International Journal of Pediatrics and Adolescent Medicine 7 (2020) 36–44

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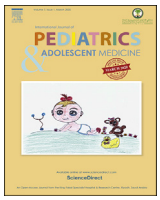
International Journal of Pediatrics and Adolescent Medicine

journal homepage: http://www.elsevier.com/locate/ijpam



Review article

Late preterm infants – Changing trends and continuing challenges

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ARTICLE INFO

Article history:
Available online 25 February 2020

Keywords:
Late preterm infants
Neurodevelopmental outcomes
Respiratory disease
Prematurity

ABSTRACT

Late preterm infants, defined as newborns born between $34^{0/7}$-$36^{6/7}$ weeks of gestational age, constitute a unique group among all premature neonates. Often overlooked because of their size when compared to very premature infants, this population is still vulnerable because of physiological and structural immaturity. Comprising nearly 75% of babies born less than 37 weeks of gestation, late preterm infants are at increased risk for morbidities involving nearly every organ system as well as higher risk of mortality when compared to term neonates. Neurodevelopmental impairment has especially been a concern for these infants. Due to various reasons, the rate of late preterm births continue to rise worldwide. Caring for this high risk population contributes a significant financial burden to health systems. This article reviews recent trends in regarding rate of late preterm births, common morbidities and long term outcomes with special attention to neurodevelopmental outcomes.

1. Introduction

Preterm birth, defined as the delivery of an infant prior to 37 completed weeks of gestation, is the leading cause of neonatal mortality [1,2]. Worldwide, about 15 million preterm babies are born annually [3]. Of the estimated 6.3 million children under 5 who died in 2013, 15.4% (around 1 million) were due to complications of preterm birth. Complications in extremely premature infants have been well studied and reported. The rate of premature births has been increasing most recently mostly secondary to an increase in the number of mature or late preterm births. It has been increasingly recognized that this population is at increased risk for various morbidities as well as mortality. In the last 15 years, this special subset of premature infants has received enhanced attention that resulted in improved clinical research as well as specific policies and guidelines for provision of care.

2. Definitions

The terminology used to classify births based on gestational age or birth weight has undergone various modifications over the last 50 years (Table 1) [4–6]. This classification has been helpful for counseling, clinical management and research. It helps identify the common causes of poor outcomes and to devise specific strategies to address them based on set criteria.

The rate of preterm birth increased by 30% between 1981 and 2003 in the United States (US). Premature babies born close to term were mostly responsible for this increase. Having recognized the increasing numbers and associated morbidities in this group and to emphasize that these infants' needs are similar to other preterm rather than term infants, a workshop conducted by National Institute of Child Health and Human Development (NICHD) defined infants born at gestational ages between $34^{0/7}$ weeks and $36^{6/7}$ weeks as late preterm infants (LPI) [7]. This replaced previous terminology of 'near term'. American Academy of Pediatrics (AAP) endorsed this definition in 2007.

3. Statistics and global burden

World Health Organization (WHO) and other United Nations (UN) agencies have developed standardized global indicators to optimize collection, reporting, and international comparisons of data on conditions and diseases. Though there is information on preterm births in general, there is limited availability of data on the trends of late preterm births in developing countries. This can be due to various factors including lack of uniform definitions,

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Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

https://doi.org/10.1016/j.ijpam.2020.02.006

Table 1
Classification of neonates at birth based on GA or weight.

Gestational Age (GA)	Birth Weight
• Preterm: < 37 completed weeks or 259 days from onset of LMP o Extreme preterm: < 28 weeks o Very preterm: $28^{0/7}$- $31^{6/7}$ o Moderate preterm: $32^{0/7}$ - $33^{6/7}$ o Late preterm: $34^{0/7}$- $36^{6/7}$ • Term: $37^{0/7}$- $41^{6/7}$ weeks o Early term −$37^{0/7}$- $38^{6/7}$ o Full term −$39^{0/7}$–$40^{6/7}$ o Late term −$40^{6/7}$–$41^{6/7}$ • Post term: > $42^{0/7}$ weeks	• Low birth weight: < 2500 gm • Very low birth weight: <1500 gm • Extremely low birth weight: <1000 gm • Micro premie: < 750 gm • Small for GA < 2 SD below mean • Large for GA > 2 SD above mean

inaccuracies in GA assessment, poor data collection and under reporting. Therefore, information on LPIs in these countries need to be extrapolated from available data elsewhere. The vast majority of data on LPIs comes from developed countries. According to 2019 National Vital Statistics report, the U.S. preterm birth rate increased to 10.02% in 2018, up from 9.93% in 2017 [8]. The preterm birth rate declined every year from 2007 (10.44%) to 2014. However, since then it has recorded an increase in 4 consecutive years mostly secondary to an increase in the rate among LPIs which increased to 7.28% in 2018 up from 7.17% in 2017. In absolute numbers, LPIs represented 276,000 total births in 2018. At the same time, earlier preterm birth rates were unchanged. Among other developed countries, the late preterm birth rates were slightly lower; 4.8% in Canada, 3.6% in Denmark, 3.3% in Finland, 3.8% in Norway and 3.6% in Sweden, between 2006 and 2014 [9]. In United Kingdom (UK) it was 5.5% in 2016, an increase from 2014. (UK office for national statistics, 2018)

WHO estimated the global preterm birth rate to be about 11% of total births (range 5–18%). South eastern Asia, South Asia, and sub-Saharan Africa contribute the majority of preterm births among developing word. In 2010, nine million preterm babies (60% of global preterm births) were born in Sub-Saharan Africa and south Asia [1]. Overall, the majority of preterm births in general and late preterm births in particular occur in resource poor settings.

