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AJA conceived and designed the study; AJA and MAA wrote the first draft of the manuscript; DMA, AMA and AMA revised the manuscript, and AJA approved the final manuscript.

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*Correspondence**Ahed J Alkhatib****Email:** ajalkhatib@just.edu.joPossible submissions [Submit your article](#) 

Preterm Birth Complications: Improving Outcomes for Extremely Premature Infants

Ahed J Alkhatib^{1,2,3*}, **Mustafa Ahmad Al-Shehabat**⁴, **Dania Mustafa Al-Shehabat**⁵, **Aya Mustafa Al-Shehabat**⁶, **Adam Mustafa Al-Shehabat**⁶

¹Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science & Technology, Jordan.

²International Mariinskaya Academy, department of medicine and critical care, department of philosophy, Academician secretary of department of Sociology.

³Cypress International Institute University, Texas, USA.

⁴Department of Physiology and Biochemistry, Faculty of Medicine, Jordan University of Science and Technology, Jordan.

⁵King Abdulla University Hospital, Jordan.

⁶Faculty of Medicine, Jordan University of Science & Technology, Jordan.

Abstract:

Preterm birth, which is birth before 37 weeks, is one of the leading causes of morbidity and mortality among neonates. This entails complicated medical, technical, and socioeconomic problems. The serious complication rates of infants born at extremely preterm gestation age (<28 weeks) are higher than the complication rates of late preterm or term infants. This paper discusses the classification, epidemiology, complications, and management of preterm birth, especially of extremely premature babies. Newborn cures and rising scientific development have demonstrated fantastic development in existence as well as long-term outcomes. Nonetheless, preterm birth remains a worldwide health issue that varies in incidence across the globe due to the differential levels of socioeconomic development. Immediate problems include pneumonia, drinking troubles, and serious infection, all while long-term troubles often involve brain trouble and long-lasting trouble. The manuscript calls for necessary interventions and enhanced clinical care and policy reforms on the burden of preterm birth, particularly in low-resource settings. By using evidence-based practices and new technologies, neonatal care will contribute to increasing the chances for better outcomes and quality of life for sick babies and their families.



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INTRODUCTION

Preterm birth is a major contributor to neonatal health and is characterized by increased medical and technical challenges associated with earlier gestational ages (Morgan *et al.*, 2022). Although late-preterm birth is the most frequent gestational age, the consequences of late-preterm birth are possibly inconspicuous (Davidesko *et al.*, 2020). In contrast, extremely premature infants less than 28 weeks of gestation are clearly at greater risk (Mitha *et al.*, 2021). As research identifies optimal strategies for improving the outcomes for infants born at the border of viability, it is important to understand the nature of the risks that these newborns face and the interventions used to decrease their complications (Mactier *et al.*, 2020).

Preterm birth is defined as birth before 37 weeks gestation (Zhu *et al.*, 2021). Subdivisions of preterm birth are classified as moderate/late-preterm birth; very preterm birth; and extremely preterm birth (Siffel *et al.*, 2022). Substantial epidemiologic trends in the gestational age at delivery are taking place (Boel *et al.*, 2020). Infants born extremely preterm have a greater likelihood of major morbidities than those born very and/or moderate/late preterm (Bell *et al.*, 2022). Approximately 1.6 million deaths in 2012 were attributable to complications of preterm birth (Nourkami-Tutdibi *et al.*, 2021). Stronger global data and research should expose the prevalence of preterm birth complications in addition to possible management strategies at lower gestational ages for low- and middle-income countries (Lincetto and Banerjee, 2020). Human infants are born 'at the edge of viability' in all countries and at every level of cost and capacity (Greenbury *et al.*, 2021).

Definition of Preterm Birth

Preterm birth is defined as birth that occurs before 37 weeks of gestation (Cheong *et al.*, 2020). A more specified classification adds categories of delivery occurring at 32 0/7, especially for pregnancies that may benefit from

antenatal corticosteroids, and between 34+0/7 and 36+6/7 weeks of gestation (the "late preterm" period) (Ohuma *et al.*, 2023). There are also subcategories of extremely, very, and moderate preterm birth used to distinguish between preterm births at varying gestational ages with these designations (Koullali *et al.*, 2020). Since survival outcomes vary widely and require different levels of preventive obstetric care and neonatal intensive care, extremely preterm birth is typically defined as birth before 28 weeks, that is, 27+6/7 weeks, of gestation (Doyle *et al.*, 2021).

