

Review Article

Ischemic Stroke during Pregnancy and Puerperium

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Ischemic stroke during pregnancy and puerperium represents a rare occurrence but it could be a serious and stressful event for mothers, infants, and also families. Whenever it does occur, many concerns arise about the safety of the mother and the fetus in relation to common diagnostic tests and therapies leading to a more conservative approach. The physiological adaptations in the cardiovascular system and in the coagulability that accompany the pregnant state, which are more significant around delivery and in the postpartum period, likely contribute to increasing the risk of an ischemic stroke. Most of the causes of an ischemic stroke in the young may also occur in pregnant patients. Despite this, there are specific conditions related to pregnancy which may be considered when assessing this particular group of patients such as pre-eclampsia-eclampsia, choriocarcinoma, peripartum cardiomyopathy, amniotic fluid embolization, and postpartum cerebral angiopathy. This article will consider several questions related to pregnancy-associated ischemic stroke, dwelling on epidemiological and specific etiological aspects, diagnostic issue concerning the use of neuroimaging, and the related potential risks to the embryo and fetus. Therapeutic issues surrounding the use of anticoagulant and antiplatelets agents will be discussed along with the few available reports regarding the use of thrombolytic therapy during pregnancy.

1. Introduction

Ischemic stroke is more common in men than in women until advanced age, when a higher incidence is observed in women [1]. When younger patients are considered, females usually exceed males under 35, a period that coincides with the prime child-bearing years [2, 3]. Pregnancy and puerperium may partly contribute to this increased rate.

Ischemic stroke during pregnancy is a rare occurrence but it could be a serious and stressful event for mothers, infants, and also their families.

A conservative approach is frequently adopted because of concerns of any adverse effects of treatment and etiological investigations on the mother and the unborn fetus.

This article describes the physiological changes that may increase the risk of cerebral complications and deepens specific mechanisms, risk factors for ischemic stroke, and management of this subgroup of patients.

2. Maternal Changes during Pregnancy Predisposing to Ischemic Stroke

Maternal physiological alterations occur during pregnancy as a consequence of the variations of the hormonal status, involving the haemostatic and hemodynamic systems. Whether this adaptation could affect the risk of an ischemic stroke is still unclear and the relationship is likely complex.

2.1. Haemostatic Adaptations. Pregnancy is normally associated with significant changes in venous flow and in the molecular mediators of haemostasis, to the extent that the overall balance shifts towards a hypercoagulant effect [4] (Table 1).

Procoagulant changes are more marked around term and in the immediate postpartum period, presumably related to the expulsion of the placenta and release of thromboplastic

TABLE 1: Modifications of haemostatic factors during pregnancy.

Procoagulant factors	
Fibrinogen (factor I)	↑
von Willebrand factor	↑
Factors VII, VIII, IX, X, XII	↑
Factors V, XIII	↑↓
Factor XI	C
Factor II	C
Coagulation inhibitors	
Protein S	↓
Protein C, antithrombin III	=
Fibrinolytic factors	
Tissue plasminogen activator	↓
Plasminogen activator inhibitor 1 and 2 (PAI-1, PAI-2)	↑
Thrombin activatable fibrinolysis inhibitor (TAFI)	↑
Others	
Platelet count	↓
Prothrombin fragment 1+2	↑
Thrombin-antithrombin complex	↑
D-dimer, fibrinopeptide-A	↑

↑: increase; ↓: decrease; =: no significant change; ↑↓: early increase followed by decrease; C: controversial data.

substances at the site of separation. Blood coagulation and fibrinolysis get back to those of the nonpregnant state approximately 3 weeks after delivery [4].

This resulting hypercoagulable state in association with a venous stasis condition may likely account for an increased risk of thromboembolic complications, in particular, during the third trimester and the puerperium.

2.2. Hemodynamic Adaptations. In the first 10 weeks of pregnancy, a volume shifting develops with an increase of total body water, that remains stably increased until 1 to 2 weeks after delivery, after which it gradually returns to normal.

This hypervolemic state combined with an increasing circulatory demands of fetus and placenta results in a rise of 30% to 50% of cardiac output, stroke volume, and heart rate. Half of this change occurs during the first 8 weeks of pregnancy, reaching a peak at 25–30 weeks. During labour, there is a dramatic change in cardiac output which increases progressively as labour advances increasing by a mean value of 30%. Heart rate also increased consistently.

