Neurologic Disease and Pregnancy

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Overview and General Considerations

Overview

Therapeutic options for neurologic disorders have grown immensely over the past decade. As a consequence, when a woman becomes pregnant, the question is no longer whether to continue or discontinue her treatments; rather, the issues are which treatments to continue and how they should be administered.

The most important message is that in the ideal case, any woman with a known, preexisting medical condition—neurologic or otherwise—should discuss her plans to become pregnant with her physician before she becomes pregnant.

This article is a collaborative effort of current and former members of the Division of Neurology at Baystate Medical Center, Springfield, Massachusetts.

The interested reader is referred (1) to other eMedicine articles to learn more about the specific disorders discussed, (2) to a recently published monograph (Washington, 2004[61]) for an indepth discussion of neurologic disorders in pregnancy, and (3) to the topic-specific references cited.

Neurologic considerations for all women of childbearing potential

All women of childbearing potential should be receiving folic acid at 0.4 mg/d, the recommendation of the US Centers for Disease Control and Prevention.

If neural tube defects occurred in a woman's previous pregnancy, increased antepartum fetal surveillance is required for the current pregnancy. This surveillance should include consultation with a geneticist and targeted fetal ultrasonography to assess the fetal spine and cranium. In addition, preconception supplementation with folic acid at 4 mg/d is recommended; this dosage is higher than that advised for a woman without such a history.

Vegetarians, particularly strict vegetarians, need to be aware of the risk of vitamin B-12 deficiency and other vitamin deficiencies. Strong consideration should be given to supplementing vitamin intake and checking levels.

Women planning to become pregnant should avoid all alcohol consumption, smoking, and use of illegal drugs (eg, cocaine) before and during the pregnancy because these may have serious deleterious effects on the fetus.

Also advisable is a review of all medications and supplements the woman is taking with the prescribing provider to assess for possible teratogenicity.

Considerations in a woman with any neurologic disease who wishes to become pregnant or who is pregnant

Any woman with an existing neurologic condition should consult her obstetrician and her neurologist before she becomes pregnant. During this consultation, the patient can be advised about the possible risks associated with her condition during pregnancy and about the possible teratogenic effects of her medications.

If the woman is already pregnant and if she did not consult her physician in advance, she needs to alert her obstetrician and neurologist. With regard to teratogenicity, her physicians should review her

current medications for their teratogenic potential, and those posing a risk should be discontinued if possible. Care should be taken to discontinue medications only when this action makes good clinical sense for the mother, not solely because they may be associated with congenital anomalies. For example, if antiseizure medications are stopped prematurely, seizure activity may increase during the pregnancy and expose the fetus to several medications at doses higher than those originally used to control the condition.

At least 2 systems are used to classify the risk associated with specific medications.

The first is the US Federal Drug Administration (FDA) risk categories, as follows:

- Category A - Controlled human studies show no risk
- Category B - No evidence of risk in humans, but no controlled human studies are documented
- Category C - Risk to humans has not been excluded
- Category D - Positive evidence of risk to humans from human and/or animal studies
- Category X - Contraindicated in pregnancy

The second system is the automatic Teratogen Information System (TERIS).[16,31]

The 2 systems are poorly correlated. According to the TERIS, the teratogenic risk in human pregnancy is undetermined for 91.2% of drug treatments approved in the United States from 1980-2000. Inadequate information is available for pregnant women and their physicians to determine whether the benefits exceed the teratogenic risks for most drug treatments introduced in the past 20 years. Therefore, in most cases, the cautionary approach (category C) is based on an absence of information, and individualized discussions between the woman and her treating physicians permit an informed joint decision.

Consider consultation with a physician who has expertise in teratogens, such as a geneticist. During this visit, the possible risks of the patient's medications can be discussed, as can the risks of the fetus inheriting the condition for which the medications were prescribed.

Breastfeeding during medical therapy

A classification of the potential effect of medications on breastfeeding infants has been described.[36] This classification is similar to the FDA classification of information regarding teratogenicity and is as follows:

- Contraindicated
- Requires temporary cessation of breastfeeding
- Effect unknown but may be of concern
- Use with caution
- Usually compatible

This system tends towards a proscriptive approach when no information is available to confirm that breastfeeding is safe and is similar in this respect to the FDA system. This absence of information results from the understandable exclusion of pregnant or breastfeeding women or of women who may become pregnant from clinical trials. The result may be overly restrictive. Hence, individualized discussions between the woman and her treating physicians may permit informed joint decision making, during which the benefits of breastfeeding can be considered and balanced with the potential risks of medications excreted in breast milk.

Medicolegal considerations

The most obvious risks are failure to diagnose a condition that develops during pregnancy, failure to preempt teratogenesis and/or avoid teratogenic medications when possible, and failure to anticipate and inform or warn the patient about the potential effect of pregnancy on the management or control of preexisting conditions (eg, epilepsy, sleep apnea).

With regard to magnetic resonance imaging (MRI) during pregnancy in the research setting, where participation is entirely voluntary and optional, the Johns Hopkins Medicine Internal Review Board

states, "MRI imaging [*sic*] is not known to cause risk to the developing fetus though there may be risks that are not known at this time. MRI contrast is known to cross the placenta and subsequent risks to the developing fetus are not known." See the Magnetic Resonance Imaging Standard Language for Consent Documents. Such language also appears to be adequate in the clinical setting when the indication for the study is clearly articulated and the risk of failure to diagnose is weighed against the unknown and hitherto undemonstrated risk to the developing fetus.

In addition, the risk of MRI must be compared with the risks of alternative imaging with ionizing radiation in that particular clinical situation. The chief concern is that an adverse outcome may occur unrelated to MRI but that it will be attributed to imaging. This risk may be minimized with appropriate documentation of the indications for the test, with a discussion of the benefits and risks with the patient, and with the patient's consent for testing.

Similar considerations apply to the clinical use of magnetic resonance angiography or magnetic resonance venography during pregnancy. The benefit of the information that may be gained from the test must be weighed against the fact that no risks are currently documented for the procedure but risks are documented (ie, radiation related) for alternative testing modalities (eg, conventional angiography, CT angiography).

These comments are provided for educational purposes; they should not be considered all-inclusive, and they should not be construed as legal advice. Clinical practice may vary.

Neurologic Complications in Women Previously Free of Neurologic Disease

This section deals with the chief neurologic complications that may occur during pregnancy or around the time of delivery in women who were previously free of neurologic disease. The reader is referred to other texts for relatively infrequent complications. Serious complications, fortunately, are rare.

Eclampsia - Seizures

Eclampsia is defined as the triad of hypertension, proteinuria, and seizures, in which seizures are the most serious consequence.

Preeclampsia is usually diagnosed because of the onset of hypertension and proteinuria that develop in the late second or third trimester. Preeclampsia can lead to eclampsia. The only known cure for this disease process is delivery. Therefore, when women develop this at term, delivery is recommended. However, when preeclampsia occurs at a premature gestational age, attempts may be made to prolong the gestation if it is thought to be in the best interest of the fetus and if the mother's condition remains stable. The obstetric conditions usually dictate the mode of delivery. In general, most patients with preeclampsia are treated with magnesium sulfate infusions during labor and for a short time after delivery to prevent eclamptic seizures.

The symptoms usually emerge during gestation. Untreated, they tend to worsen, with a peak risk at or around the time of delivery. However, the initial presentation may be involved with postpartum seizures in the absence of previously recognized hypertension or current proteinuria.

Patients who have seizures invariably undergo imaging studies to exclude bleeding secondary to hypertension or other structural pathology. Evidence of reversible posterior leukoencephalopathy (RPLE; see below) is occasionally seen on imaging studies. Brain images are usually normal.

Treatment of seizures usually includes magnesium sulfate, but benzodiazepines or rapidly acting antiepileptic drugs (AEDs), such as phenytoin, may be required.

Long-term AED treatment is not needed after the patient's blood pressure is normalized and stabilized. However, no data are available to determine the precise duration of short-term treatment, and local clinical practice prevails.

Reversible posterior leukoencephalopathy

The term reversible posterior leukoencephalopathy (RPLE) was coined relatively recently.[20] Other terms include reversible posterior leukoencephalopathy syndrome, RPLS, posterior reversible (leuko) encephalopathy syndrome, and PRES. The condition may best be understood as one in which cerebral autoregulation of blood pressure is overwhelmed, usually because of a rapid rise in blood pressure. Vasogenic edema occurs in vulnerable regions. The posterior circulation territory is thought

to be most vulnerable because it has a relatively poor ability to autoregulate.[47] Other regions may be affected, and RPLE occasionally affects gray matter.

