May

ASSESSMENT PROGRESS:  Total Questions: 10  Questions Answered: 10  Correct Answers: 1

Question 10

A 3-month-old infant is being treated for congenital tuberculosis. Recently he has been irritable and feeding poorly at the breast. The mother brings him to the emergency center after he developed a generalized clonic seizure.

Of the following, the antituberculosis drug MOST likely to have caused the infant’s seizure is:

- A. ethambutol
- B. isoniazid
- C. pyrazinamide
- D. rifampin
- E. streptomycin

Incorrect: Correct Answer: B

Perinatal tuberculosis, comprising congenital and postnatal infections, is treated with various combinations of the drugs listed in the vignette. Almost all regimens include isoniazid, which can cause pyridoxine deficiency and seizures.

Initial treatment of congenital tuberculosis often involves four drugs to reduce the emergence of drug resistance: isoniazid, rifampin, pyrazinamide, and either ethambutol or an aminoglycoside such as streptomycin. Meningitis prompts the addition of a corticosteroid for 4 to 6 weeks.

Once the susceptibilities of the organism are known, treatment can be narrowed to three drugs for 2 months, and then to two drugs, to complete a 6- to 12-month course. Adherence to the drug regimen is encouraged by using directly observed therapy and by dosing twice or three times a week instead of daily.

Isoniazid (also called isonicotinohydrazine or INH) is a small organic compound that blocks the synthesis of mycolic acid, important for construction of cell walls in tuberculosis bacilli. It can cause hepatotoxicity, peripheral neuritis, and seizures.

Pyridoxine (vitamin B6) is a water-soluble vitamin involved in the decarboxylation and transamination of amino acids, among other functions. Pyridoxine deficiency is associated...
with reduced synthesis of the neuroinhibitor γ-aminobutyric acid, leading to irritability and seizures. Other signs of pyridoxine deficiency include glossitis, cheilosis, anemia, and peripheral neuropathy.

Isoniazid inhibits the conversion of pyridoxine to its active form, and also directly disables that active form. Supplemental pyridoxine is recommended during INH treatment for exclusively breastfed infants, for children consuming meat- and milk-deficient diets, and for the pregnant woman.

Rifampin is a semisynthetic derivative of an antibiotic produced by Streptomyces mediterranei. It targets bacterial RNA polymerase. Rifampin is a large molecule to which bacteria can rapidly develop resistance, so it is used mainly in combination with other drugs. Possible side effects include hepatotoxicity, pruritus, vomiting, and thrombocytopenia.

Pyrazinamide is a small molecule whose size allows it to enter tuberculosis bacilli living in macrophages, where it contributes to bacterial killing. Its mechanism of action is disputed. Pyrazinamide can cause hepatotoxicity, hyperuricemia, and joint pains.

Ethambutol is a synthetic molecule that works against the tuberculosis bacilli by interfering with production of the cell wall, by a mechanism different from that of INH. Ethambutol can cause optic neuritis and decreased red-green color blindness.

Streptomycin, isolated from Streptomyces griseus in 1943 by a graduate student at Rutgers University, was the first aminoglycoside discovered, and it became the first antibiotic to successfully treat tuberculosis. It binds to the bacterial 16S ribosome and prevents its binding to the 60S moiety. Streptomycin usually is not used alone for treatment because it can cause ototoxicity and nephrotoxicity, and resistance emerges quickly with monotherapy.

Other drugs being used in adults include the fluoroquinolones, which target bacterial DNA gyrase, and TMC207, which targets bacterial adenosine triphosphate synthase.

References:


Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

06_Nutrition: Know the clinical and laboratory manifestations of deficiencies of water soluble vitamins

10_Infectious_diseases: Know the epidemiology, pathogenesis, and prevention of perinatal infections with Mycobacterium tuberculosis

10_Infectious_diseases: Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with Mycobacterium tuberculosis

15_Neurology: Understand the differential diagnosis and evaluation of neonatal seizures
May

Overview
Editorial Board
My Learning Plan
January
February
March
April
May
June
July
August
September
October
November
December

Evaluation
Claim Your Credit

May

My Learning Plan

ASSESSMENT PROGRESS:

Question 5

A 34-year-old woman in her first pregnancy seeks consultation at approximately 30 weeks’ gestation. She has had a history of major depression since age 24 years, for which she is being treated with a selective serotonin reuptake inhibitor (SSRI). This drug has been continued throughout her pregnancy. The woman is in otherwise good health, and her pregnancy has been uncomplicated. She inquires about the possible side effects of the SSRI on her offspring.

Of the following, the MOST serious side effect, on the offspring, of an SSRI used during pregnancy is:

- A. congenital heart disease
- B. major fetal malformation
- C. neonatal abstinence syndrome
- D. persistent pulmonary hypertension
- E. preterm birth

Incorrect:
Correct Answer: D

Each year at least 600,000 infants are born in the United States who are exposed to maternal major depression during gestation. Major depression during pregnancy may represent recurrence or exacerbation of a pre-existing psychiatric disorder, or may be the onset of a new disorder. Pharmacologic treatment is the most common mode of treatment for major depression during pregnancy. It is estimated that at least 37% of depressed pregnant women take antidepressant drugs during pregnancy. The most commonly used antidepressant drug is a selective serotonin reuptake inhibitor (SSRI). The prevalence of its use is estimated at 6.2% among all pregnant women.

The SSRIs and their metabolites have been detected in both umbilical cord

blood and amniotic fluid. The potency of placental passage of SSRI, estimated by the ratio of the drug concentration in umbilical cord blood to maternal plasma, ranges from 0.29 (for specific SSRIs such as sertraline and paroxetine) to 0.89 (for citalopram and fluoxetine). The ratio is as high as 1.1 for venlafaxine. Swallowed amniotic fluid is an additional source of SSRI for the fetus. These observations suggest that maternal SSRIs can be transferred readily to the fetus and account for their potential side effects.

