Evidence Report

Chapter 1. Introduction

This report presents the results of a systematic review of the available evidence on the benefits, risks, and costs of different strategies for managing prolonged pregnancy to avoid adverse perinatal and maternal outcomes. It was prepared for the Agency for Healthcare Research and Quality by investigators at the Duke Evidence-based Practice Center, Durham, NC.

Background

The "normal" length of gestation has traditionally been defined as 40 weeks, or 280 days, after the first day of the last menstrual period. This figure is used to calculate the "estimated date of confinement" or "due date." Postterm pregnancy is defined by the American College of Obstetricians and Gynecologists (ACOG) as a gestation longer than 42 weeks, or 294 days, from the onset of the last menstrual period (Anonymous, 1997). It has long been recognized that the risk of adverse fetal outcomes, such as stillbirth, meconium aspiration, asphyxia, and the dysmaturity syndrome, is increased as gestational age progresses beyond 42 to 43 weeks (Mannino, 1988). However, the appropriate gestational age at which a pregnancy should be considered "high risk" for reasons of advancing gestation alone is unclear for several reasons. We discuss issues surrounding the concept of "normal" gestational age in this section, then review the data on risks associated with advancing gestational age.

Normal Variation versus Pathology

The mechanisms involved in the onset of normal labor in humans are a complex interaction between the fetus, placenta, uterus, and cervix. The fetal central nervous system may play a key role. Changes in circulating hormones produced by the placenta, such as progesterone, and in local production of prostaglandin and other cytokines, intercellular communication between uterine smooth muscle cells, and changes in extracellular matrix in both the uterus and the cervix are all important, but the exact cascade of events involved remains to be elucidated. Given this complexity, normal variability in the length of otherwise uncomplicated pregnancies should be expected. Most women who have prolonged gestation likely represent one extreme of normal variability in gestational age; in other women, or in specific pregnancies in an individual woman, the mechanisms involved in preparing for labor or signaling the onset of labor may differ.

The most recent ACOG review of the subject of "postterm" pregnancy cites estimates of 3-14 percent of all pregnancies (Anonymous, 1997). Estimates of the proportion of pregnancies delivering after 41 or 42 weeks are subject to variability because of variable accuracy in dating. Randomized trials of routine screening with ultrasound in the second trimester have consistently shown that routine screening reduces the proportion of women induced for prolonged pregnancy when compared with selective screening (Crowley, 2000). Since routine ultrasound screening is not the standard of care in the United States, population-based estimates will necessarily be subject to error. The most recent available data from birth certificates (1999) suggest that 39.6 percent of all deliveries in the United States occur at 40 weeks or beyond, 18.7 percent at 41 weeks or beyond, and 7.4 percent at 42 weeks and beyond (Ventura, Martin, Curtin, et al., 2000). Because these data include women who delivered prematurely, either through spontaneous preterm labor or because of other pregnancy complications, and women who were induced for

other reasons, the data cannot be used to estimate mean or median gestational age. Interestingly, the proportion of all births between 40 and 42 weeks is somewhat lower for black women compared with white or Hispanic women, reflecting the higher risk of preterm delivery in black women. However, the proportion of women delivering after 42 weeks is similar among all three ethnic groups. If errors in gestational dating are randomly distributed among the three groups, then this suggests that true "postterm" pregnancies may be due to true differences in the biological process initiating labor in these pregnancies, rather than representing the extremes of the distribution of normal gestational length.

Even the concept of "normal" pregnancy length is more complex than it first appears. One possibility is to define it as the mean, median, or mode for all pregnancies, perhaps stratified by parity and race, with some predefined range that captures the majority of the population. This value would inevitably be skewed by preterm deliveries, both spontaneous and induced for other complications; however, this length would still be "normal" in the sense that it conveys the expected length of the gestation for any woman at the beginning of the pregnancy. Since every woman has some nonzero risk of preterm delivery at the start of the pregnancy, "normal" length defined in this manner has some meaning.

