Late preterm pathologies and prognosis

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Abstract

Infants born between 34 weeks 0 days and 36 weeks 6 days of gestation are called late preterm infants (LPTi). This group accounts for the majority of preterm infants.

Late preterm birth is associated with a higher risk of immediate clinical problems in a wide variety of organ systems. This includes the need for respiratory support, gastro-intestinal immaturity, hypoglycemia, hypothermia and hyperbilirubinemia. There are also more long-term morbidities with higher risk for neurodevelopmental problems and chronic respiratory and metabolic pathologies.

Therefore, this group is associated with high societal, emotional and financial costs. They require special attention during hospitalization and follow-up. Developing a structural care program in maternity and neonatal units can be useful.

Epidemiology

The past decades, there has been a significant increase in preterm births, especially late preterm births. Evolution in obstetric care pursues a decrease in very preterm and extremely preterm births, resulting in an increase in late preterm births. Changing maternal demographics and maternal health (e.g. higher maternal age, more obesity worldwide, …) are also possible explanations. In 2020, 7 to 8 percent of births in Belgium are premature. Late preterm infants represent one third to three quarters of this population (1-4). In singleton births, four to six percent of all deliveries occur between 34 and 37 weeks. In multiple gestation, approximately 40% of the children are born late preterm (3,4).

Late preterm infants have substantially lower mortality rates and less severe morbidities compared to very and extremely preterm infants. However, their disease burden should not be underestimated. The mortality rates among late preterm infants are 2 to 3 times higher compared to term infants (5,6). Overall morbidity rates in late preterm infants are even 7 times higher than in term infants (22% vs 3%). Given their immature respiratory and hemodynamic status, late preterm infants are at higher risk for any form of resuscitation support in the delivery room. They have higher rates of admission to NICU and have more rehospitalizations (6,7). Therefore, the terminology has changed from 'near term' infants to 'late preterm' infants to emphasize their significant immaturity and associated mortality and morbidity. They are associated with high societal, emotional and financial costs, due to their large absolute number (5,6).

In most cases (50-75%) late preterm birth occurs due to spontaneous labor or premature rupture of membranes. Potential risk factors are higher maternal age, smoking, low socio-economic status, multiparity and medically assisted reproduction (5).

Late preterm delivery is medically induced in 30% of the cases because of maternal and/or fetal conditions (5). Possible fetal indications include intra-uterine growth restriction, oligohydramnios, monochorionic twins or complicated multiple gestation. Maternal conditions are either pre-existing (e.g. hypertension, diabetes with vascular complications,…) or pregnancy related (e.g. preeclampsia, cholestasis, poorly controlled gestational diabetes,…). Uterine and placental anomalies (e.g. placenta praevia, placenta accreta, prior uterine rupture,…) can also lead to late preterm delivery (8).

Respiratory complications

An efficient gas exchange requires cleared and ventilated alveolar spaces and an increase in pulmonary blood flow to match ventilation and perfusion (7,9). In LPTi, the pulmonary development is still immature, at terminal saccular stage. This stage is characterized by maturation of dense alveolar saccules into thin, mature and more easily ventilated alveoli. Type II pneumocytes also become more prominent at 34 to 36 weeks of gestation. They are the source of pulmonary surfactant, reducing surface tension at the air-water interphase and facilitating expansion of the alveoli. In addition, pulmonary capillaries begin to bulge into the space of each terminal sac to increase pulmonary blood flow (9).

Late preterm infants more often have symptoms of respiratory distress (e.g. transient tachypnea, respiratory distress syndrome, pulmonary hypertension, pneumothorax,…) than term infants. This increases the length of neonatal stay in one third of these infants and the need for oxygen therapy, respiratory support and surfactant replacement is higher compared to term infants (6). Relative risks of nasal continuous positive pressure or mechanical ventilation requirements are respectively 9 and 5 times higher.

The incidence of respiratory problems in late preterm infants has a strong age-related trend. More than 20% of infants born at 34 weeks have respiratory distress compared to 7% in infants born at 36 weeks' gestation (1,7).

