Refining regional organisation of services in the UK to improve outcomes of pregnancies delivering at extremely low gestational age.

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Abstract

Care of pregnant women and their infants at extremely low gestational ages challenges clinical teams. The continuing rise in survival at gestational ages below 25 weeks has prompted re-evaluation of practice guidelines within the UK and other countries. This paper describes the background data that have guided our practice, the approach that has been taken to deliver optimal outcomes for pregnancies delivering at extremely low gestational age in the UK, mainly through centralising care, and discusses the research and audit data that support our practice. In particular, we emphasise the importance of a coordinated perinatal approach to both mother and infant, and careful assessment of the risks to both, to ensure that we develop the highest quality personalised care for each family, supported by national quality improvement and research evidence.

Introduction

Care for pregnant women and their babies born at extremely low gestational ages, here defined as <25 weeks of gestation, has always challenged clinical teams and practice. Few other areas of medicine have provided such ethical and moral dilemmas for all involved, as risks to the woman and her child are clear but poor outcomes are far from predictable. As care has improved and the results of a range of interventions become clearer, both parents and clinical teams have become more willing to undertake active, survival-focused care. This has resulted in neonatal mortality falling at gestations below 25 weeks. Less certainty exists about the prevalence and extent of early and later morbidity among survivors and there is limited evidence about the associated maternal morbidity that may accompany delay in delivery when aiming to achieve livebirth.

The achievement of improved outcomes at a national or regional level demands careful attention to the organisation and coordination of care. There are many different ways of achieving this, but in this paper, we describe the changes to the care of pregnant women at risk of delivering at extremely low gestational ages that have occurred in the UK over the past 20 years, discuss the supporting evidence that has driven development, and consider the implications for the care of women, their babies and the families involved.

We first describe the findings of national studies and initiatives, together with the impact this has on the model of care in our National Health Service. We then review the evidence that underpins these changes that have effectively centralised expert early care for this group. Following discussion of the ethical basis for our practice and the changing attitudes that facilitate improved outcomes, we discuss the challenges in centralising care and the leverage we have developed to ensure it happens.

Outcomes for babies born at extremely low gestational ages

In 1995 a group of neonatologists in the UK embarked on a national study of survival and health status for babies born at 25 weeks of gestation or less.[1 2] Their reasons for doing this were many but principally there had been an increase in neonatal survival at very low gestational ages, particularly since the introduction of maternal antenatal steroid and neonatal surfactant replacement therapies. There was concern and differences of opinion about the utility of providing neonatal intensive care at such low gestations. The study, EPICure, identified all births across the United Kingdom and Republic of Ireland in a 10-month period, extending in two regions to evaluate for seasonal differences, of which there were none. The resultant publications in 2000 identified low neonatal survival[1], and a high risk of impairment[2] among those who did survive. These findings provoked strong feelings[3] but revealed for the first time reliable data on outcomes at such low gestations.

In a second study of extremely low gestational age births in England during 2006 there was an improvement in neonatal survival overall of 15%[4] and in survival without impairment of 13%[5], although the proportion of babies admitted for neonatal care who survived with serious impairment remained the same. The authors noted at the time that the use of different denominators led to markedly different survival rates, being lowest when based on all births and highest when based on admissions for neonatal care. Additionally, the study reported outcomes for babies where there was evidence that intervention had occurred in the delivery room. The inclusion of babies who died following care that was not oriented to survival biases the data, as it is unknown what the outcome would have been if active interventions to promote survival had been undertaken. Using such inclusive data as a basis for counselling parents provides an unduly pessimistic picture of survival. However, using data only where active intervention has been instituted may give a somewhat optimistic view as children who are considered to be of poor prognosis may not receive intervention – this is particularly so in births before 24 weeks of gestation.

