Pregnancy and ischemic stroke: a practical guide to management

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Purpose of review
Ischemic stroke during pregnancy or the puerperium is a devastating disease during a crucial period in life and warrants a specific approach. To date, current practice is mainly based on expert opinion because of a lack of randomized controlled trials and high-quality observational studies. The present review is intended as a practical guide to (acute) management of ischemic stroke during pregnancy and puerperium.

Recent findings
Recent findings showed that the incidence of stroke during pregnancy is rising. In 2014, the first guideline for the prevention of stroke in women was released, however on many (pregnancy) related topics the evidence was too scarce to make clear evidence-based recommendations.

Summary
The risk of ischemic stroke is elevated especially from the third trimester until 6 weeks postpartum. MRI is the most accurate and well tolerated diagnostic option but low-dose CT-head is a valid alternative. Reperfusion therapies should not be withheld from a pregnant woman with moderate-to-severe stroke when benefits outweigh the risk. Aspirin up to 150 mg daily is considered well tolerated during pregnancy and lactation period. Multidisciplinary care is essential when counseling these women in the acute and later stages.

Keywords
cardiovascular disease, ischemic stroke in young women, management, pregnancy, pregnancy-complications

INTRODUCTION

Stroke during pregnancy or the puerperium (defined as the period starting from delivery up to the subsequent 12 weeks [1]) is relatively rare but is associated with significant mortality and high morbidity during a crucial and vulnerable period in life. In 16–18% of Western women and in 11% of Asian women under the age of 35 years, pregnancy with its associated risk factors including (pre)eclampsia, HELLP-syndrome, and hypercoagulability is related to the cause of stroke [2,3,4▪]. However, our understanding of the complex processes underlying pregnancy-related stroke remains limited, as illustrated by the fact that in about one fourth of these patients the exact cause remains unknown. Management of an (acute) ischemic stroke during pregnancy and the puerperium therefore poses a challenge in daily practice, also because it necessitates a different diagnostic and therapeutic approach as the clinician must take care of the health and safety of both the mother and the unborn child. This management is not supported by data from clinical trials and therefore mainly relies on expert opinion [5]. This shortcoming also applies to adequate counseling of women who would like more children after pregnancy-related stroke. In this review, we will provide a practical guide to management of stroke of presumed arterial origin during pregnancy and puerperium. We will start with an overview on the epidemiology and provide practical recommendations, regarding diagnostic and treatment options, including for lactating women. We will end with

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KEY POINTS

- Pregnancy, especially the period from the third trimester to 6 weeks postpartum, is associated with an increased risk of ischemic stroke and pregnancy-specific causes play a major role.
- MRI (with DWI/TOF) is the preferred choice of neuroimaging in case of a suspected (acute) ischemic stroke in pregnant women; CT-head is a valid option when MRI is not readily available.
- Treatment with rTPA and mechanical thrombectomy are considered effective and relatively well tolerated; benefit should outweigh the risk and decision is based on individual situation. Aspirin is well tolerated up to 150 mg daily.
- The risk of recurrent stroke in subsequent pregnancies is low, with the highest relative risk during the puerperium.

some recommendations with respect to counseling of women with stroke, who would like to have more children.

EPIDEMIOLOGY

Between 1.5 and 67.1 per 100 000 deliveries are complicated by an ischemic stroke [6–9] and the incidence is rising [10,11]. In Asian countries a comparable incidence is reported (10.2–46.2 per 100 000 deliveries) [12–14]. Pregnant (and especially postpartum) women have an estimated three-fold to nine-fold increased risk of all stroke subtypes compared to nonpregnant women [7,15]. Interracial differences have been observed; Afro-American women more often had pregnancy related stroke (52.5 per 100 000 deliveries) compared with Caucasian (31.7 per 100 000) and Hispanic (26.1 per 100 000) [7]. Higher age is a risk factor [7], whereas others have found that age under 35 years increased the risk of stroke [15,16]. About half of all strokes during pregnancy are of the ischemic subtype in Western countries (48–62%) [6,17,18], and this fraction may be slightly lower in Asian countries (25–57%)[12–14]. The risk of ischemic stroke is increased until 12 weeks postpartum, but the highest risk was found in the period starting from the third trimester [1,6,15] until the first 6 weeks postpartum [1,6,15,17]. It is important to note that the wide variation in reported incidence and age-dependent risk of stroke might also be related to study design; population or (tertiary) hospital-based study, heterogeneity with respect to inclusion of stroke subtypes, and operationalization of the postpartum period.

