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The incidence and implications of cerebral palsy following potentially avoidable obstetric complications: a preliminary burden of disease study

S Leigh,[a,b] P Granby,[a,b] M Turner,[c] S Wieteska,[d] A Haycox,[a] B Collins[a]

[a] Liverpool Health Economics, Management School, University of Liverpool, Liverpool, UK [b] Lifecode®, the Old Vicarage, Lindley, Huddersfield, UK [c] Liverpool Women's NHS Foundation Trust, Merseyside, UK [d] The Advanced Life Support Group, ALSG Centre for Training & Development, Manchester, UK

Correspondence: S Leigh, Liverpool Health Economics, Management School, the University of Liverpool, Chatham Street, Liverpool L69 7ZH, UK. Email sleigh@liv.ac.uk

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Objective To determine the extent of cerebral palsy attributable to adverse obstetric events, and estimate the lifetime mortality and morbidity expectations of these individuals relative to age-matched members of the UK general population.

Design Simulation model.

Setting UK.

Population All projected live births during 2014.

Methods Using published data regarding the incidence and aetiology of cerebral palsy, we simulated the outcomes of a hypothetical cohort of UK live births. Survival and quality of life (QoL) for those with cerebral palsy were compared with age-matched individuals representative of the UK general population, in order to estimate the number of quality-adjusted life years (QALYs) lost following asphyxia-related cerebral palsy.

Main outcome measures Incidence of asphyxia-related cerebral palsy, QALYS, QoL, and survival.

Results A total of 207 (95% CI 169–245) cases of asphyxia-related cerebral palsy were projected amongst UK children born during the year 2014, with approximately 15.2 QALYs lost per case. If these results held true in a real birth cohort, 3142 (95% CI 2321–3963) QALYs would be lost as a consequence of asphyxia-related cerebral palsy, a loss valued by the UK National Health Service at £62.9 m (95% CI £46.4–79.3 m).

Conclusions Cerebral palsy following intrapartum asphyxiation leads to significant reductions in QoL and survival; however, this may often be prevented. For those with GMFCS 1 and GMFCS 2 cerebral palsy (Gross Motor Function Classification System), lifetime QALYs accrued largely resemble those experienced by the UK general population, whereas for GMFCS 3 and GMFCS 4 QALYs are reduced considerably, and are negative in the case of GMFCS 5.

Keywords Cerebral palsy, health economics, intrapartum care.

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Introduction

It has been proposed that birth asphyxiation relates not only to maternal and fetal risk factors such as age, maternal illness, and intrauterine growth restriction, but also to the quality of obstetric care received.[1] Despite major advances in fetal and perinatal medicine, intrapartum asphyxia remains a leading cause of mortality and long-term morbidity amongst infants,[2] in part as a result of shortfalls and inconsistencies in care.[3]

There are a number of children with cerebral palsy (CP) for whom an alternative pattern of care during labour and delivery would have unequivocally improved the course of their lives. Whereas some mistakes can be remedied via additional treatment, others will result in irreversible neurological sequelae, with those receiving substandard care experiencing a three-fold increased risk of neonatal hypoxia.[1] Over 5087 successful litigation claims for substandard maternal care were made against the UK National Health Service (NHS) in the last decade, with 41% citing avoidable CP, at a cost of approximately £1.12 bn.[4] As such, birth asphyxiation remains an important and potentially preventable cause of CP and a key area of continuing research.[5]

Hypoxic ischaemic encephalopathy (HIE), the brain injury commonly caused by asphyxia, is the cause of CP in approximately 14.5% of cases,[6] yet HIE is not considered as a 'single event' but rather as an evolving process, suggesting that intervention after birth could still be of significant benefit through the prevention of delayed cell death.[7] Therapeutic hypothermia has fast become the standard of care for asphyxiated infants,[8] minimising the neurological impact of prolonged oxygen starvation to the brain and reducing the likelihood of long-term disability.[9–11]

Although therapeutic hypothermia clearly has a role, the therapeutic window is short, and those with the most severe grades of encephalopathy are unlikely to benefit.[12] As such, there exists an unmet need for interventions to lessen and avoid the effects of intrapartum asphyxia, and in order to plan research regarding potential interventions, it is important to understand the burden of ill health arising from the condition in order to estimate the associated costs.

