42. Screening for Neural Tube Defects—*Including Folic Acid/Folate Prophylaxis*

RECOMMENDATION

The offering of screening for neural tube defects by maternal serum α-fetoprotein (MSAFP) measurement is recommended for all pregnant women who are seen for prenatal care in locations that have adequate counseling and follow-up services available (*see* ***Clinical Intervention***). Screening with MSAFP may be offered as part of multiple-marker screening (see Chapter 41). There is insufficient evidence to recommend for or against the offering of screening for neural tube defects by midtrimester ultrasound examination to all pregnant women, but recommendations against such screening may be made on other grounds (also see Chapter 36). Daily multivitamins with folic acid to reduce the risk of neural tube defects are recommended for all women who are planning or capable of pregnancy (see ***Clinical Intervention***).

Burden of Suffering

Neural tube defects, including anencephaly, encephalocele, and spina bifida, account for substantial morbidity and mortality. Anencephaly is almost always lethal, usually resulting either in stillbirth or death within hours or days of birth. Spina bifida can range from mild (spina bifida occulta) to severe (myelomeningocele). The manifestations of severe spina bifida may include infectious complications, paraplegia, bladder and bowel incontinence, Arnold-Chiari malformations, hydrocephalus, and, as a complication of hydrocephalus, diminished intelligence.[1] Aggressive surgical and medical care is often necessary for severely affected cases, along with special schooling and rehabilitative services for patients with permanent disabilities. Based on 1988 cross-sectional data, the estimated lifetime cost of spina bifida is $258,000 per case.[2]

The birth prevalence of neural tube defects has declined substantially over the past 60 years.[3,4] Neural tube defects are reported in 3.6–4.6/ 10,000 live births in the United States.[3,5] These rates underestimate true incidence, however, because affected pregnancies may be spontaneously or electively aborted and because not all cases are detected and reported at birth. Popu-

lation-based active surveillance programs that include prenatal diagnoses have reported neural tube defect rates of 7.2–15.6/10,000 live-born and stillborn infants.[6] A personal or family history of a pregnancy affected by a neural tube defect is associated with an increased risk of having an affected pregnancy, as is maternal insulin-dependent diabetes, but about 90–95% of cases occur in the absence of any positive history.[7–9] The birth prevalence of neural tube defects in the U.S. is higher at younger maternal ages and is more than one third higher for whites than blacks.[5]

Accuracy of Screening Tests

Tests for neural tube defects include ultrasound examination and measurement of maternal serum α-fetoprotein (MSAFP), amniotic fluid α-fetoprotein (AFAFP), and amniotic fluid acetylcholinesterase (AFAChE). The latter two are used primarily as confirmatory tests and should not be regarded as part of routine screening of women at low risk for neural tube defects. Ultrasound examination is used both as a screening test and as a follow-up test after positive MSAFP screening.

An elevated MSAFP measured at 16–18 weeks' gestation is a good predictor of neural tube defects. Depending on the cutoff used to define an elevated level (usually 2–2.5 times the median value for gestational age, reported as multiples of the median or MoM), screening can detect between 56% and 91% of affected fetuses.[10–17] An elevated MSAFP occurs in about 1–5% of pregnant women,[9,14,15,17–20] but for a number of reasons, the likelihood of a neural tube defect given a positive screening test result is small. First, about one third of positive tests are not confirmed by a second MSAFP measurement.[9,19] Second, although the reported specificity of MSAFP when followed by appropriate diagnostic tests (i.e., high-resolution ultrasonography, AFAFP, AFAChE) approaches 100%,[12,18,21] MSAFP assays themselves are relatively nonspecific. About 90–95% of cases with confirmed elevated MSAFP are caused by conditions other than neural tube defects, such as an underestimated gestational age, other congenital anomalies, intrauterine growth retardation, multiple gestations, or fetal demise.[7,9,10,18,20,22] An ultrasound examination is necessary to rule out these explanations for an elevated MSAFP. If ultrasonography does not provide an explanation for the abnormal result (as occurs in about 50%),[10,14,15,17] an amniocentesis should be offered to measure AFAFP and/or AFAChE levels.[8] Less than 10% of these lead to the discovery of a neural tube or abdominal wall defect; the majority of the fetuses tested are normal.[9] In comparison with the number of women who must be tested, the actual number of neural tube defects detected through screening the general population is small (0.06–0.16% of pregnancies).[9,10,18,19]

