Low birth weight in the United States

Robert L Goldenberg and Jennifer F Culhane

ABSTRACT
Pregnancy outcomes in the United States and other developed countries are considerably better than those in many developing countries. However, adverse pregnancy outcomes are generally more common in the United States than in other developed countries. Low-birth-weight infants, born after a preterm birth or secondary to intrauterine growth restriction, account for much of the increased morbidity, mortality, and cost. Wide disparities exist in both preterm birth and growth restriction among different population groups. Poor and black women, for example, have twice the preterm birth rate and higher rates of growth restriction than do most other women. Low birth weight in general is thought to place the infant at greater risk of later adult chronic medical conditions, such as diabetes, hypertension, and heart disease. Of interest, maternal thinness is a strong predictor of both preterm birth and fetal growth restriction. However, in the United States, several nutritional interventions, including high-protein diets, caloric supplementation, calcium and iron supplementation, and various other vitamin and mineral supplements, have not generally reduced preterm birth or growth restriction. Bacterial intrauterine infections play an important role in the etiology of the earliest preterm births, but, at least to date, antibiotic treatment either before labor for risk factors such as bacterial vaginosis or during preterm labor have not consistently reduced the preterm birth rate. Most interventions have failed to reduce preterm birth or growth restriction. The substantial improvement in newborn survival in the United States over the past several decades is mostly due to better access to improved neonatal care for low-birth-weight infants. Am J Clin Nutr 2007;85(suppl):584S–90S.

KEY WORDS Low birth weight, preterm birth, fetal growth restriction, cerebral palsy, neonatal mortality, stillbirth

INTRODUCTION
Pregnancy outcomes in the United States and other developed countries are considerably better than those seen in many developing countries (1, 2). Stillbirth rates are in the range of 3–7 per 1000 births versus ≥30 in many developing countries. Neonatal mortality rates are ≈4–6 per 1000 newborns versus ≥40 per 1000 newborns in developing countries, and maternal mortality rates are in the range of 5–10 per 100 000 pregnancies versus rates as high as 500–1000 per 100 000 pregnancies in some developing countries. Nevertheless, despite these better outcomes in developed countries, adverse pregnancy outcomes are generally more common in the United States than in other developed countries and result in both excessive medical costs in the perinatal period and increased long-term neurologic disability (3, 4). In both developed and developing countries, low birth weight (LBW) is an important cause of perinatal mortality and both short- and long-term infant and childhood morbidity. LBW infants die at rates of up to 40 times those of infants of normal weight, and LBW infants are many times more likely to end up with long-term handicapping conditions (Figure 1). This article will explore issues related to the causes, outcomes, and interventions used to prevent LBW.

DEFINITIONS OF LOW BIRTH WEIGHT
LBW is not a homogeneous pregnancy outcome, but instead, conceptually, is composed of infants who are either born too early, ie, preterm birth, or too small, ie, with fetal growth restriction. According to the World Health Organization, a LBW infant is one born weighing <2500 g (5). Preterm infants are those born at <37 wk from the first day of the last menstrual period, regardless of birth weight, whereas growth-restricted infants are those born weighing less than the 10th percentile of birth weight–for–gestational age, regardless of whether that weight is <2500 g. Thus, it is possible for both preterm and growth-restricted infants to weigh >2500 g.

To define growth restriction, one needs a set of birth weight–for–gestational age standards with the 10th percentile birth weights defined (6). Many such standards have been published, and the 10th percentile birth weights vary substantially among them. There are many issues related to the choice of which set of standards to use (6). Although these will not be reviewed in detail here, it is clear that if one bases the standard on birth populations such as those found in Scandinavia, the 10th percentile cutoff for fetal growth restriction will be substantially higher than if the standard is based on a predominantly black birth population in the United States or a population of births from the Indian subcontinent. Within the United States, whether the birth population used to create the standard is a population at sea level or a population living at high elevations such as Denver, CO, also makes a difference. In any case, the reasons to choose one birth population to use as a standard versus another have been discussed in detail, and suffice it to say which standard to use is still a controversial topic.

