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Myelomeningocele: A Review of the Epidemiology, Genetics, Risk Factors for Conception, Prenatal Diagnosis, and Prognosis for Affected Individuals

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Although the use of folic acid before conception decreases the chance that a fetus will have an open neural tube defect, this condition still affects 0.5–1.0/1000 pregnancies in the United States. Results of a recent survey suggest that there are gaps in obstetrician-gynecologists' knowledge of risk factors for conception, strategies for prenatal diagnosis, and prognosis for affected individuals. To address these gaps this paper reviews the epidemiology, genetics, risk factors for conception, prenatal diagnosis, and prognosis for affected individuals, presents current information, and makes suggestions for expanding obstetrician-gynecologists' knowledge of myelomeningocele.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to state that despite a large amount of professional and public education on the use of folic acid in prevention of open neural tube defects (ONTDs) the incidence still affects 0.5–1.0/1000 pregnancies and recall that a recent survey conducted by the ACOG shows substantial misunderstanding and misinformation on major categories of neural tube birth defects.

Open neural tube defects (ONTDs) occur when the embryonic neural plate fails to complete its development and does not close at some point along its length (1). This process begins on day 19 with the formation of the primitive streak. Closure is accomplished as the neural folds meet and fuse in the midline to form the neural tube. Current evidence suggests that this process begins at the level of the fifth somite where the brain and spinal cord meet and proceeds both cranially and caudally as the neural folds join in a zipper-like manner. In the forebrain a second closure site appears and the fusion continues in 2 directions; meeting the zippering process advancing from the hindbrain and, at the same time, moving to close the most rostral part of the forebrain. The anterior neuropore closes on day 25 and the posterior on day 28. A lack of signaling between the neural tissue and the overlying mesoderm and ectoderm may be what leads to defects in the bony structures overlying the unfused portions of the neural tube (2).

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When the proximal end of the neural tube does not complete this fusion process, the result is an encephalocele or anencephaly. Much more commonly the dysraphic defect involves the spinal cord. ONTDs of the spine include meningoceles in which just the coverings of the brain and spinal cord protrude through the bony defect, myeloceles in which the neural elements alone protrude through the opening in the vertebral column, and myelomeningoceles in which both neural elements and meningeal elements protrude. As far as function of the spinal cord elements is concerned, it does not matter whether or not the meninges are involved, and both myeloceles and meningoceles are most commonly referred to as spina bifida. Although the incidence of spina bifida is decreasing, primarily because of elective termination and the increased use of periconceptional folic acid in women of childbearing age, it remains one of the most common significant congenital defects diagnosed prenatally.

In collaboration with the American College of Obstetricians and Gynecologists (ACOG) the authors of this paper assessed the knowledge about this condition among practicing obstetrician-gynecologists in a recent survey (3). The results indicate that there is a knowledge gap about many aspects of this condition such as incidence, risk factors, strategies for prenatal diagnosis, and prognosis for affected individuals. Although obstetrician-gynecologists do not routinely care for individuals with this condition, the study indicates that many of them provide diagnostic services during pregnancy as well as counseling for women whose fetuses have spina bifida. Thus, they should have an understanding of the epidemiology of spina bifida, the risk factors for conceiving a child with this condition, options for prenatal screening and diagnosis, and prognosis of affected pregnancies, as well as a basic knowledge of the prognosis for those with this condition. This paper addresses each of these areas and provides current information which can assist obstetrician-gynecologists in their practice.

EPIDEMIOLOGY, GENETICS, AND RISK FACTORS

In the early 1980s folic acid, a B vitamin, was first suspected as playing a role in causing ONTDs, but it was many years before clinical trials were conducted, the preventative effect was accepted, and recommended levels of consumption were specified (4–9). Although much research remains to be done on the exact mechanism of action, studies have shown that women who take at least 0.4 mg (400 μg) of folic acid a day, for at least 3 months before conception, decrease the chance that their fetus will have an ONTD by 70%–80%. For women at increased risk it is recommended that they take 0.4 mg on a daily basis and 4 mg when they are planning a pregnancy (10).

