

Chapter 143

Post-Newborn: A New Concept of Period in Early Life

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Abstract Post-newborn infants refer to infants from >28 days to <100 days after birth. During this period, infants are still completely dependent on breast milk or/and formula milk for feeding. Up to now, the concept of post-newborn has not been mentioned in classic textbooks. With the development of perinatal medicine, mortality rate of diseases in neonates such as premature infants, asphyxia, infectious diseases have decreased significantly, and consequently, issues of the quality of life for these survivors have aroused widespread concerns. The post-newborn infants have some important characteristics differing from both newborn infants and infants after the period: (1) different fatal diseases and mortality rate; (2) the diseases inherited from newborn period requiring early and prompt treatments; (3) some peculiar diseases during this period requiring much attention; (4) either similar or different immune function; (5) rapid growth and uneven development of organ systems. Establishment of the new concept of post-newborn will further reveal the nature of life, reduce the mortality rate of infants, and improve the quality of life.

Keywords Infant · Newborn · Post-newborn

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143.1 The Establishment of the Neonatal Intensive Care Unit (NICU) Could Greatly Reduce the Mortality Rate of Newborn Infant, but not Improve the Quality of Life Synchronously

In the early 1960s, the world's first NICU was established at New Haven Hospital of Yale University, which became a milestone in the developmental history of modern neonatal medicine. After that, NICU has been established in the world in succession and developed rapidly, and thus, neonatal medicine has entered a booming era. With the establishment of transfer and treatment network for the critically ill neonatal infant in the developed areas, the constant in-depth development of the relevant basic and clinical research, improvement of the treatment techniques, and especially the use of pulmonary surfactant, the mortality rate for the seriously ill newborn infants such as low birth weight newborns, extreme low birth weight newborns, severe respiratory distress syndrome have been decreased significantly. The mortality rate of the newborn in United States in 2006 has been dropped by nearly half as compared with that in 1980 (from 8.48 to 4.45 ‰) [1], where as the neonatal mortality rate in China in 2008 has been decreased by 70 % as compared with that of 1990 (from 34.0 to 10.2 ‰) [2]. However, a few surviving infants suffered from different kinds complications in the post-newborn, such as recurrent respiratory infections, physical retardation, cerebral palsy, bronchopulmonary dysplasia, retinopathy, and congenital heart disease requiring early surgical treatment [3–7]. Moreover, the complication and sequelae could change the way of life and learning of the children to some extent, affect their formation of good personality and mentality, lead to various kinds of personal and social problems in adults, add a great deal of disease burden to the countries, families and individuals [8, 9]. Although most of these children in the post-newborn have obtained some treatment and their prognosis has been improved, the post-newborn is still a very fragile, important and special stage in early life, which lacks a specific concept to define the short but crucial time.

143.2 The Definition for the Post-newborn

The post-newborn is a continuation of neonatal period. In addition to the above-mentioned sequelae and complications during the neonatal period, there is no clear distinction between the physiological and pathological condition of early infants. Because the symptoms and signs of diseases are more atypical in early infants, pediatricians should hold very cautious attitude. Nevertheless, it's lack of a specific term to cluster the infants during this period. So far most of literatures have described the early infant as “baby”, “early baby”, or “small baby”. A clear and specific concept has not been mentioned in the previous classic textbooks. With the development of perinatal medicine, the neonatal mortality rate has been

gradually decreased. Chinese Ministry of Health recently announced the infant mortality rate was run down from 32.3 ‰ in 2000 to 13.1 ‰ in 2010, achieving the UN Millennium Development Goals [10–12] ahead of schedule. Consequently the issues of quality of life for these infants surviving in the neonatal period have caused widespread concerns. The task of pediatrics is not only to focus on reducing morbidity and mortality rate, but also to guarantee children's health, improve the quality of life. The disease sequelae of the post-newborn might affect the health and well-beings of future life. Within this period, the infant have a very strong repair and remodeling capacity. When given appropriate rehabilitation, the infant could obtain unimaginable therapeutic efficacy. At the same time, early prevention of some adult diseases such as hypertension and diabetes should be paid much attention. Studies have suggested that these main diseases in adulthood have a close relationship with early infancy, especially nutritional status of the post-newborn [13]. How to further promote the growth and development and correct the complications and sequelae at the post-neonatal period, make the ill infants reach the level of normal infant development as early as possible, and reduce the incidence of adult-related diseases has become an important issue. It is necessary to carry out professional studies. For this purpose, we give the definition for this period which refers to post-newborn from >28 days to <100 days. In this period, the infant still completely depend on breast milk and/or formula milk for feeding. Up to now, the concept of post-newborn has not been mentioned in classic textbooks. The concept of post-newborn is mainly based on the following reasons:

