New Indications for Antepartum Testing:
Making the Case for Antepartum Surveillance or Timed Delivery for Women of Advanced Maternal Age

Ruth C. Fretts, MD, MPH,* and Ugonna A. Duru, MD†

Maternal age is an independent risk factor for stillbirth; a moderate number of these occur in normally formed babies near term. For a woman 40 years of age or older giving birth, her risk of having a chromosomal anomaly is 1/68. What is not appreciated is that even without medical risk factors, her risk of having a stillbirth after 37 weeks of gestation is 1/116. This article reviews the risks and benefits of the strategy of antepartum testing and timed delivery and discusses the limitations of the available data in this field.

Semin Perinatol 32:312-317 © 2008 Elsevier Inc. All rights reserved.

KEYWORDS advanced maternal age, late stillbirth, antepartum testing, active management of risk

Indications for Antepartum Testing

Antepartum testing cannot directly reduce the risk of stillbirth, but it can inform as to when to deliver the patient. Delivering the fetus incurs both maternal and fetal risks and benefits. The goal is to minimize perinatal mortality (ie, the sum of stillbirths and neonatal deaths) and include a measure of maternal morbidity, mortality, and patient preference. The current management of the most common risk conditions such as diabetes mellitus requiring insulin, the hypertensive disorders, and in utero growth restriction already include various schedules for antepartum testing. This proactive, comprehensive approach has led to the reduction of stillbirth risk, albeit at the cost of an increased risk of iatrogenic preterm birth. The role of antepartum testing in women with these conditions is summarized elsewhere in this edition of Seminars in Perinatology. In less prevalent diseases that may contribute to fetal loss, such as systemic lupus erythematosus, or in patients with a history of a previous stillbirth, there is little doubt that the clinician will include multiple modalities of antepartum testing to assess the ongoing health of the fetus. Many questions remain however. For example, should we treat women with common risk factors for stillbirth as a “high-risk pregnancy” and initiate antepartum testing and or timed delivery and, if so, what are the potential risks and benefits of this approach?

Late Stillbirths and Candidate Risk Factors for Antepartum Screening

The best opportunity for stillbirth reduction is to identify patients who have an increased risk of stillbirth, late in pregnancy, where the downside of antepartum testing and early delivery, if warranted, can be minimized. Candidate risk factors include obesity, socio-economic or racial risk factors, and advanced maternal age. Obesity has many detrimental obstetrical and maternal consequences. In a recent meta-analysis of prepregnancy maternal obesity and stillbirth, Chu and colleagues estimated the risk of stillbirth to be 1.4-fold higher in overweight women (ie, a body mass index (BMI) 25-29.9 kg/m²), and 2.1 times higher in women with a BMI of 30 or over, when compared women with a BMI of <25.1 In a Danish population, the risk of stillbirth associated with prepregnancy obesity appeared to increase late in pregnancy, and this additional risk could not be attributed to hypertension or diabetes.2 Indeed, Salihu and coworkers found obesity associated with many social, medical, and obstetric factors, which placed women at increased risk for adverse outcomes. In their study of Missouri births from 1978 to
1997, they found that women with a prepregnancy BMI of 30 or greater conferred a 1.4-fold risk of stillbirth. This increase in risk appears to be dose dependent, and black women fared worse in all weight categories when compared with whites. Black women who were extremely overweight (defined as a BMI of 40 or greater) had a 2.7-fold risk above that of normal weight white women, while similarly overweight white women had a 1.8-fold risk of stillbirth. Unfortunately, however, because cause and timing of the stillbirths associated with obesity is not well known in the American population, there are insufficient data at this time to make a recommendation for routine antepartum testing based on maternal weight alone. For now, the strategies necessary to manage these patients and minimize adverse perinatal outcomes need to be individualized, based on obesity and other comorbid conditions.