Then, in the first days after delivery, there is a strong fall of stroke volume and heart rate and cardiac output gradually decreases to 50% above prepregnancy level within 2 weeks after delivery and returns to normal by 6 to 12 weeks [5].

As a consequence of decrease in systemic vascular resistance, blood pressure starts to lower around the seventh week, hits the lowest levels at 24 to 32 weeks, and then increases progressively to prepregnancy levels at term.

Venous compliance increases throughout pregnancy, leading to decreased blood flow, increased stasis, and a tendency toward orthostatic pressure drops.

A remodelling in arterial composition with a reduction in collagen and elastin contents and a loss of distensibility that partially normalizes near term has been also observed during pregnancy [6].

3. Epidemiology

In hospital-based and community-based reports, the incidence for ischemic strokes associated with pregnancy or puerperium varies considerably ranging from 4.3 to 210 per 100,000 deliveries [7].

Potential explanations for this variability are: (1) differences in study designs, (2) small sample size of most studies, (3) inadequate consideration of referral bias, and (4) different definitions of strokes and stroke subtypes. Studies are also not uniform in definition of postpartum period. Moreover, estimation of incidence is influenced by those studies reported before neuroimaging use became widely available [8, 9]. When data published since 1985 are considered [7, 9–16], the incidence rates is reduced ranging from 4 to 41 per 100,000 pregnancies and decreases more considering only the three population-based studies, with a range from 4 to 11 cases per 100,000 deliveries [7, 9, 12] (Table 2).

The risk of stroke varies according to pregnancy stages. Kittner and coworkers estimated a relative risk of cerebral infarction of 0.7 (95% CI, 0.3 to 1.6) during pregnancy, which increased to 5.4 (95% CI, 2.9 to 10.0) during the six weeks after pregnancy (after a live birth or stillbirth) [12]. In hospital-based series, the frequency of ischemic stroke has been observed to be higher in the third trimester, with a peak in the first postpartum week [7, 14, 15].

In a large Swedish cohort of over 650,000 women with over 1 million deliveries in an eight-year time period, the greatest risk of ischemic and hemorrhagic stroke was found around delivery [33,8 (95% CI 10.5 to 84.0), two days before and one day after with an increased but declining risk over the subsequent six weeks [8.3 (95% CI, 4.4 to 14.8) [17].

The reason of a clustering of events around delivery and postpartum period is not clear but implies a possible link with the coagulation profile of this stage. The large reduction of blood volume or the rapid hormonal changes following delivery have also been suggested to influence this stroke risk timing, perhaps through hemodynamic, coagulative, and vessel-wall changes [12].

4. Risk Factors and Associated Conditions

Data from the Nationwide Inpatient Sample in United States for the period from 2000 to 2001 showed that several medical conditions resulted associated with stroke in pregnancy such as hypertension, diabetes, heart disease, sickle cell disease, anemia, thrombocytopenia, and thrombophilia. Among lifestyle factors, alcohol, smoking, and substance abuse were found to be significantly associated to stroke in pregnancy [18]. Pregnancy and delivery complications such as infection, transfusion, postpartum hemorrhage, and fluid

TABLE 2: Studies of pregnancy-related stroke since 1985.

Author, year	Methodology	Study period	Postpartum period	Deliveries N°	Total stroke N°	Ischemic stroke N°	Ischemic stroke incidence (per deliveries)	Mortality N° (%)	Ischemic stroke mortality	Notes
Wiebers and Whisnant, 1985	Retrospective population-based study	1955–1979	NR	26099*	1	1	NR	NR	NR	* Live births
Simolke et al., 1991	Retrospective single hospital-based study	1984–1990	NR	89913	15	7	1 in 10000'	2 (13,3)	1 (14,3)	* Including also cerebral venous thrombosis
Awada et al., 1995	Retrospective hospital-based study	1983–1993	15 days	NR	12	9	NR	4 (33)	1 (11,1)	
Sharshar et al., 1995	Retrospective and prospective multi-hospital-based study	1989–1992	2 weeks	348295	31	15	4,3 per 100 000	4 (13)	0	
Kittner et al., 1996	Retrospective population-based study	1988–1991	6 weeks	141243	31	17*	11 per 100 000	NR	NR	* Including cerebral venous thrombosis (1 patient)
Witlin et al., 1997	Retrospective single hospital-based study	1985–1995	4 weeks	79301	24	5	NR	7 (29,2)	NR	
Jiagobin and Silver, 2000	Retrospective single hospital-based study	1980–1997	6 weeks	50711	34	21*	41 per 100 000	3 (9)	0	* Including cerebral venous thrombosis (8 patients);
Skidmore et al., 2001	Retrospective hospital-based study	1992–1999	12 weeks	58429	36	21	NR	1 (2,7)	1 (4,7)	
Ros et al., 2001	Retrospective, records from birth register, Sweden	1987–1995	6 weeks	1003489	NR	NR	4 per 100 000	NR	NR	
Jeng et al., 2004	Retrospective single hospital-based study	1984–2002	6 weeks	49796	49	16	32,1 per 100 000	10 (20)	2 (13)	
Liang et al., 2006	Retrospective single hospital-based study	1992–2004	6 weeks	66781	26	11*	16,5 per 100000	5 (19)	1 (9,1)	* Including cerebral venous thrombosis (3 patients)

