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Duration of Gestation and Timing of Birth

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Human pregnancy lasts 9 months on average. However, an accurate estimate of gestational age in individual pregnancies is not easy to obtain. Several methods are commonly used, each of which has its advantages and disadvantages. This chapter reviews these methods and discusses the implications of errors derived from these methods.

Despite its deficiencies, gestation dating is clinically critical and usually established as early in pregnancy as possible. Many clinical decisions are gestational age–dependent because fetal maturity is directly related to the duration of gestation. When a fetus is delivered too early (i.e., preterm birth [PTB]) or too late (i.e., post-term birth), perinatal and infant long-term morbidity and mortality increase. Thanks to widespread use of ultrasonography and induction of labor, post-term birth has been mostly eliminated in many countries. However, progress in understanding the etiology of PTB, and in identifying effective prevention and treatment has been frustratingly slow. This chapter provides a comprehensive but succinct review of current knowledge in PTB. Of note, we use the terms "preterm" and "post-term" births to reflect the timing of delivery, rather than "premature" and "postmature" births, which have complex pathological meanings.

DURATION OF GESTATION

Duration of pregnancy is commonly estimated by three dating methods: last menstrual period (LMP), ultrasonography, and neonatal assessment.

Dating based on last menstrual period

Theoretically, duration of gestation should be calculated as the day of conception to the day of delivery. Although methods of ovulation monitoring, such as charting of basal body temperature, monitoring of cervical mucus, and home-based urine test kits to detect luteinizing hormone surge (Eichner 2004), are available tools to detect conception, the majority of women are not aware of the exact timing

of conception. Thus, the first day of the LMP as a landmark for calculating duration of gestation has long been used and is still the most commonly used approach, particularly in regions where an early ultrasound exam is unavailable.

It is customary to estimate the expected date of delivery by adding 1 year and 7 days to the first day of the LMP and then counting back 3 months (Naegele's rule). Gestational age is usually expressed as "completed weeks" rather than "rounded weeks." For example, if gestational age is 37 weeks plus 5 days from the LMP, it is often recorded as 37 instead of 38 weeks. Occasionally, the term *menstrual age* or *menstrual week* is used to distinguish from *embryonic age, ovulatory age*, or *fertilization age*, which are calculated from conception (Cunningham 2001).

Problems with the LMP method are well recognized. A substantial proportion of women do not remember their LMP accurately; this is especially the case among women who do not initiate prenatal care early during pregnancy (Hall 1985; Geirsson 1991). Mid-cycle bleeding and bleeding in early pregnancy may also lead to erroneous recall of LMP. Although physicians often try to confirm the LMP date by a bimanual exam of the uterine size in the first prenatal visit, this method is crude, with variability of 2 weeks or more (Resnik 2004). In addition, using LMP as the starting point of gestation has two assumptions: duration of a menstrual cycle is 28 days, and ovulation occurs on day 14 of the cycle. Such assumptions are often not met due to longer menstrual cycles, irregular menstrual cycles, and delayed ovulation (Lynch 2007). For example, only about half of women have a regular menstrual cycle of 28 ± 2 days (Geirsson 1991). Approximately 30% of women have an average cycle length of 30 days or longer (Berg 1991). Baird et al. (1995) found that only 12% of women ovulated on exactly day 14.

The errors in LMP result in inaccurate estimates of gestational duration. Mid-cycle bleeding and bleeding in early pregnancy, both occurring after the LMP, can make the duration of gestation look shorter than it actually is. On the other hand, long menstrual cycles and delayed ovulation artificially prolong the apparent duration. Erroneous recalls of LMP and irregular cycles can lead to errors in either direction.

Dating based on ultrasound measures

Using ultrasonography, researchers carefully measured fetal biometry among healthy women with regular menses and certain LMP (Hadlock 1982). Mean values of the fetal measurements at given gestational weeks were generated as the standard. Ultrasound estimation of duration of pregnancy is a reserve process. It measures fetal size to estimate gestational age. The earlier an ultrasound measurement is obtained, the more accurate the estimate of gestational age is because of the limited variability in embryonic size in early gestation. Crown–rump length is a widely accepted measure in the first trimester (Filly 2000). It can be reliably obtained from 7 to 13 weeks. Accuracy of this method in predicting gestational age is 3 to 5 days.

If an ultrasound examination is not done in the first trimester, an early second trimester ultrasound measure can still estimate gestational age with reasonable

accuracy. The basic fetal measurements used for dating are biparietal diameter, head circumference, abdominal circumference, and femoral length (Degani 2001). Although any single measure may yield an estimate of gestational age, an estimate derived from multiple measures has been found to be the most accurate (Hadlock 1987). In general, the variability (± 2 standard deviations) of ultrasound estimates between 14 and 20 weeks of gestation is within 1 week. The variability increases to 2 weeks in late second trimester and to 3 weeks in the third trimester.

To test whether the ultrasound method is more accurate than the LMP method, a number of studies compared the ability to predict timing of spontaneous onset of labor by "certain" LMP and by ultrasound estimate of gestational age (Nguyen 1999). The ultrasound dating was consistently superior to the LMP method (Lynch 2007). Thus, some authors have concluded that use of LMP even for "certain" dates offers no advantage over ultrasound estimates if they are available (Mongelli 1996).

However, it is worth noting that the ultrasound method uses size to approximate duration (time). It implicitly assumes that, early in pregnancy, all fetuses have the same size at the same gestational age. Variation in fetal size is interpreted as variation in gestational age. For instance, suppose two pregnancies are conceived on the same day. As the gestations advance, the fetal sizes may diverge. The ultrasound method assigns the larger fetus a higher gestational age and the smaller fetus a lower gestational age, introducing a systematic bias. As fetal growth abnormality can now be demonstrated as early as in the first trimester (Smith 1998; Bukowski 2007; Pedersen 2008), the systematic bias introduced by the ultrasound method can potentially distort the results (Lynch 2007). One example is the association between fetal sex and risk of preterm and post-term births (Henriksen 1995). Using reliable LMP methods, male and female fetuses had similar risks for preterm and post-term births. But using the second-trimester ultrasound method, the female fetus had a 13% higher risk of preterm delivery and a 19% lower risk of post-term delivery than did the male fetus.

The American Congress of Obstetricians and Gynecologists recommends a revision in a woman's LMP-based due date only if the LMP and ultrasound-based estimates differ by more than: ± 7 days up to 20 weeks' gestation, ± 14 days from 20 to 30 weeks' gestation, and ± 21 days at 30 weeks' gestation or beyond (ACOG 2004). By keeping the original LMP when it appears reasonably accurate, this approach may reduce the degree of the systematic bias of the ultrasound method (Lynch 2007). On the other hand, a large study showed that the combination approach still did not predict timing of spontaneous onset of labor as well as the ultrasound dating alone did (Mongelli 1996), thus suggesting that the error in the LMP dating may still be larger than the systematic bias in the ultrasound dating (Savitz 2002).

Dating based on neonatal assessment

When an antenatal estimate of gestational age is not available, physicians sometimes estimate the gestational age based on physical and neuromuscular maturity of the newborn. The Dubowitz (1970) and Ballard (1979, 1991) scoring systems are the most common methods. Studies have shown that postnatal dating is the least

accurate method, since it tends to overestimate gestations for infants born before 40 weeks, while underestimating the gestation of infants born at or after 40 weeks (Alexander 1992). With wide accessibility of ultrasonography, however, postnatal dating is now performed infrequently.

With these dating methods in mind, we may now be able to answer a timeless question: how long does an average human pregnancy last? In the early 19th century, Naegele postulated that a human pregnancy lasted 10 menstrual cycles or 280 days from the first day of the LMP (Naegele 1836). Over the years, studies based on "reliable" LMP data produced a wide range of estimated mean durations from 272 to 283 days (Kieler 1995). Smith (2001) studied 1,514 healthy pregnant women in whom the discrepancy between the LMP-based gestational age and the gestational age based on the first trimester crown–rump length was within –1 to +1 day. To overcome the problem that pregnancy may be shortened (or censored) by clinical intervention, such as induction of labor or cesarean delivery, the median duration of gestation using survival analysis was estimated to be 283 days for both fetal sexes, but varied by parity (i.e., 284 and 282 days for nulliparous and multiparous women, respectively).

