancy, an excess risk of IUD compared with that in DC twins persists throughout the third trimester[28], which is often associated with acute perimortem TTTS[29]. The prediction and prevention of these events is critical not only to improving survival but also to improving neurodevelopmental outcome, and, as yet, no clear predictors have been identified.

Conversely, selective reduction to singleton pregnancy by cord occlusion or radiofrequency ablation, compared to expectant or fetoscopic management, is associated with significantly improved neurodevelopmental outcome for the surviving twin in MC twins with sFGR or discordant anomalies. The incidence of NDI in the surviving twin may be as low as 2%[30], although the diagnosis leading to the decision to undertake selective reduction may affect the likelihood of NDI[31].

Challenges in evaluating long-term outcomes in multiples

A significant challenge in evaluating long-term behavioral and developmental outcomes in twins is the fact that twins grow and develop in a social and family environment that is substantially different from that experienced by singletons. Twins exhibit speech and language delay relative to singletons, but also frequently develop 'cryptoglossia' or a 'secret language' which the twins use with each other[32]. Bilingual children exhibit language delay without underlying pathology or alteration in quality of life[33], and the observed communication delay in multiples could be similar but requires further study. Alternatively, parenting multiples is a stressful life event that may alter the home environment, require more frequent assistance from extended family, reduce direct parent-to-child interactions or exacerbate financial strain on the household. Any of these factors could contribute to the observed differences in behavioral and developmental outcomes in multiples and could be taken into consideration in any long-term assessments.

The timing of assessment may impact the prevalence and nature of outcomes detected. Several studies have noted a particular lag in motor development in multiples on long-term follow-up to 2 years[14], but also that multiples seem to 'catch up' to their singleton peers by 2 years of age[11]. The relative lack of studies following children up to school age makes it difficult to assess whether this pattern could ultimately balance the inequalities between multiples and singletons or whether developmental and behavioral outcomes would still differ throughout life.

The majority of the above-cited studies reporting on NDI followed children for between 6 and 24 months, and yet we know that outcomes at 2 years of age only partially predict 6-year outcomes. As children grow, functional outcomes across several domains increase in relevance, including communication and independence, which are of great importance to parents and the children themselves[6]. Those parameters most important to a child's quality of life and their potential for successful independent living may be detectable only at school age, but the later the assessment the more the child's development is affected by social and environmental factors in addition to perinatal events (Figure 2).

The greatest practical challenge in the assessment of long-term outcome after complicated MC pregnancy is organizing ongoing specialist review for children not living within easy reach of the original treatment facility. Most fetal therapy centers rightly offer treatment to patients from a wide geographical region, with international travel for fetoscopic intervention being a relatively common phenomenon. There is significant variation between fetal therapy centers in the nature and duration of postnatal follow-up for MC pregnancies, which contributes to the lack of available data. In some cases, no routine follow-up occurs centrally, and, in most cases, only complicated or premature babies are followed up routinely, usually to 2 years of age.

How should we target interventions to improve long-term neurodevelopment in multiples?

The long-term neurodevelopment of a child is influenced by many factors, some of which are amenable to perinatal intervention, while others (gender, genetic make-up and socioeconomic status of parents) are not directly influenced by clinicians (Figure 3). In seeking to improve long-term neurodevelopment in multiples, we should start with reducing fetal morbidity and preterm birth and improving neonatal and infant care.