1 From Drexel University, Department of Obstetrics and Gynecology, Philadelphia, PA.
2 Presented at the conference “Maternal Nutrition and Optimal Infant Feeding Practices,” held in Houston, TX, February 23–24, 2006.
3 Reprints not available. Address correspondence to RL Goldenberg, Department of Obstetrics and Gynecology, Drexel University College of Medicine, 245 North 15th Street, 17th Floor, Room 17113, Philadelphia, PA 19102. E-mail: rgoldenberg@drexelmed.edu.
NEONATAL OUTCOMES ASSOCIATED WITH LOW BIRTH WEIGHT

The important birth outcomes related to LBW include both fetal and neonatal death, postneonatal death, short-term morbidities such as respiratory distress syndrome and necrotizing enterocolitis, and long-term morbidities such as blindness, deafness, hydrocephaly, mental retardation, and cerebral palsy. However, whether an infant is preterm or growth restricted, if it has no short-term morbidity, is discharged from the hospital at the usual time, and suffers no long-term morbidity or mortality, it matters little whether the infant was born growth restricted or preterm. Thus, many investigators use preterm birth and growth restriction as a surrogate or intermediate outcome measure for serious morbidity or mortality. Said differently, the goals of reducing growth retardation or preterm birth are important only as they reflect reductions in morbidity and mortality. It is possible, and even likely, that in some circumstances, if handicap or death is avoided, delivering an infant early is not the worst of all possible outcomes.

STILLBIRTH AND LOW BIRTH WEIGHT

The relation between stillbirth and LBW is often not considered (7). However, it is important to understand that in the United States, approximately one-half of all stillbirths occur at ≤28 wk gestational age, and another one-third occur between 28 and 36 wk (8). Thus, somewhere between two-thirds and three-quarters of all stillbirths are preterm and generally LBW. Both fetal growth restriction and preterm birth are important risk factors for stillbirth.

PRETERM BIRTH

The incidence of preterm birth in the United States is traditionally stated to be about 10%. In fact, over the past 25 y, the preterm birth rate in the United States and in most other developed countries has risen (9, 10). In the United States, this increase has been from about 9.5% to 12.5% (Figure 2). Although most other developed countries have substantially lower preterm birth rates than does the United States, many have experienced similar rises in the preterm birth rate over the past several decades.

Preterm birth is generally thought of as having 3 obstetric precursors (Figure 3). The first is an indicated preterm birth, usually for maternal or fetal indications. These births occur because the physician believes the fetus would do better in the nursery than in the uterus. Labor is either induced or the fetus is delivered by elective cesarean delivery. Common reasons for these decisions include fetal distress, which is usually determined by electronic fetal monitoring; severe growth restriction, which is usually determined by fetal ultrasound; maternal pre-eclampsia; and placental abruption. In most studies, about 25% of all preterm births occur for maternal or fetal indications. The rest of the preterm births are classified as spontaneous. These
follow premature rupture of the membranes or spontaneous preterm labor, regardless of whether the delivery ultimately is vaginal or by cesarean delivery. In most studies, about 50% of all preterm births follow spontaneous preterm labor and about 30% follow premature rupture of the membranes.

Ananth et al (11) attempted to define the reasons for the increase in preterm births over the past decade and a half. In an analysis using US vital statistics data, they concluded that a large part of the increase in preterm births in singletons is explained by an increase in indicated preterm births (Figure 4). Other authors have emphasized the considerable increase in preterm births associated with multiple births that occur after the use of various assisted reproductive techniques (12). At least one study in Canada suggested that a portion of the increase in spontaneous preterm births was associated with an increase in chorioamnionitis (13). In any case, putting together all available data, it appears as if indicated preterm births and multiple births secondary to assisted reproductive technologies account for the vast majority of the increase in preterm births noted above.

RACE, ETHNICITY, AND LOW BIRTH WEIGHT

For unknown reasons, belonging to various racial and ethnic groups is very strongly associated with both preterm birth and growth restriction. For example, in the United States, black women are approximately twice as likely to have a preterm birth and are 3 to 4 times as likely to have a very early preterm birth as women are from most other racial or ethnic groups (14). East Asian women typically have low rates of preterm birth, as do Hispanic women. Women from South Asia and especially the Indian subcontinent have very high rates of fetal growth restriction and low birth weight. Among the various groups living in the United States, the very high preterm birth rate in black women stands out and to this date remains mostly unexplained.