To date, there has been no account of the long-term implications, to both the NHS and its patients, of CP attributable to intrapartum asphyxiation. Using health-economic modelling we compared survival and quality of life (QoL) between those with asphyxia-related CP and age-matched individuals representative of the UK general population. Providing an estimate of the potential value of primary and secondary preventative measures aimed at minimising the lifelong impact of intrapartum asphyxiation.

Methods

Economic modelling was undertaken using Microsoft Excel® 2013 (Microsoft Corporation, Redmond, WA, USA) to simulate the outcomes of a hypothetical cohort of 812 970 live births. Using UK-specific epidemiological evidence where possible, this burden of illness study estimated the number of cases of asphyxia-related CP expected to occur in the UK during the year 2014, in addition to the number of quality-adjusted life years (QALYs) lost when compared with age-matched individuals representative of the UK general population.

As a composite measure of the health state of an individual, in which the benefits, in terms of survival, are adjusted to reflect the QoL experienced over that period, one QALY is equal to 1 year of life in perfect health.

We made an *a priori* assumption that ante- and/or postnatal intervention may have prevented or at least minimised the neurological impact of HIE, and with this, prevented the onset of asphyxia-related CP. This structure allowed us to quantify the complete mortality and morbidity burden arising from the irreversible and potentially preventable neurological disabilities associated with asphyxia-related CP.

Data

A comprehensive review of the English language literature was performed to provide estimates for the clinical and economic outcomes in the model. Our primary focus related to the underlying incidence of CP in the UK, the proportion of CP attributable to HIE, and the survival and QoL expectations of those with CP compared with age-matched members of the UK general population. We performed a separate literature search to identify the effect of therapeutic hypothermia as a means of preventing neurological cell death, and the subsequent onset of CP. Information was obtained through electronic databases, including the ISI Web of Science, EMBASE, and the PubMed clinical database, in addition to targeted hand-searching of the Royal College of Obstetricians and Gynaecologists (RCOG) and the National Institute for Health and Care Excellence (NICE) databases to ensure appropriate clinical retrieval.

Database searches were limited to humans, and no date restrictions were applied. For each identified publication it was initially determined whether or not the study met the predefined selection criteria based on the content of the title and abstract alone. For studies that met our criteria, or for which they were unclear, full text reports were obtained.

The reference list of all relevant publications was searched to identify further evidence, with the results of all searches combined and duplicates removed. All studies were assessed for their relevance with respect to the 'PICOS' inclusion/exclusion criteria shown in Figure S1.

Economic model

Base case

We used the 2012 number of 812 970 live births as our reference value for predicting the extent of asphyxia-related CP in the UK during the year 2014.[13,14]

The annual incidence of CP in the UK is consistently reported at around two per 1000 live births, corresponding to a 0.2% probability per birth.[8] This figure was applied in the base case to determine the total number of cases of CP expected to occur in the UK during 2014, with 14.5% of these expected to occur as a result of intrapartum asphyxiation.[6]

Therapeutic hypothermia has fast become the standard of care for HIE in the UK,[8] but data regarding long-term outcomes is absent for babies treated with hypothermia. Therefore, data were used from the pre-hypothermia era, with plausible outcomes in adulthood following therapeutic hypothermia modelled via the results of a recent meta-analysis.[15]

We assumed that therapeutic hypothermia would be initiated in all instances of HIE, resulting in a 12% decrease in the absolute risk of CP following intrapartum asphyxiation.[15]

To examine the impact of asphyxia-related CP on an individual and national basis, the severity of the disease burden, and the resulting morbidity and mortality expectations, were categorised using the Gross Motor Function Classification System (GMFCS), a five-level system describing the ambulatory functionality of children and youths with CP, on the basis of their self-initiated movement.

