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Neural Tube Defects

Neural tube defects (NTDs) are congenital structural abnormalities of the central nervous system and vertebral column. Neural tube defects may occur as an isolated malformation, in combination with other malformations, as part of a genetic syndrome, or as a result of teratogenic exposure (1). Neural tube defects are the second-most-common major congenital anomaly (2) after cardiac malformations, and their prevalence varies by geographic region, race, and environmental factors (3). Outcomes and disabilities depend on level and extent of lesion; for instance, anencephaly is incompatible with life but most infants with spina bifida will survive after surgical repair (4). Importantly, and in contrast to many other congenital abnormalities, primary prevention of NTDs is possible with folic acid. In addition, prenatal screening and diagnosis are widely available, and fetal surgery has improved outcomes for some newborns. The purpose of this document is to provide information about NTDs and make management recommendations for the pregnancy complicated by a fetal NTD.

Background

Embryology

The neural tube begins from a flat sheet of neuroepithelial cells (the neural plate), which rolls or folds in the midline to form the neural tube. This occurs at 3–4 weeks after fertilization, a time when some women do not yet realize that they are pregnant. Closure of the neural tube begins at the cervical region and extends cranially and caudally. However, the closure is complex, and as in other mammals, occurs in a discontinuous process (5). Simplistically, failure of neural tube closure at the cranial end results in anencephaly, and failure of closure at the caudal end results in myelomeningocele or spina bifida. The process of neural tube closure involves multiple cellular and molecular processes that are tightly regulated (6). Mutations in any of the genes involved in this process could result in abnormal neural tube closure and NTDs. The various types of NTDs, summarized in Table 1, include malformations of the spinal cord, meninges, and vertebra.

Epidemiology

Worldwide, approximately 300,000 infants are born annually with an NTD (7), and NTDs account for as many as 29% of neonatal deaths associated with congenital abnormalities in low-income settings (8). A recent systematic review, including data from 75 countries (3), reported a wide-ranging prevalence; the median prevalence based on World Health Organization (WHO) region ranged from 6.9 per 10,000 births in the Western Pacific, to 21.9 per 10,000 births in the Middle East. In the United States between 2004 and 2006, the prevalence of anencephaly was 0.55 per 10,000 live births and 2.54 per 10,000 live births, stillbirths, or terminations. For spina bifida, the prevalence was 3.40 per 10,000 live births and 4.41 per 10,000 live births, stillbirths, or terminations (9). As reviewed in subsequent sections of this document, the prevalence has decreased with broad use of folic acid supplementation.

Etiology

Isolated or nonsyndromic NTDs are generally multifactorial, or attributed to a complex combination of genetic and environmental factors. Specific factors associated with NTDs are environmental exposures; certain medications; maternal medical conditions; geographic and ethnic associations; genetic etiologies, including chromosomal abnormalities and single gene disorders; and family history (10).

Table 1. Neural Tube Defect Pathophysiology ⇦

Neural Tube Defect	Malformation
Cranial	
Anencephaly	Failure of fusion of cephalic portion of neural folds; absence of all or part of brain, skull, and skin
Exencephaly	Failure of scalp and skull formation; exteriorization of abnormally formed brain
Encephalocele	Failure of complete skull formation; extrusion of brain tissue into membranous sac
Iniencephaly	Defect of cervical and upper thoracic vertebrae; abnormally formed brain tissue and extreme retroflexion of upper spine
Spinal	
Spina bifida	Failure of fusion of caudal portion of neural tube, usually of 3–5 contiguous vertebrae; spinal cord or meninges, or both, exposed to amniotic fluid
Meningocele	Failure of fusion of caudal portion of neural tube; meninges exposed
Myelomeningocele	Failure of fusion of caudal portion of neural tube; meninges and neural tissue exposed
Myeloschisis	Failure of fusion of caudal portion of neural tube; flattened mass of neural tissue exposed
Holorachischisis	Failure of fusion of vertebral arches; entire spinal cord exposed
Craniorachischisis	Coexisting anencephaly and open neural tube defect, often in the cervical–thoracic region

