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Public Health Implications of Very Preterm Birth

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INTRODUCTION/BACKGROUND

Epidemiology of Very Preterm Birth

Infants born very preterm (<32 weeks gestation) are at increased risk for death, medical complications, and neurodevelopmental sequelae. The World Health Organization defines preterm birth before 37 weeks gestation with subcategories including very preterm birth, and extreme preterm birth (<28 weeks gestation).[1] Worldwide, it is estimated more than 1 in 10 infants were born preterm in 2013, accounting for approximately 15 million premature babies.[2] Among these, 1 million children younger than age 5 die annually because of complications related to preterm birth.[2] In developing countries, the measurement of very preterm birth and extreme preterm birth is more challenging and mortality is extremely high.[3]

In the United States, rates of overall preterm birth (<37 weeks gestation), calculated by last menses, increased from 10.6% in 1990 to a high of 12.8% of all live births in 2006, and 12.7% in 2007. These increases were primarily caused by a rise in late pre-term births.[4,5] Based on revised measures to improve the accuracy of gestational age, the National Center for Health Statistics revised this measure of pregnancy length from last menses to obstetric estimate.[6] Subsequently preterm birth rates were adjusted based on obstetric estimate. Based on obstetric estimate, preterm birth was estimated at 10.4% in 2007, declining to a rate of 9.6% of all births in 2014.[6,7] This decline in overall preterm birth reflected successful clinical and public health efforts to decrease late preterm birth.[8] However, recent data show new increases in overall pre-term births in 2015, 2016, and early 2017 to be 9.6%, 9.8%, and 9.9%, respectively, caused primarily by increases in late preterm births.[9–11] Nearly 400,000 preterm births occur annually among the nearly 4 million births in the United States.[9]

Preterm births less than 32 weeks gestation represent more than 60,000 births annually, yet the United States has seen little change in these rates over time.[12] In 2015, very preterm birth represented approximately 1.6% of live births but was associated with 52% of infant deaths in the United States; extreme preterm births represented 0.67% of live births and 45% of infant deaths (Table 1).[13] The lack of change in the distribution of very preterm birth may be one reason why infant mortality declines are slow and disparate. In fact, a study by Callaghan and colleagues[12] explained that although infant mortality rates declined from 2007 to 2014, the very pre-term birth weight distribution did not; yet birth weight–specific mortality rates for these tiny infants continued to decline. Causes of very preterm birth are not clear, but most are associated with premature rupture of membranes, preterm labor, and maternal medical conditions (Box 1).[14]

Mortality, Morbidity, and Neurodevelopmental Sequelae

Worldwide, survival among infants born very preterm varies by available resources for obstetric and neonatal care, and perceptions of viability.[15–17] Preterm survival at the earliest gestational ages has improved dramatically in developed countries, where the limit of viability has extended to 22 to 23 weeks gestation; yet survival at these gestational ages in developing countries is rare.[15] Improvements in the survival of very preterm infants in developed countries are the result of a variety of factors including improved insurance coverage during pregnancy; advanced obstetric and antenatal care; and improved systems of risk-appropriate care, including resuscitation and stabilization of high-risk newborns.[18–20] In a comparison of developed countries in 2010, the United States ranked second compared with 11 European countries in gestational age–specific survival at the earliest gestations (for infants born between 24 and 27 weeks gestation). However, the United States ranked 26th among 29 countries in the Organisation for Economic Co-operation and Development for overall infant survival.[21]

Because immature gestational age affects a variety of organ systems, very preterm infants are at risk for longer term medical morbidity and adverse neurodevelopmental outcomes to include motor, neurosensory, cognitive, and behavioral deficits (Box 2).[22,23] Adverse medical and neurodevelopmental outcomes are inversely correlated with gestational age. Black infants are more likely to experience preterm birth; for example, infants born to black mothers' experience 2.5 times the rate of very preterm birth compared with white infants.[10] Therefore, black infants, from a population perspective, may be more likely to experience adverse sequelae. Additional sociodemographic, genetic, and environmental risks may further affect the distribution of very and extreme preterm birth and subsequent morbidity and mortality.[22] Risks for preterm delivery may occur within families (eg, female siblings), between pregnancies, and over generations. This may be caused by shared environmental, biologic, and/or genetic factors.[22] Ultimately, prevention of very preterm birth is essential to reducing racial disparities in medical and neurodevelopmental sequelae from birth through adulthood and in subsequent generations.

