

# The clinical content of preconception care: reproductive history

Phillip G. Stubblefield, MD; Dean V. Coonrod, MD; Uma M. Reddy, MD, MPH; Raja Sayegh, MD; Wanda Nicholson, MD, MPH, MBA; **Daniel F. Rychlik, MD**; Brian W. Jack, MD

**P**reconception risk assessment includes a comprehensive evaluation of a woman's reproductive history to identify factors related to previous poor pregnancy outcomes that may be amenable to intervention before any future pregnancies occur.<sup>1,2</sup> Because an adverse outcome in an earlier pregnancy is associated with an increased risk for adverse outcomes in subsequent pregnancies, information such as previous spontaneous abortion, preterm birth, fetal growth restriction, stillbirth, surgical delivery, diabetes, and pregnancy-induced hypertension should be collected.<sup>3</sup> Preconception diagnosis and treatment of certain conditions, including maternal autoimmune disease and uterine malformations, may reduce the risk of recurrent pregnancy losses.

## Prior low birthweight infant

*Burden of suffering:* A birthweight of less than 2500 g includes infants that were born preterm (< 37 weeks) and infants that suffer from fetal growth restriction (FGR), whether born before or after 37

A history of previous birth of a low birthweight infant, previous cesarean sections, multiple previous spontaneous abortions, prior stillbirth, or uterine anomaly identifies women at increased risk for recurrent abortion, preterm birth, or stillbirth. We review the evidence for the potential benefit of reproductive history in identifying strategies for evaluation and treatment to prevent recurrent adverse pregnancy outcome. We offer evidence-based recommendations for management of women with these histories.

**Key words:** low birthweight, preconception, preterm birth, reproductive history

weeks. About 30% of preterm infants are growth restricted as well.

## Preterm birth

Preterm birth is now the leading cause of neonatal death in the United States and is the leading cause of infant mortality for nonwhite babies.<sup>4</sup> Women who have had a preterm birth have increased risk for subsequent preterm birth.<sup>5-8</sup> The earlier in gestation the first preterm birth, the greater the risk for another. Women with 1 preterm birth before 35 weeks have a 16% risk of a second preterm birth. Risk increases to 41% after 2 preterm births and to 67% after 3 pre-

term births.<sup>9</sup> Other than multiple gestations, previous preterm birth is often found as the single most important risk factor for another preterm birth among multiparous women. Multivariate analysis in a large Alabama study of a primarily low income population reported that women with previous preterm delivery had an odds ratio of 2.8 for preterm birth in subsequent pregnancy.

The only other risk factor of similar magnitude was prepregnancy maternal weight of less than 50 kg.<sup>7</sup> Early preterm delivery (23-27 weeks' gestation) was closely associated with subsequent early preterm delivery (< 28 weeks).<sup>10</sup> A population-based study from Texas concluded that prior preterm birth accounted for 10% of subsequent preterm births.<sup>9</sup> A number of conditions are associated with recurrent preterm birth: African American ethnicity, inflammatory changes in the placenta, low maternal prepregnant weight (< 50 kg) or body mass index less than 19.8 kg/m<sup>2</sup>, a large interpregnancy weight loss (> 5 kg/m<sup>2</sup>), cigarette smoking, short interpregnancy interval (< 12 months), history of cervical insufficiency, or short cervix on transvaginal ultrasound during subsequent pregnancy.<sup>8</sup> All but the first 2 could potentially be influenced before the next pregnancy. Maternal periodontal disease is associated with increased risk for preterm delivery. However, treatment during pregnancy has not been consistently beneficial. This prob-

From the Department of Obstetrics and Gynecology, Boston University Medical Center, Boston, MA (Drs Stubblefield and Sayegh), Department of Obstetrics and Gynecology, Maricopa Medical Center, Phoenix, AZ (Dr Coonrod), Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (Dr Reddy), Department of Obstetrics and Gynecology, Johns Hopkins School of Medicine, Baltimore, MD (Dr Nicholson), Fertility Treatment Center, Tempe, AZ (Dr Rychlik), and Department of Family Medicine, Boston University School of Medicine, Boston, MA (Dr Jack).

Received June 17, 2008; revised Oct. 15, 2008; accepted Oct. 17, 2008.

Reprints: Phillip G. Stubblefield, MD, Boston Medical Center, DOB 720 Harrison Ave, Suite 1105, Boston, MA 02118. [phillip.stubblefield@bmc.org](mailto:phillip.stubblefield@bmc.org).

The views expressed herein are those of the authors and do not necessarily reflect those of the Eunice Kennedy Shriver National Institute of Child Health and Human Development or the National Institutes of Health.

Conflict of Interest: Phillip G. Stubblefield, MD; Uma M. Reddy, MD, MPH; Raja Sayegh, MD; Wanda Nicholson, MD, MPH, MBA; Daniel F. Rychlik, MD; and Brian W. Jack, MD have no conflict of interest including grants, honoraria, advisory board membership, or share holdings. Dean V. Coonrod, MD, MPH is a Grant Recipient from the March of Dimes Arizona Chapter to develop an internal Care Clinic and has funding from CMS (#1HOCMS030207 101) working on compliance with the 6 week postpartum visit as a strategy to improve preconception care.