Several environmental factors have been associated with NTDs. To produce a defect, the external influence must be present during the first 28 days of development, when the neural tube is forming. Some medications, particularly those that interfere with, or deplete, folic acid, increase the risk of NTDs. For instance, the antiepileptic medication carbamazepine has been associated with an increased risk of spina bifida (11). Valproic acid, an antiepileptic medication used also for treatment of bipolar and personality disorders, has been associated with a 10-fold to 20-fold increased risk of NTDs (12). Another example of environmental exposure and increased risk of NTDs was documented in women living on the Texas–Mexico border who were exposed to the fungal toxin fumonisin (13). Maternal hyperthermia, including fever and heat exposure (such as a hot tub or sauna), also has been associated as a risk factor for NTDs. Maternal febrile illness during the first trimester may increase the risk of NTDs by as much as threefold (14). Similarly, a National Birth Defects Prevention Study demonstrated a 1.7-fold increased risk of anencephaly for women with history of hot tub use during early pregnancy (15).

Certain maternal medical conditions are associated with increased risk of NTDs. Pregestational diabetes carries a significantly increased risk of NTD (16). Maternal obesity also is associated with increased risk of NTDs (17), and there is a positive correlation between body mass index (BMI) and risk. A meta-analysis of 12 studies published between 1980 and 2007 found a 1.7-fold increased risk of NTDs for obese women (11 studies), and a 3.1-fold increased risk for *severely obese women* (defined as a BMI greater than or equal to 38 or more than 243 pounds) (five studies) when compared with women of normal BMI (18).

Racial and ethnic backgrounds and geographic location also have been associated with differences in NTD risk. Several studies have reported that in the U.S. population, the risk of NTDs is highest in the Hispanic population (19). A more recent study reported a lower risk of spina bifida in African American women but did not confirm an increased risk in the Hispanic population (20). Regarding geographic differences, Shanxi Province in China has the world's highest rate of NTDs, even after implementation of a birth defects prevention program by the Chinese government (21). These racial, ethnic, and geographic differences likely reflect a combination of genetic predispositions, dietary practices, and environmental exposures.

Although many NTDs are of multifactorial etiology, there are also genetic contributions. Chromosomal abnormalities, including trisomy 13, trisomy 18, and triploidy are associated with NTDs; certain chromosomal deletions and duplications also have been associated with NTDs (22, 23). In addition, some genetic syndromes associated with single gene disorders or chromosomal microdeletions, such as 22q11.2 deletion syndrome and Waardenburg syndrome, present an increased risk of NTDs (24). Hundreds of genes are involved in murine neural tube closure (25), and presumably the same is true in humans. General classes of genes implicated in neural tube closure include those genes related to folate metabolism; planar cell polarity genes, which are involved in cell movement during neural tube closure; and genes involved in the development of cilia that are essential for cell signaling (6).

The relationship between folic acid and NTDs has prompted interest in genes involved in the folate pathway and in the associations between gene alterations and increased risk of NTD. One gene of particular interest is

the *methylenetetrahydrofolate reductase* (MTHFR) gene, which encodes a cytoplasmic enzyme involved in the conversion of homocysteine to methionine. Specific polymorphisms, C677T, in this gene have been associated with a higher frequency of NTDs in some populations, but not others (26). Given these inconsistent associations, routine screening for MTHFR status is not recommended.

A genetic contribution to NTDs also is reflected in the association between family history and increased NTD risk. The increased NTD risk for relatives of an affected individual has been well documented, and parents who have had one child with an NTD are at significantly increased risk of having another child with the same or a similar defect (27). The risk of having a fetus with an NTD when there is an affected sibling, a second-degree relative, or a third-degree relative is 3.2%, 0.5%, and 0.17%, respectively. With two affected siblings, the risk is 10% (28, 29).

