Pregnancy, Hormonal Treatments for Infertility, Contraception, and Menopause in Women After Ischemic Stroke

A Consensus Document

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Pregnancy has been reported to be associated with an increased risk of ischemic stroke, and stroke occurring during pregnancy is one of the leading causes of maternal death.[1] Kuklina et al[2] reported that the rate of any stroke among antenatal hospitalizations increased by 47% (from 0.15 to 0.22 per 1000 deliveries) and among postpartum hospitalizations by 83% (from 0.12 to 0.22 per 1000 deliveries) when comparing the period 1994–1995 to 2006–2007.

The American Heart Association Stroke Guidelines for Women have been published recently,[3] which deal with risk factors unique to women, including reproductive factors, and those factors that are more common in women, including migraine, obesity, metabolic syndrome, and atrial fibrillation. However, the lifelong management of hormonal issues in women who have had stroke was not fully addressed regarding the following: future pregnancies, type of delivery, labor induction, and secondary prevention during future pregnancy and lactation.

This consensus provides multidisciplinary approaches compiled by stroke neurologists, gynecologists, and endocrinologists, based on a thorough review of current literature through computerized searches up until July 26, 2016.

Methods

Literature on pregnancy, secondary stroke prevention, labor induction, hormonal contraceptive therapy, ovarian stimulation, and hormone replacement therapy was reviewed. The panel collected relevant articles using computerized searches of medical literature up until July 26, 2016. The search strategy was designed to identify studies on pregnancy, delivery, labor induction, breast-feeding, ovarian stimulation, hormonal contraceptive therapy, hormone replacement therapy, and their stroke risks. The included studies were identified from the Medline/PubMed database, EMBASE, and the Cochrane Database. Additional papers were identified from reference lists of retrieved articles, abstract lists of recent scientific meetings, and Internet-based sources (http://www.tctmd.com, http://www.cxvascular.com; Figure).

A list of treatment recommendations, including evaluations of evidence strength, is provided in Table 1.

Recommendations were rated as Grades of Recommendation Assessment, Development and Evaluation (GRADE) 1 (strong: when benefit clearly outweighed risk and could be accepted with a high degree of confidence) or GRADE 2 (weak: when the benefits and risks were more closely matched and were more dependent on specific clinical scenarios) and divided into 3 categories: A (high quality), B (moderate quality), and C (low quality). Statements for issues where there was limited evidence were rated as good clinical practice.

A worldwide search was performed to select the panel members who were considered to be both expert clinicians and researchers in the fields of stroke neurology, endocrinology, or gynecology. Using the Delphi method, members of the panel were asked to evaluate their agreement on hormonal use, type of delivery, and secondary prevention treatment during pregnancy in women with previous stroke.

Recommendations were drafted when an agreement was reached among a majority of panelists. In the absence of a majority, current literature was reviewed and reanalyzed, and a new version of the document, based on suggestions furnished by the panelists, was drafted (Table 1).

Future Pregnancies and Secondary Stroke Prevention Therapy With Antithrombotics

The only data available on the risk of recurrent stroke in women of child-bearing age come from a multicenter study[4] on 373 consecutive women who had already had an ischemic stroke between 25 and 40 years of age. This study reported an overall risk of recurrent stroke of 0.5% at year 5 (95% confidence interval [CI] 0.3–0.95) in nonpregnant periods compared with 1.8% (95% CI 0.5–7.5) during pregnancy.

However, the risk of stroke was reported to be significantly higher during the postpartum period (risk ratio 9.7; 95% CI 1.2–78.9) than during pregnancy (risk ratio 2.2; 95% CI 0.3–17.5).[4] The risks of ischemic and hemorrhagic stroke have been reported to be greater in the first 6 weeks after delivery, with an overall risk estimated to be 8.1 strokes per 100 000 pregnancies (95% CI 6.4–9.7).[5] The risk of thrombotic events in the postpartum period has been reported to be markedly higher within 6 weeks after delivery (odds ratio 10.8; 95% CI 7.8–15.1).[6]

For stroke prevention treatment during pregnancy, recommendations are based on 2 scenarios: a high-risk condition that would have called for anticoagulation or a lower-risk condition that would have called for antiplatelet therapy outside pregnancy (Table 1).