The Centers for Disease Control and Prevention currently estimates the conception rate of ONTDs (anencephaly and myelomeningocele) to be between 0.5 and 1.0/1000. This represents a decrease of approximately 26% in the prevalence of ONTDs in the United States as compared with the prevalence before January 1998 when mandatory fortification of cereal grain products with folic acid was begun (11,12). Infants of Hispanic mothers have a significantly higher birth prevalence of ONTDs as compared with infants of African-American and Caucasian mothers (13,14). The birth prevalence of ONTDs is dependent not only on the conception rate, but also on the availability or prenatal diagnosis and the rates of elective termination. Both of these factors have wide regional variability, making surveillance challenging (15).

Although most cases of spina bifida occur sporadically and are felt to have a multifactorial etiology, between 2% and 16% of isolated ONTDs occur in association with a defined chromosomal or single-gene disorder (16–20). That number goes up to 24% if there are additional fetal anomalies (21). Fifty-three percent of spontaneously aborted fetuses affected with spina bifida have an abnormal karyotype which can include trisomy, triploidy, tetraploidy, ring chromosomes, or deletions (21–25). The most common aneuploidy associated with ONTDs is trisomy 18. While trisomy 13 can be associated with this condition, the most common CNS malformation seen with trisomy 13 is holoprosencephaly (23). Some cases of ONTDs are part of a genetic condition for which a specific inheritance pattern has been defined. Autosomal dominant conditions which have myelomeningocele as a feature include Lehman syndrome and the disorganization-like syndrome; among those with autosomal recessive inheritance are Meckel-Gruber syndrome, PHAVER syndrome, and VATER syndrome; and 2 that are X-linked are the Mathias laterality sequence and X-linked neural tube defects (19,23,25,26). Although not all of these conditions can currently be diagnosed prenatally, karyotype analysis should be considered when the prenatal diagnosis of an ONTD is made. Genetics consultation may allow for a more thorough understanding of the chromosomal factors operating in the index couple.

In some cases myelomeningocele occurs in the fetus secondary to environmental or maternal factors. Maternal medication use is one well-recognized risk. The anticonvulsants valproic acid and carbamezapine are known to substantially increase the chances of conceiving a child with an ONTD. The risk associated with the first trimester use of these agents may be as high as 1%–2%. Preconception care for women taking these medications should include considering discontinuing anticonvulsant use if possible, or switching to a safer medication such as phenobarbital or dilantin, which are not associated with fetal ONTDs. There is limited data on the newer anticonvulsants such as gabapentin, felbamate, levetricactem, and zonisamide (27–30). Maternal use of warfarin and vitamin A (most commonly as retinoic acid) also are risk factors for fetal spina bifida (23). Any maternal medication use should be carefully reviewed with the patient, ideally preconceptionally, and options discussed.

Prepregnancy obesity and diabetes are also associated with an increased risk of conceiving a fetus with spina bifida. Women with a prepregnancy body mass index (BMI) greater than 29 kg/m^2 have a 1.5 to 3.5 times greater chance of conceiving a child with spina bifida than those with a lower BMI. This increased risk may not be ameliorated by taking recommended doses of folic acid (14,31–34). Pregestational diabetes has long been recognized as a risk factor for spina bifida. When both maternal obesity and pregestational diabetes are present, the risk for an affected pregnancy is increased even further (35,36). Maternal hyperthermia secondary to fever or environmental factors such as hot tub or electric blanket use have been implicated as a cause of fetal spina bifida, with some reporting a doubling in the rate (37,38).

Risk factors which are the subject of much investigation are maternal mutations of various enzymes in the homocysteine remethylation pathway. One gene which has been extensively studied is 5,10-methylenetetrahydrofolate reductase (MTHFR). MTHFR plays a pivotal role in the production of the primary circulating form of folic acid. Although several allelic variants have been described, maternal homozygosity for the 677T allele or compound heterozygosity for C677T/A1298C have been associated with an increased risk for fetal spina bifida and anencephaly (39–42). Another enzyme which has been linked to an increased risk of spina bifida is methionine synthase (MTRR), the enzyme that activates cobalamin-dependent methionine synthase. Several studies of women homozygous for the MTRR 66G allele have found an increased incidence of spina bifida in their offspring and that risk was increased up to 5-fold when found in combination with low B12 levels or with one of the MTHFR mutations described above (43,44).

