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Gestational Age and Pregnancy Outcomes

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Abstract

Some of the important pregnancy outcomes such as preterm delivery, growth restriction and low birth weight (LBW) infant, stillbirth, and some long-term chronic diseases vary by race and ethnicity but also tend to be associated with gestational age of the infant at birth. In the United States, during the last 25–30 years, the rate of low birth weight has increased, as has the rate of preterm delivery among both whites and blacks. Examination of causes for these secular trends has focused mainly on changes in the distribution of maternal age, race, and certain psychosocial factors. However, gestational age at birth is associated with most of these pregnancy outcomes, particularly infant mortality, certain morbidities, birth weight, and preterm birth. In this chapter, the association between gestational age and some significant pregnancy outcomes will be discussed.

Keywords: gestational age, pregnancy outcome, infant mortality, preterm, growth restriction

1. Introduction

Before illustrating the significance of gestational age at birth and pregnancy outcomes, definitions and information about various terms to be used in the text will be provided.

Gestational age at birth: Is defined as the time between conception and birth of an infant. The most common method of measuring gestational age in weeks is by calculating the time since the last menstrual period based on dates provided by a woman at the first prenatal visit [1]. A normal pregnancy period is usually between 38 and 40 weeks.

Appropriate for gestational age (AGA): if the infant's gestational age findings after birth match the calendar age, the infant is said to be appropriate for gestational age. The weight for full-term infants born AGA is often between 2500 and 4000 g [2].

Small for gestational age (SGA): infants weighing less than 2500 g are considered small for gestational age.

Large for gestational age (SGA): infants weighing more than 4000 g are considered large for gestational age.

Low birth weight (LBW): is not a homogeneous pregnancy outcome, but, instead, is composed of infants who are either born too early, that is, preterm birth, or too small, that is, fetal growth restriction [3]. A LBW infant, according to the World Health Organization, is born weighing <2500 g [4].

Preterm birth (premature birth): is the birth of a baby at fewer than 37 weeks of gestation. Preterm birth can be spontaneous or induced [5]. **Figure 1** illustrates a combination of categories of preterm birth, low birth weight, and small for gestational age infants.

Intrauterine growth retardation (fetal growth retardation or growth restriction): growth-restricted infants or infants with intrauterine growth retardation are those born weighing less than the tenth percentile of birth weight for gestational age, regardless of whether the weight is <2500 g. Therefore, it is possible for both preterm and growth-restricted infants to weigh less than <2500. Thus to define IUGR or grow restriction, a birth weight for gestational age standard with the tenth percentile birth weight defined is needed [6, 7].

Important pregnancy outcomes include neonatal mortality, stillbirth, long-term neurologic problems, and maternal mortality [3]. Research conducted in this area indicates that many of these outcomes are associated with length of gestation or gestational age of the infant at birth. In the United States and other developed countries, pregnancy outcomes are much better than those in many developing countries, where the adverse outcomes mentioned above are increased 10–100-fold as compared to US rates [3]. However, adverse pregnancy outcomes are generally more common in the United States than other developed countries [5, 8]. Low infant birth weight, either due to preterm birth or intrauterine growth restriction, is attributed to much of the infant mortality, morbidity, and increased cost of perinatal care. Data from the US Center for Disease Control and Prevention indicates that the infant mortality rate in the United States