Pathophysiology

Defects in neural tube closure can occur at any level, as summarized in Table 1. Closure defects at the cephalic portion of the neural groove result in anencephaly. Secondary consequences of anencephaly include absent or partial development of the forebrain with degeneration of the exposed neural tissue, incomplete development of the calvarium, and abnormal facial features, including cleft palate and abnormalities of the auricular area. Typically, anencephalic infants are stillborn, or survive only a few hours or days after delivery.

Closure defects of the cervical and upper thoracic areas result in iniencephaly, with abnormalities of the associated vertebrae, retroflexion of the upper spine, defects of the thoracic cage, and abnormalities in development of the diaphragm, lungs, and heart (30). Failure of fusion at the caudal end of the neural tube results in abnormalities of the lower end of the spinal column, which may involve exposure of the meninges (meningocele), or exposure of the meninges and neural tissues (myelomeningocele); the lumbosacral regions are most commonly affected. Associated anatomic changes include hydrocephalus, abnormal head shape, decreased biparietal diameter or head circumference, and Arnold–Chiari or Chiari type II malformation (herniation of the hindbrain) (31). Talipes equinovarus (clubfoot) and scoliosis are also commonly associated with spina bifida.

Clinical Consequences

The finding of an NTD has implications for the ongoing pregnancy, neonatal management, and long-term health for the affected child. Pregnancies complicated by spina bifida require specialized care with consultation or management by a team, including maternal–fetal medicine, neonatology, pediatric neurosurgery, and genetics. Polyhydramnios can occur as a result of impaired fetal swallowing especially with anencephaly and higher-level spinal lesions and those lesions associated with aneuploidy, leading to uterine overdistention and increased risk of preterm contractions, umbilical cord prolapse, and placental abruption. Breech presentation is common at term with anencephaly and spina bifida.

For the affected newborn, the clinical consequences of spina bifida are significant. Size and location of the lesion and the presence of hydrocephalus are important prognostic factors for infants with NTDs. However, with surgical and medical management, at least 75% of infants with myelomeningocele will survive to early adulthood (32). Most infants with spina bifida and ventriculomegaly require ventriculoperitoneal shunt placement in their first year, and at least two thirds require several nonelective shunt revisions over the course of their lives (32, 33). Worsening of the Arnold–Chiari malformation, due in part to the small size of the posterior fossa, can cause severe or even lethal neurologic dysfunction. Intelligence is correlated with the level of the spinal disruption and the presence of hydrocephalus. Patients with myelomeningocele can have normal initial intelligence, but cognitive deficits are common and relate to the associated Arnold–Chiari malformation, its resultant hydrocephalus, and the status of the midbrain, cortex, and corpus callosum (34).

Ambulation is another concern for patients with spina bifida. The level of the lesion and the strength of the quadriceps, hamstring, and iliopsoas muscles generally are predictive of ambulatory function (35). A recent study confirmed that patients with motor level dysfunction at the L4 level or below have better physical function than those patients with higher-level lesions. Additionally, although scoliosis occurs in about one half of cases with spina bifida, it is not associated with decreased physical capability (36).

Impaired function of the bowel and bladder is common in patients with NTDs. Most patients with myelomeningocele have lower urinary tract dysfunction (neurogenic bladder); the level of the spinal lesion is not necessarily associated with bladder function (37). Voiding dysfunction also is associated with development of chronic renal disease, and approximately 30–40% of children with myelomeningocele eventually develop renal dysfunction (38). Renal dysfunction has been associated with death in nearly one third of patients with open spina bifida (39). Therefore, aggressive management of bladder dysfunction is important to preserve upper urinary tract function. Nearly all patients with open NTDs have innervation abnormalities of the bowel and anus

resulting in bowel dysfunction, and most will have fecal incontinence (40). Finally, at least one third of individuals with an NTD have a severe allergy to latex and can have life-threatening reactions after exposure (32).

