Advanced maternal age and the risk of antepartum stillbirth

By Joanne Stone, MD

Q. A 39-year-old G1P0 is at 30 weeks' gestation. Her pregnancy has been uncomplicated, with a normal cardiovascular system and anatomy scan. She has no underlying medical disorders. What are the risks of antepartum stillbirth associated with advanced maternal age?

A. Approximately 14.2% of women who give birth in the United States are 35 years of age or older, and 2.6% are age 40 or older. Over the last 30 years, there has been a 36% increase in first births among women aged 35 to 39, and a 70% increase among women who are aged 40 to 45.

Stillbirth, defined as fetal death at 20 weeks or more, occurs at a rate of 6.2 per 1,000 US births. Epidemiological data have consistently implicated advanced maternal age (AMA) as one of the most important contributors to unexplained stillbirth. Fretts and colleagues found that after controlling for many factors that occur more frequently in older women, such as hypertension, diabetes, abruption, and multiple gestation, AMA remained an independent risk factor for stillbirth. Women aged 35 to 39 had a 1.9-fold increased risk of stillbirth compared with women younger than 30, while women 40 years or older had a 2.4-fold higher risk.

Using a large Norwegian database of more than 575,000 women, Froen et al found that women age 35 or older had a 5.1-fold increased risk of having a stillbirth compared with women younger than 25.

After adjusting for coexisting conditions, a recent meta-analysis demonstrated that AMA was associated with an increase of 65% in the odds of stillbirth, and the odds increased with increasing age, doubling for women age 40 or older (adjusted Odds Ratio [aOR], 2.29; 95% Confidence Interval [CI], 1.54-3.41).

Given the increased risk of stillbirth for women of AMA, should antepartum surveillance be routinely performed?

Antepartum surveillance is used for women deemed to be at increased risk for fetal death. While AMA has clearly been shown to be a significant risk factor for stillbirth at term, in the absence of other co-indications (eg, maternal or fetal complications), it has not routinely served as an indication for antepartum testing.

In an analysis of stillbirth by maternal age for nonanomalous singleton pregnancies in the United States, Reddy et al found that the risk of stillbirth for women 40 or older was higher at all gestational ages, but was particularly increased after 38 weeks' gestation. They demonstrated that older women have a magnitude of stillbirth risk usually seen with postdates, but that this occurs earlier in gestation. For example, for women younger than 35, the risk of stillbirth at 41 weeks is less than that of women aged 35 to 39 at 40 weeks and that of women 40 and older at 39 weeks.

Similarly, Bahtiyar et al used a mathematical model to show that the cumulative risk of stillbirth at 38 and 39 weeks in women aged 40 to 44 was similar to the stillbirth risk in women aged 25 to 29 at 41 and 42 weeks.

Fretts et al performed a decision analysis of antepartum testing late in pregnancy for women who were at least age 35. Three strategies were compared: no testing, weekly testing starting at 37 weeks with induction after a positive test, and no testing with induction at 41 weeks. The analysis predicted that of the three, antepartum testing would be the most successful in reducing the number of unexplained stillbirths, although it was also associated with the highest induction rate. The model estimated that it would take approximately 863 antepartum tests and 71 additional inductions to prevent 1 unexplained stillbirth.
The argument in favor of antepartum surveillance starting at 37 weeks for women of AMA is that the risk of stillbirth at this gestational age is similar in frequency to other high-risk conditions for which testing is routinely performed (Table). Nulliparous women with AMA and those older than 40 may have the highest risk. Still, there is insufficient evidence to confirm that antenatal testing for the sole indication of AMA reduces stillbirth or improves perinatal outcomes. It is unknown whether antenatal testing in this population affects maternal complications either positively or negatively. Many women older than 35 will have other indications for testing. Given that approximately 15% of the population is older than 35, the potential benefit of routinely testing them must be balanced against the potential harm of increased interventions associated with testing, such as iatrogenic delivery, labor induction, and cesarean delivery.

Is there a role for earlier or timed delivery to reduce the risk of stillbirth?

To date, there are no prospective clinical trials that specifically evaluate whether timed delivery for women older than 35 without other comorbidities improves maternal or fetal outcomes.

Using a database of 11,724 women younger than 35 without known risk factors and 2,373 women 35 and older, Nicholson et al attempted to determine the optimal timing of delivery. The authors reported that the optimal time of delivery for women of AMA was 38-5/7 to 39-6/7 weeks. Proponents of timed delivery for women with AMA argue that the stillbirth risk at this gestational age threshold is similar to that in low-risk women at 41 weeks.

In a large trial of expectant management versus induction of labor for postdate pregnancies, elective induction resulted in a lower cesarean delivery rate, primarily due to fewer surgeries for nonreassuring fetal tracings, although the study was not powered to detect a difference in perinatal mortality.

A meta-analysis of 16 studies of routine versus nonroutine induction of labor in postterm patients found that routine induction after 41 weeks was associated with a nonsignificant lower rate of perinatal mortality (OR, 0.41; 95% CI, 0.14-1.18) and significant decrease in the cesarean delivery rate (OR, 0.88; 95% CI, 0.78-0.99).

Despite this reassuring information from postterm pregnancies, it is unknown whether these data can be extrapolated to women with AMA who reach 39 weeks and have no other indication for delivery. The risks of induction, particularly in nulliparous women and women with unfavorable cervices, compared with the potential risk of adverse fetal outcomes, should be taken into consideration. If delivery is considered in the absence of other indications, it should not be initiated prior to 39 weeks.

This opinion was developed by the Publications Committee of the Society for Maternal-Fetal Medicine with the assistance of Joanne Stone, MD, and was approved by the Executive Committee of the Society on March 11, 2012. Neither Dr. Stone nor any member of the Publications Committee (See the list of 2012 members at www.smfm.org) has a conflict of interest to disclose with regard to the content of this article.

(Disclaimer: The practice of medicine continues to evolve and individual circumstances will vary. Clinical practices may reasonably vary. This opinion reflects information available at the time of acceptance for publication and is not designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.)

REFERENCES


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<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Stillbirth risk (per 1,000 births)</th>
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<tbody>
<tr>
<td>All pregnancies</td>
<td></td>
<td>6.4</td>
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<tr>
<td>Chronic hypertension</td>
<td>6%–10%</td>
<td>6–25</td>
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<tr>
<td>Maternal diabetes</td>
<td></td>
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<td>Diet controlled</td>
<td>2.5%–5%</td>
<td>6–10</td>
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<tr>
<td>Insulin</td>
<td>2.4%</td>
<td>6–25</td>
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<tr>
<td>Cholestasis</td>
<td>&lt;0.1%</td>
<td>12–30</td>
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<tr>
<td>Previous stillbirth</td>
<td>0.5–1%</td>
<td>9–20</td>
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<tr>
<td>Advanced maternal age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–39 years</td>
<td>15%–18%</td>
<td>11–14</td>
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<tr>
<td>40 years</td>
<td>2%</td>
<td>11–21</td>
</tr>
</tbody>
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Adapted from Fretts, et al.*

Table Risk of antepartum stillbirth based on maternal condition