Special Theme Topic: Stroke During Pregnancy or Delivery

Endovascular Treatment in Pregnancy

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Abstract

There is an increased risk of stroke during pregnancy and the puerperium. Decisions should be made immediately upon transfer to each institution, particularly with respect to when and how to treat the patient. This review highlights the feasibility of endovascular treatment in pregnancy. Most of the pharmaceutical agents and therapeutic devices used in clinical practice can be utilized in pregnant patients. Comprehensive information on the benefits and risks of treatment should be explained to the patient and her family, with particular attention to the safety of the mother and fetus. Radiation exposure to the fetus is also a concern; the hazard can be minimized with optimal protection. Several studies have demonstrated that conventional procedures do not cause serious radiation exposure exceeding the threshold of safety to the fetus. Endovascular therapy can be safely performed for the treatment of acute stroke as in non-pregnant patients with adequate attention to pharmaceutical agents and shielding from radiation. In contrast to therapy for acute stroke, preventive endovascular treatment for asymptomatic lesions remains controversial. Several conditions, such as cerebral aneurysms and arteriovenous malformations, are known to bleed more frequently in pregnancy, but whether the benefits of preventive treatment outweigh the associated risks is unknown. The decision for preventive treatment should be carefully made on a case-by-case basis after extensive discussion with the patient.

Key words: pregnancy, stroke, endovascular treatment

Introduction

Endovascular treatment is becoming ever more important not only in the treatment of acute stroke, but also in preventive treatment. The recent introduction of various effective devices has encouraged this trend. Stroke in pregnancy is not frequently encountered by health care professionals except in specialized institutions. However, inaccurate information can negatively impact the prognosis for both the pregnant patient and the fetus. Here we describe the important considerations in endovascular treatment during pregnancy by reviewing the literature and a limited number of case reports. Safety information on medicines and agents that are currently in use will be discussed.

Medicines and Agents Used Pre-, Peri-, and Postoperatively

A wide variety of medicines and agents, particularly antiplatelets and anticoagulants, are utilized in the clinical practice of endovascular treatment (Table 1). Which substances can be safely used and which ones should be restricted in pregnant women have been described. According to the drug package inserts, no drug is completely safe for pregnant women and fetuses. The benefits and risks of each drug should be carefully discussed with the patient. The benefits should be estimated to outweigh the risks if a drug is to be administered to a pregnant woman.

I. Heparin

Heparin is one of the most important agents used in any kind of endovascular treatment to minimize the risk of periprocedural thromboembolic complications. Heparin has been proven safe to the fetus due to the absence of placental transmission and is

Table 1 Safety information on pharmaceutical agents utilized in endovascular treatment

	FDA recommendation	Teratogenicity	Lactation
Heparin	C	no	compatible
Enoxaparin, dalteparin (LMW heparin)	B	no	compatible
Protamine	C	no	probably compatible
Iohexol (iodinated contrast agent)	D	no	probably compatible
Gadolinium contrast agent	C	yes	compatible
Aspirin (low-dose)	C	no	potential toxicity
Clopidogrel	B	no	probably compatible
Argatroban	B	no	probably compatible
Alteplase (rt-PA)	C	no	compatible
Urokinase	B	no	probably compatible
Nifedipine, nicardipine	C	no	probably compatible
Dopamine	C	no	probably compatible

FDA: Food and Drug Administration, LMW: low molecular weight, rt-PA: recombinant tissue plasminogen activator.

categorized in Group C according to the recommendations of the U.S. Food and Drug Administration (FDA).⁵⁾ Heparin can be used in the same way for pregnant women as for non-pregnant women; however, the necessary dose may need to be increased due to the higher levels of heparin-binding proteins, circulatory volume, thrombotic factors, and renal clearance occurring during pregnancy. Activated clotting time should be carefully monitored during endovascular treatment. It should be noted that long-term heparin therapy during pregnancy has been associated with maternal osteopenia.¹³⁾ Low molecular weight heparin, such as enoxaparin, is recommended for patients who need heparin administration for a long period.

