Pregnancy-related strokes in southeast Turkey

Al Behcet, MD, Akıl Esref, MD, Ozkul Ozgur, MD, Acar Abdullah, MD, Aldemir Mustafa, MD.

ABSTRACT

Objectives: To evaluate the presentation, timing, etiology, risk factors, mortality, and outcome of ischemic stroke (IS), intracerebral hemorrhagic stroke (ICH/HS), and cerebral venous thrombosis (CVT) occurring during pregnancy and the postpartum period in southeast Turkey.

Methods: The study was carried out from September 2003 to September 2005 at the emergency department of Dicle University Hospital in the southeast part of Turkey. Thirty-eight stroke patients, 18-42 years of age with a diagnosis of stroke during pregnancy or within 6 weeks of delivery were included. The records were retrospectively reviewed for presentation, gestational ages, strokes subtypes and time, stroke sort, stroke place, etiology, risk factors, hospital stay, mortality, and outcome.

Results: Thirty-eight patients were identified, including 18 with IS, 15 with ICH, and 5 patients with CVT. Most events (89.5%) occurred in the third trimester and the postpartum period. A definable cause was identified in 61.1% of IS and 60% of CHS. Causes of IS include pre-eclampsia or eclampsia (22.2%), hypercoagulable states (16.7%), and a diverse array of other causes, including cardio embolism (5.5%) and hypotension (16.7%). Pre-eclampsia/eclampsia (46.7%) and ruptured atriovenous malformation (6.7%) were the primary causes of ICH. The mortality rate for all patients was 34.2%.

Conclusion: The etiology of stroke in pregnancy and the postpartum period is diverse. Strokes are most likely to occur in the third trimester and postpartum period and cluster in the first postpartum week. Mortality is high in patients with ICH. Pre-eclampsia and eclampsia are common causes of strokes.

Neurosciences 2007; Vol. 12 (3): 207-214

From the Emergency Department (Behcet, Mustafa), the Neurology Department (Esref), the Obstetrics and Gynecology Department (Ozgur), Medical Faculty, Dicle University, Diyarbakır, and the Department of Neurology (Abdullah), Batman Special Hospital, Batman, Turkey.

Received 9th October 2006. Accepted 21st February 2006.

Address correspondence and reprint request to: Dr. Al Behçet, Batman Devlet Hastanesi, Acil Tip Kliniği, Batman, Turkey. Tel. +90 (505) 2547083. Fax. +90 (488) 2211444. E-mail: behcetal@hotmail.com

Pregnancy-related stroke is a rare, but potentially devastating event. Not only do an estimated 8-15% of pregnancy-related stroke victims die,[1,2] but survivors may suffer profound, permanent disability.[3,4] Because stroke is rare in this population, the ability to estimate the incidence, identify risk factors, or report meaningful outcomes, such as mortality or disability, requires large, population-based studies. Approximately 15% of women with pregnancy-related stroke die and 10% of survivors are discharged to a facility other than home.[2] Pregnancy-related stroke accounts for 5% of all maternal mortalities, or 0.66 per 100,000 live births.[5] The incidence of stroke in non-pregnant women aged 15–44 years is 10.7/100,000,[6] although pregnancy is reported to have a 13-fold risk compared to the non-pregnant state.[7] Previously recognized risk factors for pregnancy-related stroke include hypertension, preeclampsia, infection, delivery, the puerperium, non Caucasian race, and age older than 35.[2] The pathogenesis and pathophysiology of stroke during pregnancy are not fundamentally different from that of stroke in non-pregnant patients. Pregnancy and the postpartum period are associated with prothrombotic changes, including acquired activated protein C resistance and low levels of free protein S. Cerebral blood vessel reactivity changes and hemodynamic changes may also play a role in pregnancy-related strokes.[8,9] Most stroke events during pregnancy are caused by arterial occlusions.[1] Moreover, several risk factors such as gestational hypertension, smoking habits, cesarean delivery, fluid-electrolyte and acid-based disorders, older age, and older and greater parity, premature atherosclerosis, valvular heart disease, especially thrombophilias, are known to predispose pregnant woman to stroke occurrence.[10-12] Recently, an altered maternal cardiac function and structure has been associated with fetal–maternal complications during gestational hypertension.[13] Thrombophilias comprise a group of inherited and acquired coagulation disorders that are known to predispose to vascular thrombosis and complications during pregnancy (for example, abruptio placenta and fetal growth restriction).[14] The 6 weeks postpartum and, particularly, the several days surrounding delivery are times of increased risk for all ischemic stroke (IS) types. The diagnostic approach to