NR: not reported.

and electrolyte imbalance were also linked to pregnancy-related stroke [18]. However, this study was limited to data derived from discharge record abstraction and no precise information on stroke ischemic subtype were available.

Although the risk of pregnancy-related stroke is resulted to be higher among women aged 35 years and older [18], ischemic subtype has been associated with a younger maternal age [12] and a mean age under 30 has been reported in patients with pregnancy-related stroke in hospital-based series (Table 3).

Migraine headaches have been associated with a 17-fold increased risk of stroke in pregnancy [18], a relation which is stronger with ischemic subtype (OR 30.7, 17.4 to 34.1) [19]. However, difficulties in differentiating between migraine as a manifestation or as a consequence of an ischemic stroke and others conditions such as severe pre-eclampsia, and migraine as an independent risk factor for ischemic stroke during pregnancy, limit the external validity of these findings.

Caesarean delivery has been shown to be associated with a 3–12 times increased risk of peripartum and postpartum stroke [20, 21]. Ischemic stroke risk was found to be significantly increased in women with Cesarean delivery and up to 6 months postpartum [22]. However, an increased number of caesarean delivery among patients with previous stroke or with conditions that can increase the risk of stroke such as preeclampsia-eclampsia may confound this association.

5. Etiology of Ischemic Stroke in Pregnancy

As several causes of ischemic stroke in the young have been reported in pregnancy and the puerperium [23], in most cases it is quite difficult to distinguish whether pregnancy is coincidental or plays a role in the occurrence of the cerebral infarction. Notwithstanding, there are specific conditions related to pregnancy which may lead to ischemic stroke such as preeclampsia and eclampsia, and most rare disorders such as choriocarcinoma, amniotic fluid embolism, peripartum cardiomyopathy, and postpartum cerebral angiopathy. Since most studies included small numbers of patients and authors defined strokes and stroke etiologies differently, a comparison of the conditions that contribute to ischemic stroke in pregnancy is limited. However, while a high proportion of cases, ranging from 28% to 46%, has resulted to be undetermined, preeclampsia-eclampsia and cardioembolic causes represent the conditions that mainly contribute to ischemic stroke (Table 3).

6. Pregnancy-Specific Causes of Ischemic Stroke

6.1. Preeclampsia and Eclampsia. Preeclampsia-eclampsia, also known as toxemia, is a multisystem disorder that occurs in the later stages of pregnancy and in the first 6 to 8 weeks after delivery, accounting for a substantial maternal and perinatal mortality [24].

Pre-eclampsia is characterized by the presence of elevated gestational blood pressure, proteinuria, and oedema. Although this condition is usually asymptomatic, patients

may complain of headaches, visual abnormalities, confusion, and impairment of consciousness. The onset of seizures or coma defines eclampsia [24]. About 2% to 12% of patients with eclampsia develop a HELLP syndrome [25], a life-threatening condition characterized by hemolytic anemia (H), elevated liver enzymes (EL), and low platelet count (LP). Preeclampsia occurs in about 6% to 8% of all pregnancies, whereas eclampsia has an incidence of 1/1000 to 1/2000 deliveries in the United States [26].

Preeclampsia-eclampsia increases the risk of stroke [12, 22, 27]. The proportion of patients with ischemic stroke related to preeclampsia-eclampsia during pregnancies varies from 6% to 47% (Table 3). Moreover, preeclampsia is also founded to increase the risk of stroke later in life suggesting that these patients may be closely monitored and controlled for stroke risk factors also beyond the postpartum period [27].

Patients with severe pre-eclampsia or eclampsia may manifest focal neurological deficits, consistent with a clinical diagnosis of stroke and on neuroimaging both ischemic or hemorrhagic stroke may be found.

