An overview of morbidity, mortality and long-term outcome of late preterm birth

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Background: **Preterm birth rate continues to rise around the world mainly at the expense of late preterm newborns, recently defined as births between the gestational age of 34 weeks and 36-6/7 weeks. Late preterm infants are considered to have significantly more short-term and long-term adverse outcomes than term infants.**

Data sources: **Articles concerning morbidity, mortality and long-term outcomes of late preterm infants were retrieved from PubMed/MEDLINE published during the period of 2000-2010.**

Results: **Late preterm infants are the fastest growing subgroup of neonates, comprising the majority of all preterm births. Compared with term infants, they have significantly higher risk of morbidity, mortality and adverse long-term outcomes well beyond infancy into adulthood. 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.**

Conclusions: **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.**

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Review article

Introduction

The rate of preterm birth is increasing worldwide primarily at the expense of late preterm newborns,[1-3] recently defined as births between 34 weeks and 36-6/7 weeks of gestation.[1] Late preterm infants are the fastest growing subgroup of neonates and constitute approximately 75% of all preterm births in 2009.[4,5] The birth rate of late preterm newborns has increased by 25% from 1990 to 2005 in the United States.[6] In clinical practice, late preterm newborns have been historically managed as term neonates because of their relatively large size and seemingly mature appearance.[1,7,8] However, a growing body of evidence suggests that the incidence of medical problems, either short-term or long-term, is higher among late preterm infants than term infants.[1,4,7-9] Because late preterm infants comprise the majority of preterm newborns, caring for such a large population who are prone to have unfavorable outcomes can exert a profound impact on the society. This review focused on health facets of late preterm infants to help readers understand this significant public health problem better and reevaluate our obstetric and neonatal practice.

Etiology

To date, limited studies have addressed the etiology of late preterm births. Reddy et al[10] categorized the etiology of late preterm deliveries into five groups: maternal medical conditions, obstetric complications, major congenital anomalies, isolated spontaneous deliveries and no recorded indications, which accounted for 14%, 16%, 1%, 49% and 23.2% of all deliveries respectively.[10] Laughon et al[11] reported that spontaneous labor, preterm premature rupture of membranes, and indicated deliveries each accounted for about 30% of late preterm births. These two tudies revealed three aspects. Firstly, medically indicated elective cesarean sections (CSs) were responsible for the majority of all late preterm deliveries; secondly, varied neonatal morbidities and mortalities depended upon the indications for delivery; and thirdly, a certain proportion of deliveries with unknown indications were likely patient-scheduled CS and thus potentially avoidable.[10,11]

No consensus has yet been reached on the contributing factors of the increase in late preterm births. Available data have suggested medically indicated deliveries and patient-driven factors were responsible for the increase of late preterm newborns.[10-13] Because the actual indication for delivery is recognized as a determinant in neonatal outcome,[10,11] more attention should be devoted to examine the etiology of late preterm births.

Morbidities and readmission

Late preterm neonates are at higher risk of morbidities than their term counterparts. Additionally, when they suffer from a certain disease, the condition is usually more severe than term infants with the same problem. Because neonatal disorders rise gradually as gestational age (GA) falls, immaturity remains central in the pathogenesis of diseases in late preterm neonates. Shapiro-Mendoza et al[4] found that the risk for the development of neonatal morbidities in late preterm infants was 7 times higher than in term controls. Hunt[14] also found that the incidence of apparent life-threatening events in late preterm infants was at least 8 times higher than in full-term infants. Available data have suggested respiratory distress syndrome (RDS), persistent pulmonary hypertension of newborns (PPHNs), hyperbilirubinemia, intraventricular hemorrhage (IVH), culture-proven sepsis, temperature instability, hypoglycemia, dehydration and feeding difficulties occurred more frequently in late preterm neonates than their term counterparts.[3,5,15,16] Among them, hyperbilirubinemia and RDS were demonstrated as the most frequent problems.[9] Compared with term infants, late preterm newborns are more likely to have bilirubin-induced brain injury which may occur in a fulminant way because of hyperbilirubinemia (kernicterus)[9] or in a more subtle way because of prolonged physiologic jaundice.[1] The underlying pathophysiology of RDS has been clarified as the combination of three factors: the immature capacity of the lung to produce surfactant, non-clearance of lung fluid attributable to CS, and birth prior to spontaneous labor.[17] RDS in late preterm neonates is hard to prevent because of a significant number of unavoidable elective CS, and additionally, neonates suffer from RDS are likely to develop life-threatening complications such as PPHN.[3,18] Since there is no evidence-based treatment guideline, late preterm RDS is a problem for health practitioners and it is considered one of the major drivers for increased mortality in late preterm infants.[7]