II. Protamine sulfate

Protamine is used to neutralize the anticoagulant effect of heparin. No reports of its use in pregnancy have been found.⁵⁾ Reproduction studies in animals have not been conducted.

III. Iodinated contrast agent

Iodinated contrast agent crosses the human placenta and enters the fetus.⁵⁰⁾ However, no teratogenic effects have been reported to date. In vivo animal studies have failed to show teratogenic effects from the use of iodinated contrast media in pregnancy.²⁷⁾ The iodine content can produce neonatal hypothyroidism from the direct instillation of ionic contrast agent into the amniotic cavity during amniocentesis.³⁷⁾ However, the intravascular administration of non-ionic iodinated contrast agent has been reported to have no effect on neonatal thyroid function.²⁾ Given the insufficient literature on the safety of iodinated contrast agent, the guidelines of the American College of Radiology re-

commend that it should be administered only if absolutely necessary. To our knowledge, there are no reports of clinical sequelae induced by iodinated contrast agents administered intravenously. However, maternal hydration should be carefully maintained in order to avoid fetal dehydration. A flat panel detector allows excellent density resolution. Iodinated contrast agent can be used at half strength using a flat panel detector to save on the total administered dose. A biplane equipment is also beneficial to save iodinated contrast agent and radiation exposure.

IV. Gadolinium contrast agent

Gadolinium has been shown to cross the placenta in animal studies.³¹⁾ Moreover, it has been shown to have teratogenic effects when administered at high and repeated doses.³²⁾ Contrast-enhanced magnetic resonance imaging should be avoided in pregnancy unless absolutely essential. According to the guidelines of the American College of Radiology, it should be used with "extreme" caution only if the benefit to the mother "overwhelmingly" outweighs the theoretical risks to the fetus.¹⁹⁾

V. Aspirin

Aspirin readily crosses the placenta.⁵⁾ When given near term, higher concentrations are found in the neonate than in the mother.²³⁾ Although aspirin has been used as a tocolytic agent, serious bleeding complications may occur in the newborn. The teratogenic effect of aspirin has not been proven to date. A prospective study that monitored 32,164 aspirin exposures during pregnancy did not find evidence of any teratogenic effect.⁴²⁾ Nevertheless, the use of high-dose aspirin during pregnancy should be avoided because it may affect maternal and newborn

hemostasis mechanisms. On the other hand, low doses, such as 80 mg/day, which is the dose usually used after coil embolization for unruptured aneurysms, appear to have no adverse effect. Low-dose aspirin is used for prevention of gestational hypertension, pre-eclampsia, and intrauterine growth retardation.⁵⁾ Potential complications of aspirin therapy in late pregnancy include fetal and maternal bleeding, premature closure of the ductus arteriosus, prolongation of labor, and delay in the onset of labor.

VI. Clopidogrel

Clopidogrel has been shown not to be teratogenic in two animal species,⁵⁾ but evaluation in human pregnancy is limited to one case report.²¹⁾ Moreover, it is not known if the inactive parent drug or its active or inactive metabolites cross the placenta, although the relatively low molecular weight suggests that some passage should be expected. This lack of information in humans prevents accurate assessment, but the known benefits to the woman appear to outweigh the unknown fetal risks. Therefore, if a patient's condition requires clopidogrel, treatment should not be withheld because of pregnancy.

VII. Argatroban

No studies describing the use of argatroban during human pregnancy have been located. Although the results of animal studies have been encouraging, human studies are required before an assessment can be made of the risks, including hemorrhage, that this drug represents to an embryo or a fetus. If a pregnant woman requires argatroban therapy, however, the benefits to her appear to outweigh the theoretical risks.

VIII. Alteplase (recombinant tissue plasminogen activator: rt-PA)

Limited use of alteplase during pregnancy does not suggest a significant fetal risk.⁵⁾ Nine case reports have described the use of alteplase in human pregnancy.^{5,44)} Although none of the reported human exposures occurred during organogenesis, the high molecular weight probably precludes the transfer of alteplase to the embryo. Moreover, teratogenicity has not been observed in animals. Hemorrhage is a risk of therapy at any time during gestation, but careful monitoring of the mother can prevent this from becoming a significant risk to the fetus. The most important risk to the mother is placental separation caused by bleeding in the uterus.^{11,40)} Therefore, it appears that alteplase may be used during gestation if the mother's condition requires this therapy.

