

Prediction and Prevention of Recurrent Stillbirth

Uma M. Reddy, MD, MPH

Stillbirth is one of the most common adverse pregnancy outcomes in the United States, occurring in one out of every 200 pregnancies. There is a paucity of information on the outcome of pregnancies after stillbirth. Prior stillbirth is associated with a twofold to 10-fold increased risk of stillbirth in the future pregnancy. The risk depends on the etiology of the prior stillbirth, presence of fetal growth restriction, gestational age of the prior stillbirth, and race. Categorization of the cause of the initial stillbirth will allow better estimates of individual recurrence risk and guide management. A history of stillbirth also increases the risk of other adverse pregnancy outcomes in the subsequent pregnancy such as placental abruption, cesarean delivery, preterm delivery, and low birth weight infants. Prospective studies have revealed an increased risk of stillbirth with low pregnancy-associated plasma protein A, elevated maternal serum alpha fetoprotein, abnormal uterine artery Doppler studies, and antiphospholipid antibodies. However, the positive predictive value of these factors individually is poor. Because fetal growth restriction is associated with almost half of all stillbirths, the correct diagnosis of fetal growth restriction is essential. The use of individualized or customized growth standards will improve prediction of adverse pregnancy outcome by distinguishing growth-restricted fetuses from constitutionally small, healthy fetuses. Antepartum fetal surveillance and fetal movement counting are also mainstays of poststillbirth pregnancy management.

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EPIDEMIOLOGY OF STILLBIRTH

Stillbirth is one of the most common adverse pregnancy outcomes in the United States, occurring in one out of every 200 pregnancies, which amounts to approximately 26,000 stillbirths every year (2003 data).¹ The definition of stillbirth includes the following: no signs of life present at or after birth,

Apgar scores 0/0, and at least 20 weeks of gestation. If the gestational age is unknown, a fetal death with birth weight greater than 350 g (average weight at 20 weeks of gestation) is considered a stillbirth in the United States.¹ The U.S. stillbirth rate in 2003 was 6.2 stillbirths per 1,000 live births and fetal deaths, equaling the number of infant deaths in the United States.¹ 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.¹

From the Pregnancy and Perinatology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.

Corresponding author: Uma M. Reddy MD, MPH, Pregnancy and Perinatology Branch, NICHD, NIH, 6100 Executive Blvd, Rm 4B03, MSC 7510, Bethesda, MD 20892 (express mail: Rockville, MD 20852); e-mail: reddyu@mail.nih.gov.

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PSYCHOLOGIC EFFECTS OF STILLBIRTH

Important psychologic and emotional issues arise when dealing with a pregnancy resulting in a stillbirth. Couples often experience feelings of anxiety, failure, personal guilt, and apprehension when contemplating pregnancy after having a stillborn



infant.² Many women do not receive comprehensive counseling regarding the cause of the stillbirth because an incomplete evaluation was performed, and in 50% of cases the cause remains unknown. It is difficult for clinicians to counsel, evaluate, and manage subsequent pregnancies optimally because very little is known about pregnancy outcome after a stillbirth.

RECURRENCE RISK OF STILLBIRTH

The recurrence risk for stillbirth is twofold to tenfold increased in the next pregnancy.^{3,4} Goldenberg et al⁵ evaluated the association between fetal loss in the second trimester and subsequent adverse birth outcomes. Of 95 women who had a pregnancy loss at 13–24 weeks in the index pregnancy, 39% had a preterm delivery in their next pregnancy, 5% had a stillbirth, and 6% had a neonatal death, with all outcomes worse than those found in the two control populations (previous term and previous 25- to 36-week delivery groups). There was almost a sixfold increase in the risk for stillbirth in the subsequent pregnancy for the group of women with a previous 13- to 24-week pregnancy loss compared with the term control group.

Surkan and colleagues⁶ evaluated the association between previous adverse outcomes of pregnancy and the risk of stillbirth (28 weeks of gestation or later) in the national Swedish Medical Birth Register of 410,000 deliveries. The odds ratio was 2.5 for subsequent stillbirth among women with a first stillborn infant compared with women whose first infant was not stillborn. The odds ratios for subsequent stillbirth ranged from 2.1 among women with previous live birth of a growth-restricted term infant to 5.0 among women with a live birth of a very preterm (before 32 weeks of gestation) growth-restricted infant. Previous preterm, small for gestational age (SGA) birth was clearly a more potent risk factor than previous stillbirth in the risk of stillbirth in a subsequent pregnancy. The authors speculated this difference may be attributed to heightened antepartum surveillance of women with a previous stillbirth. In fact, the decline in stillbirth rates during the past three decades coincides with the introduction of increased fetal surveillance, but it is not clear whether heightened supervision of women with previous stillbirths reduces the risk of recurrent stillbirth.

Heinonen and Kirkinen⁷ assessed subsequent pregnancy outcome in women whose stillbirth was the result of causes other than maternal conditions and fetal abnormalities. They excluded multiple gestations, structural and chromosomal abnormalities,

insulin-dependent diabetes mellitus, preeclampsia, isoimmunization, and uterine anomalies. Ninety-two deliveries after stillbirth (defined as death of fetus at more than 24 weeks of gestation or more than 500 g) were identified among 11,910 deliveries of parous women recorded in a Finnish birth registry. Stillbirth in a previous pregnancy was associated with significantly higher frequencies of the following complications in the subsequent pregnancy: placental abruption (5.4% compared with 0.7%), cesarean delivery (30.4% compared with 13.4%), preterm delivery (13% compared with 5.2%), and low birth weight infants (12% compared with 3.6%). There was no recurrence of stillbirth. The authors concluded that a history of stillbirth as a result of causes other than maternal medical conditions and fetal abnormalities confers a moderately increased risk in future pregnancies of prematurity and low birth weight. Although the overall probability of a favorable outcome is good, the history of stillbirth is an indication for more frequent surveillance because of the increased risk of adverse pregnancy outcomes.