Very preterm births incur high medical costs. The Institute of Medicine, in its 2007 report on preterm birth, estimated that infant born less than 32 weeks gestation accounted for $11 billion of excess medical costs out of the total $16 billion for all preterm infants.[24] Very

preterm infants insured through Medicaid seem to incur higher costs than those covered by commercial insurance and have higher rates of readmission after birth hospitalization, because of higher rates of morbidity.[25] In the United States, nearly 50% of pregnancies are paid for by Medicaid and these proportions vary by state (ranging from 69% in Louisiana to 24% in Hawaii).[26]

PUBLIC HEALTH'S ROLE IN THE PREVENTION OF VERY PRETERM BIRTH

Public health efforts to reduce preterm birth have focused primarily on the prevention of late preterm (between 34 and 36 6/7 weeks gestation) and early term birth (between 37 and 38 6/7 weeks gestation) using public health campaigns and policies aimed at the elimination of early elective deliveries, or nonmedically indicated deliveries before 39 weeks gestation. State, regional, and national collaborations successfully reduced late preterm births through rapid data reporting, changes in clinical practice and recommendations, and policies for reimbursement.[27–32]

Public health efforts to prevent preterm birth at earlier gestations (<34 weeks), however, have not been as robust, likely because of limited understanding of the complex causes of very preterm birth. However, innovative public health efforts can help reduce very preterm birth and associated morbidity and mortality in several ways.[33,34]

Improved Data Systems

Timely population-based surveillance systems are important to monitor trends in preterm births, associated risk factors, and outcomes. The National Center for Health Statistics now reports selective preliminary national vital statistics data, including information on gestational age, on a quarterly timeline.[11] This has been important in monitoring national trends in preterm birth more rapidly. The Pregnancy Risk Assessment Monitoring System collects state-level data on maternal experiences before, during, and shortly after pregnancy. The Pregnancy Risk Assessment Monitoring System, which is linked with vital records, can also be linked with other administrative and program data (eg, Medicaid, hospital discharge, Healthy Start, and Early Intervention registries) to monitor interventions and outcomes.[35,36] Using multiple linked data systems can inform and evaluate prevention efforts at the local, state, and national level. Statistical techniques, such as multilevel modeling, are used to assess birth outcomes caused by policies or practices.

Longitudinally Linked Data

Data systems linked over the lifespan of the mother and child can help to identify risks associated with very preterm birth and short- and long-term outcomes, assess the effectiveness of interventions, and inform strategies for improvement. Much of the research that identified the short- and long-term complications and costs associated with late preterm birth came from longitudinally linked data systems in California, Michigan, and Massachusetts, which linked vital records, maternal and infant hospital data, and program data longitudinally.[37–41] These innovative data systems help to identify the risk for infant and maternal mortality and morbidity, readmission, and developmental disabilities, and access to care.

Improving Preconception Health

Behavioral factors that are usually initiated before pregnancy, such as tobacco, alcohol, and illicit drug use, are associated with preterm birth.[22] Much chronic disease also plays a role in the risk of preterm birth, with such conditions as hypertension, diabetes, and obesity affecting maternal and fetal well-being. Shifts in the average maternal age at delivery in the United States has also increased the risk of preterm birth because mothers are more likely to be older and more likely to have a chronic medical condition.[42,43] Regardless of age, improving the health of women before pregnancy and reducing disparities in preterm birth requires a robust system of surveillance to assess preconception behaviors and access to insurance, primary care, and preventive services.[44]

Preventing Teenage and Unintended Pregnancies and Improving Pregnancy Spacing

Forty-five percent of pregnancies in the United States are unintended and nearly three-quarters of teenage births are unintended.[45] Unintended pregnancies and short interpregnancy interval (a second birth within 18 months) are associated with increased preterm birth.[46] Teenage pregnancies are at 17% higher risk for preterm birth, and teenage mothers are more likely to have a short interpregnancy interval resulting in further preterm birth risks.[47,48] Although the US birth rate for teenagers aged 15 to 19 has declined 51% since 2007 (down to 20.3 live births per 1000 women in 2016[10]), efforts to reduce teenage pregnancy need to continue, especially in African American and Hispanic communities where teenage and preterm birth rates are highest.[49] Access to a full range of effective contraceptive methods, including long-acting reversible contraception, is important to prevent unintended pregnancies, improve birth spacing, and reduce preterm birth.[50,51] Perinatal providers can help to reduce barriers to postpartum contraception access, even among mothers whose infants are in the neonatal intensive care unit, by understanding issues of availability, safety, and cost.[52,53]