In the United States, perinatal statistics are stratified by race. Obvious differences in neonatal and stillbirth rates may be due to many factors including access to obstetrical care, quality of care, stress, diet, and biological factors. Black women in the US, for example, experience a two-fold risk of stillbirth when compared with whites with a higher rate of stillbirth both early in gestation and late in gestation. There are no trials specifically addressing the potential role of antepartum testing and timed delivery in black women, although Yuan and colleagues using US data compared induction and stillbirth rates in 1997 versus 1991. Comparing the two time periods, they noted a 20% decrease in the number of stillbirths after 40 weeks of gestation, which was largely attributed to an increase in the rate of inductions after 41 weeks. These authors did note however that black women were less likely that white women to be induced before 43 weeks. This is one area in which earlier intervention could ameliorate the disproportionate stillbirth rate that is experienced by black women late in pregnancy.

Currently in the United States, approximately 15% of women giving birth are 35 years of age or older, and 2.5% are 40 years of age or older. Indeed, the birth rate to women 35 to 39 years of age has increased every year since 1978 and has risen 43% since 1990. The rate of women giving birth who are 40 years of age or older has also continued to rise. For example, based on the final birth statistics from 2003 and 2004, the rate for women 40 years of age or older rose from 8.7 births per 1000 women to 8.9 per 1000. Interestingly, the Centers for Disease Control now reports birth rates for women aged 45 to 49 and 50 to 54, but these births represent only a small fraction of total births (0.15%).

Many patients and practitioners alike have the belief that if older women are without medical problems such as diabetes or hypertension, the additional risk of conferred by advancing age is probably relatively low for adverse outcomes. Indeed small studies directed at this issue have been generally reassuring. However, a large Canadian study by Frents and coworkers, after controlling for many factors that occur more often in older women (e.g., hypertension, diabetes, previous abortion, previous stillbirth, multiple gestation, placenta previa, placental abruption, parity, and marital status), they found that advanced maternal age remained an independent risk factor for stillbirth. Women 35 to 39 years of age had a 1.8-fold risk of stillbirth when compared with women less than 30 years of age; for women 40 years of age or older the risk was 2.4-fold higher.

Using the McGill Obstetrical Neonatal database, which had over 100,000 births, Fretts and Usher found that the causes of stillbirth in older women has changed over the past three to four decades. Historically, the only specific cause of fetal death that occurred significantly more often in women 35 years of age or older, compared with younger women, was stillbirths related to congenital anomalies (OR, 3.2; 95% CI, 1.6-6.5). Later in the study period after the introduction of routine prenatal screening, diagnosis, and the availability of abortion, the number of stillbirths due to anomalies in older women reduced almost statistically below that of younger women (OR, 0.2; 95% CI, 0.003-1.5). Of course these are still significant losses, but they no longer appear in the stillbirth statistics. What was notable in the 1978-1995 period was that the unexplained stillbirth rate (i.e., an appropriately grown fetus and without obstetrical or maternal risk factors) was 2.2-fold higher in women 35 years of age or older when compared with younger women.

Froen and coworkers, using a Norwegian database of over 500,000 women, found that women 35 years of age or older to be at a 5.1-fold increased risk of having an unexplained stillbirth when compared with women less than 25 years of age (95% CI, 1.3-19.6). Huang and coworkers, also using the McGill Obstetrical Neonatal database, found that 60% of the unexplained stillbirths occurred after 36 weeks of gestation. In a separate study, this group showed that the increased risk of unexplained stillbirth late in pregnancy was notably higher in women 35 years of age or older.