Care for an individual with spina bifida is complex and typically involves frequent and lifelong medical attention with significant direct medical costs. One study estimated that the medical expenditures for children with spina bifida were 13 times greater than for those without; among adults, expenditures were six times greater for those affected by spina bifida (41). In addition, only a minority of adults with spina bifida are able to live independently (42), and there are indirect costs of disease-associated morbidity and caregiver time and expenses (43).

Role of Folic Acid in Neural Tube Development

More than four decades ago it was recognized that women with pregnancies complicated by a fetal NTD have lower plasma levels of B vitamins, including folate, than women whose pregnancies were unaffected (44). A multicenter randomized trial demonstrated that the recurrence risk of NTDs was reduced by folic acid supplementation during pregnancy; 1,817 women at high risk by virtue of a previously affected pregnancy were enrolled in the study and randomly assigned to receive folic acid, other vitamins, both, or neither. Women assigned to take 4 mg of folic acid per day before pregnancy and through the 12th week of gestation experienced a 72% protective effect (relative risk [RR], 0.28; 95% CI, 0.12–0.71) (45). Subsequently, a double-blind, placebo-controlled, randomized trial demonstrated that prepregnancy folic acid supplementation decreased the risk of a first occurrence of an NTD (46). The efficacy of prepregnancy folic acid supplementation for preventing NTDs has since been confirmed by other studies (47). The results of the MRC Vitamin Study led to the recommendation that all women contemplating pregnancy should take 400 micrograms of folate daily, and women at high risk of pregnancy affected with NTD should take 4 mg (4,000 micrograms) daily (48). In 1998, the United States began mandatory fortification of wheat flour with folic acid; several other countries including Canada, South Africa, Australia, and countries in South America followed suit. In the United States, food fortification has been linked to a 19% decrease in all NTDs, with an 11% decrease in anencephaly and a 23% reduction in spina bifida (49).

Despite years of ongoing research, the precise mechanism through which folic acid prevents NTDs has not been fully defined. Folic acid is involved in one-carbon metabolism, which includes synthesis of purines and pyrimidines for DNA replication and methyl group transfer to macromolecules. Many folate-dependent reactions are important for cell growth and proliferation, crucial processes during neural tube formation. Thus, it is biologically plausible that the interruption of folate pathways in the embryo could result in aberrant neural tube closure (2). The important role of folate in neural tube closure is illustrated by the fact that certain medications that are associated with increased risk of NTDs such as diphenylhydantoin, aminopterin, and carbamazepine interfere with folic acid metabolism (50).

The association between folic acid supplementation and decreased risk of NTDs is well established, and folate supplementation remains an important prepregnancy and prenatal recommendation. However, at least 30% of NTDs are not prevented by folic acid supplementation (51), which underscores the multifactorial etiology of NTDs. Current areas of research, many involving the use of murine models, are exploring other pathways or mechanisms, including neuronal migration pathways, cell signaling, mitochondrial folate metabolism, and inositol pathways (52).

Clinical Considerations and Recommendations

▶ ***Which folic acid supplementation regimen is recommended for preventing neural tube defects?***

It is well established that folic acid supplementation decreases the risk of a first occurrence and recurrence of isolated, nonsyndromic NTDs. The first recommendations regarding folic acid supplementation were made in 1992, when the U.S. Public Health Service recommended that reproductive-aged women reduce the risk of NTD by consuming 400 micrograms of folic acid daily in addition to eating a folate-rich diet. Several groups, including The U.S. Preventive Services Task Force, the American College of Medical Genetics and Genomics, and others have made similar recommendations (48, 53–55).

Neural tube closure occurs early in pregnancy, and at least one half of all pregnancies are unplanned (56). Thus, initiating folate supplementation at the time of missed menses is insufficient, as neural tube formation is already underway. For these reasons, all women planning a pregnancy or capable of becoming pregnant should take 400 micrograms of folic acid supplementation daily. Supplementation should begin at least 1 month before pregnancy and continue through the first 12 weeks of pregnancy (55).