Virtually all cases of anencephaly can be detected by ultrasound

alone,[24] as can many closed neural tube defects that may escape detection by MSAFP measurement. Current ultrasound techniques are less sensitive, however, in detecting other neural tube defects such as small meningomyeloceles.[11] In addition, although the published sensitivities and specificities of sonographic detection of spina bifida are high (79–96% and 90–100%, respectively),[24–28] investigators have emphasized that these data were obtained from centers with special expertise.[24] They may overestimate the sensitivity that would be expected when prenatal ultrasound is conducted with older equipment or is performed by those with less complete training,[28] which has become increasingly common as more physicians perform their own ultrasound examinations.[29] In addition, many of the published studies were of high-risk women and may not be generalizable to screening in the low-risk population. Nevertheless, recent improvements in ultrasound diagnosis of neural tube defects, with sensitivity and specificity approaching 100% when performed by expert sonographers at major screening centers, has caused some experts to recommend the use of ultrasound instead of MSAFP in pregnancies at low risk for neural tube defects.[30,31] Ultrasound and MSAFP have not been directly compared as screening tests for neural tube defects.

Effectiveness of Early Detection

The detection of neural tube defects in utero provides as its principal benefit the opportunity to inform prospective parents of the likelihood of carrying an affected fetus. Parents may be counseled about the consequences of the malformation and can make more informed decisions about optimal care for their newborn or about elective abortion. The antenatal diagnosis of a severe and/or lethal malformation (e.g., anencephaly) may spare parents some of the trauma associated with delivering such an infant. No controlled trials have been performed to prove that those screened for neural tube defects have better outcomes compared to those not screened, however. Therefore, the usefulness of this information depends to a large extent on the personal preferences and abilities of the parents.[32] Whether or not parents choose to use prenatal screening is related both to their views on the acceptability of induced abortion and their perceived risk of the fetus being abnormal.[33]

Induced abortion is sought by the majority of women who choose to be screened and whose screening tests reveal neural tube defects, thus leading to a decreased birth prevalence of affected infants among screened women.[10,14,15,34–37] Time series from the United Kingdom, where screening by MSAFP and ultrasound is widespread, have reported a 49–50% decline in the birth prevalence of anencephaly and a 32–38% decline in the birth prevalence of spina bifida attributable to elective abortion for sus-

pected central nervous system malformation.[38,39] The effectiveness of screening in reducing the number of infants born with neural tube defects is decreased by less than universal acceptance of screening, incomplete detection of affected fetuses, and varying decisions about elective abortion following early detection.[35]

Several interventional cohort studies have evaluated the effect of MSAFP programs on the birth incidence of neural tube defects. In one such study, MSAFP screening was offered to all pregnant women attending antenatal clinics during the study period (n = 15,687), of whom 70% were actually screened.[35] Of 66 total neural tube defects, 54 occurred in the screened group (4.9/1,000) and 12 occurred in the unscreened population (2.5/1,000). The higher incidence rate in the screened group suggests that women who elected screening may have been at higher risk. Offering screening resulted in the elective abortion of 56% (37/66) of all pregnancies with neural tube defects. In the screened group, 11 (20%) were not detected by screening. Six (11%) were detected but were not aborted because ultrasonography or tests on amniotic fluid mistakenly indicated an unaffected pregnancy. Screening resulted in fewer infants being born with neural tube defects (1.6/1,000 in screened women vs. 2.5/1,000 in unscreened women). In another cohort study of more than 18,000 women, MSAFP screening was accepted in approximately 85% of second-trimester pregnancies and detected 80% of open neural tube defects, all of which were electively aborted.[34] Screening in this population reduced the birth prevalence of anencephaly by 90% and of open spina bifida by 72%. In a third study, screening was performed in 72% of clinic patients and detected 59% of all affected pregnancies, 94% of which were aborted.[36] Offering screening therefore prevented the births of 55% of affected fetuses.

