Special Theme Topic: Stroke During Pregnancy or Delivery

Antithrombotic Therapy for Pregnant Women

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Abstract

Coagulability increases during pregnancy, and thromboembolism can easily occur. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. As anticoagulants in pregnant women, unfractionated heparin and low-molecular-weight heparin are recommended, but warfarin is not recommended since it has a low molecular weight and crosses the placenta. Various types of new oral anticoagulant drugs have been available in Japan since 2011. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. The guidelines on pregnant women include less information about antiplatelet drugs than anticoagulant drugs. Aspirin may cause teratogenicity and fetal toxicity, and perinatal mortality is increased. However, when low doses of aspirin are administered as antiplatelet therapy, the US Food and Drug Administration has assigned pregnancy category C, and treatment is relatively safe. Neurosurgeons and neurologists commonly encounter pregnant women with thromboembolism, such as ischemic stroke. Up-to-date information and correct selection of drugs are necessary in consultation with specialists in perinatal care.

Key words: acute stroke, anticoagulation, antiplatelet therapy, thromboembolism, venous thrombosis

Introduction

Coagulability increases during pregnancy, and thromboembolism can easily occur, primarily of the venous system. Venous thromboembolism is a cause of death in pregnant women, but arterial thrombosis such as ischemic stroke in pregnancy is also not uncommon. In pharmacotherapy for thromboembolism in pregnant women, fetal toxicity and teratogenicity must be carefully considered. However, since pregnant women are usually excluded from pharmaceutical clinical trials for ethical reasons, information on toxicity and teratogenicity in pregnancy is limited. This study presents an overview of the current status and problems with antithrombotic therapy in pregnant women, based on the “Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS

2010)”³⁾ by the Japanese Circulation Society (JCS) Joint Working Group (fiscal year 2009); and the “Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)”⁴⁾ by the same group (fiscal year 2008).

Pregnancy and Thromboembolism

Plasma fibrinogen, von Willebrand factor, and factors V, VII, VIII, IX, X, and XII are increased and activated in late pregnancy, thus increasing the risk of thromboembolism. Therefore, thromboembolism is clearly a danger in pregnant women at high risk for embolism, such as those with valvular heart disease, but thromboembolism such as cerebral sinus venous thrombosis may also occur in pregnant women without such risk factors. In addition, the effects of estrogen and elastase during pregnancy may cause evident structural changes in blood vessel walls, leading to increased fragility. For example,

patients with Marfan's syndrome tend to develop aortic dissection. The structure of cerebral and cervical blood vessel walls may also be affected. Moreover, compression of the inferior vena cava due to uterine enlargement may lead to deep vein thrombosis (DVT). Therefore, pregnancy is a risk factor for thromboembolism, particularly venous thrombosis.

Nevertheless, the safety of antithrombotic drugs as treatment, as mentioned above, has not been well established. Fetal toxicity and teratogenicity are major concerns of drug administration in pregnancy, and are affected by placental transfer of drugs and the stage of pregnancy (Table 1).

Anticoagulant Drugs in Pregnant Women

The JCS Joint Working Group provides the following recommendations for anticoagulant therapy in pregnancy.

Class I: In pregnant women with a prior history of

DVT but no other risk factors, follow-up observation until delivery and warfarin administration for 4–6 weeks postpartum is recommended.

Class IIb:

1. In pregnant women with a prior history of DVT and other risk factors (e.g., congenital or acquired blood dyscrasias), prophylactic administration of low-molecular-weight heparin or moderate dose-adjusted unfractionated heparin starting during pregnancy and warfarin administration for 4–6 weeks postpartum are recommended.

2. In all patients with a prior history of DVT, use of elastic stockings pre- and postpartum is recommended.

3. In patients requiring long-term warfarin therapy who wish to become pregnant, planned pregnancy with a switch from warfarin to dose-adjusted heparin, or promptly switching from warfarin to dose-adjusted heparin when pregnancy is confirmed at an early stage by frequent pregnancy testing is recommended.