Alternatively, "normal" length can be defined as the length of gestation in women who have uncomplicated pregnancies, labors, deliveries, and perinatal outcomes in the absence of any obstetric intervention. One could then divide pregnant women into three separate populations: (1) those with normal outcomes in the absence of intervention; (2) those requiring intervention and/or experiencing adverse outcomes associated with preterm delivery; and (3) those requiring intervention and/or experiencing adverse outcomes associated with late delivery. We did not identify any reports that characterized gestational length in this manner. Such an exercise might prove useful as an alternative method for discussing risks associated with prolonged gestation. In other words, most of the literature addresses the question: "Given gestational age, what is the likelihood of adverse outcomes?" Clinically, this is very reasonable. An alternative way to think about the problem when defining "normal" length of gestation is to ask the following two questions: "Given a good outcome without any intervention, what is the average gestational age?" And (for the two populations of preterm and term or later pregnancies): "Given an adverse outcome, what is the average gestational age?"

Errors in Dating

Menstrual Dates

Prior to the ready availability of ultrasound in the 1980s, estimation of gestational age based on menstrual dates alone was often inaccurate. For example, women who conceived soon after stopping oral contraceptives were more likely to have prolonged gestations in one series (Keng and Eng, 1982). Even with accurate recall of dates, there will be some variability in gestational age estimation because the 40-week estimate is based on an assumption of an "ideal" 28-day menstrual cycle, with ovulation on day 14. Because the follicular phase is often quite variable (ranging from 7 to 21 days), this assumption (upon which most gestational age calculators are based) will inevitably lead to some over- or underestimation of gestational age and can lead to errors in understanding the relationship between gestational age, birthweight, and pregnancy outcome (Gjessing, Skjaerven, and Wilcox, 1999).

Ultrasound

The availability of ultrasound in most sites in the United States has substantially improved the ability to estimate gestational age more precisely. Randomized trials of routine versus selective screening with ultrasound in the second trimester have consistently found a reduced incidence of induction of labor for prolonged pregnancy in the routine screening groups, presumably because of more accurate dating (Crowley, 2000). However, ultrasound itself has a nonnegligible degree of error. The error is approximately ± 1 week for scans done in the first trimester, ± 2 weeks for scans done in the second trimester, and ± 3 weeks for scans done in the third trimester (ACOG, 1997). Thus, even for women with early ultrasound dating, the "true" gestational age falls within a 14-day window of time; that is, some women with a recorded gestational age of 41 weeks will actually be 42 weeks, and some will actually be 40 weeks. In addition, because ultrasound dating is based on embryonic or fetal size, an association between size at the time of the ultrasound and later outcomes can create systematic bias in assessing gestational age-associated risk (Henriksen, Wilcox, Hedegaard, et al., 1995). For example, ultrasound dating will consistently overestimate the gestational age of larger than average fetuses. This early overestimation of gestational age could create a bias that would lead to an overestimation of the association of advanced gestational age and macrosomia. On the other hand, gestational age will be consistently underestimated for smaller than average fetuses. If some conditions that lead to low birthweight manifest themselves very early in pregnancy, then this will lead to an underestimation of the association of conditions associated with low birthweight and advancing gestational age.

The effects of uncertainty in dating pregnancy are not insignificant. Population-based estimates of the outcomes of pregnancy by gestational age, clinical trial data, and policy and clinical decisions based on these data are all dependent on the accuracy of the determination of gestational age.

The population of pregnant women with "prolonged" pregnancy thus likely represents at least two distinct groups:

1. Women in whom gestational age is overestimated because of the inherent error of all methods of dating.

2. Women whose pregnancies are correctly dated. Some of these women may represent the outer limits of normal variability. Others may have underlying defects in the mechanisms signaling the onset of labor.

It is likely that the risk of adverse outcomes varies among these groups. Many of the monitoring strategies discussed throughout this report are designed to identify fetuses at higher risk of adverse outcomes. The following section discusses the adverse outcomes associated with prolonged gestation, as well as the degree to which the risk of these outcomes is related to gestational age.

Burden of Illness: Risks Associated with Prolonged Pregnancy

Adverse fetal outcomes associated with advancing gestation can be divided into two categories:

1. Those associated with decreased uteroplacental function, resulting in oligohydramnios, reduced fetal growth, passage of meconium, asphyxia, and, potentially, stillbirth.

2. Those associated with continued normal placental function, resulting in continued fetal growth, with a subsequent increased risk of trauma during birth, including shoulder dystocia with possible permanent neurologic injury.