0002-9378/\$34.00 • © 2008 Mosby, Inc. All rights reserved. • doi: 10.1016/j.ajog.2008.10.048

lem is considered in detail elsewhere in this supplement.<sup>11</sup>

### Fetal growth restriction

Growth-restricted fetuses account for almost half of all stillbirths.<sup>12</sup> They are also at high risk for fetal asphyxia during labor, meconium aspiration, serious neonatal morbidity, and death. Risk continues into childhood and adulthood. A growing literature associates FGR birth with hypertension, coronary artery disease, diabetes, obesity, and other chronic health problems among adult survivors.<sup>13</sup>

The etiology of FGR is complex but can be described in 3 broad categories: maternal, fetal, and placental.<sup>13,14</sup> Maternal risk factors include low prepregnancy weight, malnutrition, poor weight gain during pregnancy, maternal age younger than 16 years or older than 35 years, a short interpregnancy interval, and smoking and substance abuse as well as number of chronic maternal illnesses that are detailed in other papers in this supplement.

Chronic maternal vascular disease, hypertension, renal insufficiency, diabetes mellitus, and the collagen vascular diseases (especially when complicated by preeclampsia) account for nearly one-third of FGR cases.<sup>15</sup> Fetal risk factors include chromosomal abnormalities, a number of genetic syndromes, fetal viral and protozoal infections, and multiple gestations. Placental factors include chronic placental abruption, placenta previa, placental infarctions, and chronic placental villitis. Placental mosaicism accounts for up to 25% of unexplained FGR. Malaria accounts for a high proportion of FGR births and stillbirths in areas in which transmission is high.<sup>13,15</sup> The recurrence risk of FGR is about 20%.

*How detectable is the condition?* In the United States, virtually all infants are weighed at birth, and women generally know the birthweight of their infants. Maternal illness can be identified by a careful history and obtaining the patients' medical records from the previous delivery. Transvaginal measurement of cervical length during a subsequent pregnancy identifies women with a short

cervix (< 25 mm at 20-24 weeks, < 30 mm at 16-20 weeks) who have markedly increased risk for preterm birth.<sup>8,16</sup> However, there are no validated, standardized ways to confirm a diagnosis of cervical insufficiency prior to pregnancy.<sup>17</sup> Determining the presence of placental inflammation requires obtaining a pathology report from the previous low birthweight pregnancy. Pathological examination of the placenta is not routine, although this is increasingly performed in the case of an abnormal birth outcome.

FGR is diagnosed in utero by ultrasound measurement of fetal biparietal diameter, abdominal circumference, femur length, and calculated estimates of fetal weight in comparison with standardized curves of these parameters versus gestational age. FGR is diagnosed in the neonate by birthweight corrected for gestational age. The usual criterion for defining FGR is birthweight below the 10th percentile of births at that gestational age.

*How effective are the current treatments?* Low maternal prepregnancy weight and large interpregnancy weight losses are important risks for both preterm birth and low birthweight, and weight gain prior to pregnancy might reduce risk for these women, but this has not been tested. The complex associations of body mass index with pregnancy outcomes are described elsewhere in this supplement.<sup>18</sup>

Smoking cessation programs are effective in reducing pregnancy loss.<sup>19</sup> Interpregnancy interval can be extended by contraception; however, no interventional studies exist at present.

Incompetent cervix is identifiable in some cases by a history of painless dilatation in the previous labor. Cervical cerclage procedures prior to pregnancy have been used for many years for women with a history of multiple late midtrimester losses and appear effective when compared with the same patient's past history, but there are no randomized prospective trials.<sup>17</sup> A very large international trial compared cerclage during pregnancy plus bed rest with bed rest alone and found a small but statistically

significant reduction in delivery prior to 33 weeks and very low birthweight deliveries.<sup>20</sup> With the recognition that a short cervix found by transvaginal ultrasound during pregnancy identifies women at risk for recurrent preterm delivery, there is great interest in how to treat this group. Most evidence to date is that cervical cerclage during pregnancy is not beneficial.<sup>21</sup> However, in 1 metaanalysis, risk of preterm birth was reduced by cerclage for the subgroup of women with a singleton pregnancy, prior preterm delivery, and a short cervix by ultrasound in the current pregnancy.<sup>22</sup>

Recent studies found highly significant reductions in subsequent preterm birth if women with a previous preterm infant are treated with injections of 17-hydroxyprogesterone caproate from 16 to 36 weeks of gestation.<sup>23</sup> Additional benefits include reductions in neonatal death, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis in the progesterone-treated group. Similar benefits have been reported with daily use of vaginal suppositories of natural progesterone.<sup>24</sup> A 2005 metaanalysis of 10 trials confirmed these findings.<sup>25</sup> Use of progestational agents once labor has started is not effective. Recent evidence suggests that progesterone is of benefit to women with a shortened cervix.<sup>26</sup> 17-Hydroxyprogesterone caproate is presently available only through compounding pharmacies. It has been granted orphan drug status by the US Food and Drug Administration (FDA). An FDA panel has recommended approval for the indication of preventing preterm birth.<sup>27</sup> Progesterone suppositories are also available only through compounding pharmacists.