IX. Urokinase

The use of urokinase as a thrombolytic agent during pregnancy does not appear to present a major risk to the fetus. The drug is not fetotoxic or teratogenic in rodents.⁵⁾ However, only one human case of treatment with urokinase during the 1st trimester (at 3 months) has been reported. It is not known whether the drug crosses the placenta to the fetus, but placental tissue contains proteinase inhibitors that inactivate urokinase. Placental separation and hemorrhage is a potential complication and has been reported in one case.

Maternal and Fetal Radiation Exposure

Fetal radiation effects are highly dependent on both administered dose and developmental stage at the time of exposure (Table 2).^{4,34)} During the first gestational week (0–8 days), a radiation dose of 100 mGy is believed to be lethal to the developing embryo.⁴⁾ In the organogenesis period (2–8 weeks), normal maturation may be affected by > 500 mGy.^{4,45)} During the early fetal stage (8–15 weeks), the radiation dose threshold is estimated to be 120 mGy,⁴⁵⁾ whereas the safe limit is projected at 250 mGy in the mid-fetal stage (16–25 weeks).³⁴⁾ Beyond 25 weeks, the risks of physical deformity and mental retardation are believed to be minimal unless exposure levels exceed 500 mGy.⁴⁵⁾ According to recommendations of the International Commission on Radiological Protection, the radiation threshold above which abortion should be considered is 100 mGy.¹⁶⁾

An experiment using a standard body phantom was conducted in a digital subtraction angiography suite.²⁵⁾ The scattered “uterine” dose was 11 μ Gy/min, whereas the direct “uterine” dose was 4.6 mGy/min. Assuming that the radiation exposure for the groin and for the head is 30 seconds and 45 minutes, respectively, in a general endovascular procedure, the absorbed fetal dose was measured to be 2.8 mGy. This figure is an order of magnitude below the risk thresholds mentioned above. Therefore, the risks associated with endovascular procedures appear minimal considering the threshold dose mentioned above. The adverse effects of ionizing radia-

Table 2 Threshold of radiation exposure in the fetus

Gestational week/day	Threshold (mGy)
0–8 days	100
2–8 weeks	500
8–15 weeks	120
16–25 weeks	250
> 25 weeks	500

tion should be minimized with optimal protection using a lead apron for the abdomen in pregnant women.

Subarachnoid Hemorrhage (SAH)

Ruptured aneurysm in a pregnant patient should be treated as in a non-pregnant patient. A meta-analysis demonstrated that surgical intervention for ruptured aneurysms improved not only the mother's condition, but also the fetal prognosis.⁸⁾ Whether surgical clipping or endovascular coiling is superior in the treatment of ruptured aneurysms during pregnancy remains controversial. The literature has been accumulating on surgical clipping in pregnancy.⁸⁾ One advantage of surgical clipping is that it allows aneurysm treatment and cesarean delivery in the same operating room in the same session. On the other hand, coil embolization in pregnancy has been recently reported. This minimally invasive treatment minimally affects the maternal circulatory dynamics.

Eighteen cases of coiling for ruptured aneurysms in pregnancy were found in the literature. Table 3 lists details of the 11 cases reported in the articles. Most of the aneurysms were located in the internal carotid artery, and ruptured in the 3rd trimester of pregnancy. These findings, compatible with the above meta-analysis, indicated that drastic changes in circulatory dynamics and hormone balance during pregnancy contribute to aneurysm growth and rupture.^{33,51)} In 10 of the 11 cases, the fetus was uneventfully delivered by vaginal or cesarean section before or after coil embolization. In one case, the pregnancy was electively aborted following the embolization. As described earlier, the impact of ioniz-

ing radiation on the fetus is considered to be negligible in routine endovascular procedures such as coil embolization for aneurysms.²⁵⁾ Antiplatelet and anticoagulation drugs are mostly non-teratogenic. However, heparin, routinely used in endovascular procedures, should be stopped before cesarean section to avoid hemorrhagic risk. Antiplatelet therapy should be also terminated if given in the periprocedural stage. The coils that were used in the literature reports consisted entirely of Guglielmi detachable coils (Stryker Corp., Washington, DC, USA). There is no report on stent-assisted embolization.