Therefore, unfractionated heparin or low-molecular-weight heparin is recommended in pregnant women; whereas warfarin is not recommended. Table 2 summarizes the effects of anticoagulant drugs in patients during pregnancy and breastfeeding.³⁾ Table 3 shows the US Food and Drug Administration (FDA) pregnancy categories for these drugs.¹⁾

Unfractionated heparin and low-molecular-weight heparin do not cross the placenta because of their high molecular weight and do not cause harm to the fetus. However, in Japan, the use of low-molecular-weight heparin for thromboembolism prophylaxis in patients with a history of valvular heart disease or DVT is not covered by health insur-

Table 1 Pregnancy stage, teratogenicity, and fetal toxicity

Pregnancy stage	Teratogenicity and fetal toxicity
Fertilization to day 27	no effect stage: malformations do not occur (no fertilization, no implantation, or miscarriage)
Days 28 to 50	absolutely sensitive stage: important fetal organ formation, highest risk of teratogenicity
Days 51 to 112	relatively sensitive stage: genitalia and palate formation not yet complete, teratogenicity such as cleft palate
Day 113 to delivery	potentially sensitive stage: risk of teratogenicity is rare, attention must be paid to fetal toxicity

Table 2 Effects of anticoagulant drugs in patients during pregnancy and breastfeeding

Drug	Classification	FDA category	Characteristics/adverse reactions	Teratogenicity	Breastfeeding during use	Package insert	
						Pregnancy	Breastfeeding
Warfarin	coumarin derivative	D	teratogenicity, fetal hemorrhagic complications	yes	allowed	contra-indication	contra-indication
Heparin	unfractionated heparin	C	bone demineralization with long-term administration (fractures in mothers), higher incidence of thrombosis than with warfarin, risk of heparin-induced thrombocytopenia	no	allowed	contra-indication	
Enoxaparin	low-molecular-weight heparin	B	reports of heparin-induced thrombocytopenia, not indicated for thrombus prophylaxis in cardiovascular disease	no	allowed	relative contra-indication	relative contra-indication
Dalteparin	low-molecular-weight heparin	B	reports of heparin-induced thrombocytopenia, not indicated for thrombus prophylaxis in cardiovascular disease	no	allowed	contra-indication	contra-indication

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Table 3 US Food and Drug Administration (FDA) pregnancy categories

The FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

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ance. Consequently, unfractionated heparin is generally administered. Noteworthy adverse reactions with heparin include hemorrhage, which is a common complication with all antithrombotic drugs, and heparin-induced thrombocytopenia. Another important adverse reaction in pregnant women is possible fractures due to bone demineralization caused by long-term administration of heparin. In addition, because of increased heparin-binding proteins, increased circulating plasma volume, increased clotting factors, and problems with renal clearance, the need for heparin during pregnancy is greater than in non-pregnancy. Since January 2012, home heparin self-injection in pregnant women after mechanical heart valve replacement or those with a history of DVT has been covered by health insurance.

Warfarin, the leading oral anticoagulant drug, has a low molecular weight and does cross the placenta. Therefore, warfarin administration during the absolutely and relatively sensitive stages (days 28 to 112) can cause abnormalities in fetal osteogenesis and chondrogenesis, as well as central nervous system malformations such as microencephaly. These teratogenic effects are considered dose-dependent. In addition, because enzyme systems and vitamin K-dependent clotting factors are undeveloped in the fetus, the effects of warfarin are more easily manifest

Fig. 1 Anticoagulant therapy in pregnant women with mechanical heart valve replacement. Modified with permission from the *Circulation Journal* (76: 240–260, 2012), ©2012, the Japanese Circulation Society.³⁾

in the fetus than in mothers. Therefore, to prevent teratogenicity in the absolutely and relatively sensitive stages, and to prevent complications such as fetal intracranial hemorrhage in the later period of pregnancy due to decreased clotting factors, warfarin administration is not recommended in pregnant women.

Figure 1 shows anticoagulant therapy in pregnant women after mechanical heart valve replacement,³⁾ consisting of warfarin and heparin administration from week 14 to about week 33 of pregnancy. The rationale based on guidelines is that the prophylactic effects of heparin on thrombus are uncertain.^{1,4)} Moreover, the rationale for a daily dose of warfarin ≤ 5 mg is based on the dose-dependence of warfarin teratogenicity. However, an oral warfarin dose of 5 mg is considered quite high in Japanese patients, so warfarin should be carefully administered while monitoring the prothrombin time (international normalized ratio). The guidelines from the American Heart Association/American Stroke Association²⁾ recommend that the following options may be considered for pregnant women with ischemic stroke or transient ischemic attack and high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves: adjusted dose unfractionated heparin throughout pregnancy, for example, a subcutaneous dose every 12 hours with monitoring of activated partial thromboplastin time; adjusted-dose low-molecular-weight heparin with monitoring of anti-factor Xa throughout pregnancy; or unfractionated heparin or low-molecular-weight heparin until week 13, followed by warfarin until the middle of the third trimester and reinstatement of unfractionated heparin or low-molecular-weight heparin until delivery (Class IIb, Level of Evidence C). Because home heparin self-injection is now covered by health insurance, the number of patients using heparin is thought to be increasing.