PRETERM BIRTH

Descriptive epidemiology of preterm birth

Preterm birth comprises all deliveries of less than 37 weeks completed gestation, regardless of the reason. This is not an uncommon outcome of pregnancy, affecting 11.0% of singleton live births and 12.7% of all births based on vital records in the United States in 2005 (Martin 2007), with markedly lower rates in Canada (6%–7%) and France (5%–6%), for example (Blondel 2002). Using a more stringent criterion of less than 34 weeks' completed gestation, 2.9% of singleton births and 3.6% of all births are classified as preterm. The frequency of PTB depends in part upon the method for defining gestational age, differing for last menstrual period versus ultrasound. Temporal trends show a small but steady increase over time, from 9.7% of singletons in 1990 to 10.1% in 2000, and 11.0% in 2005 (Martin 2007). The increase is driven exclusively by births in the 32- to 36-week range, with no discernible increase in births of less than 32 weeks' gestation (Behrman 2007). The rate of PTB in the United States is believed to be higher than in most other developed countries for reasons that are poorly understood, but probably includes a combination of artifacts (e.g., the method for assessing gestational age in vital records, and who is included in the vital records registration systems) as well as true differences in the presence of risk factors and clinical practice with regard to interventions leading to early delivery.

The most notable, recalcitrant health disparity in the risk of PTB pertains to the marked disadvantage experienced by African-Americans, who have notably higher risk compared to non-Hispanic whites. In 2005, 18.4% of live births to African-Americans were preterm, compared with 11.7% among non-Hispanic white women and 12.2% among Hispanic women (Martin 2007). In the most extreme

low end of the gestational age spectrum, the disadvantage for blacks is even more apparent: 1.9% of black infants versus 0.6% of white non-Hispanic infants were born prior to 28 weeks' completed gestation in 2005. The excess risk among African-Americans is not readily explained by typical indicators of socioeconomic status; nor do the few known risk factors, such as smoking, low prepregnancy weight, or bacterial vaginosis, account for the disparity. The lack of excess risk for many Hispanic groups, particularly Mexican-Americans, who also may be economically deprived, poses somewhat of a paradox, pointing to some distinctive aspect of the African-American population that confers this increased risk. However, there is increasing appreciation of ethnic variation within broad (and heterogeneous) groups of Hispanics (with higher risk among Puerto Ricans) and Asians (with higher risk among Filipinos) (Singh 1996), and recognition that risk status changes with time since immigration (Singh 1996) supporting the need for a more comprehensive consideration of the underlying reasons for such patterns.

Classification of preterm birth

Preterm birth is defined solely by the gestational age at which delivery occurs, reflecting a final common pathway for many different clinical and biological processes, resulting from diverse causal mechanisms and a wide range of candidate risk factors. Furthermore, although defined as a dichotomy divided arbitrarily at 37 weeks completed gestation, the consequences of PTB for infant health and survival vary across the continuum of gestational age within the preterm range. The entity of PTB deserves closer consideration and possible subgrouping to study both etiology and prognosis.

Preterm birth may arise from medical interventions, reflecting the judgment of the medical care provider that inducing a preterm delivery is preferable to continuing the pregnancy at that point in time. The most commonly applied basis for division of PTB has been into "spontaneous," in which preterm labor or membrane rupture begins a process culminating in preterm delivery, versus "medically indicated," in which concerns with the health of the pregnancy lead to a clinical judgment that delivery should be induced prior to term. Recent analyses suggest that the proportion of medically indicated PTBs in the United States is rising markedly over time (MacDorman 2002).

Although it is often assumed that medically indicated PTBs are limited to pregnancies that are nearing term, in fact the proportion of all PTBs due to medical indications is fairly constant across the gestational age spectrum (Savitz 2005). Both indicated and spontaneous PTBs are much rarer earlier as opposed to later in gestation, but severe complications are identified throughout the range of gestational ages of PTB that provide justification for early delivery. These indications, such as preeclampsia, fetal distress, or other serious threats to the mother's or fetus's health, lead the clinician to make the judgment that a preterm delivery is the preferred outcome, intended to reduce the risk of more severe outcomes for the mother or fetus, including stillbirth or neonatal death. In fact, interpretation of the slowly rising rate of preterm delivery must take into account the potential for a reduced rate of other more adverse outcomes, and thus this does not necessarily constitute a negative trend.

Within the category of spontaneous PTB, distinctions are sometimes made between those in which the initiating event is labor onset and those in which the initiating event is rupture of the chorioamnionic membranes (Savitz 1991; Moutquin 2003). Arguing in favor of splitting these categories is the potential for distinctive biologic mechanisms, for example, influences on uterine contractility, as distinct from influences on chorioamnionic membrane integrity. On the other hand, there is often a close relationship in time between membrane rupture and labor onset, and even when it seems that membrane rupture has initiated the process leading to early delivery, subclinical contractions may have begun. Despite efforts to identify distinctive etiologic processes using this axis for division, there are questions about the validity of the distinction (Klebanoff 1995), and the empirical support for distinctive risk factor profiles is limited (Meis 1995, 1998; Berkowitz 1998).

Other approaches to dividing births for assessing etiology have been suggested, building on our concepts of etiologic pathways. Klebanoff (1998) proposed subdividing births into those precipitated by inflammation, vascular compromise, and neuroendocrine processes. Complicating the effort to isolate these subsets based on risk factors or mechanistic pathways is the fact that predisposing attributes tend to increase both spontaneous and medically indicated PTBs. That is, the same processes that lead a clinician to intervene tend to result in spontaneous PTB if no intervention is undertaken. In addition, accurate measurement and assignment of the underlying etiology is problematic based on routinely collected data.

Another important dimension of the heterogeneity of PTB pertains to severity, with marked differences in infant health as a function of gestational age at delivery. The frequency of adverse infant outcomes, both mortality and morbidity, is inversely proportional to gestational age, with 70% of all PTBs occurring in the 34- to 36-week range and a diminishing proportion occurring earlier in gestation (Kramer 2000). On the other hand, the severity of consequences follows the opposite pattern, with profoundly different implications for survival for infants born earlier as compared with later within the period of less than 37 weeks. Compared to term births, the relative risk of infant mortality (death within the first year) is 2.9 for a 34- to 36-week birth, 6.6 for a 32- to 33-week birth, 16.2 for a 28- to 31-week birth, and 127 for a birth of less than 28 weeks. In clinical care, the focus tends to be on very early PTBs, often defined as of less than 32 weeks' completed gestation. However, from a public health perspective, the later PTBs are so much more common that even with their lower absolute risk of death, they make a substantial contribution to infant mortality (Kramer 2000; Petrini 2009).

Biologic mechanisms of preterm birth

Multiple biologic pathways are thought to contribute to the etiology of PTB, and these are considered in detail in the Institute of Medicine's report on PTB (Behrman 2007). Beyond the differing clinical presentations that manifest as preterm labor, membrane rupture, or complications leading to medical interventions, underlying biological processes need to be considered that have varying degrees of experimental and clinical support.

The most extensive support is probably for the role of ascending bacterial infection to produce inflammation that culminates in preterm delivery. This mechanism is thought to contribute to nearly half of PTBs, particularly the earliest deliveries, through infection of the chorioamnionic membranes. The proinflammatory cytokine–prostaglandin pathway is thought to play a critical role in the process culminating in PTB. Empirical evidence strongly links intrauterine infection to early delivery, and substantial evidence implicates bacterial vaginosis with PTB (Leitich 2007). However, randomized trials to screen and treat bacterial vaginosis have yielded only mixed results regarding whether intervention reduces risk of preterm delivery. In addition to the role of reproductive tract infection, there is growing evidence from observational studies that systemic infection and periodontal infection may also contribute to an increased risk of PTB, but the results from randomized trials that treat periodontal disease do not suggest benefit in reducing PTB (Macones 2008; Offenbacher 2008).

Vascular compromise, which affects placental nutrient transfer, maternal blood pressure, and other critical processes in fetal development, is an independent pathway by which risk of preterm delivery may be affected. In a sizable fraction of PTBs, particularly those associated with preterm premature rupture of the membranes, there are indications of vascular lesions in the placenta. The pathway is thought to involve thrombosis leading to ischemia. The elevated risk of PTB associated with preeclampsia (Mouldenhaur 2003) is thought to result in part through this mechanism, increasing both spontaneous and medically indicated preterm delivery.

Stress in its various forms is thought to be a contributor to PTB, mediated through neuroendocrine, immune, and/or inflammatory processes. The neuroendocrine pathway involves an increase in release of corticotrophin-releasing hormone from the placenta, which in turn is a signal to the "placental clock" for delivery (Smith 2007). When this mechanism is stimulated prior to term, preterm delivery may result. Corticotropin-releasing hormone, cortisol, and other biomarkers of stress response have been examined in relation to PTB, with mixed results.

Uterine overdistension is thought to be the mechanism by which multiple gestations result in a markedly elevated risk of PTB. There are a number of candidate mechanistic pathways by which increased volume of uterine contents could stimulate pathways that culminate in PTB.