stroke during pregnancy and the postpartum period is similar to the approach in the non-pregnant woman, although eclampsia, cardio-myopathy, postpartum cerebral venous thrombosis (CVT), and possibly paradoxical embolism warrant special consideration. Similarly, the therapeutic approach to stroke during pregnancy is similar to treatment of the non-pregnant women with some minor modifications based on consideration of the welfare of the fetus.[15] Aside from obstetrical considerations, complications of stroke in pregnancy are similar to those seen in non-pregnant patients. In the short term, the most serious risk is herniation from cerebral edema. Seizures and status epilepticus as well as aspiration, sepsis, and the consequences of immobility, such as decubitus, deep venous thrombosis, pulmonary embolism, and pneumonia, all contribute significantly to poor patient outcomes. Long-term disability, including difficulty with childcare and return to work, are important considerations in these young women.[15] In the differential diagnosis, metabolic disorders, seizures, migraine, and even psychogenic disorders need to be considered, but should be easily discerned based on history and basic labs and imaging. The most important differential consideration specific to pregnancy is eclampsia. The objective of this study was to estimate, with as complete an ascertainment as possible, the incidence, risk factors, disability, and mortality from pregnancy-related stroke in the southeast of the Anatolia Region in Turkey.

Methods. From September 2003 to September 2005, 38 stroke patients, 18-42 years of age, with a diagnosis of stroke during pregnancy or within 6 weeks of delivery applied to the emergency department of the Dicle University Hospital in the southeast part of Turkey. The total number of pregnancy-related strokes during 2003 and 2005 at Dicle University Hospital, including normal spontaneous deliveries, cesarean sections, abortions (>10 weeks of gestation), and continuo pregnancies were computed from the hospital discharge medical records. Data were abstracted to a form for each patient listing the patient name, age, presentation, gestational age, or week postpartum, location and type of infarction, demographics, presenting symptoms, cause, laboratory tests, results of imaging, parity, preeclampsia or eclampsia, stroke risk factors (history of hypertension, diabetes mellitus, cardiac diseases, anemia, thrombocytopenia, total cholesterol >200 mg/dl, history of cigarette smoking), family history and treatment received. The third trimester of pregnancy was considered to begin with the 27th week of gestation, and the postpartum week one was defined to begin at the time of delivery, regardless of the gestational age at delivery. Preeclampsia was defined by hypertension in association with proteinuria; eclampsia was defined as the occurrence of seizures or a disturbance of consciousness in a woman with pre-eclampsia. The timing of stroke onset (1st through 3rd trimester and postpartum periods), clinical manifestations, etiologies, and outcome in stroke and its subtypes were also analyzed. The diagnosis of stroke and its subtypes were based on the clinical features and the data collected by examinations, such as brain imaging (CT or MRI), cardiac imaging (transthoracic or transesophageal echocardiography), ultrasonography of extra cranial or intracranial arteries, angiography (MR or conventional angiography), and laboratory assessment of a prothrombotic state. The events were classified as IS, intracerebral hemorrhage (ICH), or CVT based on the diagnosis listed in the patient's hospital chart. Infarcts that were classified as IS or ICH were localized in the cortex, sub-cortical white matter, basal ganglia, thalamus, cerebellum, brain stem, pons or spinal cord. Treatments recorded during the hospital stays included the following: platelet antiaggregants, warfarin, heparin, tissue plasminogen activator, urokinase, antihypertensive, magnesium sulfate, or other (comprising any other event-specific treatment). The prothrombotic studies included protein C (free antigen and activity), protein S (free antigen, total, and activity), antithrombin 3 (free antigen and activity), lupus anticoagulant, anticardiolipin, and antiphospholipid antibodies. Determination of existing coagulopathy was confirmed by a follow-up prothrombotic study postpartum or positive results in other family members. All patients had CT or MRI of the brain. A diagnosis of CVT was confirmed by head MRI or cerebral angiography. The underlying etiologies were further determined in each subtype of stroke. Evaluation of the clinical presentation included evaluating medical records for the presence or absence on the initial day of presentation of 5 main symptoms; headache, focal epileptic attack, generalized tonic-clonic epileptic attack, decreased level of consciousness, or sign of lateralization. Causes were classified according to the following 8 predetermined categories: 1) arteriovenous malformation (AVM); 2) CVT; 3) hypoxia or hypotension; 4) specific hypercoagulable condition; 5) cardioembolic infarct; 6) pre-eclampsia/eclampsia; 7) other definable cause of stroke; or 8) unknown. The incidence of stroke occurring during pregnancy and postpartum was determined by dividing the number of strokes by the number of pregnancies for overall and each subtype of stroke. The number of pregnancies included the total number of normal spontaneous deliveries, cesarean sections, and abortions during the study. As our hospital is a tertiary medical center, a corrected stroke incidence was also calculated after excluding the patients who were referred from

other hospitals. The discharge disposition was assessed, and the patients were categorized as either going home, transferring to a rehabilitation center or died. Finally, patients at discharge were classified as either having or not having a neurologic deficit.