RPLE is usually identified in settings of hypertensive encephalopathy. Patients with renal failure, those with eclampsia or peripartum seizures, or those taking immunosuppressant or cytotoxic medications are especially susceptible. Metabolic imbalances (eg, hypomagnesemia) and fluid overload may lower the threshold to precipitate RPLE by rapidly elevating the patient's blood pressure.

The 2 most common clinical presentations in pregnant women are seizures and postpartum blindness.

The clinical and imaging findings usually resolve fairly rapidly with appropriate treatment to control blood pressure. The condition may progress to permanent infarct or intraparenchymal bleeding if left untreated.

Cerebral venous thrombosis

In the pregnant patient, cerebral venous thrombosis (CVT) is as common a cause of stroke as cerebral ischemia or cerebral hemorrhage. It is often encountered after delivery. Symptoms and findings are headache, stroke in a venous distribution, or both. The clinical challenges are (1) to identify CVT in patients presenting with headache alone before it progresses and (2) to recognize CVT as the correct etiology in a patient presenting peripartum with stroke.

Without treatment, the risks are emergence or progression of stroke, exacerbated dysfunction, worsening of increased intracranial pressure that leads to vision impairment, and persistence of a difficult-to-treat headache.

Treatment consists of anticoagulation with heparin, which is converted after delivery to warfarin. In rare cases, elevated intracranial pressure must be treated. However, acetazolamide is a category C drug (Data about risks in humans are not available.), and its risks in infants and children have not been studied. Hence, its use must be preceded by a clear definition of goals and by discussions with the patient and her obstetricians. CVT usually, but not always, resolves. Analgesia is permitted, consistent with usual obstetric practice.

The underlying genetic or acquired risk factors for a hypercoagulable state are often sought. Data regarding the yield of such a search in patients who have no other history of venous thrombosis or of previous fetal loss are lacking. However, the presence or absence of risk factors for hypercoagulability may contribute to decision making with regard to the length of treatment with warfarin. At present, no data are available to guide recommendations about how long the patient should take warfarin.

The question acquires particular relevance in the patient who developed CVT during pregnancy and who wishes to become pregnant again, because warfarin is a category X drug. Reports describe birth malformations in children born to mothers who were treated with warfarin during pregnancy. Furthermore, the drug passes through the placental barrier and may cause fatal hemorrhage in utero. Therefore, if the decision has been made that the patient requires anticoagulation in her next pregnancy, warfarin should be discontinued and fractionated or unfractionated heparin should be used.

Decisions must be individualized after discussions with the patient.

Back pain and posterior pelvic pain

A fair number of women have various degrees of back pain or posterior pelvic pain during pregnancy. The distinction between the conditions is that the term *back pain* refers to nonradiating pain centered in the lower lumbar region, whereas posterior pelvic pain refers to pain that is lower and more lateral (buttock). Pelvic pain also radiates to the feet in 45-65% of patients (ie, sciatica). The presumptive causes of back and pelvic pain are the added mass of a gravid uterus in the context of relaxation of the ligaments supporting the uterus.

The 3 treatment options are adaptive management, mechanical support, and symptomatic therapy. Adapt the patient's activities to avoid intolerable pain, and the obstetrician should approve any analgesics.

Compression and stretch neuropathy

Compression or stretch neuropathies occur rarely as postdelivery complications. They are disconcerting to the patient because they introduce unanticipated and unwelcome intrusions into the setting of high expectations and the joys of welcoming a new child. Dealing with the patient's and her family's disappointment becomes an important focus of therapeutic interventions. The overall prognosis for recovery is excellent, although no guarantee can immediately be given to any individual patient at presentation.

The most common locations for compression or stretch neuropathies to occur are the sciatic nerve (presumably due to positioning during natural delivery) and the femoral nerve (presumably due to retraction during cesarean delivery).

Emergence or worsening of carpal tunnel syndrome may occur during pregnancy. The presumed mechanism is pressure on the median nerve within the carpal compartment at the wrist as a result of tissue swelling, secondary to the fluid retention that occurs during pregnancy.

When spinal or epidural analgesia or anesthesia is used, the possibility of a local complication (eg, bleeding) related to the anesthesia may be raised. When adequate localization cannot be achieved by means of the neurologic examination, lumbar spinal MRI may help. MRI may be indicated if the findings suggest a diagnosis or etiology other than compression neuropathy (eg, central cause) for the symptoms.

A rehabilitation medicine specialist (physiatrist) or physical therapist should be consulted to assist in developing a plan to help the patient ambulate, to choose appropriate assistive devices, and to select appropriate range-of-motion and strengthening exercises for the different stages of recovery.

Follow-up with a neurologist, physiatrist, physical therapist, and/or primary physician must be individualized.

Headache and Migraine During Pregnancy

Migraine is extremely common among young women. Hence, optimization of its management during pregnancy is relevant to most young female migraineurs. In the ideal case, management is optimized before the patient considers pregnancy (see Migraine Headache), and the woman discusses her plans to become pregnant with the practitioner treating the migraine so that medications contraindicated during pregnancy, particularly during early gestation, can be avoided. Most preventive and mechanism-specific treatments are contraindicated before conception or during pregnancy because the small but definite risk to the fetus cannot be justified in light of the alternatives available, even if they are less effective than the contraindicated drugs.

Approximately 60-70% of migraineurs improve spontaneously during pregnancy. On occasion, the first migraine attack occurs during pregnancy.

Acceptable analgesics for acute attacks include acetaminophen, caffeine, and opioids. Caffeine is particularly effective in women who do not habitually consume caffeine and in women in whom caffeine withdrawal does not trigger migraine. Antiemetics that may be considered for use during pregnancy are prochlorperazine and promethazine. Treatment options for a severe acute attack (status migrainosus) include intravenous hydration, antiemetics, analgesics, and steroids.

For some migraine preventive medications, it may be possible to specify, at least approximately, the gestational period during which those medications present the greatest danger to the fetus. Thus, one may use them with relative safety outside of those dangerous periods.

Management of Epilepsy During Pregnancy

General considerations in anticipation of pregnancy

Most women of childbearing potential with epilepsy expect to become pregnant. Epilepsy itself is not a contraindication to pregnancy. However, seizure management should be optimized before pregnancy is considered. If the seizures are not acceptably controlled, attention to compliance is recommended. Furthermore, video and/or electroencephalographic monitoring is recommended to classify intractable seizures before conception to optimize treatment and to minimize the risk to the woman and the fetus. Patients with mixed (epileptic and nonepileptic) seizure types who are noncompliant with pharmacotherapy pose a particularly challenging management situation.

A fair amount of information is available to optimize seizure management while minimizing risk to the mother and the fetus. Preconception discussions between the woman and her health care provider and consultation with a neurologist provide the best opportunity to apply this information to a particular pregnancy.

For more information, see Seizure Disorders in Pregnancy.

Three practice parameters published in 2009 by the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) provide current information for women with epilepsy who are pregnant or planning to become pregnant.[57,59,60] The full guidelines, as well as clinician and patient summaries, are available at http://www.aan.com/go/practice/guidelines.

The guidelines affirm that in general it is safe for women with epilepsy to become pregnant, but they make specific suggestions with regards to their medication management before and during pregnancy. Preconceptional folic acid supplementation is possibly effective in preventing major congenital malformations in the newborns of women with epilepsy taking AEDs.

Antiepileptic drugs in pregnancy

The AAN/AES guidelines state that there is probably no substantially increased risk (greater than 2 times expected) of cesarean delivery or late pregnancy bleeding, and probably no moderately increased risk (greater than 1.5 times expected) of premature contractions or premature labor and delivery.

However, for women with epilepsy who smoke, there is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy.

The AAN/AES guidelines state that women with epilepsy who are seizure free for at least 9 months prior to pregnancy probably have a high likelihood (84–92%) of remaining seizure free during pregnancy.

Folic acid supplementation

The AAN/AES guidelines state that preconceptional folic acid supplementation is possibly effective in preventing major congenital malformations in the newborns of women with epilepsy taking AEDs. This is a CDC recommendation for all women of child-bearing potential. The optimal dose for women with epilepsy has not been determined, and the guidelines suggest that supplementing these women with at least 0.4 mg of folic acid before they become pregnant may be considered.