There is limited evidence evaluating ultrasound screening for neural tube defects. One randomized controlled trial of routine ultrasound examination in low-risk women reported increased prenatal detection of fetal malformations, but no differences in induced abortion rates, survival rates of anomalous fetuses, or other perinatal outcomes.[28,40] Neural tube defects were included among the anomalies detected, but the study was not designed to evaluate this outcome specifically and only 13 such defects occurred in the entire enrolled population. Of eight neural tube defects occurring in the screened group, seven were detected by screening and electively aborted, reducing the birth prevalence by 88%, to 0.13/1,000 screened women. In controls, three of five neural tube defects were detected prenatally, two of which were aborted, reducing the birth prevalence to 0.39/1,000. The numbers of fetuses affected by neural tube defects were too small for valid statistical comparison. Interventional cohort studies evaluating routine ultrasound examination as a screening test for detection of

neural tube defects have not been published, so there is inadequate information available on the acceptability and impact of ultrasound screening, confirmatory tests, and induced abortion in the general population.

Early detection of neural tube defects may also help parents to prepare emotionally, although this potential benefit has not been evaluated. It may enable clinicians to provide more intensive obstetric care and to better prepare for the delivery and care of the baby. Studies are limited, however, regarding the impact of these measures on neonatal morbidity and mortality. In a series of 208 patients aged 2–18 years with meningomyeloceles, there were no statistically significant differences in motor or sensory level, or in ambulatory function, between those delivered vaginally compared to those who had cesarean delivery.[41] On the other hand, in a retrospective population-based study of 160 fetuses with uncomplicated meningomyelocele, cesarean delivery before the onset of labor resulted in better motor function at age 2 years than vaginal delivery or cesarean delivery after a period of labor.[42] Follow-up to 4 years of age was available for 85% of the original cohort.[43] The pre-labor cesarean group continued to have a significantly greater difference between the anatomic and motor spinal cord level compared to the vaginally delivered group. Motor function was not significantly better at 4 years, however. These types of studies have important design limitations. Controlled trials evaluating early cesarean delivery for neural tube defects have not yet been published.

Another potential benefit of MSAFP screening for neural tube defects is the discovery during testing of abnormalities other than the target condition. A raised level of MSAFP, even in the absence of a congenital defect, is a risk factor for low birth weight, preterm labor, preeclampsia, and abruptio placentae;[20,44,45] early obstetric intervention for these problems may be beneficial (see also Chapter 37). Reduced levels of MSAFP are associated with Down syndrome and certain other chromosomal anomalies; MSAFP is one component of multiple-marker screening, which is recommended for the early detection of Down syndrome (see Chapter 41). The ultrasound evaluation that follows the detection of raised MSAFP may lead to a diagnosis of twins or a more accurate assessment of gestational age, and some studies suggest that acting on this information may improve neonatal outcome (see Chapter 36). Other congenital anomalies, such as diaphragmatic hernia, gastroschisis, nonimmune fetal hydrops, and obstructive uropathy, may also be detected. Discovery of a fetus affected by one of these anomalies may be useful for parental decision making, allowing the options of elective abortion or of antenatal treatment if available, planning for delivery and appropriate neonatal care. Controlled trials have not proven that early detection of these anomalies improves outcome, however. Indeed, studies suggest that fetuses with diaphragmatic hernias detected in utero have poorer outcomes than those detected after

birth,[46,47] perhaps in part because larger defects are more likely to be detected prenatally.

The potential benefits of early detection of neural tube defects must be weighed against the potential risks of screening. The most important risks include those to the fetus from amniocentesis, the psychological effects on the parents of a positive test, the complications resulting from induced abortion, and the risk of elective abortion of normal pregnancies due to false-positive test results. The risks of amniocentesis include miscarriage, puncture of the fetus, bleeding, infection, and possibly isosensitization.[9] The exact rate of fetal loss due to amniocentesis is uncertain, since women undergoing this procedure are already at increased risk of fetal loss. The procedure-related rate of fetal loss with current technique appears to be about 0.5–0.8%.[48–50] The best evidence on amniocentesis risks comes from a randomized controlled trial of screening,[48] which reported a procedure-related risk of fetal loss of 0.8% of pregnancies. This may nevertheless overestimate current rates of loss as techniques have improved. In a more recent series of patients undergoing amniocentesis as part of a clinical trial, the risk of fetal loss was 0.04%.[51] In a randomized controlled trial, neonatal respiratory distress syndrome and neonatal pneumonia were more frequent after amniocentesis, independent of birth weight and gestational age; the additional risk was about 1%.[48] A similar trend was seen in the Medical Research Council study,[52] but has not been confirmed in other studies. Infection has not been identified as a significant problem in any large studies. No clinically important effects on development, behavior, or physical status were identified in 4-year-old children whose mothers had undergone midtrimester amniocentesis.[53] Although MSAFP screening will increase the number of women undergoing amniocentesis, in cohort studies of screening programs fewer than 2% of MSAFP-screened women received amniocentesis.[10,14,15,17]