In this study, the exclusion criteria included patients with major operation in the last 6 months, brain trauma in the last 3 months, history of trauma prior to stroke (particularly for ICH), patients that were dead due to stroke at presentation to the emergency room, and patients with bleeding, for example, genitourinary bleeding, gastrointestinal bleeding, at least one time due to a hematological disorder.

Results. During the 2 year period, 38 patients of 29.2±7.23 years of age (range 18-42) experienced stroke during pregnancy and the postpartum period, including 18 (47.4%) patients with IS, and 15 (39.5%) patients with ICH. All of the patients were living in the southeast of Turkey, and were Caucasian.

Condition of consciousness on presentation. All of the patients were forwarded from second step health institutions. They arrived at our hospital within the first 10 hours from stroke occurrence. At the time of presentation, the consciousness of 26.3% of patients was open, and the consciousness of 73.3% of patients (8 somnolence, 7 stupor, 13 coma) was poor. The mortality rate was 10% for patients presenting with opened-consciousness, whereas, for patients presenting with poor-consciousness it was 44.4%. The rate of IS among the patients presenting with opened-consciousness was determined as 70%, and for ICH was 30%. The rate of IS among the patients presenting with poor consciousness was determined as 39.3%, 42.9% for ICH, and 17.8% for CVT. The highest mortality rate (69.2%) was among patients presenting with comma. The rate of ICH among the patients presenting with comma was 53.8%, 30% for IS, and 15.4% for CVT.

Complaints of patients on presentation. On presentation, 28.9% of patients had symptoms of headache, 21.1% with focal and generalized tonic colonic attacks (GTCA) (one focal attack, 7 GTCA), 26.3% with loss of consciousness, and 23.7% with lateralization symptoms. The rate of IS and ICH among the patients presenting with headache was equal (45.5%), and the mortality rate for this group was 27.3%. The IS rate in those presenting with focal or GTCA was higher (4/7); the mortality rate for this group was 42.8%. The rate of ICH in patients presenting with loss of consciousness was 70%, 20% in IS, and 10% in CVT. The highest mortality rate was detected in this group. The ratio of IS/ICH of the patients presenting with lateralization sign was 2/7, and only one patient was lost.

Gestational age, age of patients, time of stroke, and mortality. Ischemic stroke was mostly prevalent in the 18-24 age group, ICH in the >36 age group, and CVT mostly in women in the 25-30 age group. The highest mortality rate in all groups was found in the >36 group of age. One patient (2.6%) had stroke in the first trimester, 7.9% in the second trimester, 10.5% in the third trimester, 63.1% in the first postpartum week and, 15.9% within 6 weeks postpartum (except the first week postpartum). Most of the strokes (63.1%) occurred within the first 7 days of the postpartum period. Six (15.8%) patients were primiparous and 84.2% were multiparous. None of our patients had stroke in their third pregnancy. Ischemic stroke occurred in the first postpartum week in 61.1%, ICH in 66.7%, and CVT in 60% (**Table 1**).

Type of delivery, places of delivery, stroke, and mortality. Of patients with stroke, 63.2% had normal spontaneous vaginal delivery (NSVD), 13.2% through cesarean section (C/S), 13.2% through spontaneous abortion, compulsory abortion was performed on a patient due to intrauterine death. Pregnancy in the remaining 3 (7.9%) patients was ongoing. Ischemic stroked occurred in 41.7% of patients with NSVD, ICH in 54.2%, and CVT in 4.1%, the mortality rate in this group was 33.3%. Two patients with IS, and 2 patients with ICH delivered by C/S. The mortality rate was 20% among C/S patients. We found a higher rate (50%) of CVT among patients who had abortion, and the mortality was 66.7% in this group. Of deliveries, 47.1% occurred at home without any health services,

Table 1 - Gestational age, patient age, time of stroke, and mortality.

