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Clinical outcomes for babies born between 27 – 31 weeks of gestation: Should they be regarded as a single cohort?

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ABSTRACT

Preterm babies born between 27 and 31 weeks of gestation are understudied and historically, have been grouped as a single cohort. Increased evidence relating to clinical outcomes is shaping models of care for babies born ≤26 weeks of gestation. Similar consideration of births between 27 and 31 weeks of gestation is now warranted. To address this, a clear understanding of the impact of progressive maturation *in utero* on the clinical care required, and on neonatal and infant outcomes of this group of preterm babies is helpful.

In this review we highlight the spectrum of clinical presentations for babies born at 27–31 weeks of gestation. We discuss this with respect to key stages of organ/system development occurring in-utero during this five-week period and reveal a consistent trend of decreasing incidence of mortality and major morbidity with increasing gestational age at birth from 27 to 31 weeks. The clinical care required and the outcomes between babies born at either end of this gestational age range appear to be substantially different. This suggests it may be more appropriate to report outcomes by week of gestation rather than as a group in future research. Preterm health service delivery providers and decision makers need to consider this in planning services for the future, especially in environments where neonatal intensive care resources ought to be optimised for those at greatest need.

1. Introduction

Within the UK, babies born below 27 weeks of gestation are recommended to be born in maternity services attached to neonatal intensive care units (NICU). For those babies born between 27 and 31 weeks of gestation, care can be delivered in maternity services attached to either a NICU or a local neonatal unit (LNU). While the first recommendation is evidence based (Marlow et al., 2014; Watson et al., 2014), our systematic review found a paucity of evidence for optimal location of birth and care for babies born between 27 and 31 weeks (Ismail et al., 2020).

This reflects a more general lack of research aimed at babies born between 27 and 31 weeks of gestation. During our systematic review we found that most of the data available for this population comes from subgroup analyses in studies of larger gestational age ranges (Ismail et al., 2020; Lasswell et al., 2010). Of these, most report outcomes for this group as a whole rather than by gestational week (Watson et al., 2014). Neonatal research is logistically difficult, especially in relation to very preterm babies, as the population size decreases with each extra gestational week of prematurity. Therefore, it is common practice to cohort babies. While not ideal, this makes more sense for certain gestational age ranges than others.

Babies born between 27 and 31 weeks do not form a 'natural' cohort as do those born extremely preterm. There is a significant degree of heterogeneity in the clinical presentation between babies born at either end of this spectrum. Over this five-week period the foetus is undergoing significant growth and developmental changes in-utero. In this review we describe the limited available literature on the variation in clinical presentation and outcomes for babies born between 27 and 31 weeks of gestation in the context of fetal developmental biology and preterm birth. In doing so, we highlight the importance of future research reporting gestation specific outcomes for preterm babies in general, but especially this cohort.

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2. Survival and key morbidities for babies born at 27–31 weeks

Table 1 and Fig. 1 summarises outcomes for major neonatal morbidities by each week between 27 and 31 weeks of gestation. They include international mortality data from national statistical bodies. An identical trend is evident for all, demonstrating increasing incidence with decreasing gestational age and substantially different outcomes for the most preterm babies within this gestational age range compared to the most mature. There is, on average, a greater than 4-fold difference in mortality between babies born at 27 weeks of gestation compared to 31 weeks, and a 4-fold increase in rates of survival to discharge without morbidity for babies born at 30 weeks compared to 27 weeks.

3. Understanding postnatal outcomes through the lens of foetal development

The medical and nursing care required for babies in this group is likely to be more intense for those at the lower than the higher end of the gestational age spectrum, based on their degree of immaturity, and existence of co-morbidities (Table 1).

3.1. Respiratory system

Babies born at the lower end of this gestational age range are often first supported with non-invasive ventilation (NIV) if they display sufficient respiratory drive and have a good heart rate. Those that do not will be intubated and invasively ventilated within delivery suite, and a proportion of those who initially managed on NIV may require subsequent intubation and ventilation due to significant apnoea and/or respiratory failure. These babies may benefit from a dose of surfactant and regular caffeine, with the aim to extubate onto NIV as soon as appropriate, to minimise ventilator associated lung injury while still providing an adequate level of support, which may be required for several weeks. In contrast, the majority of babies born at the upper end of this gestational age range will only require a brief period of NIV, usually in the form of high flow nasal prong oxygen or continuous positive airway pressure (CPAP) support.