Sharma et al⁸ studied the risk of recurrent stillbirth using the Missouri maternally linked cohort data set containing records of births from 1978 through 1997. Of 404,180 women with information on first and second pregnancies, 1,979 (0.5%) had a stillbirth in the first pregnancy, and 402,201 (99.5%) did not. Of the 1,929 cases of stillbirths in the second pregnancy, the risk of stillbirth was significantly higher in women with a history of stillbirth (22.7 per 1,000) than in women without a prior stillbirth (4.7 per 1,000). The risk of stillbirth was almost fivefold higher in women with a prior stillbirth. Analysis across racial groups revealed that whites had a lower absolute risk for stillbirth recurrence than African Americans (19.1 per 1,000 compared with 35.9 per 1,000, $P < .05$). After adjusting for potential confounders, the risk of stillbirth recurrence in African Americans was almost three times more likely than in whites. Analysis by stillbirth subtype in the second pregnancy showed that a history of stillbirth conferred a 10-fold increased risk for early stillbirth (20–28 weeks of gestation) and a 2.5-fold increased risk for late stillbirth in low-risk women.⁹

In summary, the risk of recurrent stillbirth is increased twofold to tenfold. The risk depends on maternal race and characteristics of the prior stillbirth, 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.



CLINICAL FACTORS

There is a lack of information on how clinical factors specifically influence the risk of recurrent stillbirth. However, clinical factors that have been associated with an increased risk of stillbirth overall include previous pregnancy outcomes,³⁻⁶ advanced maternal age,¹⁰ black race,¹ maternal obesity (prepregnancy

body mass index greater than 30 kg/m²),¹¹ smoking,¹² maternal medical disease,¹³ fetal growth impairment,¹⁴ postdates,¹⁵ previous cesarean delivery,¹⁶ and infertility.¹⁷ Obesity and smoking are the most modifiable risk factors for stillbirth. Women who quit smoking from their first to second pregnancy have been shown to reduce their risk of stillbirth to

Table 1. Recurrence Risk of Disorders Associated With Stillbirth

Etiology/Associated Factors With Previous Stillbirth	Evaluation	Recurrence Risk of Disorder
Congenital anomalies ¹⁹⁻²¹	Fetal autopsy	Magnitude of increased risk depends on type of congenital anomaly and diagnosis of syndrome
Placental abnormality/fetal maternal hemorrhage	Placental pathology	
Abruption ²²⁻²⁴	+Clinical history, Kleihauer-Betke or flow cytometry, urine toxicology	9-15%
Vasa previa	+Clinical history, Kleihauer-Betke or Apt test	Undetermined, likely low
Umbilical cord abnormality ^{25,26}	Umbilical cord exam, evidence of obstruction or circulatory compromise	Undetermined, recurrent umbilical cord stricture and torsion reported in literature
Genetic disease		
Aneuploidy:		Sporadic
Turner syndrome: XO ²⁷	Karyotype	Full mutation, 1% or maternal age-associated risk, whichever is greater. Either parent translocation carrier, risk is higher
Trisomy 21,18,13 ²⁷	Karyotype	25%
Autosomal recessive disorders ^{*28}	Testing for single gene disorders	
X-linked disorders ²⁸	Rett syndrome mutations	Increased in male offspring
Infection ²⁹	Autopsy, placental histology, viral/bacterial PCR based on histology. Syphilis serology, parvovirus B19 serology	Varies by pathogen
Preeclampsia ³⁰	Clinical history	14%, recurrence risk is inversely proportional to gestational age at which preeclampsia was diagnosed in index pregnancy
Fetal growth restriction ³¹	Evaluation of dating criteria, ultrasound reports, and delivery weight at best estimated gestational age	20%
Maternal conditions		
Diabetes	Hemoglobin A1C, GTT	Maternal conditions that will likely be present in subsequent pregnancies
Chronic hypertension	Clinical history	
Antiphospholipid syndrome	Lupus anticoagulant, antiphospholipid antibodies	
Thrombophilia	Factor V Leiden mutation, prothrombin mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, hyperhomocysteinemia	
Isoimmunization	Antibody screen (indirect Coomb's test)	

PCR, polymerase chain reaction; GTT, glucose tolerance test.

* List of autosomal recessive disorders appears in Box 1.



Autosomal Recessive Metabolic Disorders Known to Cause Stillbirth

Hemoglobinopathies
 α Thalassemia
Amino acid disorders
 Glutaric aciduria, type II
Peroxisomal disorders
 Zellweger syndrome
Thrombophilias
 Homozygous
 Compound heterozygous
Storage diseases
 Sialodosis
 Galactosialidosis
 Sialic acid storage disease
 Neiman Pick type AC
 I cell disease
 GMI, gangliosidosis type I
 Gaucher's disease

This table was published in Wapner RJ, Lewis D. Genetics and metabolic causes of stillbirth. Semin Perinatol 2002;26:70-4. Copyright Elsevier 2002.

the same level as nonsmokers in the second pregnancy.¹⁸

Understanding the circumstances of the previous stillbirth is important for counseling about stillbirth recurrence risk. Categorization of the cause of the previous stillbirth will allow better estimation of individual recurrence risk of the condition that is associated with stillbirth and help guide management (Table 1 and the Box "Autosomal Recessive Metabolic Disorders Known to Cause Stillbirth").¹⁹⁻³¹ For example, for women with a previous stillbirth associated with aneuploidy, the recurrence rate of aneuploidy is 1% compared with familial DiGeorge syndrome, which has a 50% recurrence risk. These recurrence risks would influence a woman's decision to undergo chorionic villus sampling or amniocentesis. For maternal medical disorders, preconception or early pregnancy intervention can improve outcome such as optimization of early glucose control in diabetes to decrease the risk of congenital anomalies and stillbirth.

PREDICTIVE MARKERS: BIOCHEMICAL MARKERS

There are minimal data on the use of biomarkers for the prediction of stillbirth in women with a prior stillbirth. The data presented in this section are for prediction of stillbirth in either high-risk populations or in the general population.

