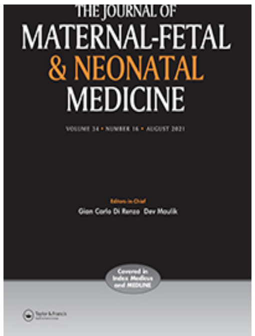

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REVIEW ARTICLE

Late preterm: a new high risk group in neonatology

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ABSTRACT

Late preterm infants are those infants born between 34 0/7 weeks through 36 6/7 week of gestation. These are physiologically less mature and have limited compensatory responses to the extrauterine environment compared with term infants. Despite their increased risk for morbidity and mortality, late preterm newborns are often cared in the well-baby nurseries of hospital after birth and are discharged from the hospital by 2–3 days of postnatal age. They are usually treated like developmentally mature term infants because many of them are of same birth weight and same size as term infants. There is a steady increase in the late preterm birth rate in last decade because of either maternal, fetal, or placental/uterine causes. There has been shift in the distribution of births from term and post-term toward earlier gestations. Although late preterm infants are the largest subgroup of preterm infants, there has been little research on this group until recently. This is mainly because of labeling them as "near-term". Such infants were being looked upon as "almost mature", and were thought as neonate requiring either no or minimal concern. In the obstetric and pediatric practice, late preterm infants are often considered functionally and developmentally mature and often managed by protocols developed for full-term infants. Thus, limited efforts are taken to prolong pregnancy in cases of preterm labor beyond 34 weeks, moreover after 34 weeks most centers do not administer antenatal prophylactic steroids. These practices are based on previous studies reporting neonatal mortality and morbidity in the late preterm period to be only slightly higher in comparison with term infants and whereas in the current scenario the difference is significant. Late preterm infants have 2–3-fold increased risk of morbidities such as hypothermia, hypoglycemia, delayed lung fluid clearance, respiratory distress, poor feeding, jaundice, sepsis, and readmission rates after initial hospital discharge. This leads to huge impact on the overall health care resources. In this review, we cover various aspects of these late preterm infants like etiology, immediate and long-term outcome.

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Introduction

Late preterm infants (34 0/7 weeks through 36 6/7 week of gestation) are developmentally and physiologically less mature and have limited compensatory responses to the extrauterine environment compared with term infants. This is particularly important because the percentage of infants born to this subgroup is growing rapidly because of many reasons. They look like their term counterpart but have immediate and long-term complications totally different from them. Late preterm infants have emerged as a new risk group like extreme and moderate preterm in neonatology, requiring close observation and future research over various aspects [1]. In this review, we will cover definition, epidemiology, etiology, short- and long-term complications of late preterm infants.

Definition of late preterm

A variety of terms have been used to describe preterm infants born at a number of different intervals between 32 and 37 weeks' gestation ("late preterm", "near term", "marginally preterm", "moderately preterm", "minimally preterm", and "mildly preterm"). The July 2005 workshop "Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant" sponsored by the National Institutes of Child Health and Human Development recommended that infants born at 34 0/7 through 36 6/7 weeks' gestation after the onset of the mother's last menstrual period be referred to as late preterm to emphasize that these infants are preterm and, as such, are at risk of prematurity related medical complications. Furthermore, use of the term "near term", which connotes that the

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infant is almost term and, therefore, almost fully mature, should be discouraged, because it might lead health care professionals to underestimate the inherent risks to these infants [2].

Epidemiology of late preterm births

Trends in late preterm birth

The preterm birth (<37 completed weeks of gestation) rate in the USA continues to rise, from 9.4% of live births in 1981 to 12.3% in 2003, increasingly divergent from the Healthy People 2010 target of no higher than 7.6%. According to the National Center for Health Statistics (NCHS), most of this (2.9%) increase is due to increase in the rates of moderately preterm births (32–36 weeks), as the very preterm rate (<32 weeks) has stayed relatively constant during the past two decades, ranging from 1.8 to 2.0% [3]. Davidoff et al. reported on the basis of the U.S. NCHS, there were 3,808,473 singleton live births in 2002, of which 394,996 (10.4%) were delivered preterm. The largest proportion of these preterm births were delivered at 36 completed weeks gestation (40.1%), with infants delivered between 34 and 36 completed weeks accounting for about 74% of the total number of preterm births. Very preterm births comprised 13.6% of all the singleton preterm births. The proportion of infants born at 40–44-week gestation within all delivery groups dropped dramatically between 1992 and 2002. After controlling for maternal age and race/ethnicity, there was an 18.6% decrease in the proportion of births at 40 and 41 weeks of gestation and a 36.6% decrease in the proportion of births at or beyond 42 weeks. Deliveries at >40-week gestation markedly decreased, accompanied by an increase in those at 34–39 weeks ($p < .001$) [3].