How can we understand this in the context of foetal development? In-utero breathing stimulates lung growth (Harding and Hooper, 1985). By 24–28 weeks, fetal breathing movements occur for 10–20% of the time, increasing to 30–40% by 30 weeks (Fraga and Guttentag, 2012). Correspondingly, during the saccular stage of fetal lung development (24–26 weeks to 36–38 weeks), surface area for gas exchange increases as does vascularisation and surfactant production. Following preterm birth, this immaturity of central respiratory drive manifests as periods of hypoventilation and apnoea, the incidence falling from 54% at 30–31 weeks to 7% at 34–35 weeks (Henderson-Smart, 1981). In those born at 24–27 weeks, apnoeic episodes are more likely to continue for longer compared to those born ≥28 weeks (Eichenwald et al., 1997). Therefore, respiratory compromise, the need for mechanical ventilation and intensive care support is more likely with increasing prematurity, with the incidence of RDS at 60–80% for babies born at 26–28 weeks, falling to 15–30% by 32–36 weeks [14]. The more immature the lung, the greater the risk of ventilator associated lung injury, abnormal development, and chronic lung disease (CLD) [15]. Its incidence is nine times greater in babies born at 27 weeks than at 31 weeks of gestation (Bolisetty et al., 2015; Egreteau et al., 2001).

3.2. Cardiovascular system

Babies born at 27 weeks of gestation who are difficult to successfully extubate will often be found to have a haemodynamically significant patent ductus arteriosus (PDA) on echocardiography (although clear evidence is lacking for a causal relationship - (El-Khuffash et al., 2019; Benitz et al., 2016)). Management protocols vary unit to unit, but many will commence pharmacological treatment with ibuprofen, or more

Table 1
Summary of outcomes from national statistical bodies ([a]personal communication and published data) and international studies showing heterogeneity with increasing gestational age at birth from 27 to 31 weeks [b]Survival to discharge with severe morbidity, which included grade III/IV IVH, PVL, at least stage III ROP in either eye or requiring surgery, stage III NEC, bronchopulmonary dysplasia (BPD) necessitating oxygen and positive pressure (via non-invasive or invasive ventilation), or >1 episode of infection [c]Severe disease, defined as disease confirmed by laparotomy, histology or autopsy, or documented as primary cause of death.

Reported outcomes		Outcome (%) by gestational week at birth				
		27	28	29	30	31
Mortality	U.K. – England and Wales (Office of National Statistics) (2013) (Office For National Statistics, 2013)	7.7	6.5	3.6	2.2	2.2
	U.K. – Scotland (NHS National Services Scotland) (2007–2012)[a]	11.6	7.1	5.5	4.2	2.0
	U.S. (Centre for Disease Control and Prevention) (2015) (Centers for Disease Control and Prevention, 2015)	6.7	5.6	3.7	2.7	2.3
	Canada (Canadian Perinatal Surveillance System) (2013–2016)[a]	6.5	4.4	2.8	2.4	1.8
	Australia (Australian Institute of Health and Welfare) (2016)[a]	5.1	3.5	2.2	1.6	0.8
	Austria (Statistics Austria) (2015–2017)[a]	7.5	6.1	4.1	3.0	1.6
	Finland (Finnish medical birth register) (2013–2016)[a]	7.9	5.3	4.0	1.4	2.5
	Portugal (Statistics Portugal) (2010–2013)[a]	14.3	7.9	4.8	3.5	2.3
	Netherlands (Infoservice Statistics Netherlands) (2014–2015)[a]	12.0	9.9	3.6	4.0	2.7
	Belgium (Statistics Belgium) (2010–2015)[a]	8.0	5.3	3.5	2.2	1.6
Survival without morbidity (Ge et al., 2013)		10	15	26	39	–
Survival with severe morbidity[b] (Ge et al., 2013)		16	12	10	8	–
Intraventricular Haemorrhage (IVH) (Brouwer et al., 2008; Synnes et al., 2001)	Any	33.0		23.0		17.0
	Severe (≥ grade III)	42.0	38.0			14.0
Periventricular leukomalacia (PVL) (Baud et al., 1999)		9.9			4.2	
Cerebral palsy (Ancel et al., 2006)		12.3	11.0	8.2	8.3	6.8
Necrotising enterocolitis (NEC[c]) (Battersby et al., 2018)		4.2	3.9	1.0	1.0	0.5
Chronic lung disease (CLD) (Bolisetty et al., 2015)		28.1	21.4	11.1	5.9	3.0
Renal failure (Walker et al., 2011)		9.2	6.0	4.0	3.9	–
Retinopathy of prematurity (ROP) (Bolisetty et al., 2015; Larsson et al., 2002)	All	30.5			11.0	
	Severe (≥ stage III)	4.6	1.5	0.2	0.1	–
Patent ductus arteriosus (PDA) (Bolisetty et al., 2015; Clyman, 2012)	Day 7 of life	68.0	33.0		2.0	
	Requiring surgery	4.5	3.0	1.5	0.8	0.4
Sepsis (Bolisetty et al., 2015; Stoll et al., 2002)	Early onset sepsis (EOS)	2.0		0.8		
	Late onset sepsis (LOS)	27.6	17.7	14.7	7.0	5.4