First-Trimester Screen

The first-trimester screen, consisting of nuchal translucency, pregnancy-associated plasma protein A (PAPP-A), and the β subunit human chorionic gonadotropin (β -hCG), is increasingly used throughout the United States for Down syndrome risk assessment. Pregnancy-associated plasma protein A is a protease for insulin-like growth factor (IGF) binding proteins 4 and 5. Low PAPP-A will lead to decreased free IGF. Insulin-like growth factors are crucial for regulation of fetal growth and trophoblast function. The First- and Second-Trimester Estimation of Risk (FASTER) trial demonstrated a 2.15-fold increased risk of stillbirth at greater than 24 weeks of gestation associated with first-trimester PAPP-A levels at less than the 5th percentile. However, low PAPP-A had a sensitivity of only 10.5% and predicted stillbirth in only 0.58% of cases.³²

Smith et al³³ also examined the value of PAPP-A less than the 5th percentile at 10 weeks for the risk of stillbirth, with a particular interest in stillbirth associated with placental dysfunction. Low PAPP-A was associated with a 9.2-fold increase in stillbirth from all causes and a 46-fold increased risk of stillbirth specifically due to placental dysfunction. Placental dysfunction was defined as abruption or unexplained stillbirth associated with growth restriction independent of maternal characteristics. However, low PAPP-A was not associated with nonplacental causes of stillbirth, and the PAPP-A positive predictive value, even for placental causes of stillbirth, was still relatively low, at 1.8%. Abnormal free β -hCG was not associated with stillbirth risk of any cause. The authors concluded that the risk of stillbirth after 24 weeks is determined by placental function as early as the first 10 weeks of conception.

Second-Trimester Screen

The role of second-trimester serum screening using alpha fetoprotein (AFP), hCG, unconjugated estriol, and inhibin-A in stillbirth prediction has been studied. Alpha fetoprotein is the major fetal oncotic protein and is synthesized in the fetal liver. Unexplained elevated maternal serum alpha fetoprotein (MSAFP) (in the absence of neural tube defect or ventral wall defect) has been associated with stillbirth via a defect in placentation. Waller et al³⁴ reviewed 21 studies and found a consistent association of AFP levels of 2.5 multiples of the median (MoM) or greater with stillbirth. Estimates of the relative risk of fetal death associated with elevated AFP ranged from 4.4 to 21.0. In a subsequent study, Wenstrom et al³⁵ found



that an elevated MSAFP 2.5 MoM or greater was associated with a 3.5-fold increased risk of stillbirth. Elevated β -hCG has also been associated with a 1.4-fold increased risk of stillbirth for every increase of 1 MoM.³⁶ Smith et al³⁷ demonstrated a 5.8-fold increased risk for stillbirth at 24–28 weeks for the top 1% for hCG. Lastly, low unconjugated estriol has been associated with stillbirth.³⁸

Because low PAPP-A at 10–14 weeks and an elevated AFP at 15–21 weeks are associated with an increased stillbirth risk, it would be logical to determine whether there is increased predictive value when they are combined. Smith et al³⁹ studied the prediction of low PAPP-A, 5th percentile for gestational age combined with a high AFP, top 5th percentile for gestational age. Low PAPP-A was not associated with high AFP, suggesting they reflect different aspects of placental dysfunction. The odds ratio for antepartum stillbirth for women with a high AFP was 2.5, for women with a low PAPP-A was 2.2, and for women with both a low PAPP-A and a high AFP was 36.7. Thus, women with a low PAPP-A and high AFP had a synergistic increase in stillbirth risk. However, because relatively few women will have the combination of a low PAPP-A and a high AFP, the sensitivity of this combined test is low and is not suitable for population-based screening for stillbirth. However, maternal serum levels of PAPP-A and AFP are widely used in Down syndrome risk assessment, and inevitably, this process will identify women who have the combination of both a low PAPP-A and high AFP. Women with this combination had a 32.1% risk of delivering a low birth weight neonate (less than 2,500 g), justifying close surveillance of these women.

In the FASTER trial, elevated AFP, hCG, and inhibin A at or above 2.0 MoMs, each showed a significant association with fetal death at more than 24 weeks of gestation. As the number of abnormal markers increased, the association became stronger. However, the presence of two or more abnormal markers, although strongly associated with fetal death at more than 24 weeks, was a poor predictor and does not support the use of quad screen markers for screening for stillbirth in a general population.⁴⁰

PREDICTIVE MARKERS: UTERINE ARTERY DOPPLER

During pregnancy the spiral arteries undergo a series of vascular transformations to ensure a more than 10-fold increase in the blood supply to the intervillous space. The trophoblast invades these blood vessels and replaces the endothelium and muscular layer. The spiral arteries are converted from small-diameter,

high-resistance vessels into larger-diameter vessels with low resistance and high compliance. Doppler ultrasonography provides a noninvasive method for the study of the uteroplacental circulation. In normal pregnancy, impedance to flow in the uterine arteries decreases with gestation, and histopathologic studies suggest that this is due to trophoblastic invasion of the spiral arteries and their conversion into low-resistance vessels. Preeclampsia and fetal growth restriction are associated with failure of trophoblastic invasion of the spiral arteries, and Doppler studies, in these conditions, have shown that impedance to flow in the uterine arteries is increased (Figs. 1 and 2).

Papageorgiou et al,⁴¹ in a review of findings of Doppler studies in unselected populations, found that abnormal uterine artery studies at 22–24 weeks was associated with increased rates of development of preeclampsia, fetal growth restriction, and perinatal death. In pooled analyses of four studies of the performance of Doppler screening in the prediction of fetal or perinatal death, the likelihood of fetal or perinatal death in those with an abnormal Doppler result was about 2.4 times higher than the background risk. The broad range of sensitivity (8–83%) of the test across studies could reflect the small number of cases in each study. These studies, including studies of one-stage screening tests at 23–24 weeks, suggest that increased impedance to flow in the uterine arteries is associated with increased risk for subsequent development of preeclampsia, fetal growth restriction, and perinatal death. In addition, women with normal impedance to flow in the uterine arteries constitute a group that have a low risk of developing obstetric complications related to uteroplacental insufficiency.