4. Etiology and risk factors

The etiology of late preterm birth is complex and multi factorial, (Table 2). Spontaneous preterm labor and/or spontaneous rupture of placental membranes is responsible for nearly 50–75% of late preterm births. Risk factors that may further contribute to preterm birth include: history of a prior preterm delivery, short cervix, multiple gestations, infection/inflammation, maternal stress, as well as uterine, placental, and/or fetal anomalies. Gestational hypertension resulting in preeclampsia or eclampsia is an important cause for delivery before 37 weeks of GA. Davidoff et al. studied the US gestational age patterns during the period of 1992–2002 and raised concerns regarding a left shift of the US singleton gestational age towards 39 weeks in 2002 as compared to 40 weeks in 1992. They also reported that increasing rates of cesarean section deliveries and birth induction contributed to this shift. In their observations, singleton late preterm births (34–36 weeks) comprised the fastest-growing segment and the largest proportion (74%) of singleton preterm births [10]. Using the 2001 US Birth Cohort Linked birth/death files, Reddy et al. reported that of a total of 292,627 late preterm births, 76.8% were a result of medically indicated or spontaneous births while the remaining 23.2% (67,909 infants) were classified as deliveries with no recorded indication. They identified older maternal age; non-Hispanic, white mother; ≥13 years of education; multiparty; or previous infant with a ≥4000-g birth weight as factors that increased the chances of late preterm birth without an indication [11]. Late maternal age at conception, Assisted Reproductive Technology (ART) and multiple births are inter-related, contributing to increasing late preterm births. The number of in vitro fertilization cycles in the US has nearly doubled from 2000 through 2013, and in 2015 nearly 1.7% of all live births in the US were the result of this technology [12]. Though the majority of infants born as a result of ART are singletons, a significant number resulted in multiple births thus increasing the rate of late prematurity as the risk of prematurity is increased by more than ten folds in twins vs singletons. A study of ART trends in 7 regions worldwide between 2004 and 2013 showed that preterm delivery rate ranged between 9.0 and 16.6% for singletons, 53.9–67.3% for twins, and 91.4–100% for triplets and higher order multiples [13].

Table 2
Etiology of late preterm births.

1. Spontaneous preterm labor and or premature rupture of membranes
2. Maternal medical conditions
   a Difficult to control chronic hypertension
   b Gestational hypertension with severe range blood pressures
   c Preeclampsia with severe features
   d Pre-gestational diabetes with vascular complications or prior still birth
   e Gestational diabetes, poorly controlled
   f Intra hepatic cholestasis of pregnancy
3. Placental/uterine conditions: placenta previa, placenta accreta/increta/percreta, vasa previa, prior classical CS, prior uterine rupture
4. Fetal/congenital anomalies
   a. Isolated or uncomplicated oligohydramnios
   b. Growth restriction with abnormal dopplers or concurrent medical complications i.e. preeclampsia or chronic hypertension
   c. Uncomplicated Multiple gestations – mono chorionic-diamniotic twins, monochorionic-monoamniotic twins, triplets or higher order
   d. Complicated multiple gestation – with growth restriction, concurrent medical complications
   e. Allo-immunization requiring intra uterine transfusion
5. Unknown or medically not indicated/iatrogenic