One study that used the Medical Birth Registry of Norway found a 25% increase in preterm births between 1980 and 1998 (4.12–5.16%) [4]. A study from Denmark reported that there was a 22% increase in spontaneous singleton preterm births between 1995 and 2004 for white European women who were 20–24 years of age (from 5.2 to 6.3% of live births). The gestational age breakdown showed that there was a 40.9% increase in extremely preterm (22–27 weeks) births, a 21.8% increase in very preterm (28–31 weeks) births, and a 21.8% increase in moderately preterm (32–36 weeks) births [5]. A meta-analysis of deliveries in the USA, Canada, and 26 other European countries reported the prevalence of moderate preterm and late preterm birth (32 0/7 to 36 6/7 day) ranging from 4.4 to 10.0% [6]. Emerging data suggest that late preterm births are becoming increasingly common throughout the world [7]. Incidence and trend in late preterm birth from India is not exactly reported but it would also be similar, as there are similar trends in other associated obstetric practices.

Etiology of late preterm birth

Why have late preterm births increased in recent times? There is no one particular explanation, but multiple factors have contributed to this rise (Table 1). Spontaneous preterm labor (PTL), preterm premature rupture of membranes (PPROMs), or maternal, placental/uterine and fetal pathology are known contributors to preterm birth; however, recent spikes in inductions, cesarean sections, and other obstetrical practices, as well as a modest change in maternal demographics, have played a key role in the increase in late preterm births [8].

Preterm labor and preterm rupture of membranes

Although the overall rate of preterm birth is on the rise, the rate of preterm delivery in the USA resulting from spontaneous PTL before 32 weeks decreased by 9% between 1992 and 2002. Paradoxically, the rate of spontaneous preterm delivery among late preterm infants increased during the same period. By 2002, more than 7% of deliveries resulting from PTL occurred between 34 and 37 weeks gestation; this represented a 12% increase in births resulting from

Table 1. Various etiology for late preterm birth.

Serial no.		Etiology
1	Maternal	Preterm premature rupture of membranes (PPROM) Preterm labor Gestational hypertension Preeclampsia Preeclampsia superimposed on chronic hypertension Assisted reproductive technology (ART) Multiple gestation (uncomplicated/ complicated) Anemia Gestational diabetes Post cesarean pregnancy Intrahepatic cholestasis of pregnancy
2	Fetal	Oligohydramnios Polyhydramnios Intrauterine growth restriction (IUGR) Alloimmunization
3	Placental/uterine	Placenta previa Placenta accrete, percreta or increta Vasa previa Previous uterine rupture Previous classical cesarean section Previous myomectomy requiring Cesarean delivery

spontaneous late PTL between 1992 and 2002. The rate of premature rupture of membranes (PROMs) between 34 and 36 weeks gestation also increased from 1992 to 2002; by 2002, 21% of cases of PROM occurred in late preterm pregnancies [3].

Standard obstetric management of PTL and PPROM may influence the percentage of these cases that result in late preterm birth beyond 34 weeks. According to practice guidelines published by the ACOG, the management of PTL should involve the use of tocolytics and glucocorticoids [9]. The management of PPROM remains controversial, but expert opinion generally recommends expectant management before 34 weeks. However, beyond 34 weeks efforts are no longer directed at prolonging the pregnancy [10]. These management strategies are based upon the fact that the survival rate of infants born at 34 weeks is within 1% of those born at term and prolongation of a pregnancy complicated by PTL or PPROM beyond 34 weeks may have unnecessary maternal and fetal risk. The practice of not aggressively attempting to treat PTL after 34 weeks of gestation may have contributed to the increasing rate of late preterm births. In addition, many actively deliver pregnancies with ruptured membranes beyond 34 weeks, or even earlier if fetal lung maturity has been documented [11–13].

Labor inductions and cesarean deliveries

Davidoff et al. found a shift toward earlier gestations among births by medical intervention (cesarean sections and inductions), with the majority of the increase seen among the late preterm (34–36 weeks) and early term infants (37–39 weeks). Although both cesarean section and induction rates increased among late preterm births (31 and 78%, respectively), cesarean rates increased more at earlier gestations, and induction rates increased more at later gestations [3].

Another factor potentially contributing to the increase in late preterm birth is the trend away from vaginal birth after a previous cesarean section (VBAC) and toward repeat abdominal deliveries. After years of a slowly increasing rate of VBAC, it began to fall in the mid-1990s. Studies have reported that in the USA, the incidence of VBAC has decreased between 1996 and 2005 [14]. With current CS rates varying from 30 to 50% in the high-income countries, a previous CS is the cited primary indication in approximately 30% of these CS [15]. This increase in the repeat cesarean section rate increased the opportunity for iatrogenic late preterm birth [16]. Assuming they were performed at term, elective deliveries may have contributed to the decreasing average gestational age at delivery but should have minimal impact on the increasing rate of late preterm births seen over the last decades. However, because of the inherent inaccuracy of pregnancy dating with margins of error of up to 3 weeks in the third trimester, inductions of labor and elective cesarean section performed at "presumed term" might inadvertently contribute to the increasing incidence of late preterm birth [17].

Reduction in stillbirth rates

Several investigators have proposed that the declining stillbirth rates and increasing preterm births are causally related. These studies imply that to prevent stillbirths, timed obstetrical interventions for at-risk groups are needed, and an increase in preterm birth rates may be the price. More work is needed, however, to ascertain the causal association between increasing obstetric interventions and decreasing stillbirths, and their combined role in increasing the overall and late preterm birth rates [18,19].