Having had a previous pregnancy with fetal spina bifida or a family history of an ONTD increases the odds that an ONTD will occur (18,19). A family history of spina bifida occulta, a condition in which the neural tube and surrounding structures are normal but there is failure of 1 or more of the vertebral bodies to completely form, and which occurs in approximately 17% of the North American population, is not known to be a risk factor for an ONTD (45–48).

SCREENING AND PRENATAL DIAGNOSIS

Women at increased risk for conceiving a fetus with an ONTD secondary to any of the factors discussed above should be informed about the availability of diagnostic ultrasound and prenatal maternal serum alpha-fetoprotein (MSAFP) screening for ONTDs. These tests can be performed between 15 and 20 weeks' gestation. Amniocentesis is a reasonable adjunct in the diagnostic process as chromosomal analysis can be performed and amniotic fluid alpha-fetoprotein (AFAFP) and acetylcholinesterase can be measured.

Women not known to be at increased risk for conceiving a child with spina bifida should be educated about and offered screening studies. MSAFP is often done as a component of a multiple marker screening test for ONTDs, trisomy 21, and trisomy 18, which also includes human chorionic gonadotropin, estriol, and inhibin A. The screen-positive cutoffs for each of the 3 screening protocols (trisomy 21, trisomy 18, and ONTD) are typically set at a false-positive rate of 5%; thus many women with an elevated MSAFP will not have a fetus with spina bifida. In some cases the fetus will be normal, and in others another abnormality such as a ventral wall defect will be present. Approximately 20%–25% of pregnancies in which there is a fetal spina bifida will have a normal MSAFP when the cutoff for an abnormal result is set at 2.5 multiples of the median (49,50). Elevated MSAFP results should initially be evaluated by confirmation of gestational age, but, if confirmed, diagnostic ultrasound with adjunctive amniocentesis as needed is indicated.

A careful diagnostic ultrasound examination may reveal the splayed vertebral arches and is even more likely to show features of the Arnold Chiari II malformation, a collection of anatomic abnormalities of

the brain which are present in virtually 100% of individuals with spina bifida. Early in pregnancy the Chiari II malformation, seen on imaging studies as the hallmark crescent or banana-like shape the cerebellum, develops when it herniates into the upper cervical region of the spinal canal (banana sign), along with an obliterated cisterna magna are frequently more obvious than the ONTD itself (51–54). Scalloping of the frontal bones, commonly known as the lemon sign, is often the most apparent feature seen on ultrasound, but it can be seen in normal pregnancies as well as in fetuses with other abnormalities, including encephalocele, Dandy-Walker malformation, cystic hygroma, diaphragmatic hernia, and fetal hydronephrosis (54,55). When the lemon sign is identified on prenatal sonography a search for related anomalies should be done and, if nothing is found, consideration should be given to repeating the scan in 2–4 weeks or to obtaining an immediate amniocentesis to measure amniotic fluid levels of AFP and acetylcholinesterase. Although the banana sign and open vertebral arches persist throughout gestation, the lemon sign often resolves by the end of the pregnancy.

Hydrocephalus resulting from the Arnold Chiari II malformation is also easily identified as is the narrow shape of the cranium. Hydrocephalus is identified when the posterior horns of the lateral ventricles exceed 1 cm in diameter. In the second trimester the biparietal diameter (BPD) and head circumference (HC) are often below the 5% for gestational age. Microcephaly has been described in up to 69% of fetuses with spina bifida when the diagnosis was made between 16 and 24 weeks' gestation (53,54). Both of these measurements usually normalize by the later part of the second trimester. Clubbed feet (talipes) can be found in fetuses affected with spina bifida, but the prognostic significance of this deformity is controversial. The sonographic features of fetal spina bifida which may be seen in the second trimester are summarized on Table 1.

TABLE 1
Sonographic features of fetal spina bifida in the second trimester

Cranial findings
Biparietal diameter less than expected
Head circumference less than expected
Frontal notching (lemon sign)
Small or absent cisterna magna
Compressed cerebellum (banana sign)
Lateral ventriculomegaly
Spine findings
Splaying of the dorsal vertebral elements
Meningocele or myelomeningocele sac

It is important to note that spina bifida lesions may be flat with no overlying meningeal sac or may have a cerebrospinal fluid-filled meningeal sac covering the placode and may contain neural elements which can be seen on ultrasound. Lesions with an overlying sac are considered to be open defects because the presence of a sac does not protect the neural tissue from damage or infection; postnatal management is the same whether or not a sac is present. When there is true skin over the defect, the lesion is considered closed or covered. Skin-covered lesions such as lipomyelomeningoceles are believed to have a different etiology than open defects and the Arnold Chiari II malformation is not found in affected individuals (56,57).