Monitoring of AED levels

The AAN/AES guidelines state that pregnancy probably causes an increase in the clearance and a decrease in the concentration of lamotrigine, phenytoin, and, to a lesser extent, carbamazepine, and possibly decreases the level of levetiracetam and the active oxcarbazepine metabolite, the monohydroxy derivative. They recommend that monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered and monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels may be considered.

Risks to the fetus of antiepileptic drug polytherapy

Monotherapy AED treatment is preferable in general and particularly during pregnancy. The risk of major malformations is as high as 25% in infants of women taking 4 or more AEDs.{Ref29}

The AAN/AES guidelines state that it is probable that AED polytherapy as compared with monotherapy regimens contributes to the development of MCMs and to reduced cognitive outcomes, and they recommend avoidance of polytherapy, if possible.

Risks of valproate to the fetus

The AAN/AES guidelines found that it is highly probable that intrauterine first-trimester valproate (VPA) exposure has higher risk of major congenital malformations (MCMs) compared with carbamazepine and possible compared with phenytoin or lamotrigine. Compared with untreated women with epilepsy, it is probable that VPA as part of polytherapy and possible that VPA as monotherapy contribute to the development of MCMs. For monotherapy, intrauterine exposure to VPA probably reduces cognitive outcomes.

Meador et al found that in utero exposure to valproate as compared with other antiepileptic agents is associated with a lower IQ in children. The study took place over 5 years in 25 epilepsy centers in the United States and the United Kingdom. The design was a prospective, observational, cohort study of pregnant women with epilepsy who took a single agent (carbamazepine, lamotrigine, phenytoin, valproate). The cohort study assessed the neurodevelopmental outcomes of children who were exposed in utero to several antiepileptic drugs. A planned interim analysis conducted when the children were 3 years of age found an increased risk of impaired cognitive function compared with other commonly used antiepileptic drugs and this association was dose dependent. The investigators concluded that valproate should not be used as a first-line agent in women of childbearing potential.[56]

Risks of phenytoin or phenobarbital to the fetus

The AAN/AES guidelines state that monotherapy exposure to phenytoin or phenobarbital possibly reduces cognitive outcomes.

Lamotrigine NAAED update and warning

An update on the teratogenicity of lamotrigine came from the North American Antiepileptic Drug (NAAED) pregnancy registry. It reported an elevated prevalence of isolated, nonsyndromic oral clefts in infants exposed to lamotrigine monotherapy during the first trimester compared with a reference population.[22]

A Dear Health Professional letter issued by the manufacturer reported 5 cases of oral clefts among 564 pregnancies exposed to lamotrigine during the first trimester, for a rate of 8.9 cases per 1000 pregnancies. The letter stated that this rate is 24 times higher than the prevalence of 0.37 case per 1000 pregnancies in the general population of the surveillance program of Brigham and Women's Hospital.

The FDA Web site (Information for Healthcare Professionals Lamotrigine [marketed as Lamictal]; accessed September 2006) states the following:

Preliminary data from the North American Antiepileptic Drug Pregnancy Registry suggest a possible association between exposure to lamotrigine monotherapy during the first trimester of pregnancy and cleft lip and/or cleft palate. The oral clefts reported were few and were not part of a syndrome that included other birth defects. Other pregnancy registries of similar size have not replicated this observation. The validity of this possible association cannot be established until further data are collected in the NAAED Pregnancy Registry, in other ongoing pregnancy registries, or through other research efforts. The clinical significance of this preliminary report is thus uncertain.

The differences among the different series may be related to the levels of lamotrigine attained in the sera of the mothers and fetuses; presumably, teratogenicity is less with lower levels, but data are lacking to confirm this hypothesis.

Specific listing of frequencies of adverse events

The following rates were reported in patients treated with an AED during pregnancy:

- Congenital heart defects - 1.5-2% (background frequency, 0.5%)
- Cleft lip and/or palate - 1.4% (background frequency, 0.15%)
- Neural tube defects
    - With valproate - 1-3.8% (background frequency, 0.1%)
    - With carbamazepine - 0-1%
- Urogenital defects - 1.7% (background frequency, 0.7%)

Data are available from the NAAED pregnancy registry with regard to major malformations associated with monotherapy. Rates are as follows:

- Phenobarbital (n = 77) - 6.5%[23]
- Valproic acid (n = 143) - 10.7%
- Other AED (n = 1048) - 2.9%
- No AED (active malformation surveillance program) - 1.62%

Data from the Lamotrigine Pregnancy Registry showed rates of 2% with monotherapy (n = 200) and 12.1% for lamotrigine plus valproic acid.

A recent study has reported a rate of fetal death or major congenital malformations of 20% for valproic acid, 11% for phenytoin, 8% for carbamazepine, and 1% for lamotrigine.{Ref33}

Mild nonspecific effects on the fetus

The AAN/AES guidelines state that neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1-minute Apgar score of <7.

Bleeding risks

Anecdotal evidence suggests an increased risk of bleeding in mothers taking AEDs and in newborns because of the potential for vitamin K deficiency due to induction by some AEDs of increased vitamin K metabolism. A possible remedy is for the mother to take vitamin K 10 mg orally during the last month of pregnancy. If this is not taken, vitamin K can be given parenterally during labor. The newborn should receive 1 mg given intramuscularly or intravenously at birth. These recommendations are not followed universally because the evidence to support them is anecdotal.

The AAN/AES guidelines state that there is inadequate evidence to determine if the newborns of women with epilepsy taking AEDs have a substantially increased risk of hemorrhagic complications.

Breastfeeding while taking AEDs

The AAN/AES guidelines state that primidone and levetiracetam probably transfer into breast milk in amounts that may be clinically important. Valproate, phenobarbital, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts.

The authors of this article suggest that the following additional information may be useful for decision making regarding breastfeeding by women taking AEDs to treat epilepsy.

Breast milk–maternal plasma ratios of AED concentration are as follows:

- Carbamazepine - 0.4
- Phenytoin - 0.45
- Phenobarbital - 0.4-0.6
- Valproic acid - 0.42
- Lamotrigine - 0.6

To illustrate the implications, consider this example: Carbamazepine is maintained at a serum level of 8 mcg/mL, 0.4 is the breast milk–serum concentration ratio, and the newborn's daily intake is 200 mL; this translates to 640 µg/d or 0.64 mg/d. For a 3.5-kg newborn, intake is approximately 0.2 mg/kg/d. However, the newborn's metabolism of carbamazepine is less efficient than the mother's, prolonging the half-life of the drug. This prolongation is equivalent to an intake of 1 mg/kg/d in a person with normal clearance. This appears to be a negligible intake.

Similar calculations may be performed for the other AEDs. However, results may be less favorable for medications with long half-lives, such as phenobarbital, lamotrigine and valproate combined, or concomitant non-AED medications associated with impaired metabolism in newborns.

One report[6] reflected nondetectable levels of antidepressants and benzodiazepines in the sera of breastfed infants of mothers who were taking these medications only during lactation. The number of mother-infant pairs was limited; the results may be dose related and may not be generalizable to mothers taking higher doses of these medications.

As a consequence, the potential risks associated with breastfeeding by a mother taking AEDs may need to be considered on a case-by-case basis. In some patients, particularly those receiving monotherapy, the risks may be related less to serum levels and more to idiosyncratic reactions. However, because the newborn is exposed to medications in utero, opportunities for idiosyncratic reactions to occur are ample even before birth, and therefore need not be overstated after birth.

Moreover, abrupt discontinuation of AEDs may pose some risks to newborns who were exposed to them in utero; effects include jitteriness (a withdrawal symptom) and, in rare cases, seizures. Withdrawal symptoms are most common with benzodiazepines.[24]

If a decision is made not to breastfeed while on AEDs, some practitioners recommend initial breastfeeding for 2 weeks, with progressive discontinuation over another 2 weeks. Because the baby was exposed for the past 9 months, the gradual downward titration of AED levels in the infant might potentially minimize withdrawal symptoms.

The official labeling of most, if not all, AEDs recommends that breastfeeding women not use them. However, this recommendation appears to be an oversimplification of the situation because the benefits of breast milk to the infant may outweigh the risks of low levels of AEDs.

Hence, an informed, patient-specific decision ideally guides a mother's choice regarding breastfeeding and concomitant use of AEDs.

Specific treatment recommendations

Specific treatment recommendations should be individualized. The risk to the fetus should be balanced with the risk to the woman due to generalized tonic-clonic seizures or, if the woman is seizure free before conception, the risk due to breakthrough seizures of any type during pregnancy.