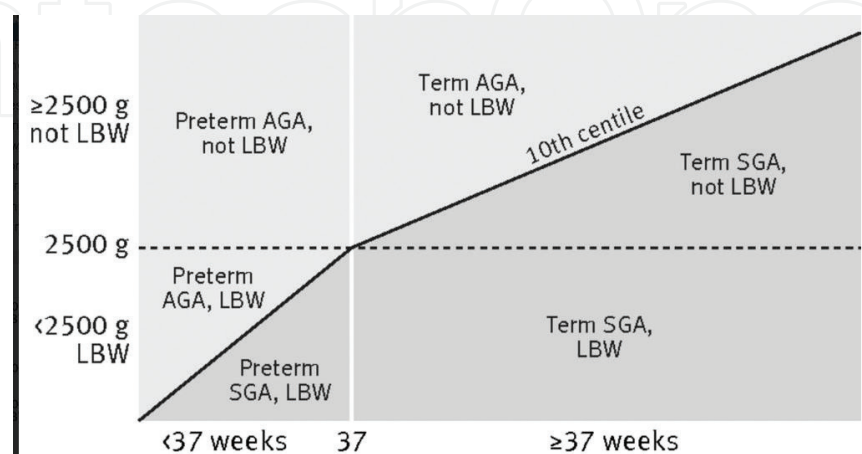


Figure 1. A combination of preterm, low birth weight, and small for gestational age infants.

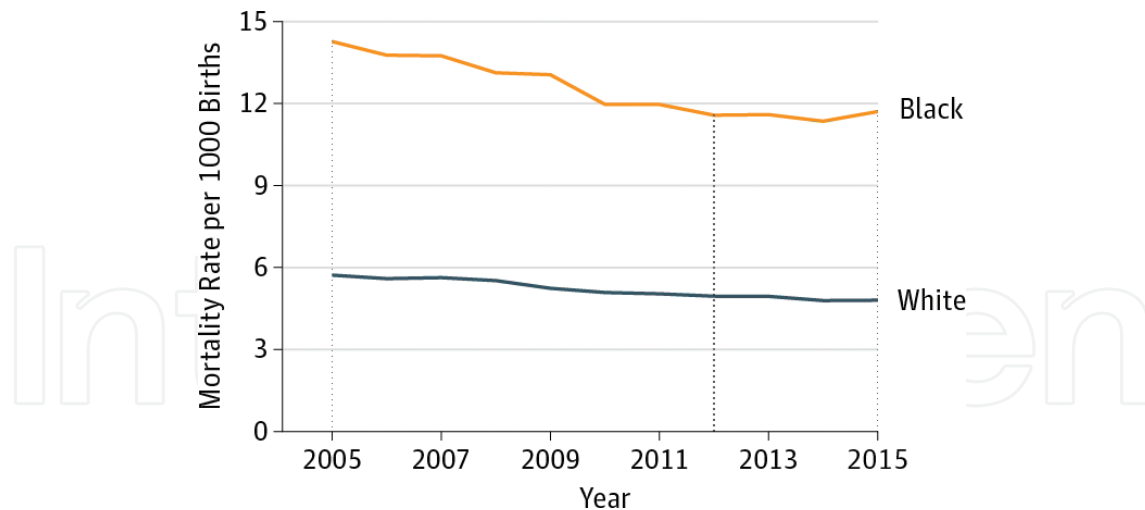


Figure 2. Infant mortality rate of black versus white infants.

during the past decade has decreased by 15% [5, 7]. Wide disparity exists in both preterm and growth restrictions among different population groups. Poor blacks, for example, have twice the preterm birth rate and higher growth restriction than do most women [5]. The infant mortality from 2005 to 2012 for non-Hispanic blacks decreased from 14.3 to 11.6/1000 births; thereafter the infant mortality rate plateaued and then increased from 11.4 to 11.7 over this time period. For non-Hispanic white infants, the rate decreased monotonically from 5.7 to 4.8/1000 births [8]. Further analyses indicate that black infants are nearly 2.2 times more likely to die than white infants during their first year of life. The trends in cause-specific mortality for four leading causes of infant death show that short gestation/low birth weight is responsible for the highest mortality rate/1000 births. Riddell et al. indicate that the gestational age at birth explains a large portion of excess deaths in black infants as compared to white infants, for example, the preterm (gestational age < 37 weeks) rate is almost 50% higher in black than to white infants [8]. Also, black infants experience nearly four times as many deaths related to short gestation and low birth weight, making it the leading cause of infant deaths among black infants during the first year of life [8]. See **Figure 2**. Thus, these results confirm that gestational age at birth is a significant factor which affects major factors resulting in poor pregnancy outcomes such as infant mortality and morbidity. The risk of adverse consequences declines with increasing gestational age [9].