Reddy and colleagues using US data from 36 states from 2001 and 2002 (N = 5,458,735) performed an analysis of the risk of stillbirth by maternal age throughout pregnancy for nonanomalous singleton pregnancies. In their study, 10.4% of their population was 35 to 39 years of age, with 8.1% reported to have a concomitant medical condition (e.g., hypertension and diabetes, which were the most commonly reported conditions). Women 40 years of age or older constituted 2.2% of births, 14.4% of which reported a medical condition. The risk of stillbirth for women 40 years of age or older was higher at all gestational ages, but the risk difference was accentuated after 38 weeks of gestation (Fig. 1). This figure demonstrates that older women have stillbirth risks usually associated with postdates but this occurs earlier in gestation. For example, for 41 weeks of gestation, the risk of stillbirth is approximately 0.95/1000 for women 30 to 34 years of age; this is the equivalent rate for women 35 to 39 years of age at 40 weeks of gestation, and for women 40 years of age and older this rate of stillbirth occurs at 39 weeks of gestation. Only about 10% women who were 35 years of age or older had reported a medical condition that might increase the risk of stillbirth, so it is useful to remember than 90% did not. When women with known medical problems were eliminated from the analysis, the results regarding stillbirth rates were unchanged. It is also importan to note that primiparous women had the highest risk of stillbirth and black women had a higher rate than white women (Table 1). These observations support a case for treating these pregnancies in a
manner similar to "postdates" pregnancies, by considering the options of antepartum testing and/or timed delivery. However, there are no prospective clinical trials however that specifically address this issue for older women, and for reasons of logistics and statistical power, it unlikely that there will be good, "Level 1" evidence in the near future. For now, the clinicians must use their clinical judgment to weigh the risks and benefits of such a strategy.

In this setting, it is a useful exercise to compare the risk of a late stillbirth to other adverse outcomes that occur in women of advanced maternal age (Table 1). Much emphasis has been placed on prenatal diagnosis to reduce the risk of having a live-born infant with a significant chromosomal anomaly. Indeed, if a woman had not been sufficiently counseled that her risk of a chromosomal anomaly was estimated to be 1/66 at the age of 40, and had not been offered invasive testing, she (and her lawyer) could easily demonstrate that her care fell outside the bounds of the standard of care. It appears that if an older woman has been able to achieve pregnancy, has been lucky enough to not have an early miscarriage, and has navigated through the many options of prenatal screening and invasive diagnostic testing, that the risk of having a late stillbirth in a normally formed baby after 37 weeks of gestation has not caught the attention of both the provider and the patient. For women 40 years of age or older having her first birth, the risk of late stillbirth after 37 weeks of gestation is 1/116 (Table 1). Given that older women have fewer reproductive opportunities, it is worth reviewing these risks with the patient and reviewing the options available to her (eg, expectant management with kick-counting, formal antepartum testing, and/or timed delivery). It is also worth mentioning that there is no standard-of-care or consensus practice guideline at the present time.

**A Strategy of Antepartum Testing at Term**

By choosing a strategy of antepartum testing, the benefit of such a strategy depends on the underlying risk of stillbirth and the sensitivity and specificity of the test. Currently there are no data to permit the generalization that antepartum testing typically used for a postdates pregnancy will function in a similar way for older women at earlier gestational ages. In general, for a postdates pregnancy, the available data to date are insufficient to guide as to which intervention(s) has contributed most to the observed reduction of stillbirths after 41 weeks of gestation. Has the often routine induction after 41

---

**Table 1 Rates of Chromosomal Abnormalities in Live-Born Compared to the Age-Related Risk of Stillbirth**

<table>
<thead>
<tr>
<th>Maternal Age at Delivery</th>
<th>Risk of Any Chromosomal Abnormality</th>
<th>Risk of Stillbirth After 37 Weeks Multipara</th>
<th>Risk of Stillbirth After 37 Weeks Nulliparous</th>
<th>Risk of Stillbirth for All Black Women After 37 Weeks with No Known Medical Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 34</td>
<td>1/1667 to 1/485*</td>
<td>1/775</td>
<td>1/269</td>
<td>1/326</td>
</tr>
<tr>
<td>35 to 39</td>
<td>1/378</td>
<td>1/192</td>
<td>1/156</td>
<td>1/247</td>
</tr>
<tr>
<td>40+</td>
<td>1/106</td>
<td>1/66</td>
<td>1/116</td>
<td>1/230</td>
</tr>
</tbody>
</table>