Antenatal betamethasone therapy decreases the rate of respiratory morbidities (1,6). However, this therapy is not routinely recommended for impending late preterm deliveries. The positive effect on the mild and frequently self-limiting respiratory morbidities doesn't always outweigh the side effects (e.g. impaired growth, hypoglycemia, …) and unknown long-term effects (10).

Transient Tachypnea of the Newborn (TTN)

TTN is defined as a late clearance of lung fluid from the alveolar space. The incidence in late preterm infants is up to 4% (7). Several explanatory mechanisms are proposed. Late preterm infants have weaker respiratory muscles and more inadequate surfactant production. This ensures that insufficient inspiratory pressures are generated, which can lead to insufficient lung aeration (11). Sodium channels in the lung epithelial cells play a role in the clearance of lung fluid. As their expression is gestational age-related with a peak expression at term gestation, late preterm infants are more at risk to develop TTN (7).

During active labor, sodium channels are activated by increased fetal epinephrine and steroid concentration. Therefore, preterm infants born by cesarean section in absence of labor and "vaginal squeeze", are more at risk to develop TTN (7).

Respiratory Distress Syndrome (RDS)

RDS is the result of qualitative and/or quantitative deficiency of pulmonary surfactant. Preterm infants have both an immature surfactant system and a quantitative deficiency (7,9). Uterine contractions enhances surfactant production, therefore birth by cesarean section in absence of labor is a risk factor for developing RDS (7).

The incidence of RDS in late preterm infants is 8 to 13-fold higher than in term infants (7).

Apnea of Prematurity

During the last 6 weeks of gestation, significant changes occur within several brainstem regions. These changes contribute to a synchronized and coordinated breathing with maturation of the upper airways and lung volume control, laryngeal reflexes, chemical control of breathing and sleep-wake cycle. Immaturity of these brainstem regions may result in apnea of prematurity. Late preterm infants are thus more at risk for central apnea (7,9). Obstructive apnea also occur at greater frequency as late preterm infants have highly compliant chest wall and upper airways who tend to collapse when the diaphragm contracts (7).

Persistent Pulmonary Hypertension of the Neonate (PPHN)

Late prematurity is a significant risk factor to develop PPHN as late preterm infants have an increase in smooth muscle cells in the walls of pulmonary blood vessels. This leads to increased pulmonary vascular resistance and eventually shunting and ventilation-perfusion mismatch (9). The presence of RDS is a risk factor due to alveolar atelectasis (7).

The overall incidence of PPHN in late preterm infants is 0.4%, compared to 0.08% in term infants. In infants with respiratory morbidities, the incidence in the late preterm group is 0.94%, compared to 0.11% in term infants (9).

Pneumothorax

Pneumothorax is more present in late preterm infants, due to the structurally immature and less compliant lungs and (invasive) ventilation support (6).

Management

As a result of these multiple risks for pulmonary complications, a close clinical monitoring is needed in late preterm infants. When signs of respiratory difficulties arise (immediately after birth or in the first hours of life), cardiorespiratory monitoring and appropriate therapy must not be delayed (6).

Gastro-intestinal complications

Gastro-intestinal problems occur in one third of all late preterm infants, compared to 7% of term infants (6). Feeding difficulties are the primary reason for prolonged hospital stay in LPTi (6, 7, 12). Poor weight gain, dehydration and failure to thrive are frequently seen in LPTi (7, 12). Possible explanations can be categorized in following domains.

Firstly, late preterm infants have an important oral motor hypotonia and are rapidly fatigued resulting in difficult persistent latching and suckling. They often require feeding support and time to reach full enteral feeding is significantly longer (6,7,12). Their orobuccal, breathing and feeding coordination is also immature with a higher risk of choking (7,12). Observing feeding moments is therefore important. If a discoordination is present, an early consultation with a speech therapist can be useful (6). Because of their delayed gastric emptying, LPTi also have a higher frequency of gastroesophageal reflux, which can contribute to reducing food intake (7).