Reducing the Risk of Higher-Order Multiples in Assisted-Reproductive Therapies

Use of fertility therapy may result in births to twins, triplets, or higher-order multiple births, which generally deliver at an earlier gestational age than singleton birth births.[22] In 2015, more than one out of every two twins and more than 9 out of every 10 triplets were born preterm or low birth weight.[9] From 2014 to 2015, the twin birth rate declined from an all-time high of 33.9 to 33.5 per 1000 live births. In addition, the triplet and higher-order multiple birth rate declined 9% from 2014 to 2015 to 103.6 per 100,000 live births. The triplet and higher-order birth rate has declined more than 40% from 1998 to 2015.[9,54] In 2014, assisted-reproductive technology in the United States contributed to 18.3% of all multiple births, 4.7% of all preterm births, and 5.0% of all very preterm births.[55] However, states with high use of assisted-reproductive therapy use had higher preterm birth rates. For example, in Massachusetts, 13.4% of all preterm and 14.7% of all very preterm births were associated with assisted-reproductive therapy use.[55] Approaches, such as elective single embryo transfer during assisted-reproductive therapy, can reduce multiple births and the risk for prematurity.[56] Understanding the contributions of other fertility therapies to multiple births is more elusive. In a study by Kulkarni and colleagues[57] in 2011, a total of 36% of twin births and 77% of triplet and higher-order births in the United States resulted from

conception assisted by nonassisted-reproductive therapy fertility treatments. Payment strategies, such as broader insurance coverage for fertility therapies, may also reduce the risk of higher-order multiples and preterm birth by reducing costs related to infertility treatment, which may in turn encourage use of treatments that result in singleton births.[58]

Improved Quality and Systems of Care

In 2016, slightly more than three out of four US women (77.2%) began prenatal care in the first trimester.[10] However, only 66.6% of black women and 63.0% of American Indian or Alaska Native women began first trimester prenatal care compared with 82.3% of white women and 80.6% of Asian women. Less than 1 in 10 (6.2%) US women had late (beginning in the third trimester) or no prenatal care.[10] Innovative group prenatal care models have held promise to reduce the risk of preterm birth. However, a recent meta-analysis showed that pregnant women who participated in group prenatal care had similar rates of preterm birth compared with traditional prenatal care models.[59] More research is needed on the content and quality of prenatal care to better understand how it might reduce the risk for early deliveries.

Access to risk-appropriate care is a proven approach to reducing death and neuro-developmental morbidity associated with very preterm births.[60] In a meta-analysis of more than 30 years of data, Lasswell and colleagues[19] found that very preterm newborns delivered outside of level III or higher facilities were at a 60% increased odds of death. One major step toward lowering death and disability to very preterm infants is to ensure an organized system of care that ensures facilities have appropriate staffing, equipment, and experience that match patient needs. Pregnant women and newborns need to receive the right care at the right place, and the right time.[61,62] Unfortunately, many very preterm infants are not delivered at appropriate facilities to meet their complex medical needs. Additionally, recent studies have demonstrated considerable variation in the quality of care among different racial/ethnic groups based on where they reside.[63,64]

Women at risk for preterm delivery need to be identified early and offered access to effective treatments to prevent preterm birth.[43,65] For example, women who have had a spontaneous preterm delivery, are at a two-fold risk for subsequent preterm deliveries. Among women with a history of spontaneous preterm birth and a singleton pregnancy, the use of 17α-hydroxyprogesterone caproate can reduce the risk of preterm birth by approximately 30%.[66] Public health collaboration with clinical providers and insurers can help identify pregnant women at risk and reduce barriers to access and use. For example, in Ohio, the state quality improvement collaborative focused on low-income women at high risk for preterm birth, with either a prior preterm birth or shortened cervix during pregnancy and provided them access to progesterone through Medicaid. This “progesterone project” aims to reduce rates of preterm birth less than 32 weeks gestation by June 2018.[67] To date, rates of progesterone administration increased from 2013 to 2016 across all races and ethnicities in Medicaid, with the highest rate being achieved in high-risk black women in 2016 (http://www.medicaid.ohio.gov/Portals/0/Resources/Reports/PWIC/PWIC-Report-2017.pdf?ver=2017-12-29-112608-887).