MANAGEMENT OF SPINA BIFIDA AND PROGNOSIS FOR AFFECTED INDIVIDUALS

The majority of pregnancies with fetal spina bifida will be uneventful. Fewer than 5% of fetuses with an isolated ONTD will be stillborn and more than 80% will be born at term (Joseph M. Centers for Disease Control and Prevention. personal communication, 2005). Survival for individuals born with spina bifida has steadily increased over the past decades. In a review of survival in 235 children born with this defect, Wong and Paulozzi found that between 1979 and 1994 the overall 1-year survival was 87.2%. When 5-year intervals were examined, survival rates were 82.7% for 1979–1983, 88.5% for 1984–1988, and 91.0% for 1989–1994 (58). Furthermore, several studies of long-term outcome for individuals with spina bifida have found the survival at 6 years to exceed 80% (59–61).

In contrast, a 2001 study by Bowman et al on the 20–25-year outcome of 118 myelomeningocele patients treated nonselectively reported that 28 (23.7%) were known to have died with 47 patients lost to follow-up (60). In 1 large British study published in 2004 which included 117 babies born with spina bifida between 1963 and 1971, also treated nonselectively, 63 (53%) had died and 54 (46%) were living, with an age range of 31–38 years (61). Determining the prognosis for long-term survival in the 21st century is problematic, however, as published studies have included individuals born in the 1960s and 1970s, and there have been several significant advances in the medical and surgical management of individuals with spina bifida in the last half of the 20th century. Before the development of adequate shunting devices in the early 1950s the leading cause

of death in children with ONTDs was complications from uncontrolled hydrocephalus. In fact, in a series of 904 patients with spina bifida treated over a 43-year period, Davis et al reported that a major factor contributing to increased survival before 1975 was the presence of a cerebrospinal fluid shunt. After 1975, survival to adolescence was similar whether or not the child was shunted (62). Urinary tract disease became the primary cause of morbidity and mortality until 1972, when Lapides et al revolutionized management of the neuropathic bladder with clean intermittent catheterization (CIC) (63). Now, with the phenomenal success of CIC in preserving renal function, complications from the Arnold Chiari II malformation and shunt problems are the leading causes of mortality for those with spina bifida (64–66).

Beyond survival, however, it is important to understand the overall picture in terms of outcome. Although spina bifida is a complex congenital condition affecting multiple aspects of physical function as well as intellectual development, the most apparent abnormality is the paralysis which occurs below the level of the defect. It is the highest level of the open neural tube which defines the degree of muscle dysfunction. While a large lesion may pose more of a challenge to the surgeon closing the defect than would a smaller one, the number of involved vertebrae or length of the lesion play no role in determining motor function. Likewise, the size of the overlying sac itself has no prognostic significance. The lower extremities are completely without muscle function when the lesion is thoracic and there is little useful leg function when the lesion is high lumbar (L1 and L2). Children so affected can be upright with the aid of specially designed standing frames or parapodiums and may walk with sophisticated braces such as the reciprocating gait orthosis (RGO) but they will never be functional walkers. In addition to paraplegia, spinal deformities such as kyphosis and severe scoliosis commonly develop when the defect occurs in the thoracic region as the muscular support of the vertebral column itself is deficient. When the lesion is mid to low lumber (L3–L5) the prognosis for long-term walking and the need for specific orthotics such as long or short leg braces as well as assistive devices such as walkers or crutches is not easy to accurately predict. The situation is complex because of the possibility of some degree of spared function of the nerves and the anatomy of innervation of the muscles about the joints of the lower extremities. For example, when the lesion is between L2 and L3 the hip flexors will be innervated while the extensors will not. When the defect is located between L3 and L4, knee extension but not knee flexion will typically be intact. Those with sacral levels have some degree of plantar flexion and will usually be able to ambulate with a very good, albeit not entirely normal, gait.

