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A 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 pregnancies over the last three decades. Advances in understanding 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-to-twin transfusion syndrome (TTTS)[3], the distinct pathological condition of the twin-anaemia-polycythaemia sequence (TAPS) has been described and management reported[4] and the classification of selective fetal growth restriction (sFGR)[5] has facilitated improved counselling and directed intervention to the highest risk of these pregnancies.

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 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 making clinical decisions 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 not only how to give their children the best chance at life, but life in all its fullness. As multiple pregnancies continue to increase in frequency[8] the impact of multiple pregnancy 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 optimise long term life and health for families after a multiple pregnancy, especially MC pregnancies.

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

We do know that children born after a multiple pregnancy exhibit differences in neurodevelopment 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 1) than dichorionic multiples,[9,10] although all are at greater risk than singletons.[11] Higher order multiples are at increased risk compared to age and gestation matched twins, although the data here is even more limited.[12,13]

Neurodevelopmental impairment in uncomplicated MC pregnancies

The prevailing assumption is that the majority of the NDI observed in multiple pregnancy is due to increased iatrogenic and spontaneous preterm birth, with the additional contribution of the special complications of monochorionicity. Around 60% of MC pregnancies will deliver close to term without TTTS, sFGR, TAPS, congenital anomalies or stillbirth (Figure 2).[14] The prognosis for these babies is usually given as good. There is, however, evidence that even uncomplicated MC pregnancies are associated with an increase in long term NDI. Using a stricter definition of NDI, NDI has been identified in 7% of children after uncomplicated MC pregnancies.[14] In this group, half of all the children with NDI were from the group of uncomplicated MC pregnancies 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 outcomes after complicated MC pregnancies

The most significant predictor of NDI in MC pregnancies remains the occurrence of MC specific complications including TTTS, sFGR, TAPS and monoamniotic (MCMA) pregnancy. The complications of monochorionicity increase the risk of NDI to variable degrees, with the highest risk being associated with acute perimortem TTTS (Figure 3). Of note, more data is 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 are continuing to improve.[2] Increasing survival has been linked to improvements in surgical technique and instruments, the learning curve as more fetal surgeons acquire significant experience of fetoscopic interventions, improved detection and referral of high risk pregnancies and improvements in neonatal unit (NNU) care.[15] After laser treatment, the risk of severe NDI has nowadays decreased to 3-6% of surviving children,[2] with mild NDI in up to 23%.[2] Of children with NDI after TTTS treated by FSLC, 35% are delivered >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 remain intra-uterine demise 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 the core outcomes of highest priority for investigators working on improving treatment of TTTS, neurological development at 18-24 months was prioritised.[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 impairment (mainly mental and behavioural impairments) cannot always be detected at younger age and often only become more apparent later on 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 centres,[19] with the role of FSLC not yet demonstrated in clinical trials. The development and validation of intervention protocols in TAPS is likely to lead to improvement in perinatal and long term outcomes, but this cannot be demonstrated if they are not measured. Importantly, 1 in 8 TAPS donors have 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 in both MC and DC pregnancies at 11-12%[20], but 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 to affect cerebral perfusion and development. The incidence of severe NDI in MC twins with birthweight discordance is reported to be as high as 42%,[22] compared to DC twins with birthweight discordance (13%) or concordant MC twins (8%). In comparison to TTTS or TAPS, however, the literature is extremely limited. The most recent systematic review of NDI in sFGR found only five studies using such heterogenous outcomes that meta-analysis was prevented. With expectant management, neurologically intact survival of both twins at 6 months is reported in 96% of Type 1 sFGR, but only 33% of Type II cases.[23] In type III sFGR, 62% had intact neurology with expectant management.[24] NDI appears to be more common in the smaller twin, presumably the twin 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 in sFGR, especially in early onset cases, but the relative effect on NDI and long term outcomes is under reported. Only 6 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 intrauterine demise (IUD) of the smaller twin, it may protect the larger twin

from the consequences of co-twin 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 most strongly associated with NDI in MC twins is the IUD of one twin, followed by death of the co-twin in 15% of cases, and severe NDI in 26%.[27] A key benefit of fetal intervention in sFGR, TAPS and TTTS is separation of the fetal circulations prior to IUD of a twin and thereby preventing the subsequent cerebral injury. Even in uncomplicated MCDA pregnancy, an excess risk of IUD compared to 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 just to improving survival but also to improving neurodevelopmental outcome and as yet no clear predictors have been identified.