*Estimates range from 20 years to age to 34 years of age.
Adapted from Reddy and colleagues,^{12} and Hook,^{13}
Table 2: Effect of Unexplained Stillbirth Risk on Outcomes of Weekly Antepartum Testing Starting at 37 Weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR 1</th>
<th>OR 2</th>
<th>OR 3</th>
<th>OR 4</th>
<th>OR 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal deaths per 1000 with no testing</td>
<td>1.6</td>
<td>3.2</td>
<td>4.7</td>
<td>6.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Fetal death per 1000 with testing</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Fetal deaths averted with testing</td>
<td>1.2</td>
<td>2.4</td>
<td>3.5</td>
<td>4.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Tests per pregnancy</td>
<td>3.4</td>
<td>3.4</td>
<td>3.3</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Tests per fetal death averted</td>
<td>2862</td>
<td>1418</td>
<td>950</td>
<td>711</td>
<td>569</td>
</tr>
<tr>
<td>Inductions per fetal death averted</td>
<td>233</td>
<td>116</td>
<td>78</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>Cesarean deliveries per fetal death averted</td>
<td>44</td>
<td>22</td>
<td>15</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

Outcomes from week 37 through 41 weeks assumes test characteristics to be 70% sensitive and 90% specific. Adapted from Fretts and colleagues.¹⁵

weeks contributed more to the stillbirth reduction or was it a “less-than-perfect” evaluation of fetal well-being that led to an induction? Crowley, for example, has estimated that, in the general population at 41 weeks, it would take 400 inductions to prevent one stillbirth.¹⁴ Since all estimates of a “true-positive test” and a “false-positive test” are driven by the fact that our interventions are designed to prevent stillbirth, a clinician will probably never know which of the 400 interventions saved a baby.

In an attempt to quantify the risks and benefits of antepartum testing late in pregnancy, Fretts and colleagues designed a decision analysis based on the week-specific risk of unexplained stillbirth the most frequent type of loss) in women 35 years of age or older having their first birth.¹⁵ Estimates of relative risk of unexplained stillbirth by maternal age were obtained from the McGill Obstetrical Neonatal Database (ie, a Canadian hospital-based data). To estimate the possible increased risk of cesarean delivery, they used the week-specific difference of cesarean delivery in labors that occurred spontaneously versus those that were induced, in two large Boston teaching hospitals.¹⁶ A sensitivity analysis of the characteristics of the test was included, varying both the sensitivity and the specificity from 70 to 90%. For the main model it assumed that the testing would begin in the 37th week, and it was assumed that 10% of women would have an abnormal test and that this would lead to an induction, regardless of cervical status. It also assumed that, despite testing, 30% of babies would die anyway and that there were no intrapartum deaths.

In this model, the odds ratio for stillbirth was the most important factor in stillbirth reduction (Table 2). Women who had an underlying five-fold increased risk, using a strategy of antepartum testing, would theoretically reduce the rate of unexplained stillbirth from 1/128 to 1/526 ongoing births. It is also useful to note women at low risk (ie, an OR = 1.0) using a similar strategy would have a more limited benefit, reducing the risk of late unexplained stillbirth from 1/625 to 1/833. For example, women 35 years of age or older having her first birth, who have an estimated rate of late unexplained stillbirth of 5.2/1,000 after 37 weeks of gestation, the model predicts that the rate of unexplained stillbirth could be reduced to as low as 1.3/1,000. This strategy however would entail 863 antepartum tests per fetal death averted, 71 inductions per fetal death averted, and 14 additional cesarean deliveries per fetal death averted (Table 3). It is interesting when one compares this approach to a strategy of no testing, but with a planned induction at 41 weeks. In this scenario, the rate of induction and cesarean delivery per fetal death averted is much greater (429 and 219, respectively) than with a strategy of antepartum testing. That is because a large portion of the stillbirths have already occurred, before 41 weeks.¹⁵

Of course this is only a model and is limited by many factors. As previously stated, it is not known if antepartum testing in women of advanced maternal age late in pregnancy will reveal abnormalities before a demise. However, if parallels can be drawn to other high-risk conditions, a strategy of implementing antepartum testing has been associated with a reduction in the risk of stillbirth in women with hypertension and diabetes to that just slightly above the general population. Another limitation is that the study model did not employ twice weekly testing (a standard protocol used for post-dates pregnancies) nor did it account for the effect of serial testing. Typically, if one test is abnormal, it would be routine to perform a second, follow-up test. This would be especially true in the setting where the patient was 35 years of age or