5. Mortality

In general, the mortality rate for LPIs is much lower than that for extreme preterm infants, but higher than their term counter parts. The increased mortality includes higher risk of dying during the first weeks of life, 1st year after birth as well as during later years. However, only few studies reported specific causes of mortality. Reddy et al. reported neonatal mortality rates of 7.1, 4.8, and 2.8 per 1000 births at 34, 35, and 36 weeks, respectively. A large population study conducted in USA and Canada reported an increased all-cause infant mortality rates among LPIs (USA: relative risk (RR) of 2.9 with 95% confidence intervals (CI): 2.8–3.0; Canada: RR of 4.5 CI: 4.0–5.0) [14]. Based on US period-linked birth/infant death files for 1995 to 2002, Tomashek and associates observed that infant mortality rates in 2002 were 3 times higher in LPIs than term infants (7.9 versus 2.4 deaths per 1000 live births); early, late, and post neonatal mortality rates were 6, 3, and 2 times higher, respectively. During infancy, LPIs were approximately 4 times more likely than term infants to die of congenital malformations, newborn bacterial sepsis, and complications of placenta, cord, and membranes. Early-neonatal cause-specific mortality rates were highly significant for deaths caused by atelectasis, maternal complications of pregnancy, and congenital malformations [15]. In a single center retrospective cohort study, McIntire et al. reported late preterm neonatal mortality rates (per 1,000 live births) of 1.1, 1.5, and 0.5 at 34, 35, and 36 weeks, respectively, compared with 0.2 at 39 weeks [16]. A recent Spanish population study concluded that one year mortality rate was higher in LPIs compared to term infants (odds ratio (OR) 4.9 (CI: 1.3–18.5) [17]. A large systematic review of studies done between 2003 and 2010, involving 2,269,071 LPIs and 25,554,246 term infants concluded that LPIs were at high risk of death in the initial 28 days of life (RR: 5.9; CI: 5–6.9). They further indicated that this risk persisted during the 1st year of life (OR: 3.7; CI: 2.9–4.6) [18]. Another study reported even higher mortality rates among LPIs compared to term infants (2.3% vs 0%) [19]. A large Swedish national cohort study of 22,590 late preterm infants, reported increased mortality in young adulthood among individuals born late preterm (adjusted Hazard Ratio 1.31; 95% CI, 1.13–1.50; $P = .001$), relative to those born full-term [20]. This data indicate an increased risk of death for LPIs globally that persists through adulthood and emphasize the importance of careful follow up for this high risk population.

6. Short term clinical outcomes

6.1. Respiratory problems

LPIs remain at much higher risk of developing respiratory problems requiring respiratory support when compared to term neonates. These include; respiratory distress syndrome (RDS), transient tachypnea of the newborn, pneumonia, apnea and bradycardia and pulmonary hypertension. The overall incidence for LPIs admitted to NICU with respiratory compromise requiring either intervention in LD or NICU was 20.5%, while 9% had respiratory morbidity on admission in one recent series and as high as 28.9% in another. The incidence and severity of respiratory compromise decreases with increasing gestational age, being highest at 34 weeks and lowest at 39 weeks [21].

6.1.1. Respiratory distress syndrome (RDS)

RDS remains one of the commonest respiratory disorder affecting LPIs with an overall incidence of 5.2%–6.4% that decreases from 10.5% at 34 weeks to 2.8% at 36 weeks compared to 0.3% at 39 weeks gestation [22]. In other words, infants born at 34 weeks have a 40 fold increase odds of developing RDS versus infants born at 39 weeks. RDS is a clinical diagnosis based on signs and symptoms of increased work of breathing, tachypnea, grunting, retractions and a typical x-ray findings of reticulogranular pattern, air bronchogram and/or atelectasis and pulmonary white out. While antenatal steroid administration has been associated with decreased incidence of RDS in very low birth weight infants, it didn't appear to cause the same decrease in LPIs [23]. Thus the increased use of antenatal steroids in LPIs after American College of Obstetrics and Gynecology (ACOG) recommendations in 2017 might not affect the overall incidence in these infants. The need for surfactant therapy was 3.8% in all LPIs and did decrease with advancing gestation age from 7.4% at 34 weeks to 0.1% at 40 weeks gestation. However, only 21.3% of all LPIs with respiratory illness in the placebo arm of randomized controlled trial of betamethasone required mechanical ventilation and surfactant therapy, signifying that the majority of these infants can be successfully managed with non-invasive respiratory support [23]. Furthermore, the incidence of BPD was very rare in LPIs which is to be expected considering the relative maturity of lung structure and minimal need for ventilator support, and did decrease significantly with the use of antenatal steroids; 0.1% after antenatal steroids versus 0.6% in placebo [23].

6.1.2. Transient tachypnea of the newborn (TTN)

During pregnancy alveolar fluid is actively secreted by chloride secretory mechanism that can be blocked by inhibitors of Na–K–2Cl co-transporter. This mechanism is important for lung development and growth and any factors that interfere with alveolar fluid secretion including diaphragmatic hernia, chest compression or pulmonary artery occlusion can result in pulmonary hypoplasia. After delivery, this alveolar fluid needs to be cleared rapidly to allow of alveolar gas exchange. The mechanism responsible for alveolar fluid clearance is developmentally regulated and starts before delivery with decreased alveolar fluid secretion and increased expression of Epithelial Na channels (ENaC) near term regulated by changes in hormonal milieu of the mother. The mechanism for clearance of alveolar is two step; first, passive movement of Na from alveolar space into the alveolar epithelium, followed by active excretion using the ENaC into the serosal space. TTN results from delayed or impaired clearance of lung fluids secondary to lack of development or lower number of ENaC [24]. The reported incidence in LPIs has ranged from 3.9% to 9.9% and like RDS the incidence decreases with advancing gestational age. The clinical picture is very similar on presentation to RDS with respiratory compromise requiring oxygen or respiratory support but characterized by rapid resolution within 48 h and a characteristic findings of retained lung fluids on chest x-ray with prominent horizontal and or/vertical fissures. Unlike RDS, TTN does decrease in response to antenatal steroids in LPIs from a baseline of 9.9%–6.7% after betamethasone.