Clinical signs and neuroradiological lesions frequently reverse completely within a few days or weeks. Brain computed tomography (CT) and magnetic resonance imaging (MRI) show subcortical white matter lesions often with posterior predominance and, to a lesser extent, in the cortical grey matter predominantly affecting the parietooccipital region, consistent with the presence of reversible vasogenic edema. The appearance of cerebral edema on brain imaging is thought to be the consequence of disturbed cerebral autoregulation with cerebral endothelial leakage in the setting of severe hypertension. These findings are similar to those found in other vasculopathies associated to pre-eclampsia such as the posterior reversible encephalopathy syndrome (PRES). MR angiography may also show reversible vasospasm of the large and medium-sized vessels.

The pathogenesis is complex and not completely understood. This condition is characterized by abnormal vascular response to placentation and by endothelial cell dysfunction which represents common response leading to instability of vascular tone with vasospasm in various organs and activation of the coagulation system with microthrombi formation [24, 28, 29] with the consequence of ischemic damage in many organs.

The management of pre-eclampsia is aimed at delivery of the fetus and placenta and drug therapy of hypertension. Magnesium sulphate should be used for the treatment of seizures and in prophylaxis may prevent or reduce the rate of eclampsia and its complications in pre-eclamptic patients [24, 30].

6.2. Choriocarcinoma. Choriocarcinoma is a malignant neoplasm that arises from placental trophoblastic tissue, usually following a molar pregnancy but also term delivery, abortion, and ectopic pregnancy. It has a tendency to early metastasize, especially to the lungs, brain, liver, and vagina [31]. Brain metastases are relatively common complication involving about one-fifth of patients. The clinical presentation of cerebral involvement includes headache, focal neurological

TABLE 3: Etiologies of ischemic stroke complicating pregnancy and the puerperium.

Author, year	Mean age, yrs	N° case	Large artery disease	Cardiac disease N° (%)	Coagulopathy N° (%)	Other causes N° (%)	Pre-eclampsia N° (%)	Other pregnancy N° (%)	Unknown N° (%)	Notes
Awada et al., 1995	30	9		3 (33%)*		1 (11%)**	1 (11%)		4 (45%)	*2 valvular heart disease, 1 postpartum cardiomyopathy with atrial fibrillation, *Nephrotic syndrome
Sharshar et al., 1995	30,2	15			1 (6,6%)*	1 (6,6%)**	7 (47%)	2 (13,2%)*	4 (26,6%)	*Protein S deficiency; **vertebral artery dissection; ***1 postpartum cerebral angiopathy, 1 amniotic fluid embolism
Kittner et al., 1996	27	17		1 (5,9%)*		6 (35,3%)**	4 (23,5%)		6 (35,3%)	*Mitral valve prolapse; **2 primary CNS vasculopathy, 1 cerebral artery dissection, 1 cerebral venous thrombosis, 1 postherpetic vasculitis, 1 thrombotic thrombocytopenic purpura;
Jiagobin and Silver, 2000	30	13	1 (8%)*	4 (30,7%)**	2 (15,3%)*		3 (23,1)*		6 (46%)	*Carotid artery dissection; *valvular heart disease, coronary artery disease, patent foramen ovale; ***deficiencies of protein C, protein S, activated protein C resistance; ****preeclampsia-eclampsia was considered as a risk factor
Skidmore et al., 2001	26,9	21		5 (23,7%)*	2 (9,6%)**	5 (23,7%)*	3 (14,4%)		6 (28,6%)	*1 pedunculated cardiac mass, 2 rheumatic heart disease, 1 valvular heart disease, 1 peripartum cardiomyopathy, **1 protein S deficiency, 1 factor VIII anomaly, ***1 cerebral vasculitis, 1 migrainous infarct, 1 mucormycosis, 1 hypotension, 1 thrombotic thrombocytopenic purpura

TABLE 3: Continued.

Author, year	Mean age, yrs	N° case	Large artery disease	Cardiac disease N° (%)	Coagulopathy N° (%)	Other causes N° (%)	Pre-eclampsia N° (%)	Other pregnancy N° (%)	Unknown N° (%)	Notes
Jeng et al., 2004	28,9	16		9 (56%)*	3 (19%)**	1 (6%)***	1 (6%)		2 (13%)	*7 rheumatic heart disease, 2 other heart diseases; ** protein S deficiency; *** giant cerebral aneurysm
Liang et al., 2006	31,5	11	1 (9%)	4 (36%)*		3 (27%)**	2 (18%)	1 (9%)***		*2 congenital heart disease, 1 rheumatic heart disease, 1 atrial myxoma; ** cerebral venous thrombosis; *** amniotic fluid embolism;

deficits, seizures, encephalopathy, signs of elevated intracranial pressure, and excessively elevated serum β human chorionic gonadotrophic hormone level [32, 33].