Dietary long-chain polyunsaturated fatty acid supplementation is discussed in the nutrition section of this supplement.<sup>18</sup> Supplementation has been found to slightly increase the mean gestational length but not with any reduction in low birthweight, preterm birth, or rate of preeclampsia.

Management of women with a history of an FGR infant includes obtaining the records of the previous pregnancy and

the infant if it survived and searching for specific neonatal and maternal conditions that may have been associated. Chronic illnesses, especially those that produce vascular disease, should be managed to optimize the mother's health before pregnancy. Maternal exposure to tobacco, alcohol, and cocaine should be eliminated if possible. Programs that reduce maternal cigarette smoking have been proven to reduce FGR births.<sup>13,15</sup> Risk for FGR decreases when women with low body mass index increase their weight between pregnancies.<sup>15</sup> Because short interpregnancy interval is associated with both preterm birth and FGR, delaying conception to allow for an interpregnancy interval of 18-24 months may be beneficial.

A portion of preterm births and FGR result from multiple births occurring after in vitro fertilization (IVF). The frequency of multiple births can be reduced by reducing the number of embryos transferred. Where FGR is associated with specific genetic syndromes, gamete donation, or IVF and preimplantation genetics may offer a solution.<sup>15</sup> Maternal periodontal disease is associated with both preterm birth and FGR, although intervention programs during pregnancy have not been consistently effective, suggesting that dental care prior to pregnancy may be necessary.

**Impact of preconception care:** Preconception care provides the opportunity to identify women at risk by determining their pregnancy history. Women with previous preterm or FGR infants should be evaluated for remediable conditions such as cervical insufficiency, cigarette smoking, and low maternal weight and chronic illness (for example, hypertension that may predispose them to another preterm or FGR delivery). Planning of pregnancies is advised to avoid short birth intervals and optimize management of maternal illness. Women with a history of preterm birth should be counseled about risk of recurrent preterm labor, the possible use of a progestational agent in the next pregnancy, and the need for early enrollment in prenatal care to make treatment possible.

**Recommendations by other groups:** The American College of Obstetricians and Gynecologists (ACOG) notes both the apparent benefits of progesterone for high-risk women and the problem of no commercial availability of 17-hydroxyprogesterone caproate. The ACOG does not make a clear recommendation to use progesterone but states that its use should be restricted to women with a documented history of spontaneous birth at < 37 weeks.<sup>28</sup>

The ACOG does not recommend preconception measures for previous FGR birth but makes detailed suggestions for screening during pregnancy and pregnancy management. Early ultrasound is advised for all women with previous FGR birth, as are subsequent ultrasounds to evaluate growth. Once FGR is diagnosed, approximately weekly fetal assessment with Doppler velocimetry, contraction stress test, biophysical profile, and nonstress testing with amniotic fluid volume assessment are recommended to reduce perinatal mortality. When tests are abnormal, daily monitoring is recommended with early delivery, despite prematurity if fetal heart rate testing and Doppler velocimetry become abnormal.<sup>29</sup>

**Recommendation.** Pregnancy history should be obtained from all reproductive-age women. Those with a history of a preterm or FGR infant should be evaluated for remediable causes to be addressed before the next pregnancy. **Strength of recommendation:** A; **quality of the evidence:** II-2.

Women with a previous spontaneous preterm birth should be informed of the potential benefit of treatment with progesterone in subsequent pregnancy. **Strength of recommendation:** A; **quality of the evidence:** I-b.

### Prior cesarean delivery

**Burden of suffering:** In the United States, cesarean delivery is the most commonly performed obstetrical procedure. Thirty percent of women undergo cesarean delivery, which is a 46% increase since 1996.<sup>30</sup> A woman considering pregnancy after a previous cesarean will be faced with deciding the mode of delivery for the next pregnancy: whether to have an

elective repeat cesarean or attempt a trial of labor (TOL). If TOL is successful, the patient can expect a faster recuperation period, shorter hospital stay, lower risk for postoperative complications (eg, bowel injury, infection, blood loss), lower risk of respiratory complications in the newborn (eg, transient tachypnea of the newborn), and higher likelihood of having a successful trial of labor in future pregnancies than a woman who undergoes elective cesarean before labor.<sup>31</sup> However, women who start a TOL may still need a cesarean during labor for failure to progress or nonreassuring fetal heart rate and are at risk for dehiscence or complete uterine rupture (incidence 1 per 200 deliveries) during labor, with expulsion of the fetus into the mother's abdomen, which may lead to death (4%) or severe disability for the infant.<sup>32,33</sup> Maternal complications of uterine rupture might include severe hemorrhage requiring blood transfusion (1 per 90 deliveries) or hysterectomy (1 per 500 deliveries).<sup>34,35</sup>

An elective repeat cesarean section prior to labor has fewer complications than the same procedure performed during labor but more than with a successful TOL.<sup>23</sup> However, multiple cesareans increase risk for later pregnancies. Rates of placenta previa have been reported to range from 0.24% in patients undergoing a first cesarean delivery to 6.74% in patients with 6 prior cesarean deliveries.<sup>36</sup> Among patients with a placenta previa, the rate of accreta can range between 3% in women with 1 prior cesarean and 61%-67% among women with 4 or more cesarean deliveries.<sup>37</sup> Placenta accreta and its more severe variations, placenta increta and percreta, can produce massive bleeding requiring emergency hysterectomy and possibly leading to death.