It has been estimated that between 16% and 58% of NTDs could be prevented by folic acid supplementation

(57). A recent case–control study reported that prepregnancy folic acid supplementation resulted in a 79% reduction in risk of spina bifida and a 57% reduction in risk of anencephaly.

Women at high risk of NTDs should supplement with a higher dose of folic acid than 400 micrograms (48). This group includes those with histories of previous pregnancies affected with NTDs, women who are affected with an NTD themselves, those who have a partner who is affected, or those with a partner with a previous affected child. Women at high risk of NTDs should take 4 mg (4,000 micrograms) of folic acid daily. The daily supplement should be initiated 3 months before pregnancy and continued until 12 weeks of gestational age (48, 53). Following the recommended supplementation in this high-risk group may reduce risk by as much as 70% (58).

Not all NTDs are preventable through folate acid supplementation. These folate-resistant NTDs include those associated with poor glucose control in the first trimester, hyperthermia, maternal obesity, and aneuploidy or genetic disorders. Although folic acid supplementation in diabetic patients may decrease the risk of NTDs, the risk is not eliminated, which emphasizes the importance of prepregnancy glycemic control (59). Similarly, prepregnancy folic acid intake in obese women may not decrease the risk of NTDs (60). Antiepileptic medication use during pregnancy, particularly valproate, also has been associated with folate-resistant NTDs. For these patients, the benefit of high-dose folic acid therapy has not been definitively proved (61), and recent guidelines for women on antiepileptic medications do not recommend higher doses of prepregnancy folate supplementation (62).

The risks of higher levels of folic acid supplementation are believed to be minimal. Folic acid is considered nontoxic even at very high doses because it is water soluble and rapidly excreted in the urine. Theoretically, supplemental folic acid could mask the symptoms of pernicious anemia and, thus, delay treatment. However, pernicious anemia is an uncommon disorder in young women and there is no evidence that supports this or other concerns regarding potential folic acid toxicity. No high-quality studies have demonstrated an association between folic acid supplementation and increased rates of twinning (55).

Some over-the-counter multivitamin supplements and most prenatal vitamins contain 400 micrograms of folic acid. Higher levels of supplementation should be achieved by taking an additional folic acid supplement and not by taking excess multivitamins. In particular, vitamin A is potentially teratogenic at high doses, and pregnant women should not take more than 5,000 international units per day, the amount that typically is found in one multivitamin and mineral supplement (63).

▶ *What are the roles of maternal serum alpha-fetoprotein testing and ultrasonography in screening for neural tube defects?*

Maternal serum alpha-fetoprotein (MSAFP) screening, usually as part of a broader screening for aneuploidy, has been used as a primary prenatal screening method for NTDs since the 1980s. Alpha-fetoprotein is a glycoprotein that is secreted by the fetal yolk sac and liver, and fetal serum concentrations are 150–200 times those of amniotic fluid (64). Levels of MSAFP increase early in pregnancy, and serum screening was optimized to differentiate normal from abnormal MSAFP results in the second trimester between 15 weeks and 18 weeks of gestation. Maternal serum alpha-fetoprotein levels are reported in multiples of the median (MoM) using unaffected pregnancies of the same gestational age as the reference group. The detection rate is expected to be greater than 95% for anencephaly and between 65% and 80% for open NTDs when MSAFP is elevated to 2.5 multiples of the median or greater, with false positive rates of 1–3% (65).

As a screening test, an elevated level of MSAFP is not diagnostic of an open NTD because it also can be explained by inaccurate gestational dating and can be found in association with other conditions, such as multiple gestation, fetal abdominal wall defects, fetal nephrosis, fetal demise, and placental conditions that increase risk of adverse events later in pregnancy. Also, MSAFP is not usually increased with closed NTDs, which limits the value of MSAFP screening.

With advances in ultrasonography and expansion of its use, MSAFP is less important for detection of NTDs when high-quality, second-trimester fetal anatomy ultrasonography is routinely used. In these cases, the value of MSAFP lies more in its screening for other abnormalities and placental complications (66, 67).