Another risk of screening is the harmful psychological effect on parents of a positive test result. This is especially important because the large majority of positive screening tests in low-risk pregnancies are false positives. There is evidence that expectant parents with normal fetuses who are informed of an abnormal MSAFP test suffer substantial anxiety during the weeks of diagnostic testing and waiting for definitive results.[54–57] The anxiety level of these women at delivery was the same as that of women who had normal screening test results, however. No published controlled trials have evaluated whether counseling and education prior to screening alleviates these psychological effects. Elective abortion of pregnancy because of a fetal anomaly may also have important psychological effects. In one small case-control study,[58] women who aborted fetuses with major malformations (including neural tube defects) experienced grief similar to those experiencing spontaneous perinatal loss, but no comparison was made to

women delivering an infant with a severe anomaly, who may also grieve for the loss of a normal infant. Most women screened will have normal results, and this may have psychological benefits for the reassured parents.

The potential complications of induced abortion must also be considered, since this is the outcome of the majority of positive diagnostic test results. The maternal case-fatality rate from legal induced abortion is 0.4/100,000 procedures, which is substantially lower than the eight to nine maternal deaths per 100,000 live births due to pregnancy and childbirth.[59–62] Rates of other major maternal complications are also lower than in pregnancy and childbirth, occurring in an estimated 0.1% of legal abortions.[62] All maternal complication rates are higher with second-trimester than with first-trimester abortions.

The most serious consequence of false-positive results, the induced abortion of a normal pregnancy on the basis of erroneous diagnostic test results, appears to be very uncommon with current diagnostic techniques (i.e., high-resolution ultrasound, AFAFP, and AFAChE). Investigators have reported false-positive results leading to elective abortion of normal fetuses in 0.006–0.07% of women screened.[10,17,18,34,38,63,64]

Primary Prevention (Folic Acid/Folate Prophylaxis)

Randomized placebo-controlled trials[65,66] and nonrandomized controlled trials[67–69] in pregnant women with a prior pregnancy affected by a neural tube defect have demonstrated that folic acid supplements substantially reduce the risk of recurrent neural tube defects. In the international, multicenter British Medical Research Council (MRC) trial, involving nearly 1,200 high-risk women, 4 mg of folic acid daily at least 1 month before conception through the first trimester reduced the risk of recurrence of neural tube defects from 3.5% to 1.0%, for a relative risk of 0.28 (95% confidence interval, 0.12 to 0.71). The MRC and two other trials tested folic acid doses of 4–5 mg/day, but the 86% risk reduction seen in one nonrandomized trial[67] that used 0.36 mg of folic acid plus multivitamins daily suggests that lower doses may also be effective.

Several case-control studies have reported a reduced risk of neural tube defects in women without a prior affected pregnancy who took daily multivitamins during the periconceptional period (from 1–3 months before conception to 0.5–3 months after conception).[70–72] One of these analyzed the amount of folic acid the multivitamins contained, which was ≥0.4 mg for most women.[71] A similar study, on the other hand, reported no protective effect of either folic acid alone or multivitamins with folic acid.[73] Stronger evidence for a benefit of periconceptional multivitamins with folic acid in low-risk pregnant women comes from a cohort study of 22,715 women.[74] The risk of neural tube defects was significantly reduced, from

