Common Problems in Critically Ill Obstetric Patients, With an Emphasis on Pharmacotherapy

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ABSTRACT: Pharmacological treatment of critically ill obstetric patients can be especially challenging due to the complexity of caring for 2 patients, with a paucity of research to support practice. This review will provide practitioners with primary recommendations for management of the critical illnesses most commonly encountered in pregnancy and will discuss the scientific and clinical merit of these recommendations. **KEY INDEXING TERM:** Pharmacotherapy. **[Am J Med Sci 2008;335(1):65–70.]**

General Guidelines

If the decision is made to try to salvage the pregnancy, further decisions regarding choices of medication will have to be made with the fetus in mind. The risk of teratogenicity is generally greater during the embryonic stage (3 to 8 weeks after fertilization). Other factors that influence fetal anomalies include the specific medication, genotype of the conceptus, mechanism of teratogenesis, different fetal manifestations, and the dose effect. In addition, our knowledge of medication risk for teratogenesis may be flawed because it is primarily based on animal studies, which may be poor predictors of human teratogenicity. As a result, the vast majority of medications introduced in the past 20 years have an undetermined teratogenic risk.[1]

Venous Thromboembolism

The diagnosis of venous thromboembolism (VTE) in pregnancy can be challenging, as signs and symptoms of VTE mimic normal findings in late pregnancy. After analysis of the data from a recent prospective, randomized, multicenter trial of patients with suspected pulmonary embolism (PIOPED II), investigators recommended that fibrin degradation fragment (D-dimer) testing with clinical assessment be performed initially, followed by venous ultrasonography before performing any studies involving ionizing radiation. If ultrasonography is negative, 69% of PIOPED II investigators then recommended pulmonary scintigraphy, and the remaining 31% recommended proceeding to contrast-enhanced computerized tomography with pulmonary angiography.[2]

Medical treatment of deep venous thrombosis and pulmonary embolism in critically ill obstetric patients is limited to unfractionated heparin, low molecular weight heparin (LMWH), and thrombolytics. There is vast clinical experience with heparin in this population, and multiple studies have shown it to be the safest anticoagulant during pregnancy.[3] Warfarin is not used because it crosses the placenta and may be teratogenic or cause bleeding.[4]

LMWH has been shown in large clinical trials to be at least as effective and safe as unfractionated heparin in the treatment of venous thromboembolism,[5] and further evidence has demonstrating both efficacy and safety in pregnancy[6] and pulmonary embolism.[7] Although heparin-induced thrombocytopenia (HIT) can occur with both medications, HIT has been demonstrated to occur less frequently with LMWH.[8] However, it must be kept in mind that the pharmacokinetics of LMWH are altered during pregnancy, due to increases in both volume of distribution and glomerular filtration rate.[9] This has been shown to lead to declines in anti-factorXa levels as pregnancy progresses with fixed dosing of LMWH.[10] Hence, anti-factor Xa levels should be monitored in critically ill pregnant patients. Finally, LMWH use should be avoided in patients expected to go into labor, require surgery or require intensive care procedures within 24 hours of injection due to prolonged anti-coagulant effect.

The rate of HIT in pregnant patients does not appear to be higher than nonpregnant patients.[8] Treatment options for HIT in pregnancy include lepirudin (recombinant r-hirudin) and danaparoid.[11] Although there is little information about lepirudin

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Submitted September 6, 2007; accepted in revised form October 22, 2007.

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use during pregnancy, use of lepirudin during the last trimester in a patient with systemic lupus erythematosus was not associated with excessive bleeding, thromboembolic events, or fetal toxicity.[12] Transplacental passage of lepirudin has been demonstrated in animal studies, but teratogenicity has not been reported. The heparinoid danaparoid may be the best option to treat HIT in pregnancy. It is an effective antithrombotic agent with less potential to induce HIT than unfractionated heparin and has not been associated with impaired fertility or fetal harm in teratology studies.[13] Although referenced in the American College of Chest Physicians Consensus Conference on Anti-Thrombotic Therapy, danaparoid is currently unavailable in the United States, but in a series of 50 pregnant patients in the German literature there were no adverse effects to the fetus noted.[14] Argatroban is a direct thrombin inhibitor derived from L-arginine that has only been tested in animal reproduction studies, with no controlled studies in pregnant women.