Although the American College of Obstetricians and Gynecologists recommends that mothers at risk for preterm delivery should be offered antenatal corticosteroids, its use is variable. Profit and colleagues[64] found that white infants generally received higher scores on the receipt of antenatal steroids within and between facilities, although these process measures should not have varied by race/ethnicity. Antenatal corticosteroids are highly effective in increasing lung maturity and has been proven to reduce respiratory distress syndrome by 66%, necrotizing enterocolitis by 46%, intraventricular hemorrhage by 54%, and death by 69% with a single course of therapy compared with control subjects.[66] Further research on more effective provider acceptance and use is needed to improve implementation of this effective intervention more equitably to diverse populations.

Perinatal quality collaboratives, through states and networks, can help to identify mothers at risk for preterm birth because of medical conditions, and/or risk for repeat preterm deliveries.[67] Approaches include[68]

- Identifying evidence-based clinical practices and processes to improve pregnancy outcomes.
- Improving maternal and fetal well-being and outcomes in the presence of maternal diseases (eg, hypertension and diabetes).
- Identifying effective interventions that may reduce the risk of very preterm birth and bring these interventions to scale (eg, use of 17-hydroxyprogesterone acetate and antenatal corticosteroids in preterm pregnancies (including late stage of labor and imminent delivery) and the use of low-dose aspirin in the prevention of preeclampsia and subsequent preterm birth).
- Improving early pregnancy assessment to improve the precision of determining gestational age to improve measurement of population-based outcomes.

Improving Social Determinants of Health

A study of preterm infants in the United Kingdom found that preterm infants living in a family with low socioeconomic status tended to score lower on cognitive assessments at 3, 5, and 7 years of age compared with term infants. But the researchers also found that the effects of low socioeconomic status and preterm birth were additive, with little or no evidence of effect modification. Additionally, they found that the magnitude of the estimate effect of poverty was so strong that term children who were living in families with poverty had lower cognitive scores than preterm children who were not living in poor families.[68]

Social determinants of health, the factors that affect health based on where an individual lives, learns, works, and ages, can influence preterm birth rates and preterm birth outcomes, by influencing health well before pregnancy.[69] This life-course perspective on birth outcomes implies that prevention of adverse pregnancy outcomes, including very and extreme preterm birth, must happen before conception and prenatal care. Although the mechanism is not completely clear, it is thought that adverse social determinants may contribute to acute and chronic stress for pregnant women possibly affecting neuroendocrine and immune pathways, leading to indolent inflammation or susceptibility to infection and an increased risk for preterm birth.[22,70]

Adverse social conditions can influence health through such factors as neighborhood poverty and hypersegregation; high crime rates; lack of goods, services, and recreational activities; limited access to quality health care; and limited opportunities for education, employment, living wages, and affordable housing.[71] Poverty is associated with chronic conditions, such as diabetes, hypertension, and obesity, and such behaviors as tobacco and illicit drug use, all of which contribute to poor pregnancy outcomes.[22] Addressing broader social issues, such as racism, discrimination, housing, employment, and education, to improve the health of mothers, particularly in African American and other communities at high risk, could possibly reduce preterm birth and associated disparities.[72] Lastly, clinical and public health interventions may operate in a social context such that implementation may be ineffective or insufficient (eg, poor access to care or lower quality of care), resulting in missed opportunities to prevent early delivery.[63,64,70]

In a commentary, Lorch[73] noted the challenges of combining health equity goals with the measurement of health care quality in perinatal care. By monitoring indicators stratified by indicators of social determinants (race/ethnicity, insurance, urban/rural), quality improvement collaboratives have the potential to improve health care quality, address health equity, and reduce disparities with thoughtful intent in the appropriate cultural context.