Smith et al⁴² studied uterine artery Doppler performed at 22–24 weeks in 30,519 women to determine the risk of placentally related stillbirth. There were 109 stillbirths, and these were subdivided into placental causes (abruption, preeclampsia, or growth restriction) or unexplained. The relative risk of placental stillbirth was increased 5.5-fold in women with a mean pulsatility index above the 90th percentile and 3.9-fold in those with bilateral notching. The relationship between a mean pulsatility index above the 90th percentile and the risk of unexplained stillbirth was weaker, and there was no association of unexplained stillbirth with bilateral notching. Because placental stillbirths occurred earlier in gestation (median 30 weeks) compared with unexplained (median 38 weeks), uterine artery Doppler was a good predictor of all causes of stillbirth up to 32 weeks (sensitivity 58% for a false-positive rate of 5%). Conversely, the



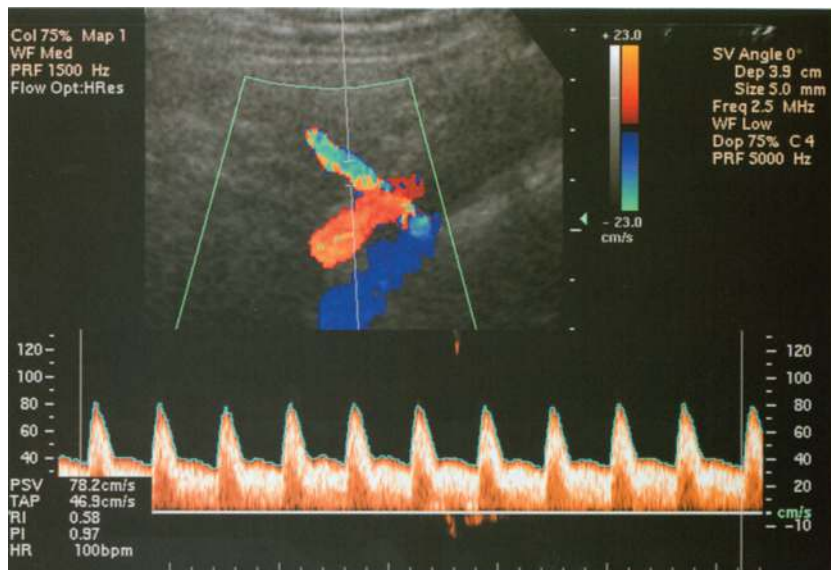


Fig. 1. The visualization of the uterine artery and its flow velocity waveform in a pregnant woman (25 weeks of gestation). Note the crossover between the uterine artery and iliac vessels. The flow velocity waveform does not have a notch. Resistance index = 0.58. This figure was published in Tekay A, Campbell S. Doppler ultrasonography in obstetrics. In: Callen PW, editor. Ultrasonography in obstetrics and gynecology. 4th ed. Philadelphia (PA): W.B. Saunders Company; 2000. p. 677–723. Copyright Elsevier 2000. Reddy. *Recurrent Stillbirth. Obstet Gynecol* 2007.

prediction of stillbirth at later gestations was poor, with a sensitivity of 7% at the same false-positive rate.

A high resistance pattern of flow in the uterine artery is associated with an increased risk of stillbirth. The association is strongest for stillbirths due to placental dysfunction and, because these occur at earlier gestations, is strongest for stillbirths occurring at extreme preterm gestations. However, uterine artery Doppler is a relatively poor predictor of unexplained stillbirth unrelated to fetal growth restriction.

PREDICTIVE MARKERS: ULTRASOUND AND FETAL GROWTH

Fetal growth restriction is the single largest category of conditions associated with stillbirth (43%) and is

found in the majority of the cases previously considered unexplained.¹³ There are no specific data on fetal growth restriction and recurrent stillbirth, so the data presented in this section deal with the occurrence of primary stillbirth. The definition of fetal growth restriction used in clinical practice differs widely: estimated fetal weight less than the 10th percentile (10% of population), estimated fetal weight more than 2 standard deviations below mean (approximately third percentile), and estimated fetal weight less than the 5th percentile.⁴³ However, fetal weight is more complex and is related to plurality, ethnicity and race, parity, fetal gender, maternal height, maternal weight, and paternal height. It has been shown that individualized or customized growth standards improve pre-

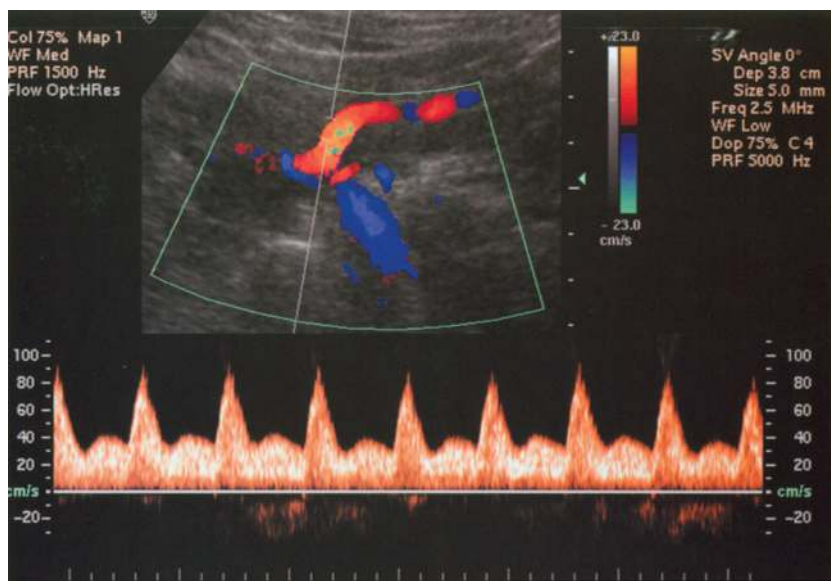


Fig. 2. Visualization of the uterine artery and its flow velocity waveform in a pregnant woman (25 weeks of gestation). The flow velocity waveform has a notch. This figure was published in Tekay A, Campbell S. Doppler ultrasonography in obstetrics. In: Callen PW, editor. Ultrasonography in obstetrics and gynecology. 4th ed. Philadelphia (PA): W.B. Saunders Company; 2000. p. 677–723. Copyright Elsevier 2000. Reddy. *Recurrent Stillbirth. Obstet Gynecol* 2007.



