Intrauterine fetal death

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INTRODUCTION — The majority of clinically recognized pregnancies have no complications and result in the birth of a healthy child. However, 15 to 20 percent tragically end in loss [1]. These embryonic and fetal losses are devastating for expectant parents at any stage of pregnancy.

The incidence, etiology, and evaluation of second and third trimester fetal death will be discussed here. Early pregnancy loss is reviewed separately. (See "Cytogenetic abnormalities in the embryo; fetus; and infant-I" and see "Spontaneous abortion").

DEFINITION — A fetal death is defined by the World Health Organization as death prior to birth (ie, expulsion or extraction of the baby from the mother) at any gestational age. The standardized definition for fetal mortality used by the United States National Center for Health Statistics (NCHS) is similar and adds that stillbirth is indicated by the absence of breathing, heart beats, pulsation of the umbilical cord, or definite movements of voluntary muscles [2]. Transient cardiac contractions and fleeting respiratory efforts or gasps are not considered signs of life. Induced abortions should be excluded unless performed to deliver an in utero fetal demise. (See "Perinatal mortality: definitions and causes").

The interpretation of comparative stillbirth data is complicated because certain states and other nations often use different criteria for reporting fetal death (eg, fetal death ≥16 weeks of gestation, fetal death ≥28 weeks of gestation, stillbirth weight ≥350 grams, stillbirth weight ≥500 grams). These differences can account for 14 to 40 percent of the variation in reported perinatal mortality rates [3]. In addition, some authors distinguish between early (less than 20 weeks), intermediate (20 to 27 weeks), and late (28 or more weeks) fetal deaths.

INCIDENCE — The most recent NCHS data available show a fetal mortality rate of 6.6 per 1000 births in 2000 [4]; approximately one-half of these deaths occurred in the third trimester. A review of a March of Dimes database of 34,350 births with careful attention to determination of gestational age and data collection found a 1.2 percent incidence of stillbirth [5]. The incidence after 20 weeks, after 28 weeks, and at term was 1/100, 1/250, and 1/500 births, respectively.

Unexplained fetal death (defined as an antepartum death unexpected by history and with no demonstrable cause after thorough autopsy and histopathological examination [6]) occurred in one in 730 pregnancies at term in a study from North East Thames [7]. By comparison, the risk of stillbirth at term from any cause was one in 529 pregnancies during the same period (1989 to 1991).

The incidence of fetal death varies according to maternal race. The rate is higher in black compared to white women (12.5 versus 5.8 per 1000 births, respectively, in the United States) [4]. Although all racial groups in the United States have been experiencing a decrease in fetal death rate, the fall has been greater in whites than blacks (30 versus 16 percent between 1980 and 1998) [4,8].

DEMOGRAPHIC FACTORS — Several maternal demographic factors are associated with an increased risk of intrauterine fetal demise. In one large multicenter study, a higher rate of fetal death compared to controls was observed for age ≥35 years (odds ratio 3.5), weight ≥85 kg (187 pounds) (OR 2.1), black race (OR 1.6), single marital status (OR 1.6), and smokers (OR 1.5) [5]. These demographic risk factors are further illustrated by the following examples:

- Advanced maternal age is a risk factor for stillbirth, even after excluding coexisting medical conditions [9,10]. As an example, one study of pregnancy outcomes in women aged 35 to 40 years found a 1.4-fold increase in stillbirth compared to younger women; the increase was 2.4-fold higher in women over age 40 [9]. The same authors noted no increased risk of fetal mortality in women less than 18 years of age [11], although others have found an association [1]. In another report, older women had a significantly higher risk for unexplained fetal death [12]. (See "Effect of advanced age on fertility and pregnancy in women").

- The relationship of prepregnancy body-mass-index (BMI) to late fetal death was examined in a population-based cohort of 167,750 Swedish women [13]. Among nulliparous women, the odds ratios for late fetal death increased threefold among women with BMI values 25 to 29.9 and fourfold in women with BMI ≥30 as compared to lean women. The mechanism(s) for this association is not known.

