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EDITORIAL

The future of perinatal research

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Abstract

Perinatal clinical, biomedical, and life sciences research are important means of improving the health and well-being of mothers and infants, and as health in infancy can establish life-long trajectories, adult health as well. In this brief paper, I will discuss the need for and importance of perinatal research, some of the many challenges facing this at the present time, the damage arising from continuing as we are, and the benefits of adopting a new approach. I suggest a way forward, accepting that this will not be easy.

Need and importance

Neonatal research is an area of great global need and universal importance. Yet, only 2.5% of trials in the Cochrane Central Register involve neonates [1], over two-thirds of Cochrane neonatal reviews are inconclusive because included trials are too small and/or methodologically weak [2], and the number of neonatal trials is diminishing [3]. Only one medicine, surfactant, has ever been developed specifically for neonates [4] and over 90% of medicines for neonates are prescribed off-label or off-license, increasing the risk of adverse effects as efficacy, safety, and dose data are inadequate [5]. Only one medicine specifically for use in pregnancy (atosiban) has been licensed in four decades and only five (amoxicillin, labetalol, diazoxidine injection, doxylamine with pyridoxine, sodium feredetate) are licensed for non-obstetric pregnancy use in the UK [6]. Astonishingly, 98% of all marketed medicines, including all covid-19 vaccines, have either insufficient or no safety data to guide dosing during pregnancy and lactation [7].

Meanwhile, a major adverse pregnancy outcome, preterm birth, is rising world-wide. The greatest burden of preterm births and deaths (over 80%) is in low-income countries, especially sub-Saharan Africa and Asia [8]; yet, these regions are rarely represented in perinatal studies. In high income countries, over 95% of very preterm infants survive to go home but though preterm survival has improved, neurocognitive outcomes have not, though the reasons are unclear [9]. This is an important knowledge gap as cognitive development is the principal determinant of adult educational, economic, and societal attainments. There is also a growing body of epidemiological evidence from around the world indicating that individuals born preterm are at higher risk of early onset of a range of chronic non-communicable diseases associated with ageing, including reduced longevity, cardiovascular, renal, and respiratory disorders, and types 1 and 2 diabetes, with typical odds ratios ranging from 1.5 to 3.0 [10–14]. These chronic conditions are now responsible for 41 million (7 out of every 10) annual global deaths [15]. Inter-generational transmission is worsening these problems, as a woman born preterm is more likely to deliver preterm, and the child of an obese mother is more likely to become obese. Thus, better understanding of the factors in early development that drive cognitive development and the risks of chronic non-communicable diseases in later life would be of enormous importance to population health around the world [16].

However, despite both need and importance, there are considerable uncertainties in the evidence to inform perinatal clinical practice; the research and development pipeline for pregnancy and newborn medicines, devices, and diagnostics is precarious; and efforts to identify preventive and public health measures and implement health policies to improve pregnancy and newborn outcomes are seriously lacking.

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Challenges

There are challenges in every aspect and every sector involved in perinatal research. A paucity of basic science research means that mechanisms of action of interventions, and targets for drug development are too often unknown. Efficacy and safety are likely to differ in relation to precision medicine factors such as sex, gestational age, and degree of growth restriction, and in high- and low-income settings given the wide variation in confounding factors. However, large-scale, internationally collaborative studies that have sufficient power to identify meaningful effects are rare. A willingness to be involved in reducing uncertainties in clinical practice requires research literacy among practitioners and public, and an understanding of the benefits of setting aside personal beliefs in favour of objective evidence-generation. Research literacy is also essential to combat the spread of false information and ability of the public and professionals to understand the nature of evidence, and assess the reliability of claims.

Business perspectives

Commercial considerations rather than disease burden and patient need, all too often drive decision-making in relation to the development of new treatments, diagnostics, and devices. Thus, the last 2 years have seen the development of promising new neonatal therapies halted at phase 2/3 stage until alternative sponsors could be identified. Instances such as this add considerably to the time, burden, and cost of getting products to market, and to the mistrust in which many parents and clinicians hold commercially sponsored studies. Notably, the development of newborn medicines remains limited despite US Food and Drug Administration and European Medicines Agency incentives to pharmaceutical industries [17].