6.1.3. Apnea and hypoxic episodes

As apnea of prematurity is a developmentally regulated disorder of control of breathing, LPIs continue to have higher incidence of extreme apnea/bradycardia and/or hypoxic episodes than term neonates until 43 weeks corrected postconceptional age [25]. Furthermore, LPIs were found to have significantly higher incidence of intermittent hypoxic events at 2–3 days versus term controlled, (2.5 ± 1.2 vs 1.0 ± 1.2; $P < .0001$). This higher tendency for intermittent hypoxemic events decreased to a similar frequency as in term infants by 45 weeks postmenstrual age [26]. While prolonged hypoxemic episodes during the first 2–3 months after birth among extremely preterm infants who survived to 36 weeks' postmenstrual age were associated with adverse neurodevelopmental outcomes at18-month [27], the long term implications of such episodes in LPIs remain to be investigated. Prolonged apnea,

bradycardia or desaturation episodes, however, do add to the medical burden and parenteral frustration of LPIs secondary to the need for observation and delayed hospital discharge.

6.1.4. Other respiratory complications

LPIs are at increased risk of other respiratory problems including need for neonatal resuscitation at birth, pneumonia and pulmonary hypertension, although they are at lower risk for meconium aspiration than term infants. They are also at increased risk for respiratory failure including the need for ECMO which, if needed, carries much worse outcomes including higher mortality and complications than in either early or full term neonates [28].

LPIs are also at increased risk for respiratory morbidity as infants and children. Lower respiratory tract infections including bronchiolitis and pneumonia were higher in LPIs as compared to term infants in a cohort of Finish children up to seven years of age with an OR of 1.51 for developing bronchiolitis and 1.25 for pneumonia as compared to term neonates [29]. Furthermore, RSV infection in children without atopic predisposition who were late preterm infants was an independent factor for wheezing at 6 years of age [30]. Additional, in a large cohort of UK children who were interviewed at 9 months of age and followed until 11 years of age, LPIs were at significantly higher risk for early (ages 3–5 years, OR 1.38) and persistent (ages 3 through 11) wheezing (OR 1.45) [31].

6.2. Hyperbilirubinemia

Similar to term infants, LPIs develop hyperbilirubinemia from increased bilirubin load secondary to short erythrocyte life span, immature conjugation and excretion and increased enterohepatic circulation. This is particularly exacerbated by poor feeding and nutrient intake. Multiple studies have reported that more LPIs develop hyperbilirubinemia requiring phototherapy during initial hospitalization [16,32–34].Wang et al. reported very high rates of jaundice in their cohort of LPIs (54% LPI vs 38% Term) [35]. More than half of the LPIs in a large based practice report developed hyperbilirubinemia needing phototherapy [36]. Furthermore, hyperbilirubinemia is the most common reason for readmissions in preterm infants following discharge.

LPIs are also at increased risk for developing Bilirubin Induced Neurologic Damage (BIND). In these infants, plasma bilirubin levels which are below the therapeutic threshold can cause auditory system damage. Bhutani et al., in a retrospective study observed that significant number of LPIs who were treated for hyperbilirubinemia in the same way as term infants were found to develop kernicterus and experienced higher rates of sequelae from hazardous hyperbilirubinemia. Current guidelines and bilirubin normograms are helpful for treating hyperbilirubinemia in infants who are born at 35 weeks or later.

6.3. Feeding difficulty

Many functional immaturities lead to poor oral intake and growth delay in this group of infants. These include immature suck-swallow coordination, fewer awake-alert periods, suboptimal oral motor skills, poor postural control at breast and immature gut motility. The energy requirement of LPIs is also increased which can place them at high risk for poor growth. Feeding problems are quite common in LPIs as compared to term infants and it is one of the leading causes for rehospitalization secondary to poor growth and dehydration. A meta-analysis of 22 studies concluded that the risk of feeding problems is high among LPIs (OR: 6.5; 95% CI: 2.5–16.9) [18]. Careful attention and vigilance to oral intake, weight gain and milk supply is clearly needed in this population to prevent added morbidity and/or rehospitalization.

6.4. Hypoglycemia

Late preterm infants are at increased risk for developing hypoglycemia secondary to various mechanisms and risk factors including; low glycogen stores, immaturity of enzymes involved in glucose release, poor feeding and inadequate nutrient intake, cold stress, infection and underlying respiratory problems. The physiologic postnatal decrease in blood glucose concentration is much greater in preterm infants compared to term infants. In addition, inadequate compensatory mechanisms contribute to higher risk for developing hypoglycemia. Despite variations among studies regarding the definition of hypoglycemia and sample size, many studies have consistently reported occurrence of hypoglycemia in LPIs. In an early small study, Wang et al. reported that hypoglycemia occurred in 16% of LPIs compared with 5.3% in term infants [35]. Kalyoncu et al. reported that LPIs were 11 times more likely to experience hypoglycemia1[19] than term neonates. The overall incidence has ranged from 8.7% to as high as 50% [32,33,36–38]. A meta-analysis further confirmed the increased risk of hypoglycemia in LPIs (OR: 7.4; 95% CI: 3–18.1), compared with term infants [18].