Because of the misleading conception that late preterm is almost term, late preterm neonates are discharged inappropriately according to the guidelines for term neonates. Early postnatal discharges (within 48 to 72 hours) are recorded in late preterm infants.[7,19,20] Early hospital discharge prevents early recognition and timely intervention of potential disorders. Thus it is not surprising that late preterm infants have a significantly higher rate of readmission than term neonates.[7,19,20] Apart from early discharge, other factors such as assisted ventilation, male sex, small gestational age (SGA) and breastfeeding also contribute to the high rate of readmission in late preterm infants.[7,19,20] McLaurin et al[21] reported that late preterm infants were almost twice as likely as their term counterparts to be re-hospitalized during the first postnatal year well beyond the neonatal period, contributing to a two-fold increase in medical cost. Jaundice, infection, feeding difficulties and failure to thrive are considered common causes of readmission.[7]

Mortality

The morbidity is significantly higher in late preterm infants than in term ones, thus it is not surprising that

Table 1. Risk of mortality in late preterm infants compared with term infants

References	Year of patients' birth	Country	Age to follow-up	Mortality rate (%)	RR (95% CI)
Guasch et al[2]	1992-2008	Spanish	Until discharge	0.5	4.7 (2.3-9.5)
Mathews et al[22]	2003	USA	1 y	0.7	nd
Swamy et al[23]	1967-1988	Norway	1 y	7.0	For girls: 6.3 (5.7-6.9) For boys: 5.7 (5.3-6.2)
Swamy et al[23]	1967-1989	Norway	6 y	0.8	For girls: 1.6 (1.2-2.0) For boys: 1.5 (1.2-1.8)
Swamy et al[23]	1967-1990	Norway	13 y	0.3	For girls: 1.5 (1.0-2.1) For boys: 1.2 (0.9-1.6)
Swamy et al[23]	1967-1991	Norway	18 y	0.4	For girls: 1.3 (0.9-1.9) For boys: 1.0 (0.8-1.4)
Kramer et al[24]	1995	USA	1 y	7.6	2.9 (2.8-3.0)
Kramer et al[24]	1992-1994	Canada	1 y	4.9	4.5 (4.0-5.0)
Pulver et al[25]	1999-2005	USA	1 y	0.8	10.5 (7.1-15.3), 7.2 (5.1-10.4) and 5.3 (3.8-7.2) for infants born 34, 35 and 36 weeks, respectively

nd: no data available; RR: relative risk; CI: confidence interval.

the survival rate of late preterm infants is significantly reduced as reported (Table 1).[2,22-25] The mortality in the early neonatal (age 0-6 days), late neonatal (age 7-27 days) and postneonatal (age 28-364 days) periods was 6, 3, and 2 times higher respectively in late preterm infants than in term infants.[26] During infancy, late preterm infants were 3 times more likely to die than term infants.[26,27] A population-based longitudinal study[23] demonstrated that the mortality rate of late preterm infants was higher than that of term infants from infancy to late childhood (age 6-12.9 years) [adjusted RR (95% CI) for boys and girls was 1.2 (0.89-1.6) and 1.5 (1.0-2.1) respectively]. The mortality rate of late preterm infants is decreased as GA increases, which was demonstrated in a study that the neonatal mortality rates per 1000 live births were 1.1, 1.5, and 0.5 at 34, 35 and 36 weeks respectively, compared with 0.2 at 39 weeks.[15] The common causes of death are congenital malformations, immaturity, sepsis, atelectasis, maternal complications and sudden infant death syndrome (SIDS).[26,27] SGA is suggested to substantially increase the mortality rate.[24]