Each of these mechanistic hypotheses has resulted in important, contributory laboratory and clinical research, identifying candidate modifiable risk factors and suggesting possible interventions, some of which have been rigorously evaluated. For example, the potential role of inflammation has led to the study of infectious processes and genes controlling inflammatory response in relation to PTB (Engel 2005), yet trials of antibiotics have not consistently provided the anticipated benefit of such treatment (Varma 2006). Analogously, the neuroendocrine mechanism has generated abundant research on candidate biomarkers, stress, social support, and other psychological pathways, but with little clarity or consistency in the empirical findings.

One of the important distinctions to be made in relating biological mechanisms to epidemiologic findings is the challenge of distinguishing *markers* of risk from *causal determinants* of risk. In the course of pregnancy that is predisposed

to culminate in early delivery, biologic changes can be reflected in biomarkers that are strong, empirical predictors of early delivery. These include fetal fibronectin (an indicator of placental dysfunction), elevated cortisol, increased uterine activity, and others. Examined in the usual way, these markers appear to be strong risk factors for early delivery, yet the evidence that they are on the causal pathway and thus amenable to intervention is lacking. That is, they reflect an etiologic process that is in progress, which allows for preparation for impending PTB (including administration of antenatal steroids to promote lung maturation) but do not necessarily provide an opportunity to prevent the PTB from occurring.

Risk factors for preterm birth

Epidemiologic research on risk factors for PTB is quite substantial in volume and increasingly of high quality, yet with very limited success in identifying causal influences that are strong and amenable to intervention. The clearest predictors of PTB, not directly modifiable, are multiple gestation, with over half of such infants delivering preterm; prior preterm birth, associated with a two- to threefold increased risk; and African-American ethnicity, associated with around a twofold increased risk. The leading indicators of risk that are well-established and offer more potential for preventive measures are bacterial vaginosis, associated with around a twofold increased risk; cigarette smoking, associated with a 1.3- to 2-fold increased risk; and low prepregnancy body mass index (BMI), associated with around a 1.5-fold increased risk (Behrman 2007).

The extensive research concerning other well-studied candidate risk factors warrants mention, even though the work has not yet culminated in preventive measures or, in most instances, in trials of prevention. In the realm of health behaviors (Savitz and Murnane, 2010), a large body of research has considered the potential adverse effects of alcohol, caffeine, and illicit drugs, with only cocaine showing reasonably consistent evidence of an association with increased risk. Low levels of vitamin C, folate, and lack of multivitamin use have been associated with increased risk, with iron providing mixed results depending on the indicator that is used. Leisure time physical activity has been associated with decreased risk. Sexual activity during pregnancy has been linked to both increased and decreased risks.

Psychosocial factors have generated considerable interest and attention, in large part because of the compelling mechanistic pathways discussed earlier. Various indicators of stress and responses to stress (both psychosocial and biological) have been investigated repeatedly, with at best mixed empirical evidence for an increased risk of PTB with higher stress indicators. Depression has also been evaluated, as well as anxiety, lack of social support, neighborhood crime, racial discrimination, and other related constructs, all with mixed empirical support for an association. These constructs are so challenging to measure accurately that the potential remains for an important effect that has not yet been captured in the level of detail that would be required to generate compelling empirical support.

A potentially important but incompletely understood influence on PTB is the rapidly increasing use of assisted reproductive technologies (ART). Beyond the well-known increased risk of multiple gestation and resulting increase in PTB,

there is growing evidence that singleton births conceived through medical interventions may carry an increased risk of PTB. A meta-analysis published in 2004 (Helmerhorst 2004) reported a pooled relative risk estimate of 2.0 (95% confidence interval [CI] 1.8, 2.3) for PTB among singletons conceived through ART, even more pronounced for very preterm births of less than 32 weeks completed gestation (relative risk = 3.3, 95% CI = 2.0, 5.3). Whether the underlying infertility that resulted in assisted conception or the medical treatment to achieve conception is responsible is not clear.

The limited progress in identifying causes of PTB, despite extensive epidemiologic research, calls for thoughtful examination of the reasons. It is, of course, possible that the important determinants of PTB are not strongly affected by the "usual suspects" in the behavioral, social, and medical arenas, yet the persistent racial disparity for African-Americans and the plausible biological mechanisms for a number of these risk factors (infection and stress, for example) argues otherwise. Heterogeneity in the causes of PTB may be an important limitation in studying etiology, analogous to searching for the causes of adult morbidity or mortality in the aggregate—a multiplicity of pathways and risk factors that need to be subdivided in order to identify strong influences. Combined with the rather crude tools used to assess behavior, psychosocial processes, and diet, the mixed results should not be overinterpreted as demonstrating that these factors are *not* contributors to the etiology of PTB.

Prevention strategies

Multiple preventive strategies have been considered, often with a strong rationale and great optimism, yet with one exception—all have failed. The rationale for prevention strategies has been to focus on early identification of preterm labor or other evolving indications that the biological process that may lead to PTB has begun. These efforts include primary prevention, reducing risk factors such as stress (through social support), bacterial vaginosis (through antibiotic treatment), and nutritional deficiency (through supplementation and counseling). A more medically based model for prevention begins with biologic signs of preterm labor based on monitoring of uterine contractions (with pharmacologic efforts to postpone labor onset), identification of cervical insufficiency (treated with cervical cerclage), or biomarkers of incipient early delivery such as detection of fetal fibronectin or a rise in cortisol levels.

During the 1980s, it was thought that if subclinical premature contractions indicative of impending preterm delivery could be detected early enough, and antitocolytic treatment initiated, PTB could be averted. However, despite some early promise, large randomized trials based on early detection through patient education or electronic monitoring failed to result in a decreased risk of PTB. No matter how effective the ability to identify women at high risk of premature onset of labor, the pharmacologic tools available for postponing delivery for days rather than hours are quite limited at present.

Prenatal care, social support, and reduction of physical activity have been considered as more general approaches to reducing risk of PTB by screening and

treating for medical conditions, providing counseling regarding healthful behaviors such as smoking cessation, and reducing stress. One of the common recommendations for women who are identified as being at elevated risk of PTB is bed rest, which has not been demonstrated to be of clinical benefit in preventing PTB as intended. Although there may very well be multiple medical and psychological benefits to such care and attention, there is no indication that PTB rates are reduced as a result.

Most promising and most extensively investigated is the strategy of screening to identify bacterial vaginosis and treating it with antibiotics to eliminate the condition. In the past, a number of reproductive tract infections, including group B streptococcus, *Chlamydia trachomatis*, and *Trichomonas vaginalis* were suspected of causing PTB, but for some time, the main focus has been on an imbalance in the vaginal microflora, labeled as *bacterial vaginosis*. Whatever the origins may be, identification of the presence of bacterial vaginosis during pregnancy has been shown in an extensive array of observational studies to be empirically predictive of an increased risk of PTB (Leitich 2007). Furthermore, medications are available that alter the vaginal flora to assume a normal profile, even if there is some tendency for bacterial vaginosis to recur once the antibiotics are no longer in use. Given this promising evidence, a series of large, randomized trials to screen asymptomatic women in pregnancy and intervene to eliminate bacterial vaginosis have not demonstrated a consistent reduction in the risk of PTB. It seems that bacterial vaginosis is a marker of increased risk and reflective of contributions of infection and inflammation to the etiology of PTB, but the relation is not so simple as cause and effect.

The one strategy that has been proven effective is weekly progesterone injections for women who have a history of prior PTB. In a large, well-designed, randomized controlled trial, women who received progesterone experienced a 40%–55% reduction in the risk of PTB (Meis 2003). The short-term neonatal sequelae associated with PTB were correspondingly reduced, and there is every reason to believe that the results reflect a real and clinically meaningful benefit. The treatment is only proven effective for women at high risk and involves a rather demanding intervention protocol, but nonetheless offers some of the first concrete evidence that PTB can be prevented.

Limited epidemiologic evidence suggests that vitamin C may help to reduce risk, based on mechanistic support for its potential benefit based on its role in collagen cross-linkages and thus in maintaining the integrity of the chorioamnionic membranes. A recent trial addressed the role of antioxidants in the prevention of preeclampsia, but also examined impact on PTB (Poston 2006). However, once again, a promising intervention strategy failed to show benefit.

Short- and long-term consequences of preterm birth

Preterm birth is closely associated with an increased risk of infant mortality, both neonatal (first 28 days) and postneonatal (28 days to 1 year). Figure 8.1 shows the pattern of neonatal mortality by gestational age for black and white infants in the United States for two time periods, 1989 and 2005, across the PTB range.