Variable	IS	ICH	CVT	Total	Exitus
Age groups					
18–24	7	2	-	**9**	3
25–30	3	4	4	**11**	4
31–36	6	3	1	**10**	3
>36	2	6	-	**8**	3
Number of pregnancies					
First pregnancy	4	1	1	**6**	1
Second pregnancy	3	4	1	**8**	3
Third pregnancy	-	-	-	**0**	-
Fourth pregnancy	5	4	3	**12**	5
Fifth pregnancy	3	3	-	**6**	3
>6 pregnancies	3	3	-	**6**	1
Time of strokes					
First trimester	1	-	-	**1**	1
Second trimester	2	1	-	**3**	1
Third trimester	1	2	1	**4**	2
First postpartum week	11	10	3	**24**	9
Sixth postpartum week (except postpartum week one)	3	2	1	**6**	-

IS - ischemic stroke, ICH - intracranial hemorrhage, CVT - cerebral venous thrombosis

and 52.9% occurred in hospital. The incidence of IS, ICH, and CVT was higher among deliveries in hospital compared with deliveries at home. The mortality rate for home deliveries was 31.2%, compared with 38.8% for hospital deliveries.

Etiology, risk factors, family history, emerging strokes, and mortality. The etiology of 34.2% of patients was determined as preeclampsia/eclampsia. Of the eclampsia cases, 46.1% resulted in death. Ischemic stroke occurred in 30.8% of this group, ICH in 53.8%, and CVT in 15.4%. The mortality rate due to pre-eclampsia/eclampsia in IS was 33.3%, 50% in ICH, and 16.7% in CVT. There was hypercoagulability in 3 patients and protein S deficiency was also observed. Ischemic stroked occurred in all 3 patients with hypercoagulability and one was lost. In one of the 2 patients with cardio embolic origin there was mitral valve replacement, and in the other arterial fibrillation was observed. The former was recorded in connection to ICH and the latter to IS. Only in one patient was arteriovenous malformation (AVM) observed, ICH developed in this patient and was lost. Ischemic stroke due to hypotension (<50/30 mm Hg) developed in 3 patients, and all 3 survived. A distinctive reason could not be found in 16 (42.1%) patients, 6 of which had IS, 3 had ICH, and 3 had CVT. Three patients of this group were lost (**Table 2**). The determinable risk factors for strokes related to pregnancy in our study were DM due to pregnancy and hypertension, the stroke attacks experienced before, pre-eclampsia/eclampsia, cardiac diseases, abnormal laboratory values (<25% hematocrit, <50 L/UL platelet, >80 U/L aspartate aminotransferase/alanine aminotransferase (AST/ALT) = hemolysis, elevated liver enzymes, low platelets (HELLP), 200 mg/dl hypercholesterolemia) and smoking. The blood pressure in 18 patients (47.4%) was above 155/105 mm Hg. The mortality rate was 33.3% in those with pregnancy induced hypertension. Diabetes mellitus due to pregnancy developed in 4 patients. Pre-eclampsia/eclampsia was observed in 13 patients (34%). The mortality in this group was 46%. Two patients had already had stroke attack due to cardio emboli. One presented due to ICH and the other due to IS; both died. Mitral valve replacement was observed in one patient before the stroke, arterial fibrillation in another, both had a history of hypertension. One patient with hypertension was lost due to ICH. On first laboratory evaluation, 4 of 7 patients (57.1%) had <25% of normal hematocrit range. Both of the 2 patients with platelet ranges of < 50 K/L, 6 of the 20 patients (30%) with >200 mg/dl cholesterol range, and 3 of the 4 patients (75%) with >80 U/L AST and ALT ranges were lost. Three patients had a smoking habit before and during pregnancy, and none were lost (**Table 2**).

Table 2 - Etiology, risk factors, familial history, drug use in pregnancy, hospitalization stay, developed strokes, and mortality.

Variable	IS	ICH	CVT	Total	Exitus
Etiology					
Eclampsia/preeclampsia	4	7	2	**13**	6
Hypercoagulability	3	-	-	**3**	1
Cardio emboli	1	1	-	**2**	2
Arteriovenous malformation	-	1	-	**1**	1
Hypotension	3	-	-	**3**	-
Unknown	7	6	3	**16**	3
Risk factors					
Gestational DM	1	3	-	**4**	3
Gestational hypertension	6	10	2	**18**	6
Prior stroke	1	1	-	**2**	1
Eclampsia/preeclampsia	4	7	2	**13**	6
Cardiac diseases	1	1	-	**2**	2
<25% hematocrit	3	3	1	**7**	4
<50 K/UL platelet	1	1	-	**2**	2
>200 cholesterol	9	8	3	**20**	6
>80 U/L AST/ALT	2	2	-	**4**	3
Cigarette smoking	2	-	1	**3**	-
Hospitalization stay					
72 hours	6	5	1	**12**	10
3-10 days	4	4	1	**9**	2
11-20 days	5	4	1	**10**	1
>20 days	3	2	2	7	-
General mortality n (%)	5 (27.8%)	6 (40%)	2 (40%)	**13 (34.2%)**	