Since this report, perinatal surveillance in the UK now includes survival data based on whether or not intervention was planned in the delivery room and the current Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) data report such outcomes with surprising results (Figure). Although the annual numbers surviving at these low gestations across the UK is small (in 2016, it was 15 babies at 22 weeks, 101 at 23 weeks and 270 at 24 weeks) it is clear that where interventions are undertaken that survival is significantly higher than previously believed. Given these data and the increasing move to use more factors than simply gestational age to assess the chances of survival,[6 7] the UK national framework for practice[8] was revised and published in 2019.[9] This framework is new for many units in the UK but reflects how practice and care have changed over the 25 years since the first EPICure study. The data mirror the practice in Sweden, where a move to provide interventions at extremely low gestations has been in place for some time and had produced further increases in survival in babies born at 22, 23 and 24 weeks.[10] In contrast there have been few changes in outcomes at extremely low gestations in France between the two national EPIPAGE studies in 1997 and 2011, and national guidance in France and several other countries is not to provide survival focused care below 24-25 weeks.[11 12]

Evolution of the Neonatal Care Model in the UK

What is guiding these changes across the UK and other countries? There are a range of drivers but mainly an increasing realisation among perinatal teams that survival at 24 weeks or less is possible and frequently sought by parents. There is also a societal change in how impairment or disability are viewed, and a consensus that using the composite “neurodevelopmental impairment” variable to counsel women and families overstates the burden that a woman and her family are weighing up against the alternative – death.[13] This ethical view is not at odds with the published ethical recommendations[14], which were based on the original EPICure study data from 1995. There have been no further national studies of developmental outcomes to guide parents since the 2006 EPICure cohort, although national guidance has recommended standardised follow up[15]. Follow up reporting at 2 years is improving but is not yet at a level to start regular outcome reporting.[16] Outcome data from the EPICure2 study of 2006 births[5] describe the proportions of children with impairment that are similar to those in other national and large population reports,[9 11] and with similar prevalence of impairment to the children who were born in 1995.[17]

Neonatal intensive care in the UK grew from local initiatives and in 1995 was dispersed and delivered in most hospitals. With the realisation that service quality needed to be developed to ensure babies had the best care[18], initiatives were begun that led in 2004 to the establishment of formal neonatal networks.[19] These have been refined over the ensuing years and England (approx. 600,000 births per year) is now covered by 10 “operational delivery networks”; this system of networks is commissioned centrally and managed regionally,[20] and is subject to published annual audits and quality improvement initiatives[16]. All networks are now coordinated with local maternity systems to ensure that organisational issues consider the whole perinatal pathway.

It is against this background that we should evaluate how services may be best organised to benefit this vulnerable group to optimise their outcomes within our society.

Is there evidence that centralising care improves neonatal outcomes?

For births in 2006, EPICure2 provided an opportunity to evaluate neonatal outcome against the complexity of care undertaken in the hospital of birth and the effect of antenatal or neonatal transfer between hospitals for babies <26 weeks of getsation.[21] Hospitals were classified by the network-designated type of hospital where Level 1 was a special care service (no long-term intensive care), Level 2 was a local neonatal service (agreed limits to intensive care activity) and Level 3 was a full neonatal intensive care service, and by "activity", high activity defined as carrying out ≥2000 days respiratory support (ventilation or continuous positive airways pressure) per year, and more than four consultants with >50% of their time dedicated to neonatology. Despite a complex analysis that was confounded by transfer policies, the data showed that only 56% of births 22-26 weeks of gestation occurred in Level 3 units, and that there was a 25% increase in the adjusted odds of survival without neonatal morbidity (BPD, ROP, NEC, Brain injury) for babies that were delivered in a Level 3 as opposed to a Level 2 unit. Furthermore, survival at 23 and 24 weeks was significantly higher for babies cared for in high activity units compared to medium activity, and that postnatal transfer from Level 2 to Level 3 for neonatal care significantly increased the risk of mortality. The reduction in mortality in level 3 deliveries was also seen among deaths before delivery. The implications of this were that women at risk of preterm delivery at extremely low gestations should be transferred to hospitals with Level 3 neonatal facilities. It is at these hospitals that expertise in pregnancy management will also have been developed to optimise care for the mother, including when to intervene to expedite delivery.