The authors' approach is to try to achieve monotherapy before pregnancy, if possible, by aiming for the best medication for the seizure type.

Valproic acid and phenobarbital are avoided, if possible. Concomitant nonepileptic medications are reviewed, and the elimination of those that can be eliminated is advised.

They prescribe supplementation with folic acid at a dose of 4 mg/d. (No evidence supports the use of this dosage rather than a lower dosage, such as 0.4mg/d.)

In addition, increased fetal surveillance is recommended if the woman requires treatment with AEDs. This surveillance should include a detailed anatomic survey by using high-resolution ultrasonography, fetal echocardiography, and maternal serum screening for alpha-fetoprotein, which assists in diagnosing neural tube defects.

The authors prefer to check AED levels frequently (eg, every month) because levels may drop during pregnancy and rise after delivery. The dosage is adjusted if needed.

Sleep Disorders During Pregnancy

Symptoms related to sleep are more common in pregnant women than in nonpregnant women. Pregnant women are most likely to snore and to have insomnia and daytime sleepiness. A variety of factors may contribute to this increase in symptoms, including weight gain, hormonal changes, nutritional stress, and nocturnal discomfort.[45]

Insomnia

Insomnia is most prevalent in the first and third trimesters and affects a substantial minority of pregnant women. Causes of insomnia include urinary frequency, low back pain, nocturnal cramps, fetal movements, and restless legs syndrome (RLS) or periodic limb movements of sleep.

Urinary frequency often occurs early in pregnancy and may result in repeated bouts of nocturia.

Low back pain is a common symptom among pregnant women. The weight of the enlarging uterus stresses the spine and changes lumbar posture. Sleeping position may need to be altered to find one that minimizes backache. Specially shaped pillows have been recommended and offer some benefit. Water exercises, physical therapy, and acupuncture also may reduce discomfort, improve function, and lessen insomnia.

Nocturnal cramps occur more frequently during pregnancy than in other stages of life. The cause of these painful, sleep-disrupting attacks usually cannot be determined. Several trials of vitamin and mineral supplements have been published, but little benefit from such treatments is documented. The available data give greatest support to the use of magnesium salts to decrease cramps.

Fetal movements become increasingly prominent as pregnancy progresses, and they may contribute to nocturnal arousals in certain patients.

RLS may occur throughout life, but the prevalence during pregnancy is unusually high.[32] In this disorder, the patient reports a distinctly unpleasant, nearly continuous urge to move her legs late in the day and at night. The symptoms can be a major obstacle to falling asleep. Once asleep, a patient may have periodic leg movements that can cause several arousals.

Data from epidemiologic and other investigations have supported the notion that iron deficiency may play a role in the genesis of restless legs. Iron is a cofactor in the endogenous production of dopamine in the CNS. Dopamine, in turn, plays a role in modulating movement. The altered dopaminergic balance can result in restlessness. This is seen in association with Parkinson disease and in the akathisia that may accompany the use of neuroleptic drugs, which are known to block dopamine receptors. Folate is another nutrient that may play a role in the prevention of RLS. In a group of pregnant women, those with low serum folate levels were most likely to have restless legs.

Dopamine receptor agonists have been highly effective in relieving RLS, but their safety during pregnancy has not been demonstrated. Other proven treatments include narcotics, benzodiazepines, certain AEDs, and clonidine. The risks of these agents to the fetus are given in the Table.

Risks of Drug Therapies for RLS in Pregnancy

Open table in new window

Drug Class	Generic Name	Level of Risk in Pregnancy
Dopaminergic	Carbidopa-levodopa	C
	Bromocriptine	B
	Pergolide (Removed from US market March 29, 2007*)	B
	Pramipexole	C
	Ropinirole	C
Opioid	Oxycodone	B
	Propoxyphene	C (D for long-term use)
	Tramadol	C
Benzodiazepine	Clonazepam	D
	Diazepam	D
	Lorazepam	D
Antiepileptic	Gabapentin	C
	Carbamazepine	D
Alpha-agonist	Clonidine	C
Drug Class	**Generic Name**	**Level of Risk in Pregnancy**
Dopaminergic	Carbidopa-levodopa	C
	Bromocriptine	B
	Pergolide (Removed from US market March 29, 2007*)	B

	Pramipexole	C
	Ropinirole	C
Opioid	Oxycodone	B
	Propoxyphene	C (D for long-term use)
	Tramadol	C
Benzodiazepine	Clonazepam	D
	Diazepam	D
	Lorazepam	D
Antiepileptic	Gabapentin	C
	Carbamazepine	D
Alpha-agonist	Clonidine	C

Because RLS has a benign prognosis and because it often resolves after pregnancy, most women are reluctant to receive pharmacologic treatment. Increased supplementation of iron and folate may be the best approach. Because the serum ferritin level may not directly reflect the availability of iron in the CNS, iron supplementation to achieve a ferritin level above the minimal normal level should be considered. Additional folate intake beyond the recommended daily allowance of 400 mcg also may be warranted.

* Note: Pergolide was withdrawn from the US market March 29, 2007, because of heart valve damage resulting in cardiac valve regurgitation. It is important not to abruptly stop pergolide. Health care professionals should assess patients' need for dopamine agonist (DA) therapy and consider alternative treatment. If continued treatment with a DA is needed, another DA should be substituted for pergolide.

Sleep apnea

Although elderly men are at greatest risk for obstructive sleep apnea compared with other persons, sleep disordered breathing may occur in pregnant women.[42] The prevalence of loud snoring is reported to increase during the late months of pregnancy. Women who gain excessive weight and/or develop fluid retention may be at particular risk for reduced airflow (ie, apneic and hypopneic events). Such irregularities in breathing degrade the quality of nighttime sleep and may lead to daytime sleepiness.

A second respiratory issue for pregnant women is the possibility of nocturnal oxygen desaturation, especially during rapid eye movement (REM) sleep. REM sleep characteristically produces a generalized loss of tone of muscles except of the diaphragm. Because of this, patients with restrictive lung disease (due to obesity, scoliosis, muscular dystrophy, or other conditions) may breathe at abnormally low lung volumes during REM sleep. When lung volumes are low, blood may be shunted through underventilated lung tissue, and oxygen desaturation may result. The abdominal distention caused by a gravid uterus may produce or add to a preexisting restriction.

Sleep apnea is now recognized as a risk factor for hypertension. It possibly causes recurrent activation of the sympathetic nervous system in response to airway obstruction and hypoxemia. Women with preeclampsia are most likely to have narrow upper airways and to be snorers; this observation suggests that increased upper airway resistance or the resultant snoring or apneas may contribute to pregnancy-induced hypertension. A greater degree of sleep-disordered breathing has been shown in preeclamptic than non–preeclamptic women.[52] Pregnant women who have an elevated apnea-hypopnea index can be successfully treated with nasal continuous positive airway pressure therapy, and their blood pressure can be decreased.

Hypersomnia

Daytime sleepiness is another common symptom during pregnancy, but its severity and effect on well-being have not been thoroughly studied. Hormonal changes are suspected to be a contributing factor in the first trimester. Later than this, disrupted nighttime sleep may be a substantial factor. Sleep apnea may be the cause in an obese woman who snores. Particularly in the presence of hypertension, nocturnal polysomnography (multichannel sleep study) may be warranted to diagnose the disorder.

Treatment with nasal continuous positive airway pressure therapy may be started, if indicated, based on the severity of the condition.

Patients with previously diagnosed narcolepsy or idiopathic CNS hypersomnia may become pregnant and require changes in their treatment. Commonly used stimulants have not been shown to be safe in pregnancy, and they should be withdrawn from most patients before conception. An inability to drive safely and an overall decline in functional status may result. For stimulants dextroamphetamine, methylphenidate, and modafinil, the level of risk to the fetus is category C.

Since 2002, sodium oxybate (gamma-hydroxybutyrate) has been available to treat narcolepsy. This is a highly sedating compound that is known as a drug of abuse. It is taken only at night and reduces both cataplexy and daytime sleepiness by means of unknown mechanisms. The absence of teratogenicity in animal studies has led to it being classified as category B. This information suggests sodium oxybate might be preferable to stimulants during pregnancy, but this preference has not been demonstrated in clinical trials. Because of its potential for respiratory suppression, sodium oxybate could be harmful to pregnant women with sleep apnea, hypoxemia, or hypoventilation. The maximum recommended dosage is a daily sodium load of 1.6 g, which may be undesirable in pregnant women with edema or hypertension.