IS - ischemic stroke, ICH - intracranial hemorrhage, CVT - cerebral venous thrombosis, DM - diabetes mellitus, AST - aspartate aminotransferase, ALT - alanine aminotransferase

Family history, drug usage during pregnancy, stroke, and mortality. There was cerebrovascular incident (SVI) in the history of 3 patients. One had IS, one ICH, and the other had CVT. Ischemic stroke developed in 3 patients with a history of familial hypertension. All patients with hypertension and SVI on family history survived. Ten patients were observed to have kept using drugs throughout the pregnancy due to various reasons. Four patients had been using only antihypertensive agents, 4 antihypertensives with anti diabetics, and 2 antihypertensives with anticoagulant agents. Four patients (40%) from this group were lost (**Table 2**).

Duration of hospitalization, time of mortality, strokes, and general mortality. The average duration of hospitalization for IS was 10.6 days, for ICH was 9.5 and for CVT was 14.8. In general, for all patients the average duration of hospitalization was 10.7 days. Seventy-seven percent of deaths occurred within the first 72 hours, 15.4% in the following 3-10 days, and 7.7% occurred between 10-12 days after hospitalization. All deaths were due to ICH and CVT, and 57.1% of deaths due to IS occurred within the first 72 hours of hospitalization. The mortality rate was lower among those with hospitalization (**Table 2**).

Table 3 - The outcome and the regions of stroke occurrence.

Region	Outcome			
	Exitus	Discharged with deficit	Discharged with complete recovery	Total
Ischemic stroke				
Right hemisphere infarct	-	-	1	1
Right hemisphere hemorrhagic infarct	1	3	3	7
Left hemisphere infarct	2	3	1	6
Left hemisphere hemorrhagic infarct	2	1	-	3
Brain-stem-cerebellum infarct	-	1	-	1
Intracranial hemorrhage				
Right hemisphere hemorrhage	2	1	4	7
Left hemisphere hemorrhage	3	3	-	6
Pons hemorrhage	1	-	-	1
Arteriovenous malformation	-	1	-	1
Cerebral venous thrombosis				
Sagittal sinus	2	2	-	4
Transverse sinus	-	-	1	1
Total	**13**	**15**	**10**	**38**

Location of strokes and outcome. Fifty percent of IS developed in the left hemisphere with 44.4% in the right hemisphere; 46.7% of ICHs developed in the right and 40% in the left hemisphere. Eighty percent of CVTs developed in the sagittal sinus. Forty-four percent of IS patients, 33.3% ICH patients, 40% of CVT patients, and a total of 39.5% of all patients were sent to the physical treatment and rehabilitation center due to neurological deficit after being discharged from hospital. Twenty-eight percent of IS patients, 26.7% of ICH patients, 27% of CVT patients, and a total of 26.3% of all patients showed full recovery on discharge. The mortality rate among all the patients due to IS was 27.8%, 33.3% due to ICH, and 20% due to CVT. The general mortality rate was observed as 34.2% (**Table 3**).

Discussion. Although it is widely believed that pregnancy is associated with an increased risk of stroke, there are no consistent findings regarding the incidence of stroke during pregnancy and postpartum.[7,16,17] The presenting signs and the proportion of subtypes of strokes may be different from each other. In Frank et al's study,[18] the incidence of loss of consciousness, headache, and deep coma in patients with ICH was 73%, 64%, and 45%. It is reported in this study that the majority of patients with IS presented with headache; and 20% of patients with CVT presented with loss of consciousness. In our study, most of the patients presented with somnolence, stupor, and coma. The incidence of ICH, IS, and CVT in patients presenting with coma was 53.8%, 30.8%, and 15.4%. The majority of complaints determined at presentation were headache and of loss conscious.