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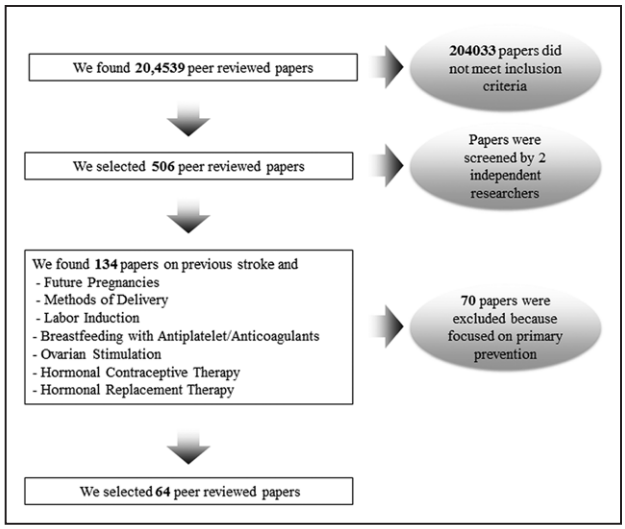

Figure. Flow chart of the research strategy.

Anticoagulants

Neither unfractionated heparin (UFH) nor low molecular weight heparin (LMWH) cross the placenta and, therefore, do not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the utero-placental junction has been reported.[7]

The use of UFH has been associated with maternal risks, including heparin-induced thrombocytopenia and osteoporosis. Furthermore, the administration of therapeutic doses of UFH requires regular laboratory monitoring of the activated partial thromboplastin time.

However, LMWH offers several advantages over UFH because of its better bioavailability, longer plasma half-life, more predictable dose response, and improved safety profiles, especially for osteoporosis and heparin-induced thrombocytopenia.[7]

Unlike heparin, coumarin derivatives (such as warfarin) can cross the placenta and, therefore, can lead to bleedings in the fetus and teratogenicity.[7] These have been reported to occur when oral anticoagulants (OA) are administered between the 6th and 12th weeks of gestation, whereas OA are less likely to be fetopathic when administered in the first 6 weeks of gestation.[8] Finally, warfarin has been reported to lead to fetal bleeding during delivery.[9]

A systematic review[9] in patients with mechanical heart valve (MHV) reported that the use of OA throughout pregnancy was associated with warfarin embryopathy in 6.4% (95% CI 4.6%–8.9%) of live births. The substitution of heparin at or prior to 6 weeks, and continued until the 12 week, eliminated this risk. Overall risks for fetal wastage were similar in women treated with OA throughout pregnancy, compared with those treated with heparin in the first trimester. Maternal mortality occurred in 2.9% (95% CI 1.9%–4.2%). Major bleeding events were recorded at 2.5% (95% CI 1.7%–3.5%) of all pregnancies, with most occurring at the time of delivery. The use of OA throughout pregnancy was associated with the lowest risk of valve thrombosis (3.9%; 95% CI 2.9%–5.9%), whereas heparin use between weeks 6 and 12 was associated with the highest risk of valve thrombosis (9.2%; 95% CI 5.9%–13.9%; Table 2).[9] Moreover, data collected from the Registry of Pregnancy and Cardiac disease comparing patients with MHV to those with tissue heart valves and those without prosthetic valves reported a maternal mortality rate of 1.4% in patients with MHV, 1.5% for those with tissue heart valve (P=1.000), and 0.2% for those without prosthetic valve (P=0.025). MHV thrombosis complicated pregnancies in 10 MHV patients (4.7%), 5 in the first trimester, which had been switched to some form of heparin. Hemorrhagic events were reported to occur in 23.1% of patients with MHV, 5.1% of those with a tissue heart valve (P<0.001), and 4.9% of those without prosthetic valve (P<0.001). Only 58% of MHV patients had no serious adverse events compared with 79% of those with a tissue heart valve (P<0.001) and 78% of those without a prosthetic valve (P<0.001). OA use in the first trimester compared with heparin was associated with a higher rate of miscarriage (28.6% versus 9.2%; P<0.001) and late fetal death (7.1% versus 0.7%; P=0.016).[10]

New Anticoagulants

Regarding the use of new anticoagulants during pregnancy, there are no available data because pregnancy was an exclusion criteria for the randomized controlled trials that these agents were tested in.[11–14] However, the German Embryotox Pharmacovigilance Center identified 63 exposed pregnancies associated with rivaroxaban use during childbearing age. All the women had discontinued rivaroxaban after the confirmation of pregnancy, mostly in the first trimester, whereas one patient continued therapy up until week 26. The registry recorded only one major fetal malformation in a mother who had had a previous fetus with cardiac malformation without exposure to rivaroxaban. Finally, a case of bleeding after a retrospective report of surgery for missed abortion was reported in this series.[15]

Aspirin

A meta-analysis of 73 studies[16] and a large (>9000 patients) randomized controlled trial[17] both suggest that 60 to 150 mg/d of aspirin administered during the second and third trimesters of pregnancy is safe for the mother and fetus.