Parasomnias

Sleep walking, night terrors, and other parasomnias may occur in women of childbearing age. A few systematic studies have been conducted to investigate the effect of pregnancy on these disorders. Data about whether symptoms may increase or decrease during pregnancy are conflicting. Because benzodiazepines are often given to treat parasomnias and because they may be harmful to the fetus, an attempt should be made to withdraw these agents before conception or early in the first trimester in unplanned pregnancies.

Pregnancy and Multiple Sclerosis

Effects of multiple sclerosis on pregnancy

Complications of pregnancy are generally thought to affect women with multiple sclerosis (MS) no more often than they affect women in the general population. This notion extends as far back as 1948.[14] Data from numerous subsequent studies of fertility, pregnancy, and delivery have substantiated this theory.[5] Data also suggest that the risk of spontaneous abortions, congenital malformations, stillbirths, and complications of pregnancy (eg, preeclampsia, premature delivery) is not increased.

Although many findings refute the risk of low birth weight, a retrospective study of the Norwegian National registry[12] showed an increased rate of neonates being small for their gestational age. These neonates had a reduced mean birth weight and length but normal head circumference. The etiology was unclear, although the subtle morphologic changes in the pelvic organs of women with MS may result in suboptimal intrauterine conditions that influence fetal development. The data also suggested an effect on deliveries. Although the number of planned cesarean deliveries increased, women delivering vaginally had an increased incidence of slow labor progression requiring interventions. This result may have been partly due to perineal weakness and spasticity and fatigue related to MS.

These findings were countered in a 3-year prospective study.[51] This study reported normal distributions of weight and head circumferences in babies born to mothers with MS. Rates of infant mortality, congenital anomalies, and cesarean deliveries were also similar to those of the general population.

Reasons for the discrepancies in these studies are unclear. The differences in the severity and localization of disease in the patient populations of each study could certainly play a role in the outcomes, particularly if perineal and bladder involvement differed. Factors increasing the frequencies of pelvic infections may also play a role.

Although MS is unlikely to seriously affect pregnancy, each patient should be evaluated on an individual basis. Patients with clinically significant bladder and perineal involvement and excessive fatigue should to be counseled about possible interventions that may help facilitate delivery.

Effects of pregnancy on MS

Disease activity

An Israeli study of 338 women was conducted to evaluate the relapse rate during each trimester of pregnancy and 6 months after delivery. Of 199 completed pregnancies in 66 women, 85 relapses occurred (20 during pregnancy, 65 postpartum). The relapse rate was definitely reduced in the third trimester.[28]

In 2004, Salemi et al reported on the effects of pregnancy on MS by using a questionnaire. They collected information concerning the age at the onset of MS, disease duration, the number of relapses during the prepregnancy period, the number of relapses during pregnancy, and the first 3 months after delivery. Among 350 patients, 70 had 98 pregnancies. This study showed a significant reduction in the relapse rate during pregnancy (P = .006).[43]

The Pregnancy in Multiple Sclerosis (PRIMS) study was the first multicenter prospective study of MS in pregnant women, and it is the largest natural history study of pregnant women to date.[10] The researchers evaluated 254 women with relapsing-remitting MS during and after 269 pregnancies. Patients were examined at 20, 28, and 36 weeks of gestation to determine the relapse rate in each trimester. The relapse rate declined by approximately 70% during the third trimester of pregnancy compared with the rate observed in the year before conception.

In 1993, Roullet et al reported on the severity of relapses in 125 French women, who were followed via an MS clinic over 10 years. The women had 32 full-term pregnancies. Relapses occurring during pregnancy tended to be mild, resulting in minimal or no residual deficits.[41]

Patients with MS appear to fare better while they are pregnant than when they were not, particularly in the third trimester, with a decrease in the number and severity of relapses. Although some claim that the suppression of MS during pregnancy may be more potent than that achieved with currently available treatments[4], the decision whether or not to forgo treatment with immunomodulatory agents must be made on an individual basis. Given the potential risks of these treatments on the pregnancy, the decision to treat should be reserved only for exceptional cases (see Treatments later in this section).

Postpartum period

In 1959, Millar et al evaluated 45 pregnancy-associated relapses in 170 pregnancies. Thirty-nine women experienced relapses in the postpartum period.[34]

In 1994, Worthington et al reported a 3-year prospective study of the level of disability, severity, and distribution of relapses in 15 women with MS diagnosed before pregnancy compared with 22 nulliparous women with MS as control subjects. Relapses were most frequent during the first 6 months after pregnancy. Fewer relapses than expected occurred in postpartum months 6-24.[51]

In a study of 338 women reported in 1984, Korn-Lubetzki et al found that postpartum exacerbations were 3 times more common in patients than in control subjects.[28]

In 2004, Salemi et al retrospectively determined that the relapse rate increased in the first 3 months after delivery, although the change was not statistically significant (relative risk = 1.36, 95% confidence interval = 0.79-2.20).[43]

In the PRIMS study, the relapse rate increased by approximately 70% and then returned to the prepregnancy rate.[10] Neither breastfeeding nor epidural analgesia affected the rate of relapse or progression of disability.

In 2004, Vukusic et al reported on a study of 227 women enrolled in the PRIMS study for an additional 2 years after delivery.[49] Women with increased disease activity in the year before pregnancy and those who had additional relapses during pregnancy were most likely to have postpartum relapses. They did not find a single predictor (including breastfeeding or epidural anesthesia) that helped in accurately identifying women with MS who would have relapses in the first 3 months after delivery. In the second postpartum year, the relapse rate was similar to that of the year before pregnancy. In addition, pregnancy, delivery, and the postpartum period did not ultimately increase overall disability from MS.

In 1993, Roullet et al found that relapses during the postpartum period were most severe, as reflected by a change in the Expanded Disability Status Scale (EDSS) score of more than 1 point.[41] Worthington et al confirmed this result in 1994, finding that relapses were most severe during the first 6 months after pregnancy.[51] No overall significant differences in the severity of relapses were found in patients

compared with controls, as measured by using the median EDSS score after the pregnant and postpartum periods.

Relapses appear to increase in frequency and severity in the first 3 months after delivery, although they return to the prepregnancy state afterward. Because the decrease in MS activity during pregnancy offsets this change, pregnancy does not seem to change the overall course of the disease from the perspective of disability. Patients with relatively severe disease before and during pregnancy appear to be at greatest risk for relapses in the postpartum period. No other single predictor was identified. In these patients, therapies that may reduce the likelihood of relapses should be considered.

Epidural anesthesia

Epidural analgesia did not appear to affect the rate of relapse or progression of disability in both the PRIMS trial[10] and its 2-year extension[49]. This finding suggests that despite anecdotal reports stating otherwise, epidural analgesia is safe and does not carry a significant risk when it is used for deliveries in patients with MS.

Breastfeeding

In a questionnaire-based retrospective study, the onset of MS, relapse frequency, and breastfeeding was studied in 438 women. Half the patients breastfed their children for a mean of 6.3 months.[37] The relapse rate in the breastfeeding group was not significantly different from that of control subjects (37.5-30.5%). The mean time to relapse was not delayed with breastfeeding. In fact, 69% of relapses in the breastfeeding group occurred while the patient was still breastfeeding. The study data suggested that breastfeeding did not extend the protective effects of pregnancy on exacerbations of MS.

On the contrary, Vukusic et al reported in 2004 that women who chose to breastfeed had fewer relapses than other women.[49] However, they also found that the women who chose to breastfeed also had relatively mild disease. Conversely, women with active disease (and additional relapses) chose not to breastfeed.

The incidence of various infantile illnesses at age 6, 9, and 12 months was evaluated in a study of 140 breastfeeding and 35 nonbreastfeeding mothers.[18] Infants that were not breastfed had significantly increased incidences of otitis media, lower respiratory tract illnesses, constipation, milk intolerance, and allergies.

Breastfeeding does not appear to have a notable effect on the activity of MS. However, breastfeeding lowered incidences of infantile illnesses, as listed above, suggesting a protective effect for the infant. This finding potentially supports the consideration of breastfeeding and the delay of immunomodulating therapy until breastfeeding is stopped in patients with MS. These potential benefits should be weighed against the risks of delaying treatment on a case-by-case basis.