diction of adverse pregnancy outcome by distinguishing between fetal growth restriction and small healthy infants.⁴⁴ The use of population-based tables for weight percentiles does not account for an individual's inherent growth potential. A 6-lb infant may be appropriate for families with constitutionally small children but represents lagging fetal growth in families destined to have larger infants.⁴⁵

Claussion et al⁴⁴ performed a population-based study from Sweden comparing population based growth curves adjusted only for gestational length and fetal gender with customized growth curves, based on the prediction of optimal growth in each individual pregnancy. There was a sixfold increase in stillbirth when a fetus was SGA by customized growth charts. There was no increase in the risk of stillbirth when a fetus was SGA by population-based curves. There was also a dose-response effect, with the more profound the SGA, the greater the risk for fetal death. Use of customized growth charts reduces false positives, helping to minimize obstetric interventions on constitutionally small fetuses.

Improved antenatal detection of fetal growth restriction is crucial to having a positive impact on stillbirth prevention. In up to 75% of pregnancies, fetal growth restriction may be missed⁴³ and is incorrectly diagnosed about 50% of the time.⁴⁶ Without the correct diagnosis of fetal growth restriction, the necessary antenatal surveillance may not be performed, and timely delivery of the fetus at risk for stillbirth from an unfavorable intrauterine environment will not be effected.

Even with the correct identification of fetal growth restriction, the management of preterm fetal growth restriction is a major clinical challenge; balancing the risks of a potential stillbirth against those of an indicated preterm delivery with attendant neonatal morbidity and mortality is difficult. Based on the literature, Doppler velocimetry is useful in pregnancies complicated by fetal growth restriction with improved management and timing of delivery of preterm fetuses. There is a natural progression of findings in Doppler studies in fetal growth restriction. Initially, there are abnormal umbilical artery Doppler studies reflecting increased resistance in placental vessels. Absence or reversal of end diastolic velocities in the umbilical artery represents further deterioration. Subsequently, there is blood flow redistribution resulting in "brain sparing," which is reflected in abnormal middle cerebral artery Doppler studies. With further deterioration, there is cardiac failure with retrograde flow in the venous circulation resulting in abnormal venous Doppler studies. The final

steps manifest in central nervous system damage with abnormal antenatal testing (nonstress test or biophysical profile) and then fetal death.

Multiple randomized control trials and meta-analyses of Doppler studies demonstrate a reduction of perinatal mortality by 38% and reduction in cesarean deliveries for fetal distress.⁴⁷ Therefore, Doppler studies should be used in conjunction with other tests of fetal well-being in the management and timing of delivery in preterm fetal growth restriction. Early recognition of fetal growth restriction is likely a prerequisite to the prevention of some stillbirths, but the optimal clinical approach to the compromised, very preterm fetus with growth restriction remains unclear.

ANTIPHOSPHOLIPID ANTIBODIES

Antiphospholipid antibodies are a heterogeneous group of autoantibodies that recognize epitopes expressed by negatively charged phospholipids, proteins, or a protein-phospholipid complex. The best characterized antiphospholipid antibodies are lupus anticoagulant and anticardiolipin antibodies. These antibodies cause anticoagulation in vitro and thrombosis in vivo. Lupus anticoagulant is detected by phospholipid-dependent clotting tests: activated partial thromboplastin time, dilute Russell viper venom time, Kaolin clotting time, and plasma clotting time. Anticardiolipin antibodies immunoglobulin (Ig)G, medium or high positive titers (more than 20 IgG binding units) or IgM (more than 20 IgM binding units), or positive lupus anticoagulant are considered significant, and along with prior fetal death are criteria to diagnose antiphospholipid syndrome.⁴⁸ Prospective cohort studies indicate there is an increased risk of fetal death in unselected women, as well as in high-risk populations with antiphospholipid antibodies.⁴⁹⁻⁵¹

PREVENTION: ANTEPARTUM TESTING

The history of stillbirth has been recognized as an important risk factor for adverse pregnancy outcome, and these patients usually undergo antepartum testing.⁵² There is a paucity of evidence on the optimal time to start antepartum testing. Weeks et al⁵³ reviewed the antepartum testing database over a 12-year period, involving 70,000 tests on 15,000 patients. Three hundred healthy women with previous stillbirth were identified. Fetal testing in the subsequent pregnancy was studied. In the 300 women with a previous stillbirth, there was one recurrent stillbirth and there were no neonatal deaths, for a perinatal mortality rate of 3.3 per 1,000, less than half the general



U.S. rate for stillbirth of 7.5 per 1,000 at the time. However, one fetal death occurred despite normal antepartum testing, suggesting that in some instances fetal death cannot be predicted despite close antepartum surveillance.