LOW-BIRTH-WEIGHT OUTCOMES

One of the very large success stories in the United States and other developed countries is the improved survival in very LBW infants over the past 3 decades. For example, if one focuses on infants born weighing between 500 and 1000 g, in 1975, survival for those infants was ≈15%. At the present time, survival for the same group of infants approaches 80%. Improvement in survival over the past decades for infants between born weighing between 1000 and 2500 g is equally impressive. With these improvements, mortality in infants born weighing 1000 to 2500 g is quite rare, and when one examines the distribution of neonatal mortality by birth weight group, ≈60% of all neonatal mortality is found in infants weighing <1000 g. Thus, if we are to have a really large effect on neonatal mortality in the United States, our major goal must be to reduce mortality in infants born weighing <1000 g.

There are several long-term outcomes associated with both preterm birth and fetal growth restriction. Among the best studied are neurologic outcomes such as cerebral palsy, blindness, deafness, and hydrocephaly. The earlier the gestational age and the lower the birth weight, the greater the risk of all complications and especially cerebral palsy (15). For example, as shown in Figure 5, that in infants born weighing >2500 g at term, the risk of cerebral palsy is 1 to 2 per 1000 births. On the other hand, for infants born at the edge of survival (at about 23–24 wk and at 500–600 g), the prevalence of cerebral palsy is as high as 250 per 1000 births. In 1998, Lorenz et al (16) performed a meta-analysis of studies that presented survival and the prevalence of disability in extremely LBW infants. As shown in Figure 6A, from 1975 to 1995, survival among these extremely small infants increased substantially. On the other hand, the prevalence of disability among the extremely small survivors remained virtually unchanged over time, averaging about 25% (Figure 6B). Thus, because the survivors increased and the prevalence of disability among the survivors stayed the same, the absolute number of survivors with disability increased (Figure 6C). In an attempt to show how this might play out for all births in the United States, we constructed Table 1. It can be seen that from 1960 to 2000, ≈20 000 infants were born each year weighing <1000 g. However, survival increased from ≈1% in 1960 to ≈80% in 2000. The number of survivors has increased accordingly. Since the percentage of survivors with cerebral palsy or with any disability has remained approximately the same, one can see that among the 20 000 infants born each year weighing <1000 g, the number of survivors with cerebral palsy and the number of survivors with other disabilities has increased substantially over the years. Thus, the major success related to preterm birth is a reduction in mortality. There obviously has been no
In relation to growth restriction, it appears that long-term disability is related to the degree of growth restriction (17). Those infants born between the 5th and 10th percentiles, for example, have little increase in long-term neurologic damage. On the other hand, infants born below the 3rd and especially below the 1st percentile are at considerably greater risk. The prevalence of long-term handicap also depends on the gestational age at which the growth restriction became established. For example, when growth restriction is documented before 26 wk, the infants are considerably more likely to have cerebral palsy or other neurologic damage than are infants who grew appropriately the past 26 wk and then ceased growing normally. In any case, the risks of cerebral palsy associated with growth restriction (<1%), especially if the infant is born close to term, are considerably less than for preterm infants born weighing 500–1000 g, for which overall risk is ≈8%.

CHRONIC DISEASES ASSOCIATED WITH LOW BIRTH WEIGHT

In recent years, there has been a great deal of interest in the relation of LBW and each of its components to the development of long-term chronic medical conditions, such as hypertension, diabetes, and heart disease. Termined the Barker Hypothesis, this relation has been studied extensively, and although its existence is controversial, it is supported by the results of several epidemiologic studies (18). However, no interventions have been shown to reduce the long-term chronic diseases potentially associated with LBW.