6.5. Temperature instability and cold stress

Large surface area when compared to body weight, immature insulation, low amount of both brown and white fat, immaturity in thermogenesis and inefficient compensatory mechanisms place the LPIs at increased risk for hypothermia. Temperature instability is one of the main causes for prolonged hospital stay as well as for increased readmission rates. Significant number of LPIs experience temperature instability and cold stress during birth hospitalization. Wang et al. reported hypothermia in 10% of near term infants in their small study [35] while AWHONN study showed that more than half of their LPIs were diagnosed with hypothermia during the initial hospitalization [36]. Hypothermia was cited as the primary reason for admission to NICU in 5.2% of all LPIs [39].

6.6. Immunological response and sepsis

Some of the underlying mechanisms for increased rate for sepsis among LPIs include immature innate immunity, poor immunological responses, maternal infection including chorioamnionitis, and invasive procedures in intensive care units. As the group B streptococcal (GBS) screening is not performed prior to 36 weeks gestation, LPIs are more likely to get sepsis work up and treatment with antibiotics if admitted for other reasons like respiratory distress, hypoglycemia or hypothermia. In a large US observational cohort study by the Pediatrix medical group, the cumulative incidence of early and late onset sepsis was 4.42 and 6.30 episodes per 1,000 admissions, respectively. Gram-positive organisms caused the majority of early and late onset sepsis episodes. In a meta-analysis LPIs were reported to have a fourfold increased risk of undergoing sepsis evaluations and a fivefold higher risk of culture-positive infections, compared with their term counterparts [18]. The odds of developing meningitis (OR: 21; 95% CI: 1.1–406) and pneumonia (OR: 3.5; 95% CI: 1.4–8.9) were in general low but higher than full-term infants [18]. Infants with early onset gram negative sepsis(OR: 4.39; 95% CI: 1.71–11.2) and late onset sepsis (OR: 3.37; 95% CI: 2.35–4.84) were more likely to die than those without culture-proven infection [40].

6.7. Intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL)

Though the incidence of severe intraventricular hemorrhage

(IVH) or PVL is low in LPIs when compared to very preterm and extreme preterm infants, they are still at higher risk when compared to term neonates. Due to lack of standard guidelines for screening neuroimaging in LPIs, there is a large variation in the reported rates of IVH and or PVL. Though severe forms of cystic PVL are rare in LPIs, subtle forms may still be seen due to associated conditions like maternal chorioamniontis, cardiovascular instability, and hypoxic-ischemic insults. McIntire et al. reported rates of grade 1 and 2 IVH in LPIs of 0.5% at 34 weeks, 0.2% at 35 weeks and 0.06% at 36 weeks. In a review of 22 studies by Teune et al., intracranial hemorrhage occurred more frequently in LPIs (OR: 4.9; 95% CI: 2.1–11.7). The rate of either grade 3 or 4 IVH was extremely low in LPIs [16], however, it remained higher than term neonates, 0.01% vs. 0.004% [18].

7. Long term neurodevelopmental outcomes

The brain undergoes rapid growth between 34 and 40 weeks of intrauterine life. Cortical volume is nearly half, and brain weight is about 65% of that of term neonate at 34 weeks gestation. Similarly, neuronal proliferation and synaptogenesis are rapidly developing in the last trimester making the brain more susceptible to injury. This susceptibility is further exaggerated by hypoxic episodes, inadequate nutrition and maternal infection/inflammation. LPIs were found to have widespread brain white matter microstructural alterations compared with controls at term-equivalent age, in patterns consistent with delayed or disrupted white matter microstructural development [41]. This may explain some of the developmental delays in this population.

Various epidemiological studies have reported long term neurodevelopmental outcomes in LPIs. The majority of these studies were retrospective, while some also included moderate preterm infants born between 32 and 34 weeks of GA. The developmental assessment tools and age at assessment also differed among the studies and many were conducted nearly 20 years ago. Despite these limitations, most of the studies have highlighted the increased risk for long-term developmental delay in LPIs.