Assisted reproductive technology and multiple births

There has been an approximately two-fold increase in rate of ART in 2002 compared with 1996. As an unintended consequence of ART increases the incidence of multiple pregnancies, a well-recognized risk factor for preterm births, increasing rates of ART use can be causally linked to increasing overall late preterm birth rates. It is also known that ART increases the risk of preterm births even among singleton pregnancies [5]. Multiple births contribute significantly to this problem of prematurity. Many twin and high-order multiple pregnancies are delivered between 34 and 37 weeks' gestation either secondary to PTL or obstetrical complications necessitating intervention [18]. Virtually, all the principal obstetric complications are higher in multifetal pregnancies and they include gestational diabetes, hemorrhage, preeclampsia, abruption, IUGR, and LBW. Many of these medical conditions may necessitate delivery and serve as common indications for delivery in the late preterm period [20]. Blondel et al. studied the impact of the increasing number of multiple births on the rates of preterm birth and low birth weight and found that when compared with singleton births, multiple births are five times more likely to be born late preterm. The mean age at delivery for singletons is 38.8 weeks but 35.3 weeks for twins, 32.2 weeks for triplets, and 29.9 weeks for quadruplets [21].

Preeclampsia

Gestational hypertension–preeclampsia is the most common medical complication of pregnancy and is a major cause of maternal mortality and morbidity, preterm birth, perinatal death, and intrauterine growth restriction (IUGR) [22]. The majority of cases occur in healthy primiparous women with a reported incidence in this group of 3–7 and 1–3% in multiparous. The rates are even higher in women with certain risk factors [23]. Preeclampsia may affect both the mother and fetus. As there is no effective cure for preeclampsia other than delivery; delivery is always the treatment of choice for the mother. In general, delivery is recommended for women who develop gestational hypertension–preeclampsia at 37 weeks or more. In addition, because of the concern about maternal and fetal safety, delivery is recommended for all women with severe preeclampsia at >34 weeks' gestation, and at 35–37 weeks' gestation in the presence of risk factors in women with mild gestational hypertension or mild preeclampsia but who do not deliver before 35-week gestation, expectant management is recommended with close maternal and fetal evaluation [24]. Knuist et al. [25], Hauth et al. [26], and Sibai et al. [27] evaluated the rates of preterm delivery in women who developed mild gestational hypertension. The rates of preterm delivery did not exceed 7% in any of the studies and the rate of preterm delivery approached 22% in women who developed recurrent preeclampsia. Barton et al. found that 15% of women with mild gestational hypertension are delivered between 34 and 36 weeks when community hospitals are included [28].

Placental/uterine conditions

Many placental and uterine conditions lead to late preterm birth for a better fetal outcome. The common conditions include placenta previa, placenta accreta, percreta, or increta and previous uterine rupture [29].

Fetal conditions

Fetal conditions also lead to the birth of late preterm infant as risk outweighs the benefit of prolonging delivery to 39 weeks or further. The fetal conditions that lead to it include oligohydramnios, polyhydramnios, IUGR and alloimmunization [29].

Complications of late preterm infants

Neonatal morbidity

During the initial birth hospitalization, late-preterm infants are four times more likely than term infants to have at least one medical condition diagnosed and 3.5 times more likely to have two or more conditions diagnosed (Table 2). Late-preterm infants are more prone to complications like temperature instability, hypoglycemia, respiratory distress, apnea, jaundice, and feeding difficulties than term infants [30]. Using a population-based cohort study, Tomashek et al. evaluated the risk of neonatal morbidity (defined as hospital readmission, observational stay, or both) in all vaginally delivered, live-born singleton late preterm and term infants who were discharged home early (< 2-night hospital stay). They found that 4.3% of late preterm and 2.7% of term infants were either readmitted or had an observational stay. Late preterm infants were 1.5 times more likely to require hospital-related care and 1.8 times more likely to be readmitted than term infants. They suggested that the late preterm infants discharged early experience significantly more neonatal morbidity than term infants discharged early [31]. Using the same dataset, Shapiro-Mendoza et al. found that of the 9552 late preterm, "healthy" infants, 4.8% had inpatient readmission and 1.3% had an observational stay [32].

Despite their increased risk for morbidity, late preterm newborns are often cared for in the well-baby nursery after birth and are discharged from the hospital by 2–3 days of age. Understanding which characteristics of late preterm infants pose the greatest risk for neonatal morbidity is essential for preventing post-discharge complications. Knowledge of risk factors for neonatal morbidity among "healthy" late preterm infants can be used to identify infants needing closer monitoring and earlier follow-up after hospital discharge [33,34]. Shapiro-Mendoza et al. also compared late-preterm and term infants with and without selected maternal medical conditions and assessed the independent and joint effects of these exposures on newborn morbidity risk. Eight selected maternal medical conditions were assessed (hypertensive disorders of pregnancy, diabetes, antepartum hemorrhage, lung disease, infection, cardiac disease, renal disease, and genital herpes) in relation to newborn morbidity. They concluded that late-preterm birth and, to a lesser extent, maternal medical conditions are each independent risk factors for newborn morbidity. When combined, these two factors greatly increased the risk for newborn morbidity compared with term infants who were born without exposure to these risks [35].

Table 2. Late preterm common complications after birth.