Adverse physical consequences to the mother resulting from prolonged gestation include those associated with increased fetal size, including an increased risk of short-term trauma to the pelvic floor, vagina, and perineum (as well as a possible longer-term risk of pelvic floor dysfunction), and postpartum hemorrhage. Interventions performed to reduce the risk of perinatal morbidity and mortality, such as induction of labor or cesarean section, have iatrogenic risks, such as infection, hemorrhage, and surgical injury. In addition, any adverse outcome for an infant will obviously have significant emotional impact on the mother.

Risk of Perinatal Mortality

The risk of perinatal death decreases with advancing gestational age until some point between 38 and 41 weeks, when it begins to increase again. The gestational age at which the risk begins to increase and the degree of risk involved have been subject to a reconsideration in several recent publications (Table 1). Yudkin, Wood, and Redman (1987) examined data from 40,888 deliveries in the Oxford Health District in England between 1978 and 1985. When unexplained stillbirth rates were calculated using the number of total deliveries within a given gestational age period, the rate per 1,000 births was 2.14 from 37 through 38 weeks, 0.43 from 39 through 40 weeks, and 1.24 from 41 weeks on. When estimated using a different denominator, the number of continuing pregnancies (i.e., the number of pregnancies still at risk of having a stillbirth), rates were different: 0.42/1,000 for 37 and 38 weeks, 0.29/1,000 for 39 and 40 weeks, and 1.24/1,000 for 41 weeks and later.

Hilder, et al., examined data from 171,527 births from the North East Thames Region in London (Hilder, Costeloe, and Thilaganathan, 1998). Stillbirth rates calculated as a percentage of all deliveries declined from 6.2/1,000 at 37 weeks to 1.5/1,000 at 40 weeks, then began to increase again with advancing gestational age (1.7 at 41 weeks, 1.9 at 42 weeks, and 2.1 at 43 weeks or more). The pattern was slightly different when risk was estimated as stillbirths per 1,000 ongoing pregnancies: 0.34 at 37 weeks, 0.70 at 38 weeks, 0.83 at 39 weeks, 1.57 at 40 weeks, 1.48 at 41 weeks, 3.29 at 42 weeks, and 3.71 at 43 weeks and beyond.

Cotzias, Paterson-Brown, and Fisk (1999) performed a reanalysis of the data set used by Hilder's group. In addition to estimating the number of stillbirths in a given gestational age divided by the number of ongoing pregnancies, the authors also estimated the "prospective

stillbirth risk," the total number of stillbirths at or beyond a given gestational age divided by the total number of pregnancies at or beyond that age, multiplied by 1,000. Other data sets were used to estimate the proportion of singleton births and the proportion of stillbirths occurring in singleton pregnancies, as well as the proportion of stillbirths that were unexplained by anomalies or other recognized fetal and maternal complications. Using this methodology, the risk for unexplained stillbirth in singleton pregnancies was highest at 37 weeks (1.55/1,000), declined to a low of 1.08/1,000 at 40 weeks, then increased again to 1.58/1,000 at 43 weeks. The high rates at lower gestational ages may reflect this methodology.

Most recently, Smith (2001) analyzed data from Scotland for the period 1985 through 1996. This analysis has several advantages over the previous ones. First, the number of deliveries is considerably larger, resulting in greater precision of risk estimates. Second, stillbirths are divided into antepartum and intrapartum stillbirths, a distinction that has clinical relevance, since clinical strategies for preventing each of these might be quite different. Third, congenital anomalies were explicitly excluded. Fourth, life table methods were used to account for censoring resulting from deliveries within a given observation period. Fifth, the time period is considerably later, making the results more likely to reflect current clinical management, at least in the United Kingdom. Finally, cumulative probabilities for stillbirth at each gestational age were estimated.

Estimates of antepartum stillbirth in this paper show the conditional probability increasing as gestational age increases (Table 1), while the probability of intrapartum stillbirth does not change significantly with increasing gestational age. Smith (2001) also found that cumulative probability increases, from 0.4/1,000 at 37 weeks to 2.2 /1,000 at 40 weeks to 11.5/1,000 at 43 weeks. The risk of any perinatal death, when calculated as a cumulative probability, begins to increase at 39 weeks; when calculated as a risk per total births in a given week, it does not begin to increase until after 42 weeks. Risks did not appear to differ when deliveries between 1985 and 1990 were compared with those between 1991 and 1996; however, risks for antepartum stillbirth were increased significantly for primigravidas compared with parous women.