Antenatal fetal surveillance is gestational-age dependent. At 28 weeks of gestation, only approximately 60% of normal fetuses will have reactive nonstress testing. This is not a result of uteroplacental insufficiency but reflects the immature fetal autonomic nervous system. In the study by Weeks et al,⁵³ 13.6% of deliveries were performed after abnormal or positive test results. Women with earlier prior stillbirths (32 weeks or less) had more antepartum testing and more abnormal tests, but the incidences of intervention for an abnormal test, cesarean delivery for fetal distress, and fetal growth restriction were similar to those in whom the prior stillbirth occurred at 36 weeks or later. Therefore, the authors concluded that there was no relationship between the gestational age of the previous stillbirth and abnormal antepartum testing in subsequent pregnancies. The authors proposed initiating antepartum surveillance at 32 weeks or later, acknowledging that a rare patient with earlier fetal compromise may be missed. However, starting at 32 weeks or later will significantly diminish the need for repeated backup testing and the attendant increase in patient and physician anxiety. The American College of Obstetricians and Gynecologists (ACOG) supports this conclusion and states that starting antepartum testing at 32–34 weeks is appropriate in healthy pregnant women with a history of stillbirth. However, in pregnancies with multiple or particularly worrisome high-risk conditions (eg, chronic hypertension with suspected intrauterine growth restriction), testing may begin as early as 26–28 weeks of gestation.⁵⁴

It is customary to recommend that patients with prior stillbirth be instructed on fetal movement assessment, with patients who report decreased fetal movement undergoing follow-up fetal surveillance. Because stillbirths may be preceded by a reduction or cessation of fetal movements, recognition of decreased fetal movement, followed by action to confirm fetal compromise and expedite delivery, may prevent such deaths. This observation is the rationale for fetal movement assessment by the mother (“kick counts”) as a means of antepartum fetal surveillance. Reviews of stillbirth indicate that nearly half occur in low-risk pregnant women with structurally normal fetuses, pregnancies that are not candidates for traditional antepartum testing.⁵⁵

The efficacy of fetal movement counting to prevent stillbirth in the general population is controversial. Moore and Piacquadio⁵⁵ conducted a prospective

evaluation of the effectiveness of a fetal movement screening program in reducing the fetal mortality rate. During a 7-month control period when no formal fetal movement assessment was done, the fetal mortality rate was 8.7 per 1,000 births. During the study period, subjects were instructed to perform fetal movement counts. Patients who experienced fewer than 10 fetal movements over 2 hours were instructed to report to labor and delivery for further evaluation. The fetal mortality rate was 2.1 per 1,000 ($P<.01$) during the study period. The authors concluded that the count-to-ten fetal movement screening program is simple and effective in reducing the stillbirth rate.

Two randomized trials have studied the role of fetal movement counting in decreasing the stillbirth rate. The first was a prospective trial conducted in a mixed-risk population of 3,111 Danish women who, after 32 weeks of gestation, were randomly assigned to an experimental (counting) group or a control group. Women in the experimental group were asked to count fetal movements for 1 hour three times a week and to contact their hospital immediately if they detected fewer movements than their previously established baseline. Women in the control group were given no special fetal movement assessment instructions but were asked about fetal movement at their prenatal visits. Of the 1,562 women in the counting group, three experienced stillbirths of normally formed infants weighing more than 1,500 g compared with 12 stillbirths among the 1,549 women in the control group ($P<.05$). The authors concluded that fetal movement probably reflects fetal well-being and that all women should be taught to count fetal movement after 32 weeks of pregnancy.⁵⁶

The second study to evaluate fetal movement randomized 68,000 women at 28–32 weeks of gestation regardless of risk category to a counting policy in which normal fetal movement was defined as the perception of 10 movements within 10 hours or to routine care in which no special counting policies were employed. Women in the counting group with fewer than 10 movements in 10 hours for two successive days were instructed to alert their care provider, at whose discretion further evaluation was undertaken. Overall fetal death rates were low in this trial and did not differ significantly between the two groups (2.9 per 1,000 in the counting group compared with 2.7 per 1,000 in the control group). The authors concluded that routine fetal movement counting, followed by appropriate action when movements are reduced, seems to offer no advantage over informal inquiry about movements during standard antenatal



care and selective use of formal counting in high-risk women.⁵⁷

Despite the lack of conclusive evidence that fetal movement counting is an effective independent surveillance technique for predicting stillbirth in the low-risk obstetric population, most clinicians recommend that women with a previous stillbirth monitor fetal movement. The recommendation that all women with a prior stillbirth should be instructed to begin fetal movement assessment at 26–28 weeks of gestation and that those who report decreased fetal movement should have follow-up fetal surveillance⁵³ appears reasonable. Most women are compliant when they understand the rationale for fetal movement counting and are informed that the procedure usually requires no more than 1 or 2 hours per day. Continued encouragement by a consistent health care professional yields the best compliance. Research is urgently needed to understand the performance of fetal movement counting to optimize its benefits in reducing fetal mortality in high-risk and general obstetric populations.⁵⁸

THERAPY FOR PREVENTION OF RECURRENT STILLBIRTH

Improved treatment of maternal medical disorders such as diabetes and hypertension decreases the risk of stillbirth in these situations. The risk of stillbirth associated with antiphospholipid antibody syndrome is likely to be decreased with treatment with prophylactic heparin or low molecular weight heparin and low-dose aspirin.⁴⁸

Thrombophilia

Heritable coagulopathies or thrombophilias, involving deficiencies or abnormalities in anticoagulant proteins or an increase in procoagulant proteins, similar to antiphospholipid syndrome, have been associated with an increased risk of vascular thrombosis and stillbirth. Case series and retrospective studies have reported an increased stillbirth risk associated with factor V Leiden mutation, the G20210A mutation in the promoter of the prothrombin gene, and deficiencies of the anticoagulant proteins antithrombin III, protein C, and protein S. The prevalence of a particular thrombophilia in the general population varies greatly and depends on race and ethnicity (Table 2).⁵⁹

Thrombophilias have been associated with a 3.6-fold increased risk of stillbirth.⁶⁰ In most studies, thrombophilias are more strongly associated with losses after 10 weeks of gestation than with early pregnancy losses. In a recent meta-analysis of 31

Table 2. Prevalence of Hereditary Thrombophilia in the General Population

Thrombophilia	Prevalence (%)
Factor V Leiden mutation	5–9*
Prothrombin mutation G20210A	2–4
Protein C deficiency	0.2–0.5
Protein S deficiency	0.08
Antithrombin III deficiency	0.02–0.2
Hyperhomocystinemia	1–11

* For African Americans, about 1%; for whites, 6–11%.