Such recommendations are not new, regionalisation has been recommended since 1975[22] but effectively not practised in many areas. In a systematic review of regionalisation, Lasswell and colleagues confirmed in a meta-analysis that for very preterm or very low birthweight infants there was a 60% reduction in the odds of neonatal death for births in Level 3 centres compared to births outside these centres. For extremely low birthweight babies (<1000g), this reduction in risk of mortality was even higher (80%).[23] The challenge therefore is how to achieve this.

The ethical basis for survival-focused management at extremely low gestational ages

For many years, clinicians have used a series of gestational age thresholds to guide practice of "active neonatal intervention", although they vary widely around the world.[24 25] The use of such thresholds is always controversial and may remove both clinician and parental discretion from the decision making,[12] whereas other recommendations suggest a "grey" zone where discretion may be used.[14] Some may point to a lack of cost effectiveness but there are few data to support such a view. Finding a balance between clinical futility and respecting the wishes of parents is challenging[7 13 14], but it seems clear that for the infant:[9]

- Survival is possible even down to 22 weeks of gestation for some infants
- The frequency of severe impairment/disability is about one in three, or two in three do not have severe impairments at follow up

- A proportion of survivors without severe impairment will have developmental challenges but be able to live independently
- Within each gestational week band there is a range of outcomes dependent on the precise age within the week, the sex of the infant, fetal growth and plurality (some of which is not precisely quantifiable), as well as the effect of a range of other maternal factors including chorioamnionitis
- The administration of antenatal corticosteroids and delivery in an appropriately resourced specialist maternity and neonatal setting may significantly enhance survival.

Hence it is considered that the ethical basis for undertaking survival-focused care at extreme low gestations exists but must include clinical and parental agreement; a full discussion should be had between the clinical team (which includes obstetric, neonatal and midwifery teams) and parents to agree a plan of clinical care following an assessment of the risk to the mother and the infant. That plan will require re-evaluation as gestation advances and in light of changing clinical condition, but consensus should be maintained to achieve optimal care for both mother and infant.

It also demands that attention is paid to comfort-focused or palliative care in situations where it is considered that the situation is of extremely high risk to either baby or mother. Indeed, little consideration has been given to the risks of extremely preterm birth to the mother,[26] which are certainly not trivial,[27] see below.

Influence of professional attitudes

Attitudes of neonatologists and neonatal nurses to care at low gestational ages varies widely.[28 29] This is reflected in variation in the engagement of parents in the development of national guidance.[25] Neonatal teams appear more optimistic than obstetric/midwifery teams[30] which may reflect neonatal team exposure to the whole neonatal journey for a variety of different patient scenarios and their appreciation of the changes in mortality and long term outcomes for the child. In contrast, maternity teams' attitudes are likely to be influenced by their exposure to the immediate outcomes at birth, and their experience of the maternal morbidity associated with birth at extreme preterm gestations. Although much of the emphasis is on neonatal outcome, it is vital that healthcare professionals do not lose sight of the pregnant woman and her healthcare needs in the face of delivery of her baby at extremely low gestations. Maternal morbidity is rarely considered but comprises an important part of the decision-making equation. Despite this, consideration of the outcome for the woman may be frequently secondary to the decisions made about the fetus and baby.

One aspect of the provision of care is the principle of "fairness" and therefore equality of access. The perception of outcomes as quoted are interpreted by the receiver in different ways. Parents desperate for their child to survive are frequently pitted against clinical teams that consider the mother to be at high risk of severe morbidity with an infant at very high risk of death, and for whom active care is futile. Each present with prior beliefs that need to be managed. There may be differences of opinion between the referring and receiving hospital as to the most appropriate intervention and indeed of the risk to the fetus and mother.