The decision to have a TOL or elective repeat cesarean can best be made after careful consultation with an obstetrician or other expert health care provider and is based on information about the previous cesarean, most especially the type of uterine incision (whether low transverse, low vertical, T incision, or classical) and type of repair (whether single layer or 2 layer). Every effort should be made to

obtain the official operative report for the first cesarean.

The outcome of TOL is influenced by a variety of factors:

- The type of incision. Transverse uterine incision and lower segment vertical incisions have the least risk for rupture, whereas classical vertical incisions and T incisions increase risk for rupture and are contraindications to TOL.<sup>38</sup> Rates of uterine rupture range between 4% and 9% in women with prior classical or T-shaped incisions. Lower rates have been reported in women with prior low vertical (1-7%) or low transverse incisions (0.2-1.5%).<sup>30,39,40</sup> Most studies present prior cesarean delivery as a composite variable, essentially grouping all non-transverse incisions into 1 category. Therefore, it is difficult to provide relative risks for each type of incision.
- Type of repair. Whether the incision was repaired with a single vs double-layer uterine closure may be another determinant of risk. Single-layer closures have been reported to confer a 4- to 8-fold adjusted increase in risk for uterine rupture during TOL over the risk with a conventional 2-layer uterine closure.<sup>33,41</sup> However, 4 retrospective studies and 1 case-control study with a total of 1372 patients reported no substantial differences in uterine rupture with single- vs double-layer closure.<sup>42-46</sup>
- Maternal characteristics. Maternal obesity increases risk<sup>35</sup> as does maternal age over 30 years.<sup>47</sup>
- Time since last cesarean. A short inter-delivery interval (defined as months from the previous delivery to the index delivery) increases risk. One study found this effect for interdelivery intervals of less than 24 months,<sup>48</sup> another for interdelivery intervals of less than 18 months,<sup>49</sup> and a third for interpregnancy intervals (defined as months from delivery to the subsequent conception) of less than 6 months.<sup>50</sup> These data suggest a reasonable minimal interval from delivery to the next conception to be approximately 15 months.<sup>50</sup>

- Labor initiation. Induction of labor, especially with prostaglandin E2, is associated with a substantial increase in the risk of uterine rupture.<sup>51-53</sup> Induction with misoprostol appears associated with even more risk.<sup>46</sup>
- Number of prior cesarean sections. Previous preterm cesarean delivery appears to increase risk for rupture, even when the incision was transverse.<sup>52</sup> Multiple cesarean deliveries, all with lower-segment transverse incisions, do not appear to significantly increase rate of uterine rupture during TOL compared with those with a single prior operation.<sup>53</sup>

Shipp et al<sup>54</sup> combined many of these risk factors in a simple formula to predict risk for uterine rupture during a TOL. They assigned numerical scores to the various factors: adding 2 points for 2 or more prior cesareans, 1 point for inter-delivery interval 18 months or less, 1 point for maternal age 30-39 years, and 2 points for maternal age 40 years or greater, and subtracting 1 point for a prior vaginal delivery and 1 prior cesarean. Women with the lowest score (-1) had a 0.26% risk of rupture during TOL, whereas women with scores of 0, 1, 2, 3, and 4 had uterine rupture risks of 0.25, 1.11, 2.43, 3.70, and 14.29, respectively. This work, if validated by others, may simplify discussion of risk with patients.

*How detectable is the condition?* Women are aware of whether they have undergone prior cesarean delivery but may not know the type of scar or details of the repair.

*Impact of preconception care:* A preconception visit prior to a subsequent pregnancy would allow discussion of the potential maternal and newborn risks and benefits of a TOL vs elective repeat cesarean delivery. Ideally this discussion should begin prior to discharge after the cesarean and continue at the postpartum visit and should include a description of the type of uterine incision and repair the patient just experienced.

Because uterine rupture with TOL is reduced by a delay of 18 months or more from previous cesarean, a discussion of

family-planning methods is strongly indicated. A review of potential operative morbidity with multiple cesarean deliveries and an appraisal of long-term risks of placental previa or placental accreta with multiple cesarean deliveries should also be discussed along with interventions for management and potential maternal complications.<sup>55</sup>

*Recommendations by other groups:* The ACOG issued a 2006 committee opinion on the evaluation and management of women with prior cesarean delivery, recommending that when labor induction is needed, the patient be informed of increased risk of uterine rupture and that use of misoprostol or other prostaglandins and oxytocin in sequence be avoided.<sup>51</sup>

*Recommendation.* Preconception counseling of women with prior cesarean delivery should include counseling about waiting at least 18 months before the next pregnancy and about possible modes of delivery so the patient enters the next pregnancy informed of the risks and options. Ideally the counseling should begin immediately after the cesarean and continued at postpartum visits. *Strength of recommendation: A; quality of evidence: II-2.*

### Prior miscarriage

*Burden of suffering:* There are 2 forms of spontaneous abortion to consider in the preconception period. One is sporadic pregnancy loss, which occurs at random throughout reproduction in 10-15% of clinically recognized pregnancies.<sup>56</sup> Another is recurrent abortion, which is defined as 3 or more consecutive spontaneous abortions and occurs in about 1% of fertile couples.