The advantage of cumulative probability is that it captures the risk of death in preceding gestational ages. Smith (2001) uses the metaphor of Russian roulette to explain the difference between conditional probability and cumulative probability: the risk with each pull of the trigger is 1 in 6, but the risk of death for someone taking his fifth shot is greater than for someone taking his first shot. For example, Smith estimated the conditional probability of stillbirth at 43 weeks as 6.3/1,000 ongoing pregnancies, while the cumulative probability was 11.5/1,000 ongoing pregnancies. This difference represents the effects of stillbirths occurring before 43 weeks. The potential clinical significance of this is that achieving the absolute minimum cumulative stillbirth probability may require interventions at earlier gestational ages.

Consistently, the risk of stillbirth in the above-described studies rises with advancing gestational age, and this increase appears to begin at 39-40 weeks when estimated using the number of ongoing pregnancies as the denominator. One limitation of these studies is that they were all performed in the United Kingdom, and the degree to which the risks would differ in a different population with different clinical management is unclear. Another limitation is that other potential causes of perinatal mortality, such as maternal diabetes or hypertension, are not explicitly accounted for in these data sets. Also, autopsy verification that fetal anomalies or other anatomic causes of death did not occur was not performed. However, a recent Norwegian case-control study of unexplained stillbirth, in which autopsy verification was performed and logistic regression was used to control for documented maternal disease, found that increasing gestational age remained a significant risk factor for unexplained stillbirth, along with maternal

age, smoking, obesity, and low educational level. Interestingly, parity was not a risk factor in the multivariate analysis (Froen, Arnestad, Frey, et al., 2001).

It should be pointed out that the risk of stillbirth in these studies remains quite low at an absolute level. The point at which the risk becomes unacceptable and justifies intervention is unclear and is likely to be influenced by each couple's feelings about the tradeoffs between intervention and no intervention.

Two other studies provide additional indirect evidence of increased risk of death with prolonged gestation. Bastian, Keirse, and Lancaster (1998) compared outcomes of all planned home births in Australia from 1985 through 1990 with all Australian births in the same time period and home births in other countries. The planned home birth perinatal death rate was 6.4/1,000 (46/7,002 total home births). Of the 44 deaths with known gestational age, seven (15.9 percent) were greater than 42 weeks. On chart review, six of these deaths, or 28.6 percent of the total, were classified as due to intrapartum asphyxia; prolonged pregnancies represented 10.7 percent of all home births. Overall, the mortality rate for home births in infants over 42 weeks was twice that for other home births. The authors point out that other conditions associated with perinatal mortality are much less common in the home-birth population, so that the excess mortality observed is unlikely to be solely due to the confounding effects of other complications, such as preeclampsia or diabetes.

Mehl-Madrona and Madrona (1997) reviewed self-reported data from midwives in the western United States between 1970 and 1985. A total of 4,361 midwife-attended home births were compared with 4,107 family-practitioner-attended home births performed in California and Wisconsin during the same time period. Sampling frames and response rates were variable, as were the data collection instruments. Deliveries were matched by maternal age, insurance status, parity, and presence of risk factors. Midwives were significantly more likely to deliver postdate pregnancies, defined as gestational age greater than 42 weeks, than were family practitioners (midwives also were more likely to deliver breech and twin pregnancies). Mortality rates were significantly higher for midwives compared to family practitioners, a difference that was attributable entirely to more postdate, twin, and breech deliveries in the midwife group.

Both of these studies are limited by issues concerning accuracy of dating, completeness of reporting, confirmation of causes of death, and in the case of the Mehl-Madrona paper, a rather complicated sampling scheme and questions about the true comparability of groups. There also are concerns about generalizability in terms of current midwifery practice in the United States. However, patients who select home birth are, by definition, low-risk patients. They also are unlikely to have undergone antepartum testing. The excess mortality seen in women with prolonged pregnancy delivering at home in these two studies is consistent with an independent effect of increasing gestational age on perinatal mortality.