Survival analyses have shown that each of the domains of QoL primarily affected by CP (ambulation, manual dexterity, cognitive ability, hearing, and vision) possesses similar predictive power with regard to mortality;[16,17] however, GMFCS scores for ambulatory disability are the most common within the survival and QoL literature. We assumed that following the onset of CP, 22.5, 12.5, 18, 25, and 22% would experience ambulatory disability (GMFCS levels 1–5, respectively), as demonstrated by Young et al.[18]

As long-term QoL data were unavailable for those with CP, we extrapolated point estimates of QoL for those with differing extents of CP-related disability (GMFCS 1–5),[19] in order to represent the QoL experienced by those with CP over their entire lifetimes, as shown in Table 1. The point estimates used applied to those with a mean age of 33 years, and these were extrapolated at a decreasing rate over time from age 33 years until death, in order to model the negative effects of ageing on QoL. We also made the assumption that as CP is considered to be a non-progressive disorder,[20] if impediments to adult QoL do exist, they would necessitate similar impediments during childhood. As such, for ages less than 33 years we extrapolated the QoL weights with a gradual increase towards age zero, again to reflect the fact that QoL is generally greater during youth and gradually decreases with age. The rate at which QoL decreased over time mirrored that exhibited by the UK general population,[21] and as such we made the assumption that ageing has no greater effect on QoL for those with CP than otherwise healthy members of the UK general population.

Both the CP and general population QoL weights were expressed using the EuroQoL-5D (EQ-5D), the gold standard for UK health-economic evaluations, where individuals value their current health state with respect to depression/anxiety, ability to undertake usual activities, mobility, pain/discomfort, and self-care.

Survival data for the UK general population cohort were obtained from Office for National Statistics (ONS) life tables,[22] whereas those with CP (GMFCS 1–5) had their survival emulated using a 30-year survival analysis conducted in the UK.[23] In order to acknowledge that mortality varies by age, three periods were covered: 0–10 years, 11–20 years, and 21–30 years. Survival during each of these periods was converted into an annual mortality rate using the function below, with the resulting base-case mortality data shown in Table 2:

$$\text{Instantaneous rate of death} = -[\ln(1 - \text{mortality risk ratio at time}\,(t))]/\text{time period covered}\,(t).$$

We assumed that all deaths occurring in the CP cohort occurred at a constant rate over the 30-year period covered, with survival beyond 30 years expected to mirror that of the UK general population, without any longer-term evidence to suggest otherwise.

The health state differences between those with and without CP, measured by the difference in EQ-5D valuations for each year of life lived, were discounted at the NICE recommended rate of 3.5%, and then combined with the survival estimates for each hypothetical cohort. This revealed the difference in the number of years lived, weighted by the QoL experienced during that period, expressed in terms of QALYs.

The corresponding monetary value of the QALY losses attributable to asphyxia-related CP was calculated by applying the lower limit of the NICE cost-effectiveness threshold, equal to £20,000 per QALY, an estimation of the

Table 1. EQ-5D values for those with CP and age-matched individuals representative of the UK general population

Age	EQ-5D norms[25]	Cerebral palsy				
		GMFCS1	*GMFCS2*	*GMFCS3*	*GMFCS4*	*GMFCS5*
20 years	0.940	0.888	0.706	0.534	0.081	−0.248
30 years	0.935	0.883	0.702	0.532	0.08	−0.249
33 years	0.932	0.88	0.70	0.53	0.08	−0.25
40 years	0.892	0.842	0.669	0.507	0.077	−0.261
50 years	0.825	0.779	0.619	0.469	0.071	−0.279
60 years	0.790	0.746	0.593	0.449	0.068	−0.288
70 years	0.757	0.714	0.568	0.430	0.065	−0.297

Table 2. Expected survival for those with CP and age-matched healthy individuals representative of the UK general population

Age	ONS UK survival[18] (%)	Cerebral palsy survival (%)				
		GMFCS1	*GMFCS2*	*GMFCS3*	*GMFCS4*	*GMFCS5*
20 years	99.4	98.6	97.6	96.6	94.2	68.1
30 years	99.1	97.5	97.1	96.6	88.7	56.2
40 years	98.5	97	96.5	96.1	88.6	51
50 years	97.2	95.7	95.2	94.8	87.3	49.9
60 years	93.9	92.4	92	91.6	84.4	48.2
70 years	86.5	85.2	84.7	84.3	77.8	44.5

amount that the NHS would be willing to pay today in order to avoid the mortality and morbidity impediments associated with asphyxia-related CP.