This emphasises the need for pre-counselling clinical discussions with the whole perinatal team and parental involvement in the development of care plans, including the receiving staff if antenatal transfer is being contemplated. Despite the availability of outcome data for infants born at extremely low gestational ages and the use of on-line risk calculators[6], individual hospitals have differing attitudes and experience towards the provision of active care[31] leading to wide variation in mortality between units.[16 31] By reducing the number of units at which decisions are made and thereby increasing the expertise of these units, more consistency can be brought to this area.

Challenges to centralisation of care

Care is not solely about the baby, as emphasised above. There should be awareness of maternal risks, the risk profile may change as the clinical picture worsens, care must be taken to ensure safety during transfer at what is a critical period in the pregnancy and the ability of regional centres to manage the population and provide for the families, who provide essential support for women, are all important considerations.

The mother should be the first priority in all discussions, since if the mother is unwell, the fetus is surely compromised. Extremely low gestational age birth is not a natural event and serious complications of pregnancy have occurred to precipitate delivery that themselves will require expert care. Delaying delivery to achieve maturation in gestational age at birth and increased birthweight can come at the expense of maternal health. Thus, any transfer into a regional centre has implications for obstetric practice, alongside the challenging decisions that need to be made for the infant. Increasingly pregnancy is complicated by pre-existing maternal disease. Among 132 women presenting for preterm delivery with a live fetus at 22-26 weeks of gestation at University College London Hospital, only 17 (13%) had no co-existing maternal medical conditions or antenatal complications. Multiple pregnancy was common (28%). Over 1-in-4 mothers had serious complications of labour and/or delivery, commonly postpartum haemorrhage (10%), sepsis (8%), and placental abruption (6%). Eleven fetuses developed intrapartum complications (cord prolapse, unanticipated delivery and head entrapment) and there were 5 intrapartum fetal deaths.[27] Care for women presenting at extremely low gestational ages is accompanied by complex care needs and senior input is necessary. The RCOG has reviewed the evidence base to support care at 23-24 weeks of gestation and suggests a strategy.[26]

Given there are potential risks for the mother in the process of extremely preterm delivery, planning for all possible clinical scenarios requires careful documentation so that all healthcare professionals are briefed. While waiting to achieve viability, women may develop life-threatening sepsis and bleeding complications. The maternal clinical picture often changes rapidly with the result that healthcare professionals may need to act urgently, for example, to expedite delivery in a woman developing chorioamnionitis.

Communication prior to transfer is a critical part of care and it is good practice to involve the receiving team in the early discussions with the family so that consistent messaging is provided, and the timing of transfer and immediate perinatal care can be optimised. However, it is also important to emphasise that transfer does not necessarily mean survival-focused care for the child, particularly if the mother's condition is deteriorating.

A second issue is that of the capacity of regional centres to care for this population, which requires careful planning. Prognostic tests for threatened preterm labour are developing through big multicentre studies[32 33] which give more confidence in their use to triage women for antenatal transfer, but objective measures of fetal infection and wellbeing are lacking. Most regional operational delivery networks in the UK have developed maternity and neonatal cot finding services with clear primary and secondary pathways for transfers within the network area. Networks are working hard to cultivate the mindset that all high-risk preterm infants should have equal access to tertiary maternity and NICU care no matter where they live in the network. The “Just Say Yes” philosophy strongly encourages tertiary maternity and neonatal services to always accept very high-risk premature infants unless they would have to transfer out a similar case presenting directly to their own hospital.

Family support structures are required to ensure that what can become extended stays in the receiving centre are supported appropriately and managed to reduce the stress of separation. Frequent issues arise over the move to repatriate care closer to home; when the time comes to return to their local hospital, variation in care practices between centres and can be confusing for parents. In England, we have appointed family care coordinators to manage this area and promote consistent practice across our managed networks.