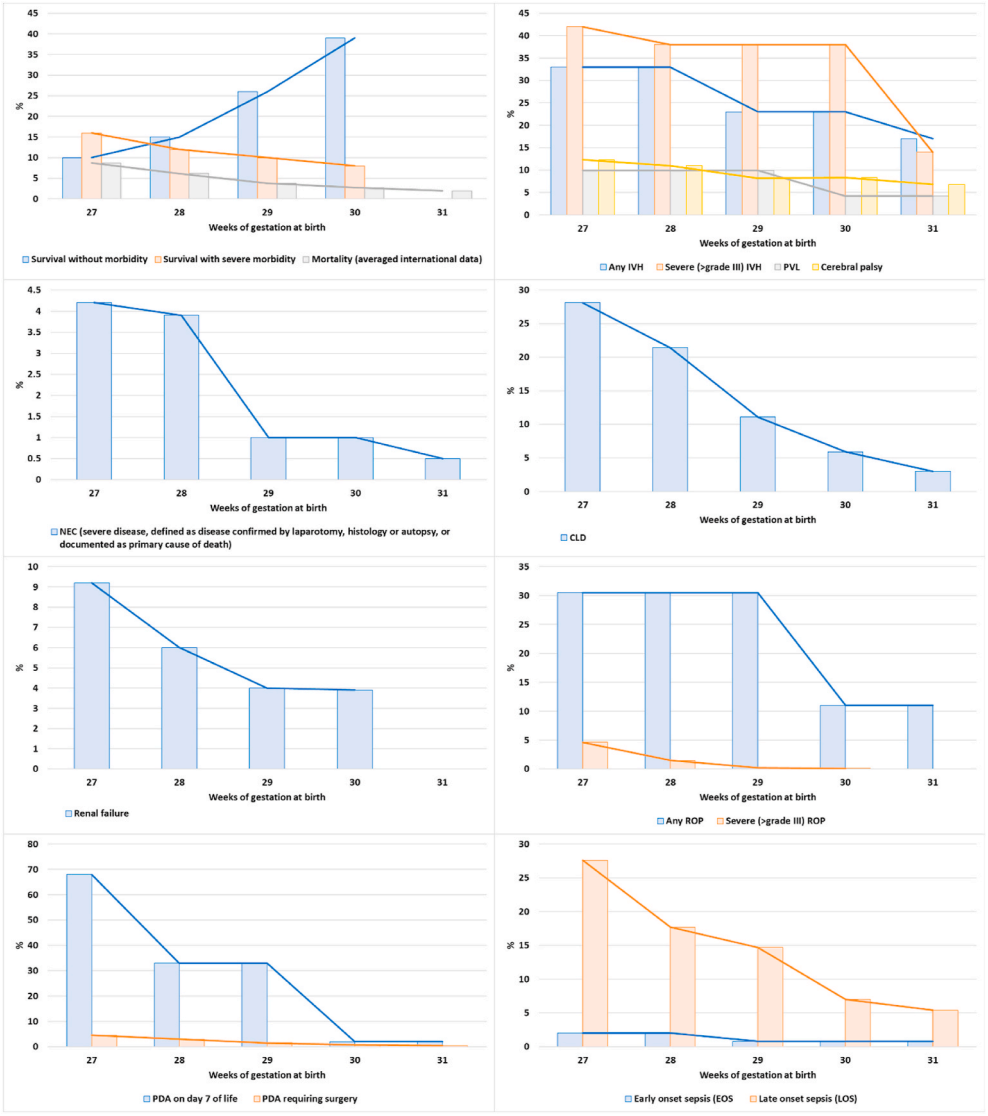

Fig. 1. Graphical representation of mortality and morbidity data (from Table 1) for babies born between 27 and 31 weeks by gestational week of birth.

recently paracetamol. If this is unsuccessful, and on serial echocardiograms there is evidence of developing heart failure, the baby will be referred for surgical ligation. While some babies born at 31 weeks may have clinical signs of a PDA (i.e., a murmur, easily palpable femoral pulses), it is unlikely to be haemodynamically significant and can be left to close on its own. If at the time of discharge these signs are still present, an echocardiogram can provide a definitive diagnosis to arrange appropriate follow-up.