Adapted from American College of Obstetricians and Gynecologists. Thromboembolism in pregnancy. ACOG Practice Bulletin 19. Washington (DC): ACOG; 2000. Data from Lockwood CJ. Heritable coagulopathies in pregnancy. *Obstet Gynecol Surv* 1999;54:754–65.

studies, factor V Leiden mutation was associated with late nonrecurrent fetal loss (odds ratio [OR] 3.26, 95% confidence interval [CI] 1.82–5.83). Prothrombin G20210A gene mutation (OR 2.30, 95% CI 1.09–4.87) and protein S deficiency (OR 7.39, 95% CI 1.28–42.63) were also associated with late nonrecurrent fetal loss. The range of gestational ages included as late nonrecurrent fetal loss varied between studies. Methylenetetrahydrofolate mutation associated with hyperhomocystinemia, protein C deficiency, and antithrombin III deficiency was not associated with pregnancy loss in this meta-analysis.⁶¹ Alfirevic et al⁶² performed a systematic review of the relationship between maternal thrombophilia and unexplained stillbirth, defined as unexplained fetal loss after 20 weeks. In his pooled analysis of five studies, factor V Leiden, protein S deficiency, and activated protein C resistance were significantly associated with stillbirth.

The occurrence of thrombophilia and fetal death is different from thrombophilia alone. It is important to be cautious when attributing fetal death to thrombophilias in women who test positive for these conditions. These conditions are extremely common in normal individuals, and prospective studies have failed to demonstrate an association between the factor V Leiden mutation and fetal death.⁶³ Thrombophilia is more likely to contribute to a fetal death if there is objective evidence of placental insufficiency such as fetal growth restriction, placental infarction, or abnormal Doppler velocimetry.

Clinicians are often faced with the difficult clinical situation of what to do with a woman with a previous adverse pregnancy outcome, such as stillbirth, who has tested positive for a thrombophilia. Gris and colleagues⁶⁴ performed a small multicenter randomized controlled trial of 160 women with one prior pregnancy loss at more than 10 weeks and thrombophilia (factor V Leiden, prothrombin mutation, or protein S deficiency).



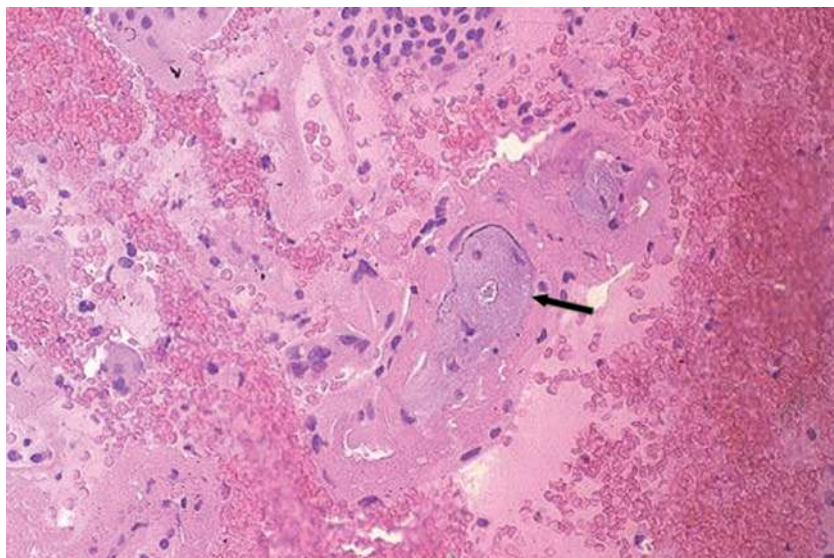


Fig. 3. Thrombosed placental vessel in a patient with antiphospholipid antibody syndrome. Thrombosis of placental vessel indicated by arrow. Slide is courtesy of Dr. Robert Silver.

Reddy. *Recurrent Stillbirth*. *Obstet Gynecol* 2007.

All women received 5 mg folic acid daily preconception and were randomized to low-dose aspirin (100 mg daily) or enoxaparin (40 mg daily at 8 weeks). The use of enoxaparin, a low molecular weight heparin, was associated with a significantly improved odds ratio for live birth (15.5), 86% live birth rate in the enoxaparin group compared with 29% for the low-dose aspirin group. The improvement in live birth rates with enoxaparin was similar for each thrombophilia. Lower birth weight occurred in the low-dose aspirin group. Although promising, there is an urgent need for larger studies to determine whether thromboprophylaxis with low molecular weight heparin improves fetal outcome in women with previous unexplained stillbirth who test positive for thrombophilia.

Aspirin Therapy

There has been interest in the use of low-dose aspirin in improving the outcome of subsequent pregnancies after fetal death. Low-dose aspirin is an antiplatelet agent that irreversibly inhibits platelet cyclo-oxygenase and thus decreases the production of thromboxane A₂, a potent vasoconstrictor. Low-dose aspirin was first used to treat recurrent pregnancy loss in women with antiphospholipid syndrome. Aspirin use was prompted by the recognition that thrombosis was central to the pathophysiology of antiphospholipid syndrome (Fig. 3).