3.3/1,000 to 0.9/1,000 women, with daily intake of multivitamins containing 0.1–1.0 mg of folic acid during the first 6 weeks of pregnancy. In an unadjusted analysis, taking multivitamins with folic acid both in the 3 months before conception and in the first trimester was also protective against neural tube defects. In a random sample of the multivitamin users, about two thirds consumed multivitamins containing a daily dose of at least 0.4 mg of folic acid and 95% consumed at least 0.1 mg of folic acid daily. A randomized double-blind controlled trial of the efficacy of daily periconceptional multivitamin-multimineral supplements containing 0.8 mg of folic acid in preventing first occurrences of neural tube defects was conducted in Hungary, enrolling 4,753 women planning pregnancy.[75,76] Full supplementation was defined as taking them from 28 days before conception to at least the second missed menstrual period. The average daily consumption of dietary folate was 0.18 mg, which is similar to the estimated average intake of 0.2 mg/day by women aged 19 to 34 years in the United States.[77] The supplemented group experienced a significantly decreased prevalence of neural tube defects (0 of 2,104 vs. 6 of 2,052), congenital malformations as a whole (13.3 compared to 22.9/1,000), and major congenital abnormalities other than neural tube defects and genetic syndromes diagnosed by 8 months of age (14.7 vs. 28.3/1,000). Three observational studies provide limited evidence for the effectiveness of dietary folate at levels higher than 0.1–0.25 mg/day in preventing the occurrence of neural tube defects.[70,71,74] All three studies reported a protective effect of greater dietary folate intake, although not all results were statistically significant or adequately reported.

Research on adverse effects from folic acid supplementation is limited. Evidence that folic acid supplements in daily doses of 1–5 mg can mask the hematologic manifestations of vitamin B_{12} deficiency, possibly delaying its diagnosis and treatment thereby leading to permanent neurologic consequences, is limited to uncontrolled intervention studies[78–80] and case reports.[81–83] Hematologic improvement in pernicious anemia has also been reported in some patients taking folic acid doses <1 mg, but the response is not consistent, particularly at lower doses.[79,84–86] Nevertheless, this has been advanced as one reason to avoid universal supplementation or food fortification with folic acid. It has also been argued, however, that it is unreasonable to maintain anemia to make it easier to diagnose B_{12} deficiency while some neural tube defects occur that are potentially avoidable by supplementation.[87] Limited evidence supports independent associations of low-normal folate and B_{12} levels, and high homocysteine levels, with neural tube defects,[88,89] suggesting that a causal mechanism for these defects may be an abnormality in methionine synthase, a folate- and B_{12}-dependent enzyme. If these results are confirmed, supplementation with both folic acid and B_{12} may be appropriate to prevent neural tube defects. This could re-

duce the potential for adverse effects of folate supplementation in B_{12}-deficient patients.

Folic acid supplementation may also reduce intestinal absorption of zinc.[90] A randomized trial in which 50 women received either 10 mg folic acid or placebo daily showed no effect on plasma zinc concentrations after 2 and 4 months, however.[91] One cross-sectional study found a significant correlation between pregnancy complications and high folate and low zinc concentrations in the plasma of 450 pregnant women,[92] but confirmation is needed. Patients under therapy with medications that interfere with folic acid metabolism (e.g., treatments for cancer, asthma, arthritis, AIDS, and psoriasis) may be adversely affected by folic acid supplementation, but this risk has not been adequately assessed.[93] Folic acid supplementation might theoretically provoke convulsions in epileptic women by interfering with the activity of certain anticonvulsants; this potential risk has not been well studied.

None of the trials of healthy pregnant women reported serious adverse effects associated with folic acid supplementation. In the Hungarian trial,[94] infants born to women who received a multivitamin-multimineral supplement with folic acid did not differ from those born to women receiving only trace elements in mortality, somatic development, mental and behavioral development, or total serious or chronic disorders, at 8–21 months (mean 11 months) of age. The rate of atopic dermatitis, asthma, and wheezy bronchitis was significantly increased in the group whose mothers received multivitamins (16 vs. 5/1,000), but more affected infants in the supplemented group also had a positive family history for these disorders. This difference may also be a chance effect due to the large number of comparisons made. A series of 91 children born to women who had taken daily multivitamins containing 0.36 mg of folic acid to prevent neural tube defect recurrences revealed no adverse effects on health, auditory, visual, growth, or developmental status at age 7–10 years, compared with the general population.[95] The study found significant increases in neurotic traits, but whether this was attributable to folic acid or to other causes (e.g., increased parental anxiety related to having had a previously affected pregnancy) is unknown.