The incidence of pregnancy-related stroke varies in different studies. In a study reported by Jeng et al,[19] the incidence of pregnancy-related stroke was 46.2 per 100,000 pregnancies. For this study, the incidence of IS, ICH, and CVT during pregnancy or postpartum was 16.0, 18.1, and 10.0 per 100,000 pregnancies. In addition, the rate of stroke occurrence was significantly higher in the postpartum period than in each trimester of pregnancy. In another study,[18] the rate of IS, ICH, and CVT was determined as 58.3%, 30.6%, and 11.1% during pregnancy and the postpartum period. In our study, the incidence of IS, ICH, and CVT of pregnancy-related stroke during pregnancy and postpartum was 20.1, 16.8, and 5.6 per 100,000 pregnancies. The higher incidences of stroke, especially infarction, noted in our study, and those of Jeng et al,[19] and Jaigobin and Silver,[1] were similar. When the entirety of pregnancy and the postpartum state are considered, there is an increased rate of all forms of stroke.

Controversy exists in the literature regarding the timing of stroke in pregnancy and postpartum. Some studies have reported that the risk of stroke is increased only in the postpartum period and not during pregnancy.[12,20] A study conducted in the Baltimore-Washington areas reported a 5.5-fold increase in IS, an 18.2-fold increase in ICH, and a 7.9-fold increase in all stroke for puerperal (postpartum period) women.[21] Another study in Sweden revealed that increased risks of circulatory diseases, including stroke, were confined to the immediate pre-delivery and postnatal period.[12] Sharshar et al,[22] in a French population study, concluded that the prevalence of non hemorrhagic stroke does not seem to be much increased during pregnancy and postpartum, however, they found an

increased rate of hemorrhagic stroke (ICH). Kittner et al[20] found an increase in both ICH and IS in the postpartum period, but no increase in the rate of cerebral infarction during the pregnancy itself. In Frank et al's study,[18] it was identified that the majority (86%) of pregnancy-related strokes occurred after the onset of the third trimester. It is stressed in this study series of patients that, pre-eclamptic/eclamptic related events occurred as early as 30 weeks gestation and as late as the second postpartum week. According to the Baltimore-Washington Cooperative Young Stroke Study,[20] the risk of IS or ICH during pregnancy and the first 6 weeks postpartum was 2.4 times greater than during a comparable period for nonpregnant women of similar age and race. More importantly, this study reported no increased risk of IS during pregnancy, but showed a relative risk of 8.7 during the 6 weeks postpartum. Intracerebral hemorrhage showed a small relative risk of 2.5 during pregnancy, but increased dramatically to a relative risk of 28.3 in the 6 weeks postpartum. In our study, the majority of pregnancy-related strokes (31.6%) occurred in the fourth pregnancies of patients. Nine of 13 deaths occurred among the patients who had 4 or more pregnancies. Seventy-eight percent of IS, 80% of ICH, and 80% of CVT occurred in the postpartum period. In addition, 61.1% of IS, 66.7% of ICH, and 60% of CVT occurred within 7 days after delivery. In our series, 63.1% of strokes occurred within the first postpartum week. The majority (50%) of pregnancy-related strokes that occurred in the third trimester were ICH. For all subtypes, only 4 stroke events occurred in the first and second trimesters.

The risk factors for pregnancy-associated stroke have been examined in several studies. Older age, cigarette smoking, and older and greater parity were each associated with an approximate 2-fold increase in the risk of stroke during pregnancy and the postpartum period.[11,12,23] Cesarean section and preeclampsia were associated with an approximate 6-fold increase in stroke risk. Different studies,[2,24,25] examined risk factors such as hypertension, infection, non-Caucasian race, and age older than 35. The risk factors stressed in different studies[26-39] are determined as migraine headaches, thrombophilia, lupus, heart disease, sickle cell disease, thrombocytopenia, diabetes, substance abuse, smoking, anemia, blood transfusion, and high levels of estrogen. Frank and colleagues[18] determined that the most common cause of IS (23.8%) in their case series was cardio embolism. In this study, the incidence of cardio embolic strokes due to valvular heart disease was 14.2%. In our study, the most common (34.2%) cause of strokes was pre-eclampsia/eclampsia. Six of 13 deaths were among the patients whose etiology determined pre-eclampsia/eclampsia. Apart from pre-eclampsia/eclampsia, the causes of strokes we determined were hypercoagulable state (7.9%), cardio embolism (5.3%), hypotension (7.9%), and AVM (in only one patient). Sixteen of 38 patients (7 IS, 6 ICH, and 3 CVT) had no definable cause. The other determinable risk factors in our series were gestational diabetes mellitus, gestational hypertension, prior strokes, pre-eclampsia/eclampsia, hearth diseases, anemia, thrombocytopenia, and hypercholesterolemia.