When compared with MSAFP alone, second-trimester fetal two-dimensional ultrasonography has a higher detection rate for NTDs. In a series of 189 cases of NTD, MSAFP was abnormal in only 75% of the 102 patients who were screened. In contrast, ultrasonography identified the NTDs in 96% of the 130 women who had their ultrasound examinations either without MSAFP or before results of MSAFP screening were known (68).

Because of the high sensitivity for NTD detection, the presence of typical findings on two-dimensional ultrasonography is considered diagnostic of an NTD, and additional studies are usually not necessary to confirm the diagnosis. Amniocentesis with measurement of acetylcholinesterase can help differentiate open NTDs from closed NTDs in cases that are not straightforward.

Three-dimensional ultrasonography does not appear to be superior to two-dimensional ultrasonography for diagnosis, although it may be better for defining the upper limit of the lesion in some cases (69).

Ultrasonography in the second trimester is recommended for all pregnant women (70); the optimal time for a single ultrasound examination is 18–22 weeks, allowing for confirmation of gestational age and screening for anomalies, including NTDs. An earlier ultrasound examination also may be indicated for the patient with an abnormal MSAFP or other high-risk condition. In a fetus with anencephaly, features visible by ultrasonography in the second trimester include the absence of a fetal cranium and significant facial dysmorphology. In a fetus with spina bifida, the primary ultrasound findings include abnormal posterior vertebral arches and a protuberant myelomeningocele sac for open and closed NTDs, although these may not be as evident with closed spinal abnormalities. Associated findings of open spina bifida are seen at 18–22 weeks of gestation in more than 95% of cases, including an abnormal skull shape (the "lemon sign"), an abnormal cerebellum and posterior fossa (the "banana sign"), and ventriculomegaly (71).

First-trimester ultrasonography also has been investigated as a screening tool for NTDs. Although it is possible to detect some NTDs in the first trimester, the detection rate appears to be much lower than with second-trimester ultrasonography (72). Therefore, a normal first-trimester ultrasound examination should not be substituted for a screening ultrasonography at 18–22 weeks of gestation. Fetal magnetic resonance imaging (MRI) has been useful mainly as an adjunct to the primary ultrasonography when confirmation is needed for equivocal ultrasonographic findings or when a more detailed evaluation of the central nervous system is indicated for prenatal counseling and planning antenatal management (73). Fetal MRI is not recommended as a primary screening modality for NTDs or for routine evaluation of NTDs that are detected by ultrasonography.

▶ *How should a pregnancy affected with fetal neural tube defects be managed?*

When an NTD is suspected or detected, the patient should be referred to a maternal–fetal medicine unit for a specialized ultrasound examination for diagnosis or confirmation, to define the location and size of the lesion, to ascertain whether secondary findings such as hydrocephalus are present, and to determine whether the fetus has other structural abnormalities. Given the increased risk of other abnormalities, fetal echocardiography should be considered.

Counseling should include a discussion of the nature of the lesion and the range of expected outcomes. Anencephaly is incompatible with long-term survival, and patients should understand the anticipated outcome. Outcomes with open spina bifida are highly variable and depend on a number of factors, including the location and size of the lesion, the presence of hydrocephalus or other anomalies, and whether a genetic abnormality is present. Counseling should be individualized and as specific as possible. A patient with a fetus with an NTD should be offered the management options of pregnancy termination, expectant management with neonatal surgical repair, and in utero fetal repair for appropriate candidates. For the patient who elects to continue the pregnancy, genetic evaluation by amniocentesis for chromosomal microarray should be recommended because the identification of a genetic abnormality in a fetus with an NTD has important implications for counseling regarding prognosis, pregnancy management, and determining whether the patient is a candidate for in utero NTD repair (74, 75). Measurement of amniotic fluid acetylcholinesterase helps to differentiate between open and closed NTDs and is a component of many preoperative evaluations for fetal repair. Fetal MRI also may be considered for assessment of unclear findings on ultrasonography (76). Pregnant women with an ongoing, nonlethal fetal NTD should be referred to a tertiary center for full spectrum care, including maternal–fetal medicine in collaboration with neonatology, pediatric neurosurgery, and genetics.