Serial no.	Morbidities	Etiology	Prevention/management
1	Low Apgar score/birth asphyxia	Neurological immaturity Maternal or fetal indication for preterm delivery	Birth attendant by doctor well versed in neonatal resuscitation
2	Feeding difficulties	Immature brain development Low oromotor tone Incoordination of the suck-swallow-breathe sequence Sleepy behavior Gastrointestinal dysmotility Immature suction pressure Higher incidence of gastro-esophageal reflux	Lactational counseling and support Parent's education over feeding habits Frequent feeding Monitoring of enteral intake, weight gain, urine, and stool output
3	Hypoglycemia	Immature hepatic enzymes for glycogenolysis, gluconeogenesis, and ketogenesis Decreased hepatic glycogen stores Immature adipose tissue lipolysis Unregulated insulin secretion during hypoglycemia Associated morbidities	Sugar monitoring for initial 24 hours Frequent feeding Following standard and latest guidelines for treatment
4	Hypothermia	Decreased brown adipose tissue stores and hormones necessary for breakdown Less subcutaneous white adipose tissue Nonkeratinized thin skin Increased body-surface area to body–weight ratio Immature response to temperature receptors	Providing thermo-neutral temperature in delivery room Skin to skin contact Delayed bathing and educating parents Kangaroo mother care
5	Hyperbilirubinemia	Reduced red cell life Reduced hepatic uptake Decreased conjugation of bilirubin Increased enterohepatic circulation	Frequent breastfeeding Pre-discharge risk assessment Phototherapy Exchange transfusion
6	Respiratory morbidities	Functional deficiencies in surfactant Reduced ability for lung fluid clearance Delay in postnatal adaptation Apnea secondary to decreased ventilatory response	Oxygen support Continuous positive airway pressure (CPAP) Surfactant Invasive ventilation Antibiotics Pulmonary vasodilator
7	Infection	Impaired host defense mechanisms Limited amounts of protective endogenous flora on skin and mucosal surfaces Reduced maturity and barrier function of neonatal skin Use of invasive procedures and devices Exposure to broad-spectrum antibiotics	Hand hygiene Prevention of central line associated bloodstream infection
8	Readmission	Secondary to Jaundice Feeding problems Respiratory illness Infections	Parent education Follow up
9	Mortality	Secondary to various morbidities	Morbidities need to be managed
10	Intraventricular hemorrhage (IVH) and periventricular leucomalacia (PVL)	Brain immaturity Cerebro-vasculature Associated morbidities	Prevention of factors leading to IVH Treatment of associated morbidities Ultrasound head

Low Apgar score

These late preterm infants are prone to have a low Apgar score at birth and perinatal/birth asphyxia. This could be because of neurological immaturity and maternal or fetal indication for preterm delivery. It can be prevented by identification and follow up of high-risk pregnancy with early identification of any complications. Such birth should be attended by clinicians who are well versed in resuscitation of such high-risk infants [36]. Wang et al. in their retrospective record analyzed 90 near term and 95 full-term infants, found that median Apgar scores at 1 and 5 min were 8 and 9, respectively, for both near-term and full-term infants and no study patient had a score at 5 min assigned <3 [37]. Jaiswal et al. showed that Apgar scores at one and 5 min were significantly lower in late preterm infants when compared to term infants [38]. Bulut et al. similarly reported significantly higher incidence of perinatal asphyxia in late preterm infants [39].

Feeding difficulty

Late-preterm infants also have an immature gastrointestinal function and feeding difficulties that predispose them to an increase in enterohepatic circulation, decreased stool frequency, dehydration, poor weight gain, and hyperbilirubinemia [31,32,40]. Feeding during the birth hospitalization may be transiently successful but not sustained after discharge [41]. They can have feeding difficulties secondary to immature brain development leading to low oromotor tone, incoordination of the suck–swallow–breathing sequence, sleepy behavior, gastrointestinal dysmotility, and immature suction pressure [42]. Late preterm infants also have higher incidence of gastroesophageal reflux when compared to term counterparts due to transient relaxation of the lower esophageal sphincter leading to dehydration and hypernatremia [43]. Ten percent of late preterm infants have significant apnea of prematurity and they frequently have delays in establishing coordination of feeding and breathing. Obstructive and mixed apnea also occur at greater frequency and severity compared with infants born at term [44–46]. Management of feeding difficulties in late preterm infant includes parent's education over feeding habits, frequent feeding, and providing them special attention to provide safe and effective oral feedings [47]. Close monitoring of adequate enteral intake in the form of weight gain, wet diapers, and number of stools need to be done in this high-risk group [48]. For the late preterm infants who are breastfed, lactation support to the mother is critical because of the increased risk of difficulty in establishing effective breastfeeding and mothers are at risk for delayed onset of lactation [49]. These infants need to be started on supplementation with vitamin D and iron which are required for bone mineralization, growth, and development of the brain and nervous system [48].