- The fetal death rate in single women is twice as high as in married women (11.4 versus 6.0 per 1000 births) [14]. The higher stillbirth rate among unmarried women may be more closely related to a relatively disadvantaged status than to their marital state. Unmarried mothers, for example, are more likely to be black and have poorer socioeconomic situations and inadequate prenatal care compared to married women [15].

Smoking is associated with several adverse pregnancy outcomes, including stillbirth, abruption, and fetal growth restriction [14,16]. (See "Smoking and pregnancy"). High parity, long interpregnancy interval, and years of maternal education are other purported risk factors for fetal death in some [14,17-20], but not all, studies [5]. (See "Interpregnancy interval and pregnancy outcome").

ETIOLOGY — Causes of fetal death are typically categorized according to the compartment primarily responsible for the pathologic process:

- Fetal (Table 1)
- Maternal (Table 2)
- Placental (Table 3)

Fetal Risk Factors For Fetal Death

Congenital anomaly
Chromosomal abnormalities
Infection
Fetomaternal hemorrhage
Hemoglobinopathy
Erythroblastosis fetalis
Fetal growth restriction
Postmaturity
Nonimmune hydrops
Coagulation disorder
Male sex
Oligohydramnios

Table 1

Maternal Risk Factors For Fetal Death

Antiphospholipid antibody syndrome
Isoimmunization
Hypertensive disease
Vascular disease
Infection
Insulin requiring diabetes mellitus
Cholestasis
Chronic renal disease
Substance abuse
Cyanotic heart disease
Severe anemia

Table 2

Placental And Umbilical Cord Causes of Fetal Death

Abruptio placentae
Umbilical cord accident
Twin-twin transfusion syndrome
Uteroplacental insufficiency
Chronic villitis
Maternal floor infarction
Massive chorionic intervillositis

Table 3

The process may be acute (eg, abruption, umbilical cord compression), subacute (eg, infection, fetomaternal hemorrhage), or chronic (eg, uteroplacental insufficiency) [21-24]. Some disorders cause death directly (eg, infection), while others are indirectly related to the fetal demise (eg, fetal growth restriction).

The types and frequencies of disorders responsible for fetal death in a series of 66 carefully examined, consecutive stillbirths are shown in Table 4 [25]. By comparison, the frequencies of disorders causing

fetal death reported in the literature are highly variable because of differences in the populations studied. Many of these etiologies are also interdependent, for example, uteroplacental insufficiency is related to maternal hypertension and fetal growth restriction.

Causes Of Fetal Death From A Series of Sixty-six Consecutive Cases†

Cause	Frequency (percent)
Infection	15.2
Congenital anomalies	10.6
Preeclampsia	9.1
Fetal growth restriction	7.6
Umbilical cord complication	7.6
Fetomaternal transfusion	6.1
Nonimmune hydrops	6.1
Abruption placentae	4.5
Asphyxia during labor	4.5
Twin to twin transfusion	4.5
Coagulation disorders	4.5
Isoimmunization	1.5
Uterine rupture	1.5
Antiphospholipid syndrome	1.5
Postdates	1.5
Sjogren's syndrome	
Unexplained	12.1

†Adapted from data in Ahlenius, I, Floberg, J, Thomassen, P. Acta Obstet Gynecol Scand 1995; 74:115.

Table 4

The major pathologic processes that cause fetal death are uteroplacental insufficiency leading to fetal asphyxia [26,27], chromosomal and congenital abnormalities [28], antepartum hemorrhage [29], and infection [30,31].

Intrauterine asphyxia — Acute or chronic intrauterine asphyxia is the final common pathway for most causes of fetal death. In one series of 765 stillbirths, hypoxia accounted for 43 percent of deaths; the remainder were due to antepartum hemorrhage, congenital anomalies, diabetes mellitus, trauma, or unclassified/miscellaneous [29]. The subgroups and frequencies of hypoxia-related fetal death were fetal growth restriction (26 percent), cord accidents (18 percent), maternal hypertension (17 percent), placental insufficiency (17 percent), postmaturity (13 percent), and other (13 percent). (See "Clinical features and prognosis of preeclampsia-I", see "Definition; classification; and etiology of fetal growth restriction", and see "Inherited thrombophilias in pregnancy-I").