*How detectable is the condition?* A careful obstetric history can determine the number and gestational age of the spontaneous abortion(s). Recurrent abortion is defined as 3 or more consecutive spontaneous abortions; some recommend not including biochemical pregnancies (pregnancies with a pregnancy test and missed menses as the only manifestation) in this count.<sup>57</sup>

*How effective are the current treatments?* Patients with sporadic abortion should be reassured that the prognosis is good for future pregnancies and offered routine preconception care. Those with a loss at a gestational age greater than 14 weeks may benefit from consideration that their loss was due to preterm birth or fetal loss. Women with recurrent early pregnancy loss (RPL; < 15 weeks' gestation) should be offered a work-up including measurement of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody), parental karyotyping, and imaging of the uterus with pelvic ultrasound (sonohysterography or 3-dimensional ultrasound) or hysterosalpingogram. No recommendation can be made about thyroid testing, glucose tolerance, or luteal phase defects because data are not conclusive about their association with RPL.

No randomized controlled studies have shown any benefit from measuring infectious agents, antinuclear antibody, paternal leukocyte antigens/antipaternal antibodies, or their associated treatments and thus cannot be recommended. Those with elevated antiphospholipid antibodies may benefit from treatment with heparin and low-dose aspirin; 2 small trials found rates of spontaneous abortion reduced by 54% for treatment with both vs aspirin alone.<sup>57</sup> There is also evidence of improved blood flow on histopathologic data with these treatments.

Couples with an identified chromosomal anomaly should be offered genetic counseling and prenatal testing of the fetus in subsequent pregnancies. Preimplantation embryo testing can identify specific chromosomal abnormalities (such as translocations or specific gene defects) and may be an option for those couples with access to assisted reproductive technology. This therapy is not recommended for screening of aneuploidy or without a known genetic defect.

Those diagnosed with a uterine septum on imaging can undergo resection of the septum via hysteroscopy with reported rates of live births of 70-85% based on case series data. Similarly, removal of uterine fibroids is an option when they are identified and felt to be

contributing to RPL, such as a large submucous fibroid, which deforms the cavity. All surgical treatments are largely based on case series, so the actual treatment effect is unclear. When no cause is identified, the prognosis is still favorable.

Couples can be reassured that a successful pregnancy occurs in a next pregnancy in 50-75% of women. Although no randomized controlled studies exist, psychological support and tender loving care have been shown to improve outcomes in RPL patients.<sup>58</sup> One study demonstrated an 86% rate of successful pregnancy with specific counseling and support vs 33% with no specific care.<sup>59</sup> Another study found miscarriage rates of 26% vs 51% for those with and without supportive therapy, respectively.<sup>60</sup> Because of the noninvasive nature of this therapy, it should be offered to these patients to help them through this difficult time.

*Impact of preconception care:* Work-up for recurrent spontaneous abortion is done in the preconception period. Surgical correction of uterine anomalies such as a septum must be corrected in the preconception period. Some treatments such as heparin therapy are initiated early in pregnancy, so identification of antiphospholipid antibodies must be accomplished prior to pregnancy. Those with a loss at a gestational age greater than 14 weeks may benefit from consideration that their loss was due to preterm birth or fetal death and receive a comprehensive workup for these etiologies as discussed below.

*Recommendations by other groups:* ACOG recommends the work-up cited in previous text and treatment with heparin and aspirin in those with repeated (2 abnormal results 6-8 weeks apart) antiphospholipid antibodies. The European Society for Human Reproduction and Embryology states that treatment of antiphospholipid antibodies with aspirin or heparin requires further randomized trials, citing design issues of existing studies.<sup>60</sup> They recommend testing thyroid function and glucose intolerance based on benefits for overall fetal development and low cost. Neither group rec-

ommends routine karyotyping of abortus tissue in future pregnancies,<sup>60</sup> nor does either recommend therapy with progestational agents. Both, in addition to the American Society for Reproductive Medicine, recommend against treatment with intravenous immunoglobulin.<sup>58,61</sup>

*Recommendation.* Women with sporadic spontaneous abortion should be reassured of a low likelihood of recurrence and offered routine preconception care. Those with 3 or more early losses should be offered a work-up to identify a cause. Therapy based on the identified cause may be undertaken. For those with no identified cause, the prognosis is favorable with supportive care. *Strength of recommendation: A; quality of evidence: I-a.*

### Prior stillbirth

*Burden of suffering:* The definition of stillbirth includes the following: "death prior to the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy, and that the fetus does not breathe or show other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles."<sup>62</sup> Reporting of fetal deaths is required in most states if it involves "a fetal death of 350 g or more, or if weight is unknown, of 20 completed weeks' gestation or more."<sup>62,63</sup> The US stillbirth rate in 2003 was 6.2 stillbirths per 1000 live births and fetal deaths, equaling the number of infant deaths in the United States.<sup>62</sup> Stillbirths constitute half of all perinatal mortality and 50% have an undetermined cause of death. There is significant racial disparity in the stillbirth rate; the rate for non-Hispanic black women is more than double that of non-Hispanic white women.<sup>63</sup>