Whether coil embolization or delivery of the fetus should be performed first should be carefully considered on a case-by-case basis. Vaginal delivery can be safely performed after coiling for ruptured aneurysms with low-grade SAH. However, in a patient with high-grade SAH with maternal circulatory instability, cesarean delivery should be considered if the fetus is mature enough. Delivery of the fetus makes it possible to avoid possible adverse effects caused by the various agents used in the intensive management of high-grade SAH.

Fetal monitoring during the procedure is useful in near-term pregnancy.⁴⁹⁾ However, cesarean delivery has several limitations in the angiographic suite with limited equipment. A hybrid operating room equipped with a full-spec digital subtraction angiography machine is considered to be useful.²⁸⁾

Ischemic Stroke

Ischemic stroke includes arterial infarction and venous infarction. The former is more likely to occur in the 1st and 3rd trimester and the latter tends to

Table 3 Case reports of cerebral aneurysms treated with coil embolization in pregnancy

Author (Year)	Patient age (yrs)	Gestational week	WFNS grade	Location	Used coils	Delivery	Fetus outcome	Maternal mRS
Meyers et al. (2000) ²⁶⁾	34	30	III	PCA	GDC	vaginal, 38 wks	healthy	1
	36	31	I	BA bif	GDC	vaginal, 36 wks	healthy	0
	36	34	I	ICA-Pcom	GDC	cesarean, 34 wks	healthy	0
Shahabi et al. (2001) ⁴¹⁾	36	38	I	BA bif	GDC	cesarean, 38 wks	healthy	0
Piotin et al. (2001) ³⁵⁾	28	32	I	ICA bif	GDC	cesarean, 32 wks	healthy	0
	31	22	III	ICA paraclinoid	GDC	vaginal	healthy	0
Kizilkilic et al. (2003) ²⁰⁾	25	10	I	ICA-Pcom	GDC	aborted	aborted	0
	39	18	I	ICA-ophthalmic	GDC	vaginal, 34 wks	healthy	0
	26	28	I	Acom	GDC	vaginal, 38 wks	healthy	0
Pumar et al. (2010) ³⁶⁾ (8 cases)	30	32	III	BA bif	GDC	cesarean, 38 wks	healthy	0
Tarnaris et al. (2012) ⁴⁶⁾	21	29	III	ICA-Pcom	GDC	cesarean, 38 wks	healthy	1

Acom: anterior communicating artery, BA: basilar artery, bif: bifurcation, GDC: Guglielmi detachable coil, ICA: internal carotid artery, mRS: modified Rankin scale, PCA: posterior cerebral artery, Pcom: posterior communicating artery, WFNS: World Federation of Neurosurgical Societies.

Table 4 Case reports of acute ischemic stroke treated with endovascular treatment in pregnancy

Author (Year)	Age (yrs)	Gestational week	Strategy	Dose	Complications	Maternal outcome	Fetal outcome
Elford et al. (2002) ⁹⁾	28	1	IA rt-PA	15.5 mg	groin hematoma	poor	good
Johnson et al. (2005) ¹⁸⁾	39	37	IA rt-PA	15 mg	none	good	good
Murugappan et al. (2006) ²⁹⁾	43	37	IA rt-PA	21 mg	none	good	good
	28	6	IA UK	0.6 MU	hematoma	poor	good
	25	1 st trimester	local UK	0.7 MU	asymptomatic ICH	good	aborted
Li et al. (2012) ²⁴⁾	24	11	IA rt-PA	NR	none	poor	NR

IA: intraarterial, ICH: intracerebral hemorrhage, NR: not reported, rt-PA: recombinant tissue plasminogen activator, UK: urokinase.

occur postpartum.¹⁸⁾ Review of 102 ischemic strokes in 7 articles summarized the causes of ischemic stroke as: 1) pre-eclampsia and eclampsia (37.3%), 2) cardiac disease (25.5%), 3) coagulopathy (7.8%), and 4) atherothrombotic disease (2.0%). These are very different from the causes in the non-pregnant population.