Following preterm birth, constriction of the ductus arteriosus is less likely to occur because of reduced vessel tone and pulmonary clearance of prostaglandins, to which the ductus in preterm babies is more sensitive (Clyman, 2012). This explains the increase in incidence of patent ductus arteriosus (PDA) at day 7 of life with reducing gestation (68%, 33%, and 2% at 26–27 weeks, 28–29 weeks, and ≥30 weeks, respectively) (Clyman, 2012), and a 10-fold increase in the likelihood of requiring surgery for a clinically significant PDA in those born at 27 weeks gestation when compared to those at 31 weeks (Bolisetty et al., 2015).

3.3. Ocular system

Babies born at the lower end of this gestational age range most often require supplemental oxygen as part of their respiratory support. This is carefully titrated to maintain saturations in the target range (91–95%), with aggressive weaning if saturations are consistently >95%. Babies born at the upper end of this gestational age range less frequently require supplemental oxygen, or if they do, for a shorter duration.

In preterm babies, oxygen halts retinal vascularisation through suppression of vascular endothelial growth factor (VEGF) and erythropoietin (Hellstrom et al., 2013; Taeusch et al., 2005). Continued retinal growth and resulting hypoxia restarts VEGF and erythropoietin production causing abnormal neovascularisation, i.e., retinopathy of prematurity (ROP). Gestational age is the most important risk factor (OR 1.79, 95% CI 1.42–2.25) (Larsson et al., 2002). In babies born at 27 weeks who survive to discharge there is a 46-fold increase in incidence of severe ROP compared to those born at 31 weeks (Bolisetty et al., 2015).

3.4. Gastrointestinal system

Birth weights at 27 and 31 weeks reflect a period of rapid in-utero growth, with approximately a 725g averaged difference for babies born on the 50th centile (representing an increase of ~72.5%). Babies born at the lower end of this gestational age range are unlikely to rapidly establish enteral feeds. Therefore, on admission to the neonatal unit central lines are inserted to commence total parenteral nutrition. The

importance of expressing breastmilk for their preterm babies is stressed to the mother, with colostrum being used for mouthcares and trophic feeds, ideally from birth, to prime the gut and establish an appropriate microbiome. Over subsequent days, if supply of mother's milk is lacking parents may be consented for use of donor breastmilk, avoiding use of preterm formula. As enteral feeds are being established, not infrequently an episode of bilious aspirate or abdominal distension will cause the baby to be put nil-by-mouth for several days as part of conservative management of suspected necrotising enterocolitis (NEC). In contrast to this, most babies born at the upper end of this gestational age range will more often be commenced on a peripheral infusion of glucose to maintain hydration and blood sugar levels while nasogastric tube feeds of either mother's milk or preterm formula are quite rapidly established.

Within the third trimester intestinal length doubles and there is an even greater increase in surface area (Neu, 2007). Before 31 weeks there is delayed gastric emptying and intestinal smooth muscle contractions are disorganised (Bisset et al., 1988; Riezzo et al., 2000). From 31 to 34 weeks, contractions begin to cluster, propagation increases from 50% to 90% and gastric emptying time shortens to term equivalent. From 26 to 34 weeks, secretion of digestive enzymes (e.g., maltase, glucoamylase, sucrase), reach 70% of adult levels, and lactase is at 30% of newborn levels (Lebenthal and Lebenthal, 1999). Pancreatic lipase is detected from 30 weeks onward (Lebenthal et al., 1983; Manson and Weaver, 1997), while bile acid concentration is 33%–50% that of term babies. Monosaccharide absorption by day 14 of life is higher in babies born between 28 and 32 weeks compared to <28 weeks (Rouwet et al., 2002). These anatomical, motor, digestive and absorptive functions manifest clinically, with preterm babies born at <29 weeks of gestation taking a longer time to establish full enteral feeds (Kempley et al., 2014).