Wang et al. demonstrated that nearly 27% of late preterm infants had a clinical condition requiring intravenous fluid compared to only 5% of term infants (OR: 6.48; 95% CI: 2.27–22.91; $p = .0007$) and 76% of late preterm infants with poor feeding experienced a delay in discharge to home, whereas 28.6% of term infants with poor feeding had delayed discharge (95% CI: 0.94–93.4; OR: 7.3; $p = .029$) [37]. Vachharajani and Dawson found that approximately 7.3% of infants at 35-week gestation were admitted to the NICU for feeding difficulties [50]. Escobar et al. studied incidence of rehospitalization after discharge in the neonates who were admitted at the time of birth and reported that nearly 26% of the late preterm and term infants required rehospitalization for feeding difficulties and late preterm infants were more likely to get readmitted (4.4% in late preterm versus 2% in term) [51]. Tomashek et al. reported that when breastfed late preterm infants were compared with term counterpart, they were 1.8 times more likely to require hospital-related care and 2.2 times more likely to be readmitted. The authors concluded that late preterm infants discharged early experienced significantly more neonatal morbidity when compared to early discharged term infants [31].

Hypoglycemia

Newborn infants produce glucose primarily by hepatic glycogenolysis and gluconeogenesis and these late preterm infants have immature hepatic enzymes for glycogenolysis, gluconeogenesis, and ketogenesis. They too have decreased hepatic glycogen stores, which are normally accumulated in the third trimester. There is also immature adipose tissue lipolysis in these infants. In addition, hormonal regulation and insulin secretion by pancreatic β cells are immature, resulting in unregulated insulin secretion during hypoglycemia. This quick depletion of the inadequate glycogen stores, with associated conditions such as cold stress, sepsis, and feeding difficulties, in the late preterm infants puts them at increased risk for hypoglycemia [52]. The clinical signs of neonatal hypoglycemia include lethargy, poor feeding, abnormal cry, jitteriness, irritability, hypothermia, diaphoresis, hypotonia, lethargy, seizures, pallor, tachypnea, apnea, and cardiac arrest. Management depends upon both the clinical presentation and glucose concentration [53–55].

The incidence of hypoglycemia is correlated inversely with gestational age, with late preterm infants having a greater risk than term infants. In a study by Wang et al., hypoglycemia (blood glucose <40 mg/dl) was three times more common in late preterm infants than term infants (15.6 versus 5.3%; OR: 3.30; 95% CI: 1.1–12.2; $p = .028$) [37]. Rather et al. reported in their study that late preterm had significant higher hypoglycemia incidence when compared to term infants (16 versus 6.5%; OR: 2.74; 95% CI: 2.07–3.63; $p < .0001$) [56]. Similarly studies conducted by Jaiswal et al. and Bulut et al. showed significant higher incidence of hypoglycemia in late preterm cohort [38,39].

Hypothermia

Term infants can generate heat by breaking down brown adipose tissue with the help of hormones, such as norepinephrine, prolactin, triiodothyronine, and cortisol, which peak at term gestation [57,58]. Late preterm infants have decreased brown adipose tissue stores and hormones necessary for their breakdown. They also have less subcutaneous white adipose tissue, have nonkeratinized thin skin and increased body-surface area to the bodyweight ratio, putting them at risk for increased heat loss. These infants have immature response to temperature receptors located in posterior thalamus for releasing thermogenic hormones like thyroxine and norepinephrine, thus making them more susceptible for hypothermia [59,60]. Cold stress can lead to poor respiratory transition in late preterm infants and exacerbate hypoglycemia, prompting work-ups for sepsis, which require further laboratory tests and antibiotics. Temperature regulation is important in late preterm infants and, if not properly managed, can lead to significant morbidity and mortality. Hypothermia can be prevented by providing thermo-neutral temperature, skin to skin contact with mother, delayed bathing and educating parents about hypothermia [61–63]. Kangaroo mother care (KMC) has shown to be effective in management and prevention of hypothermia in these infants [64]. Cochrane meta-analysis reported that with the use of KMC, there was significant reduction in incidence of hypothermia [65].

Wang et al. found that late preterm infants were more likely to present with temperature instability compared to term (10 versus 0%; OR: infinite; $p = .0012$) [37]. In another study by Vachharajani and Dawson, hypothermia was cited as the primary reason for admission in 5.2% of all late preterm infants who were admitted to the NICU [50].

Hyperbilirubinemia

Hyperbilirubinemia in the late preterm infant is caused by a higher rate of bilirubin production because of reduced red cell life, reduced hepatic uptake, decreased conjugation of bilirubin secondary to decreased activity of hepatic uridine diphosphate glucuronyl transferase enzyme and increased enterohepatic circulation caused by immature gastrointestinal function and motility [66]. This condition puts them at risk for high serum bilirubin levels and sometimes severe, prolonged jaundice, and kernicterus [67]. Lavanya et al. showed that in late preterm infants large for gestation, lower gestational age, birth trauma, and previous sibling with jaundice predicted risk for severe jaundice in the cohort [68]. Mothers should be counseled for frequent breastfeeding and these infants should have predischarge risk assessment, need to be kept in followup and if develops significant hyperbilirubinemia above the threshold of gestational age, than management involves phototherapy or rarely exchange transfusion [69].