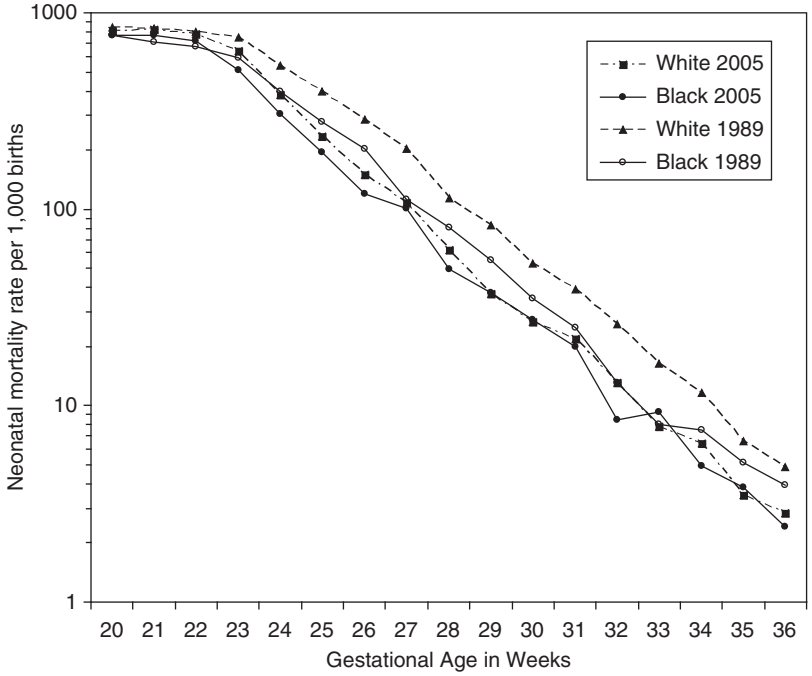

Figure 8.1 Neonatal mortality rates in 1989 and 2005 by gestational age and race.

Noting the log scale, the mortality rate increases exponentially as gestational age at birth declines, lower for the more recent calendar time period.

Beyond the fatal conditions with which PTB is strongly linked, many serious medical conditions are increased among those preterm infants who survive. These include pulmonary complications (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, chronic lung disease), gastrointestinal disease (e.g., necrotizing enterocolitis), immune deficiencies that leave the preterm infant more vulnerable to infection, cardiovascular abnormalities (e.g., patent ductus arteriosis), auditory and visual deficits, and an extensive array of neurodevelopmental abnormalities, many of which are irreversible as more fully described in Chapter 12. Major neurodevelopmental impairments such as cerebral palsy and mental retardation are associated with PTB, as well as more subtle deficits, as reflected in diminished cognitive performance in the form of lower intelligence quotient (IQ) scores throughout life. Aggregate measures of newborn well-being, such as length of hospital stay, are reflective of the increased morbidity of preterm infants as well. As has been found for mortality, the risks of sequelae for the late preterm (born at 34–36 weeks' completed gestation) are elevated relative to term infants, but not as dramatically as for more severely preterm infants. However, the increased frequency of marginally compared to severely PTBs leaves a substantial public health burden in terms of health status, medical services, and/or quality of life.

POST-TERM BIRTH

Prevalence

Post-term gestation is defined as any pregnancy that lasts 294 days (42 completed weeks) or more. The incidence of post-term gestation varies greatly, depending on which dating method is used. Recent studies showed that the incidence of post-term gestation was 10%–12% based on the LMP, but only about 3% based on the ultrasound dating (Taipale 2001; Savitz 2002). The incidence was further reduced from 3.7%, based on the early second-trimester ultrasound dating, to 2.7%, based on the first-trimester ultrasound dating in a recent study (Caughey 2008). It should be noted, however, that the above incidence figures may have been affected by an increasing temporal prevalence for induction of labor in the United States, especially in 41 weeks of gestation.

Etiology and risk factors

The mechanism of onset of parturition in humans has yet to be fully elucidated. However, several risk factors have been identified for post-term gestation. The most important factor "causing" post-term gestation by far is an error in estimating gestational age. Studies show that the mean duration of the follicular phase is 16–18 days, with a standard deviation representing 6–8 days (Lynch 2007). Women are more likely to have delayed ovulation (or later than day 14 of the cycle) than early ovulation in any given cycle (Baird 1995). Thus, even in women who have an accurate LMP, post-term pregnancy may be erroneously diagnosed due to delayed ovulation arising from menstrual cycle lengths greater than the so-called norm of 28 days.

In most cases of true post-term pregnancy, the cause is not known. Nulliparity, maternal overweight and obesity, and history of previous post-term birth are the only established risk factors. Lynch et al. (2007) showed that nulliparous women had a 1.4 to 2.0-fold increased risk to have a post-term birth in comparison to multiparous women. The relative risk for overweight and obese women was 1.3 to 1.4, using normal weight women as the reference group. One population-based study showed that, after one prolonged pregnancy, the risk of a second such pregnancy in the subsequent birth increased from 10% to 27% (Mogren 1999). If there have been two successive prolonged pregnancies, the risk in the subsequent birth rises to 39%.

More recent evidence suggests that genetics also plays a role. For example, if the mother was born after a prolonged pregnancy, her daughter is also at increased risk of a prolonged pregnancy (relative risk [RR] = 1.3, 95% CI 1.0–1.7) (Mogren 1999). A Danish twin study showed that the concordance rate for female twin pairs for a post-term gestation was higher for monozygotic than for dizygotic twin pairs (Laursen 2004). Biometric modeling suggested that genetic factors account for 23%–30% of prolonged gestations. On the other hand, paternal genes had no obvious effect. Some rare conditions also predispose women to post-term pregnancy, such as placental sulfatase deficiency (an X-linked recessive disorder characterized

by a low level of estriol), fetal adrenal insufficiency or hypoplasia, and fetal anencephaly (Norwitz 2007).

Effect on perinatal outcomes

Post-term pregnancy is associated with an increased risk of stillbirth and neonatal and infant mortality (Hilder 1998). As the placenta ages with advancing gestation, placental insufficiency, fetal acidemia, and preeclampsia are more common among post-term births. Approximately 1 in 5 post-term infants has "fetal postmaturity syndrome," characterized by decreased subcutaneous fat, skin desquamation, and long fingernails, often with yellow meconium staining of the nails, skin, and vernix. These pregnancies are more likely to have oligohydramnios, nonreassuring fetal status, intrauterine passage of meconium, and neonatal complications (e.g., hypoglycemia, respiratory insufficiency, and seizures). Meconium aspiration syndrome is mainly a complication in post-term infants. Consequently, the risk of perinatal mortality in ongoing pregnancies at 42 weeks of gestation is twice that at 40 weeks and increases fourfold at 43 weeks and five- to sevenfold at 44 weeks (Norwitz 2007).

Post-term fetuses are often larger than term fetuses, which increase the risk of prolonged labor, cephalopelvic disproportion, and shoulder dystocia. These intrapartum complications in turn increase the risks of both neonatal and maternal morbidity. For instance, cesarean delivery rates double for post-term births (Rand 2000). Also raised are the risks of other maternal complications such as perineal laceration, endometritis, hemorrhage, and thromboembolic disease (Norwitz 2007). With the common practice of preventive induction at 41 weeks, perinatal morbidity and mortality related to post-term gestation is decreasing (Yoder 2002).

In summary, ultrasonography has improved the accuracy of gestation dating substantially. Frequent induction of labor, coupled with accurate dating, prevents the majority of post-term births in many regions. However, preterm birth is still a major problem with few effective prevention or treatment strategies. It remains a high priority for perinatal research.

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9

Fetal Growth: Measurement and Evaluation

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Fetal size and growth reflect critical dimensions of fetal health, and abnormal growth is strongly associated with perinatal death and serious neonatal morbidity. However, defining what constitutes appropriate fetal growth presents a challenge for several reasons: the normal variations in fetal size, proportions, and growth associated with parental and environmental factors; a limited ability to obtain accurate measurements of the fetus in utero; and the choice of reference for defining abnormal size or patterns of growth can influence the interpretation.