CAUSE OF PREGNANCY-RELATED ISCHEMIC STROKE

According to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) [19] classification system, the causes of stroke during pregnancy can be classified as large artery atherosclerosis (9–10%, mainly in Asian studies [13,20]), cardioembolism (19%, but up to 56% in Asian studies [12,13,20]), and other determined causes (31–65%), such as hypercoagulability (7–18%), arterial dissection (5–7%), and preeclampsia (24–47%) [6,17,18]. In a quarter to a third of Western women and in one fifth of Asian women, the cause remains cryptogenic [12,17,18,20]. A selection of pregnancy-related causes will be highlighted below (for further reading see Table 1).

Cardioembolism

During pregnancy, the body has to accommodate profound hemodynamic changes such as increase in blood volume (30–40%), cardiac output (45%), and a cardiac remodeling resulting in a physiological (left) ventricular hypertrophy. It has been suggested that an inability to adapt to these changes can put pregnant women with known cardiac disease at greater risk of cardiovascular complications, but also can reveal a (previously unknown) underlying cardiac disease [21,22]. Peripartum cardiomyopathy (PPCM) is a specific pregnancy-related dilated cardiomyopathy of unknown cause typically occurring during the third trimester until up to 6 months after delivery [23]. Rheumatic valvular heart disease is now a rare disease in Western countries but frequent in developing countries [24], and still reported as a major cause of pregnancy related stroke in Taiwanese patients [12].

Other determined causes: hypercoagulability

Especially in the third trimester (in preparation for delivery) and shortly postpartum a physiological hypercoagulable condition develops (Table 2), with an attendant increased risk of ischemic stroke [25]. In the presence of a hypercoagulable state (such as the antiphospholipid syndrome) this risk is even higher [26].

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HPD) is an umbrella term for a group of potentially life threatening pregnancy-specific disorders that are highly associated with ischemic stroke [27], namely gestational hypertension (defined as a blood pressure of >140 mmHg systolic and/or 90 mmHg diastolic typically resolving within 12 weeks after delivery),

Table 1. Risk factors and causes of ischemic stroke during pregnancy and puerperium[a] categorized following TOAST-classification

Risk factor or cause	Specific high-risk period (when applicable)
Cardioembolism	
Peripartum cardiomyopathy	Third trimester, puerperium (up to 6 months after delivery)
Cardiomyopathy, congestive heart failure	During pregnancy, delivery
Rheumatic valvular heart disease	During pregnancy, delivery
Mechanical heart valves	First trimester, third trimester, delivery, puerperium (possibly because of suboptimal anticoagulant therapy)
Other determined causes	
Arterial (cervical/intracranial) dissection	Delivery
Postpartum angiopathy	Puerperium
Coagulation disorders	Third trimester, delivery, puerperium
Systemic lupus erythematosus (SLE)	
Antiphospholipid syndrome (APS)	
Factor V Leiden (FVL)	
Sickle cell anemia	
Proteïn C/S deficiency	
Air embolism	Delivery, puerperium
Amniotic fluid embolism	Delivery, puerperium
Caesarean delivery[b]	Delivery
Blood transfusion	During or directly after delivery
Gestational hypertension	From second trimester
(Pre)eclampsia/HELLP syndrome	From second trimester, puerperium
Migraine	During pregnancy
Choriocarcinoma	No specific high risk period
(Postpartum) infection	Puerperium

[a]Puerperium is defined as the period between delivery and 12 weeks after delivery.
[b]May in part be attributed to an increased likelihood of caesarean delivery in already high risk patients [66]. Abbreviations: TOAST, trial of ORG 10172 in acute stroke treatment; HELLP, hemolysis elevated liver enzymes and low platelets. Source: Data extracted from Frontera *et al.* 2014 [30], James *et al.* 2005 [7], Lanska *et al.* 2000 [66], Leffert *et al.* 2015 [11], Miller *et al.* 2017 [67], and Wabnitz *et al.* 2015 [68].