Even when research has provided answers, implementation can be slow and in the case of public health measures, often blocked by commercial lobbying and/or siloed decision-making, e.g., despite clear evidence from a landmark randomised controlled trial carried out a quarter of a century ago, of the effectiveness of supplementation in reducing neural tube defect pregnancies, the introduction of folic acid fortification of foodstuffs has still not been implemented in the majority of countries including across Europe [18].

Waste and cost

Research waste occurs when studies do not generate meaningful outcomes. Research waste was estimated to cost US$85 billion in 2009 and there has been little improvement [19, 20]. Even the most casual perusal of Cochrane Library reviews makes evident the large number of trials that are methodologically weak or are too small to be able to identify clinically important differences in outcomes. This is also damaging to trust because parents who give their consent to the participation of their baby do so in the belief that the study will provide information that will improve the care of other infants. Studies may be done with the best of intentions, but they must be designed to reach reliable conclusions if they are to benefit patients. This does not necessarily mean mega-trials are the only meaningful approach; for example, a small study can be designed with a planned meta-analysis in mind; this requires expertise in trial design and analysis. Phase 3 effectiveness studies will often require international collaboration but variation in regulatory requirements, data sharing permissions, and the reluctance or inability of many public sector funders to combine forces with agencies in other countries, adds considerably to the difficulty in conducting such studies. These problems are not insurmountable, but they do pose major challenges.

The cost of bringing new medicines to market has been widely discussed in relation to industry-led research and development. A "Clinical Trial Cost Study" conducted in 2016 indicated the median cost of a study from protocol approval to final report at US$3.4 million for phase I trials, $8.6 million for phase II trials and $21.4 million for phase III trials [21]. The same study estimated that staff costs make up 37% of the total for an average phase III trial, outsourcing and preparation of contracts approximately 20% each, with the remaining fifth assigned to an "other costs" category.

Less has been said about the costs of research to resolve uncertainties in clinical practice, large-scale effectiveness trials, and other studies that benefit patients and public health. These are of enormous importance but usually only funded by public sector agencies and charities with limited resources. Identification of long-term effects can take many years, adding further to the cost and burden of perinatal studies. Reducing costs and making research more efficient is thus essential [22].

A skilled workforce

Another important barrier to good research is a lack of skilled personnel. Successful research requires the expertise of basic scientists, methodologists, trialists, statisticians and health economists, the involvement and engagement of patients, parents and the public, and the skills of administrators, project managers, and data managers, no less the acumen of clinicians able to identify important evidence gaps and patient needs.

Few countries have defined career pathways for clinical academics or other research personnel. The UK benefited enormously from having a clear clinical academic training pathway for doctors and nurses, and joint appointments

across universities and the National Health Service (https://www.medschools.ac.uk/studying-medicine/after-medical-school/academic-medicine). Personal discussion with colleagues across Europe, Asia, and the Americas, indicates that globally there is a huge lack of structured training and secure career progression opportunity for clinical academics. A particularly pernicious, but little discussed obstacle is the perception in some countries, especially those that have a strong private healthcare sector and a weak public health system, that a wealthy physician with a large private practice is held in higher esteem than a clinical academic.

Clinician bias

Clinicians strive to do their best for their patients, The Hippocratic Oath requires practitioners to "first do no harm". Through this dictum remains true, the way in which practitioners must "first, do no harm" has altered. The Hippocratic oath was formulated in a bygone era, long before the concept of evidence as the basis for safe and effective practice was recognised, in a time when individual experience was paramount. With an appreciation of the necessity for evidence, has come a responsibility to help generate evidence. I have suggested that the responsibility to "strive to reduce uncertainties in care" should be recognised as a modern-day addition to the Hippocratic oath [23]. The need for such recognition is illustrated by the continued, and understandable, problem of clinician bias. Clinicians have personal views and beliefs. But these can get in the way of attempts to obtain objective evidence. Individual clinicians often continue to hold fast to strongly held views and are unwilling to put these uncertainties to the test of randomisation. Poorly evidenced clinical practice, although often endorsed by expert opinion, is a patient safety issue. I have argued that where there is uncertainty in relation to treatments already in wide use, randomisation is the most ethical approach. This is because randomisation gives every infant a fair and equal chance of receiving the unknown optimal treatment. In contrast, clinician bias imposes the same treatment on every patient with the risk that this might be the wrong choice, and the inevitable consequence that the uncertainty will continue. By way of example, I point to the protracted resistance to putting the routine use of 100% oxygen for neonatal resuscitation to the test of randomisation [24]. When trials were finally completed, this practice of decades, taught to countless millions of practitioners, was shown to be harmful; routine oxygen supplementation is no longer advised.