There are no well-designed studies that have assessed the value of antenatal fetal surveillance in pregnancies complicated by spina bifida. However, serial ultrasound examination may be considered for monitoring fetal growth, head size, and progression of hydrocephalus, if present. The fetus with spina bifida is not at increased risk of placental insufficiency, and there are no data to support the routine use of antenatal fetal surveillance in these pregnancies. Delivery of a fetus with nonlethal spina bifida should be planned to occur in a hospital that provides tertiary neonatal care and has personnel capable of managing the spinal defect and any immediate complications; evidence suggests that outcomes are better in such settings (77).

▶ *What is the optimal timing and mode of delivery of a fetus with a neural tube defect?*

Most pregnancies complicated by fetal spina bifida will result in delivery at term unless there is a maternal or obstetric complication that requires early delivery. Generally, delivery at term is preferred. However, a late-preterm to early-term delivery is indicated if in utero fetal surgery has been performed because of the high risk of uterine rupture, similar to patients with a previous

classical cesarean delivery. Rapidly increasing ventriculomegaly also may prompt delivery before term so that a ventriculoperitoneal shunt can be placed. Each case should be managed individually in consultation with the pediatric neurosurgery and neonatal intensive care teams caring for the newborn.

Breech presentation, resulting from fetal neurologic dysfunction or hydrocephalus with an enlarged head, is common in pregnancies complicated by fetal spina bifida. For the breech fetus with an NTD, planned cesarean delivery is standard (78). The best delivery route for the fetus with a normal head size in cephalic presentation remains controversial. No prospective randomized trial of vaginal delivery versus cesarean delivery for vertex fetuses with spina bifida has been performed. All studies in the current literature are retrospective, with various biases. Regardless, the overwhelming majority of the published evidence suggests that vaginal delivery does not adversely affect neonatal outcome with meningomyelocele (78, 79).

Most studies regarding mode of delivery also are limited by lack of long-term follow-up, which is essential in evaluating medical care for these infants because loss of function and other neurologic reversals are common even when surgery is performed early to correct an NTD. Because it is not clear whether or how significantly the neurologic outcome is affected by the method of delivery in these infants, decisions about the timing and route of delivery should be made individually in consultation with personnel with experience and knowledge of NTDs, which may include maternal–fetal medicine specialists, neonatologists, and pediatric neurosurgeons. A special consideration in the delivery and care of infants with an NTD is the use of latex-free gloves because individuals with an NTD are at risk of developing a severe, potentially life-threatening allergy to latex (32).

▶ *What is the role of fetal surgery for neural tube defects?*

The neurologic damage in myelomeningocele is thought to be due to two sequential processes, the so-called "two-hit hypothesis." The "first hit" is the primary developmental abnormality that causes the open spina bifida; the "second hit" is a combination of the inflammation to the spinal cord from exposure to amniotic fluid and direct trauma to the exposed cord (80, 81). The rationale for fetal surgery is that damage to the exposed spinal cord is progressive with advancing gestation. Therefore, early repair of the lesion, in utero, can reduce damage from the second hit and, thus, improve clinical outcomes.

The first successful human fetal surgery for spina bifida repair was reported in 1998 (82) and was followed by the Management of Myelomeningocele Study (MOMS), a prospective randomized clinical trial that compared standard postnatal repair of myelomeningocele to intrauterine repair of the defect in the second trimester. All fetuses were between 19 0/7 weeks and 25 6/7 weeks of gestation at randomization with a normal karyotype and an upper border of the spina bifida between T1 and S1, and all had evidence of an Arnold–Chiari malformation on ultrasonography and fetal MRI. All fetal repairs were done at one of three sites in the United States. A total of 158 patients were randomized and evaluated at 12 months after delivery. In utero spina bifida closure resulted in a lower incidence of the composite outcome of fetal or neonatal death or need for shunt placement by 12 months (68% versus 98%, RR, 0.70; 97.7% CI, 0.58–0.84) and a lower incidence of hindbrain herniation at 12 months (64% versus 96%, RR, 0.67; 95% CI, 0.56–0.81). Children who had prenatal surgery were more likely to have a level of function that was two or more levels better than expected and were more likely to be able to walk without devices or orthotics. There were no differences between the groups with regard to cognitive test scores (83).