Table 3: Base-Case Results for Nulliparous Women Aged 35 Years and Older

<table>
<thead>
<tr>
<th>Outcome of Unexplained Fetal Deaths</th>
<th>No Testing</th>
<th>Weekly Testing Starting at Week 37</th>
<th>Induction at 41 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal deaths/1000</td>
<td>5.2</td>
<td>1.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Fetal deaths averted</td>
<td>--</td>
<td>3.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Test per pregnancy</td>
<td>--</td>
<td>3.3</td>
<td>--</td>
</tr>
<tr>
<td>Test per fetal death averted</td>
<td>--</td>
<td>863</td>
<td>--</td>
</tr>
<tr>
<td>Induction per fetal death averted</td>
<td>--</td>
<td>71</td>
<td>469</td>
</tr>
<tr>
<td>Cesarean deliveries per fetal death averted</td>
<td>--</td>
<td>14</td>
<td>219</td>
</tr>
</tbody>
</table>

Outcomes from week 37 through 41 weeks assumes test characteristics to be 70% sensitive and 90% specific. Adapted from Fretts and colleagues.¹⁵
older, at 37 weeks, with an unfavorable cervix. Contrast this with the threshold to induce in the setting of a 43-year-old woman with mild oligohydramnios at term, where the clinician might be relieved that at 39 weeks there is now an “indication” for delivery. This decision analysis does not address the type and the cost of antepartum testing, the potential maternal risks of additional cesareans, nor the effect of antepartum testing on maternal anxiety and confidence.

In summary, the sensitivity and specificity of antepartum testing has been greatly debated. In this model, however, if the specificity were lowered from 90 to 70% (thereby increasing the “false-positive” rate to 30%, and consequently increasing the induction rate), there was a reduction of stillbirths, reminding us once again that if the patient is delivered, she is no longer at risk for stillbirth.13

**Optimal Timing of Testing and Delivery**

Theoretically, each medical condition has an optimal time to start antepartum testing, and an optimal time for delivery, after taking into account both fetal and maternal factors. For pregnant women with insulin-dependent diabetes, Rouse and colleagues estimated the optimal timing to begin antepartum testing was about 34 weeks of gestation.17 Similarly, Weeks and colleagues, using results of antepartum testing in 300 women with a previous stillbirth, estimated in otherwise healthy women that antepartum surveillance be initiated after 32 weeks of gestation.18 Early interventions led to an increased risk of admission to the neonatal intensive care, but delaying fetal evaluation and delayed delivery can increase the risk of stillbirth or delivery of a baby in poor condition. Postdates pregnancies can also put the mother at risk for increased obstetrical trauma, because of the increased rate of fetal macrosomia. Nicholson and colleagues, for example, compared maternal and fetal outcomes in women with good dating, who were at term and who were eligible for a vaginal birth.19 The database included 11,724 women without any known risk factors, who were less than 35 years of age, and 2373 women who were 35 years of age or older. Six hundred thirty-five women had a diagnosis of hypertension, and 460 women had diabetes. Women with multiple risk factors were included in each subgroup. The study was not powered to look at perinatal mortality. The investigators evaluated the maternal cesarean section rate, the newborn admission rate, the incidence of maternal 3rd- and 4th-degree tears, and the 5-minute Apgar of 0 to 6 rate. The most important component of this study’s outcomes that defined the lower limits of the optimal time of delivery was the admission rate to the neonatal intensive care unit. The outcome that largely defined the upper limit of the optimal time of delivery was the maternal cesarean section rate. Given the design of this study, including the prespecified goals of minimizing both neonatal admissions and cesarean sections, these investigators described the optimal time of delivery to be where these risks intersected the 95% CI around these points. The “optimal times of delivery” were described as 37 1/7 to 41 0/7 weeks for low-risk women, 39 2/7 to 40 1/7 weeks for women with hypertension, and for women 35 years of age or older, the optimal timing of delivery was 38 5/7 to 39 6/7 weeks of gestation. Interestingly their model did not work well for diabetic women, because a large proportion of babies born to diabetics spent time in the neonatal intensive care unit, presumably to monitor the baby’s glucose, monitoring that was not routinely performed on infants born to nondiabetic mothers. This study, while interesting, did not assess the impact of antepartum testing or induction. There were also many questions on how competing outcomes should be weighed and how patient preference might have altered these outcomes.