Episodes of NEC (confirmed or suspected) also contribute towards this delay. Poor absorption and gut stasis leading to bacterial overgrowth in the context of a pathogenic microbiome and impaired gut wall integrity (Choi, 2014). Diastolic steal from the coeliac/mesenteric system secondary to a large PDA has also been hypothesised as a possible risk factor (Ruoss et al., 2020). The incidence of developing severe NEC for babies born at 27 weeks of gestation is 8 times that at 31 weeks (Battersby et al., 2017, 2018).

3.5. Immune system

Babies born at the lower end of this gestational age range are routinely commenced on first line antibiotics for potential early onset sepsis (EOS). Depending on the context of preterm birth, successive C-reactive protein (CRP) tests and blood culture (BC) results, chest radiograph findings and clinical progress, the duration of antibiotics is not infrequently extended. A significant proportion will receive one or more further courses of antibiotics prior to discharge, to treat episodes of late onset sepsis (LOS) and central line associated bloodstream infections (CLABSI). While babies born at the upper end of this gestational age range would also receive antibiotics at birth, the majority do not have any evidence of infection, remain clinically well, and finish the course at 36 h.

Sepsis is a major cause of mortality in preterm babies (Bolisetty et al., 2015; Stoll et al., 2002). There is a >2-fold increase in the incidence of early onset sepsis in babies born at 27 weeks of gestation compared to 31 weeks, and a 5-fold increase in the incidence of late onset sepsis. Neonates rely largely on their innate immune system to protect them from infection (Adkins et al., 2004; Marodi, 2006).

Endothelial cells and neutrophils from babies born between 30 and 36 weeks show reduced adhesion molecule expression and selectin mediated capture, decreasing further in babies born <30 weeks (Nussbaum et al., 2013). Plasma concentrations of the FcRIII receptor (involved in neutrophil phagocytosis (Carr and Huizinga, 2000)) is at 15% term equivalent between 24 and 32 weeks (Carr et al., 1992). Monocytes in babies born <29 weeks have reduced expression of CD14 cell surface markers (Kan et al., 2016). Such antimicrobial pattern recognition receptors (including toll like receptors) continue development until 33 weeks, however, for up to 28 days after preterm birth at <30 weeks, toll like receptor responses are significantly reduced (Marchant et al., 2015). Regarding the complement system, average levels of terminal pathway components, C5, C6, and C8 in preterm babies are at 60–73%, 36–39%, and 29%, respectively, compared to adult levels (McGreal et al., 2012). Considering overall functional capacity, CH50 assay results increase from 32 to 36% at 26–27 weeks, to 52–81% at term.

Physical and external contributing factors, such as skin barrier integrity, repeated invasive procedures and indwelling plastic catheters, are also related to degree of prematurity.

3.6. Renal system

Babies born at the lower end of this gestational age range receive a significant proportion of their hydration/nutrition intravenously, while simultaneously exposed to nephrotoxic drugs, e.g., gentamicin for treatment of suspected EOS, ibuprofen for treatment of a haemodynamically significant PDA, and vancomycin for treatment of CLABSI, warranting close monitoring of their electrolytes, renal function, and fluid balance. In contrast, babies born at the upper end of this gestational age range relatively quickly establish enteral feeds and much less frequently require treatment with nephrotoxic drugs.

The incidence of renal failure is 2-fold higher for a baby born at 27 weeks compared with 30 weeks of gestation (Walker et al., 2011; Jetton et al., 2017). Two thirds of new nephrons form between 28 and 36 weeks, after which no new glomeruli develop (Stritzke et al., 2017; Hinchliffe et al., 1991). Following preterm birth, nephrogenesis can continue for up to 40 days (Rodriguez et al., 2004; Black et al., 2013), but a significant proportion of new glomeruli have cystic dilatation of the Bowman's capsule (Sutherland et al., 2011).

3.7. Neurological system

As routine, babies born at the lower end of this gestational age range will have a cranial ultrasound scan (CrUSS) within the first few days of life, which will be repeated two to three times within the first month. It is not uncommon to diagnose uni/bilateral grade I-II intraventricular haemorrhage (IVH) and increased echogenicity in the periventricular areas even in those babies without any discernible risk factors except prematurity. However, for the more unwell (who may have required a degree of resuscitation, intubation and invasive ventilation, periods of hypoxaemia, hyper/hypocapnia and acidosis, and hypotension requiring fluid expansion and inotropic support), more severe grades of IVH (III/IV) and cystic periventricular leukomalacia (PVL) are more common. This would necessitate increasing the frequency of scanning to monitor for complications (e.g., post-haemorrhagic hydrocephalus) and plan for longer term neurodevelopmental follow-up and support. Babies born at the upper end of this gestational age range are much less likely to experience this degree of homeostatic disturbances and so are routinely scanned once within the first week of life and may not have a second scan until term equivalent or ready for discharge.