Based on their well-documented ability to decrease clot burden and improve hemodynamics, thrombolytics are recommended in patients with pulmonary embolism and cardiopulmonary collapse unless an overwhelming contraindication is present.[15] Although there is a possibility of hemorrhage with any thrombolytic, there is no evidence to suggest that this complication is increased in pregnancy. A review of the literature on pregnant patients treated with thrombolytic therapy (172 cases) has shown a maternal mortality rate of 1.2%, a pregnancy loss rate of 5.8%, and an 8.1% rate of maternal hemorrhagic complications (versus 6.3% in nonpregnant patients).[16] Of the 3 thrombolytic agents used in gravid patients (streptokinase, urokinase, and tissue plasminogen activator), the most information is available on streptokinase. The use of streptokinase during pregnancy has been described in more than 150 case reports.[17]

Administration of streptokinase during the first half of gestation may result in early placental separation. Furthermore, because streptokinase is a bacterial protein, it can induce allergic reactions including anaphylaxis.[17] There is limited information on the use of urokinase during pregnancy, but there are case reports of successful results in treatment of pulmonary emboli using this agent in pregnant patients.[18] Tissue plasminogen activator does not cross the placenta, and use in pregnant patients for a variety of indications including pulmonary embolism has not been associated with higher complication rates than in nonpregnant patients.[19]

The literature on the use of thrombolytics during pregnancy for pulmonary embolism is limited, and, therefore, their use should be limited to life-threatening situations. Although the most experience is with streptokinase, tissue plasminogen activator remains the most practical choice, because it is the most commonly used thrombolytic and can be given over 1 to 2 hours in the setting of pulmonary embolism, as opposed to 24 hours with streptokinase.

Vasopressors for Sepsis

Common pregnancy-related causes of sepsis include endometritis, pelvic thrombophlebitis, septic abortion, and infection related to obstetric procedures.[20] These conditions mandate aggressive fluid resuscitation, antibiotics, and, oftentimes, vasopressors. Although fetal effects of vasopressors have been extensively studied in animals, there are minimal data in human pregnancy to dictate the optimal choice of vasopressor in the hypotensive gravid patient.

Based on available data, the safest vasopressor for use in pregnancy is ephedrine. It stimulates not only α-1 but also β-2 adrenergic receptors and is the only vasopressor clearly shown to increase uterine blood flow.[21,22] In addition, ephedrine has been shown to improve fetal hypoxemia and acidosis caused by human maternal hypotension during spinal anesthesia.[23] However, it is generally not practical for treatment of sustained hypotension in the intensive care unit because it has a short duration of action and is only administered in periodic boluses. In addition, data on its use are extrapolated from caesarean-section literature rather than direct evaluation in the intensive care unit. Consequently, ephedrine is generally reserved for transient episodes of hypotension that can be treated with short-term bolus injections.

Dopamine is commonly given to treat hypotension due to sepsis in pregnant patients. There have been several small studies on the use of this drug in pregnant women that support its use.[24–26] The effect of dopamine on human uterine perfusion remains inadequately evaluated, but in a complex clinical situation such as septic shock, the overall increase in blood pressure associated with its stimulation of α-adrenergic, β-adrenergic, or dopaminergic receptors should lead to relative improvement in uterine blood flow.

Norepinephrine (a precursor to epinephrine) stimulates both α- and β-adrenergic receptors but has less effect on β receptors than epinephrine. As with dopamine, cardiovascular effects are dose dependent. It is primarily an inotrope at low doses (β-receptor effects), but with higher doses, vasoconstrictor (α-receptor) effects predominate. In nonpregnant patients, norepinephrine has been shown to increase blood pressure, increase intestinal pH, and lower mortality in septic shock compared with dopamine.[27,28] However, there is inadequate information on fetal toxicity or teratogenicity. Transplacental passage is possible, but diffusion across the blood-brain barrier does not occur. Norepinephrine can induce uterine contractions and decrease uterine blood flow; but in patients unresponsive to dopamine, norepinephrine should be considered. The

benefit to maternal blood pressure may outweigh or overcome the other effects.