7.1. Cognitive delays

Multiple studies have reported the increased risk for neurodevelopmental delay in LPI. Petrini et al., using ICD criteria, reported rates of developmental delay of 12.2 per1000 live births in 8341 LPI as compared to 9.2 in term infants, with an adjusted odds ratio of 1.36 (CI: 1.11–1.66) [42]. Woythaler et al., using Bayley Scale of Infant Development (BSID) short form at 2 years of age, reported lower scores for both Mental Developmental Index (85 versus 89) and Psychomotor Developmental Index (88 versus 92) in LPI (n = 1200) versus full term infants (n = 6300). Furthermore, a higher proportion of LPIs compared with term infants had an MDI <70 (21% versus 16%; $P < .0001$) and PDI <70 (6.1% versus 6.5), with an adjusted OR for developmental delay of 1.52 (CI: 1.26–1.82) [43]. These findings seem to persist into childhood as Talge et al. concluded that at six years of age, late-preterm infants were twice as likely than term controls to have full scale and performance IQ scores below 85, a threshold that marks borderline intellectual functioning. These findings were independent of socioeconomic factors and maternal IQ [44]. On the other hand, few other studies did not find a significant difference in cognitive scores between LPIs and term infants [45–47] .

7.2. Speech delay

Few studies addressed the speech and language delay in LPIs. Using parental questionnaires to assess the speech and language skills, Stene-Larsen et al. (LPI -1673, term −7,109) found that LPIs were at increased risk for speech and language delays at 18 and 36 months [48]. In a similar study, Nepomnyaschy et al. concluded that LPIs scored lower than full-term children on language use at 2 and 4 years [46]. In a retrospective cohort study based on ICD-9 codes, Rabie et al. assessed the rates of developmental speech or language disorders (3270 LPIs vs. 24,000 term infants). Late preterms were at increased risk of developmental speech and/or language delay (AHR 1.36 (1.23–1.50) [49]. However, Brown et al. (LPI 3083, FT 2479), using Peabody Picture Vocabulary test, found that rate of receptive vocabulary delay in children aged four to five years was not statistically significant between late preterm and term infants, 13.1% vs 12.7%, respectively [50].

7.3. Cerebral palsy

Despite lower rates of high grade IVH and cystic PVL in neonatal period, LPIs were found to be at high risk for developing cerebral palsy (CP) during early childhood. In a large Finnish national register study, the incidence of CP was found to be 0.6% in LPI versus 0.1% in the term group for infants born between 1991 and 2008. In this study, factors predictive of an increased CP risk in the LPI group included resuscitation at birth, antibiotic treatment during the first hospitalization, 1 min Apgar score <7 and intracranial hemorrhage [51]. In a retrospective study using ICD criteria, Petrini and colleagues reported that LPIs were more than three times as likely to be diagnosed with CP when compared to term infants by five years of age [42].

7.4. School age outcomes

Many studies have evaluated school performance in late preterm birth. Using population based UK Millennium Cohort study data, Quigley and colleagues reported school outcomes at the end of first and again during the 3rd year of school. They used foundation stage profile (FSP) at school year one and Key stage 1(KS1) for school year 3 assessments. They found that at the end of 1st year of school, 59% of LPIs had not reached a good level of overall achievement compared to 51% of full term children [52]. On 3rd year assessment, they noted that LPIs were at 36% increased risk for poor performance compared to term born children [53]. In a cohort study of 5–6 year olds born in 2001, Woythaler et al. found that LPIs had significantly worse total school readiness, reading and math scores compared with FTI. Lipkind and colleagues concluded that children who were born as LPIs had 30% higher adjusted odds of needing special education than those born at full term. They also had lower math and English scores on 3rd grade standardized tests [43]. In another study, Chyi et al. reported that LPIs had lower reading scores than full term infants in Kindergarten (K) and first grade and risk for poor reading and math scores remained elevated through first grade. They further showed that teacher evaluations of math skills from K to first grade and reading skills from K to fifth grade were worse for LPIs with higher odds for below average skills for math in K and for reading at all grades. Special education participation was also higher for LPIs at early grades [54]. Morse and associates reported that the risk for suspension in kindergarten was 19% higher for LPIs. LPIs were also found to be at 10–13% increased risk for disability in prekindergarten at 3 and 4 years of age, lower exceptional student education, and retention in kindergarten [55].

7.5. Neurobehavioral problems

7.5.1. Attention deficit hyperactivity disorder (ADHD)

It has been recognized that LPIs are at higher risk for eliciting

symptoms of ADHD. However, like many other epidemiological studies, this relationship was evaluated retrospectively and using variable diagnostic methods. In a large Swedish national register study, there was a step wise increase in odds ratio for ADHD medication usage at 6–19 years of age with increasing degree of immaturity at birth. Higher ADHD medication usage rates were also noted in children born LPIs when compared to children born at full term [56]. Talge et al. reported that late-preterm birth was associated with higher levels of internalizing and attention problems. These children also were at higher risk for teacher reported behavioral problems, associations that were most consistently observed in the attention and internalizing problem domains. Internalizing problems in early childhood have been prospectively linked with risk for a variety of psychiatric disorders in adolescence and adulthood [44].

Rabie et al. reported that LPIs born secondary to a medical indication had a higher risk for hyperactivity and higher global index scores for ADHD [49]. However, when all late preterm infants were combined, the authors did not observe any increase in the risk of ADHD symptoms. Others did not find a statistically significant differences in the cumulative incidence of ADHD or learning disability (LD) between the late preterm (N = 256) and term (N = 4419) groups [57].