Causes of Perinatal Mortality in Prolonged Pregnancies

Analysis of data from the Medical Birth Registry of Norway from 1978 to 1987 found that the risk of perinatal death was over five times higher in infants below the 10th percentile of birthweight for their gestational age (odds ratio [OR], 5.68; 95 percent confidence interval [CI], 4.37 to 7.38) than in infants from the 10th to 90th percentile (Campbell, Ostbye, and Irgens, 1997), after adjustment for a variety of potential confounding variables, such as maternal complications like diabetes. Maternal age ≥ 35 years was also a risk factor in multivariate analysis (OR, 1.88; 95 percent CI, 1.22 to 2.89). Infants above the 90th percentile in weight had a

decreased mortality risk (OR, 0.51; 95 percent CI, 0.26 to 1.00). A similar relationship between perinatal mortality in prolonged pregnancy and low birthweight was found in a review of Swedish registry data from 1987 through 1992 (Divon, Haglund, Nisell, et al., 1998). These observations are consistent with a hypothesis that decreased uteroplacental function, leading to growth restriction, oligohydramnios, and eventually asphyxia, is one of the major risks of advancing gestational age, although changes in weight occurring after death and prior to delivery may explain some of this phenomenon. What is not clear is whether the decreasing uteroplacental function is an inevitable result of advancing gestational age, or whether failure to go into labor is somehow a marker for some forms of uteroplacental insufficiency.

The Norwegian data are limited by the population (results may not be generalizable to a more diverse U.S. population), accuracy of dating (gestational age in the registry is based on last menstrual period), and time (obstetric management has changed somewhat since 1987). However, the observed association between low birthweight and perinatal mortality in a genetically homogeneous population with a relatively high standard of living and level of access to prenatal care suggests that this is at least partly a reflection of changes in the biology of the uterus, placenta, and/or fetus associated with prolonged pregnancy.

Another issue that should be considered in reviewing recent population-based data on perinatal mortality is the degree to which observed perinatal deaths are preventable. It is unclear from population-based administrative data what proportion of unexplained stillbirths after 40 weeks gestation occurred in women undergoing some form of antenatal surveillance. This information is important for two reasons. First, in order to estimate the benefits of antenatal surveillance at different gestational ages quantitatively, the baseline gestational-age-specific risk, in the absence of surveillance, is needed. Second, if current mortality data reflect mostly women who are undergoing surveillance, then the limits of currently available technology may have been reached; in this case, the only strategy available for further reducing perinatal mortality would be elective induction of labor at a predefined gestational age. This is supported by the findings of a Cochrane meta-analysis (Crowley, 2000), which showed an excess of perinatal mortality in the testing arms. Conversely, if current mortality data reflect women who are not undergoing surveillance, then greater efforts are needed to ensure access to currently available technologies.

Perinatal Morbidity

In the Norwegian database, risks for fetal distress in labor (relative risk [RR], 1.68; 95 percent CI, 1.62 to 1.72) and shoulder dystocia (RR, 1.31; 95 percent CI, 1.21 to 1.42) were significantly increased in infants born after 42 weeks compared with infants born between 39 and 42 weeks (Campbell, Ostbye, and Irgens, 1997). Others also have noted an association between prolonged pregnancy and increased fetal weight and/or shoulder dystocia (Acker, Sachs, and Friedman, 1985; Eden, Seifert, Winegar, et al., 1987; Nocon, McKenzie, Thomas, et al., 1993; Sarno, Hinderstein, and Staiano, 1991).

Data on longer term outcomes of infants born after prolonged gestations are relatively sparse. One Irish case-control study reported an association between prolonged pregnancy and neonatal seizures (Curtis, Matthews, Clarke, et al., 1988). In a study of British children with cerebral palsy, there was a strong association between maternal gestational age greater than 41 weeks and the presence of neonatal encephalopathy (defined as having both signs of neonatal neurological abnormalities and depression at birth, defined as a 1-minute Apgar score less than 6) (OR, 3.5;

95 percent CI, 1.0 to 12.1). This risk was particularly marked in primigravid women (OR, 11.0; 95 percent CI, 1.5 to 102.5). The infants studied also were more likely to have had induction of labor (indications not specified), long second stage of labor, meconium-stained amniotic fluid, and emergent cesarean section or operative vaginal delivery.

On the other hand, prospective studies have not shown an association between prolonged pregnancy and adverse physical or mental development at 1 or 2 years, even when stratified by presence or absence of the dysmaturity syndrome (Shime, Librach, Gare, et al., 1986).