Care is needed in addressing distinctions between what is a measure of fetal size or status and what is a measure of growth, as well as among prevailing concepts, such as those embodied in the terms *small-for-gestational age* (SGA), *large-for-gestational age* (LGA), *fetal growth restriction* (FGR), *intrauterine growth restriction* (IUGR), or *macrosomia*. The former two terms refer to the size of the fetus or neonate (at a particular gestational age) in relation to some normative reference and could indicate a constitutional phenomenon or an abnormality of fetal growth. A fetus suffering from growth restriction, on the other hand, does not have to be SGA, since the growth restriction may refer to a pattern of inadequate growth over time, resulting in the fetus not reaching its potential size, while remaining above the cutoff for absolutely small size. Both of the constructs, FGR and IUGR, were formally defined in the literature as "fetal growth retardation" and "intrauterine growth retardation," but over the past several decades, in recognition that a small fetus is actually more likely to be constitutionally small (biologically or physiologically restricted by parental size, for example) than growth retarded—which implies a pathological cause—the more general term "restriction" has gained favor.

At the other end of the fetal growth spectrum, a different but important clinical distinction is made between the LGA fetus and one in whom growth in one or more compartments has been accelerated and is macrosomic (≥4,000 or 4,500 g). Macrosomic growth is of relevance to obstetrics, given the association of macrosomia with gestational diabetes mellitus (GDM) and a higher propensity for birth trauma. For these and related reasons, measurement and evaluation of fetal size and growth represent a complex and evolving area of research that has an important bearing on obstetric practice and population health.

ROLE OF THE PLACENTA

Fetal blood circulation occurs within a closed system that exchanges oxygen, nutrients, and waste products with the maternal circulation through a placental interface. The role of the placenta extends far beyond that of a physical structure for this exchange, however, and includes the production of steroid and protein hormones in a greater amount and diversity than any other endocrine tissue (Cunningham et al. 2005; Murphy et al. 2006; Salafia et al. 2006). The placental hormones that play an important role in fetal growth include human placental lactogen, growth hormone variant, growth hormone-releasing hormone, and leptin. Human placental lactogen is a major hormone of pregnancy and is responsible for mobilizing maternal nutrient stores through maternal lipolysis and an anti-insulin–like action, which facilitates transport of amino acids to the fetus. It also functions to secrete angiogenic hormones and plays a role in the formation of the fetal vasculature (Cunningham et al. 2005).

Fetal size and growth are associated with several gross aspects of placental structure, including its shape, morphology, and size. Placental size is generally correlated positively with fetal size, although notable exceptions occur that may seem counterintuitive. For example, with maternal anemia, the placenta may be enlarged in relation to the size of the fetus, as the placenta hypertrophies in response to a relatively anoxic environment. The normal placenta is disc shaped, and abnormal lobulation is seen with maternal smoking and other conditions typically associated with poor fetal growth. The location of umbilical cord insertion into the placenta (central vs. peripheral); placental diameter, thickness, and weight; gross placental infarcts; and microscopic lesions in the placental villi (which can lead to restricted umbilical arterial blood flow) also correlate closely with fetal growth (Murphy et al. 2006). Abnormal placentation is more commonly seen in the placentas of twins, and vascular connections within the placenta of monochorionic twins that cause abnormal shunting of blood can lead to one fetus becoming growth restricted and anemic, while the other becomes polycythemic and hydropic (twin-to-twin transfusion syndrome) (El Kateb and Ville 2008).

SOURCES OF INFORMATION ABOUT FETAL GROWTH

Two complementary sources of information are available about fetal size and growth. The first is indirect (no measurement of the fetus in utero) and based on the anthropometric measurement of the abortus (Birkbeck et al. 1975; Kaul et al. 1986), stillbirth (nonmacerated), or live-born neonate, with a weight immediately at delivery (i.e., birth weight) being the most common and reliable measurement and the one most commonly reported to vital registries. Although birth weight is the most reliable measurement, it is not measured totally without error or variation, depending upon the timing of the measurement. For example, weight at birth can be affected by meconium or urine passage or the timing of any feeding relative to weighing.

Birth length, head circumference, and chest circumference are also usually measured in the neonatal nursery and recorded as part of the medical record, but are

rarely included in vital registries. The measurement of birth length can be biased by the fact that, at delivery, the neonate is in a flexed state that only relaxes after several days. As the degree of flexion decreases over the first few days after birth, measured length increases (Shinwell and Shlomo 2003), such that mean measured length increases significantly by approximately 0.2 cm between admission and age 1 day and by a further 0.2 cm by age 2 days. Head molding at delivery can bias measurements of head circumference and may not resolve for several days. In addition to weight, length, and head circumference, the same anthropometric techniques and measurements that are used for children and adults (e.g., trunk and limb circumferences, skinfold thicknesses, and the calculation of limb fat and muscle areas) have been used in neonates to determine if pregnancy complications have affected fetal growth in proportions or compartments (Catalano et al. 1995; Stetzer et al. 2002). There are also a score of other specialized cranial and somatic measurements for which normative references exist (Meany and Farrer 1996), but these are primarily of interest to dysmorphologists and geneticists who use them to diagnose birth defects or confirm the presence of genetic syndromes.

Anthropometry at birth can be augmented by various methods that more directly measure body composition or compartments (e.g., lean body mass, fat, water, bone mineral density), such as bioelectric impedance analysis (BIA), dual energy x-ray absorptiometry (DXA) (Beltrand et al. 2008), and air displacement plethysmography (Ma et al. 2004; Ellis et al. 2007; Ellis 2007), although these latter two especially are rarely used outside of research studies because they require specialized laboratory conditions and equipment. Bioelectric impedance analysis is the only one of the methods that might be useful in clinical or field situations. Bioelectric impedance analysis is based on the principle that lean tissues that contain water and free electrolytes conduct an applied electrical signal more readily than fat tissue, and BIA has been proposed as a measure to track the efficacy of hydration therapies in growth-restricted neonates (Gartner et al. 1994). Its widespread use in neonates has been hampered, however, by the lack of adequate reference data.

The other source of information is direct and obtained from fetal imaging. Fetal imaging was originally done using radiographs and was complicated by the limitations and static nature of the x-ray filming. Even well-defined fetal parameters, such as head circumference and bone lengths, could be difficult to measure if the fetus was not fortuitously positioned, and the fetus was generally not even seen radiographically until after the first trimester. Imaging is now done primarily by ultrasonography, which is not only safer (Duck 2008), but more sensitive and flexible and allows for visualization in multiple planes. The gestational and yolk sacs can be seen as early as 4 to 6 weeks' gestation, and fetal crown–rump length (CRL) is measured in the first trimester to establish dates. Thereafter, a number of equations employ various combinations of ultrasound-measured fetal head circumference (HC), abdominal circumference (AC), biparietal diameter (BPD), and femur length (FL) to estimate fetal weight in relation to gestational age (Anderson et al. 2007) as an indicator of fetal growth and well-being.

Ultrasound methods have advanced over the past 20 years to become increasingly more sensitive, such that not only are bony dimensions and ossification centers (Gottlieb and Galan 2008) visualized as they once were on x-rays, but also elements

of fetal body composition, such as cross-sectional subcutaneous fat layers and muscle (Larciprete et al. 2003; Parretti et al. 2003), and organ dimensions (e.g., kidney, liver) can be measured using two-dimensional (2D) ultrasonography and have been for research purposes. Volumes can be obtained using three-dimensional (3D) ultrasound and are beginning to be used for fetal body composition studies (Lee et al. 2009) and to study organ development in relation to growth restriction or macrosomia, although there appears to be, to date, limited improvement of 3D approaches over conventional 2D in terms of clinical care and diagnostics.

FETAL GROWTH AS AN OUTCOME

Despite its limitations, weight at birth is still used as the primary indicator of neonatal status and reflects broadly the outcome of fetal growth processes and complications. A number of cutoffs, indices, and ratios have been devised to relate birth weight to risk of mortality and morbidity (Table 9.1). One of these metrics, low birth weight (LBW), an outcome defined as a birth weight below 2,500 g (5 lb, 8 oz), is by far the most common and is used worldwide in surveillance (UNICEF 2007) and in epidemiologic studies. Although given the advances in perinatal care, the 2,500 g cutoff now seems arbitrary, historically it was the level below which neonatal mortality was seen to be significantly increased. About two-thirds of LBW infants are preterm by dates, and all term LBW infants are considered to be growth restricted. Low-birth-weight infants are at increased risk for complications at birth, including a number of severe conditions, such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), especially if they are also preterm. Very-low-birth-weight (VLBW) infants, born below 1,500 g are almost exclusively preterm, and their risks for severe conditions are proportionately higher.

The problem with the LBW construct is that it represents a mixture of both preterm deliveries and growth-restricted infants and is not very useful when the outcome or disease of interest may be differentially related to prematurity or abnormal growth. It also conveys no information about patterns, growth velocity, or the timing of growth-restricting complications. Similarly, using an absolute cutoff for a high birth weight alone (e.g., ≥4,500 g) might underestimate the proportion of neonates whose mothers had gestational diabetes and who were delivered at a late preterm (35–36 weeks) or early-term gestation to avoid delivery complications.