*How detectable is the condition?* Stillbirth is readily recognized at birth by the absence of any signs of life. Women generally know if they have had one. The risk of recurrent stillbirth is increased 2- to 10-fold for women with a history of prior stillbirth(s) over the risk for women with no such history.<sup>64-66</sup> The risk depends on maternal race and characteristics of the prior still-

**TABLE**  
**Estimates of maternal risk factors and risk of stillbirth**

Condition	Prevalence (%)	Estimate rate of stillbirth per 1000	Odds ratio <sup>a</sup>
All pregnancies		6.4	1.0
Low-risk pregnancies	80	4-5.5	0.86
Hypertensive disorder			
Chronic hypertension	6-10	6-25	1.5-2.7
Pregnancy-induced hypertension			
Mild	5.8-7.7	9-51	1.2-4.0
Severe	1.3-3.3	12-29	1.8-4.4
Diabetes			
Treated with diet	2.5-5	6-10	1.2-2.2
Treated with insulin	2.4	6-35	1.8-4.4
Systemic lupus erythematosus	< 1	40-150	6-20
Renal disease	< 1	15-200	2.2-30
Thyroid disorders	0.2-2	12-20	2.2-3.0
Thrombophilia	1-5	18-40	2.8-5.0
Cholestasis of pregnancy	< 0.1	12-30	1.8-4.0
Smoking > 10 cigarettes	10-20	10-15	1.7-3.0
Obesity (before pregnancy)			
BMI 25-29.9 kg/m <sup>2</sup>	21	12-15	1.9-2.7
BMI ≥ 30 kg/m <sup>2</sup>	20	13-18	2.1-2.8
Low educational attainment (< 12 y vs ≥ 12 y)	30	10-13	1.6-2.0
Previous growth-restricted infant (< 10%)	6.7	12-30	2-4.6
Previous stillbirth	0.5-1	9-20	1.4-3.2
Multiple gestations (current pregnancy)			
Twins	2.7	12	1.0-2.8
Triplets	0.14	34	2.8-3.7
Advanced maternal age (reference < 35 y)			
35-39 y	15-18	11-14	1.8-2.2
≥ 40 y	2	11-21	1.8-3.3
Black women compared with white women	15	12-14	2.0-2.2

BMI, body mass index.

Source: Fretts RC. Etiology and prevention of stillbirth. *Am J Obstet Gynecol* 2005;193:1923-35.<sup>68</sup> Used by permission.

<sup>a</sup> Odds ratio with the factor compared with the risk factor absent.

Stubblefield. *The clinical content of preconception care: reproductive history*. *Am J Obstet Gynecol* 2008.

birth, including etiology, gestational age, and the presence of fetal growth restriction. In addition, a history of stillbirth increases the risk of a range of adverse pregnancy outcomes in the subsequent pregnancy.

*How effective are the current treatments?* Present management is based on a search for risk factors during the subsequent

pregnancy, with intensive prenatal care based as much as possible on what is known of the causes of the previous stillbirth. During the preconception or initial visit, the obstetric provider obtains a detailed medical and obstetrical history; reviews the evaluation of the prior stillbirth; determines recurrence risk based on available information; and discusses

the risk of other obstetrical complications, such as placental abruption, preterm delivery, and cesarean delivery.<sup>67</sup> The Table lists common maternal factors associated with stillbirth from a recent systematic review of the medical literature.<sup>68</sup>

There is little evidence to form recommendations for the management of sub-

sequent pregnancy after stillbirth. Counseling is individualized to the patient's particular circumstances or risk factor. For example, if a couple experienced a previous second-trimester stillbirth as a result of a cystic hygroma and nonimmune hydrops caused by Turner's syndrome, they can be reassured that Turner's syndrome is a sporadic condition and is not associated with advanced maternal age. However, in the subsequent pregnancy, one can offer nuchal translucency ultrasound to provide reassurance to the couple.

First-trimester sonograms are advised for accurate dating. Although the predictive value for maternal serum screening in the first trimester is low, performing maternal serum pregnancy-associated plasma protein-A may provide some reassurance regarding the recurrent risk of stillbirth from placental causes.<sup>69</sup> If not previously performed as part of the work-up for the initial stillbirth, early diabetes screen, anticardiolipin antibodies, and thrombophilia work-up may be performed. For example, a woman with a previous stillbirth associated with fetal growth restriction or placental pathology significant for thromboses may benefit from thrombophilia testing and treatment with aspirin and heparin if thrombophilia testing is positive.<sup>70,71</sup>

In the second trimester, a fetal anatomic survey may be performed at 18-20 weeks. Similar to the first-trimester screen, the predictive value of second-trimester analytes for stillbirth (maternal serum alpha-fetoprotein [MSAFP], human chorionic gonadotropin [hCG], estriol, and inhibin-A) is poor but may provide additional information. MSAFP testing may be associated with the presence of a placental abnormality if it is elevated in a structurally normal fetus.<sup>72</sup> Likewise, an abnormally elevated B-hCG may be associated with an increased risk of stillbirth but has poor predictive value.<sup>73</sup>