Uteroplacental insufficiency — Chronic maternal underperfusion of fetal villi often results in a small (eg, placental weight <10th percentile) ischemic placenta. The villi become smaller and smaller as ischemia progresses and numerous large syncytial trophoblastic knots develop. Chronic underperfusion ultimately results in placental infarcts, which are clinically severe (eg, associated with fetal growth restriction or stillbirth) if 20 percent or more of the placenta is affected. These findings can occur with maternal hypertensive disorders, cardiovascular disease, and hereditary and acquired thrombophilias. The relationship between early and late pregnancy loss and a maternal prothrombotic state is actively under investigation [32-35]. (See "Inherited thrombophilias in pregnancy-I").

Umbilical cord complications — These are common causes of fetal demise in the third trimester [22,36,37] because they are mostly unpredictable and unpreventable.

- **Knots —** In one study, the incidence of umbilical cord knots was 1 percent [38]. The fetal mortality rate was higher in cords with a knot compared to knot-free cords, 2.7 versus 0.5 percent, respectively [38]. Although a knot is present, it is not necessarily the cause of fetal death. Further evaluation is usually warranted.

- **Nuchal cords —** The presence of a nuchal cord antepartum is often transient [39]; nevertheless, nuchal cords are associated with increased risk to the fetus [40]. One series found that single nuchal cords were present in one quarter of deliveries and multiple nuchal cords were present in 3.7 percent [41]. An increase in blood flow resistance has been noted with even a single nuchal coil, oxygen saturation of umbilical cord blood can be altered, and a persistent nuchal cord can be associated with reduction in the middle cerebral artery S/D ratio (suggesting redistribution of blood flow to the brain) [39,41]. As a result, nuchal cords can be associated with fetal distress in labor, passage of meconium, growth restriction, and lower Apgar scores [42], although most fetuses with a nuchal cord are not severely stressed [39].

It is important to note, however, that the mere presence of one or multiple coils is rarely associated with fetal mortality [40,43]. An

important distinction should be made between the types of coiling (ie, type A or B) to assess the degree of risk. A type A encirclement can undo itself, as the placental insertion end crosses over the umbilical insertion end. By comparison, in a type B coil the placental end crosses under the umbilical end, and it therefore becomes locked [44]. It is thought that type B encirclements, therefore, are the ones that increase the risk of fetal mortality.

- **Insertion abnormalities** — Insertion abnormalities such as marginal insertion and velamentous insertion can also cause fetal death. Marginal insertions, which occur in 5 to 7 percent of pregnancies, appear more prone to vessel rupture or compression, thereby resulting in fetal demise [45,46]. Velamentous cord insertions, which occur in approximately 1 percent of singleton births, are susceptible to folding and torsion of umbilical vessels; those that traverse the internal cervical os are prone to rupture and infection [22].

- **Prolapse** — Umbilical cord prolapse can result in fetal death from compression of the cord between the fetus and uterus or maternal pelvis. It is most common during labor and in women with preterm premature rupture of membranes. (See "Umbilical cord prolapse").

- **Constriction** — Umbilical cord constriction has been implicated as a rare cause of fetal death [22,47-50]. The major pathological features are an extremely narrow segment at the fetal end of the cord (rarely the placental end) with absence of Wharton's jelly, stenosis, torsion, intravascular cord thrombosis, or obliteration of cord vessels [22,47].

Antiphospholipid antibody syndrome — The presence of maternal antiphospholipid antibodies has been linked to recurrent first trimester abortions and fetal demise (usually occurring in the early second trimester) [51]. Some, but not all, studies suggest that women with antiphospholipid antibodies and systemic lupus erythematosus and/or history of fetal loss, as well as those with specific types of antiphospholipid antibodies, may be at an increased risk for adverse obstetrical outcomes. The mechanism is unclear; direct cytotoxic effects, vasculopathy, and placental thrombosis may all play a role.