Sensitivity analysis (Monte Carlo simulation)

Owing to the large number of variables included in the model, and the extensive variation in parameter estimates reported in the literature, our base-case model was subject to a considerable degree of uncertainty. A Monte-Carlo simulation was conducted to account for this parameter uncertainty in the model inputs, which would invariably lead to variation in the model outputs, in terms of the number of cases of asphyxia-related CP and the associated QALY losses.

Sample values for each input parameter were randomly and repeatedly drawn from representative distributions of feasible values, shown in Table S1. These distributions were determined not only by the mean values reported in the literature, but also by the degree of certainty surrounding these values, as demonstrated by their 95% confidence intervals (95% CIs). This process was repeated 10 000 times, with the dispersion of results representing the range of probable outcomes, weighted by their likelihood of occurrence.

Results

The prevalence and implications of asphyxia-related CP in the UK

In the base case, it was estimated that approximately 208 cases of asphyxia-related CP (of any severity) would occur in the UK during the year 2014. Applying the CP severity expectations from Young et al.,[18] this was further categorised as 47, 26, 37, 52, and 46 with ambulatory disability classifications GMFCS 1–5, respectively, as shown in Figure 1.

The impact of CP on quality of life

Over a lifetime, those with asphyxia-related CP were shown, on average, to experience a QoL that was 63% lower than that experienced by the UK general population. When taking into account the potential for variation in the severity of CP-related impairments, however, QoL expectations varied considerably.

For those experiencing GMFCS-1 CP, QoL largely resembled that of the general population, with only a 5% reduction in QoL over a lifetime; however, QoL decreased considerably as the level of ambulatory disability increased. Those with GMFCS 2, 3, and 4, each exhibited reductions in QoL of 25, 43, and 92%, respectively, whereas those with the maximum level of CP-related disability (GMFCS 5) faced even further reductions in QoL.

The impact of CP on survival

For those with GMFCS-1 CP, our base-case analysis suggested that survival, much like QoL, largely mirrored that exhibited by the UK general population, with only a 1.5% decrease in survival by the age of 50 years. Those with GMFCS-2, 3, and 4 CP, however, faced mortality rates of 4.8, 5.2, and 12.7%, respectively, some 1.7, 1.9, and 4.5 times that of the UK general population. As expected, those with the greatest burden of disease (GMFCS 5) not only faced the largest detriment to QoL, but also the largest reduction in survival. These individuals faced a risk of death some 17 times greater than age-matched members of the UK general population, with more than 50% expected to die before the age of 50 years.

The NHS-wide impact of CP attributable to asphyxiation

In the base-case model, our hypothetical cohort of 208 individuals expected to develop asphyxia-related CP accrued a total of 2002 QALYs over a 102-year time horizon, approximately equal to 9.6 QALYs in the life of the average person with CP attributable to asphyxia.

Taking into account the varying severities of CP that could be experienced (and with this, the wide variation in QoL and survival that these individuals may experience), this 9.6 QALY 'average case' was considered a highly insensitive pooled estimate. For the 47 individuals expected to develop GMFCS-1 CP, 1103 QALYs were expected to be