Various types of new oral anticoagulant drugs have been available in Japan since 2011, and these can be clinically used in patients with non-valvular

atrial fibrillation and those undergoing lower limb orthopedic surgery. These new agents include the direct thrombin inhibitor dabigatran and the activated factor X inhibitors edoxaban, rivaroxaban, and apixaban. In large-scale clinical trials, these new oral anticoagulants have reduced hemorrhagic complications to the same or greater extent than warfarin, and in particular, the incidence of intracranial hemorrhage compared to warfarin is markedly decreased.⁵⁾ In addition, argatroban, an intravenous direct thrombin inhibitor, is now widely used as an alternative to heparin for treatment of the acute phase of cerebral infarction and in heparin-induced thrombocytopenia. However, the Japanese package inserts for these anticoagulants advise quite cautious administration in pregnant women. In other words, dabigatran, edoxaban, and apixaban should only be used when the benefits outweigh the risks, and rivaroxaban should not be given to pregnant women. Argatroban has been assigned pregnancy category B by the FDA, but the Japanese package inserts specify that argatroban should not be administered to pregnant women.

Antiplatelet Drugs in Pregnant Women

Venous thrombosis occurs more often than arterial thrombosis in pregnant women, and the guidelines include less information about antiplatelet drugs than anticoagulant drugs. Table 4 summarizes the effects of antiplatelet drugs in patients during pregnancy and breastfeeding.³⁾ Aspirin, the leading antiplatelet drug, may cause teratogenicity and fetal toxicity such as premature closure of the ductus arteriosus, and perinatal mortality is increased. But when low doses of aspirin are administered as antiplatelet therapy, the FDA has assigned pregnancy category C, and treatment is relatively safe. However, the drug package insert says “contraindicated (regardless of dose) in pregnant women within 12 weeks of the expected date of delivery (pregnancy week 28 or later).” Therefore, a full explanation and

Table 4 Effects of antiplatelet drugs in patients during pregnancy and breastfeeding

Drug	FDA category	Characteristics/adverse reactions	Teratogenicity	Breastfeeding during use	Package insert	
					Pregnancy	Breastfeeding
Aspirin (low dose)	C	considered relatively safe, do not use in pregnancy week 28 or later regardless of dose	no	potential toxicity	relative contraindication	contraindication
Dipyridamole	B	hypotension, worsening of angina pectoris	no	probably allowed	relative contraindication	contraindication
Ticlopidine	B	hemorrhage, liver dysfunction	no	potential toxicity	relative contraindication	contraindication

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Table 5 Information in Japanese package inserts regarding use of antiplatelet drugs in pregnant women

Drug	Guideline for use in pregnant women
Aspirin	up to week 28: may be used if risks outweigh the benefits, week 29 and later: do not use
Clopidogrel	may be used if risks outweigh the benefits
Ozagrel	may be used if risks outweigh the benefits
Cilostazol	do not use in pregnant women
Ticlopidine	do not use in pregnant women

informed consent are necessary for administration in the third trimester of pregnancy.

The Japanese package inserts for clopidogrel and ozagrel recommend use only when the benefits outweigh the risks (Table 5). Cilostazol and ticlopidine are contraindicated in pregnant women. On the other hand, aspirin and ozagrel are reported to be effective in preventing placental thrombosis in pregnant women with autoimmune disorders such as antiphospholipid syndrome.

Conclusion

In the present paper, the author, who is not a specialist in perinatal medicine, has discussed using antithrombotic drugs in pregnancy based on guidelines and package insert information. Searching the literature often found disagreement between information in FDA categories, Japanese guidelines, Japanese package inserts, and overseas package inserts, but this was not further pursued. Neurosurgeons and neurologists also commonly encounter pregnant women with thromboembolism, such as ischemic stroke. Up-to-date information and correct selection of drugs are necessary in consultation with specialists in perinatal care.

Conflicts of Interest Disclosure

The author declares that he has no conflict of in-

terest.

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