From neonatal measurements, a number of other indices and ratios have been promoted as being more useful in evaluating fetal growth outcomes and more sensitive in indicating growth retardation or excessive growth than birth weight alone (Table 9.1). A fetal growth ratio, which assesses birth weight in proportion to the mean or median (50th percentile) for gestational age, can be constructed from any birth-weight-for-gestational age reference. Where means and standard deviations (SD) of birth weight are available by gestational age, a relative birth weight (*z*-score or standard deviation unit, SDU) can be calculated. Because these indices and ratios are based on a measure of gestational age, in developing countries where

Table 9.1 Measures and Common Indices of Birth Size Based on Neonatal Anthropometry

Measure	*Definition and comments*
Neonatal Anthropometry	
Birth weight	Weight in pounds or grams at delivery
Birth length	Recumbent length in inches or centimeters measured at or shortly after delivery; normal neonatal flexed condition may bias the measurement shorter in the first 2 days of life
Head circumference	Head circumference in inches or centimeters measured at or shortly after delivery; head molding at delivery may bias measurement
Chest circumference	Chest circumference in inches or centimeters measured at or shortly after delivery, measured at the level of the nipples
Neonatal Indices-Continuous	
Fetal growth ratio	Percent of mean or median (100%) birth weight for gestational age calculated using means or medians by gestational age (and usually by gender)
Relative birth weight	*Z*-score (SDU) birth weight for gestational age calculated using means and standard deviations by gestational age (and usually by gender)
Weight-for-length	2000 CDC reference percentiles, cutoffs usually at <10th percentile (low weight-for-length) and ≥90th percentile (high weight-for-length); weight-for-length at birth by gender determined for infants <1,500 g
Ponderal index	Calculated as (weight (g)/length^3 (cm)) × 100 or (weight (kg)/length^3 (m)), cutoffs at <10th percentile (low ponderosity-for-length) and ≥90th percentile (high ponderosity-for-length)
Neonatal Indices–Categorical	
Birth weight categories	Low birth weight (LBW) <2,500 g (5 lb, 8 oz) Very low birth weight (VLBW) <1,500 g (3 pounds, 5 ounces) Extremely low birth weight (ELBW) <1,000 g (2 lb, 3 oz) or <500 g (1 lb, 2 oz) High birth weight or macrosomia ≥4,000 (8 lb, 13 oz) or 4,500 g (9 lb, 14 oz)
Birth-weight-for-gestational age	Small-for-gestational age (SGA) <10th, 5th, 3rd, or 2nd percentile [same as small-for-dates (SFD)] Large-for-gestational age (LGA) ≥90th, 95th, 97th, or 98th percentile [same as large-for-dates (LFD)] Appropriate-for-gestational age (AGA) as reference
Growth restriction proportionality	Asymmetric = wasted, –2 SD weight-for-length (or ponderal index) Symmetric = stunted, –2 SD length-for-age, normal ponderal index

there is limited access to prenatal care and determination of gestation, categories based on birth weight alone are still used predominantly for surveillance of birth outcome and determination of historical trends. Other indices, such as the ponderal index (PI), rely on neonatal measures of length, and birth length is only sporadically available in birth registries or from vital statistics. Reference percentiles for PI at birth by gestational age have been constructed for local populations (e.g., Landmann et al. 2006), but have not been widely used.

The Centers for Disease Control and Prevention (CDC) growth charts for the United States (Kuczmarski et al. 2000) include percentile and *z*-scores for birth weights, birth lengths, and weight-for-length at birth on the charts specific to birth

to 36 months of age. These percentiles are applicable for birth weights of greater than or equal to 1,500 g. The World Health Organization (WHO) standards have available both percentiles and *z*-scores for weight and length for well-grown term neonates at birth (WHO 2006).

MEASURING AND DATING ISSUES

Ultrasound measurement of fetal size has become a reliable tool not only for evaluation of fetal well-being and pregnancy prognosis, but also for confirming menstrual dates or dating pregnancies when menstrual dates may be unknown or in error (Table 9.2). In the first trimester, fetal CRL correlates closely with gestational age and is often used as the gold standard for dates (Hadlock et al. 1992; Daya 1993). The CRL has the added advantage of not being biased by gender differences or ethnic differences at these early gestational ages (Sahota et al. 2009), and the variation is small. However, CRL measurements are not in perfect agreement with dates. The discrepancy between known menstrual dates (expected size) and CRL (observed size) has been shown to be predictive of later growth, such that a greater observed size than expected for dates is associated with a larger birth weight at term and a smaller observed size for dates with a lower birth weight and preterm delivery (Smith et al. 1998, 2004; Bukowski et al. 2007).

After the first trimester and up to about 24–26 weeks' gestation, fetal size (weight) as estimated using a variety of biometric parameters, singly or in combination

Table 9.2 Ultrasound Biometric Parameters for Determination of Fetal Growth and Size, and to Establish dates

Parameter	*Applicable Weeks*		*Reference*
	Used to Date	Used for Fetal Growth	
Crown-rump length (CRL)	7–13	7–13	Hadlock et al. 1992; Daya 1993
Biparietal diameter (BPD)	13–24	13–40	
Head circumference (HC)	13–24	13–40	Hadlock et al. 1991;
Femur length (FL)	13–24	13–40	Anderson et al. 2007
Abdominal circumference (AC)	13–24	13–40	
Transcerebellar diameter (TCD)*	15–24	15–40	Goldstein et al. 1987
Fetal foot length	10–24	24–40**	Drey et al. 2005
Other nomograms			
Orbital diameters	14–36	14–36	Goldstein et al. 1998
Clavicle	14–41	14–41	Sherer et al. 2006
Scapula	16–41	16–41	Dilmen et al. 1995
Radius, ulna, tibia	13–24	13–40	Chitty & Altman 2002
Kidneys	24–38	24–38	Konje et al. 2002
Thymus		19–38	Cho et al. 2007

*May be best for dates because of brain-sparing and the preferential shunting (blood flow) to cerebellum

**Of value later in gestation to predict nasotracheal tube length in neonates (Embleton et al. 2001)

(Table 9.2), is still closely associated with dates and can be used to confirm or modify estimated gestational age. After that point in gestation, the differences in fetal size associated with gender, ethnicity, and a number of other maternal factors, such as cigarette smoking, so affect fetal growth rates as to increase the variance and significantly bias estimates of gestational age based on size (Henriksen et al. 1995; Dietz et al. 2007). Gender differences in fetal size, particularly in head dimensions (BPD, HC), with male fetuses having larger dimensions than female fetuses, are measurable on the average by 12–14 weeks' gestation and significant by 24 weeks (Parker et al. 1984; Davis et al. 1993). Based on head size alone, then, in the third trimester, female fetuses would tend to be dated as younger than males (Henriksen et al. 1995).

Also as early as the second trimester, the ethnic differences in body proportions that are evident in children and adults are already seen in the fetus, which can further bias estimates of gestational age or complicate evaluation of fetal proportions for birth defects screening, depending on the reference used. Beginning in the second trimester (15–20 weeks), the FL of non-Hispanic black fetuses are already longer than those of non-Hispanic white fetuses of the same gestational age (Davis et al. 1993; Shipp et al. 2001), whereas the FL of Asian fetuses are shorter than those of non-Hispanic whites (Shipp et al. 2001), and these differences are magnified in the third trimester. Likewise for the arm, the humerus lengths (HL) of non-Hispanic black fetuses tend to be longer than those of non-Hispanic whites, which are longer than those of Asians (Mastrobattista et al. 2004). Because a short HL is used as a marker, along with other sonographic findings, for the prediction of Down syndrome (Schluter and Pritchard 2005) care should be taken in the second and third trimester that suitable ethnic-specific references are used for dimensions or proportions that are considered indicators of birth defects (Meany and Farrer 1986).

MEASUREMENT APPROACHES FOR DETERMINING ABNORMAL FETAL GROWTH

Two different approaches are used to create charts or nomograms to evaluate fetal, infant, or child size and growth velocity. The first is construction of a *reference*. Growth references are considered to be descriptive (how a fetus or child *is* growing) and population-specific. They can be based on a representative sample, but still include abnormal cases or those who have exposures or conditions that may affect growth. The second approach is to create a *standard* of growth. In contrast to a reference, a standard is proscriptive (how a fetus or child *should* be growing) and is generally not population-specific. Samples for a standard are chosen because they are growing under optimal conditions, and cases that have exposures or conditions that may affect growth are excluded. Unlike in a reference, the variance in a standard is restricted, and the cutoffs or other distributional parameters may be very different. Care should be taken then, before using either a reference or a standard to evaluate fetal growth, to understand the selection of the source sample or population and the assumptions of construction.