Follow up of women who deliver at extremely low gestations is also necessary to bring some closure to what for many couples is a traumatic event, and also to plan optimal management of any future pregnancy.[34] This requires co-ordination between the local and tertiary units to provide comprehensive support to families.

What leverage is there to achieve centralised care?

National and regional organisation and audit of services are key aspects of quality improvement in these areas. In a review of the geospatial organisation of perinatal care in the USA, one-in-five obstetric critical care services had no adjoining neonatal service, and a similar proportion of neonatal services were not co-located with obstetric services. [35] In the UK all level 3 neonatal services are co-located with an obstetric/fetal medicine service and, following the publication of criteria for designation of services[36] [37], all neonatal services are part of a clinical network managed as part of an operational delivery network. The advantage to this system is that regional commissioning of services and national quality assurance can be used to monitor service performance.

Pathway monitoring for all high-risk infants admitted to neonatal units is in place in all neonatal networks and in most networks is done in real time, as details on all neonatal inpatients are entered into a single linked electronic system on a daily basis. Exception reporting is used by networks to ensure any breaches in agreed pathways have had a full case discussion with the tertiary NICU and are clearly documented. There is potential to withhold payment for care in inappropriate centres. More recently, networks have developed mechanisms for feedback and exception reporting of high-risk infants born outside the NICUs back to the local maternity oversight committee for independent standardised review of the case. Lessons learnt are regularly fed back to all obstetric and midwifery staff in the region. This has resulted in a significant increase in the percentage of high risk infants <27 weeks born in centres with an NICU from 56% in 2006[21] to 78% in 2019.[16]

The National Neonatal Audit Project is a nationally commissioned audit running in the UK since 2008, to enable key process and outcome data to be compared across regions.[16] The published and unanonymised annual report includes case studies for successful QI initiatives from different units and enables units to compare themselves with any other unit or network in the UK in addition to seeing changes and progress within their own unit over time. The audit is compulsory for all units and key metrics are subject to outlier analysis with formal feedback of positive and negative outliers to chief executives in provider units, with real time interrogation of the data available to units. Since 2016, a similar approach has been adopted for national maternity audit through the National Maternity Perinatal Audit.[38]

Both these audits contain key process measures for improving optimal management around the time of birth for the extreme low gestational age infant to support local QI and improve outcomes for this vulnerable group. In addition, the British Association of Perinatal Medicine (BAPM) has produced a series of Quality Improvement Toolkits to support improvements in antenatal optimisation and early neonatal management.[39] The National Maternity and Neonatal Safety Collaborative[40] is a national support service for local and regional perinatal QI, resulting in a rapid improvement for some perinatal metrics, including administration of maternal peripartum MgSO4 <30 weeks of gestation, administration of which has increased from 64% to 82% in appropriate deliveries over the 2 year period 2017-19. It is anticipated that the NHS England National GIRFT (Getting it Right First Time) program which is underway in England and uses a series of national benchmarking data to support clinician to clinician discussions regarding quality improvement will provide further support and encouragement to improve outcomes in this vulnerable group.[41]

Research has an important role to play in improving care. In the UK we have been able to confirm the findings of the influence of place of birth[42], the importance of neonatal nurse staffing[43] and of transfer[44], and the impact of networks themselves.[45] A study to assess the feasibility of a trial for mode of delivery for preterm birth is ongoing[46] but more basic research is needed into markers of maternal and fetal wellbeing to best plan when and how to deliver women. Central real time monitoring is key to ensuring steady and continuing improvement in care and that the desired developments occur.

Further leverage can be actioned by ensuring that patient/parent representatives are closely involved in these processes to give legitimacy and context to national and regional policy. To that end all of our Network boards and national oversight groups have affiliated parent groups attached to them as part of their structure.