Table 2. Physiological alterations in coagulation and fibrinolytic factors during pregnancy

Hemostatic changes during pregnancy	
Procoagulants	
Factor I (fibrinogen)	↑
Factor II	=?
Factor V	= /mild ↑?
Factors VII, VIII, IX, X, XII, XIII	↑
Factor XI	(Mild) ↓
Von Willebrand factor	↑
D-dimer	↑
Plasminogen activator inhibitor 1 and 2 (PAI-1/PAI-2)	↑
Anticoagulants	
Protein S activity	↓
Antithrombin III	=/ mild ↓?
Protein C activity	=

↑, increase; ↓, decrease; =, unchanged; ?, contrasting or insufficient data. Source: Data extracted from Bremme (2003) [25], Brenner *et al.* (2004) [69], and Cerneca *et al.* (1997) [70].

preeclampsia (progression to a combination of gestational hypertension and proteinuria >300 mg/24 h), eclampsia (occurrence of seizures in preeclamptic women [28]) and HELLP-syndrome (hemolysis, elevated liver enzymes, and low platelets). These pregnancy complications are pathophysiologically not yet fully understood, but are thought to be the result of a dysfunction of the placenta or placental development leading to systemic endothelial damage [29]. Also, during the second trimester the blood pressure is supposed to decrease because of a decreased vascular resistance, but when these mechanisms fail this results in gestational hypertension.

Postpartum cerebral angiopathy

Postpartum cerebral angiopathy (PPA) is also referred as (a form of) reversible cerebral vasoconstriction syndrome (RCVS), marked by a postpartum temporarily vasoconstriction of the cerebral arteries resulting in focal neurological deficits, usually after an uncomplicated pregnancy with imaging features

such as ischemic stroke and subarachnoid hemorrhage [30].

Amniotic fluid embolism

Cerebral embolism because of amniotic fluid entering the maternal circulation (during (traumatic) delivery or disruption at the site of placental insertion) is considered a very rare but specific cause of stroke [31].

Choriocarcinoma

Choriocarcinoma is a rare malignant neoplasm arising from placental trophoblastic tissue with a high tendency to metastasize to the brain. Ischemic stroke is possibly caused by trophoblastic embolism or direct vascular damage because of cerebral metastases [32].

DIAGNOSTIC APPROACH

Clinicians need to carefully consider the diagnostic options and should limit the risk of radiation and contrast exposure to the fetus as much as possible. No diagnostic imaging should be withheld when indicated, but the benefit should outweigh the risk [33▪]. Uncertainty of modality choice might cause unnecessary delay in the diagnostic process. Here, we provide guidance on diagnostic approach.

Magnetic resonance imaging

MRI is the first choice of imaging modality with a high diagnostic yield without radioactive radiation, which can also be used to rule out other diagnoses. MR-angiography [i.e. time-of-flight (TOF) sequence without contrast agent] can be used for vessel imaging and diffusion weighted imaging (DWI) to detect acute ischemia [33▪,34].

Computed tomography

When MRI is not readily available or in case of contraindications (e.g. pacemaker), CT-scan is a valid option, preferably with a low radiation technique. Fetal radiation exposure because of a regular CT head/neck is approximately 1.0–10 mGy, whereas an expected threshold dose for negative effects on the fetus is considered to be above 50 mGy [33▪]. This (indirect) radiation exposure is therefore rarely of concern.