Choriocarcinoma is a highly vascular tumor and is extremely prone to hemorrhage. In the brain, trophoblasts may invade blood vessels, just as they would in the uterus. Cerebral ischemic damage may be the result of thrombotic process in damaged vessels or consequence of trophoblastic cerebrovascular embolism [23].

6.3. Amniotic Fluid Embolism. Amniotic fluid embolism (AFE) is a rare complication of pregnancy, related more frequently to advanced age and multiparity. AFE occurs in the setting of a disrupted barrier between the amniotic fluid and maternal circulation. Why this entry into maternal circulation occurs in some women and not in others is not clearly understood.

The mortality rate varies from 61 to 86% and accounts for approximately 10% of all maternal deaths in the United States [34]. AFE usually presents at term during labour and should be suspected in any pregnant patient, specifically those with ruptured membranes, who develop sudden onset dyspnea with hypoxia, acute hypotension, and/or cardiac arrest followed by a profound coagulopathy; a large percentage of survivors has a permanent hypoxia-induced neurological damage [34]. Paradoxical cerebral amniotic fluid embolism is possible [23]. Seizures is present in 10%–20% of cases and may be at times the first manifestation.

6.4. Postpartum Cerebral Angiopathy. Postpartum cerebral angiopathy is characterized by prolonged but reversible vasoconstriction of the cerebral arteries, usually associated with acute onset, severe, recurrent headaches, with or without additional neurologic signs and symptoms. It has been described using various labels, including postpartum angiopathy [35, 36], postpartum angiitis [37], and puerperal cerebral vasospasm [38]. Although the pathophysiology is scarcely understood, a disturbance in the control of cerebral vascular tone seems to be a critical element, features similar to those observed in preeclampsia or eclampsia [39]. Most patients have a history of uncomplicated pregnancy and normal labor and delivery, followed within days to a few weeks by acute onset of headache with or without various neurologic signs and symptoms. The brain MRI in patients with postpartum angiopathy may show areas of T2/FLAIR hyperintensity in any location, but especially in watershed areas between vascular territories. Multifocal segmental narrowing of large and medium-sized cerebral arteries may be present on both magnetic resonance angiography (MRA) and CT angiography. Arterial abnormalities are better visualized with CT angiography and conventional invasive catheter angiography; both of which require the use of iodinated contrast material. The MRI and MRA features may normalize with time, although extensive infarction may develop [36].

6.5. Peripartum Cardiomyopathy. Peripartum cardiomyopathy is a rare dilating cardiomyopathy, that develops in the

last gestational month of pregnancy or in the first 5 months after delivery, with no identifiable cause for heart failure and in the absence of heart disease. Early development of a cardiomyopathy during pregnancy has also been described with similar clinical presentation and maternal outcome but with a higher incidence in twin pregnancies, shorter duration of pregnancy, and lower birth weight [40].

The true incidence of this condition is unknown; the reported rate is of 1 in 3000 to 1 in 4000 live births in the United States but there are geographical differences being rare in Europe and more common in Africa [41–43].

Risk factors include advanced age (>30 years), multiparity, obesity, twin pregnancies, preeclampsia, and severe hypertension during pregnancy [40, 44, 45]. The etiology remains uncertain. Suggested hypotheses include myocarditis, abnormal immune response to pregnancy, maladaptive response to the hemodynamic stresses of pregnancy, stress activated cytokines, viral infection, and prolonged tocolysis.

Clinical features consist of heart failure with dilated cardiac cavities. However, the diagnosis remains a challenge because many normal women in the last month of a normal pregnancy experience dyspnea, fatigue, and pedal edema, symptoms similar to early congestive cardiac failure. Peripartum cardiomyopathy is a diagnosis of exclusion, distinguished by rapid onset, occurrence in the peripartum period, and significant improvement in up to 50% of affected women.

Systemic and pulmonary embolization is frequently associated with this condition with an estimated incidence ranging from 25% to 40% [23]. Neurologic deficits caused by thromboembolism can rarely be the presenting symptoms [46–48]. The incidence of ischemic stroke is about 5% [23]. Additionally, cerebral infarction may result more rarely from cerebral hypoperfusion secondary to cardiac failure [49]. Prognosis is dependent on recovery of systolic function. The majority of patients recover partially or completely but the mortality rate is high and the rate of heart transplantation is about 11% [50]. Recurrences during subsequent pregnancies are common.