In summary, available data are insufficient to quantify the degree of excess risk, if any, of perinatal morbidity (including neurological morbidity) associated with prolonged pregnancy.

Maternal Outcomes

Maternal risks of obstetric trauma and hemorrhage are increased in prolonged pregnancy compared with term pregnancy (Campbell, Ostbye, and Irgens, 1997). Labor abnormalities also are increased. All three of these may be related to an increased risk of macrosomia. Another potential reason, as stated above, is that some women who do not go into labor within the "normal" length of gestation have differences in the physiology of labor and delivery compared with women who begin labor earlier in gestation.

Interventions performed to prevent adverse outcomes associated with prolonged gestation have the potential for complications, most notably hyperstimulation resulting from too frequent uterine contractions, infection, bleeding, or organ injury from cesarean section.

Summary: Risks of Prolonged Pregnancy

Prolonged gestation is associated with an increased risk of perinatal death, as well as perinatal morbidities related to either uteroplacental insufficiency or fetal macrosomia. Direct maternal risks are potentially related to fetal macrosomia or to interventions used in the management of prolonged pregnancy. The gestational age at which the risk of adverse direct perinatal or maternal outcomes justifies the costs and potential complications of active intervention is unclear.

Scope and Purpose

The purpose of this evidence report is to review the evidence regarding strategies to reduce the risks of adverse maternal and fetal outcomes associated with advancing gestational age. Because of the issues discussed above, we did not limit our review to interventions performed after a predefined gestational age cut-point. Although "postterm" pregnancy technically refers to gestations beyond 42 weeks, and "postdate" to pregnancies beyond 40 weeks, others have used the phrase "prolonged pregnancy." The appropriate gestational age range upon which this report should focus proved a lively topic for debate among the members of the project's advisory panel of technical experts. However, consensus was reached that the primary focus should be on managing those risks associated with advancing gestational age, with an attempt at quantifying the gestational-age-specific risk. Because of this scope, we use the term "prolonged pregnancy" throughout this report, to avoid confusion with terminology associated with specific gestational age definitions. We use "postterm" and "postdate" only when specifically referred to in articles under discussion.

There is an inherent uncertainty associated with any estimate of gestational age. However, risks of certain adverse outcomes for both mother and infant clearly increase as gestational age increases after 37-38 weeks. Strategies to minimize these risks may themselves carry certain risks. The ultimate goal of this report is to provide a framework for rationally comparing these competing risks, and to help patients, clinicians, and policymakers decide for themselves the best options for managing prolonged gestation in their particular situation.

Key Research Questions

The key research questions addressed in the report were developed by the Agency for Healthcare Research and Quality (AHRQ) and our report partner, ACOG, and refined in consultation with AHRQ, ACOG, and the project's advisory panel of technical experts. The questions were as follows:

1. What are the test characteristics (reliability, sensitivity, specificity, predictive values) and costs of measures used in the management of prolonged pregnancy to (a) assess risks to the fetus and mother of prolonged pregnancy, and (b) assess the likelihood of a successful induction of labor?

2. What is the direct evidence comparing the benefits, risks, and costs of planned induction versus expectant management at various gestational ages?

3. What are the benefits, risks, and costs of currently available interventions for the induction of labor?

4. Are the epidemiology and outcomes of prolonged pregnancy different for women in different ethnic groups, different socioeconomic groups, or in adolescent women? This question reflects AHRQ's programmatic interest in identifying health disparities attributable to age, race/ethnicity, and socioeconomic status.

Our approach to addressing each of these questions was to identify and evaluate the relevant literature and supplemental data (if any); report the results; and where evidence was lacking or methodological limitations in the available sources precluded drawing firm conclusions, identify the issues needing resolution in order to answer the question.

Because the primary focus of the report is on clinical issues surrounding advancing gestational age, we did not systematically review the basic science literature on the initiation of labor, the physiology of the gravid uterus and cervix, placental function, or any of the other topics critical to a comprehensive understanding of these issues. The Duke team, AHRQ, ACOG, and the advisory panel all agreed that the time, effort, and additional expertise required to systematically review this literature precluded their inclusion in this evidence report.

Interventions Assessed

Based on the key research questions, our preliminary review of the literature, and discussions with the advisory panel, we considered the following interventions to reduce risks to the fetus or mother associated with advancing gestational age.