(See "Clinical manifestations and diagnosis of the antiphospholipid antibody syndrome in pregnancy").

Chromosomal abnormalities — Abnormal fetal karyotypes are associated with fetal loss at all stages of pregnancy. In one series, for example, karyotyping of a combined group of 823 stillbirths and neonatal deaths found a major chromosomal abnormality in 6.3 percent [28]. The frequency of abnormal karyotype in macerated stillbirths, nonmacerated stillbirths, and neonatal deaths was approximately 12, 4, and 6 percent, respectively. The abnormalities reported were mostly comprised of trisomies 18, 13, and 21; sex chromosome aneuploidy; and unbalanced translocations. The frequency of chromosomal abnormality in this combined group was approximately 10-fold higher than that observed in live births (0.7 percent). (See "Cytogenetic abnormalities in the embryo; fetus; and infant-I").

The rate of karyotypic abnormalities is increased in the following situations:

- Fetal deaths at earlier gestational ages. The prevalence of chromosomal abnormalities in clinically recognized first trimester losses appears to be in the range of 60 to 90 percent and is strongly correlated with maternal age [52-55]. The prevalence falls to 50 percent at 12 to 15 weeks, 24 percent at 16 to 19 weeks, 12 percent at 20 to 27 weeks, and 6 percent among stillborns near or at term [56].

- Structurally abnormal fetuses. The frequency of chromosomal abnormalities is higher in structurally abnormal fetuses, with the highest frequencies among those with the most severe anomalies [57]. Genetic amniocentesis performed after ultrasonographic identification of a fetal malformation yields an 11 to 35 percent rate of karyotypic abnormality.

- Growth restricted fetuses. Abnormal karyotypes are primarily found in fetuses with **both** growth restriction and structural abnormality. As an example, in a series of 458 growth restricted fetuses at 17 to 39 weeks of gestation who were karyotyped, the risk of chromosomal abnormality was twenty-fold higher in fetuses with

ultrasonographic evidence of fetal malformations than in those with isolated growth restriction, 40 versus 2 percent, respectively [58].

Genetic versus chromosomal abnormalities — The presence of a normal karyotype does not exclude the possibility of a genetic defect (eg, cystic fibrosis, Tay-Sachs, sickle cell disease). Therefore, a pregnancy loss may still be due to a genetic cause even though the karyotype is normal. Presence of trophoblast inclusions, which are abnormal infoldings of the villus trophoblast bilayer, have been proposed as a marker of such genetically abnormal gestations. [59]. This finding could be clinically useful by removing the pregnancy loss from the unexplained category when a karyotype was not, or could not, be performed.

Congenital anomalies — Fifteen to twenty percent of stillbirths have a major malformation. Malformations associated with fetal demise, but unrelated to structural chromosomal abnormalities, include abdominal wall defects, neural tube defects, Potter syndrome, achondrogenesis, and amniotic band syndrome.

Infection — Infectious agents may lead to fetal demise as a result of severe maternal systemic illness (eg, influenza), placental dysfunction from placental infection (eg, malaria), or fetal systemic illness (eg, Escherichia coli) [60]. Infection is more commonly associated with early, as opposed to term stillbirth.

Fetal infection, acquired transplacentally or transcervically, is a common cause of neonatal morbidity and, less often, of fetal mortality [61-66]. (See "Pathogenesis of preterm birth"). Several types of viral, bacterial, fungal, parasitic, and protozoal organisms have been associated with fetal/congenital infection (Table 5).