In this chapter, pregnancy outcomes and its relationship to gestational age will be limited to pregnancy outcomes associated with preterm birth, race and ethnicity, low birth weight, still-birth, small for gestational age (fetal growth restriction), and certain chronic diseases.

2. Preterm births and gestational age at birth

As noted before, preterm birth is defined as infants born before completing gestational age of 37 weeks. In 2010, an estimated 14.9 million babies were born preterm, 11.1% of all live births worldwide, ranging from about 5.5% in most European countries to 18% in some African

countries [10]. Preterm birth also affects affluent countries, for example, the United States has high rates and is 1 of 10 developed countries with the highest number of preterm births [10]. Preterm birth can further be subdivided on the basis of gestational age: extremely preterm (<28 weeks), very preterm (28–32 weeks), and moderate or late preterm [32–37] completed weeks of gestation. Since decreasing gestational age is associated with increasing mortality, disability, and cost due to intensity of neonatal care, these subdivisions are important [7]. As stated before, the risk of adverse consequences declines with increasing gestational age [9]. There are a variety of causes of preterm birth which can be broadly classified into (1) provider initiated preterm birth (induction of labor or elective cesarean section) before 37 weeks of gestation for maternal or fetal indications, (2) spontaneous preterm labor with intact membranes, and (3) preterm rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by cesarean section [9]. Births that follow spontaneous labor and PPRM are together referred to as spontaneous preterm births. As indicated in most studies, approximately 25% of all preterm births occur for maternal or fetal indications [5]. The contributions of the causes of preterm birth to all preterm births differ by ethnic groups. PPRM most commonly is the cause of preterm birth in black women, but spontaneous preterm birth is most commonly caused by preterm labor in white women [11]. In most studies, about 50% of all preterm births follow spontaneous preterm labor, and approximately 30% of preterm births result from premature rupture of the membranes. Obstetric intervention or iatrogenic preterm birth explains much of the increase seen in preterm births [12, 13]. Also, prior spontaneous preterm delivery is strongly associated with recurrence in the current pregnancy. An early prior spontaneous preterm delivery is a better predictor of recurrence and is most strongly associated with subsequent early spontaneous preterm delivery [14].

Ananth et al. tried to explain the reasons for the increase in preterm births over the last two decades by using large United States vital statistics data and concluded that a large part of increase in preterm births is explained by indicated preterm births [15]. Also a considerable increase is associated with multiple births that occur due to the use of various assisted reproductive techniques. Demographic and socioeconomic factors associated with increased risk of preterm birth include ethnicity, the presence of indicators of low socioeconomic status, and extreme maternal age among other factors [9]. A country-based study conducted in Italy showed an association between preterm birth and certain maternal outcomes as BMI, employment, previous abortions, previous preterm delivery, and previous cesarean section [16]. Some researchers believe preterm labor to be a syndrome initiated by multiple mechanisms, including infection or inflammation, utero-placental ischemia or hemorrhage, stress, and other immunologically mediated processes [11, 17]. A more concise mechanism is difficult to establish in most cases; therefore factors linked with preterm birth have been analyzed to explain preterm labor. Since many of the risk factors result in systemic inflammation, increasing infection or inflammation pathway might explain some of the variance in increase in preterm births associated with multiple risk factors [18]. Maternal BMI is an important risk factor for preterm birth and is of public health importance independently. Some researchers have shown an increase in preterm birth with low BMI or BMI <18.5 kg/m² [19–21]. Others support an increase in provider initiated preterm birth with increasing BMI [22, 23]. Cole-Lewis et al. suggest that there is evidence that pregnancy-specific stress is associated with preterm birth. They examined this relationship by measuring

pregnancy-specific stress measured in the second and third trimesters in 920 black and/or Latina young women. Their findings emphasize the importance of measuring pregnancy-specific stress across the pregnancy. The longitudinal change from the second to third trimesters was significantly associated with the length of gestation measured both as a dichotomous variable (preterm birth) and a continuous variable. The results of the Cole-Lewis et al. study indicate that change in pregnancy-specific stress between the second and third trimesters was significantly associated with increased risk of preterm delivery and shortened gestational age, even after adjusting for important biological, behavioral, psychological, and sociocultural risk factors [24]. **Figure 1** depicts the sequelae of preterm birth.