7.5.2. Autism

Very few studies reported the rates of autism in LPIs. In an UK population cohort study of 548 late/moderate preterm infants (32–36 weeks) and 761 term infants, Guy et al., using the modified checklist for autism questionnaire reported that a total of 14.5% of late/moderate preterm infants versus 9.3% of term controls scored above the clinical cut-off for ASD at two years of age. The risk of true positive failure rate was 2.4% and 0.5% for late-preterm and full-term infants, respectively, on follow-up interview. The higher risk for autism persisted after excluding infants with neurosensory impairments [58].

7.6. Adult and adolescent outcomes

Data on adolescent and adult outcomes of LPIs are mostly based on data from Scandinavian national health registries of LPIs born 40–50 years ago. Moster et al. reported long term outcomes, at 20–36 years of age, in a large Norwegian retrospective cohort study involving 29,000 LPIs and nearly 800,000 term infants. They concluded that adults born as LPIs had a 13% higher risk for failure to complete high school compared to those born at full term [59]. In another large Norwegian retrospective cohort study involving only males at 18–19 years, who were in Military service, late preterm boys had higher chances for lower IQ when compared to boys born full term. This difference persisted even after adjusting for social confounders and adult body size [60]. In a similar study from Sweden, 18–19 year old boy born as LPIs had lower mean cognitive scores. However, the difference disappeared after adjusting for socioeconomic status [61]. In an extensive review of 53 long term follow up studies involving mostly late preterm and early term infants, Kajantie et al. concluded that as adults, LPIs were at higher risk for all-cause mortality and as well as other disorders including; type 2 diabetes, asthma, lower physical fitness, lower cognitive abilities, and several mental health disorders [62].

8. Financial and economic burden

The vast majority of LPIs do well both short and long term. However, given the large absolute number of LPIs, there has been an increased utilization of health care resources leading to increased financial burden. In 2006, the Institute of Medicine estimated a total cost of nearly $26 billion (USD) for all preterm births per year. Due to their large number and need for extra care, LPIs contributed a major portion of this economic burden. Based on data from 84,540 late preterm and 92,241 term infants in California in 1998–2000, Phibbs and associates estimated that delaying delivery at 34 weeks gestation by one week would result in mean economic savings of $4528 USD [63]. McLaurin and associates reviewed insurance database and found that the cost for initial hospitalization for 33–36 week infants was $26,000 USD compared to $2000 USD for term infants. They also reported that total first year costs were, on average, 3 times as high among LPIs ($12,247 USD) compared with term infants ($4,069 USD) [64]. In a UK prospective population based study, Khan and colleagues concluded that mean total societal costs from birth to 24 months were £5823 GBP for children born late preterm compared with £2056 GBP for children born at term. This difference remained significant even after controlling for clinical and socio-demographic characteristics, where late preterm birth increased societal costs by £1963 GBP compared with birth at full term [65]. A study from Netherlands compared the initial hospitalization costs for LPIs and term infants. The costs were nearly 2–8 fold higher for LPIs. Similarly the costs were significantly higher for LPIs born as multiples when compared to singleton LPIs [66]. In a Canadian study of costs and morbidities of late preterm births, the mean total cost during the first 2 years of life was $2568 CAD compared with $1285 CAD for term infants [67]. Mean costs of initial hospitalization were did decrease with increasing gestational age at they cost $18,617 USD $15,864 USD, $12,305 USD and $6,368 USD for infants born at 34, 35, 36 and $\geq$ 37 weeks respectively, in the US state of Michigan in 2003 [68].

9. Readmissions

Readmission rates are higher for LPIs following initial birth hospitalization. Escobar et al. looked at hospitalization rates of LPIs discharged from neonatal intensive care units and found that infants 33–36 weeks' gestation with a length of stay of less than 4 days had an increased chances of getting readmitted (OR 2.94 (1.87–4.62) compared with term infants. As discussed previously, jaundice was the main cause for readmission in 71% of the patients [69]. Tomahawk et al. studied 1000 LPIs and 24,000 term infants and concluded that LPIs were 1.8 times more likely to be readmitted than term infants. Jaundice and infection were the main reasons for readmissions especially in breast fed LPIs [70]. Shapiro-Mendoza et al. reported readmission rates of 5.5%, 6.9% and 5.8% for 34, 35 and 36 week infants respectively. They identified initial hospital stays less than 4 days, breastfeeding, Asian/Pacific Islanders, first-born infants, and public payers at the time of delivery as risk factors for readmissions [71]. In the United Kingdom, Oddie et al. reported higher risk of readmission in infants born at 35–37 weeks compared with term infants (AOR 1.72, (1.15–2.57). Interestingly, infection was the leading cause for readmission. Further, early discharge was not associated with increased readmissions while breast feeding was associated with lower rates of readmission [72]. In a large cohort study using California Kaiser Permanente database, including 19,494 LPIs from 2003 through 2012, Kuzniewicz et al. showed that compared with term infants, LPIs were at higher risk for being readmitted secondary to jaundice, feeding problems (RR 2.41; 95% CI, 2.29–2.55) or sepsis (RR 1.66; 95% CI, 1.50–1.83) [73]. In a study from Spain, readmissions were found to be higher in the late preterm group at both 30 days (9.0% versus 4.4%) and at one year (22.0% versus 12.4) [17]. Jaundice and bronchiolitis were the main diagnoses at 30 days and 1 year readmission, respectively [17]. In a recently published large population based cohort study from Canada, Isayama and associates studied 75,364 LPIs and concluded that LPIs had more frequent admissions than term