PREDICTING PRETERM BIRTH

In the United States, many studies have focused on the prediction of preterm birth in the hope that being able to predict preterm birth would lead to its prevention (19). Conceptually, the predictors for preterm birth might be divided into 1) demographic characteristics such as race and poverty, 2) adverse health behaviors such as smoking, 3) maternal physical characteristics such as body size and especially low body mass index (BMI; in kg/m²), 4) medical obstetric history such as having a prior preterm birth, 5) biophysical characteristics such as the length of the cervix as determined either by physical examination or ultrasound, and 6) a large number of biological fluid markers. Among the strongest predictors of preterm birth are black race, maternal thinness as measured by a low BMI (<20), a history of a prior preterm birth and especially an early preterm birth, a short cervical length as measured by ultrasound, and a positive test result for cervical or vaginal fluid fetal fibronectin (20, 21). Unfortunately, knowledge of the presence of any of these characteristics has not been helpful in reducing the incidence of preterm birth.

INFECTION AND PRETERM BIRTH

Over the past 20 y, it has become apparent that many of the early spontaneous preterm births are associated with and probably caused by intraterine bacterial infections (22–24). The organisms are usually vaginal in origin and ascend into the uterus either before or early in pregnancy. The organisms are often of low virulence and the infections tend to be chronic, persisting for weeks or months before the preterm labor or membrane rupture initiates a spontaneous preterm birth. Ureaplasma urealyticum
and *mycoplasma hominis* are the 2 most common organisms, but >30 different bacteria have been identified. Many of these organisms are components of a chronic vaginal infection called bacterial vaginosis, a common condition associated with a 2-fold increase in preterm birth. About 85% of spontaneous preterm births of fetuses weighing <1000 g are thought to be caused by an intrauterine infection, but few of the later preterm births are associated with this condition. Many attempts have been made to reduce preterm birth by using antibiotics, either in the prenatal period or during early labor. Although the results of a few studies have been positive, most have failed to show a reduction in preterm birth, and no authoritative US agency recommends the use of antibiotics to achieve a reduction in preterm birth (24).

### NUTRITIONAL ISSUES

Because this is a conference devoted to nutritional issues, it is appropriate to briefly explore the relation between maternal body habitus and LBW. In recent years, it has become clear from many studies that thin women have a higher risk of having both preterm and growth-restricted infants than do average-sized women (25, 26). In fact, the relation seems to be essentially linear in that the thinner the woman, the greater the risk of both preterm birth and fetal growth restriction. Conversely, the heavier the woman, the lower the risk. However, the heavier the woman, the greater the risk of a wide variety of pregnancy-related complications such as chronic hypertension, preeclampsia and eclampsia, and diabetes. In Figure 7, which is derived from data from the National Institute of Child Health and Human Development Preterm Prediction Study, it can be seen that as maternal BMI increases, the rate of spontaneous preterm birth decreases (26). Some evidence suggests that the relation between BMI and preterm birth is mediated through cervical length, in that women who are overweight and obese tend to have longer cervices, which seem to protect against spontaneous preterm birth (19).

Several interesting observations have related various risk factors to growth restriction mediated by maternal BMI. For example, higher BMIs appear to protect the fetus against the effect of smoking on growth restriction (27). Similarly, higher BMIs protect the fetus from the effect of maternal stress on growth restriction (28). In a randomized clinical trial, low doses of aspirin increased birth weight and newborn abdominal circumference, but this relation occurred only in thinner women (29). Finally, in another randomized clinical trial, zinc supplementation increased birth weight substantially, but only in thinner women (30). Thus, some evidence suggests that maternal thinness is a risk factor for spontaneous preterm birth and fetal growth restriction. Furthermore, at least 2 treatments that might reduce fetal growth restriction and preterm birth seem to work only in women who are thin. High BMIs seem to protect against 2 risk factors for growth restriction, maternal smoking, and maternal stress. Another interesting observation relating maternal BMI to an adverse pregnancy outcome is that women with high BMIs are more likely to have infants with neural tube defects, and folate supplementation increased birth weight substantially, but only in thinner women (31). Thus, the relation of maternal body habitus, various risk factors, and various interventions to improving outcomes should be explored further.