Treatments

The strategy for treating pregnant women with MS is controversial. Some claim that the suppression of MS during pregnancy is more potent than that achieved with currently available treatments for this disease.[4] However, the validity of this argument in all cases is unclear.

Interferon beta-1a and interferon beta-1b - Category C

High doses of interferon beta-1a in rhesus monkeys were not teratogenic, but they had a dose-dependent abortive effect.[35] In a longitudinal, 3-pronged cohort study involving 1 group exposed to interferon beta-1a and interferon beta-1b, a disease-matched unexposed group, and a healthy control group, mean birth weight decreased and rates of miscarriages and stillbirths increased in the exposed group versus the control group (39.1% vs 5%). Two major malformations were also identified: an X chromosomal abnormality and Down syndrome.[7]

In another study, 41 pregnancies involving interferon beta-1a exposure resulted in 20 healthy full-term infants, 1 healthy premature infant, 9 induced abortions, 8 spontaneous abortions, and 1 fetal death. One patient had hydrocephalus. One patient was lost to follow-up. These findings were in stark contrast to those of the 22 control subjects who were exposed to interferon beta-1a before but not during pregnancy. These subjects had 20 full-term healthy infants, 1 healthy premature infant, and 1 birth-related complication (Erb palsy).[44]

Although interferon beta-1a and interferon beta-1b are category C, data from published reports are sufficient to recommend that they should not be used in pregnant patients because they impose a high frequency of serious risks on the fetus.

Glatiramer acetate - Category B

An abstract presented at a meeting of the American Academy of Neurology in 2003 suggested that glatiramer acetate does not impose any substantial risk in pregnancy, with no abortifacient or teratogenic effects. This drug is not known to be excreted in breast milk. Evidence suggests that glatiramer acetate might be safe in pregnancy and breastfeeding. However, caution should be exercised if one decides to treat patients with this drug.

Mitoxantrone - Category D

Mitoxantrone was associated with low birth weight and abnormal fetal kidney development in animal studies. Rats treated with mitoxantrone had an increased incidence of preterm labor.[30] Because of its known risk in pregnancy, mitoxantrone should not be used in pregnant patients.

Intravenous immunoglobulin - Category C

In 1999, Orvieto et al suggested that intravenous immunoglobulin (IVIg) has no known teratogenic effects.[38] It also does not have any apparent effect on the immune system of the fetus or newborn.

If necessary, consider treatment with IVIg, although the potential risks must be carefully assessed.

Azathioprine - Category D

Azathioprine is rated category D. Despite this rating, some believe it is potentially useful for treating MS in pregnancy. Although the drug crosses the placenta, the fetus lacks the enzymes that convert it into its active metabolites; this lack potentially protects the fetus from the potential teratogenic effects of the drug.[8,53] However, because azathioprine is category D, its use in pregnancy should be avoided if at all possible.

Methotrexate - Category X

Methotrexate has known risks for causing malformations and abortifacient effects.[15] It is category X and should not be used in pregnant patients.

Cyclophosphamide - Category D

Cyclophosphamide is teratogenic in animals. In humans, its teratogenicity has not yet been clearly determined.[15] It is, however, category D and therefore should be avoided in pregnant patients.

Corticosteroids (methylprednisolone) - Category C

The PRIMS study included 16 pregnant women who received corticosteroids. No adverse effects were noted in either the patients or their children.[10] The use of corticosteroids (methylprednisolone) in pregnancy may be safe. Use of these drugs in pregnant patients should be considered carefully and avoided unless they are deemed necessary.

Possible postpartum treatments

Corticosteroids (methylprednisolone) - Category C

In one study from 1996-1998, 22 patients who did not receive any treatment after delivery were compared with 20 patients from 1999-2001 who were treated with 1 g of intravenous corticosteroids monthly for the first 6 months of the postpartum period. Although the relapse rate increased during the first 3 months in both groups, it was higher in the untreated group than in the treated group, with a mean of 2 ± 0.66 compared with 0.8 ± 0.41 (P = .018).[55]

This finding suggests that prophylactic treatment with intravenous corticosteroids may be beneficial during the first 3 months after pregnancy. However, to the authors' knowledge, no studies have been conducted to adequately assess its safety in breastfeeding.

Intravenous immunoglobulin

Nine patients with a history of postpartum acute exacerbations were treated with IVIg for 5 consecutive days in the first week after childbirth and at 6 and 12 weeks afterward. None had a relapse during the 6 months after delivery.[1]

In 2004, Achiron et al retrospectively studied IVIg treatment during pregnancy and the postpartum period in 108 pregnant patients with relapsing-remitting MS. The subjects were assigned to an untreated group, a group treated with IVIg in the first week after delivery with booster doses after 6 and 12 weeks, and another treated continuously with IVIg during and after pregnancy. Relapse rates for patients treated with IVIg for the entire pregnancy versus the untreated group revealed a positive effect, as follows: first trimester, 0.43 versus 0.72; second trimester, 0.15 versus 0.61; third trimester, 0.0 versus 0.41; and postpartum period, 0.28 versus 1.33 (P <.05). Relapse rates also decreased in patients treated with IVIg only after delivery versus untreated patients, 0.58 versus 1.33 (P = .012). No significant adverse events were associated with IVIg treatment in patients or newborns.[2]

In 2000, Haas reported on treatment with IVIg to prevent exacerbations after delivery.[19] IVIg was administered within 3 days after delivery and then monthly to patients thought to be at high risk for exacerbations. They were compared with patients in the PRIMS study, who, for this study, served as control subjects. The exacerbation rate after delivery in treated individuals was reduced by 33%.

IVIg treatment may be effective as a treatment to reduce the incidence of pregnancy- and postpartum-related relapses. Again, the potential risks and benefits must be carefully assessed before treatment is started, especially because the medication is category C. Its safety in breastfeeding is unknown.

Myasthenia Gravis and Pregnancy

Autoimmune myasthenia gravis (MG) is an uncommon disease of the neuromuscular junction characterized by striated muscle fatigue and weakness. MG frequently affects young women of childbearing age (20-40 y), and pregnancy creates potential risks for both the mother and fetus.[21]

During pregnancy, the course of disease is unpredictable. In a series of 69 pregnancies in 65 women with MG treated in a single obstetrics department, 15% had deterioration during pregnancy and 16% had deterioration during the puerperium.[13]

In a report of 64 MG pregnancies in 47 women, 39% of those treated improved, 42% were unchanged, 19% had deterioration, and 17% of those not receiving therapy had deterioration. Myasthenic symptoms of 28% women worsened after pregnancy.[13] Therefore, successful management requires the clinician to plan therapy while recognizing the potential for myasthenic crisis, optimizing anticholinesterase or immunosuppressive medication treatment, and preparing for the possibility of transient neonatal MG.

Management of pregnancy and delivery

The risks and benefits of continuing medication or other immunosuppressive therapy should be discussed, and counseling ideally begins when the pregnancy is planned. Treatment of MG should be optimized, and clinical improvement should be maximized. The need for immunosuppressant treatment depends on the severity of illness and should be modified given the duration and severity of the patient's symptoms of MG. If possible, physicians with experience in treating patients with MG should perform the delivery at a hospital with the capability to treat both women and infants with complications of MG.

In the Medical Birth Registry of Norway 1967-2000, a population-based cohort study, the potential for cesarean delivery doubled in 127 births by 79 mothers with MG versus a reference group (17.6% vs 8.6%).[3] The number of births requiring medication to induce labor was not increased. Five children of mothers with MG had serious birth defects, but the rate was not significantly greater than that of a reference group. Preterm rupture of the amniotic membranes was the only complication that occurred more frequently in the MG group than in a comparison group. Rates of neonatal mortality, birth weight, or prematurity did not differ. Pregnancy did not worsen the long-term outcome of MG.[46] Cesarean delivery is recommended if necessary for obstetric reasons, and regional anesthesia is safe with correct drug selection.[9]

Immunosuppressive medication should be discontinued if possible, or the dose minimized, to reduce the potential for adverse effects on the fetus. However, little information is published on this topic. Although some information is derived from the treatment of patients with other autoimmune disorders,

separating the effects from potential risks of the treated illness is difficult. Prednisone or prednisolone is associated with a less than 1% increased risk of cleft palate. Premature rupture of amniotic membranes may be associated with the use of high-dose corticosteroids.[9] Fetal malformations may be associated with methotrexate, and use of this drug is not recommended during childbearing years.[3] Although women taking azathioprine have generally been advised against pregnancy, no teratogenicity or specific malformation pattern is definitively demonstrated with therapeutic doses in humans.[3,9]