**Risk of Induction Near Term**

While there is no measurable long-term neonatal mortality associated with delivery after 37 weeks, there is an increase in the incidence of neonatal respiratory distress and transient tachypnea at term, and the rate is higher before 38 weeks of gestation and with those having a cesarean delivery.20 Multifetal women of advanced maternal age are at an increased risk of stillbirth late in pregnancy, but for them induction near term does not materially increase the cesarean section rate.18 The greater management dilemma is for nulliparous women. There are many cohort studies addressing the role of induction in nulliparous women. While most have not included information on cervical status or the use of cervical ripening agents, there appears to be an approximately twofold increased risk of cesarean delivery when comparing women who present in spontaneous labor compared with those that are induced.18 The most appropriate comparison however is to compare elective induction (with cervical ripening) to expectant management. With the nadir of cesarean section being between 38 and 39 weeks, expectant management is associated with both larger babies and an increasing opportunity for late placental dysfunction.22 In an elegant analysis, Caughey and coworkers, using a retrospective cohort of women eligible for a vaginal delivery at University of California San Francisco, demonstrated how using the traditional comparison of spontaneous versus induced labor generated a two-fold increase in cesarean sections for nulliparous women.23 However, when the cesarean section rate of induced women was compared with the total risk of a cesarean delivery over the last weeks of gestation (i.e., "the prospective risk of cesarean" similar to the "prospective risk of stillbirth"), it appears that induction may actually reduce the risk of cesarean delivery (Table 4).

A novel approach called the "Active Management of Risk in Pregnancy at Term" (AMOR-IPAT), used by groups at the University of Pennsylvania, does show some promise.24 They published a cohort study comparing outcomes in AMOR-IPAT (N = 100) and non-AMOR-IPAT groups (N = 300). In the active management group, early dating was performed. At term, a risk assessment was performed that included the presence or absence of factors that might increase uterine and placental dysfunction (eg, hypertension, diabetes, advanced maternal age, smoking, size-less-than-dates, and other factors). They also included risk factors for cephalopelvic disproportion (eg, BMI >30, short stature, gestational diabetes, size-greater-than-dates,
Cervical ripening was used for all women with a Bishop score less than 5. The AMOR-IPAT group had a median gestational age at delivery which was significantly lower than the non-AMOR-IPAT group (38.9 versus 40.1 weeks; P < 0.001), as well as a significantly higher induction rate (63% versus 25.7%; P < 0.001), but they also had a surprisingly low cesarean section rate (4% versus 16.7%). The active management group also had a statistically lower rate of 3rd- and 4th-degree tears and a lower NICU admission rate. If this approach were to be widely adopted, the result would be a sea of change for obstetrics, necessitating a very high induction rate. While the utility of this approach needs to be confirmed and validated, issues of patient acceptability will also be an important measure. Modern obstetrics is often accused of medicalization of the birthing process; it is not clear what proportion of women would embark on a strategy that would involve a 60% induction rate.

**Summary**

While there is no “level 1” evidence to recommend antepartum testing or timed delivery in patients with an increased risk of stillbirth late in pregnancy, we need to appreciate that this is a gap in our knowledge. Many times we as practitioners must function in the “gray” area of imperfect knowledge. It is important however to accurately assess risk. The 40-year-old woman having her first baby should be told that her risk of stillbirth in late pregnancy is 1/16. When she and her practitioner travel down the “gray” roads together, it behooves the practitioner to describe the risks and benefits of these approaches within the limits of our knowledge.

**References**