Secondly, breastfeeding is frequently complicated due to both inappropriate lactogenesis in the mother following maternal pregnancy complications and latching difficulties in preterm infants. Given the normal delay in full maternal milk supply, breastfeeding problems can initially go unrecognized until a larger amount of breastmilk is required. This may lead to an inadequate intake resulting in failure to thrive (6).

The incidence of initiation and maintenance of breastfeeding in late preterm infants is significantly lower than in term infants. Therefore, both support and education from lactation consultants and kangaroo or skin-to-skin care are crucial (12).

Lastly, the nutritional requirements of late preterm infants have not been specifically evaluated. Higher energy expenditure and thus higher nutritional needs are expected, as derived from those of very preterm infants (8). Close monitoring of weight is essential to evaluate the need for active nutritional support (parenteral nutrition, gavage feeding, fortifiers, supplements, …) (7,12). The requirements for vitamins, minerals and trace elements are also likely to be higher in LPTi, but insufficient data is available to make concrete recommendations. The incidence of vitamin D deficiency is higher in LPTi suggesting that higher vitamin D supplementation could be useful. Late preterm infants are also at risk for developing iron deficiency and associated microcytic anemia because of their lower iron stores related to the shorter duration of pregnancy, lower birthweight and multiple blood sampling (12). A better neurological development is also seen in late preterm infants who receive early routine prophylaxis (13). Tubules of LPTi excrete a significantly higher amount of sodium compared to tubules of term infants, due to an immature renal function (14). This may play a role in the presence of failure to thrive in LPTi as serum sodium is correlated with weight gain. Monitoring is thus recommended.

Metabolic complications

Hypothermia

Neonates rely on non-shivering thermogenesis to maintain body temperature. Brown fat, which is produced from the 28th week of pregnancy, is the source of this thermal regulation, together with hormonal regulation. Efficiency of temperature regulation is therefore dependent on gestational age and is defined by the amount of brown fat and the maturity of the hypothalamus. In addition, preterm infants have more heat loss because of a higher surface area to weight ratio, less white adipose tissue and an immature epidermal barrier (15). Rigorous monitoring of the temperature and prevention of heat loss is of importance. In the first hours, this might be supported by early skin-to-skin contact with one of the parents, thorough drying of the skin and the use of caps and warm blankets. During the rest of the hospital stay, close follow up and adjustment of room temperature and clothing remains important. Incubators, warming beds or heat tables decrease the risk of temperature instability. Skin to skin contact is still advised during the whole hospitalization.

Hypoglycemia

Late preterm infants have reduced glycogen stores and an immature hepatic glycogenolysis and gluconeogenesis in combination with inappropriately high secretion of insulin. The sudden discontinuation of maternal glucose supply after birth may therefore cause hypoglycemia when there is an insufficient metabolic response. Limited enteral intake due to immaturity, higher glucose need (hypothermia, infection, hypoxia), less alternative energy sources (intrauterine growth restriction) or higher circulating insulin in case of unbalanced maternal diabetes may further contribute to the higher risk of hypoglycemia (15). Therefore, systematic monitoring of the glycemia is recommended in late preterm infants during the first 24 hours of life as well as early feedings and support of breastfeeding. In some situations, transient intravenous glucose administration might be needed to insure proper levels of serum glucose (16).

Hyperbilirubinemia

Due to an immature liver function with slower bilirubin conjugation and increased enterohepatic circulation, jaundice occurs more often and can be more prolonged in late preterm infants. Concurrent infections or feeding difficulties with secondary dehydration can further increase the risk of hyperbilirubinemia.

The blood-brain barrier in late preterm infants is more permeable. This, in combination with lower circulating albumin, can make them more vulnerable for neurological complications at lower bilirubin levels (17).

Guidelines for phototherapy incorporate those risks and a lower threshold for initiation of therapy is recommended in late preterm infants (18).

Infectious complications

The late-preterm infant is more vulnerable for infections because of an immature immune system, less transplacental maternal antibodies and associated comorbidities.

The innate as well as the adaptive immune system is less developed in preterm infants, partly because of a deficient production of immunoglobulins, complement proteins and a less effective cellular response to infections (19).