General approach for creating fetal growth references and standards

Clinical growth charts for infants and children, whether references (Kuczmarski et al. 2000) or standards (WHO 2006), are based on measured values, with the 3rd percentile (or the approximately equivalent mean minus 2 standard deviations) and the 97th percentile (or the approximately equivalent mean plus 2 standard deviations) used clinically as cutoffs for growth faltering or excessive growth. Birth-weight-for-gestational age references, on the other hand, have tended to use the 10th percentile and the 90th percentile of birth-weight-for-gestational age as the cutoffs for the identification of SGA and LGA infants, respectively. The higher-percentile cutoff for fetal growth references (typically created using vital statistics data) accounts for the mixed normal and abnormal population (i.e., infants from complicated and uncomplicated pregnancies) used in creating the reference.

Traditional birth weight-for-gestational age versus ultrasound-based references

Traditionally, fetal growth references have been created by measuring the birth weights of a relatively large numbers of live-born babies at each gestational week and identifying a cutoff that signifies poor or excessive growth using distributional assumptions. With the 10th, 50th, and 90th percentile thereby determined for each gestational week, fetal growth "curves" have been developed that chart the expected fetal weight through pregnancy. The drawback with this methodology is the extrapolation implicit in using cross-sectional information (weight at birth) for modelling a longitudinal experience. If preterm delivery is more likely to occur among a subset of fetuses whose growth patterns or velocities are different from the subset that continues in utero, this would bias the information in the fetal growth curve derived from birth weights (Hediger et al. 1995; Bukowski et al. 2001; Hutcheon and Platt 2008).

As mentioned, ultrasonographic techniques have been increasingly used to measure fetal size in recent decades. Estimation of fetal weight requires biometric measurements of the fetus including measurements of head size (head circumference, biparietal diameter), abdominal circumference, and FL (Platz and Newman 2008). These measures are combined using one of any number of available formulae (Anderson et al. 2007), the most commonly used being the one proposed by Hadlock and colleagues (1991). The addition of other biometric measurements does not appear to improve the accuracy of fetal weight estimation. Validation studies show that fetal weight estimated by these techniques yields reasonable results for fetuses weighing between 1,500 and 3,999 g. Outside these bounds, however, there is tendency to overestimate or underestimate fetal weight, with errors as high as 25% between the actual and predicted weights (Platz and Newman 2008).

Both birth-weight-for-gestational age and ultrasound-based references, and particularly the trajectories of the percentile curves of interest (e.g., 10th or 90th percentile), have been used to derive *rates* of growth and make inferences about fetal growth in relation to complications. However, because of substantial interindividual variation in the timing and tempo of growth and measurement error, increments

or interval growth inferred from cross-sectional estimated fetal weights sampled at different gestational ages and smoothed percentiles will underestimate variation and inflate the proportion growing abnormally. Assessment of rates of growth should ideally be made against an actual velocity reference, but only a couple of small series of fetuses have been evaluated by ultrasound longitudinally to estimate growth velocity (Owen et al. 1996; Milani et al. 2005). A current need still exists for a properly constructed longitudinal ultrasound reference or standard for interval growth.

Customized and individualized fetal growth standards

It is generally acknowledged that male fetuses have patterns of growth that are distinct from those of female fetuses; females infants have lower birth weight for gestational age and also lower perinatal mortality rates than do male infants. For this reason, most traditional fetal growth references are customized by sex; that is, they provide different SGA and LGA cutoffs for male and female fetuses (Zhang and Bowes 1995; Kramer et al. 2001), although references are available for the sexes combined (Alexander et al. 1996) as well. Gardosi and coworkers (1992, 1995) extended this concept and proposed fetal growth standards that predict optimal growth and are simultaneously customized not only for fetal sex but also for maternal height, weight, parity, and ethnicity. A previous variation of this theme involved the individualization of the fetal growth curve based on two ultrasound measurements in early gestation (Deter and Rossavik 1987). This latter proposition assumed that fetal growth patterns deviate from the norm only in late gestation.

Other ultrasound-based approaches for assessing fetal growth problems

Numerous other approaches have been proposed to identify growth restriction including combinations of biometric measures, such as an elevated FL-to-AC ratio (FL/AC), an elevated head-to-AC ratio (HC/AC), or elevated transverse cerebellar diameter-to-AC ratio (TCD/AC) (Gottlieb and Galan 2008; Platz and Newman 2008). The HC/AC is particularly useful for detecting asymmetric growth. Another approach for diagnosing fetal growth restriction is based on the amount of amniotic fluid measurable, with decreased amniotic fluid indicative of poor perfusion of the fetal kidneys and associated growth restriction. Currently, the most useful clinical approach for the diagnosis of compromised fetal growth involves umbilical artery Doppler velocimetry among fetuses found to be growth restricted by biometric methods (Cunningham et al. 2005; Zhang, J. et al. 2010).

Controversies and alternative approaches for assessing growth patterns

One intriguing feature of traditional fetal growth standards is the decline in fetal weight that is observed at late gestation. Do fetuses at post-term gestation lose weight, or is this phenomenon a consequence of cross-sectional information being

used to model longitudinal fetal growth? Some fetal growth references have deployed methods that have eliminated this decline in fetal weight at late gestation (Kramer et al. 2001).

Customized fetal growth standards (Gardosi et al. 1992, 1995), although popular, have also elicited some controversy. Proponents claim that such standards perform better than other references in terms of predicting perinatal mortality (Clausson et al. 2001; McCowan et al. 2005; Ego et al. 2006), but others have argued that this is merely an artifact of the method used, which leads to a higher proportions of preterm births within the customized SGA subset (Zhang et al. 2007; Hutcheon et al. 2008).

The relatively simple methodology required for the creation of fetal growth references (determining percentiles using data from a vital registry, or perinatal or ultrasound database) has led to a plethora of fetal growth references in the literature. Should each county have its own reference or standard of fetal growth? This question is controversial, given the recent creation of a standard for infant and child growth (WHO 2006) that was designed for universal application. The more general question regarding the selection of factors that require customization is also thought-provoking because percentile-based methods could be used to produce separate references for infants of mothers who smoke, for singletons and twins, and for a host of other factors that affect birth weight. This issue reiterates the profound difference between a descriptive reference and a normative standard.

Alternative approaches to fetal growth reference creation have been proposed recently and include one advocating epidemiologic modeling for addressing the missing data problem in traditional fetal growth references (Hutcheon and Platt 2008). Since traditional birth-weight-for-gestational age charts are created based on live births at each gestation, they do not reflect the weights of the large proportion of undelivered fetuses. The weight of these "missing" fetuses needs to be incorporated into the fetal growth chart if the reference is to reflect the growth patterns that prevail in utero.

Another proposed approach to the creation of standards attempts to determine the optimal birth weights at each gestational age over which serious neonatal morbidity and mortality rates are lowest and then determine relevant cutoffs (Joseph et al. 2009). Among singleton males at 40 weeks, serious neonatal morbidity/mortality rates were lowest between 3,012 and 3,978 g. The low end of this optimal birth weight range for females was 37 g less (consistent with a priori expectations). The low end of the optimal birth weight range was 152 g less for twins compared with singletons, suggesting that there might be plurality-specific thresholds for obstetric intervention and for neonatal growth monitoring and nutritional supplementation (Joseph et al. 2009).

FETAL GROWTH AND PRETERM DELIVERY

It has long been recognized that poor fetal growth increases the risk of preterm delivery and that the proportion of growth-restricted infants is likely to be substantially higher among preterm live births than that defined by a birth-weight-for-gestational

age reference and SGA categorization (Goldenberg et al. 1985; Ott 1993; Hediger et al. 1995; Smith-Bindman et al. 2002). This is not surprising, given that fetal compromise and fetal growth restriction are indications for iatrogenic preterm delivery. However, studies have shown that, even within spontaneous preterm live births, there is a relative preponderance of infants with a birth-weight-for-gestational age that is substantially different from the mean weight as defined using an ultrasound-based reference (Morken et al. 2006). Interestingly, in preterm gestational age categories of less than 34 weeks, this preponderance is restricted to infants with birth weights that are much lower than the mean birth weight for gestational age, whereas at 34–36 weeks' gestation, there is an excess of infants with birth weights that are significantly smaller and significantly larger than the mean (Morken et al. 2006).

