Suggested Title: Time to address the knowledge gaps for late preterm birth

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Late preterm babies, born between 34+0 and 36+6 weeks of gestation, account for around 6-7% of all births and for three quarters of all preterm births. It is perhaps surprising therefore that for years, such a large population of babies, has been regarded with a degree of disinterest by clinicians. However, the large majority appear well at birth, spend only a short time in hospital compared with their very preterm counterparts, and for the most part do not cause anxiety for neonatologists and paediatricians; in addition, many do well in the long term. Their larger size and apparent maturity, and presumed good outcomes have all led to these babies being managed postnatally in much the same way as those born at term.

It is only in relatively recent years that the appropriateness of this approach has been questioned, prompted first by the finding that mortality was increased in this population compared with those born at 37 or more weeks of gestation[1]. Since then, interest has grown immensely and retrospective and prospective studies have consistently confirmed an increased risk of adverse outcomes in terms of mortality and both neonatal and long-term morbidity in the late preterm group[2-4]. Indeed, it now appears that a gradient of risk exists across the whole spectrum of gestational age, with even early term birth at 37-38 weeks associated with measurable increased risks compared with birth at 39 -41 weeks, which is now regarded as full term[5]. In this issue, two papers address the challenges of late preterm birth.

Luna et al use population-based data from Spain to retrospectively compare outcomes at discharge from hospital in the neonatal period, at 30 days and at one year between hospitalised healthy late preterm infants and hospitalised normal term-born infants [6]. The authors comment that, although described as healthy, infants in the control group were hospitalised. This suggests that they may have been more likely to have had minor or suspected morbidities or transitioning difficulties in than non-hospitalised babies. This selection bias is likely to explain their finding that only poor fetal growth and disorders associated with prematurity were increased in the late preterm group. This is

in contrast to most previous studies, which have reported increases in most neonatal morbidities in late preterm compared with term born babies. For hospital readmissions, however, we see a pattern emerging that is more similar to the findings of other researchers[7]. Readmission rates are commoner in the late preterm group at both 30 days and one year; jaundice, possibly driven by feeding difficulties, is the most common cause in the first month of life, and there are high rates of respiratory admissions in infancy. They also highlight a vulnerability, which has been described previously[8], to respiratory syncytial virus (RSV) infection, in these babies who do not meet criteria for RSV prophylaxis in many health care systems. The authors conclude that late preterm birth *per se* should be viewed as a high-risk condition for morbidity and mortality when compared to healthy term newborn infants.

Since outcomes have become better defined and there has been an increasing research focus on late preterm birth, the question that is now taxing researchers is why, in this population previously regarded as low risk, should outcomes be worse and perhaps more importantly, what should be done about it? As an area of research however, it is still developing and so understandably, much of the available data from observational studies simply describes the outcomes. Few studies have sought to tease out whether adverse outcomes in this population are attributable solely to immaturity, or whether there are some groups of babies at greater risk than others. Bonnevier and colleagues report such a study in which they used data from singleton births in Sweden, with the aim of determining the impact of maternal and pre-pregnancy conditions and the effect of gestational age on health of late preterm infants[9]. They used a hierarchical system to explore relationships between late preterm infant outcomes and the underlying reasons for delivery, including PPROM, hypertensive disease, pre-gestational diabetes and placental disorders. As might be expected, over half of late preterm births and more than 90% of term births did not have complications. Almost a quarter of deliveries were by caesarean section. The results demonstrated an increased risk of

morbidities in the late preterm group compared with the term group, and decreasing risk with increasing gestational age as shown in previous studies. On closer investigation using multiple regression with adjustment for potential confounders, they found a relationship between neonatal morbidity and underlying medical conditions in a substantial proportion of births. Where PPROM was the cause of preterm birth, in the absence of other major complications the risk in this study was lowest. Respiratory disease appeared to be related to prematurity per se.

There are still large gaps in knowledge about late preterm birth and its associated outcomes and a two-pronged approach is needed to develop a robust evidence base. It is encouraging to see researchers now exploring the potential reasons for adverse outcomes in late preterm infants. While the results of the small number of studies to date do not provide sufficient evidence to influence practice, they represent an important move in the right direction and will serve to fuel further research. It is neither feasible nor necessary to provide intensive monitoring in the neonatal period or long-term follow-up for all late preterm babies, so some method of identifying higher risk groups is crucial to allow targeted care and intervention for those who need it. However, there is also substantial uncertainty about how to optimise neonatal care for these babies to minimise the risk of adverse outcomes. There are few, if any, data from randomised controlled trials of neonatal or early childhood interventions in this population and therefore delivery of care and management of common conditions is subject to huge variation. In contrast, the effects of very preterm birth have been extensively studied over many years and the balance should be redressed. Although long-term morbidities in the late preterm population are generally less severe than those of very preterm babies, they are measurable and may have important far reaching consequences for much larger numbers of babies and for health care services. There is a need both to understand the mechanisms by which adverse outcomes occur and also to develop clinically and cost effective management and treatment strategies to improve care for affected babies.

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