Epinephrine, an endogenous catecholamine produced and released from the adrenal gland, binds to both α- and β-adrenergic receptors in tissues. It is typically used in patients who have refractory hypotension after traditional agents fail, but at a potential cost of impaired end-organ perfusion. It crosses the placenta but not the blood-brain barrier.[29] Epinephrine can inhibit contractions and delay childbirth, and myometrial hyporeactivity may continue even after the agent is discontinued. Severe adverse effects include uterine atony, bleeding, and fetal anoxia.[30,31]

Phenylephrine is selective for α-1 adrenergic receptors and has been shown to compromise uteroplacental blood flow in sheep with subsequent fetal anoxia and bradycardia.[32] These data have long been extrapolated to humans, and the use of phenylephrine was avoided in gravid patients. However, in multiple recent clinical trials comparing phenylephrine to ephedrine, no differences were found in the incidence of fetal acidosis or neonatal Apgar scores.[33] Therefore, the use of phenylephrine is becoming more common in the hypotensive pregnant patient. It should be noted that all of the clinical trials that compared ephedrine and phenylephrine were in the setting of spinal anesthesia–induced hypotension rather than septic shock.

Although studies are limited, some general rules can be derived from the currently available information. Ephedrine or dopamine should be the agents first tried for treatment of septic shock in pregnant patients. The body of evidence supporting phenylephrine for hypotension in pregnancy is increasing, and its use in septic shock is likely still unsupported. Norepinephrine is a suboptimal choice but may be used if the patient is refractory to other agents. Epinephrine should be avoided unless fetal compromise is deemed inevitable.

Treatment of Hypertensive Emergencies

Hypertensive emergencies are severe elevations in blood pressure with evidence of target organ dysfunction and require immediate admission to the intensive care unit. Treatment of hypertensive emergency in pregnancy is unique because the clinician must be aware of compromising placental perfusion with antihypertensive medications.

The most clinical experience is with hydralazine, but this drug lost favor when a recent meta-analysis concluded that its use was associated with worse maternal and perinatal outcomes as compared with labetalol and nifedipine.[34] Although generally safe, its use has been associated with the development of thrombocytopenia and lupus-like syndrome.[35]

Labetalol is now more commonly chosen because as a selective α1 and nonselective β-adrenergic blocker it both slows the heat rate and decreases systemic vascular resistance. Unlike pure β-blockers, it does not decrease cardiac output but does decrease myocardial oxygen consumption. Reported neonatal side effects include hypotension, hypoglycemia, hypothermia, and bradycardia. However, it has not been found to affect the uteroplacental blood flow or fetal hear rate.[36]

If oral agents are an option, oral but not sublingual nifedipine may be considered. A randomized, controlled trial comparing nifedipine (n = 24) with hydralazine (n = 25) concluded that nifedipine was associated with more stable blood pressure control and shorter neonatal intensive care unit stays.[37] Sublingual nifedipine is contraindicated because it can induce hypotension in the treatment of hypertensive urgencies,[38] and increased mortality has been associated with its use in non–intensive care unit patients.[39]

Magnesium is often used in pre-eclampsia or eclampsia to prevent or treat seizures, but it also lowers the mean arterial pressure.[40] This effect must be carefully considered in patients treated with nifedipine, as magnesium may potentiate the effect of calcium channels blockers and cause severe hypotension.

Nitroglycerin may have the advantage of improving uterine perfusion.[41] However, if used without concomitant volume expansion, the hypotensive effect is achieved at the cost of a reduction in cardiac index. Volume expansion is problematic as it significantly reduces the hypotensive effect of nitroglycerin.[42] In addition, there is the potential risk of methemoglobinemia.