Enriching Postnatal Infant Development

Health care providers should be aware of the variety of public health resources available to families of preterm infants to support postnatal infant development, particularly for low-income families. Programs include the following:

- Breastfeeding support
- Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)
- Early intervention services
- Healthy Start
- Home visitation programs
- Head Start
- Literacy initiatives (eg, Reach out and read)

SUMMARY

Preterm birth is a global public health priority. Developed countries have seen dramatic improvements in the survival of very preterm infants with declines in infant mortality. Yet, in the United States, total preterm birth rates are rising while the proportion of very preterm infants born in the United States has not changed substantially over the last several decades. To continue to reduce infant mortality and associated medical and neurodevelopmental disability, the complex issue of early preterm birth and associated racial/ethnic disparities need to be addressed. Public health approaches in collaboration with diverse stakeholders can improve population-based data and identify effective interventions with impact to

improve the health of women before, during, and after pregnancy and reduce death and disability among newborns.

Several national organizations are leading initiatives to reduce preterm birth:

- March of Dimes (MOD) (www.marchofdimes.org). MOD has established five multidisciplinary centers to research the complex causes of preterm birth. In 2017, MOD launched the Prematurity Collaborative, a national effort to reduce preterm birth through improving health equity. The Collaborative has more than 200 members with focused strategies on equity, research, clinical and public health interventions, policy, and communications. Lastly, the MOD's "Road-map to 2020 and 2030 Goals" identified 16 states with preterm birth rates greater than 11.5% with substantial racial/ethnic disparities and approximately 100,000 births per year to reduce modifiable risk factors by bundling various interventions through the Healthy Babies are Worth the Wait Community Program.
- Association of State and Territorial Health Officials Healthy Babies Initiative (www.astho.org):
- Collaboration on Innovation and Improvement Network (www.mchb.org):
- National Network of Perinatal Quality Collaboratives (https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pqc.htm)

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KEY POINTS

- Although very preterm births (<32 weeks gestation) represent approximately 1.6% of all US live births, they account for 52% of infant deaths, substantial medical complications, neurodevelopmental disability, and associated health care costs.
- Clinicians and health systems should be aware of population-based risks, including disparities, associated with very preterm birth and data available to inform decision-making.
- Public health engagement and collaboration offers opportunities to address social determinants to improve the quality of care and health of reproductive-age women and their newborns.

Risks associated with preterm delivery

Maternal demographic characteristics

- Young or advanced maternal age
- Black race
- Low socioeconomic status

Unhealthy lifestyle

- Tobacco use
- Substance abuse
- Low or high prepregnancy body mass index

Pregnancy history

- Short interpregnancy interval
- Previous preterm delivery
- Multiple gestations

Pregnancy complications

- Placental abruption or previa
- Polyhydramnios
- Oligohydramnios

Maternal medical disorders

- Thyroid disease
- Obesity
- Asthma
- Diabetes
- Hypertension

Mental health

- Psychological or social stress
- Depression

Fertility treatments

- Assisted-reproductive technology
- Nonassisted-reproductive technology fertility treatments

Intrauterine infection

- Premature rupture of membranes

Fetal factors

- Fetal anomalies

Adapted from Shapiro-Mendoza CK, Barfield WD, Henderson Z, et al. CDC grand rounds: public health strategies to prevent preterm birth. MMWR Morb Mortal Wkly Rep 2016;65:828; with permission.

Medical complications of preterm birth

Respiratory

Respiratory distress syndrome

Transient tachypnea

Bronchopulmonary dysplasia

Pneumonia

Apnea and bradycardia

Pulmonary interstitial emphysema

Cardiovascular

Patent ductus arteriosus

Gastrointestinal/hepatic

Jaundice

Feeding intolerance

Necrotizing enterocolitis

Immune/infectious

Infection/sepsis

Meningitis

Central nervous system

Retinopathy of prematurity

Intraventricular hemorrhage

Posthemorrhagic hydrocephalus

Periventricular leukomalacia

Cerebral palsy

General

Inability to regulate body heat

Anemia

Table 1

Percent preterm birth by gestational age categories, United States, 2007, 2010, and 2015

Year	Total Preterm[a]	34–36 wk	32–33 wk	28–31 wk	≤27 wk
2015	9.62	6.87	1.17	0.91	0.68
2010	9.98	7.15	1.18	0.94	0.71
2007	10.44	7.51	1.22	0.97	0.74

[a]Preterm defined as <37-wk gestation.

Data from Centers for Disease Control and Prevention. User guide to the 2015 period linked birth/infant death public use file. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/DVS/periodlinked/LinkPE15Guide.pdf. Accessed January 31, 2018.