In the general population, thrombolytic therapy with alteplase is the first-line option with the strongest evidence. Due to its large molecular size, rt-PA does not cross the placental barrier, and animal studies have not shown any teratogenic effect. To date, the experience in pregnant patients is limited to case reports and case series. The FDA recommendations categorize alteplase in Group C (indicated if benefits outweigh risks). Seven cases of intravenous rt-PA therapy (0.9 mg/kg) have been reported in 5 reports.^{6,22,29,47,52)}

Endovascular treatment is considered beneficial because it may eliminate the need for thrombolytic agents or allow a decrease in the dose. rt-PA can act on the placenta, leading to premature labor, placental abruption, or fetal death. Ionizing radiation to the fetus should be minimized by an optimal shield. There have been 6 cases reported of intra-arterial thrombolytic therapy in pregnancy (Table 4).^{9,18,24,29)} The administered thrombolytic agents were rt-PA in 4 cases and urokinase in 2 cases. Good recovery was obtained in 3 of 6 pregnant patients with intra-arterially administered rt-PA at a dose of 15.5–21 mg. This dose is smaller than the dose of intravenous rt-PA (0.9 mg/kg). The fetus of each of the 4 patients who received rt-PA was reported healthy except the unreported case and the aborted fetus. Abortion was chosen due to a chromosomal abnormality detected, which was not associated with the thrombolytic therapy.

Mechanical thrombectomy devices such as the Merci Retriever® (Concentric Medical, Inc., Mountain View, California, USA)⁴³⁾ and the Penumbra system (Penumbra, Inc., Alameda, California, USA)¹²⁾

have been used with or without intra-arterial rt-PA therapy. Moreover, stent-type retrievers, such as the Solitaire™ (ev3 Endovascular, Inc., Plymouth, Minnesota, USA)³⁹⁾ and Trevo® (Stryker Corp.)³⁰⁾ have been recently introduced. The procedure time from placement of a guiding catheter to recanalization is reported to be 36 minutes with the Solitaire™.³⁹⁾ The short procedure time appears beneficial in pregnant patients because it may decrease radiation to the fetus. To date, there have been no reports on use of these devices in pregnant patients.

Unruptured Cerebral Aneurysm

Whether or not to treat unruptured aneurysms during pregnancy for the purpose of preventing SAH is controversial. There are several reports that cerebral aneurysms have grown during treatment procedures.^{33,51)} The increased cardiac output, increased circulatory volume, increased systemic blood pressure, and change of hormonal balance during pregnancy most probably contribute to the rapid growth of cerebral aneurysms during pregnancy, particularly in the 3rd trimester. While several reports have stated that the rate of aneurysm rupture is similar to that in the non-pregnant population,⁴⁸⁾ it is necessary to check for possible growth of any known aneurysms.

If a pregnant woman with unruptured aneurysms desires coil embolization, the most important problem is not radiation to the fetus, but administration of antiplatelet agents. With optimal shielding, a routine endovascular procedure such as coiling does not cause radiation exposure over the threshold that leads to consideration of abortion.²⁵⁾ It is recommended that antiplatelet drugs be administered for a certain period after the endovascular procedure, particularly after coiling for unruptured aneurysm.¹⁰⁾ However, these medicines may increase hemorrhagic risks during delivery. The Japanese drug package insert recommends to stop

aspirin administration after the 28th gestational week because it may produce adverse effects in the mother: anemia, antepartum or postpartum hemorrhage, prolonged gestation, and prolonged labor.⁵⁾ If coiling is to be performed during pregnancy, the timing should be carefully discussed with the patient so that antiplatelet therapy can be safely stopped near term. Stent-assisted coiling, which usually needs a longer period of antiplatelet therapy of more than a year, should be avoided during pregnancy.