Ultrasonographic studies that have followed the growth patterns of twins have shown that slow growth for one or both twins was associated with higher rates of preterm delivery (Hediger et al. 2005). Another large study of South American singletons showed a more complex relation between growth patterns and preterm delivery. Larger estimated fetal weight prior to 23 weeks and larger estimated fetal weight between 23 and 28 were both associated with significantly higher rates of preterm birth. This pattern was reversed between 28 and 33 weeks, and fetuses with a higher estimated fetal weight at this gestation had significantly lower rates of preterm delivery (Lampl et al. 2009).

FETAL GROWTH IN MULTIFETAL PREGNANCIES

The trajectory of fetal growth in twins throughout gestation has been observed and described, both using ultrasonography and ultrasonography combined with birth weight, with the finding that the trajectory indicates a slowing of growth relative to singletons for almost all twins after 28 weeks' gestation (Min et al. 2000; Smith et al. 2001). Before 28 weeks' gestation, however, all twins should be expected to grow at rates comparable with singletons. Even twins who had been growing at rates similar to singletons before 28 weeks may show slowed rates of growth in the third trimester (Buckler and Green 1994; Ananth et al. 1998; Glinianaia et al. 2000; Gielen et al. 2008; Joseph et al. 2009).

The major determinant of variation in twin fetal growth is not zygosity, but instead chorionicity. The approximate 65% of monozygotic twin pairs that are dichorionic show patterns of fetal growth similar to dizygotic twins. On the other hand, monozygotic, monochorionic twin pairs tend have a growth trajectory that falls below even that of dichorionic twins, not to mention singletons. A couple of birth-weight-for-gestational age references (Naeye et al. 1966; Ananth et al. 1998) have stratified by chorionicity, but this factor is usually not considered in references for twin fetal growth because chorionicity is generally not included in vital statistics and obstetric databases, and because monochorionicity is considered a risk factor for poor fetal growth that should be evaluated by comparison with normal references, either twin or singleton.

It has been hypothesized that the pattern of growth for even well-growing twins in the third trimester is a normal down-regulation in response to a constricted

uterine environment or limited nutrition and may underscore the need for an ultrasound or birth-weight-for-gestational age reference that is specific for twins. The primary rationale for a separate reference is that optimal intrauterine growth and development is achieved earlier in gestation for twins than for singletons and at a lower birth weight (Luke et al. 1993; Dodd et al. 2003; Joseph et al. 2009), but as for singleton births, it appears that such slow-downs may be associated with earlier delivery and a greater risk for morbidity associated with premature birth (Hediger et al. 2005). This would argue against a separate reference for twins, or, at least, for the development of a growth velocity reference for singletons and twins to allow for the accurate assessment of interval growth.

RISK FACTORS FOR ABNORMAL FETAL GROWTH

Recognizing risk factors for abnormal fetal growth allows clinicians to anticipate potential problems and institute more careful screening regimens. From the community medicine standpoint, knowledge of risk factors helps to explain temporal trends in fetal growth, and to develop policy initiatives to optimize health and to anticipate future trends.

Causes of poor fetal growth

The causes of poor fetal growth may be categorized into maternal, fetal, and placental factors (Das and Sysyn 2004; Maulik 2006). Maternal factors include maternal diseases and pregnancy complications, the most common of which are hypertensive disorders in pregnancy. These include chronic hypertension, preeclampsia, and the other hypertensive variants that lead to a decrease in uteroplacental perfusion. Other maternal diseases that can lead to growth restriction include autoimmune disease (such as antiphospholipid syndrome and systemic lupus erythematosus), diabetes, and renal and cardiac diseases, among others.

One important maternal risk factor for poor fetal growth in industrialized countries is cigarette smoking. It is estimated that the average birth weight among infants of women who smoke is 150 g less than the average birth weight of infants born to nonsmoking women (Kramer 1987). In some South Asian and other less industrialized countries, where some rates of LBW are 29% (UNICEF 2007), maternal prepregnancy size and related factors are responsible for high levels of poor fetal growth. Another factor associated with SGA live births is low socioeconomic status (Joseph et al. 2007). Poverty represents a collection of behavioral and other factors (in addition to maternal smoking) that contributes to poor fetal growth, including higher rates of substance abuse, hard physical work, short interpregnancy interval, and poor maternal health. Various medications, including antiepileptic agents and multiple courses of antenatal steroids (Murphy et al. 2009), are also associated with higher rates of poor fetal growth.

Chromosomal anomalies (such as Down syndrome and trisomy 18) and other congenital malformations of the fetus are strongly associated with poor fetal growth. Chromosomal anomalies in particular are associated with symmetrical

growth restriction (unlike other causes in which the head is spared). Multiple malformations, anencephaly, microcephaly, cardiac defects (such as tetralogy of Fallot), and abdominal wall defects are also associated with high rates of poor growth. Perinatal infections due to protozoan parasites (such as malaria) and viruses (such as rubella, cytomegalovirus, and human immunodeficiency virus [HIV]) are important causes of fetal growth restriction worldwide. The many maternal and fetal factors listed here often exert their adverse effects on fetal growth by affecting the placenta and reducing uteroplacental circulation. Other abnormalities of the placenta, such as placenta previa and placental abruption, are also associated with growth restriction (as causes or as consequences). Placental factors also play an important role in the poor fetal growth seen in multifetal pregnancy.

Causes of excessive fetal growth

The main maternal causes of excessive fetal growth are diabetes mellitus and maternal obesity (Das and Sysyn 2004; Maulik 2006). Uncontrolled maternal diabetes mellitus, which can be preexisting type 1 or type 2, or gestational, leads to maternal hyperglycemia and consequently fetal hyperglycemia. The higher output of fetal insulin produced as a response leads to excessive uptake of glucose by fetal tissues and an increase in fetal growth. Maternal obesity is also associated with excessive fetal growth, although the macrosomic infants of diabetic mothers have a different morphology compared with macrosomic infants of mothers who do not have diabetes mellitus. Some genetic and chromosomal disorders, such as Beckwith-Wiedemann syndrome, are also associated with LGA infants (Taeusch et al. 2004).

Temporal trends in fetal growth

Fetal size has increased in industrialized countries in recent years. Much of this change has occurred due to reductions in SGA live births and increases in LGA live births among term births (Kramer et al. 2002). The factors that have acted to increase fetal growth at the population level include increases in maternal weight, body mass index (BMI, weight-for-height^2), increases in gestational weight gain, and reductions in maternal smoking. Factors that have adversely affected fetal growth trends include increases in maternal age, hypertension, and diabetes. However, some of the documented changes could be a consequence of improvements in the accuracy of gestational age ascertainment due to the increasing use of ultrasonography (Kramer et al. 2002). In recent years, rates of macrosomia have decreased because of increases in early delivery (i.e., by labor induction and/or cesarean delivery), which have reduced post-term birth rates and pregnancy duration even among term pregnancies. Mean birth weight among term births has also begun to decline after increasing steadily for decades (Zhang X. et al. 2010). Figure 9.1 shows temporal trends in singleton SGA and LGA live births in Canada, from 1995 to 2004 (Public Health Agency of Canada 2008).

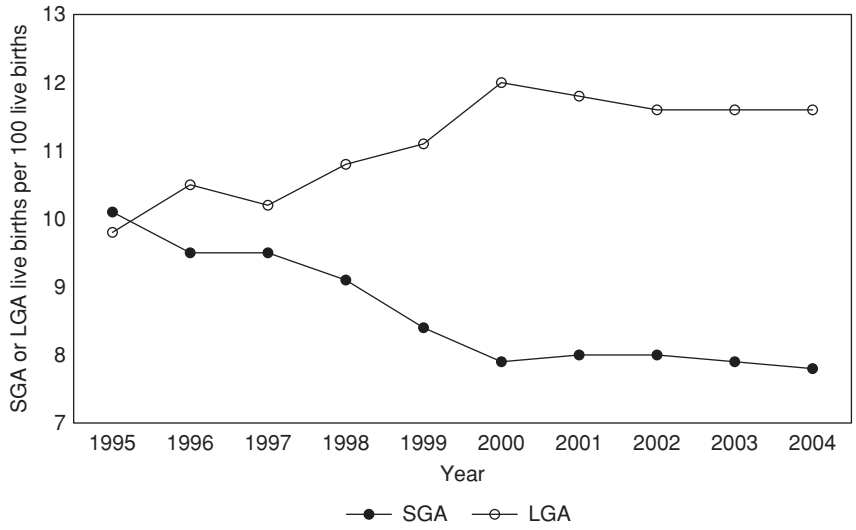

Figure 9.1 Temporal trends in rates of small-for-gestational age (SGA) and large-for-gestational age (LGA) live births in Canada (excluding Ontario), 1995 to 2004 (Public Health Agency of Canada, 2008).

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