Research regulation

A paternalistic approach to research regulation in which the protection of the research "subject" often outweighs reasonable consideration of the rights of pregnant women and infants to benefit from research is another barrier. The COVID-19 pandemic underlined many of the consequences of this prevailing paradigm. Lack of trial data driven by the exclusion of pregnant and lactating women from the first wave of clinical trials even though there was little biological justification to do so, led inevitably to inconsistent messaging from authorities around the world, contributing to the lack of protection afforded to many women and their babies, and increasing vaccine hesitancy [25]. In an editorial in the British Medical Journal, we recently described clear routes to improvement including a requirement for "maternity investigation plans", similar to the "Paediatric investigation plans" introduced in 2007 in Europe through legislation [26]. These would require the default inclusion of perinatal populations in clinical trials unless there are clear scientific grounds not to do so, prioritisation of developmental and reproductive toxicology studies at the start of the development of a medicine, physiologically based pharmacokinetic modelling, ensuring the right mix of experts in trial development, and steering and monitoring committees, and requiring the involvement of women and organisations representing their and their babies' interests [27].

Doing better

These many challenges are stifling attempts to improve perinatal health and care, and in so doing are undermining health in adults, their economic and societal contributions, and increasing the transmission of health disadvantage to subsequent generations. Recognition of the need to strengthen research to improve perinatal health and care would bring benefits not only to individuals, but also to societies and economies worldwide [28].

Bringing about change requires both vision and strategy. The vision must be progressive prevention of adverse pregnancy outcomes, and incremental improvement in the evidence-base for clinical practice. The strategy must be presentation of a multi-faceted pipeline encompassing investment in basic perinatal science, building, and sustaining a research workforce, growing research literacy among the public and the clinical workforce, creating collaborative infrastructure, persuading funders to eschew a national focus in favour of collaborative international studies and addressing the reluctance regulators to tailor requirements to the need of mothers and infants.

Ensuring studies deliver patient benefit requires scrutiny by expert, unbiased panels, and often powerful advocacy directed at government agencies. Research involving mothers and babies would benefit from the inclusion in panels of members with good understanding of perinatal issues, no less a cadre of investigators able to compete successfully in a highly competitive funding arena. It also requires political

will to ensure industry receives a just—not excessive—return on research and development, and that their standards of practice are such that clinician, patient, and public trust in their efforts is justified.

To bring this vision about is no small undertaking. So, it is pertinent to ask whose responsibility is it to improve matters? Infants cannot speak for themselves; they cannot lobby like many adult patient groups have done so effectively; they need advocates. Effective advocacy requires an understanding of the need for evidence, and the wide personal and societal benefits that would result from improved newborn health and wellbeing. I suggest that professional societies, in collaboration with parents, are best placed to lead the charge. All major perinatal societies recognise the importance of research. However, their contributions to-date have generally been limited to disseminating research at conferences and occasionally providing limited research funding. They understand the need and can assemble the collaborative voices of clinicians, families, educators, scientists, and economists, to define a long-term strategy for perinatal research, and present a compelling case to funders, regulators, policy-makers, and politicians. I have the privilege to be president-elect of the European Society of Perinatal Research. I invite other societies to join with us to tackle this challenge.

Author's Contributions NM wrote this article following an invitation from the journal editors.

Declarations

Ethics approval Not applicable.

Competing interests NM is president-elect of the European Association of Perinatal Medicine and past-president of the Neonatal Society, Academic Paediatrics Association of Great Britain and Ireland, Medical Women's Federation, British Medical Association and Royal College of Paediatrics and Child Health. The views expressed are her own.

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