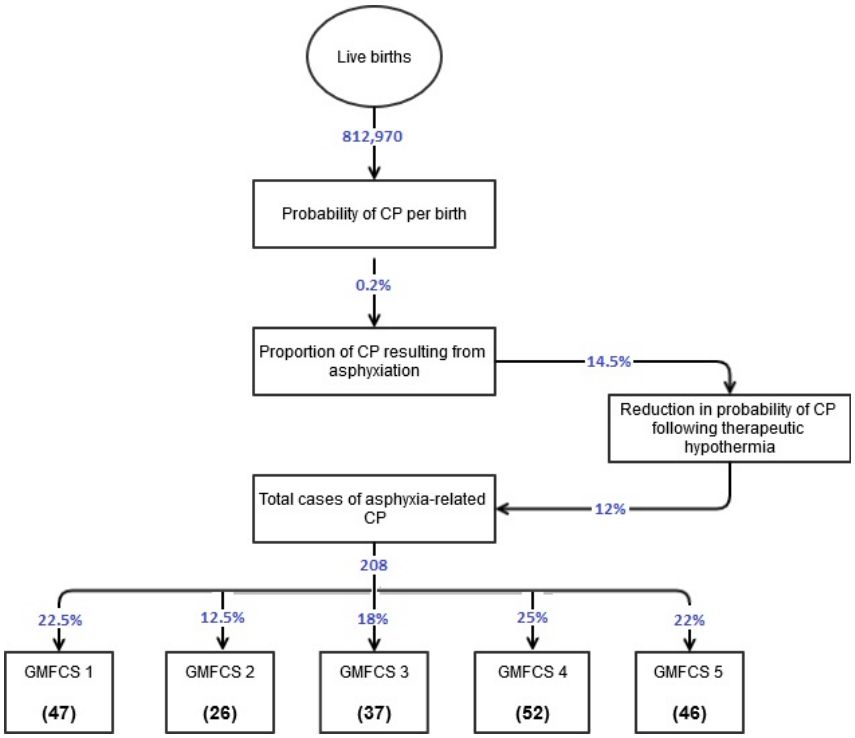

Figure 1. Results of the hypothetical patient simulation model: base case.

accrued, equating to an average of 23.4 QALYs per person. This decreased to 18.6, 14.0, and 2.0 for those with GMFCS 2–4, respectively, as shown in Table 3, whereas those with GMFCS-5 CP effectively accrued −4.5 QALYs.

By comparison, the same hypothetical cohort of 208 individuals could have accrued 5203 QALYs over the same period, given that the events that led to asphyxiation were managed in such a way that could have prevented the onset of CP.

As such, those suffering from CP experienced approximately 3201 less QALYs than the age-matched cohort representing the UK general population, with this difference representing the mortality and morbidity burden of all cases of asphyxia-related CP expected to occur in the UK during the year 2014.

Using the lower limit of the NICE willingness-to-pay threshold, equal to £20,000 per QALY gained, this difference has a net present value of £64 m, the value that the NHS would be willing to pay today in order to generate increases in survival or QoL of equal magnitude to those lost following asphyxia-related CP occurring during 2014.

Sensitivity analysis

With the exception of the underlying incidence of CP in the UK (regardless of aetiology), the reported values of each parameter used within the model showed a considerable degree of variation within the obstetric literature. To incorporate this variability in the estimates reported and the corresponding uncertainty regarding the true population values, 10 000 Monte Carlo simulations were

Table 3. QALY expectations for hypothetical birth cohort differentiated by severity of CP

	Size of Cohort	QALYs accrued	QALYs per individual	QALY loss per case vs. general population	NHS valuation of forgone QALYs (per case)	NHS valuation of forgone QALYs (total)
GMFCS 1	47	1,103	23.4	1.6	£32,000	£1.50 m
GMFCS 2	26	483	18.6	6.4	£128,000	£3.33 m
GMFCS 3	37	517	14.0	11.0	£220,000	£8.14 m
GMFCS 4	52	105	2.0	23.0	£460,000	£23.92 m
GMFCS 5	46	−206	−4.5	29.5	£590,000	£27.14 m

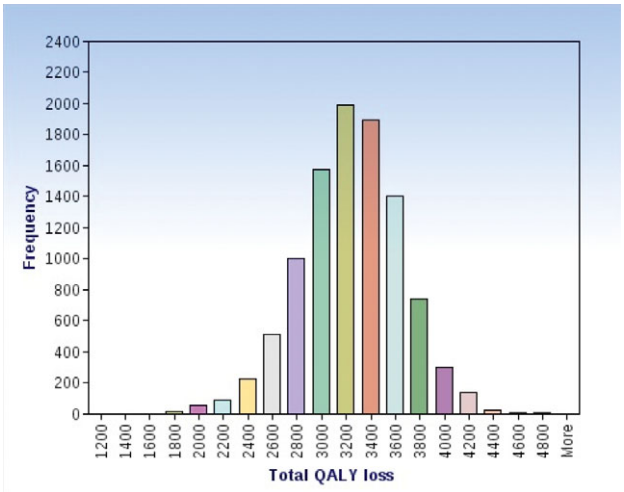

Figure 2. Total QALYs lost as a result of asphyxia-related cerebral palsy: results of 10 000 Monte-Carlo simulations.

performed to establish the combined effect of changes in the values of any or all of the parameters employed, and how these would ultimately affect the results of the model.