Much of the information regarding the side effects on the offspring of mothers using SSRIs during pregnancy is based on observational and case-control studies, as randomized placebo-controlled trials would be unethical to perform. These studies, at best, can show associations between maternal SSRI use and specific fetal/neonatal outcomes. Although delineation of biologic plausibility for these outcomes can strengthen the validity of the associations, the cause-effect relationship between maternal SSRI and fetal/neonatal effects cannot be confirmed. With these caveats, a close survey of individual studies and metaanalyses can allow one to draw conclusions regarding the use of SSRIs during pregnancy and their side effects on the offspring.

The most serious known side effect on the offspring of a mother using SSRI during pregnancy is persistent pulmonary hypertension. As reported by Chambers and associates in a case-control study, newborns with persistent pulmonary hypertension were more likely to have been exposed to SSRI during pregnancy after the 20th week of gestation than newborns without persistent pulmonary hypertension (adjusted odds ratio [OR], 6.1; 95% confidence interval [CI], 2.2-16.8). It is speculated that the fetal lung acts as a reservoir for antidepressant drugs, and substantial amounts of an SSRI can accumulate in the lung. Serotonin has not only vasoconstrictive properties that increase pulmonary vascular resistance, but also mitogenic effects on pulmonary vascular smooth muscle cells. Thus, higher circulating concentrations of serotonin in the fetus and accumulation of serotonin in the fetal lung might result in the proliferation of pulmonary vascular smooth muscle cells that is characteristic of persistent pulmonary hypertension of the newborn.

An additional potential pathway to persistent pulmonary hypertension is through the inhibitory effect of an SSRI on the synthesis of nitric oxide, a vasodilator that regulates pulmonary vascular smooth muscle tone and reactivity both in utero and during postnatal life. The incidence of respiratory distress is estimated at 30% among newborns with late prenatal exposure to an SSRI; at least a part of this outcome might be attributed to the occurrence of persistent pulmonary hypertension.

Use of SSRI during pregnancy has not been associated with congenital heart disease in the offspring. As reported by Wichman and associates in a retrospective review, the incidence of congenital heart disease was 0.4% among offspring of women exposed to an SSRI during pregnancy as compared with 0.8% among those not exposed to an SSRI (P=.23). As reported by Alwan and associates for the National Birth Defects Prevention Study, maternal exposure to an SSRI from 1 month before to 3 months after conception (periconceptional exposure) was associated with no increase in the incidence of any type of congenital heart defect (Table 1).

<table>
<thead>
<tr>
<th>Congenital heart defect</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conotruncal</td>
<td>1.3 (0.8-2.1)</td>
<td>.19</td>
</tr>
<tr>
<td>Septal</td>
<td>1.1 (0.7-1.6)</td>
<td>.51</td>
</tr>
<tr>
<td>Right ventricular outflow obstruction</td>
<td>1.3 (0.7-2.2)</td>
<td>.38</td>
</tr>
<tr>
<td>Left ventricular outflow obstruction</td>
<td>0.9 (0.5-1.7)</td>
<td>.82</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.

Use of SSRI during pregnancy has not been consistently associated with major fetal malformations. As reported by Kulin and associates in a prospective controlled multicenter study, the incidence of major fetal malformations was 4.1% among offspring of women exposed to an SSRI during pregnancy as compared with 3.8% among those not exposed to an SSRI (relative risk, 1.06; 95% CI, 0.43-2.62). In contrast, Alwan and associates, in the National Birth Defects Prevention Study, found that maternal periconceptional exposure to an SSRI was associated with three types of birth defects (Table 2), but the absolute risks for
these defects were small.

<table>
<thead>
<tr>
<th>Major fetal malformation</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>2.4 (1.1-5.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>2.5 (1.5-4.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>2.8 (1.3-5.7)</td>
<td>.005</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.

* Absolute risks for these fetal malformations were small.

As reported by Louik and associates for the Slone Epidemiology Center Birth Defects Study, SSRI use during pregnancy was associated with no increase in the incidence of major fetal malformations, including craniosynostosis (adjusted OR, 0.8; 95% CI, 0.2-3.5) and omphalocele (adjusted OR, 1.4; 95% CI, 0.4-4.5). These authors suggest that individual SSRIs may confer increased risks for specific defects, but the implicated defects are rare and the absolute risks are small.

Use of SSRI during pregnancy has not been associated with preterm birth. The metaanalysis by Lattimore and associates showed that the incidence of preterm birth was 8.8% among mothers exposed to an SSRI compared with 5.3% among mothers not exposed to an SSRI (adjusted OR, 1.85; 95% CI, 0.79-4.29; P=.1295).

A cluster of symptoms has been observed in some newborns (up to 30% of cases) exposed to maternal SSRI use during the third trimester of pregnancy. These symptoms, resembling neonatal abstinence syndrome, include irritability, tremors, hypertonia, feeding disturbance, and altered sleep pattern. Seizures, abnormal posturing, and shivering may be seen in rare cases. These symptoms are generally mild and transient, typically resolving within 2 weeks after birth with supportive care.

References:


**American Board of Pediatrics Content Specification(s):**

01_Maternal_Fetal: Know the effects on the fetus and/or newborn infant of maternal psychiatric disorders and their treatment

04_Respiratory: Know the pathogenesis, pathophysiology, pathologic features, and risk factors for persistent pulmonary hypertension

15_Neurology: Know the significance and differential diagnosis of jitteriness and irritability in neonates

18_Pharmacology: Recognize drugs that cross the placenta and are known to present health risks to the developing fetus or to the newborn infant