In a retrospective review of pregnancy outcomes, infants exposed to azathioprine might develop reversible leukopenia, anemia, thrombocytopenia, reduced immunoglobulin levels, infection, and/or thymic atrophy.[3,9] Babies born to mothers treated with azathioprine have an increased risk of myelosuppression and immunosuppression.[9]

Cyclosporine increases the risk of low birth weight, prematurity, and spontaneous abortions.[3,9] Nausea and vomiting early in pregnancy may interfere with pyridostigmine dosing. Drug schedules may need to be altered because of increased renal clearance, expanded blood volume, and erratic gastrointestinal absorption.[39] Discontinuation of maternal immunosuppressants can worsen or improve MG. If needed, plasma exchange or human IVIg are effective and can be safely administered during pregnancy. In theory, plasma exchange can induce premature delivery because of large hormonal shifts.[3]

Although MG does not directly affect the uterine smooth muscle, the striated abdominal muscles that contract with the effort of delivery during the second stage of labor may fatigue and weaken more easily than they do without MG. Acetylcholinesterase drugs should probably be given parenterally because of their unpredictable oral absorption. Neuromuscular blockers may exaggerate and prolong muscular weakness and should be avoided if possible. Epidural anesthesia is considered relatively safe for vaginal and cesarean deliveries. Magnesium sulfate is used to prevent seizures in patients with preeclampsia, to treat eclampsia, and to prevent preterm birth in patients with preterm labor; this drug can precipitate weakness by interfering with neuromuscular transmission. Maternal deaths are reported with its use to treat MG in women with preeclampsia.[9] Consultation with an anesthesiologist should be considered for all pregnant patients with MG.

Newborn complications

Neonatal MG may result from passive transplacental transfer of antibodies to the nicotinic acetylcholine receptor from the myasthenic mother to the fetus. However, not all infants with detectable levels of antibodies to acetylcholine receptor develop neonatal MG.

The severity of symptoms varies and ranges from mild hypotonia to respiratory distress. Clinical symptoms develop in the first few hours after birth and usually resolve within 2-3 weeks.[9] In the Medical Birth Registry of Norway, 21.3% of children of mothers with MG needed transfer to intensive care units compared with 2% of the reference group. Other studies have shown a neonatal incidence of MG of 10-21%, and neonatal MG was reported in 4% but probably affected 12% of the Norway registry cohort.[21] Children of mothers with MG need careful observation in the first few days after birth, and symptoms may respond to anticholinesterase medication.[9] Women with MG should deliver in a facility with a neonatal intensive care unit.

Arthrogryposis multiplex congenita, characterized by multiple joint contractures in utero, occasionally complicates the pregnancy of a mother with MG. Circulating antibodies may inhibit the function of fetal acetylcholine receptors, with little effect on adult acetylcholine receptor function, and may be responsible for this condition.[40] A high titer ratio of antifetal-to-antiadult muscle antiacetylcholine receptor antibodies is predictive of neonatal MG in the first child of a mother with MG.[17] Elevated alpha-fetoprotein levels may inhibit acetylcholine antibody binding capacity, and this may explain the delay to onset of neonatal MG symptoms after birth.[9]

Summary

The challenging care of a woman with MG who is contemplating pregnancy should begin with careful planning and the collaboration of obstetricians and neonatal intensive care specialists. Counseling should address current knowledge, risks, and available treatments. Women with MG who decide to become pregnant should receive prenatal care from providers with experience in treating patients with MG, and delivery should be performed at a hospital that can manage complications should they

arise.[3,25,21,9]

For more information, see Myasthenia Gravis and Pregnancy.

Cerebrovascular Disease in Pregnancy

Introduction

Stroke is the third leading cause of death and the primary cause of adult disability in the United States. Cerebrovascular disease is thought to be uncommon in pregnancy. However, it is an important cause of maternal and fetal morbidity and mortality, causing 3.5-26 instances of neurologic dysfunction per 100,000 deliveries, and it is associated with greater than 12% of maternal deaths.[50] The incidence of stroke during the childbearing ages alone is 10.7 cases per 100,000 women. Some have questioned if the risk of stroke increases in association with pregnancy itself[11]; however, evidence suggests that the postpartum period is associated with an increased risk of ischemic stroke.[26,27]

Etiologies

Strokes can be classified as ischemic or hemorrhagic. For related information, see eMedicine articles Stroke, Ischemic and Stroke, Hemorrhagic.

Ischemic stroke

Ischemic strokes account for 85% of all strokes.[27] Causes of ischemic stroke in pregnancy can be put into 2 categories: pregnancy-specific etiologies and stroke-in-the-young factors. The first category includes causes such as preeclampsia and/or eclampsia, which are present in 24-47% of ischemic strokes and 14-44% of intracranial hemorrhages.[26,50] Other pregnancy-specific causes include choriocarcinoma, amniotic fluid embolism, peripartum cardiomyopathy, and postpartum cerebral angiopathy. Postpartum cerebral angiopathy is rare and reversible. It causes narrowing of the blood vessels, which can lead to ischemia.[46,50]

Causes of stroke in a young person include atherothrombotic etiologies, cardioembolic events, lacunar disease, other vasculopathy (eg, fibromuscular dysplasia [FMD], dissection, arteritis), hematologic disorders, drugs (eg, cocaine), migraine, and unknown causes. Some causes in this category are less common in stroke than in other settings; they occur most frequently in relatively young women.[27]

Systemic lupus erythematosus (SLE) is one of the disorders that is most common in women. SLE is associated with cerebrovascular events due to hypercoagulability associated with antiphospholipid antibodies or vasculitis. Thrombus may come from a cardiac origin or from within the intracranial vasculature.[27]

Antiphospholipid antibody syndrome is associated with stroke in young women and with SLE and other collagen-vascular diseases. The patient's medical history is important in diagnosing the disorder and should include a pertinent history of spontaneous abortions or intrauterine fetal demise (especially if multiple), thrombotic events, a family history of stroke or antiphospholipid antibody syndrome, and thrombocytopenia. Treatment usually consists of anticoagulation.[27] See eMedicine article Antiphospholipid Antibody Syndrome and Pregnancy.

Other hypercoagulable states that occur in young women, include such conditions as antithrombin III deficiency, protein C or S deficiencies, resistance to activated protein C, dysfibrogenemia, homocystinemia, and plasminogen and plasminogen-activator deficiency. Because pregnancy itself results in a hypercoagulable state, the risk for thrombotic events increases in patients with a known preexisting hypercoagulable condition. These disorders should also be considered in young women with stroke and should be investigated if suspected.[27,50]

Vasculitis is a rare condition that may occur in women of childbearing age and that may result in stroke if it involves the cerebral vessels. In addition to focal symptoms of ischemia (stroke), cerebral vasculitis may cause nonfocal symptoms such as headache and encephalopathy. If suspected, particularly in the setting of known systemic vasculitis, the patient should be evaluated with appropriate laboratory and imaging studies. Primary CNS vasculitis is extremely rare.

Other forms of vasculopathy have been related to stroke in females of childbearing age. This category of noninflammatory vascular disease includes FMD, arterial dissection, and moyamoya disease. Arterial dissection causes symptoms of stroke secondary to embolic fragments from the dissection site. Causes of a dissection include FMD, trauma, hypertension, or spontaneous etiologies. Treatment

for vasculopathy is disease specific and may involve anticoagulation or surgical intervention.[27,50] Migraine headaches are common in young women and can be associated with stroke, but these instances are rare. It is a diagnosis of exclusion.