Conclusions

Improved neonatal outcomes after birth at extremely low gestational ages can only be achieved by integrated teams working across health structures, supported by parent representatives and in close liaison with commissioners. Coordinated investment in services, transparent monitoring processes and structured quality improvement support are required to drive quality for this vulnerable and very high-risk group with the clear aim to improve long term outcomes for both the mother and her infant.

Knowledge Gaps (•) and Research Priorities (o)

- Information about maternal outcomes following extremely preterm birth is lacking
    - Studies of neonatal outcomes should include key maternal morbidities
    - Trials of maternal management and interventions during labour and delivery focussing on maternal outcomes are required
- Continual reporting of extremely preterm mortality and neonatal/infant morbidities based on regional populations is critical to understanding the effects of regionalisation
    - Monitoring and regular publication of regional outcomes will provide accurate and contemporary outcome data on which to base counselling
- Effective systems for triaging women at risk of extremely preterm birth, to avoid pressure on regional centres, are required
    - Trials of different strategies to make decisions on transfer are needed
- Professionals would benefit from training in communication to ensure that prospective parents are engaged in a shared decision-making process
    - Studies of real counselling conversations and training in communication strategies will improve engagement of parents

Conflict of Interest

NM declares Consulting fees with Novartis and Takeda outside the published work, other authors declare no conflicts of interest.

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Figure: Survival in the UK for births 22-26 weeks of gestation in 2016: data abstracted from MBRRACE-UK supplemental report for births in 2016[47]

References

1. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR, Grp EPS. The EPICure study: Outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000;**106**(4):659-71 doi: 10.1542/peds.106.4.659[published Online First: Epub Date]|.
2. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. The New England Journal of Medicine 2000;**343**(6):378-84 doi: 10.1056/NEJM200008103430601[published Online First: Epub Date]|.
3. Silverman WA. 'Acceptable' and 'unacceptable' risks. Paediatric and perinatal epidemiology 2002;**16**(1):2-3
4. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012;**345**:e7976 doi: 10.1136/bmj.e7976[published Online First: Epub Date]|.
5. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ 2012;**345**:e7961 doi: 10.1136/bmj.e7961[published Online First: Epub Date]|.
6. Tyson JE, Parikh NA, Langer J, et al. Intensive care for extreme prematurity--moving beyond gestational age. The New England Journal of Medicine 2008;**358**(16):1672-81 doi: 10.1056/NEJMoa073059[published Online First: Epub Date]|.
7. Mercurio MR, Carter BS. Resuscitation policies for extremely preterm newborns: finally moving beyond gestational age. Journal of Perinatology 2020;**40**(12):1731-33 doi: 10.1038/s41372-020-00843-4[published Online First: Epub Date]|.
8. Wilkinson AR, Ahluwalia J, Cole A, et al. Management of babies born extremely preterm at less than 26 weeks of gestation: a framework for clinical practice at the time of birth. Archives of Disease in Childhood. Fetal and Neonatal Edition 2009;**94**(1):F2-5 doi: 10.1136/adc.2008.143321[published Online First: Epub Date]|.
9. Mactier H, Bates SE, Johnston T, et al. Perinatal management of extreme preterm birth before 27 weeks of gestation: a framework for practice. Archives of Disease in Childhood. Fetal and Neonatal Edition 2020;**105**(3):232-39 doi: 10.1136/archdischild-2019-318402[published Online First: Epub Date]|.
10. Norman M, Hallberg B, Abrahamsson T, et al. Association Between Year of Birth and 1-Year Survival Among Extremely Preterm Infants in Sweden During 2004-2007 and 2014-2016. JAMA 2019;**321**(12):1188-99 doi: 10.1001/jama.2019.2021[published Online First: Epub Date]|.
11. Torchin H, Morgan A, Ancel P-Y. International comparisons of neurodevelopmental outcomes in infants born very preterm. Seminars in Fetal and Neonatal Medicine 2020; Jun;25(3):101109. doi: 10.1016/j.siny.2020.101109.
12. De Proost L, Ismaili M'hamdi H, Verhagen A, Reiss I, Geurtzen R, Verweij EJJ. On the limits of viability: toward an individualized prognosis-based approach. Journal of Perinatology 2020;**40**(12):1736-38 doi: 10.1038/s41372-020-00793-x[published Online First: Epub Date]|.
13. Wilkinson D. *Death or Disability?: The 'Carmentis Machine' and decision-making for critically ill children*. Oxford: OUP, 2013.
14. Nuffield Council on Bioethics. Critical care decisions in fetal and neonatal medicine: ethical issues. Report of a Working Group. London: Nuffield Council on Biothethics, 2006.
15. National institute for Health and Care Excellence. Developmental follow-up of children and young people born preterm. London: NICE 2019.
16. National Neonatal Audit Programme. National Neonatal Audit Programme (NNAP) 2020 annual report on 2019 data. London: Healtcare Quality Improvement Partnership, 2020.
17. Marlow N, Ni Y, Lancaster R, et al. No change in neurodevelopment at 11 years after extremely preterm birth. Archives of Disease in Childhood. Fetal and Neonatal Edition 2021; 2021 Jan 27;fetalneonatal-2020-320650.