- (1) The supplementary food is usually introduced from the 4th month after birth. After this period, the gastrointestinal function of infant begins to adapt to the supplementary food and has significant changes.
- (2) After 100 days, most of the common neonatal diseases and complications have been cured.
- (3) For most infant medications at this period, no reference for dosage has been made yet, which is not consistent with evidence-based medicine: whether the application of various drugs has an effect or not? How the level of such drug's effect is produced? Is there any possible side effects or delayed benefits? The emphasis on this period is helpful for promoting the drug research and development in this specific period. After this period, most of the medications have some reference usage, which has greatly enhanced the safety.
- (4) In this period, the antibody levels of infants from breast milk are high, while its own immune function is low, and there are few autoimmune diseases. Investigation of the immunity and its tolerance in this period is expected to provide new treatment methods for immunological disease/rheumatic diseases in the future.
- (5) People in a lot of countries usually have the historical tradition and habit to invite relatives and friends to congratulate the baby on the 100th day after birth on spending the most vulnerable period of life. The time is easy to remember.

143.3 The Post-newborn Infants Have Some Important Characteristics Differing from the Newborn and Infant After this Period

143.3.1. **Post**-newborn infants have different fatal disease and mortality. An important indicator for reflecting children's health issue is the infant mortality. However, due to different kinds of reasons, there is no infant mortality reported within 3 months alone. It is reported that in some Asian developing countries, neonatal disease is still the first cause of death, and infectious disease is the major killer after the neonatal period. In western developed countries, the first cause of death is the congenital malformation, and the death age of those infants is not at the neonatal period [1, 14]. Because of high infant mortality rate and various kinds of complicated diseases, this indicator can not fully reflect the health level of infants. Clinical practice experience suggests that most of the deaths occurred in younger infants after the neonatal period, especially within 100 days. In the United States, sudden infant death syndrome is one of the main causes of infant mortality [15], the peak age of death appeared in 2–4 months after birth, and the infant mortality rate decreased after 4 months [16, 17].

143.3.2. The disease inherited from neonatal period requires early and prompt treatment. There might be a distinct defect in terms of the time concept for neonatal period. Although during neonatal period, a few of the mother-born diseases have been corrected, such as hemolytic disease of newborns, premature rupture of membranes, gestational diabetes etc. [18], it is impossible for the sequelae and complications of neonatal diseases to be fully corrected in this period. How to better diagnose and treat these diseases in post-neonatal period is the issue which the pediatricians have to pay much attention to. These diseases often require the full co-operation of many specialties including screening and correcting for hearing anomalies, treatment of persistent pathological jaundice, rehabilitation for hypoxic ischemic encephalopathy, screening and treatment for retinopathy, therapy for repeated infection of bronchopulmonary dysplasia, congenital heart disease requiring early surgical treatment due to repeated or fatal respiratory infections affecting infant growth and development.

143.3.3. In this period, some special diseases need attention, such as late-onset vitamin K deficiency, which is frequently present in infant with exclusive breastfeeding, chronic diarrhea, and malnutrition. It is prone to have fatal intracranial hemorrhage, and the survivors often leave behind the neurological sequelae, seriously harming the health of babies. During this period, the nerve myelin development is obvious. Early diagnosis and treatment of cerebral palsy can help reduce neurological sequelae.

143.3.4. The immune function has similarities and differences. The common point of post-neonatal infant and other infancy stages is the low immune function. During this period, the non-specific immunity, humoral and cellular immune function are very immature, and levels of sIgA and IgG are low, with low resistance to infection, prone to have various bacterial and viral infections. Clinical

manifestations of pneumonia in the post-newborn is more insidious than those of children's pneumonia, The post-newborn infants suffering from pneumonia have usually very light and a typical symptoms such as refusing milk or milk feeding decreasing, no weight increasing, weak cry, and some even lack any clinical manifestation but with rapid disease progress. The difference between neonatal and post-neonatal infants is that the neonatal babies have significantly increased resistance because of colostrum feeding. As the time going on, the maternal antibodies decrease obviously, leading to a variety of infectious diseases such as respiratory syncytial virus, EB virus and EV71 virus.

143.3.5. There is a conflict between the rapid development and growth and uneven development of organ systems during the post-newborn period. This period is the stage for extremely strong growth. The weight of infant has been more than doubled that at the birth. The nutritional requirements are relatively high. At the same time, the uneven development of organ systems, especially the digestive system is often difficult to adapt to a large number of food digestion and absorption. It has been suggested that both nutritional deficiencies and overnutrition are able to significantly affect adult metabolic diseases [13, 19, 20]. The fine mapping of the human genome indicated that diseases were genetically related. Not only genetic (congenital) disease but also risk of acquired and some so called adulthood-starting diseases (such as diabetes, hypertension) might start to be increased before birth or at the infancy and childhood. Moreover, it has made people realize that gene could not be the only factor to decide the human disease. Through epigenetic modifications of gene, early nutrition and its regulation could alter genetic pathway, and then prevent or inhibit the occurrence of disease in adulthood. Classical genetics indicated that individuals of the same gene should have exactly the same phenotype, but the truth is not the case. One pair of identical twins often has the differences in terms of appearance, personality of many aspects, which might be the result of epigenetic modifications. The epigenetics has made the research that under the situation gene DNA sequence has not changed, the gene expression has the inheritable changes. The epigenetics has three important features: (1) not involving DNA changes; (2) gene functions have changed; (3) the change of gene function has heritability and reversibility. Food, as a source of methyl donor may change the gene expression and thus affect the development of various organ systems, possibly through epigenetic methylation modifications.