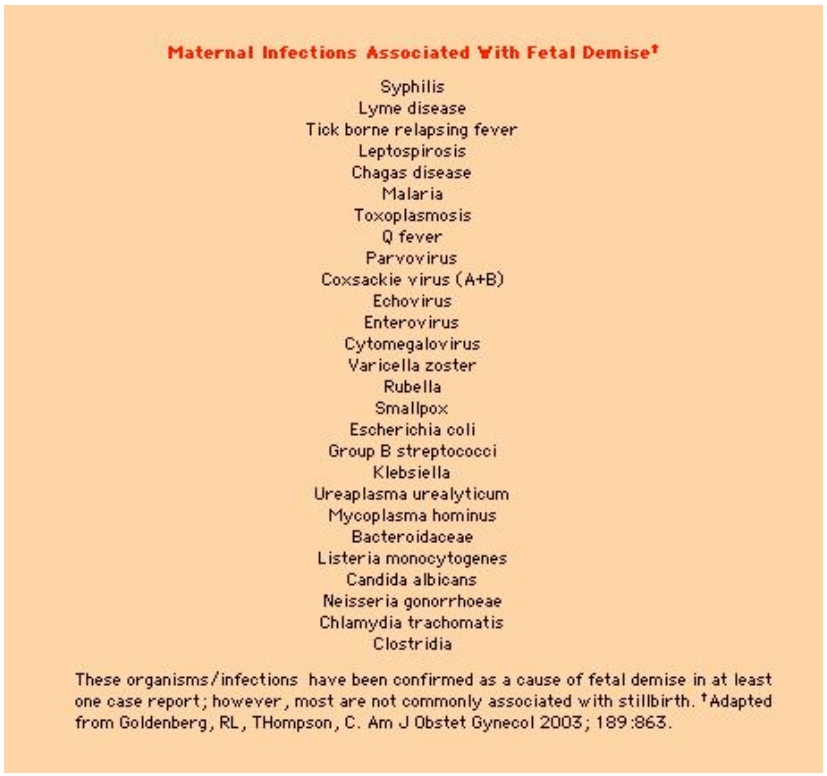

Table 5

The vaginal flora, which may ascend into the uterine cavity and infect the fetus, are the usual source of fetal infection associated with premature rupture of membranes. Group B streptococcus and Gram negative rods are the most common pathogens. Lethal fetal infection acquired from maternal hematogenous seeding of the placenta most often is due to parvovirus, listeria, and cytomegalovirus [67,68]. (See "Placental infections" and see individual topic reviews on these infections).

Other — The incidence of late fetal death in pregnancies complicated by diabetes mellitus has been steadily falling [69]. Although fetal mortality was 50 percent prior to the development of insulin, the stillbirth rate in women with optimal glycemic control now approaches that of nondiabetic women [70]. (See "Medical management of type 1 and type 2 diabetes mellitus during pregnancy").

Abruptio placenta, placenta previa, and vasa previa may also result in fetal demise; the mechanism is decreased placental surface for gas

exchange in the former two disorders and exsanguination in the latter. (See "Abruptio placentae" and see "Placenta previa-I").

Fetomaternal hemorrhage sufficiently large to cause death has been reported in up to 5 percent of stillborns [71].

Unexplained fetal deaths — The causes of fetal death are often complex and sometimes unknown; as many as 12 to 50 percent of stillbirths have no identifiable etiology [72]. Some causes of fetal demise have a higher incidence during specific periods of gestation. The major causes of fetal loss in each of the trimesters can be summarized as follows:

- First trimester: genetic abnormalities
- Second trimester: fetal infection and placental thrombosis
- Third trimester: cord accident and placental thrombosis

DELIVERY — Most women (80 to 90 percent) will spontaneously enter labor within two weeks of fetal demise. Prolonged retention of a dead fetus can cause consumptive coagulopathy due to gradual release of thromboplastin from the products of conception into the maternal circulation [73]. Induction of labor is typically initiated soon after diagnosis of fetal death because of the emotional distress associated with this event and the prospect of carrying a dead baby.