Another meta-analysis of 8 studies, 7 observational and 1 randomized, on the risk of congenital anomalies with aspirin exposure during the first trimester reported no overall risk of congenital malformations associated with aspirin use.[18] However, aspirin use during the first trimester was associated with a 2-fold increased risk for gastroschisis. This risk estimate was calculated without taking into consideration variables, including concomitant drug use and the selection of controls. Furthermore, diagnosis was not confirmed in all patients.[18] Notably, another meta-analysis on preeclampsia suggests that aspirin is also beneficial in preventing preeclampsia when started before week 16.[19]

The effects of alternative antiplatelets, such as clopidogrel, ticlopidine, dipyridamole, prasugrel, and ticagrelor, during pregnancy have never been systematically investigated (Table 2).

Most available data on clopidogrel use during pregnancy comes from case reports on patients who had undergone coronary stent placement after a myocardial infarction either during or before pregnancy. Only 1 case report has been published on a successful gestation and delivery during clopidogrel use for secondary stroke prevention.[20]

Regarding dipyridamole, the use of dipyridamole together with low doses of aspirin during pregnancies at high risk for preeclampsia has been reported to lower the incidence of preeclampsia, fetal loss, and fetal growth retardation, whereas abnormal bleeding was not reported for mothers and neonates.[21]

Only single case reports on women with previous myocardial infarction using prasugrel or ticagrelor during pregnancy without negative results have been recently published.[22,23]

Methods of Delivery

Antithrombotic Discontinuation During Labor

UFH can cause a persistent anticoagulant effect at the time of delivery; therein, its use prior to labor is not without risk.[24] The bleeding risk associated with UFH can be assessed by activated partial thromboplastin time; however, during pregnancy, its response to heparin is often attenuated because of increased levels of factor VIII and fibrinogen.[25]

Bleeding complications have been rarely reported with LMWH.[26] Friedrich et al have reported antifactor Xa activity levels to be subtherapeutic in pregnant women receiving a twice daily regimen of therapeutic enoxaparin.[27] Regarding aspirin, it can readily cross the placenta and, when given near term, can lead to higher concentrations in the neonate compared with the mother.[28]

Choice of Delivery for Women With a History of Stroke

Caesarean delivery has been reported to be an independent risk factor for stroke.[29] We found few studies that had analyzed the modality of delivery in women with previous stroke.[4,30] One of these studies interviewed 115 women as to their past method of child delivery: 88 (77%) vaginal, 19 (17%) caesarean sections, and unknown for

Table 1. Recommendations

Questions	Recommendations	Grade	Level
Point 1: (a) Future pregnancies (b) Secondary prevention	For women with a history of stroke, future pregnancies are not contraindicated based on available data.	2	B
	Pregnant women with defined low-risk condition may be considered for treatment with UFH or LMWH throughout the first trimester, followed by low-dose aspirin for the remainder of the pregnancy	2	B
	In pregnant women with defined low-risk conditions, no recommendations on other types of antiplatelets other than aspirin can be given	2	C
	In pregnant women with defined high-risk conditions, vitamin K antagonists should be avoided between the 6th and 12th weeks of gestation and close to term to avoid the delivery of an anticoagulated fetus. LMWH or UFH should be used either during these above periods alone and alternated with vitamin K antagonists that have the same target INR based on previous prescription or during the entire pregnancy.	2	B
	High-risk condition women on NOAC treatment should be prescribed LMWH or UFH between the 6th and 12th week of gestation, while warfarin can be administered in the other periods. The vitamin K antagonist target INR needs to be based on the underlying pathology. Alternatively, UFH or LMWH may be prescribed throughout pregnancy	2	C
Point 2: Methods of delivery	Natural birth may be preferred to caesarean section. Caesarean section should be performed based on obstetric indications and not on previous history of stroke	2	C
Point 3: Labor induction	When labor is pharmacologically induced, aspirin therapy may be continued	2	C
	Therapeutic doses of UFH/LMWH should be discontinued 24 h prior to inducing labor and restarted within 24 h if no contraindications exist	2	C
	Vitamin K antagonists may be restarted after 24 h after delivery without a loading dose	2	C
Point 4: (a) Breast-feeding during antiplatelet treatment (b) Breast-feeding during anticoagulant treatment	Low-dose aspirin use during breast-feeding may be recommended	2	C
	No recommendations on antiplatelets besides aspirin during breast-feeding can be given	2	C
	Vitamin K antagonist use during breast-feeding may be recommended.	2	C
	UFH/LMH during breast-feeding during breast-feeding may be recommended.	2	C
	NOACs should be avoided during breast-feeding and when necessary substituted with LMWH/ UFH or vitamin K antagonists	2	C
Point 5: Ovarian stimulation	In women with previous stroke, no recommendation on ovarian stimulation could be given	2	C
Point 6: Hormonal contraceptive therapy	OC should not be recommended to women with previous stroke	1	B
Point 7: (a) Hormone replacement therapy and alternative strategies	HRT should not be recommended to women with previous stroke	1	A
	In women with previous stroke Gabapentin may be recommended for hot flashes.	2	C
	In women with previous stroke, no recommendation on the use of SSRI for hot flashes could be given	2	C
	Smoking habit, physical inactivity, and a BMI above normal should be discouraged in menopausal women with previous stroke	2	B