We can act to reduce fetal morbidity, starting from the moment of conception in pregnancies conceived by assisted reproduction. Reducing the incidence of NDI associated with multiple pregnancy should include considered use of assisted reproductive technologies and clear and honest counseling of prospective parents[34]. Fetal morbidity can be further reduced by improving antenatal detection of complications, including improving the understanding of how MC placentation itself affects fetal cerebral development and the risk of unexpected IUD or cerebral injury in an apparently uncomplicated MCDA pregnancy. It is possible that the number and nature of placental anastomoses and their associated

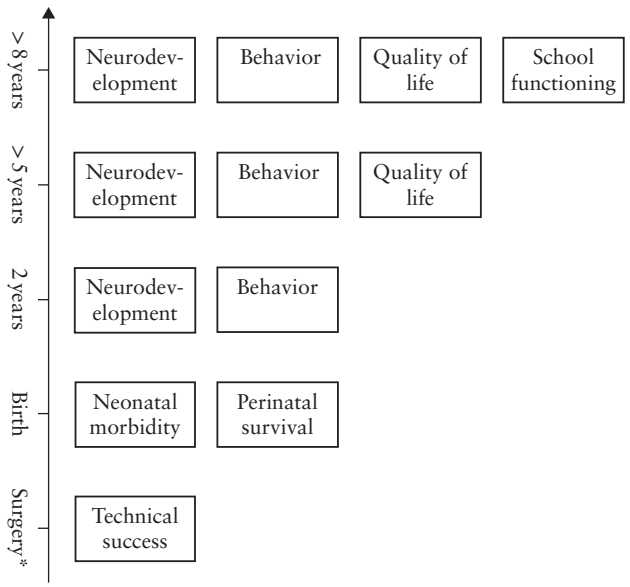

Figure 2 Timeline of outcome in monochorionic twins. *When performed.

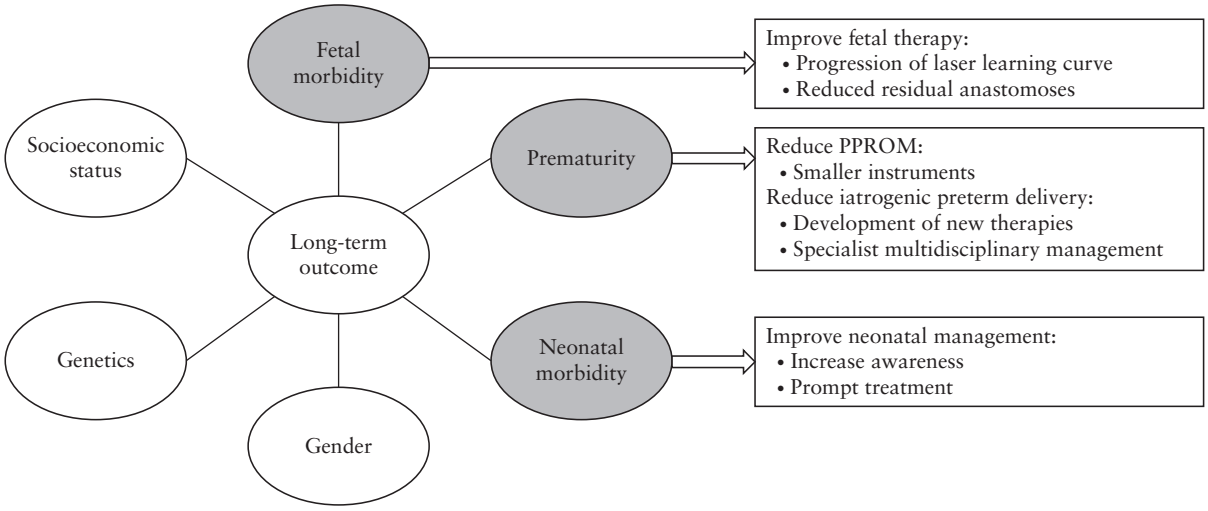

Figure 3 Long-term neurodevelopmental outcome in monochorionic twins: risk factors and possible interventions. PPROM, preterm prelabor rupture of membranes.

acute and chronic hemodynamic changes may contribute to adverse neurological outcomes in complicated MC twin pregnancies. However, the association between these hemodynamic disturbances in the donor and recipient twins and an increased risk for adverse neurological outcome is yet to be fully understood.