The mean of our 10 000 simulations suggested that a total of 207 (95% CI 169–245) cases of asphyxia-induced CP could be expected in the UK during 2014, compared with the 208 cases estimated in the base case. The dispersion of results is demonstrated in Figure S2, with the long-term impact of these cases shown in Figure 2. As such, our probabilistic sensitivity analysis suggested that approximately 3142 (95% CI 2321–3963) QALYs will be lost as a result of asphyxia-related CP occurring during the year 2014, compared with the 3201 QALYs estimated in the base case.

Discussion

Main findings

In this study, an analysis was conducted (for the first time) examining the lifelong impact of asphyxia-related CP on QoL and survival. Our findings suggest that, when compared with the UK general population, asphyxia-related CP results in a lifetime reduction in QoL of approximately 63%; however, this may be as high as 92% for those with GMFCS-5 CP.

These individuals are also, on average, six times more likely to die by the age of 50 years, with those experiencing the most severe forms of impairment (GMFCS 5) facing a risk of death 17 times greater than that of the UK general population.

At the national level, this combination of reduced QoL and survival is expected to result in a 3142 QALY loss (95% CI 2321–3963) amongst those developing asphyxia-related CP during 2014. This corresponds to approximately 15.2 QALYs lost for every case, with a total net value of £62.8 m (95% CI £46.4–79.3 m), the amount the NHS would be willing to pay today in order to generate improvements in QoL and survival equal to those lost as a result of asphyxia-related CP.

Strengths and limitations

The main strength of this study is that this analysis is the first of its kind in the UK and across the World. No previous health-economic analysis has examined the long-term morbidity and mortality impediments attributable to asphyxia-related CP, nor has there previously been an estimation of the extent of this disability in the UK. Our methods and results are reported with reference to the consolidated health economic evaluation reporting standards statement (CHEERS),[24] and as such can be considered transparent and readily reproducible and adaptable in the event of new information becoming available.

The limitations of this study lie in the fact that shortages of data inevitably resulted in a number of assumptions in order to model the effect of CP over a lifetime.

Although it has been reported that QoL is significantly affected by CP few estimations of the magnitude of this effect were found, particularly when using the EQ-5D. The health utilities index (HUI3) is the preferred tool for measuring QoL in adults and children with CP,[18,25,26] as it explicitly measures the domains of QoL predominantly affected by CP that the EQ-5D does not, including vision and hearing. Although there exists a greater availability of evidence using the HUI3, there is currently no set of population norms for the HUI3 in the UK, meaning that comparisons against the UK general population are not possible. In using the EQ-5D to measure QoL in those with CP, we proceeded with the assumption that although the EQ-5D does not explicitly account for a number of the principally affected domains of QoL, these would still be acknowledged indirectly, for example through the impact of blindness on self care and the ability to perform one's usual activities.

Furthermore, given that survival analyses amongst those with CP only commenced during the mid-20th century, assumptions concerning the longer-term survival of these individuals were also essential. Unaccounted for reductions in all-cause mortality between the time these studies were undertaken and the present day may have led to an overestimation of the impact of CP on survival, whereas assuming that all cases of HIE are treated with hypothermia may have led to an overestimation of the number of individuals with HIE who successfully avoided the onset of CP.

We also made the assumption that all cases of asphyxia-related CP are amenable to primary or secondary prevention; however, the reality of this assumption is

dependent upon effective interventions being implemented by fully integrated perinatal services with a national reach, and thus our results represent the 'best-case' scenario.