### NUTRITIONAL INTERVENTIONS

Because maternal thinness has been associated with preterm birth and growth restriction, several studies have been made of nutritional interventions to reduce adverse pregnancy outcomes. First, it is clear that folic acid reduces the prevalence of certain congenital anomalies (32). It is also clear that in certain developing countries where near-starvation diets are common, nutritional supplementation improves several outcomes, including reducing mortality as well as decreasing preterm birth and growth restriction (33). However, in the United States, virtually all nutritional interventions used to reduce low birth weight or its components, preterm birth and growth restriction, have failed (34, 35). In fact, protein supplementation appears to have a negative effect on pregnancy outcome. Nutritional counseling programs have had minimal effects, if any, on pregnancy outcomes, and caloric supplementation programs including WIC (the Special Supplemental Nutrition Program for Women, Infants, and Children) have been associated with only small increases in birth weight, but no other important improvements in outcome. Supplementation during pregnancy with various minerals such as...
iron, calcium or zinc, and various vitamin preparations have not consistently reduced preterm birth or growth restriction.

**STRATEGIES USED TO REDUCE LOW BIRTH WEIGHT**

Many other strategies have been used in an attempt to reduce LBW (34). These include a general increase in prenatal care and many of its components. Home uterine contraction monitoring, for example, has not generally led to any decrease in preterm birth and often is associated with an increase in the use of various interventions that by and large have not been effective (34, 36). Programs aimed at reducing adverse health behaviors, such as the use of drugs, alcohol, or tobacco, have by and large not had a major effect on reducing preterm birth or growth restriction (34). We should emphasize here, however, that tobacco use is more distinctly associated with growth restriction than with preterm birth (37), and it is likely that the recent decline in tobacco use during pregnancy is associated with an overall increase in birth weight. Many other interventions such as bed rest, use of antibiotics to treat infection, home uterine activity monitoring to search for uterine contractions before labor, and various treatments of preterm labor such as intravenous hydration, various tocolytic agents, etc, have not been associated with a reduction in preterm birth (34, 36, 38). Similarly, strategies used to prevent growth restriction and especially growth restriction associated with preeclampsia, such as bed rest, calcium supplementation, antihypertensive medications, etc, have generally failed as well. Two recent studies suggest that the use of a prostaglandin agent prenatally might reduce preterm birth in women with a history of prior preterm birth (39, 40). However, because only a small fraction of preterm births derive from this population, the overall effect of this intervention is likely to be small. Therefore, because most strategies aimed at preventing preterm birth and preeclampsia have not been shown to be effective when applied to defined populations, it is not surprising that the preterm and low birth weight rates have not declined.

**REGIONALIZATION OF PERINATAL CARE**

Because it is obvious that the programs aimed at reducing preterm birth have not been successful, a question often asked is, “Is anything that we do worthwhile?” Clearly, when equivalent gestational ages are considered, survival among preterm infants in the United States is as good or better than anywhere else in the world. What is being done well in the United States is the provision of medical care for high-risk women and their newborns. The concept of regionalization of perinatal care arose in the 1960s and 1970s with a goal of having the mother and infant delivered to an appropriate institution. Regionalization, together with improvements in technology, especially for high-risk, LBW infants, is responsible for most of the improvements in preterm newborn survival described above. Advances on the maternal side include the use of corticosteroids to mature the fetal lung and other organ systems and fewer traumatic preterm deliveries (41). On the neonatal side, a wide range of improvements in care include the use of surfactant, the use of antibiotics, and a better understanding and use of newborn respirators and oxygen delivery (42).

**SUMMARY**

In summary, the issue of LBW, and especially its preterm birth component, has proven to be one of the most difficult pregnancy-related issues to address. Although survival has improved, the proportion of births born before term continues to increase and the rate of disability among the preterm survivors has not decreased. Continued research aimed at reducing the preterm birth rate and disability among survivors is crucial if we are to achieve substantial improvements in pregnancy outcome in the United States.

RLG performed the literature review, presented the data at the conference, and wrote the first draft of the paper. JFC helped to conceptualize the project, reviewed the data before presentation, and edited both the presentation and the paper. Neither of the authors had any financial interest or conflict of interest with the study.

**REFERENCES**

16. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of growth restriction and especially growth restriction associated with preeclampsia, such as bed rest, calcium supplementation, antihypertensive medications, etc, have generally failed as well.