Patients with hyperglycemia and high blood pressure should pay more attention for strokes during pregnancy. In addition, for adult male, and female patients in general, the risk of hemorrhagic stroke correlates directly with the degree of elevation of systolic blood pressure and is less related to, but not independent of, diastolic blood pressure.[36] So many studies[39-41] recommend receiving antihypertensive agents when systolic blood pressure is more than 155 mm Hg or diastolic blood pressure is sustained at more than 105 mm Hg, or both. Chesley[42] could have prevented not only convulsions, but also could have prevented cerebrovascular hemorrhage by using antihypertensive agents for patients with pre-eclampsia and eclampsia. In our study, 10 patients whose systolic blood pressure were more than 155 mm Hg or diastolic blood pressure were more than 105 mm Hg or both, received antihypertensive agents. For this group, stroke occurred in 6 patients (2 IS, 4 ICH). Four patients with a level of blood glucose higher than 160 mg/dl received antidiabetic agents. In addition, 2 patients received anticoagulant agents due to heart diseases.

It is understood from different studies that the mortality incidences of pregnancy-related strokes vary from 0-38%. It has been estimated that, overall, cerebrovascular disorders contribute to as many as 12% of maternal deaths.[43] Only a few studies, however, have elaborated on maternal and fetal outcomes. In 1968, Cross and colleagues[21] reported a 26% maternal death rate from pregnancy-related stroke. More recently, the Ile de France study[22] based on a small number of cases, reported no maternal deaths in patients with IS. In Frank et al's study,[18] only one of 36 patients died. In Lanska and Kryscio,[2] and James et al's[26] studies, the mortality rates were reported as 3.3% and 4.1%. Differences in management of stroke in pregnancy in different populations may account for differing estimations of mortality. In the study of Witlin et al,[37] (which found a mortality rate of 29%), 10 of 24 cases were complicated by patient delay in seeking medical attention. In our study, the mean hospital stay was 10.6 days. The majority (76.9%) of the deaths occurred within 72 hours after the event. The mortality for IS, ICH, and CVT were 27.8%, 40%, and 40%. The mortality for all patients was 34.2%.

Functional outcome in women after pregnancy-related stroke is quite varied. In the Ile de France study,[22] half of surviving women were left with mild to moderate deficits, while the remaining half recovered completely. Lanska et al[2] discharged 10% of survivors to a facility other than home. In another study,[18] it was reported that a similar proportion of IS and ICH (68% and 64%) had clinical deficits at discharge from the hospital. Morbidity, however, was greater in patients with ICH. The majority of their patients with ICH required discharge to a rehabilitation center or nursing home. The majority of patients with IS were discharged home, as were 3 of 4 patients with CVT. In our study, 44.4% of IS, 33.3% of ICH, and 40% of CVT left the hospital with neurologic deficits, so they were transported to the rehabilitation center. However, 27.8% of IS, 26.7% of ICH, and 20% of CVT were discharged home with complete recovery.

In conclusion, in this investigation of women in Southeast Turkey women with pregnancy-related stroke, we found the first postpartum week and the several days surrounding delivery are times of increased risk for IS, ICH, and CVT. Pre-eclampsia/eclampsia, gestational hypertensive, and gestational diabetes mellitus, and heart diseases were the most common causes of IS, ICH, and CVT. The mortality rate among patients with ICH is the highest. We believe that women who have severe preeclampsia or eclampsia and severe systolic hypertension (> 155 mm Hg), and diastolic hypertension (>105 mm Hg) are at special risk for ICH and CVT. These patients deserve immediate and special attention, intensive care, and antihypertensive therapy to reduce their risk of such strokes. Understanding the cause of pregnancy-related stroke and identification of women at risk are the first steps.