18. BAPM. Standards for Hospitals providing Neonatal Intensive Care. London: British Association of Perinatal Medicine, 1996.
19. Marlow N, Gill AB. Establishing neonatal networks: the reality. Archives of Disease in Childhood-Fetal and Neonatal Edition 2007;**92**(2):F137-F42 doi: 10.1136/adc.2005.086413[published Online First: Epub Date]|.
20. NHS England and NHS Improvement. Implementing the Recommendations of the Neonatal Critical Care Transformation Review. London: NHS England, 2019.
21. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. Archives of Disease in Childhood. Fetal and Neonatal Edition 2014;**99**(3):F181-8 doi: 10.1136/archdischild-2013-305555[published Online First: Epub Date]|.
22. Ryan GM, Jr. Toward improving the outcome of pregnancy Recommendations for the regional development of perinatal health services. Obstetrics and Gynecology 1975;**46**(4):375-84
23. Lasswell SM, Barfield WD, Rochat RW, Blackmon L. Perinatal regionalization for very low-birth-weight and very preterm infants: a meta-analysis. JAMA 2010;**304**(9):992-1000 doi: 10.1001/jama.2010.1226[published Online First: Epub Date]|.
24. Shahroor M, Lehtonen L, Lee SK, et al. Unit-Level Variations in Healthcare Professionals' Availability for Preterm Neonates <29 Weeks' Gestation: An International Survey. Neonatology 2019;**116**(4):347-55 doi: 10.1159/000501801[published Online First: Epub Date]|.
25. Gallagher K, Martin J, Keller M, Marlow N. European variation in decision-making and parental involvement during preterm birth. Archives of Disease in Childhood. Fetal and Neonatal Edition 2014;**99**(3):F245-9 doi: 10.1136/archdischild-2013-305191[published Online First: Epub Date]|.
26. RCOG. Perinatal Management of Pregnant Women at the Threshold of Infant Viability– the Obstetric Perspective Scientific Impact Paper London: RCOG, 2014.
27. Morgan AS, Waheed S, Gajree S, Marlow N, Davi. AL. Maternal and infant morbidity following birth before 27 weeks of gestation: a single centre study. Scientific Reports 2021; 11:288 https://doi.org/10.1038/s41598-020-79445-1
28. Gallagher K, Marlow N, Edgley A, Porock D. The attitudes of neonatal nurses towards extremely preterm infants. Journal of Advanced Nursing 2012;**68**(8):1768-79 doi: 10.1111/j.1365-2648.2011.05865.x[published Online First: Epub Date]|.
29. Gallagher K, Aladangady N, Marlow N. The attitudes of neonatologists towards extremely preterm infants: a Q methodological study. Archives of Disease in Childhood. Fetal and Neonatal Edition 2015 doi: 10.1136/archdischild-2014-308071[published Online First: Epub Date]|.
30. Chan K, Kean L, Marlow N. Staff views on the management of the extremely preterm infant. EJOG 2006;**128**(1-2):142-47
31. Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. The New England Journal of Medicine 2015;**372**(19):1801-11 doi: 10.1056/NEJMoa1410689[published Online First: Epub Date]|.
32. Stock SJ, Wotherspoon LM, Boyd KA, et al. Study protocol: quantitative fibronectin to help decision-making in women with symptoms of preterm labour (QUIDS) part 2, UK Prospective Cohort Study. BMJ Open 2018;**8**(4):e020795 doi: 10.1136/bmjopen-2017-020795[published Online First: Epub Date]|.
33. Watson HA, Carlisle N, Kuhrt K, et al. EQUIPTT: The Evaluation of the QUiPP app for Triage and Transfer protocol for a cluster randomised trial to evaluate the impact of the QUiPP app on inappropriate management for threatened preterm labour. BMC Pregnancy and Childbirth 2019;**19**(1):68 doi: 10.1186/s12884-019-2210-1[published Online First: Epub Date]|.
34. England N. Saving Babies' Lives Version Two: A care bundle for reducing perinatal mortality. London: Maternity Transforamtion Programme, 2019.