There is a paucity of information on the use of low-dose aspirin for prevention of stillbirth. Two studies shed light on the possible impact of aspirin therapy, but recurrence of stillbirth was not the focus of either study. Rai et al⁶⁵ assessed the effect of low-dose aspirin (75 mg daily) on pregnancy outcome in women with recurrent pregnancy loss in a nonran-

domized study. Of 250 women with a history of at least one late pregnancy loss at more than 13 weeks of gestation and negative testing for lupus anticoagulant and anticardiolipin antibodies, there was almost a twofold increase in live births for those taking low-dose aspirin. Frias et al⁶⁶ had similar findings in an uncontrolled retrospective cohort of 230 women with previous unexplained fetal death, defined as intrauterine demise of a conceptus known to be alive at or beyond 10 weeks of gestation. Women with antiphospholipid syndrome were excluded from the study. In univariate analysis, low-dose aspirin was associated with an OR of 0.41 (95% CI 0.25–0.68) for subsequent pregnancy loss. After controlling for confounders in a multivariate analysis, low-dose aspirin was associated with an OR of 0.12 (95% CI 0.05–0.32) in women 35 years of age or older. The authors speculated that low-dose aspirin may improve the uteroplacental circulation, decreasing the risk of placental thrombosis, infarction, and insufficiency that have been associated with fetal death.

Both of the above studies suggest that low-dose aspirin may have a role in improving subsequent pregnancy outcome. However, because the majority of previous second-trimester fetal deaths were at less than 20 weeks of gestation and there was an increased proportion of women with recurrent pregnancy loss in these studies, these results may not be directly applicable to women who have experienced a stillbirth that occurs at 20 weeks of gestation or later. More research is necessary to determine if low-dose aspirin administration in women with a previous stillbirth improves pregnancy outcome.



MANAGEMENT OF THE SUBSEQUENT PREGNANCY

There is little evidence to inform recommendations for the management of subsequent pregnancy after stillbirth. During the preconception or initial visit, the obstetric provider should obtain a detailed medical and obstetric history, review the evaluation of the prior stillbirth, determine recurrence risk based on available information, and discuss the risk of other obstetric complications such as placental abruption, preterm delivery, and cesarean delivery. Counseling should be individualized to the patient's particular circumstances. For example, if a couple experienced a previous second-trimester stillbirth as a result of a cystic hygroma and nonimmune hydrops due to 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 ultrasonography to provide reassurance to the couple.

First-trimester sonogram should be performed for accurate dating. Although the predictive value for maternal serum screening in first trimester is low, performing maternal serum PAPP-A may provide some reassurance regarding the recurrence risk of stillbirth from "placental causes." If not previously performed as part of the workup for the initial stillbirth, early diabetes screen,⁶⁷ anticardiolipin antibodies, and thrombophilia workup may be performed.⁶⁸ 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.⁶⁸

In the second trimester, 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 (MSAFP, hCG, estriol, and inhibin-A) is poor but may provide additional information. Maternal serum alpha fetoprotein testing may be associated with the presence of a placental abnormality if it is elevated in a chromosomally normal fetus. Likewise, an abnormally elevated β -hCG may be associated with an increased risk of stillbirth but has poor predictive value. Women with a prior stillbirth will already be counseled and monitored clinically based on their previous history of stillbirth. Although there is no evidence to support further alteration in the management plan based on abnormal serum screening, the clinician may consider increasing the frequency of antepartum surveillance.

Management of Subsequent Pregnancy After Stillbirth

- Preconception or initial prenatal visit
 - Detailed medical and obstetric history
 - Evaluation/workup of previous stillbirth
 - Determination of recurrence risk
 - Discussion of increased risk of other obstetric complications
 - Smoking cessation
 - Weight loss in obese women
 - Genetic counseling if family genetic condition exists
 - Support and reassurance
- First trimester
 - Dating ultrasonography by crown-rump length
 - First-trimester screen: PAPP-A, hCG, and nuchal translucency*
 - Diabetes screen
 - Antiphospholipid antibodies
 - Thrombophilia workup depending on previous pregnancy circumstances
 - Support and reassurance
- Second trimester
 - Fetal anatomic survey at 18–20 weeks
 - Quadruple screen: MSAFP, hCG, estriol, and inhibin-A*
 - Uterine artery Doppler studies at 22–24 weeks*
 - Support and reassurance
- Third trimester
 - Serial ultrasonographies to rule out fetal growth restriction, starting at 28 weeks
 - Fetal movement counting starting at 28 weeks
 - Antepartum fetal surveillance starting at 32 weeks or 1–2 weeks earlier prior to gestational age of previous stillbirth as clinically appropriate.
 - Support and reassurance
- Delivery
 - Elective induction at 39 weeks or before 39 weeks if desired by the couple and fetal lung maturity documented by amniocentesis

PAPP-A, pregnancy-associated plasma protein A; hCG, human chorionic gonadotropin; MSAFP, maternal serum alpha fetoprotein.

** Provides risk modification but does not alter management.*

Because nearly half of all stillbirths are associated with fetal growth restriction, serial sonograms for fetal growth should be performed, starting at 28 weeks. If there is evidence of fetal growth restriction, then the frequency of ultrasonography to monitor fetal growth should be increased, usually to every 2–4 weeks, and Doppler studies and antepartum fetal testing per-



formed. The ACOG technical bulletin on intrauterine growth restriction outlines management strategies.⁴⁶

In all women with a previous stillbirth, maternal assessment of fetal movement or fetal kick counts may be started at 28 weeks of 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 as clinically appropriate. Caution must be used when interpreting the antepartum fetal surveillance of a fetus at less than 32 weeks of 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 of gestation or earlier delivery with documented fetal lung maturity may be appropriate.

Stillbirth is a tragedy for the mother, the family, and obstetrician. Management of subsequent pregnancy after a couple has experienced a stillbirth is difficult for both the clinician and the couple. There is a clear need for research into improved prediction and management of subsequent pregnancy after stillbirth. The tendency for adverse pregnancy outcomes to be repeated in successive births is well known, and the risk of stillbirth is estimated to increase by a factor of 2–10 among women with a prior stillbirth. As discussed in this paper, there is limited information to support each step of the management schema outlined in the Box “Management of Subsequent Pregnancy After Stillbirth.” The key for the clinician is to understand clearly the circumstances of the previous stillbirth, individualize management of the subsequent pregnancy, be vigilant in monitoring for the development of pregnancy complications, and provide support and reassurance to a couple likely to be anxious during their next pregnancy.

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