Conversely, selective reduction to a singleton pregnancy by cord occlusion or radiofrequency ablation is associated with a significantly improved neurodevelopmental outcome for the surviving twin compared to expectant or fetoscopic management of sFGR or discordant anomalies in MC twins. 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 behavioural and developmental outcomes in twins is the fact that twins grow and develop in a social and family environment substantially different to that experienced by singletons. Twins exhibit speech and language delay relative to singletons, but also frequently develop ‘cryptoglossia’ or a ‘secret language’ the twins use with each other.[32] Bilingual children also 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 observed differences in multiples and could be considered in any long term assessment.

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 in long term follow up to two years,[14] but also that multiples seem to ‘catch up’ to their singleton peers by 2 years of life.[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 behavioural outcomes would still differ throughout life.

The majority of the studies reporting NDI cited above followed children up for between 6-24 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 potential for successful independent living may only be detectable at school age, but the more distant the assessment the more the child’s development is affected by social and environmental factors in addition to perinatal events (Figure 4).

The greatest practical challenge to assessment of long term outcomes after complicated MC pregnancies is organising ongoing specialist review for children not living within easy reach of the original treatment facility. Most fetal therapy centres rightly offer treatment to patients from a wide geographical region, with international travel for fetoscopic intervention a relatively common phenomenon. There is significant variation between fetal therapy centres 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 only complicated or premature babies are routinely followed up, usually to 2 years of age, excluding those 'uncomplicated' MC twins.

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 amenable to perinatal intervention and others (gender, genetic make-up, socio-economic status of parents) that are not directly influenced by clinicians (Figure 5). In seeking to improve long term neurodevelopment in multiples we should start with reducing fetal morbidity, preterm birth and improving neonatal and infant care.

We can act to reduce fetal morbidity, starting from the moment of conception in the case of pregnancies conceived after assisted reproduction. Reducing the incidence of multiple pregnancy associated NDI should include considered use of assisted reproductive technologies and clear and honest counselling of prospective parents.[34]

Fetal morbidity can further be reduced by improving antenatal detection of complications, including improving the understanding of how MC placentation in 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 its associated acute and chronic hemodynamic changes may contribute to adverse neurological outcomes in complicated MC twin pregnancies. However, the association of these hemodynamic disturbances in the donor and recipient twin and increased risk for adverse neurological outcomes is yet to be fully understood.

We have seen a continuous improvement in surgical techniques in FSLC for 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 must be clarified in high quality prospective studies reporting the core outcomes identified for these conditions,[17,35] including long term follow up.

Reducing preterm birth must be the cornerstone of any strategy to reduce NDI in multiple pregnancy. Spontaneous preterm birth could be reduced with improved surgical techniques to reduce 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 into 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 pregnancies[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. Lastly, specialist multidisciplinary management of MC pregnancies is recommended[38] and is likely to reduce unnecessary iatrogenic preterm birth. Disappointingly, relatively few obstetric units in the UK provide this service at present,[39] and we call on policy makers to increase the availability of specialist multiple pregnancy services to benefit the long term health and wellbeing of multiples and their families.

Once born, continuing input of clinicians with expertise in multiple pregnancy can facilitate both prevention and earlier intervention for NDI. Given the incidence of NDI in well MC twins, 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 behavioural 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 of these infants will facilitate crucial early interventions but 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 maximising the real clinical impact of academic work is systematic involvement of patients and families throughout research development and reporting. Where an outcome is so important to the end users of research, it falls to us as clinicians and researchers not to dismiss it as impractical but 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 must be seized.[41] Telemedicine in paediatric clinics has already been trialled[42] and does not only facilitate 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 centres? What other innovative tools could be developed to create family centred care to the lifelong benefit of these children?