Wang et al. showed that late preterm were clinically jaundiced more often (54.4 versus 37.9%; OR: 1.95; 95% CI: 1.04–3.67; $p = .027$) [37]. Similarly, Tomashek et al. also found that of late preterm infants who were readmitted to the hospital in the neonatal period, 45.7% had a principal diagnosis of jaundice [31]. The studies conducted by Jaiswal et al. and Rather et al. also reported significant higher incidence of jaundice in late preterm cohort when compared to term counterpart [38,56]. A retrospective study by Newman et al. reported that infants born at 36-week gestation had nearly four time the odds for developing serum bilirubin levels >20 mg/dl when compared to those born at 39–40 weeks. In this study, gestational age was a strong predictor of severe jaundice, indicating that physicians were treating late preterm infants with less aggressive treatment protocols applicable to term infants [70]. In another retrospective study, Maisels and Kring reported that infants at 35–36, 36–37 weeks, and 37–38-week gestation were 13.2, 7.7, and 7.2 times more likely to be readmitted to the hospital and require phototherapy for significant hyperbilirubinemia than those ≥40-week gestation [71]. Sarici et al. showed that late preterm infants were 2.4 times more likely to develop significant hyperbilirubinemia than term infants, and nearly one in four late preterm infants required phototherapy for jaundice. In this study, late preterm had significantly higher bilirubin levels on day 5 and day 7, indicating relatively delayed bilirubin peak with a tendency to persist for a longer duration in them [72].

Bhutani and Johnson compared the clinical profile and health care experiences related to the management of newborn jaundice and hyperbilirubinemia in preterm infants (<37-week gestation) who are cared for as term infants (≥37 weeks) and develop acute and/or chronic posticteric sequelae using Data from Pilot Kernicterus Registry (1992–2003). The authors found that no targeted attention was accorded to preterm infants during their neonatal health care experiences as related to predischarge risk assessment, feeding, discharge follow-up instructions, or breastfeeding, regardless of the known vulnerability of preterm infants to safely transition during the first week after birth. Large for gestational age and late preterm infants disproportionately developed kernicterus as compared with those who were appropriate for gestational age and term [73].

Respiratory morbidities

Late preterm infants are born during the transition from the terminal sac period to the alveolar period of lung development. During the terminal sac stage, terminal respiratory units are composed of alveolar saccules lined with cuboidal type II (source of surfactant) and flat type I epithelial cells [74]. From 34 to 36 weeks' gestation, terminal respiratory units of the lung develop to mature alveoli lined primarily with extremely thin type I epithelial cells (alveolar stage). In the alveolar stage, pulmonary capillaries also start bulging into the space of each terminal sac, and surfactant amount is increased in lungs. Therefore, in these late preterm functional deficiencies in surfactant and management of lung fluid also occur [52]. These preterm infants surfactant lacks phosphatidylglycerol predisposing them to develop respiratory distress syndrome (RDS) [75,76]. In the last 6 weeks of gestation, the fetus starts developing synchrony and control over breathing, thus such immature structural and functional deficiencies predispose late preterm infants to respiratory failure [77]. The cardiopulmonary transition that is necessary immediately after birth for postnatal adaptation may be delayed in late preterm infants, which is reflected by higher rates of retained fetal lung liquid syndrome (transient tachypnea) and RDS than in term counterparts [78,79]. Traditional explanations such as vaginal squeeze and starling forces may play some role and can only account for a fraction of the fluid that is absorbed [80]; studies show that the epithelium sodium channels (ENaCs) play an important role in the transepithelial movement of fetal lung fluid [81]. Increased number and activation of the ENaC channels close to birth and after birth leads to movement of sodium from the alveolar lumen across the apical membrane into the cell, with subsequent extrusion out of the cell by Na^+/K^+-ATPase [82]. Peak expression of the ENaC channels occurs at term gestation; late preterm infants are therefore born with lower expression of ENaC, which reduces their ability to clear lung fluid after birth [83,84].

Late preterm is also prone to develop persistent pulmonary hypertension (PPHN) and apnea. Apnea in late preterm is secondary to decreased ventilatory response to increased carbon dioxide levels; biphasic ventilatory response to hypoxia and very compliant chest wall and upper airway [43,85]. Teune et al. conducted meta-analysis and reported that the incidence of apnea was 0.9% in the late preterm and was 0.05% in the term infants [86]. Studies have reported that PPHN is more commonly seen in late preterm infants who develop RDS after birth when compared to infants born at 32 weeks' gestation. This predisposition is attributed to a developmental increase in smooth muscle in the walls of pulmonary blood vessels. Hibbard et al. in their retrospective study reported the incidence of PPHN being 0.38% in late preterm infants when compared with 0.08% in term infants, and the incidence of respiratory failure being 0.94% in late preterm infants compared with 0.11% in term infants [87]. When the cause of preterm delivery is fetal infection or maternal chorioamnionitis, this predisposes late preterm infants to neonatal sepsis and pneumoniae [43]. The incidence of pneumonia in infants born at 34 weeks' gestation is significantly higher compared with infants born at 39-week gestation (1.5 versus 0.1%) [87]. Management of respiratory issues includes oxygen, continuous positive airway pressure, surfactant, invasive ventilation, antibiotics, or pulmonary vasodilator depending upon the etiology [88,89].