7. Brain Imaging Ischemic Stroke during Pregnancy

Imaging studies as part of the workup should be based on neurological indications but several concerns about fetal exposure to radiation arise for the clinician. The harmful effects of radiation depend on the stage of gestation at which the fetus is exposed, the total dose of radiation absorbed, and the rate at which the dose is absorbed [51]. Fetal exposure to ionizing radiation from CT of the maternal head is extremely low. Potential risk of birth defects due to radiation are limited to the first few weeks, the embryogenesis period, when the patient may not be aware of the pregnancy. Radiation-protection precautions for the developing fetus should be used whenever the question of pregnancy arises.

A CT perfusion study should be avoided due to a significant increase of the X-ray exposure and to the necessity

of administering intravenous contrast unless the information is critical to guide therapy. The use of iodinated contrast material during pregnancy may pose some risk to the fetus.

There are no evidence of adverse fetal effects in humans to the magnetic field exposure for magnetic resonance imaging (MRI). It has been hypothesized that some risk for the fetus may raise due to exposure to very powerful magnetic fields, minimal increases in body temperature, and loud tapping noises of the coils [52]. Although a possible teratogenic effect has been found in some studies on animal models [53, 54], MRI is the preferred imaging option in pregnancy.

Regarding the use of gadolinium during MRI study, toxic effects are not known but depositions of the gadolinium ions in fetal tissue raises concerns. Moreover, animal reproduction studies showed that gadolinium at high dose have teratogenic effects [52, 55]. Therefore, the use of gadolinium should be avoided in a pregnant woman unless specifically indicated in particular situation where the decision must be made after a well-documented and thoughtful risk-benefit analysis [56, 57].

8. Treatment of Ischemic Stroke during Pregnancy

The choice of therapy for an ischemic stroke in pregnancy is complicated by potentials of fetal toxicity, in particular during the first trimester when the risk of teratogenicity is the highest. Therapeutic intervention is influenced by the identification of underlying etiology and the related effectiveness of the treatment, the possibility of adverse outcomes both to the mother and the fetus, and by the consideration of the term of pregnancy.

8.1. Prevention Treatment. Therapeutic decision is made difficult by the lack of randomized controlled trials that adequately compare treatment options for this group of patients. Therefore, the choice of agents for prophylactic strategies is largely based upon inferences from others studies, primarily on prevention of deep vein thrombosis and the use of anticoagulants in women with high-risk cardiac conditions.

According to the American Heart Association (AHA) guidelines for pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions such as coagulopathy and mechanical heart valves, three possible therapeutic alternatives may be considered: (a) adjusted-dose unfractionated heparin (UFH) throughout pregnancy, (b) adjusted-dose low molecular weight heparins (LMWHs) throughout pregnancy, (c) either UFH or adjusted-dose LMWHs until week 13, then restarted from the middle of the third trimester until delivery and warfarin at other times [58]. For lower risk conditions, either UFH or LMWH therapy is recommended in the first trimester, followed by lowdose of aspirin for the remainder of the pregnancy [58].

8.2. Anticoagulant Treatment. UFH and LMWH do not have teratogenic effects since they do not cross the placenta

and are not causes of fetal hemorrhage, although bleeding at the utero-placental junction is possible. Several studies strongly suggest that UFH/LMWH therapy is safe for the fetus [59–62]. By contrast, warfarin cross the placenta and can cause bleeding and malformation in the fetus [61, 63]. This agent is probable safe if administered during the first 6 weeks of gestation, but confers a risk of embryopathy if given between 6 weeks and 12 weeks of gestation [63]. In addition, warfarin cause an anticoagulant effect in the fetus, which is a concern, particularly at the time of delivery, when the combination with the trauma of delivery can lead to bleeding in the neonate. Therefore, warfarin is best avoided during pregnancy.