Although sodium nitroprusside has no known teratogenicity with short-term use, pregnancy is a relative contraindication to its use due to potential fetal cyanide toxicity.[43,44] It may be used for brief periods in patients unresponsive to other agents. Due to the frequency of coexistent renal dysfunction in the critically ill and decreased glomerular filtration rate in pregnant patients, cyanide and thiocyanate levels should be monitored. If used antepartum, cord blood should be assayed for cyanide and thiocyanate levels.

Angiotensin converting enzyme inhibitors are contraindicated because they are associated with fetal renal failure and teratogenic effects, and diuretics are relatively contraindicated because of their association with fetal thrombocytopenia and hypoglycemia.

Seizure Management

One of 3 women with a history of epilepsy will have increased seizure frequency during pregnancy. New-onset seizures may be the initial manifestation of a variety of diseases including eclampsia, oxytocin-induced water intoxication, toxicity of local anesthetics, and amniotic fluid embolus, in addition to diseases not attributable to the pregnant state. Many antiepileptic medications are highly protein bound, and when plasma proteins decrease in preg-

nancy, the serum concentrations of free drug increase and are more rapidly excreted through the kidneys. In a clinical study of over 100 women, total serum antiepileptic drug levels were found to decline as pregnancy progressed. Dosage adjustments were required at different stages of pregnancy, depending on the antiepileptic agent used. Other factors which may lower antiepileptic drug levels include a dilutional effect of fluid retention and increased hepatic microsomal activity.[45] It is problematic to predict free drug concentrations because levels tend to increase in some and decrease in others as pregnancy progresses.[46]

Seizures associated with severe pre-eclampsia should be treated with magnesium sulfate. It is not clear if magnesium can be classified as a true anticonvulsant, but it has been shown to reduce cerebral ischemia.[47] In addition, magnesium has been shown to decrease recurrent seizures and may be superior to benzodiazepines and phenytoin for this purpose.[48,49]

The "fetal anticonvulsant syndrome" has been described with hepatic enzyme-inducing anti-epileptic drugs. This syndrome includes major malformations, minor anomalies, microcephaly, cognitive impairment, intrauterine growth retardation, and infant mortality. The most common major malformations are cleft lip/palate, heart defects, and neural tube defects.[50] It is generally recommended that Vitamin K (10 mg per day orally) be administered in the last 4 weeks of pregnancy for women taking these drugs to reduce the incidence of these malformations (phenytoin, phenobarbital, primidone, carbamazepine, topiramate, and oxcarbazepine).[51]

Although teratogenic effects mentioned above have classically been associated with prenatal use of phenytoin, these effects are associated with long-term use. If the patient is in a life threatening situation such as status epilepticus, these side-effects should not deter one from using this medication. In addition to malformations, hemorrhagic disease of the newborn has occurred after fetal exposure to phenytoin[52] and may result from either drug-induced fetal vitamin K deficiency[53] or thrombocytopenia.[54] The pharmacokinetics of phenytoin is significantly altered during pregnancy. Studies show that the clearance of phenytoin is somewhat increased during pregnancy, possibly due to enhanced conversion of the parent drug to hydroxyphenytoin.[45] In addition, plasma albumin concentrations are reduced during pregnancy making the amount of unbound phenytoin in the blood higher. However, although total serum concentrations of phenytoin have been shown to decline throughout pregnancy,[45] free serum concentrations are not significantly reduced.[46]

Phenobarbital is often used as an adjunctive agent for seizures that are refractory to benzodiazepines and phenytoin. Fetal anticonvulsant syndrome has also been reported in infants of mothers treated with large doses of phenobarbital.[55] Changes in cognitive skills have been demonstrated in both animal and human studies.[56] Also, neonates exposed in utero to phenobarbital have experienced barbiturate withdrawal within 2 weeks of birth.[57]