Because nearly half of all stillbirths are associated with FGR, serial sonograms for fetal growth are customary, starting at 28 weeks. If there is evidence of fetal growth restriction, then the frequency of ultrasound to monitor fetal growth is increased, usually to every 2-4 weeks, and

Doppler studies and antepartum fetal testing are recommended. The ACOG technical bulletin on intrauterine growth restriction outlines management strategies.<sup>74</sup>

In all women with a previous stillbirth, maternal assessment of fetal movement or fetal kick counts may be started at 28 weeks' gestation. Antepartum fetal testing, such as twice-weekly nonstress tests and amniotic fluid index or biophysical profiles, may be initiated at 32 weeks or 1-2 weeks before the gestational age of the previous stillbirth.<sup>75</sup> Caution must be used when interpreting the antepartum fetal surveillance of a fetus of less than 32 weeks' gestation.

The delivery plan should be discussed with the couple well in advance of the third trimester. The timing of the delivery depends on maternal anxiety, cervical ripeness, and the cause of the previous stillbirth. In most cases, elective induction at 39 weeks' gestation or earlier delivery with documented fetal lung maturity may be appropriate.<sup>76</sup>

*Impact of preconception care:* Many women do not receive comprehensive counseling with regard to the cause of the stillbirth because either an incomplete evaluation was performed or because in 50% of cases with complete evaluation, the cause remains unknown. The most important preconception intervention begins with a comprehensive assessment at the time of the stillbirth and this should be undertaken in all cases. This recommendation is based on stillbirths defined as fetal deaths occurring at or after 20 weeks of gestation or more than 350 g birthweight. However, early second-trimester intrauterine fetal demise may not differ in etiology from stillbirths occurring after 20 weeks and a comprehensive evaluation as described in this section may be useful.

The single most important tests are an autopsy and pathologic examination of the placenta. If the parents refuse autopsy, they may accept a limited physical examination of the neonate by a perinatal pathologist. Postmortem magnetic resonance imaging may be useful. Cytogenetic studies are essential. The highest yield of viable cells is from an amniocen-

tesis taken after recognition of the fetal death and prior to birth.<sup>77</sup> Additional useful laboratory tests may include maternal fasting glucose, a Kleihauer-Betke test to detect fetal-maternal hemorrhage, urine toxicology, hemoglobin A<sub>1c</sub>, and a thrombophilia work-up in normally formed infants.<sup>68,78</sup>

A preconception visit to review the circumstances and work-up of the previous stillbirth is important. Review of available reports of the fetal autopsy, placental pathology, and appropriate testing is important to guide management of the subsequent pregnancy and in some cases may suggest interventions that should be undertaken prior to the next pregnancy. Because many stillborn infants have had fetal growth restriction, the interventions to prevent FGR discussed in previous text may be appropriate. Examples of possible interventions include maternal dietary supplementation with folic acid to prevent recurrence of neural tube defects, tight control of blood glucose for diabetic women to prevent other major fetal malformations, and management of other genetic conditions by preimplantation genetics and embryo selection. Because cigarette smoking is related to growth restriction and stillbirth, smoking cessation is an important preconception intervention.<sup>79</sup> Couples often experience feelings of anxiety, personal guilt, and apprehension when contemplating pregnancy after having a stillborn infant and may require additional psychosocial support.

*Recommendations by other groups:* The ACOG issued a 2007 committee opinion providing detailed suggestions for the evaluation of stillbirth at the time that it occurs. These include a detailed review of the mother's medical history; obstetric history; history of the prenatal course; physical examination of the fetus with weight, head circumference, and length; multiple photographs of the infant and placenta; placental pathology; fetal karyotype; whole-body X-ray and autopsy if possible; and documentation of findings. The findings should be communicated to the family.<sup>78</sup>

*Recommendation.* At the time of the stillbirth, a thorough investigation to de-

termine causation should be performed and communicated to the patient. At the preconception visit, women with a previous stillbirth should receive counseling about the increased risk of adverse pregnancy outcomes and may require referral for support. Any appropriate work-up to define the etiology of the previous stillbirth should be performed if not done as part of the initial work-up. Risk factors that can be modified prior to the next pregnancy should be addressed, for example, smoking cessation. *Strength of recommendation:* B; *quality of evidence:* II-2.

### Uterine anomalies

*Burden of suffering:* Two to four percent of fertile women with normal reproductive outcomes are believed to have congenital mullerian anomalies.<sup>80,81</sup> The prevalence of such anomalies in women with history of poor reproductive performance (recurrent first- and second-trimester losses) is estimated at 13%.<sup>82</sup> Prevalence rates as high as 7-8% in the general population and 25% in the recurrent pregnancy loss population have been reported in series in which minor anomalies were included (eg, minor arcuations and "hypoplastic" uteri).<sup>83</sup> It has also been estimated that a congenital uterine malformation complicates 1 in 594 pregnancies.<sup>84</sup> The most common uterine anomalies are septate (35%), bicornuate (26%), and arcuate or subseptate (18%), but these proportions may vary, depending on the specific population studied and the methodology used to ascertain the diagnosis.<sup>81</sup> The overall live birth rates in patients with mullerian anomalies are lower than average and are estimated around 60% for the bicornuate and septate uterus and 40% for the unicornuate and didelphic uterus. It is generally agreed that the rates of prematurity, growth restriction, postpartum hemorrhage, cervical incompetence, malpresentation, pregnancy-associated hypertension, dystocia, uterine rupture in labor, and cesarean deliveries are higher in patients with mullerian anomalies.