3. Race and ethnicity and low birth weight

There is a strong association between both growth restriction and prematurity in newborns in women who belong to various ethnic and racial groups. Reasons for this association are not clear. In the United States, the rate of preterm birth in black women is about twice that of women from most other racial or ethnic groups. Similarly, black women are three to four times more likely to give birth to a very early preterm infant as compared to other racial groups [5, 25]. Women from South Asia and especially the Indian subcontinent have very high rates of growth restriction and low birth weight. In the United States, among all the groups, in black women the relationship between gestational age at birth of an infant and a particular pregnancy outcome, that is, low birth weight due to preterm, is very high, and to date this very high-preterm birth rate in black women is mostly unexplained.

4. Low birth weight and gestational age at birth

Infants born weighing <2500 g who are either born too early, that is, preterm birth, or too small, that is, fetal growth restriction, are referred to as low birth weight (LBW). LBW is an established factor associated with increased risk of infant mortality and morbidity, also a recognized proxy for maternal health [26, 27]. Garcia et al. have shown that after controlling for maternal age, parity, smoking, and maternal BMI, a significant difference was noted in infant mean birth weights and gestational age and hence rate of preterm birth between British and Indian, Pakistani, and Bangladeshi infants. This study confirms the evidence that South Asian women typically give birth to infants of lower birth weight than white British women, and a large variance in birth weight can be explained by a shorter gestational age in Indian mothers as compared to white British mothers [28]. One of the success stories in the United States and other developed countries is the improved survival in very LBW infants over the last three and a half decades. The survival for infants weighing between 500 and 1000 g in 1975 was approximately 15%. At present, survival for the same group of infants is 80%. Improvement in survival for infants born weighing between 1000 and 2500 g is also impressive. Approximately 60% of neonatal mortality is seen in newborns weighing <1000 g when the distribution of neonatal mortality by birth weight group is looked at [5].

The distribution of newborn the decreased rate of LBW in the United States is not seen across all 50 states. Some places like Washington DC and other mostly relatively poor southern states currently have a much higher rate of LBW rate than that of the United States (7.1%). The latest 2017 Alabama Kids Count Data Book, noted mixed results Statewide for children from 2005 to 2015 [29]. In Tuscaloosa County, Alabama, though the number of LBW babies has decreased from 12.6% during the last 10 years, the percentage is still higher than the state average of 10%. Unfortunately, the improvement in infants weighing between 1000 and 2500 g is not due to improvement in factors related to increased gestational age or reduction in rate of preterm birth. Highly sophisticated instruments and techniques are responsible for survival of these low and very low birth weights, without improving the factors associated with low birth weight, for example, increased length of gestation.

There are several long-term outcomes associated with low birth weight. The most common among them are neurological outcomes such as blindness, cerebral palsy, deafness, and hydrocephaly and several severe respiratory difficulties because of the poor lung development due to a short gestation. As indicated before, the earlier the gestational age and lower birth weight, the greater the risk for all complications and especially cerebral palsy [5, 7].