Future research should be aimed at clarifying areas for which the level of available evidence was low. Longitudinal research concerning the mortality and morbidity expectations of those with CP would add significantly to the robustness of future conclusions regarding the extent and implications of asphyxia-related CP in the UK. Furthermore, when available, information relating to the novel methods of primary and secondary prevention for HIE currently under trial will enable reliable estimates of the potential to reduce the mortality and morbidity detriments that can be attributed to potentially avoidable obstetric complications.

Interpretation in light of other evidence

In order to plan research regarding interventions to reduce the impact of asphyxia-related CP, it is first important to understand the burden of ill health arising from the condition, in order to estimate the potential for improvement. Until now, the majority of publications focusing on the causes of CP have placed little weight on the relative contribution of intrapartum complications, the consensus being that the events of labour and delivery only represent a small proportion of all causes of CP,[27–29] and have instead stressed the relative importance of genetic factors and events occurring during the growth and development of the fetus.

These most common antecedents of CP are, however, exogenously determined, and as such largely unmodifiable and unavoidable. However, the adverse intrapartum events associated with lifelong conditions such as CP, no matter how uncommon, result in significant detriments to QoL and survival, and may in fact be amenable to primary and secondary prevention. One example is the growing body of evidence demonstrating a positive association between practical simulation training for use in obstetric emergencies, and clinically significant improvements in neonatal outcomes,[30–33] with one retrospective study of 19 460 neonates in the UK demonstrating a 50% reduction in the incidence of HIE following the implementation of obstetric training.[34]

Given the considerable QALY losses associated with asphyxia-related CP, primary prevention by means of obstetric training may lead to significant improvements in health, particularly if training were focused on areas that at present account for a large proportion of the disabilities arising from substandard care.[35] One example is cardiotocography (CTG) misinterpretation, which is relatively common within the NHS and is associated with inexperienced staff and night-shift working patterns.[36] As CTG misinterpretation is reportedly responsible for over 70% of successful litigation claims against the NHS that cite avoidable CP,[4,36] implementing obstetric training in those institutions where CTG misinterpretation is relatively common may help to minimise the considerable QALY losses associated with asphyxia-related CP in the UK.

Although training has shown positive outcomes, it has been argued that intensive education is not a sustainable approach in most clinical settings, and that other systems are required that are less reliant upon individual motivation, thus removing the potential for human error. Such technologies currently under trial in the UK include enhanced continuous electronic fetal monitoring (Guardian®; K2 Medical Systems, Plymouth, Devon) and the addition of Xenon gas inhalation to standard treatment with hypothermia or melatonin.[37–39]

These technologies may also potentially reduce the incidence and implications of asphyxia-related CP significantly; however, it will be some time before the effectiveness of these secondary preventative measures is known and decisions regarding their cost-effectiveness and implementation can be made.

Conclusion

Cerebral palsy resulting from intrapartum asphyxiation leads to significant reductions in QoL and survival; however, this condition may often be prevented. For those with GMFCS 1 and 2 cerebral palsy, lifetime QALYs accrued largely resemble those experienced by the UK general population, whereas for those experiencing GMFCS 3 and 4, QALYs are reduced considerably, and are negative in the case of GMFCS 5.

Disclosure of interests

SW is the chief executive officer of the charitable institution the Advanced Life Support Group (ALSG). This charity provides education and training for use in obstetric emergencies, amongst other areas, and provided the funding for the original research from which this article was created.

Contribution to authorship

SL, SW, AH, and BC conceived of the need for this research. Planning of the clinical and economic research was performed by SL, PG, MT, AH, and BC, with the original underlying economic model designed by SL, with assistance from PG, AH, and BC. All research and the creation of the economic model was performed by SL, along with all analysis and the write-up. Following review by a clinical expert (MT), the economic model was adapted and the clinical research expanded. The final article was reviewed and subject to minor content editing from PG, MT, SW, AH, and BC.

Details of ethics approval

No ethical approval was sought. This article is a review and interpretation of existing published data, and relies on no previously unpublished patient data.

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None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Model parameter values for base case and Monte-Carlo simulation.

Figure S1. Identification of research question using PICOS analysis.

Figure S2. Cases of asphyxia-related CP: results of 10 000 Monte-Carlo simulations. ■

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