Fetal surgery is not without maternal and obstetric risks. It requires two hysterotomies in the affected pregnancy, the first under general anesthesia for the fetal repair and a second for the cesarean delivery; additionally, because of uterine rupture risk, all future pregnancies require cesarean delivery before labor. In the MOMS trial, one half of the women who had fetal surgery gave birth before 35 weeks, and 11% delivered before 30 weeks; 44% had spontaneous rupture of membranes, 20% had oligohydramnios, more than 11% had partial or complete dehiscence of their hysterotomies, 9% required transfusion at delivery, and 5% developed pulmonary edema (84). Similar outcomes have been reported from other series of patients who underwent in utero surgery for a variety of indications (85). Endoscopic repair of lumbosacral myelomeningocele has been reported and, as techniques evolve, maternal morbidity may decrease (86).

Despite the maternal and obstetric risks, in utero repair is an option for women who meet appropriate criteria. Counseling should be nondirective and include all options, with full disclosure of all potential benefits and risks for the fetus and woman, including the implications for future pregnancies (87). Fetal repair of myelomeningocele should be performed only in an established fetal therapy center with the expertise, multidisciplinary team, facilities, and services that are required, and with an adequate volume of procedures to establish and maintain competency, and should follow standard procedures derived from the MOMS trial (87, 88).

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- All women planning a pregnancy or capable of becoming pregnant should take 400 micrograms of folic acid supplementation daily. Supplementation should begin at least 1 month before pregnancy and continue through the first 12 weeks of pregnancy.
- Women at high risk of NTDs should take 4 mg (4,000 micrograms) of folic acid daily. The daily supplement should be initiated 3 months before pregnancy and continued until 12 weeks of gestational age.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Ultrasonography in the second trimester is recommended for all pregnant women; the optimal time for a single ultrasound examination is 18–22 weeks, allowing for confirmation of gestational age and screening for anomalies, including NTDs.
- Although it is possible to detect some NTDs in the first trimester, the detection rate appears to be much lower than with second-trimester ultrasonography. Therefore, a normal first-trimester ultrasound examination should not be substituted for a screening ultrasonography at 18–22 weeks.
- A patient with a fetus with an NTD should be offered the management options of pregnancy termination, expectant management with neonatal surgical repair, and in utero fetal repair for appropriate candidates.
- For the patient who elects to continue the pregnancy, genetic evaluation by amniocentesis for chromosomal microarray should be recommended because the identification of a genetic abnormality in a fetus with an NTD has important implications for counseling regarding prognosis, pregnancy management, and determining whether the patient is a candidate for in utero NTD repair.
- Pregnant women with an ongoing, nonlethal fetal NTD should be referred to a tertiary center for full spectrum care, including maternal–fetal medicine in collaboration with neonatology, pediatric neurosurgery, and genetics.
- Delivery of a fetus with nonlethal spina bifida should be planned to occur in a hospital that provides tertiary neonatal care and has personnel capable of managing the spinal defect and any immediate complications.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Because it is not clear whether or how significantly the neurologic outcome is affected by the method of delivery in these infants, decisions about the timing and route of delivery should be made individually in consultation with personnel with experience and knowledge of NTDs.
- Despite the maternal and obstetric risks, in utero repair is an option for women who meet appropriate criteria. Counseling should be nondirective and include all options, with full disclosure of all potential benefits and risks for the fetus and woman, including the implications for future pregnancies.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More–Info/NTD.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. These resources may change without notice.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–August 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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