Drugs administered for induction of labor, particularly near term, can be given according to standard obstetric protocols. (See "Induction of labor: Indications, techniques, and complications-I"). However, these regimens are often unsuccessful remote from term. Options for second and early third trimester medical termination of pregnancy include:

- For gestations less than 28 weeks, prostaglandin E2 (PGE2) suppositories (20 mg inserted vaginally every four hours) are administered until labor is induced. Pretreatment with acetaminophen, compazine, and diphenoxylate is useful to minimize fever, nausea, vomiting, and diarrhea, which invariably occur. The PGE2 dose should be reduced to 5 to 10 mg if used at a more advanced gestation (off label use) as uterine sensitivity and the risk of uterine rupture increase with gestational age [74]. The risk of uterine rupture is highest in women

with a hysterotomy scar; these drugs should be used judiciously or, preferably, not at all in this situation [75-77].

- High dose oxytocin (200 units in 500 mL saline at 50 mL per hour) [78]. The mother should be observed for signs of water intoxication and maternal electrolyte concentrations should be monitored at least every 24 hours. Nausea and malaise are the earliest findings of hyponatremia, and may be seen when the plasma sodium concentration falls below 125 to 130 meq/L. This may be followed by headache, lethargy, obtundation and eventually seizures, coma and respiratory arrest.

- Misoprostol (50 to 200 mcg vaginally every 4 to 12 hours up to four doses or 400 mcg orally every 4 hours) can induce labor and result in successful expulsion in 80 to 100 percent of cases, but data are limited [79-83]. It is not approved for this indication by the United States Food and Drug administration. The American College of Obstetricians and Gynecologists recommends that misoprostol **not** be used for cervical ripening or labor induction in women with prior uterine incisions [76].

Early second trimester losses (less than 24 weeks of gestation) can be managed as second trimester termination of pregnancy. (See "Termination of pregnancy: Second trimester-I"). Maternal morbidity is similar to that observed in pregnancies without a fetal demise [84].

MOURNING — Grief and mourning are normal reactions to loss of a child. Limited observational studies also describe psychological sequelae in subsequent pregnancies, such as depression, post-traumatic stress disorder, and anxiety, as well as deleterious effects on maternal-child attachment [85]. In general, grieving parents want staff to appreciate the severity of their loss, offer understanding and support, and allow them to talk about the death. Although it is commonly assumed that seeing and holding the stillborn infant is conducive to the mourning process, the value of this practice has recently been questioned [86]. An appropriate policy consists of empathetic, honest communication between parents and hospital staff that acknowledges the specific needs and cultural practices of individual couples [87].

VALUE OF PATHOLOGIC EXAMINATION — The cause of fetal death can often be determined through gross and histopathologic examination of the fetus and placenta [21,88-92]. Determining the cause of death is important because sooner or later parents will want to know "Why did this happen?" and "Will it happen again?" Answers to these questions are often impossible without information gained from pathologic examination [93-95]. For example:

- The clinical utility of the perinatal autopsy was illustrated in a study of 77 fetal deaths [93]. The pathologic diagnosis confirmed the clinical diagnosis in 29 percent of patients, changed or significantly added to the diagnosis in 34 percent, and was inconclusive in 38 percent.

- In another series of 1477 stillbirths, autopsy findings identified the cause of death in 46 percent of cases [95]. Among the 1239 stillborns with any positive findings, new information resulting from complete postmortem examination was obtained in 51 percent. This new information influenced management of a future pregnancy: the recurrence risk estimate changed in 40 percent of cases and recommendations were changed for preconceptional care (9 percent), prenatal diagnostic procedures (21 percent), prenatal management (7 percent), and neonatal management (3 percent).

Components of the perinatal autopsy — Compassionate parental counseling is important to obtain informed consent before the pathologic examination and to communicate the findings afterwards.

A perinatal autopsy consists of the following [96,97]:

- Review of the medical record to obtain the clinical history. Informational gaps may be provided by the patient or her clinician.