CVT can cause symptoms of focal dysfunction that mimic those of ischemic stroke. Because of the hypercoagulable state during pregnancy, it is more common at this time than at others. The postpartum period has the highest risk for CVT. One study demonstrates that the risk of intracranial venous thrombosis was 11.66 cases per 100,000 deliveries.[50] Treatment of CVT usually consists of anticoagulation and close monitoring.[27]

Use and abuse of legal and illegal drugs have also been associated, probably causally, with ischemic stroke and intracerebral hemorrhage. The drugs most specifically related to strokes are ephedrine, pseudoephedrine, phenylpropanolamine, heroin, cocaine, amphetamines, and alcohol. These drugs may cause stroke by means of several mechanisms, such as hypertensive surges, arterial vasospasm, arrhythmias, hypercoagulopathy, and embolization of diluent particles. Treatment should be focused on stopping use of the drug and on rehabilitation.[27]

Hemorrhagic stroke

Women at risk for intracerebral hemorrhage in pregnancy are those with eclampsia, vasculitis, or an aneurysm or vascular malformation. High blood pressure is the most important risk factor for intracranial hemorrhage in pregnancy. Prevention is the key. Blood pressure should be monitored closely during pregnancy.[27]

Clinical evaluation

History and physical examination

Obtaining a history and performing physical examination are important aspects of evaluating the type of cerebrovascular event that may have occurred. Important historical points include pain (headache, neck pain), trauma, fluctuating neurologic symptoms, seizures, mental status changes, recent fevers, and drug use. A complete history should include a medical history of previous stroke or risk factors for stroke, spontaneous abortions, collagen-vascular disease, and a family history. In addition, a history of complications that developed during the current and previous pregnancies should be obtained. The patient should undergo a complete physical examination, including funduscopic, cardiovascular, skin, and full neurologic examinations.

Diagnostic testing

Imaging studies are required to evaluate stroke. Several imaging studies are available. CT scanning is the most useful study to rule out an acute hemorrhage. It is also useful in the evaluation of ischemic stroke. CT angiography and CT venography can also be useful in evaluating the cerebral vasculature. CT studies produce results quickly, but they do pose a small radiation risk to the fetus. Evaluation of bleeding due to ruptured intracranial aneurysms or arteriovenous malformations (AVMs) may require extensive imaging studies, including cerebral arteriography.

MRI is useful in evaluating stroke in a pregnant patient. It does not carry the risk of radiation exposure, and the contrast material required for some studies is associated with few reports of adverse reactions, unlike the contrast material used for CT studies. MRIs take longer to perform than CT scans; however, they offer more details of the brain tissue (especially the posterior fossa) than do CT scans. In addition, the diffusion-weighted images increase accuracy in diagnosing acute ischemic events.[50]

Other diagnostic tests that may be used to evaluate a patient with ischemic stroke include carotid Doppler imaging, transesophageal or transthoracic echocardiography, ECG, and, occasionally, transcranial Doppler imaging.[27]

Laboratory testing

Laboratory studies depend on the mechanism of the stroke and on whether the arterial or venous system is involved. Studies may include hemoglobin electrophoresis, fasting homocysteine level determination, a cholesterol panel, anticardiolipin and/or antiphospholipid antibody tests, thrombin time determination for dysfibrogenemia and for factor V Leiden, prothrombin G20210A mutation tests, protein C or S tests, and antithrombin III assays. Of note, protein S activity is decreased during

pregnancy. If possible, the protein study should be performed 6-8 weeks after delivery. Other studies may be indicated to investigate for SLE, other etiologies of vasculitis, and other systemic diseases.

Differential diagnosis

Differential diagnoses of stroke in young women include seizure, brain tumor, RPLE, MS, and migraine. In appropriate settings, infectious causes (eg, Lyme disease, bacterial endocarditis) may need to be considered.

Treatment

Ischemic stroke

Treatment of stroke may minimize neuronal damage and is aimed at preventing recurrences. In pregnancy, factors such as maternal risk versus benefit and fetal risks must be taken into account. The stroke etiology also must be considered when determining the best treatment.

Use of thrombolytics in acute ischemic stroke

Tissue-type plasminogen activator (tPA) is category C in pregnancy. The effects of tPA on humans and animals during pregnancy have not been adequately evaluated, and, at this point, tPA is considered to be contraindicated.[27,50] Although other interventional techniques are being developed to treat acute stroke, information about treating the pregnant patient with stroke with these modalities is limited. When any of these modalities is considered in a pregnant woman, the known risks of withholding treatment must be balanced against the unknown risks of treatment. The stage of the pregnancy (ie, gestational age) likely factors into the considerations. From a dosing standpoint, targeted intra-arterial treatment might be safer than other routes, but it presents radiation risks to the fetus because of the use of x-ray fluoroscopy during the treatment.

The major categories of medications used in stroke prophylaxis are anticoagulants and antiplatelet agents. Anticoagulants are heparin, heparinlike compounds, and warfarin.

Heparin is considered category C in pregnancy. It is used routinely during pregnancy when anticoagulation is needed because it does not cross the placenta. It takes effect quickly and can be stopped abruptly. Associated risks and adverse reactions include heparin-induced thrombocytopenia, osteoporosis (with the use of low molecular weight heparin or unfractionated heparin), and bleeding.

Warfarin is category X in pregnancy. It crosses the placenta and can cause complications with organogenesis. Maternal-fetal bleeding can occur with warfarin, as can spontaneous abortions and still births.

Antiplatelet agents include aspirin, clopidogrel, and a combination therapy composed of dipyridamole and aspirin. Prolonged treatment with high doses of aspirin can result in fetal complications. Therefore, it is not used for long-term treatment with an antithrombotic agent in pregnancy. Adverse events appear to be dose related; hence, a low dose (60 mg) was used in studies. It was not strongly associated with pregnancy-related complications. Clopidogrel is an antiplatelet agent that is category B in pregnancy. Adequate studies in human pregnancies have not been performed with this medication. Dipyridamole is also category B in pregnancy. At moderate doses, it did not cause clinically significant teratogenic effects in animals. Further studies of its safety must be performed. The aspirin-dipyridamole combination has limited use in pregnancy because of the adverse affects of aspirin.[27,50]

See eMedicine article Thrombolytic Therapy in Stroke.

Hemorrhagic stroke

The management of hemorrhagic stroke depends on its location and the etiology. General measures include discontinuation of antithrombotics or anticoagulation, blood pressure management, and general supportive measures. Ruptured cerebral aneurysms or AVMs that have bled may need to be treated urgently either with open surgery or with endovascular interventions. It is easiest to proceed with these treatment decisions if all parties agree that the life of the mother takes precedence, because it may be impossible to safeguard the fetus from all risks when treatment is optimized for the mother.

Prevention

All women may decrease their risk of stroke by avoiding smoking, by maintaining a health body mass index, by avoiding excess alcohol use, by avoiding use of all illegal drugs, and by having their blood

pressure checked periodically to detect hypertension. If they are at particular risk for diabetes or elevated cholesterol levels, periodic checks by their primary health care provider may be indicated. If hypertension, diabetes, or hypercholesterolemia is diagnosed, meticulous treatment lowers their risk of stroke.

Women with known cerebrovascular diseases who are pregnant or who plan to become pregnant may take steps to maximize the safety of their pregnancy. If they previously had a cerebral infarction, its cause should have been or should be determined, preferably before the pregnancy occurs, so that appropriate measures can be instituted to minimize the risk of recurrence.

The following is a summary of available antithrombotics and anticoagulants and their safety profiles during pregnancy:

- Aspirin - Category D (but low dose relatively safe)
- Clopidogrel - Category B
- Dipyridamole - Category B (but formulated in combination with aspirin, which is category D)
- Heparin and heparinlike compounds - Category C
- Warfarin - Category X (crosses the placenta and is particularly problematic during organogenesis, ie, week 6-12 of gestation)

In patients with a known cerebral aneurysm, clipping or coiling should be performed, if possible. Consider cesarean delivery. In patients with a known AVM, resect or embolize the lesion. The preferred mode of delivery has not been established.

Opinions regarding the best treatment of women with hypercoagulable states (thrombophilia) diverge. Some reserve anticoagulant treatment for those with severe thrombophilias by considering the specific etiology and past clinical symptoms, particularly those during previous pregnancies. Patients who previously took warfarin because of recurrent venous thrombotic events need to be converted to heparin or a heparinoid before conception; this should be maintained throughout the pregnancy. Some authorities add low-dose aspirin to manage relatively severe thrombophilias. Decisions in treating mild or moderate thrombophilias must be individualized, with some reserving the use of anticoagulation for the peripartum period.

Keywords

neurological disease, neurologic disorders, neurological disorders, neurologic considerations in pregnancy, teratogenicity, teratogens, genetic consultation, eclampsia, seizures, preeclampsia, reversible posterior leukoencephalopathy, RPLE, cerebral venous thrombosis, CVT, back pain, posterior pelvic pain, compression, stretch neuropathy, headache during pregnancy, migraine during pregnancy, epilepsy, anticipation of pregnancy, lamotrigine, sleep disorders during pregnancy, insomnia, hypersomnia, parasomnia, multiple sclerosis in pregnancy, MS in pregnancy, myasthenia gravis, MG, stroke

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