In addition to the risk of adverse outcomes and neurodevelopmental deficits, a complicated preterm birth may affect the immediate, acute, and infant and juvenile health of the neonate (Sullivan and Cummings, 2022). As such, perivable (22+0/7-25+6/7 weeks) and extremely preterm (22+0/7-27+6/7) are milestones in obstetrics and provide guidelines as to when ongoing pregnancy should be attempted if maternal interests align with infant survival (Seasely *et al.*, 2024). The decision to actively manage the labor of a healthy pregnant patient at these gestational ages while exploring and demonstrating the risks and benefits is an important area of ongoing research (Sullivan *et al.*, 2022). Nursing staff needs to have a clear understanding of gestational age classifications, perivable versus extremely preterm, and outcome variability (Ireland *et al.*, 2021).

Epidemiology of Preterm Birth

Prevalence estimates for preterm birth range from about 2.1% to 3.0% in the Czech Republic to about 18.1% in Malawi among low-income countries (Chersich *et al.*, 2020). The current global rate of preterm birth has increased by 8% in less than a decade, and future trends might shift the rate up to 11% by 2025 (Quenby *et al.*, 2021). The absolute number of preterm births is projected to continue rising (Perin *et al.*, 2022). The profound public health and societal implications of preterm birth have piqued the interest of many researchers and the general public (Betran *et al.*, 2021). The causes of

preterm birth are intrinsic as well as extrinsic to women worldwide, as preterm births affect all socioeconomic strata and ethnic groups (Been *et al.*, 2020). A major contributor to the global preterm birth burden is excluded, uninsured, underinsured, illegal immigrants of childbearing age and their offspring (Ugai *et al.*, 2022). A considerable number of women in several of the populations most tested in the world have no health coverage. Unfettered in the realms of maternal health, access to prenatal care is a reliable determinant of preterm birth rates in both pregnant adolescents and women (Hug *et al.*, 2021).

Variability in preterm birth rates among different populations and different geographical areas can stem from the level of socioeconomic development (Deng *et al.*, 2021). Therefore, apparent differences in preterm birth rates have led researchers to interpret the incidence of preterm birth in different countries as being driven by differences in such occurrences in single pregnancies, and they argued that the data should be interpreted with caution (Menon *et al.*, 2020). Factors including the preterm birth incidence by population and last menstrual period dating reference are possibly the most unfair within-population variation due to biases in population and gestational length (Cao *et al.*, 2022). Almost identical Irish data were interpreted as representing differences in pregnancy dating: for the population-based incidence of single fetuses, the relative difference between last menstrual period, clinical, and ultrasound dating was significant (Roman *et al.*, 2020). The differences between the self-reported and the clinically recorded gestational age at delivery were not narrowed down (Joo *et al.*, 2021). Based on gestational age distribution, they estimate a preterm birth rate reduced the nationwide rate in Europe within a few countries to two pregnancies in Europe due to registries closer to the stated prevalence (Egesa *et al.*, 2020). Despite the fact that others declared that ultrasound dating has an unquestionably lower preterm birth rate than last menstrual period dating, a lack of other data indicated that the series rate of preterm birth in

the case of other articles was still lower than the rate of more gestations (Mekuriyaw *et al.*, 2020). Increases in multiple gestation pregnancies are a major cause of increased preterm birth and low birth weight worldwide and increases in the late 20th century (Abadiga *et al.*, 2021).

Preterm birth is the primary determinant of the degree of morbidity and mortality of the newborn, and a significant amount of the clinical data on preterm labor centers on very immature infants (Egesa *et al.*, 2020). The rapid decline in mortality among mid-preterms and late-preterms has been made possible through dramatic advances in obstetric and neonatal care, as early as mid-pregnancy and pre-pregnancy (Kannaujiya *et al.*, 2022). There is support for the measurement of interventions from these mortality data to evaluate intervention thresholds (Jana *et al.*, 2022). The degree of immaturity has direct implications for the provision of care to the preterm newborn and is therefore of critical importance (Abebaw *et al.*, 2021).