143.4 Strengthening Investigation of Post-newborn Could Further Reveal the Nature of Life and Improve Life Quality of Children

Pediatrics is the only vertical division of subject in clinical medicine in accordance with the process of human life (age group). The division of each age group has accordingly promoted the research progress of the stage. Especially the

establishment of neonatology and its specialties has made remarkable achievements. The infant stage, especially post-newborn is one of the critical periods for individual physique and neurogenesis, with time and spatial differences. Not only the normal anatomy and physiology have the characteristics, but also diseases in different system in terms of etiology, clinical phenotype, assessment method, diagnosis and treatment are quite different from those newborns, children and adults. The research on the developmental law of post-neonatal infants will help to find new diagnosis, treatment and prevention methods for the diseases of children and adults.

The task of the post-newborn research remains how to better promote physical and neurological growth and development of the infants, which are the most basic features and the most common issues in children's life course. The physical development integrates child nutrition, endocrine and metabolic diseases, genetics and environmental medicine. Nutrition is the material basis for physical growth and development, whereas environmental factors are the important aspect affecting development. Researches have revealed that developmental abnormalities are related to human abuse of the environmental substances such as melamine and phthalate esters, whose mechanism may be through endocrine and epigenetic modification. It's important to maintain the balance of nutrients, trace elements, minerals and vitamins. The neurological development is the essence of life quality, which includes the prevention and treatment of children's neurological diseases and mental illness, and promotion of neural development level. Although neurological rehabilitation medicine has been significantly improved, the number of children with neurological and intellectual disabilities has been not significantly decreased because the mortality for neonatal disease, especially preterm infants, severe asphyxia, severe respiratory distress syndrome has been dropped significantly and many survivors suffer from neurological complications. It is a big challenge for pediatrician to carry out the early identification and intervention for the infants with the intellectual disability and high risk factors, and finally reduce the incidence of children with intellectual disabilities.

Prevention of infectious disease and immunization is important for infants during post-newborn. Infectious diseases once led to the death of large number of infants. Along with development of antibiotics and vaccine work, infectious diseases have been obviously under control. However, a few of infectious diseases such as tuberculosis and measles have flared up in recent years. More seriously, at the same time, new resistant strains such as the production NDM-1 "super bacteria" have been emerged constantly. In addition, a number of newly-emerging viruses including H1N1 avian flu virus, EV71 virus, SARS virus have brought forward new challenges. The strengthening of the development for anti-infective drugs, vaccines and vaccination during this period will help decrease the illness of infant, reduce costs for health care, lower the social and family burden, and thus abate infant mortality.

The strengthening of the post-newborn research, especially the research on translational medicine [21], may help to find new ways and methods for the treatment of diseases in infants, children, and adult caused by nutritional

abnormalities. The nutritional abnormalities could cause disease by means of epigenetic modification. DNA methylation depends on the dietary intake of methionine and folate which are subject to individual nutrient levels. Low dietary intake of methionine in rats could lead to the occurrence of DNA demethylation, more prone to liver cancer [22]. It has been suggested that mammals should have a critical developmental period before and after birth, and nutrition as well as other environmental stimuli have an impact on developmental processes and cause permanent change in terms of metabolism and susceptibility to chronic disease [23–26]. A few of population epidemiological and animal model experimental data support this view, but the complex biological mechanism is still unclear. Future research in this area is to select possible target goal to improve the nutritional regulation of intestinal development, namely the detailed understanding of the relationships among nutrients, epithelial cells, intestinal flora, enteric nerves and endocrine. It's of great value to find what nutrients and metabolic pathways get involved in regulation of early life and adult dietary regulation of epigenetic mechanisms. More importantly, epigenetic modifications might occur in the critical window period of early life, especially in the post-newborn.

The premise of research is to enhance the degree of concerns on post-newborn. First of all, it is to strengthen the promotion of concept of post-newborn. In the 1980s, the textbook set the “newborn of diabetic mothers” as the independent chapter for etiological diagnosis, which caused a high degree of perinatal medical attention, hence greatly contributed to the research on this disease. For this reason, it's strongly recommend that post-neonatal should be defined as an independent age group and be regulated. The post-newborn should be write into pediatric articles and textbooks. In addition, the relevant theoretical system should be built in time. At the same time, specialized training courses and academic conferences should be held to study on the basis of post-newborn so that the concept of post-newborn could go deep into the field.

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