A major bleeding was reported in about 2% of the pregnant women treated with UFH [62], which is consistent with the observed rate in nonpregnant women receiving UFH and warfarin therapy. Since the possibility of a persistent anticoagulant effect (for up to 28 hours after the last injection of heparin), the use of UFH prior to labor may complicate the delivery increasing the risk of bleeding and contraindicates epidural analgesia. By contrast, LMWH therapy is rarely related with bleeding complications and in particular, it is not associated with an increased risk of severe peripartum bleeding [64]. LMWH has also the advantages of producing a more stable coagulant response and lower incidence of osteoporosis. In about 3% of non pregnant patients, the UFH therapy can cause the development of the heparin-induced thrombocytopenia (HIT), an acquired immune condition IgGmediated, which is frequently complicated by extension of the preexisting thrombotic phenomena or new arterial thrombosis [60]. In pregnant women who developed HIT and require ongoing anticoagulant therapy, use of the heparinoid danaparoid sodium is recommended because it is an effective antithrombotic agent, does not cross the placenta, and has much less cross-reactivity with UFH and, therefore, less potential to produce recurrent HIT than LMWH [65].

Heparin and LMWHs do not reach the maternal milk and can be safely given to nursing mothers [65]. The use of warfarin is also safe during breastfeeding [65].

8.3. Antiplatelet Treatment. Whether treatment with aspirin during the first trimester of pregnancy is safe remains unclear. Although some retrospective studies reported an increased risk of fetal malformations in pregnant women using aspirin during first months, prospective studies did not confirmed this result.

A meta-analysis of eight studies (seven observational and one randomized) evaluated whether aspirin use during the first trimester of pregnancy is associated with an increased risk of congenital malformations and found no evidence of an overall increase in rates of major congenital malformations, suggesting that aspirin is safe even when used early in pregnancy [66]. This analysis, however, showed that exposure to aspirin may be associated with an increased risk of gastroschisis, but the reliability of this result should be biased because of the limitations of the studies involved related to the use of other drugs, the selection of control

TABLE 4: Case reports describing the use of thrombolytic treatments in ischemic stroke during pregnancy and puerperium.

Author, year	Thrombolysis	Dosage	Maternal age	Gestational age	Maternal complications	Fetal outcome	Associated conditions
Dapprich, 2002	IV rt-PA	0,9 mg/kg	31 y	12 week	minor hemorrhagic imbibition of infarct area	good	Protein S deficiency
Elford, 2002	IA rt-PA	15.5 rng	28 y	I week	hematoma in basal ganglia	good	Ovarian hyperstimulation syndrome
Johnson, 2005	IA rt-PA	15 rng	39 y	37 week	none	good	Undetermined cause
Leonhardt, 2006	IV rt-PA	0,9 mg/kg	26 y	23 week	basal ganglia infarction	good	Elevated IgG and IgM anti-cardiolipin
Murugappan, 2006	^a IV rt-PA	0,9 mg/kg	37 y	12 week	intrauterine hematoma	MTP	Antibodies
	^b IV rt-PA	0,9 mg/kg	31 y	4 week	none	MTP	Mitral valve replacement decreased protein S activity
	^c IV rt-PA	0,9 mg/kg	29 y	6 week	death from dissection during angioplasty	died	Aortic valve replacement
	^d IA rt-PA	21 rng	43 y	37 week	none	good	AT III, protein C and S deficiencies
	^e IA UK	600 000 U	28 y	6 week	buttock hematoma	good	protein C and S deficiencies, PFO
	^f local UK	700 000 U	25 y	frst trimester	asymptomatic ICH	SA	bacterial endocarditis
Wiese, 2006	IV rt-PA	0,9 mg/kg	33 y	13 week fifteen hours after cesarean delivery 6 days after	none	good	mitral valve replacement
Mendez, 2008	IA UK	100 000 U	37 y		none		Undetermined cause
Ronning, 2010	IA rt-PA	20 rng	29 y	delivery	none		Peripartum cardiomyopathy

IV: intravenous; IA: intra-arterial; rt-PA: recombinant tissue plasminogen activator; UK: urokinase; ICH: intracerebral hemorrhage; MTP: medical termination of pregnancy; SA: spontaneous abortion.

subjects, and failure to definitively confirm the diagnosis in all patients [66]. Potential complications of aspirin therapy in late pregnancy include fetal and maternal bleeding, premature closure of the ductus arteriosus, prolongation of labour, and delay in the onset of labor. According to data reported in another meta-analysis of 14 randomized studies including a total of 12,416 women, there is no evidence of fetal and maternal adverse effects of low-dose aspirin therapy (60 to 150 mg/d) administered during the second and the third trimester of pregnancy in women at risk for pre-eclampsia [67].

Therefore, available evidence suggests that low-dose aspirin (<150 mg/die) can be used safely during the second and third trimester; by contrast, the safety of higher dose of aspirin and/or aspirin ingestion during the first trimester is controversial.