Complications of Preterm Birth

Each year, over half a million births occur in the United States, with more than 10% involving premature deliveries (Kvalvik *et al.*, 2020). Complications of preterm birth remain a significant cause of morbidity and mortality (Crump, 2020). These complications are often related to or result in chronic health issues during growth and development and may require frequent and lasting medical care (Pusdekar *et al.*, 2020). Extreme normal growth and development continue post-term and during infancy. Thus, complications from preterm birth predominantly have immediate and long-term effects on the developing infant (Trickett *et al.*, 2020). The complications from preterm birth can be divided into those that result from the immediate effects of prematurity and those that result from complications of being born preterm (Pusdekar *et al.*, 2020).

The complications related to the immediate effects of being born too soon typically affect the infant's ability to breathe and gain weight. These complications may be temporary or permanent

and vary in severity (Trickett *et al.*, 2020). In terms of long-term complications resulting from the stress of being born too soon, the most prominent is related to neurodevelopment (Schnider *et al.*, 2020). Survivors of extremely preterm birth frequently suffer from cognitive, emotional, and behavioral disabilities, in addition to special educational needs and psychiatric illnesses that last into adulthood (Perez *et al.*, 2020).

Premature delivery associated with specific medical risks, such as exposure to an infection and difficulty feeding, often requires a longer hospital stay. Premature infants require care to decrease the likelihood of severe infection (Benestad *et al.*, 2022). Additionally, these infants frequently require oxygen and may need surfactant to prevent lung damage (Brunson *et al.*, 2021). Feeding premature infants is challenging, and slow growth is often a reflection of poor nutrition as well as organ immaturity (Youn *et al.*, 2021). Though every parent loves their new infant, many mothers describe emotional responses such as sadness or feelings of disappointment and failure and will request to hold the infant to bond and increase milk production despite the absence of reliable evidence that kangaroo care improves breastfeeding success (Singer *et al.*, 2021). Infant complications related to preterm birth increase the demand for well-trained physicians and nurses to improve outcomes (Tso *et al.*, 2023).

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is the major complication of preterm birth and primarily affects infants born before 28 weeks of gestation (Barrantes *et al.*, 2021). The pathophysiology of RDS is mainly due to surfactant deficiency in premature infants, which affects inspiratory function and prevents alveolar collapse (Chen *et al.*, 2021). Normally, surfactant facilitates the modulation of surface tension within the alveoli, thereby preventing their collapse during expiration (Parker and Dalziel, 2020). The absence or deficiency of surfactant leads to

increased work of breathing, which is the primary cause of the clinical manifestation of RDS due to lung immaturity (Shi *et al.*, 2020). The tachypnea and visible signs of distress are largely classified as type II respiratory failure, marked by oxygen desaturation, hypercapnia, and even respiratory acidosis (Ko *et al.*, 2021). Classification is significant for key clinical features and intervention, allowing for timely diagnosis and a multidisciplinary plan of care that addresses both the underlying lung immaturity and support with respiratory distress symptoms (De Luca *et al.*, 2022).

Current management options for premature infants with RDS include antenatal corticosteroids, surfactant replacement therapy, and ventilatory support (Ng and Shah, 2021). Nasal continuous positive airway pressure has also been shown to be effective in preventing the progression of RDS by leaving end-expiratory pressure in the airway (Hallman *et al.*, 2022). Interventions associated with lower rates of complications in untimely infants include C-section delivery and prenatal steroids (De Luca, 2021). The combination of high-frequency ventilation and surfactant replacement therapy is beneficial for prematurely born infants (Bhandari *et al.*, 2023). The long-term effect of RDS is suboptimal pulmonary development. Nutritional management is clearly affected, often delivering inadequate calories and protein (Ismailova and Khodjamova, 2024). Preventing premature birth is not solely possible with obstetric interventions as the etiology of premature birth is multifactorial and often idiopathic (Greiner *et al.*, 2021). This emphasizes the need for advanced medical care (Van Wyk *et al.*, 2020). To improve outcomes for infants with RDS, public awareness of the nature of the problem and the potential role that advanced neonatal care can offer is an important part of this discussion (Ekhaguere *et al.*, 2022).