1. Testing:
   a. Tests to determine risk of stillbirth or compromise related to prolonged gestation:
      - Maternal measurement of fetal movement.
      - Nonstress test (NST).
      - Contraction stress test (CST), using either nipple stimulation or oxytocin.
      - Amniotic fluid measurements.
      - Biophysical profile, using either five measures (reactive NST, breathing, tone, movement, amniotic fluid) or two measures (NST, amniotic fluid).
      - Doppler measurements of umbilical or fetal cerebral blood flow.

   b. Tests to determine the risk of macrosomia.
      - Estimation of fetal weight:
        - Maternal judgment.
        - Clinical examination.
        - Ultrasound.

   c. Tests to estimate likely success of induction of labor.
      - Clinical estimation of cervical ripeness (Bishop score).
      - Fibronectin.

After discussion with the advisory panel, we did not include tests of fetal well-being that are no longer in widespread clinical use, such as estriol.

2. Management options other than testing:
   - No intervention (neither induction nor testing).
   - Interventions to prevent prolonged pregnancy:
     - Scheduled sweeping of membranes.
   - Planned induction:
     - 41 weeks.
     - 42 weeks.
     - Later timing
   - Testing for fetal well-being (using tests described above):
     - Varied time of initiation (40, 41, 42 weeks).
     - Varied frequency.

3. Specific agents/interventions used for the induction of labor:
   - Amniotomy.
   - Castor oil.
   - Extra-amniotic saline instillation.
   - Relaxin.
   - Sweeping of the membranes.
   - Foley catheter.
   - Nipple stimulation.
   - Oxytocin.
   - Prostaglandins:

    - Prostaglandin E_2 (gel, tablets, and inserts).
    - Misoprostol.
- Mifepristone.

We did not systematically review certain other interventions that may play a role in managing prolonged pregnancy. Although we discuss the effect of ultrasound estimation of gestational age on the diagnosis of prolonged pregnancy above, we did not attempt to systematically review the literature on the other potential benefits, risks, and costs of routine ultrasonography in early pregnancy. Attempting to place the potential benefits of accurate gestational dating for managing advancing gestational age in the context of the other possible outcomes associated with routine ultrasound screening was well beyond the scope of the report and beyond the resources available. Similarly, we did not systematically review the literature on intrapartum interventions used in the management of common complications of prolonged pregnancy (such as oligohydramnios or meconium-stained amniotic fluid) unless identified articles clearly included data on prolonged pregnancy.

Patient Populations

The primary patient population considered in this report was pregnant women with a single fetus in the vertex position, approaching or past the estimated date of confinement, without any other medical or obstetrical complications, where the only potential factor increasing the risk of an adverse perinatal or maternal outcome was advancing gestational age. We also examined the potential interaction of this risk with age and race/ethnicity. Our findings are specifically not applicable to women with prior cesarean section, for several reasons:

- Prior cesarean section was an exclusion criteria in the vast majority of the randomized trials of management strategies and induction agents; thus, we are unable to generalize these results.

- Recent observational data (Blanchette, Nayak, and Erasmus, 1999; Lydon-Rochelle, Holt, Easterling, et al., 2001; Plaut, Schwartz, and Lubarsky, 1999) suggest that risk of uterine rupture is increased in women with prior cesarean section undergoing induction of labor, especially with prostaglandins. Incorporating an evaluation of this evidence into the report would have required an additional consideration of the general risks and benefits of vaginal birth after cesarean section, which is well beyond the scope of this report.

Practice Settings

Practice settings where the interventions discussed in this report may potentially be considered for use include:

- Hospitals.
- Free-standing birthing centers.
- Patients' homes.
- Prenatal clinics or other facilities where ambulatory prenatal care is delivered.

Target Audiences

The primary target audiences for the evidence report are groups involved in writing guidelines or educational documents on management of prolonged pregnancy for health care professionals. Secondary audiences include:

- Health care professionals providing care for pregnant women (obstetricians, family physicians, nurse-midwives, nurses, childbirth educators, etc.).
- Policymakers involved in coverage/payment decisions.
- Agencies, foundations, and other groups involved in funding research.
- Media involved in dissemination and education about health issues.
- Patients with an interest in reviewing the state of the art of the medical literature concerning management of prolonged pregnancy.