Clopidogrel has not been found to cause significant fetotoxicity in animal studies at high doses, but there are no adequate and well-controlled studies in pregnant women so far. Only few case reported pregnant women who had successful outcome while taking clopidogrel [68, 69]. Thus, there are insufficient data to evaluate its safety in this setting.

Although dipyridamole has not been found to cause significant fetal adverse effects, there are no adequate data regarding safety or effectiveness of dipyridamole in humans during pregnancy.

8.4. Thrombolytic Treatment. No data are available about the use of thrombolytic treatment in pregnancy since this conditions was an exclusion criteria from clinical trials that validated these therapies. To date, the experience is limited only to case reports and case series, including different thromboembolic conditions such as pulmonary embolism, thrombosis of cardiac valve prosthesis, myocardial infarcts, and deep venous thrombosis, but also ischemic stroke [70]. Due to its large molecular size, recombinant human tissue plasminogen activator (rt-PA) does not cross the placental barrier and studies on animal model have not shown teratogenic effects [71, 72]. However, fetal adverse effects remain largely unknown. Obstetric concerns are also raised by the possible effects on the placenta resulting in premature labor, placental abruption, or fetal demise.

In the last years, thrombolysis for acute ischemic stroke in pregnancy has been described in only 11 patients [70, 73–77] (Table 4). In most cases, patients received thrombolysis during the first trimester, sometimes inadvertently. One of six patient treated with systemic rt-PA died; the other five women were treated with catheter-based therapy (three intra-arterial rt-PA, one intra-arterial urokinase, and one local urokinase). Four patients did not have complications, while three had cerebral hemorrhage with clinical worsening in one case. Hemorrhagic complications also included intrauterine hematoma in one case and buttock hematoma in another one. Two women had an elective therapeutic abortion and one a spontaneous miscarriage.

Moreover, thrombolysis in the postpartum period was also reported, within fifteen hours after a cesarean delivery in one case and after six days from delivery in another one, without complications for the patients [78, 79].

However, because of the differences in etiologies, as well as in thrombolytic agents used and in the way of administration, it is difficult to draw any conclusion regarding safety or effectiveness although favorable maternal outcome was shown in many cases. Therefore, thrombolytic therapy should not be withheld for potentially disabling stroke during pregnancy, but in each clinical situation, since experience is limited, the ultimate choice of therapies must be based on careful assessment of the maternal and fetal risks and benefits.

9. Prognosis and Recurrence

In a previous study of late sixties, the maternal mortality immediately after stroke was reported to be 26% [8]. Subsequently, maternal mortality following cerebral infarction has been reported not to exceed 14% and some studies reported no maternal deaths secondary to an ischemic stroke [7, 14]. However, a reliable estimate is difficult as a consequence of small number of events and different characteristic of published studies (Table 2).

In the Ile de France study, about half of the patients had a mild to moderate residual neurological deficit, with a modified Rankin score ranging from 1 (3 patients) to 2 (2 patients) [7]. Skidmore and coworkers reported that 73% of the patients were discharged home [15]. Fetal outcome showed a death rate of about 12% [7].

Data regarding the influence of pregnancy on the risk of recurrent stroke are scarce, thereby making difficult to counsel women with a history of ischemic stroke about future pregnancies.

A multicenter French study on a group of 489 consecutive women aged 15 to 40 years with a first-ever arterial ischemic stroke or cerebral venous thrombosis showed that the risk of stroke recurrence associated with subsequent pregnancies is relatively small [80]. In this study, twenty-eight patients (of 373 with arterial ischemic stroke) had the initial ischemic event during pregnancy or the puerperium. During a mean followup period of 5 years, 13 of the whole cohort had a recurrent stroke but only two of these occurred in a subsequent pregnancy, related to rare definite causes of stroke such as essential thrombocythemia and primary antiphospholipid syndrome. No woman whose initial stroke occurred during pregnancy had a recurrent stroke during subsequent pregnancies. The postpartum period, not the pregnancy itself, is associated with an increased risk of recurrent stroke (RR 9.68, 95% CI 1.2, 78.9), but these results may be limited by small number of observed events, lack of prospective record of recurrent events and subsequent pregnancies, and by a selection bias related to follow-up lost.

In line with these results, a descriptive study of a series of 23 patients with a history of a previous ischemic stroke showed no recurrence of ischemic stroke during subsequent pregnancy or after delivery [81].

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