infants in the first 5 years of age. This was noted in both singletons (adjusted incidence rate ratio (aIRR) (95% confidence interval) 1.46 (1.42–1.49)) and twins (1.21(1.11–1.31). Neonatal jaundice was the most common admission diagnosis during the neonatal period, while lower respiratory tract diseases, gastro intestinal problems or infection after the neonatal period [74].

10. Emergency room (ER) visits

Similar to increased readmission risk, LPIs also have higher odds of being seen in an ER. Jain et al. reported an ER visit rate of 17.7% for LPIs. In fact, the majority of LPIs presented to ER during the 4th week of life were of 36 week GA. The most common diagnoses were feeding problems, respiratory problems, fever and jaundice [75]. Kuzniewicz et al. sho wed that when compared to term infants, LPIs were more likely to be seen at ER (RR 1.20 (1.12–1.29). They also reported that when compared to term infants, LPI visits to ER were more likely to result in an admission [73].

11. Management and discharge

Caring for LPIs requires collaboration through a multidisciplinary team approach which includes parents, nursing, lactation services, dieticians, therapy services and neonatal providers. The infants' care need to be directed utilizing guidelines based on the best available medical evidence. A check list of discharge criteria should be completed in each infant; this should include, but not limited to, clinical stability for minimum of 48 h, feeding assessment, hypoglycemia, hyperbilirubinemia, temperature stability, car seat safety, critical congenital heart disease, parental education and follow up visits [76]. Additional useful measures can include; maternal screenings for depression, drug use, safe home environment, and presence of social support. Selective high risk LPIs with additional morbidities like severe SGA, asphyxia, in utero drug exposure and genetic syndromes should be referred to neurodevelopmental follow up clinics and other relevant specialist services.

12. Prevention

A plethora of basic and clinical research has contributed to our current understanding of the pathogenesis of, and strategies to prevent, preterm birth. Some evidence-based strategies that can be useful in decreasing the incidence of preterm birth in general, and late preterm birth in particular, include; smoke prevention, use of 17- hydroxy progesterone (17-OHP) and/or cerclage in women at risk due to short cervix, judicious utilization of fertility treatments – both ART and non-ART, prevention of non –medically indicated deliveries, improving prenatal care and pre-conceptional health, promoting longer inter-pregnancy intervals and life style modifications to reduce chronic medical conditions [77]. Administration of betamethasone to pregnant women at risk for late preterm delivery has been shown to reduce respiratory complications. However, careful monitoring for hypoglycemia is required in these infants [23].

13. Future

As most of the research on LPIs was retrospective, there is a need to study the morbidity and long term outcomes in a prospective manner using standard assessment tools. Research is also needed to look at the outcomes in sick LPIs needing intensive care compared to healthy LPIs as controls. There is an urgent need for collection and reporting of data on LPIs using standard definitions in middle and low income countries. Due to technological advances, telehealth is fast becoming an attractive and feasible option for follow up through 'virtual visits'. This should be explored for post-discharge follow up care of LPIs. Further research into pathogenesis and prevention strategies of all preterm but in particular late preterm birth clearly is need.

14. Conclusions

The number of late preterm births are increasing worldwide. They represent more than three quarters of all preterm infants. Late preterm infants are at increased risk of various morbidities and mortality. The common morbidities include respiratory distress and failure, feeding difficulties, poor growth, hypoglycemia, hyperbilirubinemia and hypothermia. These morbidities not only cause a prolonged hospital stay but also increase the risk for readmission following hospital discharge. Suboptimal neurodevelopmental outcomes in LPIs are a cause for concern indicating the sequelae of earlier insults to the developing brain. This emphasizes the need for long-term follow-up. Over all, majority of LPIs do well both in short term and long term. However, due to their absolute high numbers, they contribute a significant burden to heath care cost. Multi-faceted approach is required which includes, but not limited to, avoiding late preterm births without a medical reason, comprehensive evaluation of the infants during hospital stay, development of care pathways, parental education and diligent follow up.

Author contributions

All authors contributed equally to the writing of the first draft, and its revisions.

Declaration of competing interest

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

None.

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Screen at 2 Years of Age ASD Autism spectrum disorders LMPT Late and moderately preterm M-CHAT Modified Checklist for Autism in Toddlers RR Relative risk SES Socioeconomic score n.d. https://doi.org/10.1016/j.jpeds.2014.10.053; 2015.
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