Cerebral Arteriovenous Malformation (AVM)

There are several reports that pregnancy does not affect the annual rate of hemorrhage in patients with cerebral AVM.^{1,15)} However, recent studies found an increased rate of hemorrhage.¹⁴⁾ At the very least, intervention should be considered in patients with ruptured AVM, particularly in pregnant patients with AVM who present with intracerebral hemorrhage, in the same manner as non-pregnant patients. If a patient with cerebral AVM desires preventive treatment, surgical resection may be the first choice. The preventive effect against hemorrhage can be achieved immediately after surgical resection, while it takes several years with radiotherapy. Partial embolization has no preventive effect. However, direct surgery for cerebral AVM usually incurs a risk of intraoperative bleeding, and may also pose a risk to the fetus. Pre-surgical embolization may be considered in order to lessen the intraoperative bleeding risk.

It is difficult to know what is the best embolic material to be used for treatment during pregnancy. Onyx® (ev3 Endovascular, Inc.) and n-butyl cyanoacrylate (NBCA) are available, but are not indicated for pregnant women according to the device package inserts. None of these devices are mentioned in the FDA recommendations because they are not considered to be drugs. However, some chemical components may be absorbed into the blood after being implanted into the cerebral arte-

ries. There are several reports that cerebral AVMs have been treated with Onyx®^{7,17)} or NBCA³⁸⁾ (Table 5).

Onyx® is known to achieve a rather higher rate of complete occlusion compared with NBCA. Onyx® liquid embolic agent is ethylene-vinyl alcohol copolymer dissolved in the organic solvent dimethyl sulfoxide (DMSO). Ethylene vinyl alcohol is considered to be chemically inert, but there is no data available on its teratogenic potential. Several studies have shown that DMSO is not teratogenic in mammals except at extremely high doses, which are not encountered in clinical situations.³⁾ However, DMSO diffuses into the blood after being injected into a cerebral AVM. A measurable amount of DMSO may enter the circulatory blood pool in pregnant patients. DMSO, a lipophilic solvent with low molecular weight, can cross the placental barrier. The dose during the procedure should be very carefully considered. Moreover, AVM embolization with Onyx® generally requires a longer procedure time compared with aneurysm embolization. A pregnant woman was treated for an AVM at the 20th gestational week.⁷⁾ Embolization with Onyx® was performed in 2 sessions, and the patient successfully delivered a healthy fetus at the 36th gestational week. The embolized nidus was successfully resected 4 months later. The radiation exposure to the patient's head was measured to be 8154 mGy. The calculated fetal dose was as low as 1.9×10^{-30} mGy from scatter. Nevertheless, it remains very important to protect the abdomen with an optimal lead shield and minimize the use of fluoroscopy and angiography.

Conclusions

The accumulated evidence on endovascular therapy in pregnancy has been reviewed. It is feasible to perform endovascular therapy safely with respect to both the mother and fetus with comprehensive knowledge of the utilized agents and devices, and an effort to minimize radiation exposure. Careful dis-

Table 5 Case reports of arteriovenous malformations treated with embolization in pregnancy

Author (Year)	Age (yrs)	Gestational week	Material	Resection	Complications	Maternal outcome	Fetal outcome
Salvati et al. (2011) ³⁸⁾	23	19	NBCA	no	none	good	good
	30	2 wks post-cesarean section	NBCA	no	none	good	good
Dashti et al. (2012) ⁷⁾	17	20	Onyx®	yes	catheter entrapment (managed with aspirin)	good	good
Jermakowicz et al. (2012) ¹⁷⁾	23	22	Onyx®	yes	none	good	good

NBCA: n-butyl cyanoacrylate.

cussion should be conducted with patients on whether to treat asymptomatic lesions during pregnancy. Endovascular treatment should be administered only if the benefits are considered to outweigh the risks associated with treatment.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of the Japan Neurosurgical Society (JNS) have registered online self-reported conflict of interest disclosure statement forms through the website for JNS members.

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