BMI indicates body mass index; HRT, hormone replacement therapy; INR, international normalized ratio; LMWH, low molecular weight heparin; NOAC, new anticoagulants; OC, oral contraceptives; SSRI, selective serotonin reuptake inhibitors; and UFH, unfractionated heparin.

8 (6%). Out of these 115 deliveries, 3 live births were reported in the first year after the index stroke, while 2 recurrent strokes during pregnancy; one because of essential thrombocytemia and the second because of primary antiphospholipid syndrome.[4] Another study reported that among 29 pregnant women with a history of stroke, 21 had full-term deliveries while 8 were preterm. Nine deliveries (31.1%) were caesareans, 1 (3.4%) forceps-assisted, and 19 (65.5%) noninduced vaginal deliveries. No recurrent strokes were reported.[31] Crovetto et al[30] reviewed the clinical reports of 24 pregnant women with previous stroke, reporting 11 caesarean sections and 13 vaginal deliveries. No recurrence of stroke was reported for these cases. The decision to perform caesarean section was based on obstetric indications and not on previous history of stroke.

Resumption of Antithrombotics

No randomized controlled trials or registry data are available on the resumption of antithrombotics after delivery. Yet, after minor general surgery or an invasive procedure, warfarin is generally resumed on the first evening after the procedure at the maintenance dose without a loading dose. However, LMWH, UFH, or new anticoagulants are generally resumed 12 to 24 hours after minor general surgery.[32]

Labor Induction

Literature is lacking data regarding the benefit/risk of uterotonic drug–induced deliveries in women with previous stroke. However, oxytocin does not significantly influence ATP-induced platelet aggregation, while prostaglandin $F_{2\alpha}$ competitively inhibits ATP-induced platelet aggregation.[33]

Breast-feeding and Antiplatelets or Anticoagulants

Warfarin

Warfarin is not detectable in either maternal milk or infant plasma.[34]

New Anticoagulants

New anticoagulants during breast-feeding have not been studied for infant safety.[11–14]

Table 2. Associated Teratogenic Risks From Antithrombotic Therapies

Antithrombotic Drugs	Placental Transfer	First Trimester	Second and Third Trimester
Low-dose aspirin (60–150 mg/d)	Yes	Contraindicated (risk of gastroschisis)	Not contraindicated
Other antiplatelets	No data	No data	No data
Warfarin	Yes	Contraindicated (teratogenic)	Not contraindicated
			Regular check of INR
UFH	No	Not contraindicated	Not contraindicated
		Risk of HIT	Risk of HIT
			Regular check of APTT
LMWH	No	Not contraindicated	Not contraindicated
NOAC	Dabigatran: yes	No data	No data
	Rivaroxaban: yes		
	Apixaban: no data		
	Edoxaban: no data		

APTT indicates activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWH, low molecular weight heparin; NOAC, new anticoagulants; and UFH, unfractionated heparin.