In addition to some level of paralysis in the lower extremities, almost all individuals with spina bifida, including those with sacral defects, will have some degree of bowel and bladder dysfunction because the low sacral nerves innervate the distal bowel, anal sphincter, bladder, and internal and external bladder sphincters. This situation poses a social problem when the child is not dry, but the critical task in the management of a denervated bladder and sphincter is the prevention of vesicoureteral reflux and upper tract damage. For those with a flaccid sphincter the issue is one of continence, as they cannot hold a significant quantity of urine. It is in those with bladder sphincter dysynergia and/or an increased leak point pressure in whom the upper tracts are at risk. Resultant vesicoureteral reflux can damage the upper tracts and lead to renal failure over time (67,68). In many cases, CIC alone is very effective in preserving upper tract function as the bladder is emptied before the intravesical pressure can increase sufficiently to cause reflux and kidney damage (62,69). If an acceptable level of dryness is not obtained with CIC alone, the next step is to add anticholinergic agents to decrease bladder spasms or to use them in combination with alpha-adrenergic agents which are used to increase outlet resistance (70,71). Even in a patient who is dry on CIC, anticholinergic agents may be needed to control reflux. There are several surgical options for those individuals in whom medical management does not result in a satisfactory degree of urinary continence. These include the Kropp procedure which increases the length of the urethra, periurethral collagen injections which increase urethral pressure, the Mitrofanoff procedure in which a continent catheterizable abdominal stoma is created, and implantation of an artificial sphincter (72–76). There are additional surgical procedures such as bladder augmentation which can be used to decrease bladder spasms and increase volume.

Whereas management of the neuropathic bladder is a medical as well as a social issue, bowel dysfunction presents a primarily social problem. Although some individuals with spina bifida will develop life-threatening complications secondary to severe constipation, incontinence is the chief problem. High-fiber diets or fiber supplements are frequently used to improve stool consistency and a program of digital stimulation and/or extraction, en-

emas, or timed evacuation is successful for many (77–79). There are also more invasive solutions such as the antegrade continence enema (ACE) procedure in which the appendix is used to make a continent abdominal stoma through which an enema can be administered (80,81).

The neurologic effects of myelomeningocele go beyond those related to abnormal spinal cord development, as this is a condition which causes abnormalities throughout the central nervous system. The Arnold Chiari II malformation is a complex abnormality of the brain found in virtually 100% of those with a myelocele or myelomeningocele (82). Hallmarks of the Arnold Chiari II include a small posterior fossa, medullary kink, beaked tectum, and a tube-like elongation of the fourth ventricle, but it is the herniation of the brainstem which the most significant threat to those with spina bifida. The cerebellum, in a relatively herniated position, causes an obstruction to the flow of CSF which may be partial or relatively complete. When CSF is produced more quickly than it is able to drain, hydrocephalus results. It is, therefore, not surprising nor is it a sign of a more severe or complicated case of spina bifida when hydrocephalus is diagnosed on prenatal ultrasound. In fact, some degree of hydrocephalus is seen on prenatal ultrasound in over 75% of cases. In the majority of those who have no ventricular dilatation before birth, hydrocephalus develops soon after the ONTD is closed. The mere presence of hydrocephalus does not mean that treatment with a shunting device will be necessary, however. Even in the presence of the Arnold Chiari II, approximately 10%–15% of those with spina bifida will not develop a degree of hydrocephalus requiring treatment. The lower the level of the defect, especially when it is sacral, the greater the chances that shunting will not be necessary (83). In the 85%–90% of children in whom progressive ventricular enlargement occurs, placement of a ventricular shunt is the accepted mode of treatment (84). Endoscopic third ventriculostomy remains a controversial approach to management of hydrocephalus in children. It can be technically difficult to perform given the abnormal anatomy of the brain and the signs and symptoms of failed diversion, which can be subtle, are often less obvious than they are with traditional mechanical shunting (85). Although shunts are a necessary life-saving device for those with progressive hydrocephalus, there is significant potential for associated morbidity and mortality. Shunts may need revision because of proximal or distal obstruction, under or over drainage, infection, or mechanical failure. In a 2003 study of long-term outcome of hydrocephalus in 189 children with myelomeningocele born between 1987 and 1996, Tuli et al reported that in 120 (64%) the median time to the first episode of shunt failure was 303 days. Overall, 61 (32.2%) had 2 episodes of shunt failure, 38 (20.1%) had 3 episodes, and 36 individuals (19%) had 4 or more episodes of shunt failure. Infection at the time of placement was calculated at 15% and, overall, shunt infection caused failure in 29 (24%) of the patients (86). Multiple shunt revisions can threaten optimal intellectual development, but it is shunt infection which poses the greatest threat in this area (87–89).