Beyond direct clinical care, we should also consider our role as advocates for our patients. We recognise 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 pregnancies, 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 rigour to improve outcomes that matter to families.

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FIGURE LEGENDS

Figure 1. Definition of cerebral palsy and neurological impairment

Figure 2. Complications of monochorionic twin pregnancies

Figure 3. Incidence of neurodevelopmental delay in monochorionic twins

Figure 4. Long-term neurodevelopment outcome: Why and When?

Figure 5. Long-term neurodevelopment outcome: Risk factors and possible interventions

Cerebral palsy and neurological impairment

Cerebral palsy

- Persistent disorder of movement and posture attributable to a non progressive disturbance of brain development
- Diagnosed on the basis of abnormal muscle tone in ≥ one extremity
- Spastic diplegia, hemiplegia, and quadriplegia

Neurodevelopmental impairment

- Subnormal Mental Developmental Index (<70)
- Cerebral palsy
- Deafness requiring amplification
- Blindness (unilateral or bilateral)

Figure 1

Bax M Dev Med Child Neurol. 1964

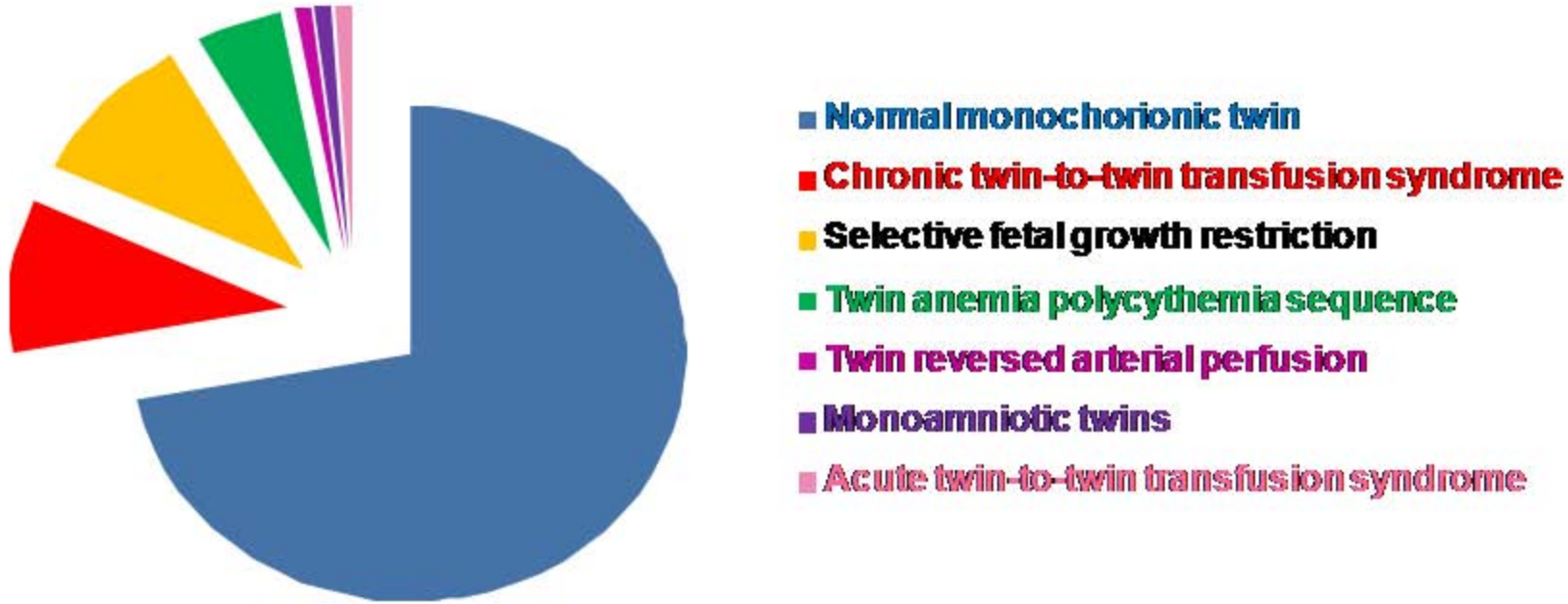

Figure 2

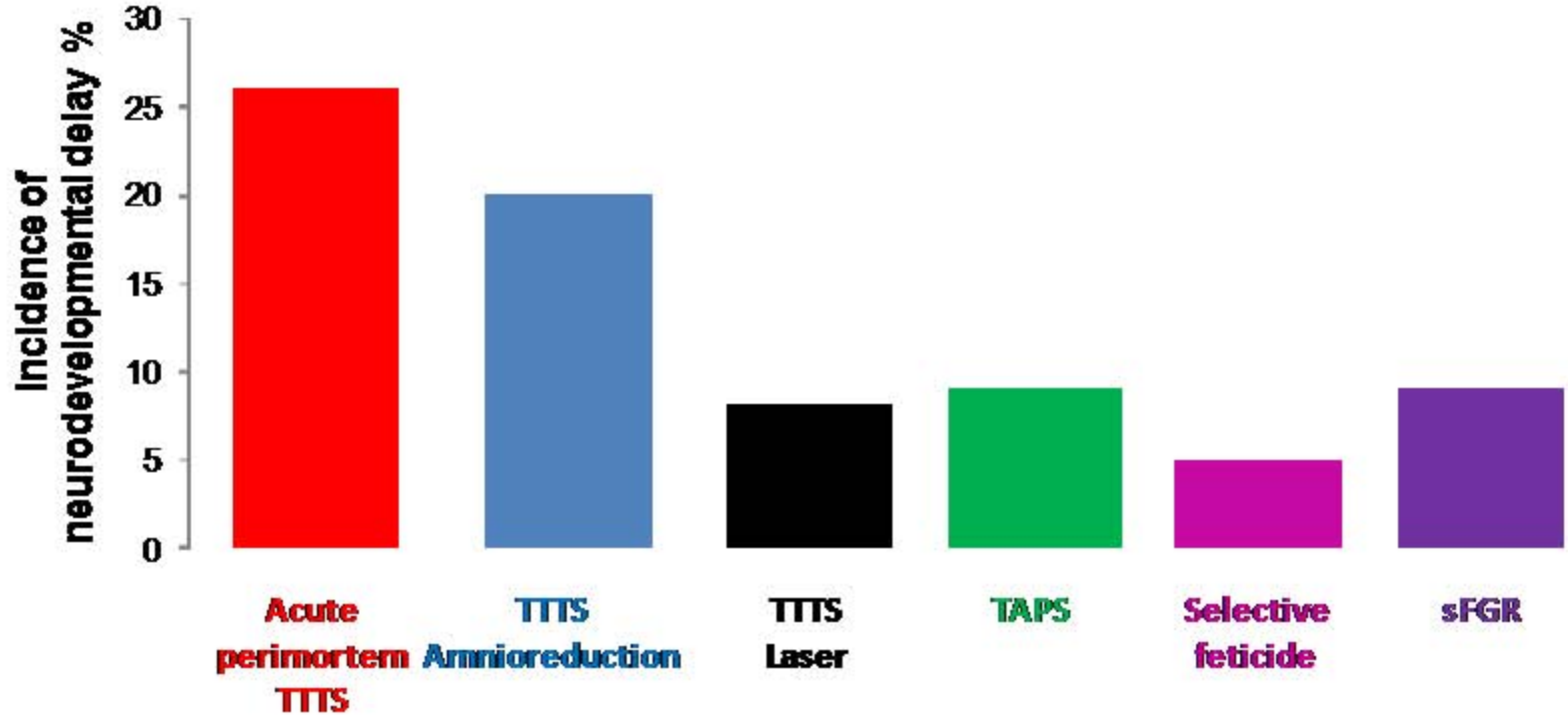

Figure 3

Long-term neurodevelopment outcome: Why and When?