Current Treatment and Care Practices

The mission of healthcare professionals caring for the extremely preterm infant often involves a medical and psychosocial juggling act aimed at

preventing or managing the potentially acute or chronic complications that are a part of the daily life of the very preterm infant in the neonatal intensive care unit (Lee *et al.*, 2020). Guidelines for best practices to improve the likelihood of a healthy outcome, being alive without disability, when a resuscitated infant reaches school age are provided (Croop *et al.*, 2020). For the rest of the NICU care days, the standard of care follows a multitude of best practices, evidence-based interventions, and individualized care recommendations by a multidisciplinary team of healthcare professionals who provide infant and family-centered care (Poindexter *et al.*, 2021). Neonatal medicine encompasses three major focuses, including: (1) maintenance of normal body temperature of the infant in the incubator or on a warm blanket (2) replacement of normal fetal functions with intravenous or enteral feeds and parenteral nutrition support (3) prevention, identification, and management of infections, also termed "sepsis." (Organization, 2022).

In the last 50 years, neonatal disruptive technologies have evolved with innovations such as commercial incubators as the "go-to" care model for the preterm infant, mechanical ventilator care to help with respiration, and monitoring devices that measure vital physiological parameters (Kajantie *et al.*, 2021). Of the many care interventions after birth, early food support required to achieve a faster growth increase in premature infants has been a high research priority. Human milk is the go-to food support for the extremely preterm infant (Kleinhout *et al.*, 2021). Of the many guidelines and recommendations to accomplish the big-picture goal of decreasing morbidity and mortality, financial considerations occur in both high-income and low-resource countries (Organization, 2020). In the United States, the complete costs for very low birth weight care and hospital discharge vary according to demographic information, ranging overall from a specified amount. When a child leaves the neonatal intensive care unit, many will receive ongoing outpatient clinic care (Cordova and Belfort, 2020).

Innovations in Neonatal Care

Innovations in neonatal care have led to significant advancements in the survival and development of extremely premature infants (Batey *et al.*, 2024). Technologies and practices that have been developed, well studied, and are now affecting the treatments for infants include the following aspects (Taha *et al.*, 2023). For respiratory care, new non-invasive techniques for supporting respiration in the newborn require smaller and less invasive endotracheal tubes or none at all, reducing the need for surfactant and potentially reducing bronchopulmonary dysplasia, the most prevalent and serious long-term respiratory consequence of preterm birth (Dumka and Bhandari, 2021). New strategies for nutritional support have been studied with a specific eye on the optimal support of brain growth during and after neonatal intensive care (Hysinger and Ahlfeld, 2023). Drug therapy has been an intensive area of research, and basic research is still investigating new treatment modalities (Sahni and Bhandari, 2023). For developmental support of preterm infants, care practices such as skin-to-skin care and relaxation therapy for mothers and infants have been widely studied in clinical trials (Atag *et al.*, 2020). Increased use of telemedicine in the NICU is allowing the expansion of needed advanced clinical care to rural areas where exceptional care for sick newborns is needed (Boel *et al.*, 2022). Importantly, the research that has led to these new therapies has not only stood the test of time but has also required repetitive clinical trials to fully understand (El-Ferzli *et al.*, 2023).

All of these advances are costly (Shah *et al.*, 2020). Obtaining the full benefits of these can only be achieved through adequately funding them and by expanding the number of trained staff in neonatal care (Olatunji *et al.*, 2024). For example, although we now have top-notch ventilators and non-ventilator respiratory support, daily management decisions made by nurses and therapists can help or hinder infants in their NICU course (Fang *et al.*, 2020). Staff need proper training in these latest technological

therapies and how they affect long-term outcomes (Palmer *et al.*, 2020). Constant research and improvement in clinical practice and innovative trials are needed in the area of management strategies for preterm birth complications (Torous *et al.*, 2021). It is our hope that this critical review of the major developments in the field will inspire further exploration and investment in innovations focused on the very first interventions for newborn babies born sick (Mehta *et al.*, 2021).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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