Heparins

The only published data on whether LMWHs are secreted in breast milk comes from a case series of 15 women receiving LMWH after caesarean section, where small amounts of heparin were detected in the breast milk of 11 patients.[35]

Aspirin

It has been reported that 4% to 8% of the aspirin dose directly reached the nursing infant,[36] often causing toxic accumulation because of the long elimination half-life of aspirin.[37] Moreover, high doses of aspirin (2–4 g/d) have been associated with metabolic acidosis, theoretical risks of platelet dysfunction,[38] gastrointestinal bleeding, and Reye's syndrome in infants.[39] However, low-dose aspirin intake on the part of the mother seems to be safe for the platelet function of neonates during breast-feeding.[40]

Clopidogrel

The use of $P2Y_{12}$ receptor blockers during pregnancy and their possible effects on breast milk have yet to be investigated. However, clopidogrel has been reported to be successfully resumed after delivery.[20] Furthermore, prasugrel has been maintained for 15 months after delivery without complications,[23] while ticagrelor use has never been investigated during breast-feeding.

Ovarian Stimulation

Studies investigating the effects of ovarian stimulation in women with previous stroke have yet to be performed because women with previous stroke probably are unlikely to be offered ovarian stimulation. However, it has been hypothesized that elevated estradiol levels during ovarian stimulation with gonadotropins may cause a state of hypercoagulability, which could determine arterial or vein thrombosis.[41] Strokes have been more frequently described in women with ovarian hyperstimulation syndrome,[42] but episodes have also been described in its absence.[43]

Hormonal Contraceptive Therapy

Regarding women with previous stroke on OCs, we were unable to find any data on safety because current guidelines recommend against the use of OCs in women with previous stroke.

Hormone Replacement Therapy

Limited data are available on the effects of estrogen therapy or hormone replacement therapy as secondary stroke prevention—this type of data has only been derived from the HERS (Heart and Estrogen/Progesterone Replacement Study),[44] WEST (Women's Estrogen for Stroke Trial),[45] and ESPRIT (Oestrogen in the Prevention of Reinfarction Trial)[46] trials on women with major past cardiovascular events (either myocardial infarction or stroke). The data indicates that neither are statistically significant.

However, most of these studies have investigated on the effects of conjugated equine estrogens, currently substituted by estradiol, for which data are extremely limited.

However, for herbal medicinal products, a Cochrane Database review examined all types of phytoestrogens, including red clover extracts, dietary soy, and soy extracts, and concluded that there was no evidence to support a benefit for climacteric symptoms.[47] None of these alternative therapy studies examined their benefit on vascular prevention, but several of them have reported that biochemical markers, including arterial wall stiffness and apolipoprotein B, are influenced by alternative treatment.[48]

It has been reported that gabapentin, which does not increase vascular risk, can reduce hot flushes.[49] Randomized placebo-controlled trials have shown that selective serotonin reuptake inhibitors can reduce menopausal vasomotor symptoms within 4 weeks of treatment.[50] However, selective serotonin reuptake inhibitor exposure has been reported to be associated with increased risks of intracerebral and intracranial hemorrhage.[51] On the other hand, a meta-analysis on the use of selective serotonin reuptake inhibitors in stroke survivors reported a nonsignificant excess of bleeding (risk ratio 1.63; 95% CI 0.20–13.05).[52]

Regular physical activity, no smoking habit, limited alcohol habit, and body mass index in the norm improve climacteric symptoms and reduce vascular risk. In fact, The American Heart Association's "Life's Simple 7"[53] defines ideal cardiovascular lifestyle as not smoking, regular physical activity, healthy diet, maintaining normal weight, and controls of cholesterol, blood pressure, and blood glucose levels. The achievement of Life's Simple 7 goals has been associated with lower long-term risk of dying after stroke.[53]

Discussion and Considerations for Future Research

This multidisciplinary expert consensus provides evidenced-based recommendations on the lifelong management of hormonal issues in women with previous stroke. Most of these recommendations are of limited strength and are based on observational data, and it is unlikely that randomized

controlled trials will provide data on these issues in the near future.

This thorough review of current literature leads its authors to recommend that women with past stroke be better followed up over their lifetimes to determine both the underlying role of pregnancy in stroke and its impact on the lifelong vascular risks for both mother and child through the application of this expert-based consensus document, together with the participation in a future planned international registry for women with past stroke in childbearing age.

The research community would benefit from pooling their data on pregnant women and stroke victims to realize a clearer picture on global trends concerning secondary prevention and risk profiles, both of which are responsible for death and disability rates worldwide. Data of this nature would provide the much-needed insight into the treatment safety and efficacy regarding antiplatelet selection and dosage and could aid in better defining predictive factors.

An additional priority of future research should be to investigate on the role of ovarian stimulation on the vascular state because this therapy is widely sought out by women because of falling fertility rates worldwide.

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