Intravenous contrast agents

Administration of contrast during pregnancy should be done with caution. Gadolinium and ionidated contrast pass the placenta and are found to be potentially harmful to the fetus in animal models [31,35], although there are also reports of safe administration in pregnant women [36]. In a lactating woman intravenous contrast can be safely administered and breastfeeding can be continued [33▪,34,37].

Ultrasonography

Duplex ultrasonography of the carotids is frequently performed for the detection of carotid dissection or (atherosclerotic) carotid stenosis. Concerns of tissue temperature elevation produced by the sound waves reaching the fetus are of no concern when ultrasonography is performed outside the pelvic area [33▪].

TREATMENT OF ACUTE ISCHEMIC STROKE

Recombinant tissue plasminogen inhibitor

Pregnancy and the postpartum period are formal contra-indications of treatment with recombinant tissue plasminogen inhibitor (rTPA), because all randomized controlled studies on safety and efficacy of acute stroke treatment have excluded pregnant patients. However, in animal models no teratogenicity was found, which was in line with pharmacological studies that reported that rTPA does not cross the placenta [38]. This is in line with studies that reported that rTPA was safely administered during pregnancy and had a comparable effect and risk of complications in pregnant women compared to nonpregnant women [39,40]. Note that these statements rely on case reports [41,42] and retrospective analyses [43] with the risk of confounding by indication or publication bias. To overcome the lack of reliable information, the Safe Implementation of Treatments in Stroke-Fertile Women Stroke Thrombolysis Study (SITS-FW) was initiated and especially addresses the safety of thrombolysis in pregnancy [44]. Until these results become available, the current expert opinion is to consider treatment with rTPA in moderate-to-severe ischemic stroke in pregnancy and to balance the risks against the potential benefits [41,45,46].

Intra-arterial procedures

Mechanical thrombectomy is proven to be effective in patients with acute ischemic stroke with an occlusion of one of the proximal intracranial vessels of the anterior circulation [47], but pregnant women were excluded from this trial. The procedure appears as well tolerated as in nonpregnant women, but

Table 3. Ischemic stroke treatment: recommendations during pregnancy, delivery, and lactation period

Medication	Period		
	Pregnancy	Delivery	Lactation
Recombinant tissue plasminogen activator (rt-PA)	Relative contra-indication, however individual decision, benefit should outweigh risk (level of evidence C)	Limited evidence: within 48 h after delivery considerable risk of fetal and maternal bleeding (level of evidence C)	Limited evidence: temporarily discontinuation advised (level of evidence C)
Aspirin	Safe up to 150 mg in second and third trimester, in first trimester no consensus[a] (level of evidence B)	Discontinue at 36th week or 1 week prior to a scheduled delivery (level of evidence C)	Safe up to 150 mg (level of evidence C)
Other antiplatelet agents (dipyridamole, ticagrelor, clopidogrel)	Limited evidence, do not use (level of evidence C)	Limited evidence, do not use (level of evidence C)	Limited evidence, do not use (level of evidence C)
Heparin (LMWH, UFH)	Safe, LMWH preferred over UFH (level of evidence B)	Discontinue 24 h prior to delivery, or as soon as possible in case of contractions/spontaneous rupture of membranes. Restart within 12–24 h after delivery (level of evidence B)	Safe, not secreted in breast milk (level of evidence UFH: A, level of evidence LMWH: B)
Vitamin K antagonists (warfarin, acenocoumarol)	Teratogenic, convert to LMWH/UFH especially in first and third trimester (level of evidence B) In case of high cardioembolic risk (mechanical heart valves): adjusted-dose UFH/bid LMWH or UFH/LMWH until 13th week, then vitamin K antagonists until close to term, then resume UFH/LMWH. [60,67] (level of evidence A)	Discontinue close to delivery (in case of high cardioembolic risk), restart 1–3 days after delivery (level of evidence C)	Safe (level of evidence A)
Direct oral anticoagulants (DOAC) (apixaban, rivaroxaban, dabigatran)	Limited evidence, do not use (level of evidence C)	Limited evidence, do not use (level of evidence C)	Evidence of secretion in breast milk, do not use (level of evidence C)
Statins	Discontinue. Limited evidence, therapy not essential during pregnancy (level of evidence C)		Limited evidence, do not use (level of evidence C)
Antihypertensive treatment	(intravenous) Labetalol, nifedipine and methyldopa well tolerated and effective (level of evidence A) Avoid Atenolol, angiotensin receptor blockers and direct renin inhibitors (level of evidence C)		Widely used and compatible with breastfeeding (consult Lactmed[b] for complete summary): -Beta blockers: propranolol, labetalol, metoprolol; -Calcium channel blockers: nifedipine, nicardipine; -Methyldopa; - ACE-inhibitors: captopril, enalapril, quinapril-Avoid diuretics: can inhibit milk production (*Level of evidence C*)