35. Brantley MD, Davis NL, Goodman DA, Callaghan WM, Barfield WD. Perinatal regionalization: a geospatial view of perinatal critical care, United States, 2010-2013. AJOG 2017;**216**(2):185 e1-85 e10 doi: 10.1016/j.ajog.2016.10.011[published Online First: Epub Date]|.
36. Department of Health. Toolkit for High Quality Neonatal Services. London: Department of Health, 2009.
37. Neonatal Critical Care Clinical Reference Group. Neonatal Service Specification. Secondary Neonatal Service Specification 2015. https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-e/e08/.
38. HQIP. National Materity and Perinatal Audit. Secondary National Materity and Perinatal Audit 2020. https://maternityaudit.org.uk/pages/home.
39. BAPM. Secondary 2020. https://www.bapm.org/pages/191-resources.
40. England N. Secondary 2020. https://healthinnovationnetwork.com/projects/maternity-neonatal-health-safety/.
41. NHS Improvement. Secondary 2020. https://www.gettingitrightfirsttime.co.uk/medical-specialties/neonatal-intensive-care/.
42. Watson SI, Arulampalam W, Petrou S, et al. The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: retrospective population-based cohort study. BMJ Open 2014;**4**(7):e004856 doi: 10.1136/bmjopen-2014-004856[published Online First: Epub Date]|.
43. Watson SI, Arulampalam W, Petrou S, et al. The effects of a one to one nurse to patient ratio on the mortality rate in neonatal intensive care: A retrospective, longitudinal, population-based study. Archives of Disease in Childhood Fetal & Neonatal Edition 2016;**101**:F195-200
44. Helenius K, Longford N, Lehtonen L, et al. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. BMJ 2019;**367**:l5678 doi: 10.1136/bmj.l5678[published Online First: Epub Date]|.
45. Gale C, Santhakumaran S, Nagarajan S, et al. Impact of managed clinical networks on NHS specialist neonatal services in England: population based study. BMJ 2012;**344**:e2105 doi: 10.1136/bmj.e2105[published Online First: Epub Date]|.
46.Cassava Study 2019. https://www.ed.ac.uk/centre-reproductive-health/cassava.
47. Smith LK, Draper ES, Manktelow BN, Fenton A, Kurinczuk JJ, Collaboration. obotM-U. MBRRACE-UK Supplementary report on survival up to one year of age of babies born before 27 weeks gestational age for births in Great Britain from January to December 2016. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester., 2019.