Several studies have consistently shown that late preterm infants are at higher risk for transient tachypnea of the newborn (TTN), RDS, PPHN, and respiratory failure than term infants [33,90–92]. Wang et al. showed that late preterm infants had nine times the odds of respiratory distress than term infants (28.9 versus 4.2%; OR: 9.14; 95% CI: 2.9–37.8; $p < .001$) [37]. Recently published data from the British Columbia Perinatal Database Registry by Khashu et al. found that late preterm infants had 4.4 times relative risk (95% CI: 4.2–4.6) of respiratory morbidity than term infants [93]. In other large population-based study, Gilbert et al. found the incidence of RDS to be 7.4% at 34 weeks, 4.5% at 35 weeks, and 2.3% at 36 weeks with 6.3% infants required mechanical ventilation at 34 weeks, 3.6% at 35 weeks, and 2.3% at 36 weeks, thus showing decrease in respiratory morbidity with every week increase in gestational age [94]. Hibbard et al. reported that in preterm neonates born at 34 weeks, the odds for developing RDS were increased 40-fold; and the risk decreased with each advancing week of gestation until 38 weeks [87].

Prematurity by itself is responsible for significant respiratory morbidity, but when coupled with the cesarean section and absence of labor, it can exaggerate the incidence of respiratory distress. Several studies of term infants have shown increased odds of respiratory distress for births by cesarean section without labor; this risk increases substantially with a drop in gestational age [95,96]. Morrison et al. found that the incidence of respiratory morbidity was significantly higher for the group delivered by cesarean section before the onset of labor (35.5/1000) compared with vaginal delivery (5.3/1000) (OR 6.8; 95% CI 5.2–8.9; $p < .001$) [97]. A large Dutch study similarly found increased odds of severe respiratory distress with decreasing gestational age; at 37 weeks, infants born by cesarean section without labor had five times the odds of severe respiratory morbidity than those born by vaginal delivery at 39 weeks [98].

Infection

Late preterm neonates have unique susceptibility to infection and have higher incidence of early-onset sepsis and nosocomial infection [99,100]. These neonates are at high risk for sepsis secondary to impaired host defense mechanisms, limited amounts of protective endogenous flora on skin and mucosal surfaces, reduced maturity and barrier function of neonatal skin, the use of invasive procedures and devices during NICU stay, and frequent exposure to broad-spectrum antibiotics [84]. Hand hygiene and prevention of central line associated bloodstream infection, are the two most important intervention to reduce incidence of sepsis [101,102]. Wang et al. found that late preterm infants have approximately four times the odds for being screened for sepsis than term infants (36.7 versus 12.6%; OR: 3.97, CI: 1.82–9.21; $p < .01$); the majority of the late preterm infants screened for sepsis were treated with antibiotics and were likely to be treated longer (30 versus 17% in term infants). The likelihood of having a positive sepsis screen increases with decreasing gestational age [37]. McIntire and Leveno found that 33 versus 12% of infants were screened for sepsis at 34 and 39 weeks respectively and only 0.4% of those screened had culture-proven sepsis [79]. Tomashek et al. also found that of late preterm infants who were readmitted to the hospital in the neonatal period, 31.4% had a principal diagnosis of infection [31]. Similar results of higher incidence of neonatal sepsis in this group of neonate have also been reported by other authors too [38,39,56]. Late preterm infants often have conditions such as mild RDS, TTN, hypoglycemia, and hypothermia, which are all related to their prematurity, but these conditions may be enough to prompt the clinician to screen and treat these infants for suspected sepsis [33,103].

Readmission

Several case-control studies designed to evaluate risk factors for neonatal hospital readmission after the birth hospitalization has identified late-preterm birth as a significant risk factor. Studies that compared neonatal hospital readmission rates among late-preterm infants and term infants have found that late-preterm infants are more likely to be readmitted than term infants and the incidence varies from 1.5 to 3 times when compared to term infants [32,51,104]. The two most common causes of rehospitalization are neonatal jaundice and feeding difficulties [105]. A large study in the United Kingdom, Oddie et al. found that infants born at 35 through 37 weeks' gestation were 1.7 times more likely to be readmitted during the neonatal period than were infants born at 38 through 40 weeks' gestation (OR: 1.7; 95% CI: 1.2–2.6) [106]. Late-preterm infants with short NICU stays may be at increased risk of hospital readmission after the birth hospitalization compared with all other NICU survivors. A study by Escobar et al. that assessed outcomes among all newborn infants discharged alive from six NICUs found that preterm infants of 33–36 weeks' gestation with a hospital stay of less than four days had higher hospital readmission rates than all other groups, including the most preterm group [107]. Tomashek et al. also found that late-preterm infants who are discharged early (< 2-night hospital stay) from the hospital after a vaginal delivery may be at increased risk of neonatal morbidity compared with term infants who are discharged early [31]. The reason for readmission in these preterm infants include jaundice, feeding problems, respiratory illness, and infections [108].

Mortality

Birth/infant death files from 1995 to 2002 in the USA showed that despite significant declines in mortality rates for late preterm infants than term infants since 1995, the infant mortality rate in 2002 was three times higher in late preterm infants when compared to term infants (7.9 versus 2.4 deaths/1000 lb) [31]. Young et al. showed a higher rate of neonatal mortality in late preterm infants and there was also increasing mortality and relative risk of death for every decreasing week in GA <40 weeks. This relationship was seen in both early neonatal mortality (days 1–7), neonatal mortality (days 1–28), and infant mortality rates. The most common cause of mortality was birth defects [109]. Pulver et al. compared neonatal and infant mortality rates of SGA, AGA, and LGA late preterm, early term, and term newborns using same dataset. Late preterm SGA infants were 44 times more likely than term AGA newborns to die in their first month and 22 times more likely to die in their first year. Therefore, authors concluded that being SGA substantially increases the already higher mortality of late preterm and early-term newborns [110]. Similar results have been published by Rather et al. [56], McIntire and Leveno [79], and Kramer et al. [111] in addition to mortality, this group of late preterm infants add a substantial burden to the neurocognitive and pulmonary morbidity rates in premature infants [111].