[a]Data on safety in first trimester are limited, aspirin crosses the placenta, inconsistent reports of birth defects but potential benefits may warrant use of the drug in pregnant women despite potential risks [55]. Abbreviations: LMWH, low-molecular weight heparins; UFH, unfractioned heparin; ACE, angiotensin converting enzyme. Data extracted from: Bates *et al.* [60], Caso *et al.* [63▪], Demaerschalk *et al.* [45], Kernan *et al.* [55], [b]Lactmed [51], Nishimura *et al.* [71], Reprotox® [72] and Toxnet [50].

evidence on this treatment modality is based on case reports with the risk of publication bias [37,48]. In case of an occlusion of a proximal intracranial artery in a pregnant woman, primary mechanical thrombectomy may be considered without prior administration of rTPA. [49]. Treating clinicians should be aware of the intraprocedural radiation that is used during angiography and should limit the exposure of scattered radiation on the fetus using low dose or pulsed fluoroscopy and protection with radiation shields [37].

SECONDARY PREVENTION DURING PREGNANCY AND LACTATION

Secondary prevention treatment after ischemic stroke in pregnant women is generally indicated but the choice depends on the cause, risk of recurrence, gestational age, and/or whether a woman is lactating. This will result in an individualized treatment strategy, based on shared decision making. We strongly advise to use a drug database (such as Toxnet [50], Lactmed [51], and Reprotox [52]) prior to actual prescribing any medication during pregnancy and/or lactation but in general the following recommendations can serve as a guidance (Table 3).

Antiplatelet therapy

There is extensive experience with the use of aspirin, which crosses the placenta without teratogenic effects and thus can be used in low daily doses (50–150 mg/day) during the second and third trimester, and during the lactation period [53–55].

Data on safety in the first trimester are limited; there are some but inconsistent reports of birth defects such as gastroschisis [55]. The effects of other antiplatelet agents (e.g. dipyridamole, ticagrelor, clopidogrel) on the fetus or breastfed newborn are unknown because of limited data and should not be prescribed [56,57].

Anticoagulant therapy

Vitamin K antagonists cross the placenta and are found to be teratogenic (especially before 12 weeks of gestation) and thus contraindicated during pregnancy, but are well tolerated when a woman is lactating [58]. The new direct-acting oral anticoagulants (DOAC) such as dabigatran, rivaroxaban, and apixaban are found to cross the placenta in animal models, but to date there are insufficient data on toxicity during both pregnancy and lactation period and DOAC should therefore be avoided [59]. Alternatively, low-molecular weight heparins (LMWH; preferred) and unfractioned heparin (UFH) are recommended as they do not cross the placenta and are not secreted in breast milk [60].

Antihypertensive treatment

Almost all classes of antihypertensive drugs cross the placenta. For the treatment of hypertension during pregnancy labetalol, nifedipine, and methyldopa are considered the most safe and effective options. Atenolol, angiotensin receptor blockers, and direct renin inhibitors are contraindicated in pregnancy [5].