Neurodevelopmental problems

Late preterm neonates who survived should not be considered a normal population free from medical problems. They have more adverse long-term outcomes than term infants including neurodevelopmental sequelae, since the brain is the most susceptible one in all immature organs to preterm birth.[1] Epidemiologic studies[28,29] have shown that the survival of preterm infants is increased significantly over these years, but at the expense of various neurodevelopmental sequelae such as cerebral palsy, developmental delay/mental retardation, seizure or epilepsy, neurosensory disabilities.[25] A retrospective cohort study[27] revealed that late preterm infants were 3 and 1.47 times more likely than term infants to be diagnosed with cerebral palsy and developmental delay/mental retardation at 5.5 years of age, respectively. The risk might be underestimated because of the improper inclusion criteria.[27] Moster et al[28] found that cerebral palsy, mental retardation and schizophrenia were 2.7, 1.6 and 1.3 times more frequent in late preterm infants than in term infants, respectively. It has been suggested that infants of all GA, including term, are at risk of having neurodevelopmental problems, and the prevalence of neurodevelopmental sequelae in late preterm infants is between that of very premature neonates and term neonates.[30] Because late preterm neonates comprise the majority of preterm population and their number keeps increasing, the impact to be exerted on society by those with neurodevelopemental problems can never be overestimated.

In addition to apparent neurodevelopmental problems, there are developmental lags not severe enough to be defined as sequelae such as cognitive

Table 2. School performance of late preterm infants

Author, year	Participants			Accessing methods	Outcomes	Statistical results
	n	Arms	Follow-up			
Swamy et al, 2008[23]	1 167 506	Late preterm *vs.* term infants	28-34 y	Registry data with Medical Birth Registry of Norway	Not finishing high school	Adjusted RR (95% CI) was 1.13 (1.1-1.17) for women, 1.09 (1.06-1.12) for men
Moster et al, 2008[28]	903 402	Late preterm *vs.* term infants	20-36 y	Data extraction from Norwegian National Education Database	Not completing high school, bachelor's degree and postgraduate degree	Adjusted RR (95% CI) was 1.0 (1.0-1.0), 1.0 (1.0-1.0), 1.0 (0.9-1.0), respectively
Nomura et al, 2009[31]	1619	Late preterm *vs.* term infants	over 30 y	Wechsler Intelligence Scale for Children, Short Form (Wechsler, 1949)	IQ, reading, spelling and arithmetic scores	Scores were 88.9 *vs.* 93.5, 28.8 *vs.* 31.8, 21.0 *vs.* 22.8, 17.7 *vs.* 19.5, respectively
Huddy et al, 2001[32]	187	Late preterm infants, no control	7 y	Self-designed questionnaires and SDQ	Poor speaking/listening, writing/composition, fine motor skills, mathematics, reading, physical education and hyperactivity	Percentage was 19%, 32%, 31%, 29%, 21%, 12% and 19%, respectively
Kirkegaard et al, 2006[33]	5776	33-36 wk *vs.* 39-40 wk infants	10 y	Self-designed questionnaires	Reading, spelling and mathmatic difficulty	Adjusted RR (95% CI) was 1.19 (0.61-2.34), 1.61 (0.86-3.00), 0.95 (0.34-2.69), respectively
Morse et al, 2009[34]	159 813	Late preterm *vs.* term infants	6 y	Data extraction from several local databases and educational staff	Developmental delay/disability, disability in prekindergarten at age 3 and 4, not ready to start school, exceptional student education, retention and suspension in kindergarten	Adjusted RR (95% CI) was 1.36 (1.29-1.43), 1.13 (1.08-1.19), 1.10 (1.05-1.14), 1.04 (1.00-1.09), 1.10(1.07-1.13), 1.11(1.07-1.15), 1.19 (1.10-1.29), respectively

SDQ: Strengths and Difficulties Behavior Questionnaire; IQ: intelligence quotient; RR: relative risk; CI: confidence interval.

deficits, behavioral problems and learning difficulties. Late preterm infants were shown to have worse school performance than their term counterparts in every aspect (Table 2).[23,28,31-34] However, unanimous conclusions are difficult to make on account of the wide heterogeneity among these studies concerning enrolled cohorts, ages at follow-ups, assessing methods, adjusted confounders, definitions and severities of reported school problems.