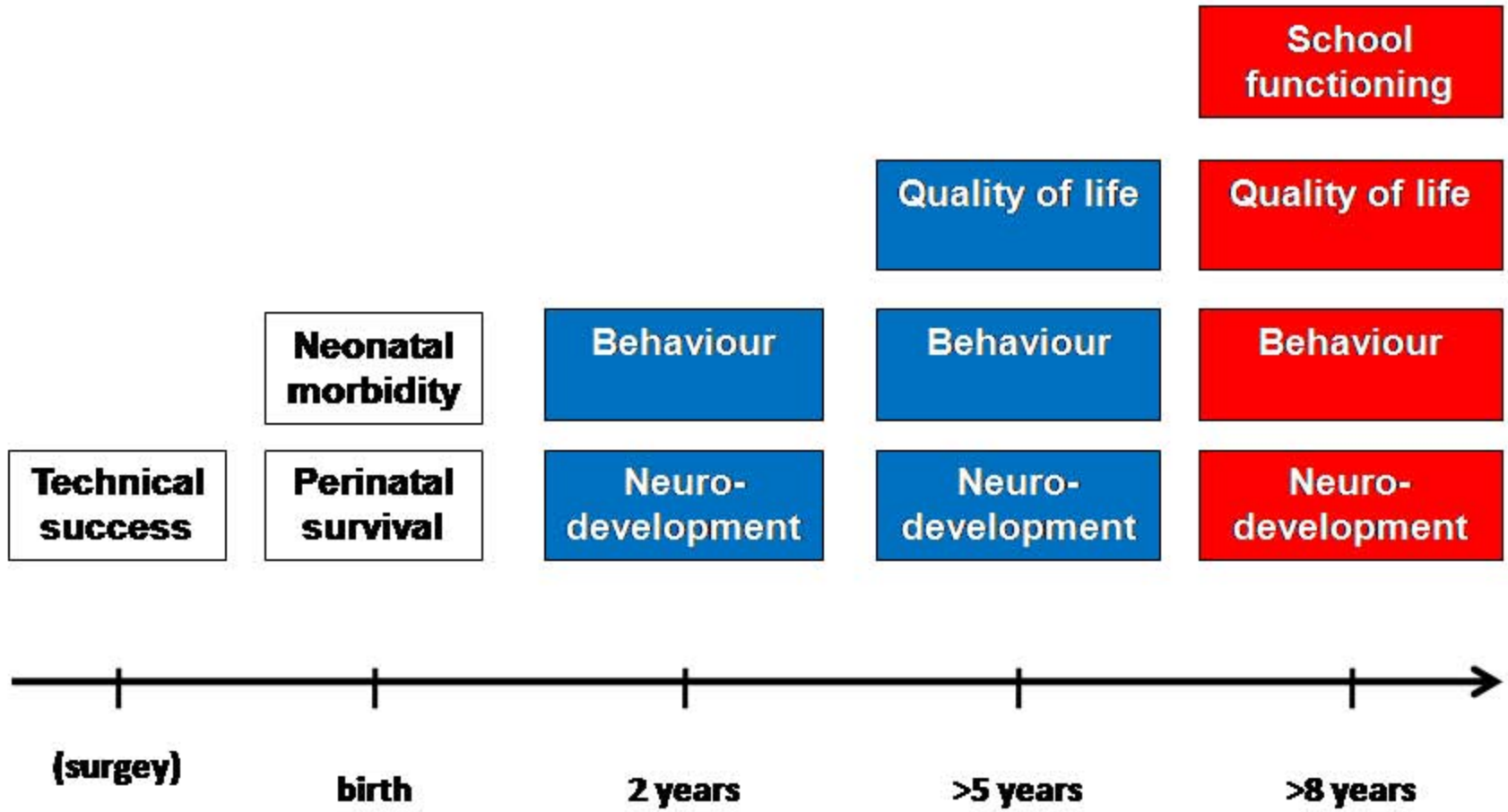

Figure 4