An infant is protected with passive immunity by transplacental passage of antigen-specific immunoglobulins in the third trimester. This transfer increases with fetal age, so preterm and late preterm infants have lower levels of circulating maternal IgG's. The use of human milk is therefore crucial to support the preterm infants' immature immune system after birth. It contains high concentrations of secretory IgA and IgG as well as human milk oligosaccharides and many other immunomodulatory components. These components are suggested to compensate for the deficiencies in the neonatal immune system (20).

Higher incidence of intrauterine inflammation in preterm infants as well as the need for vascular access and respiratory support devices further increase the risk of infections like sepsis and pneumonia in this vulnerable population (19).

Neurological complications

Brain weight at 34 weeks is only 65% of that of the term baby. Between 34 and 40 weeks of gestation, the brain experiences significant growth and development with intense synaptogenesis, dendritic arborization and myelination. The cortical surface growth is exponential at those ages with the development of sulci (21,22).

Ultrasound screening is not always routinely performed in late preterm infants because of the low prevalence of acute neurological problems. However, intraventricular hemorrhage does occur more often than in term infants (0.41% vs. 0.09%). Therefore imaging should be done on clinical suspicion and with low threshold (23).

Long term complications

Different studies reported that late preterm infants have a threefold increased risk for cerebral palsy compared with term infants and are also more vulnerable for minor psychomotor impairments such as cognitive difficulties, language and praxis problems, social interaction disturbances and attention-deficit disorders (21,23,24).

At preschool age, two studies report significantly lower communication and gross motor scores for late preterm infants, both at 12 month corrected age and at 3 years of age (25,26).

At school age, a descriptive meta-analysis reported a moderate deficit concerning neurological impairment, school skill and requirement of early intervention program (27). However, these differences were only significant for infants with a complicated neonatal course and not significant for babies with an easy neonatal course (24-27).

Late preterm infants have a higher respiratory vulnerability than term infants, even in the absence of acute respiratory impairments after birth. Within the first years of life, they have a higher incidence of respiratory interventions and need respiratory support more frequently. Late preterm gestation is also associated with asthma as the lung function of these infants is compromised with a persistent decreased forced expiratory flow and forced vital capacity with a higher residual volume (8).

The incidence of an Apparent Life Threatening Event (ALTE) and sudden infant death syndrome (SIDS) is also higher in late preterm infants compared to term infants (8-10% vs <1% for ALTE and 1,36/1000 vs 0,69/1000 for SIDS) (7).

This group also has a higher risk for respiratory infections in the first two years of life. Because of this vulnerability, they benefit from an adapted vaccination scheme. In Belgium, a supplementary dose of conjugated pneumococcal vaccination is administered at the age of 12 weeks and the booster vaccinations of 15 months are given at 12 months of age. Influenza vaccination is recommended for infants older than 6 months. Passive immunization for RSV with palivizumab is recommended in late-preterm infants with more than 48 hours of respiratory support in the NICU if they are less than 6 months old at the beginning of the RSV season.

To further protect this population, influenza and pertussis vaccination is advised for family members and caretakers of infants <6 months of age.

In adulthood, higher incidences of arterial hypertension, obesity and metabolic syndrome have been described (1,5,23). Preventive measures should be taken where possible.

Conclusion

It is important to recognize the increased risk for complications in the late preterm infant and try to avoid them. This can be done antenatally by interdisciplinary consultation to correctly indicate the need for preterm delivery and betamethasone administration. Postnatally it is important to implement preventive measures and monitor for known complications including respiratory adaptation difficulties, hypothermia, hypoglycemia and to initiate appropriate treatment where necessary.

This group of infants also requires a specific and close follow-up as they are at higher risk for long-term neurodevelopmental impairment and other chronic problems. Developing a structured care program after discharge can therefore be useful for both acute and chronic impairments. At the same time focusing on non-separation between parents and infants can facilitate bonding and benefit breastfeeding. It is important to keep mother and child together as much as possible by stimulating kangaroo care and creating units with the possibility of rooming-in (28).

Disclosure

There is no conflict of interest for any of the authors.

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