This variation in scanning frequency is based on the inverse correlation gestational age at birth has with risk of IVH (Brouwer et al., 2008; Synnes et al., 2001). Babies born at 27–28 weeks have a 2-fold increased risk of developing intraventricular haemorrhage (IVH) of any grade, compared to those born at 31 weeks (Brouwer et al., 2008; Synnes et al., 2001). Severe IVH (stage III/IV) is three times more common in those born at 27 weeks than 31 weeks.

The germinal matrix has a dense supply of fragile blood vessels that are prone to rupture with fluctuations in cerebral blood flow, causing the bulk of what is described in the literature as IVH. The risk is increased due to immature cerebral autoregulation, in which hypoxaemia, hypercapnia, hypocapnia, and acidosis cause pressure passivity (Soul et al., 2007; Tsuji et al., 2000). This, combined with increasing severity of

respiratory illness and homeostatic disturbances in the more preterm baby, may explain the inverse correlation of IVH with gestational age.

The trend is similar for periventricular leucomalacia (PVL) (Luan-ying, 2011). Non-cystic PVL is characterised by hypomyelination (Volpe, 2009). By 28–30 weeks, increasing differentiation of oligodendrocyte progenitors (pre-OL) coincides with the start of myelination (Jakovcevski et al., 2009; Tau and Peterson, 2010), stimulated by microglia that are also proliferating (Menassa and Gomez-Nicola, 2018; Gould and Howard, 1991; Billiards et al., 2006). Hypoxia, infection or inflammation cause pathogenic activation of microglia and death of pre-OL cells through release of reactive nitrogen and oxygen species (RNS/ROS) (Merrill et al., 1993; Haynes et al., 2003).

Preterm babies with severe IVH (grade III/IV) and cystic PVL are at increased risk of cerebral palsy (Himmelmann and Uvebrant, 2014). There is a nearly 2-fold increase in incidence of cerebral palsy for a baby born at 27 weeks compared with 31 weeks of gestation, but the absence of cranial ultrasound abnormalities does not always mean normal neurodevelopment for babies born preterm. *In utero*, cortical volume increases from 13% at 28 weeks to 53% at 34 weeks. Babies born preterm have reduced growth trajectories of their cerebrum, cerebellum, and brainstem compared to the foetus within the last trimester (Bouyssi--Kobar et al., 2016). Each extra week of maturity at birth between 27 and 32 weeks is associated with an increased IQ of 2.5 points (Johnson, 2007).

4. Implications for practice

The degree of clinical support that a preterm baby may receive is graded into intensive care, high dependency and special care (BAPM, 2011). Most babies born at the lower end of this gestational age spectrum require some degree of intensive care support, based on the clinical manifestations of their prematurity. In contrast, the majority of 'well' preterm babies at the upper end may never require intensive care support, but rather high dependency and special care support. This dichotomy in their clinical presentation means that grouping them into a single cohort may have the following consequences:

a) Cohorting this group in terms of decision-making regarding place of birth and care may mean over utilisation of intensive care support for those babies at the upper end of the spectrum. This in turn may limit intensive care availability for those babies who need it, especially in resource and cost constrained environments.
b) Grouping them as a single cohort in the literature makes it more likely significant outcomes for babies at the lower end of this spectrum will be obscured.

5. Conclusion

This review highlights the variation and range of clinical profiles and associated outcomes for babies born between 27 and 31 weeks of gestation, and how these relate to key aspects of organ/system development occurring in-utero during this 5-week period. The data summarised in Table 1 and graphically represented in Fig. 1 consistently demonstrate a gradient of risk across multiple outcomes with rates of mortality and morbidity increasing from birth at 31 to 27 weeks. Outcomes at the two extremes of this range may differ significantly, yet babies born between 27 and 31 weeks of gestation are often regarded as a single entity with respect to place of birth and care, and for research purposes. In future studies relating to very preterm birth, understanding gestation specific morbidities and outcomes may be more informative, compared to outcomes as a single collective group. This may be a useful concept for policy makers involved in preterm health service delivery, and might allow more finely tuned, appropriate utilisation of resources for this group of babies.

Author contributions

AQTI wrote the initial draft of the manuscript. AQTI, EMB, and TP were involved in editing and writing subsequent versions of the manuscript. All have approved the final, submitted version.

Disclosure of interest

The authors have no conflicts of interest to declare.

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