Propofol and midazolam infusions have been used as treatment alternatives for status epilepticus. Since placental glucuronidation may be minimal,[58] there is probably little metabolism of propofol by the placenta. After propofol administration during the first trimester of pregnancy, serum concentrations of the drug are twice greater in the mother than in the fetus, as propofol does not concentrate in amniotic fluid.[59] Propofol has been shown to have no known teratogenic effects in humans and does not accumulate during maternal anesthesia.[59]

Of the benzodiazepines, midazolam is an alternative in the obstetric patient who requires an additional agent for status epilepticus or sedation. Exposure to certain benzodiazepines before delivery has resulted in respiratory depression,[60] lower Apgar scores, hypothermia, poor sucking ability, and need for ventilation in the neonate.[61] In addition, prenatal exposure has been associated with minor anomalies, growth deficiency, and central nervous system abnormalities.[62] Minimal exposure to midazolam and discontinuation before delivery is recommended, as the risk appears to be greater for the fetus than the mother. Midazolam is soluble in lipids at physiologic pH, highly bound to serum proteins, and may have a greater volume of distribution in women than in men.[63] Midazolam concentrations have been compared after administration to patients in the last trimester of pregnancy and after administration to patients in labor. Higher levels were observed in the parturients.[64] Midazolam and its metabolite diffuse across the placenta at a slower rate than diazepam or lorazepam.[65] Teratogenicity has not been demonstrated in animal studies. However, because midazolam is transferred transplacentally, the medication can result in neonatal central nervous system depression and, like other benzodiazepines, should be used only when absolutely necessary.

Intravenous valproate is now a third or fourth-line agent in the treatment of status epilepticus. In pregnancy, it should only be used as a last resort given its association with links to spina bifida (1% to 7%), especially in the first trimester of pregnancy.[66] If valproate is given in the third trimester, levels should be monitored considering the higher likelihood of seizures occurring in patients with subtherapeutic levels.

Levetiracetam (Keppra) is an antiepileptic drug that is increasingly used as second line therapy for seizures. The most common adverse effects are somnolence, asthenia, and dizziness, which usually appear early after initiation of therapy and generally resolve without medication withdrawal.[67] Studies of the pharmacokinetics in pregnant patients have found increased elimination of levetiracetam in pregnant patients resulting in marked decline in

plasma concentration. Consequently, measurement of drug levels may be useful.[68] In addition, it appears that there is considerable transplacental transport of levetiracetam and fairly slow elimination in the neonate.[68] It is classified as a Pregnancy Category C drug, and it is unknown if it can be used safely in human pregnancy. In a study of 117 exposed pregnancies, 3 infants developed major malformations. However, in all 3 of these cases there was also exposure to other anti-epileptics.[69]

There is a significant risk of fetal toxicity associated with most of the antiepileptic agents, but uncontrolled seizures can cause permanent maternal and fetal injury. The goal of therapy is the same for both pregnant and nonpregnant patients: achievement of adequate seizure control at the lowest effective drug doses.[70] According to a report from the Epilepsy Research Foundation Workshop, the initial therapy for seizures related to pre-eclampsia is magnesium sulfate. The initial therapy for status epilepticus not due to eclampsia is a midazolam. Second-line therapy is phenytoin sodium, and third or fourth line therapies are propofol and phenobarbital. Dosing guidelines from nonpregnant patients are extrapolated to critically ill pregnant patients, because there are no specific guidelines published for treatment of status epilepticus in pregnancy. The lowest effective dose to maintain seizure control is recommended.[66]

Conclusions

There is limited information available concerning pharmacotherapy for critical ill patients during pregnancy. Most data about medication safety in the pregnant patient have been derived from animal studies, retrospective analyses, and case reports. It is unlikely that there will be randomized controlled trials for drug evaluations in this population because of legal and ethical issues related to the mother and fetus. To optimize medical management, the clinician must consider the known safety profile and potential risks associated with use of any drug in the pregnant woman. The risks to a mother and fetus with pulmonary embolus, septic shock, and status epilepticus outweigh potential adverse teratogenic effects, so, unless alternatives are available, standard pharmacologic therapy is indicated.

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