*How detectable is the condition?* Because of increased use of ultrasound and mag-

netic resonance imaging (MRI) for miscellaneous gynecological complaints, mullerian anomalies are being increasingly detected in women whose reproductive performance has not been previously tested. In women with recurrent pregnancy loss, however, the gold standard for the diagnosis and accurate classification of uterine anomalies is a hysteroqram (HSG) followed by a laparoscopy and hysteroscopy if the HSG is abnormal. More recently the use of MRI and 3-dimensional ultrasound have emerged as noninvasive alternatives for the diagnosis and classification of anomalies with a good degree of specificity and sensitivity.<sup>85,86</sup> It should also be noted that approximately 20% of women with mullerian anomalies harbor a coexistent renal or ureteral anomaly that should be ruled out with either a renal scan or intravenous pyelogram.

*How effective are the current treatments?* The literature concerning the effectiveness of treatments on reproductive outcomes in women with Mullerian anomalies is mostly observational and retrospective. In women with anomalies whose reproductive performance has not been previously tested, the course of action should be individualized and depends on the nature and complexity of the anomaly and associated gynecologic symptoms. Although there is no evidence that proactive interventions improve outcomes, most authorities favor hysteroscopic incision of a uterine septum when identified.

The best results appear to occur in women with history of recurrent pregnancy loss who have a uterine septum greater than 1 cm long. In those patients, hysteroscopic resection/incision of the septum restores a normal live birth rate of about 80-90% and reduces miscarriage rates to background levels of 15-20%.<sup>82,87,88</sup> There is anecdotal evidence that excision of coexisting vaginal septum may be beneficial in reducing risk of dystocia and cesarean delivery in subsequent pregnancies. There is no credible evidence that surgical correction of a unicornuate, bicornuate, didelphic, or T-shaped uterus improves pregnancy and live birth rates. Some individual pa-

tients, however, with bicornuate or didelphic uteri who have had repeatedly poor outcomes despite intensive obstetric management may benefit from a Strassman reunification metroplasty.<sup>89</sup>

*Impact of preconception care:* Preconceptional identification of a uterine septum usually calls for hysteroscopic resection to improve subsequent pregnancy outcomes, particularly in the recurrent loss population. Identification of a coexistent renal or ureteral anomaly should also call for heightened awareness during the next pregnancy because of an increased risk of hypertension, recurrent urinary tract infections, and urinary tract injury during cesarean. Although there is no strong evidence of overall benefit,<sup>90</sup> intensive obstetrical and sonographic surveillance of subsequent pregnancies could theoretically allow early identification of risk markers for preterm labor and incompetent cervix and deployment of interventions that may optimize fetal outcomes (eg, bed rest, progesterone use, cerclage placement, tocolysis, and steroid use). Because of a reported increase in the risks of ectopic pregnancy in women with mullerian anomalies, early pregnancy tracking by hCG levels and sonography is also warranted for early detection and noninvasive management of ectopics.<sup>91</sup>

In patients with anomalies who require assisted reproductive technologies to conceive, the overall pregnancy rates after IVF appear to be lower than in the general population, although the series are small.<sup>91</sup>

Occasional difficulties may arise during egg retrievals (because of unusual ovarian position in the pelvis) and embryo replacement (because of cervical stenosis or deformity) that require special skills to overcome. Extra care should also be taken by the IVF team to minimize the risk of multiple pregnancies because of the increased baseline risk of preterm labor.

*Recommendation.* A uterine septum in a woman with poor prior reproductive performance should be hysteroscopically corrected before the next conception. All other anomalies call for specific delineation of the anomaly and any asso-



ciated vaginal and renal malformations. Although surgical correction may be advised in some, heightened awareness and surveillance during a subsequent pregnancy and labor should help optimize outcomes. *Strength of recommendation: B; quality of evidence: II-3.*

## Conclusion

A large number of specific conditions that increase risk of preterm birth or adverse pregnancy outcome can be diagnosed based on reproductive history. Many of these can be successfully treated prior to pregnancy or early in a subsequent pregnancy to reduce risk. There is good evidence for some treatments, for example, smoking cessation and use of 17-hydroxyprogesterone caproate after previous preterm birth. Case series show the often dramatic benefit of hysteroscopic resection of uterine septa after recurrent miscarriage, and we recommend this, but there have been no randomized trials.

Placental inflammation exists in most extremely preterm deliveries and is a central problem, but intrauterine growth restriction and stillbirth are major problems that can result from many different etiologies. Reduction of risk requires a program of searching for possible causes, managing those causes, and closely monitoring the subsequent pregnancy with ultrasound and antepartum fetal heart rate monitoring. However, truly proving that such management leads to the improved outcome would require withholding care from some. This poses a very difficult ethical dilemma for investigators. Concerted application of our present knowledge should help reduce adverse pregnancy outcomes, but much more remains to be done to understand causes and develop effective therapies. ■

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