- Birth weight and external measurements (eg, foot length, head and chest circumference, crown-to-foot length)

- Photographs and x-rays

- Gross external examination of the stillborn, placenta, and cord

- Gross examination and weight of major fetal organs
- Microscopic examination of fetal organs, placenta, and cord
- Bacterial cultures of fetal blood and lung

The gross external examinations should be performed promptly. (See "Placental anatomy and examination"). Cytogenetic, biochemical, and molecular genetic studies and viral cultures can be obtained as indicated. (See "Histopathology of placental disorders", see "Placental infections", and see "Cytogenetic abnormalities in the embryo; fetus; and infant-I"). One study evaluating a protocol for postmortem examination of stillbirths concluded that gross examination, photography, radiography, and bacterial cultures should be performed in all cases, while karyotyping and microscopy could be reserved for subjects abnormal on gross examination [98]. However, this protocol might fail to detect some nongenetic disorders, such as viral infection [99].

Specimen collection — Cytogenetic studies may be performed on fetal blood, tissue, or body fluids, as long as the cells are viable. Fetal blood can be collected from the umbilical cord; at least 3 mL should be placed in a heparinized tube. Skin samples are obtained by washing the skin with alcohol or sterile saline, drying the area with sterile gauge, and removing one square centimeter of tissue with underlying dermis. Fascia samples are usually taken from the Achilles tendon or thigh, using sterile technique. Tissue samples should be placed in sterile medium (eg, Hanks balanced salt solution) from the cytogenetics laboratory or sterile saline solution and kept at room temperature (do not use fixatives such as formaldehyde). Another 1 cm tissue sample can be frozen for future studies, if required.

Laboratory testing — The following maternal tests are recommended for women with an intrauterine fetal demise:

- Random glucose concentration
- Complete blood count (includes platelet count)
- Antibody screen
- Syphilis testing
- Kleihauer-Betke

- Urine toxicology screen

Thyroid function tests, cytomegalovirus titer (IgM, acute and convalescent IgG), toxoplasmosis titer (IgM, acute and convalescent IgG), parvovirus titer (IgM), Listeria culture, lupus anticoagulant and anticardiolipin antibody titers, and thrombophilia evaluation should be obtained in selected patients. (See "Placental infections", see "Parvovirus B19 infection during pregnancy", see "Overview of thyroid disease in pregnancy", and see "Clinical manifestations and diagnosis of the antiphospholipid antibody syndrome in pregnancy").

PROGNOSIS — The risk of recurrent fetal demise is not known, but clearly depends upon the cause of the index death. For example, the risk of Trisomy 21 (47,+21) in a subsequent fetus is approximately one percent, whereas recurrent nonimmune hydrops from alpha-thalassemia is likely in 25 percent of offspring.

There were no recurrences in one series of 92 deliveries after stillbirth [100]. By comparison, another study found an 8 percent rate of repeat stillbirth, particularly among women with hypertension and diabetes [101]. A third report in which 300 women with a previous history of stillbirth were followed with antepartum fetal surveillance noted one unexplained fetal death in a woman with two previous, unexplained fetal deaths [102]. Thus, in most cases of fetal death in which the etiology is known, a recurrence risk can be determined and sometimes prenatal diagnosis and prevention are possible. Women with an unexplained fetal death can be reassured that the risk of recurrence is low.

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Keywords

Abruptio placentae
Antiphospholipid antibody syndrome
Bereavement
Blacks
Body mass index
Chromosomal abnormalities
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Fetal loss;Major topics;Major topics;Pathogenesis
Fetomaternal hemorrhage
Intrauterine asphyxia;Major topics;Major topics
Intrauterine growth restriction
Karyotype
Kleihauer Betke test
Labor induction
Maternal age
Meconium
Meconium induced vascular necrosis;Moderate topics
Miscarriage
Nuchal cord;Major topics
Perinatal asphyxia;Major topics
Perinatal autopsy;Major topics
Perinatal infection;Moderate topics
Pregnancy
Second trimester
Stillbirth=Stillborn;Major topics;Major topics
Third trimester
Umbilical cord
Umbilical cord knot
Umbilical cord prolapse
Uteroplacental vasculopathy;Moderate topics