5. Stillbirth and gestational age at birth

The relationship between stillbirth and LBW and hence gestational age at birth of the infant is not studied frequently [30]. In the United States, approximately half of all still births occur at <28 weeks of gestational age. The other one-third occurs between 28 and 36 weeks of gestation [31]. Therefore, somewhere between two-thirds and three-quarters of all still births are mostly LBW and preterm. Thus both fetal growth restriction and preterm birth are significant risk factors for still birth. The risk of stillbirth after 32 weeks of gestation increases with gestational age, and half of these late fetal deaths occur at term [32]. Rosenstein et al. [33] and other researchers have reported that the risk of stillbirth at term increases with gestational age from 2.1/10,000 ongoing pregnancies at 37 weeks of gestation up to 10.8/10,000 ongoing pregnancies at 42 weeks of gestation. Also, at each gestational age beyond 38 weeks of gestation, the mortality risk of expectant management is higher than the risk of delivery, thus 39 weeks of gestation, 12.9 compared to 8.8/10,000; 40 weeks of gestation, 14.9 compared with 9.5/10,000; and 41 weeks, 17.6 compared with 10.8/10,000.

6. Fetal growth restriction and gestational age at birth

One of the major purposes of antenatal care is assessment of fetal growth. Caregivers need to distinguish between fetuses which are smaller than expected growth in utero; while some fetuses are constitutionally small, others have failed to meet their growth potential, that is, they are growth restricted (small for gestational age). While in the United States and other affluent countries, severe growth restriction is not common, the consequence of it not being recognized may include severe morbidity and in some cases even perinatal death [34]. According to the

Child Health Epidemiology Reference Group (CHERG) dataset which uses INTERGROWTH-21st standard, in 2012, an estimated 23.3 million or 19.3% infants were born small for gestational age in low- and middle-income countries [35]. Among these, 11.2 million were term and not LBW, 10.7 million were term and LBW, and 1.5 million were preterm. Also, in these low- or middle-income countries, an estimated 606,500 neonatal deaths were attributed to infants born too small for gestational age, 21.9% of all neonatal deaths. The prevalence in South Asia was highest. About 34% and approximately 26 of neonatal deaths were due to infants born too small for gestational age or growth restricted. Thus, in low- and middle-income countries, about one in five infants is born small for gestational age (as compared to 16% among blacks and 9% SGA in 200 in the United States), and one in four deaths is among such infants [36]. Growth restriction in infants can be due to many factors including poor maternal nutrition, maternal infections, congenital defects, smoking, and placental conditions [36]. SGA can also arise from genetic predisposition to small size. The genetic and constitutional contributions to SGA are generally small relative to the other factors mentioned above, particularly in low- and middle-income contexts. Infant survival strategies should direct resources toward leading causes of infant and child mortality, with attention focusing on infectious and neonatal causes. More rapid decrease from 2010 to 2015 will require accelerated reduction for most common causes of death, particularly, preterm and growth-restriction complications. Last but not least, gathering of high-quality data and enhanced estimation methods will be very useful for future estimates [37].

7. Chronic diseases and low birth weight and gestational age

Recently there have been many studies on the relation of LBW and gestational age at birth to the development of long-term chronic conditions, such as hypertension, diabetes, and heart disease. Termed as the Barker hypothesis, proposed in 1990 by the British epidemiologist David Barker that intrauterine growth retardation, low birth weight, and premature birth have a causal relationship to the origins of hypertension, coronary heart disease, and noninsulin-dependent diabetes [38]. Although its existence is controversial, it is supported by several epidemiological studies [39, 40].

8. Summary

The important pregnancy outcomes associated with gestational age at birth include both fetal and neonatal deaths, postnatal death, and short-term morbidities such as the respiratory distress syndrome and necrotizing enterocolitis. The long-term morbidities such as deafness, blindness, hydrocephaly, mental retardation, and cerebral palsy are among other chronic diseases discussed before. Many investigators use preterm birth (associated with gestational age) and growth restriction as an intermediate outcome measure for serious morbidity or mortality, that is, the goals of reducing growth retardation, preterm delivery, or length of gestational age are worthwhile only if they reflect reduction in morbidity and mortality. Thus, in some circumstances, if handicap or death is avoided, delivering an infant early is not the worst of all possible outcomes.

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