Mechanisms underlying the neurodevelopmental problems of late preterm infants remain uncertain. Immature brain and secondary brain damage induced by various neonatal disorders were considered to be important factors.[3,35] It is widely recognized that the last 6 weeks of gestation is the critical time for brain growth and development.[1,3] In particular, active myelination persists in late preterm period and for an additional 24 postnatal weeks.[36] Between 34 and 40 weeks of GA, significant growth is observed in the gyri, sulci, synapses, dendrites, axons, oligodendrocytes, astrocytes, and microglia, which contributes to the 50% increase of cortical volume and the 25% increase of cerebellar development.[37,38] In clinical studies, white matter volume reduction was detected in preterm infants born appropriate for GA (AGA) without brain injuries,[39] and significant periventricular leukomalacia was found in late preterm infant autopsies.[40] It has been demonstrated that significantly decreased volumes of sensorimotor, parieto-occipital and midtemporal cortices in preterm brains were associated with decreased full-scale, verbal, and performance IQ scores.[41,42] Late preterm infants are born with definite immature brains and they are more likely to have neonatal disorders which may cause damage to the underdeveloped brain than term infants. Thus, it is not difficult to explain the higher incidence of neurodevelopmental problems observed in late preterm neonates than their term counterparts.

Growth development problems

The first two years after birth is considered prime time for catch-up growth of preterm infants.[15] It is suggested that severe morbidities in late childhood and adolescence, even chronic diseases such as hypertension, hyperlipidemia and high level of blood glucose in adulthood may be partly due to abnormal growth patterns in fetal and infant life.[43,44] To our knowledge, there are limited investigations regarding the growth development of late preterm infants. Santos et al[45] found that the risk of being underweight, stunted and wasted were at least two folds higher for late preterm infants than their term controls. Reasons for faltering growth in late preterm infants remain unclear. Data have suggested the immature gastrointestinal function and a high rate of morbidities were possible causes.[8,15,46] In order to delineate the growth pattern of late preterm infants, multi-center longitudinal researches are required.

Other long-term outcomes

It was reported that receiving a low job-related income and social security benefits were 1.1 times more likely to occur among people born late preterm than their term controls.[28] However, it is difficult to conclude that people born late preterm are at significantly higher risk of having social problems than people born term because the influence of other unadjusted biological and socioeconomic factors on adulthood outcomes can not be ruled out.[28]

It is noteworthy that people born late preterm also have problems in reproduction. The cohort study conducted by Swamy et al[23] compared people born at 33-36 weeks of GA with term controls, finding that the adjusted risk (95% CI) of preterm birth, fetal stillbirth and infant death among offspring were 1.4 (1.3-1.5), 1.1 (0.95-1.4), 1.1 (0.81-1.4) times for women and 1.1 (0.81-1.4), 0.96 (0.74-1.2), 1.4 (1.1-1.9) times for men who were born near term. Whether reproduction problems are results of being born preterm needs further investigation, since reproductive abilities are strongly affected by complicated psychosocial and economic factors apart from the biologic background.

Conclusion

Late preterm infants were a newly defined fast-growing subgroup of preterm neonates who attract increasing attention worldwide. According to current data, they are not as vulnerable as neonates born very premature but have a significantly higher risk of developing either short-term or long-term adverse outcomes than term infants. In view of the great impact of late preterm infants exerting on society, World Health Organization and American Academy of Pediatrics have called for a long-term evaluation, monitoring and follow-up of this vulnerable population.[1] Key areas for future researches include:[1,7,47,48] (1) Educating health care personnel that seemingly mature late preterm infants are to be considered physiologically immature and should be carefully evaluated, monitored and followed; (2) Depicting the epidemiology and etiology of late preterm infants and assessing possibly preventable births, thus to establish an evidence-based delivery indication guideline for late preterm gestations; (3) Describing

gestational-age-specific morbidities and mortalities for late preterm infants; (4) Conducting studies to understand the influence every additional gestational week may exert on developing individual well beyond childhood into adulthood and establishing evidence-based intervention guidelines for every certain neonatal disease, especially respiratory disorders; (5) Assessing the total cost of late preterm birth in short-term and long-term medical, educational and social services, to evaluate the cost effectiveness of delayed deliveries during late preterm period.

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