Recommendations of Other Groups

The American College of Obstetricians and Gynecologists (ACOG),[8] the American Society of Human Genetics,[96,97] the American Academy of Pediatrics (AAP),[98] the Canadian Task Force on the Periodic Health Examination,[99] and an international expert consensus conference[11] have recommended that MSAFP screening be offered to all pregnant women at

16–18 weeks' gestation, provided that it is accompanied by adequate counseling and follow-up and is performed in areas with qualified diagnostic centers (conventional and high-resolution ultrasound, amniocentesis) and high-quality standardized laboratories. The Canadian Task Force also recommends that high-resolution ultrasonography may be adequate for low-risk women.[99] The AAP and ACOG recommend that patients with a personal or family history of neural tube defects be offered amniocentesis at 15–16 weeks' gestation with AFAFP testing.[100] The recommendations of the American Academy of Family Physicians (AAFP) on screening for neural tube defects are currently under review.

The AAP,[101] Canadian Task Force,[99] and U.S. Public Health Service (USPHS)[102] recommend that all women of childbearing age who are capable of becoming pregnant take 0.4 mg of folic acid daily to reduce the risk of having a pregnancy affected with a neural tube defect. The AAP,[101] Canadian Task Force,[99] ACOG,[103] and the USPHS[104] recommend that patients who have had a previous pregnancy affected by a neural tube defect and who are planning to become pregnant should be offered treatment with 4 mg of folic acid daily starting 1–3 months prior to planned conception and continuing through the first 3 months of pregnancy. The recommendations of the AAFP on folate supplementation for the prevention of neural tube defects are currently under review.

Discussion

MSAFP is a sensitive screening test for neural tube defects. When positive results are followed by appropriate diagnostic tests, such as high-resolution ultrasound, AFAFP and AFAChE, MSAFP is highly specific as well. Early detection leads to a reduced birth prevalence of severely affected fetuses and may reduce complications due to labor and delivery in affected infants. It can also detect several other conditions, for some of which effective interventions exist. While MSAFP screening is a relatively safe procedure, neural tube defects are relatively uncommon, and in certain low-prevalence populations it is possible for the complication rate from screening and its follow-up diagnostic tests to equal or exceed the detection rate for the target condition. Some have expressed concern that the relatively small number of neural tube defects detected through screening may not justify the potential risks of amniocentesis and parental anxiety for the large majority of normal fetuses.[32] The increased risk may, nevertheless, be acceptable to parents with strong fears of having an abnormal child.[105] Whether or not to receive MSAFP screening therefore depends on the preferences of the individual patient, who must receive adequate counseling regarding potential risks and benefits of screening before being screened in order to make an informed decision. Ultrasonography performed by expert sonog-

raphers at major screening centers also appears to be a sensitive and specific screening tool, but these findings may not be generalizable to sonographers in other settings. Ultrasound has not yet been adequately evaluated as a routine screening test for neural tube defects.

Identification and abortion of pregnancies affected by neural tube defects raises important ethical concerns, a full discussion of which is beyond the scope of this chapter. These concerns include the implicit message that having a neural tube defect is an undesirable state, the interpretation of induced abortion in eugenic terms by some persons, and societal and economic pressures that may stigmatize families with a member who has a neural tube defect. These issues highlight the importance of offering screening and prenatal diagnosis of neural tube defects in a value-sensitive fashion with emphasis on reliable information about the defects themselves as well as about the potential risks and benefits of screening and diagnostic procedures.

For a woman who has had a previous pregnancy affected by a neural tube defect, there is good evidence that folic acid supplementation begun at least 1 month prior to conception and continued through the first trimester decreases the risk of recurrence. The only dosage adequately studied is a daily supplement of 4 mg, although some evidence suggests that lower dosages may be effective. For low-risk women who are planning pregnancy, a randomized controlled trial and several observational studies indicate that periconceptional intake of multivitamin-multimineral or multivitamin preparations containing 0.4–0.8 mg of folic acid can significantly reduce the risk of first occurrence of neural tube defects. All of these studies indicate the need to start supplementation at least 1 month before conception and to continue daily supplements through the first 2 to 3 months of pregnancy. There is limited evidence that dietary folate intake of greater than 0.1–0.3 mg/day reduces the risk of neural tube defects. No studies have directly compared the effectiveness of multivitamins with folic acid to increased dietary folate intake for the primary prevention of neural tube defects, but the evidence supporting use of multivitamins with folic acid is of higher quality. The current estimated average daily consumption of only 0.2 mg of dietary folate by American women aged 19–34 years[77] suggests that achieving adequate dietary intake may be more difficult for some women than taking supplements. It is unknown whether women who already have a diet that meets or exceeds 0.4 mg/day of folate would gain additional benefit from vitamin supplements. The effort required to assess dietary folate intake adequately may outweigh the costs and potential harms from routine supplementation.