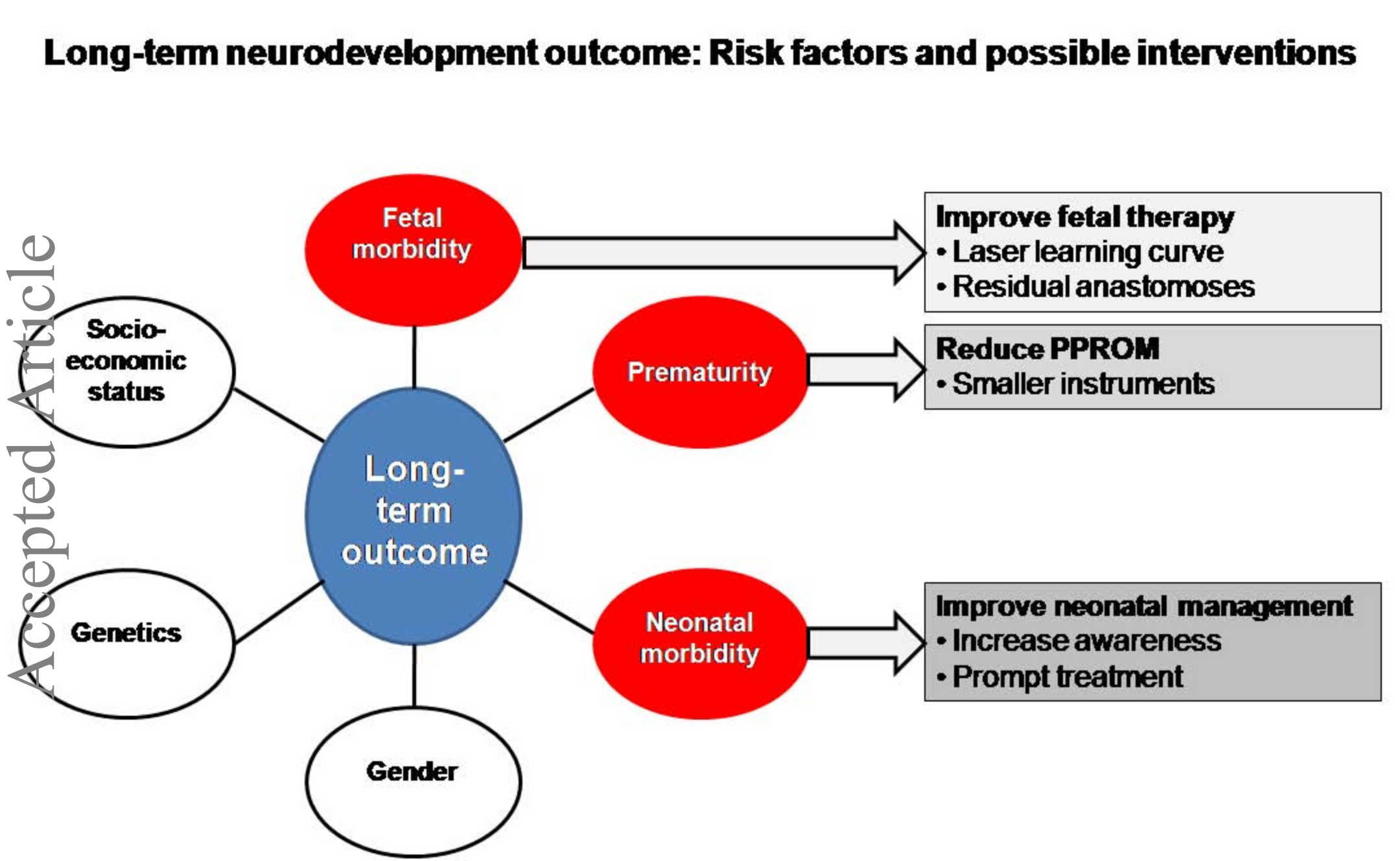

Figure 5