Intraventricular hemorrhage (IVH) and periventricular leucomalacia (PVL)

Germinal matrix hemorrhage–intraventricular hemorrhage (GMH–IVH) are common in very preterm and extremely preterm infants and its incidence decreases with increase in gestational age [112]. Cranial ultrasonography is not routinely performed in late preterm infants, therefore, the true incidence of IVH is underestimated in this cohort [85]. McIntire and Leveno in their retrospective cohort study reported that incidence of GMH–IVH grades 1 and 2 (Papile classification [113]) decreased with advancing gestational age from 0.5% at 34 weeks to 0.2% at 35 weeks, 0.06% at 36 weeks, and 0.01% at 39 weeks [79]. As per the current evidence, any GMH–IVH or severe GMH–IVH occurs infrequently in moderately preterm and late preterm infants [85]. Teune et al. conducted systematic review of 22 studies and reported that IVH occurred more frequently (OR: 4.9; 95% CI: 2.1–11.7) in late preterm infants. Similarly rates of severe IVH (grades 3–4) were also higher (0.01 versus 0.004%) in late preterm infants [86]. PVL has been defined as focal periventricular necrosis associated with diffuse reactive gliosis and microglial activation in the surrounding cerebral white matter [114,115]. There was very scarce data of PVL in late preterm infants because of infrequent head ultrasound in this cohort [85].

Long-term outcome

Late preterm infants have a higher risk of all cause hospital admission from neonatal to adolescence period [116]. These late preterm infants are at increased risk of neurologic impairments, developmental disabilities, school failure, behavioral and psychiatric problems from infancy to adulthood [117]. These infants have underdevelopment of multiple organ systems including brain. The second half of gestation is an important period of brain growth and there is five-fold increase in brain volume between 35 and 41 weeks [114,118]. The process of brain maturation including neurogenesis, synaptogenesis, and dendritic arborization occurs during the last weeks of pregnancy and this process is interrupted with infant birth [114]. These late preterm are more likely to be readmitted or visit emergency department after hospital discharge because of multiple reasons [119,120]. Barros et al. compared the neurobehavior of healthy late preterm and full-term infants and reported that late preterm infants when compared to term neonates, had lower scores for attention ($p = .041$), arousal ($p = .011$), regulation ($p < .001$), quality of movements ($p < .001$) and higher scores for nonoptimal reflexes ($p < .001$) and hypotonicity ($p = .029$). Thus showing that preterm have a more immature neurobehavioral performance at 24–72 h of life in multiple areas compared to term neonates suggesting a need for careful follow-up [121]. Woythaler et al. showed that at 24 months of age late preterm infants when compared with term infants had lower mental index scores (MDI) (85 versus 89) and psychomotor index scores (PDI) (88 versus 92), both $p < .0001$, respectively. A higher proportion of late preterm infants compared with term infants had an MDI <70 (21 versus 16%; $p < .0001$). Late preterm infants had higher odds of mental (OR: 1.52, 95% CI: 1.26–1.82, $p < .0001$) or physical (OR: 1.56, 95% CI: 1.30–1.89, $p < .0001$) developmental delay [122]. Late preterm has increased the risk of cerebral palsy, mental retardation, and schizophrenia when compared with term infants [86,123]. Shah et al. reported that children born in the late preterm period demonstrated less optimal scores in preschool reading ($p = .0006$), preschool mathematics ($p = .0014$), and kindergarten reading ($p = .0007$) compared with infants born at term gestation [124]. Dusing and coworker conducted systematic review and concluded that late preterm infants are at an increased risk of neurodevelopmental delay between 1 and 18 years of life when compared to those born at term and this delay was most evident in the cognitive domain of neurodevelopment. They also concluded that these infants were also at risk of delayed language development, motor development, and lower academic performance [125].

Conclusions

Late preterm infants are the fastest growing subgroup of neonates, comprising the majority of all preterm births. They look alike term infants but, they are at significantly higher risk of various morbidity, mortality, and adverse long-term outcomes well beyond infancy into adulthood. These infants need careful observation soon after birth. However, epidemiology and etiology of late preterm births, the magnitude of their morbidity, the long-term life quality, and public health impact have not been well studied. The growing number of late preterm neonates substantiates the importance to better understand and medically approach this special preterm subgroup. A long-term evaluation, monitoring, and follow-up of late preterm infants are needed to optimize neonatal care and improve human health status. Understanding the morbidity pattern in late preterm infants not only helps the newborn care providers to anticipate the risks and monitor them for timely intervention but also provides guidelines for obstetrical decision making. As majority of the time minimal infrastructure, monitoring, and support would suffice to stabilize them, even in resource-limited countries a large difference can probably be made to neonatal morbidity and mortality by giving adequate attention to late preterm babies compared to small premies who need more specialized care.

Disclosure statement

No potential conflict of interest was reported by the authors.

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