Since half of pregnancies in the U.S. are unplanned,[106] all women capable of becoming pregnant would need to take multivitamins with folic acid (or increase their dietary folate intake) to maximize prevention of

neural tube defects. It is likely that in the observational studies evaluating the association between multivitamins with folic acid and reduced risk of neural tube defects, many of the women evaluated had unplanned pregnancies, providing indirect evidence in support of this intervention. The ability of clinicians to convince women not contemplating pregnancy that they should take multivitamins with folic acid in order to prevent neural tube defects is unknown. Many women of childbearing age who are not planning pregnancy may not take supplements or pursue diets adequate in folate, particularly those who are poorer and less educated. Some authorities suggest that food fortification with folate has greater potential to reach the entire population at risk.[101–111]

The results of controlled trials indicate that folic acid supplementation will not prevent all neural tube defects. The Centers for Disease Control and Prevention estimates that low-dose folic acid supplementation of all women capable of pregnancy would reduce the incidence of neural tube defects in the U.S. by 50%.[102] Therefore, the use of periconceptional folic acid supplements does not preclude offering screening for neural tube defects, although the cost-effectiveness of such screening is likely to be reduced given a lower risk of occurrence.

CLINICAL INTERVENTION

The offering of screening for neural tube defects by maternal serum α-fetoprotein (MSAFP) measurement at 16–18 weeks' gestation is recommended for all pregnant women who are seen for prenatal care in locations that have adequate counseling and follow-up services, skilled high-resolution ultrasound and amniocentesis capabilities, and reliable, standardized laboratories ("B" recommendation). Women with elevated MSAFP levels should receive a second confirmatory test when time allows (i.e., before 18 weeks of gestation), and high-resolution ultrasound examination by an adequately trained and experienced examiner before amniocentesis is performed. Screening with MSAFP may be offered as part of multiple-marker screening (see Chapter 41). There is currently insufficient evidence to recommend for or against the offering of screening for neural tube defects by routine midtrimester ultrasound examination in pregnant women ("C" recommendation). Recommendations may be made against such screening, except when conducted by expert sonographers at major screening centers, based on its unproven accuracy in other settings, the availability and proven effectiveness of MSAFP screening, and cost. See Chapter 36 for additional recommendations regarding routine ultrasound examination in pregnancy. Pregnant women at high risk of neural tube defects (e.g., those with a previous affected pregnancy) should be referred to specialized centers for appropriate diagnostic evaluation, including high-resolution ultrasound and amniocentesis.

Folic acid supplementation at a dose of 4 mg/day beginning 1–3 months prior to conception and continuing through the first trimester is recommended for women planning pregnancy who have previously had a pregnancy affected by a neural tube defect, to reduce the risk of recurrence ("A" recommendation). It is also recommended that all women planning pregnancy take a daily multivitamin or multivitamin-multimineral supplement containing folic acid at a dose of 0.4–0.8 mg, beginning at least 1 month prior to conception and continuing through the first trimester, to reduce the risk of neural tube defects ("A" recommendation). Taking a daily multivitamin containing 0.4 mg of folic acid is also recommended for all women capable of becoming pregnant, to reduce the risk of neural tube defects in unplanned pregnancies ("B" recommendation). Women taking drugs that interfere with folate metabolism (e.g., methotrexate, pyrimethamine, trimethoprim, phenytoin), women at increased risk of vitamin B_{12} deficiency (e.g., vegans or persons with AIDS), and those with epilepsy whose seizures are controlled by anticonvulsant therapy, should consult with their clinician regarding potential risks and benefits prior to considering folic acid supplementation. There is currently insufficient evidence to recommend for or against counseling women planning or capable of pregnancy to increase their dietary folate consumption to 0.4 mg/day as an alternative to taking multivitamins with folic acid ("C" recommendation). Offering counseling to increase dietary folate intake to women who do not wish to take folic acid supplements may be recommended on other grounds, including low risk, low cost, and likely benefit.

The use of periconceptional multivitamins with folic acid does not necessarily obviate the need to offer screening for neural tube defects during pregnancy, since not all defects will be prevented by prophylaxis.

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