We have seen continuous improvement in surgical techniques for FSLC in TTTS that may be transferable to invasive therapy for TAPS and sFGR. The relative benefits of FSLC, selective reduction and delivery for TAPS and sFGR should be clarified in high-quality prospective studies reporting the core outcomes identified for these conditions[17,35], including long-term follow-up.

Reducing the rate of preterm birth should be the cornerstone of any strategy to reduce NDI in multiple pregnancy. The rate of spontaneous preterm birth could be reduced with improved surgical techniques to lower the risk of procedure-related complications and preterm rupture of membranes. A key contributor to NDI after FSLC for TTTS is spontaneous preterm birth, and, as yet, our ability to predict and prevent this is limited. Interventions, including cerclage in women with a short cervix after FSLC or progesterone supplementation, may offer benefit, but have rarely been reported in complicated MC pregnancies. It is important to emphasize that evidence derived from uncomplicated MC twin pregnancies cannot be extrapolated to complicated MC twin pregnancies, particularly after fetal interventions, because the nature of the prenatal insults and natural history of each MC twin pregnancy complication is different from the natural history of uncomplicated MC twin pregnancy[36,37]. The need for iatrogenic preterm delivery could be reduced by the development of new therapies for sFGR and TAPS to prevent fetal deterioration requiring delivery. Furthermore, specialist multidisciplinary management of MC pregnancies is recommended[38] and is likely to reduce the rate of unnecessary iatrogenic preterm birth. Disappointingly, relatively few obstetric units in the UK provide this service at present[39], and we call on policymakers to increase the availability of specialist multiple-pregnancy services to benefit the long-term health and wellbeing of multiples and their families.

After delivery, the continuing input of clinicians with expertise in multiple pregnancy can facilitate both prevention and earlier intervention for NDI. Given the incidence of NDI in MC twins that are seemingly well at birth, cranial imaging in the neonatal period should be considered in all MC infants. Treatment from occupational therapists, speech and language therapists and child psychologists can significantly improve longer term development for these children, and even simple parent-delivered behavioral interventions can be of benefit. Since even uncomplicated MC pregnancies are at increased risk of mild-to-moderate NDI, there is a strong argument for ensuring longer term follow-up for all MC twins. Long-term follow-up clinics for these infants will facilitate crucial early interventions and also provide key long-term data for refining and improving care of MC pregnancies in the future. Ultimately, we cannot improve long-term neurodevelopment in multiples unless we measure it.

Listening to patients and families as an essential research paradigm

A sweeping call to expand long-term follow-up to all MC twins is certainly daunting in scope, with major resource and service-configuration implications. Nonetheless, multiple stakeholder consensus projects have shown us that long-term outcomes are both of great significance to parents[17,35,40] and under-reported in our existing literature[16,26]. We acknowledge that that the key to maximizing the real clinical impact of academic work is systematic involvement of patients and families throughout research development and reporting. When an outcome is of great importance to the end users of research, it falls to us as clinicians and researchers not to dismiss it as impractical but rather to consider how we

can alter our practice to answer the questions that matter to parents and families.

These are times of great change and, in these moments, the opportunity to develop new and valuable patterns of care should be seized[41]. Telemedicine in pediatric clinics has already been trialed[42] and not only facilitates increased access to specialist review for geographically dispersed patients[43] but also offers the additional insights of reviewing children in their own homes and with their families. Why not adapt similar methods for the long-term follow-up of MC pregnancies by central fetal therapy centers? What other innovative tools could be developed to create family-centered care to the lifelong benefit of these children?

Beyond direct clinical care, we should also consider our role as advocates for our patients. We recognize the importance of social and economic support for the parents of multiples in promoting optimal development and equal life chances for children born after multiple pregnancy, and we call on clinicians and academics worldwide to highlight the special needs of these families.

Long-term neurodevelopment in MC twins is under-reported, poorly understood and a growing public health concern. It is time to combine clinical excellence and academic rigor to improve outcomes that matter to families.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Definition of cerebral palsy and neurological impairment.

Figure S2 Complications of monochorionic twin pregnancies.