Although pressure on the brainstem is relieved with appropriate ventricular shunting, some children still suffer from cerebellar and upper cervical nerve dysfunction with resultant abnormalities in oromotor function, swallowing, vocal cord motion, and upper extremity function. Life-threatening central hypoventilation and/or apnea as well as vocal cord paralysis and airway obstruction can result, necessitating oxygen supplementation and, in severe cases, tracheostomy and artificial ventilation (90–93). Unfortunately, the severity of any Arnold Chiari II symptoms frequently do not correlate with the degree of hindbrain herniation present, making it impossible to determine prenatally which children will have problems secondary to the Chiari II and which will not.

Spina bifida is, indeed, a complex congenital defect affecting many body systems and as such it is not possible to accurately predict many of the physical challenges and medical complications a particular individual with spina bifida will face. It is even more difficult, however, to predict their ultimate level of intellectual functioning. Overall, those who do not require ventricular shunting have a much better outlook in terms of intelligence. In those with shunts, studies have shown that the rate of profound mental retardation (IQ below 20) is 5% or less and the average IQ is about 80 which is in the low normal range (84,94). When profound mental retardation is seen, it is usually the result of significant medical complications such as shunt infection or severe problems secondary to the Arnold Chiari II, such as apnea or chronic hypercarbia and/or hypoxia. The picture is much more complex than looking at simple IQ, however. Verbal IQ is often significantly higher than performance IQ and even those with a normal IQ have abnormalities in language function. They often learn meaningful words at a slower rate than expected for age, and have poor memory and retrieval abilities (95–97). Math skills, as estimated by the performance IQ, are recognized as a weaker area for

those with myelomeningocele. Computational accuracy and speed as well as problem solving are challenging (98). All of these verbal and performance issues in combination serve to construct a complex picture of intellectual ability. It is difficult to predict the level of function and ultimate independence in individuals with an overall normal IQ but significant intellectual deficits.

Overall health and well-being can be undermined by the appearance of a whole host of medical complications. The survivors in the studies discussed above as well as those followed by other researchers have suffered from a wide range of medical and surgical problems including, but not limited to, epilepsy, latex allergy, tethered cord, and scoliosis. Common degenerative disorders such as osteoarthritis often affect individuals with spina bifida decades earlier than is routinely seen (60,61,84,99).

There are several exciting areas of research in the area of ONTDs. Atala et al have engineered bladder tissue which they successfully transplanted into 7 myelomeningocele patients with end-stage bladder disease (100). Prenatal closure of ONTDs has shown promise (101–103). The ongoing National Institute of Child Health and Development-funded Management of Myelomeningocele Study (MOMS) is a randomized trial designed to further investigate the risks and potential benefits of the fetal procedure. Researchers have used embryonic stem cells and embryonic ventral spinal cord cells to reinnervate muscles in experimental animals (104,105). In the next decade there is more potential for significant medical advances in the management of individuals with spina bifida than were realized in the last half-century.

CONCLUSION

Myelomeningocele is, indeed, a complex congenital defect. There are many issues to consider in making the correct diagnosis and providing accurate information to the family in whom the diagnosis is made. The fact that this condition affects so many body systems coupled with constant advances in diagnosis and treatment make keeping up-to-date challenging. Obstetrician-gynecologists should, therefore, take advantage of the multiple avenues for continuing medical education available to them. In addition, when the diagnosis of an ONTD is suspected, referral to a maternal-fetal medicine specialist should be considered. If the diagnosis is confirmed, medical personnel experienced in the management of affected individuals such as multidisciplinary spina bifida programs and pediatric neurosurgeons can be invaluable sources of information for the family and are available in most areas of the United States.

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