Cholesterol lowering therapy

For the treatment of hypercholesterolemia, there is a lack of knowledge on the consequences of statin use. As there is no direct maternal risk when these medications are temporarily interrupted, they should best be avoided during pregnancy and breastfeeding [61].

PERIPARTUM MANAGEMENT

There are no specific data on the most optimal management of (type of) delivery in a woman with a history of pregnancy-related ischemic stroke. In general, these women will be admitted to a hospital to monitor labor. There are no studies that investigated whether vaginal or caesarean section is safer in case of ischemic stroke during pregnancy, and this decision will generally be made based on an obstetric indication. When stroke is the consequence of (pre)eclampsia or HELLP syndrome, the best treatment for both the mother and the unborn child is to induce labor as early as possible [28]. It is advised to temporarily interrupt aspirin at the 36th week or 1 week prior to a scheduled delivery and anticoagulant medication (UFH/LMWH) preferably 24 h prior to labor to prevent bleeding complications. After labor, heparins can be restarted after 12–24 h. Vitamin K antagonists can be initiated after 1–3 days (Table 3) [62,63▪].

RISK OF RECURRENT ISCHEMIC STROKE DURING SUBSEQUENT PREGNANCIES

The absolute risk of a recurrent ischemic stroke during a subsequent pregnancy was found to be low (0–1.8%) [17,64,65], but to date there are no large studies available. In general, the postpartum period is associated with a higher recurrence risk than during pregnancy in women with a history of an ischemic stroke (risk ratio 9.7 vs. 2.2, respectively) [64]. This risk depends on the underlying disease or cause of stroke. Especially among women with stroke because of the antiphospholipid syndrome, the risk of recurrence was found to be high (15%) in a small study with only three events in 20 patients [26]. Based on the (limited) findings on the actual risk of stroke recurrence in pregnancy, future pregnancies do not need to be discouraged in women after stroke, but adequate counseling is advised.

COUNSELING OF WOMEN WHO ARE STILL AT A REPRODUCTIVE AGE AFTER PREGNANCY-RELATED STROKE

When a woman with a history of stroke has a desire to have children, they are generally referred to a gynecologist for preconceptional consultation, although this is solely based on expert opinion. There is no consensus on whether or not to start/continue antithrombotic prophylactic therapy in a pregnant woman with a history of stroke, especially during the embryonic phase (first trimester). Despite the presumed low risk of recurrent stroke during a subsequent pregnancy, the general opinion based on a survey among 230 neurologists was to prescribe antithrombotic prophylaxis during the first trimester of pregnancy in women after a pregnancy related stroke (88% of participants favored the prescription of some form of antithrombotic therapy) [56]. Recent AHA guidelines recommend that for pregnant women 'In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH/LMWH or *no* treatment may be considered during the first trimester of pregnancy depending on the

clinical situation (Class IIb; Level of Evidence C), followed by aspirin 50–150 mg/d for the remainder of the pregnancy (Class IIa; Level of Evidence B) [p. 2209] [55]. For women at high risk of embolism, continuation of anticoagulant therapy is preferred and in such cases it is generally recommended to administer LWMH twice daily or adjusted dose UFH [55].

CONCLUSION

Pregnancy-related ischemic stroke warrants a specific management for both mother and the unborn child. Pregnancy-specific risk factors are the hypertensive disorders of pregnancy and hypercoagulability. Diagnostic imaging with MRI is preferred, but low-dose CT is also a valid option. Therapeutic management should be based on risk–benefit analysis, but intravenous rTPA and mechanical thrombectomy should not be withheld from a pregnant woman with moderate-to-severe acute ischemic stroke when indicated. Aspirin (50–150 mg/daily) is well tolerated during pregnancy and the lactation period. The risk of recurrent stroke during subsequent pregnancies is considered low but continuation of antithrombotic or anticoagulant therapy is preferred. Multidisciplinary care with a team consisting a neurologist, an obstetrician and a radiologist/interventionalist is essential.

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Conflicts of interest

There are no conflicts of interest.

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