References

1. Jaigobin C, Silver FL. Stroke and pregnancy. ***Stroke*** 2000; 31: 2948-2951.
2. Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. ***Stroke*** 2000; 31: 1274-1282.
3. Kappelle LJ, Adams HP Jr, Heffner ML, Torner JC, Gomez F, Biller J. Prognosis of young adults with ischemic stroke: a long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa Registry of Stroke in Young Adults. ***Stroke*** 1994; 25: 1360-1356.
4. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Anderson CS. Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989-1990. ***Stroke*** 2002; 33: 1033-1040.
5. Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, Seed KA, et al. Pregnancy-related mortality surveillance-United States, 1991–1999. ***MMWR Surveill Summ*** 2003; 52: 1-8.
6. Pettiti DB, Sidney S, Quesenberry CP, Bernstein A. Incidence of stroke and myocardial infarction in women of reproductive age. ***Stroke*** 1997; 28: 280-283.
7. Wiebers DO. Ischemic cerebrovascular complications of pregnancy. ***Arch Neurol*** 1985; 42: 1106-1113.
8. Hellgren M. Hemostasis during normal pregnancy and puerperium. ***Semin Thromb Hemost*** 2003; 29: 125-130.
9. Cipolla MJ, Vitullo L, McKinnon J. Cerebral artery reactivity changes during pregnancy and the postpartum period: a role in eclampsia? ***Am J Physiol Heart Circ Physiol*** 2004; 286: 2127-2132.
10. Lanska DJ, Kryscio RJ. Peripartum stroke and intracranial venous thrombosis in the National Hospital Discharge Survey. ***Obstet Gynecol*** 1997; 89: 413-418.
11. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. ***BMJ*** 1993; 306: 956-963.
12. Ros HS, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in the late pregnancy and puerperium. ***Epidemiology*** 2001; 12: 456-460.
13. Novelli GP, Valensise H, Vasapollo B, Larciprete G, Altomare F, Di Pierro G, et al. Left ventricular concentric geometry as a risk factor in gestational hypertension. ***Hypertension*** 2003; 41: 469-475.
14. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. ***N Engl J Med*** 1999; 340: 9-13.
15. Helms AK, Kittner SJ. Pregnancy and Stroke. ***CNS Spectr*** 2005; 10: 580-587.
16. Mas JL, Lamy C. Stroke in pregnancy and the puerperium. ***J Neurol*** 1998; 245: 305-313.
17. Knepper LE, Giuliani MJ. Cerebrovascular disease in women. ***Cardiology*** 1995; 86: 339-348.
18. Frank MS, Linda SW, Kevin DF, Robert JA, Jose B. Presentation, Etiology, and Outcome of Stroke in Pregnancy and Puerperium. ***J Stroke Cerebrovasc Dis*** 2001; 10: 1-10.
19. Jeng JS, Tang SC, Yip PK. Incidence and Etiologies of Stroke during Pregnancy and Puerperium as Evidenced in Taiwanese Women. ***Cerebrovasc Dis*** 2004; 18: 290-295.
20. Kittner SJ, Stern BJ, Feeser BR, Hebel R, Nagey DA, Buchholz DW, et al. Pregnancy and the risk of stroke. ***N Engl J Med*** 1996; 335: 768-774.
21. Cross JN, Castro PO, Jennett WB. Cerebral strokes associated with pregnancy and the puerperium. ***Br Med J*** 1968; 3: 214-218.
22. Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium. A study in public hospitals of Ile de France. ***Stroke*** 1995; 26: 930-936.
23. Ros HS, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Pulmonary embolism and stroke in relation to pregnancy: how can high-risk women be identified? ***Am J Obstet Gynecol*** 2002; 186: 198-203.
24. Li C, Engstrom G, Hedblad B, Berglund G, Janzon L. Risk factors for stroke in subjects with normal blood pressure: a prospective cohort study. ***Stroke*** 2005; 36: 234-238.
25. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, et al. Stroke in a biracial population: the excess burden of stroke among blacks. ***Stroke*** 2004; 35: 426-431.
26. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. ***Obstet Gynecol*** 2005; 106: 509-516.
27. Soh Y, Yasuhi I, Nakayama D, Ishimaru T. A case of postpartum cerebellar infarction with hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. ***Gynecol Obstet Invest*** 2002; 53: 240-242.
28. Harscher S, Witte OW, Moller U, Bloos G, Pfleiderer SO, Terborg C. Cerebral vasospasms with hemodynamic infarctions as a complication of HELLP syndrome [in German]. ***Nervenarzt*** 2003; 74: 1122-1126.

29. Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. ***Stroke*** 2002; 33: 1202-1208.
30. Gordon MC. Maternal physiology in pregnancy. In: Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: normal and problem pregnancies. 4th ed. New York (NY): Churchill Livingstone; 2002. p. 63-92.
31. Bushnell CD. Migraine and risk of ischemic stroke: an evidence-based medicine review. ***J Clin Outcomes Manag*** 2001; 8: 33-39.
32. Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. ***Neurology*** 2001; 57: 1805-1811.
33. Schwaag S, Nabavi DG, Frese A, Husstedt I-W, Evers S. The association between migraine and juvenile stroke: a case-control study. ***Headache*** 2003; 43: 90-95.
34. Zeller J, Frahm K, Baron R, Stingele R, Deuschl G. Platelet-leukocyte interaction and platelet activation in migraine: a link to ischemic stroke? ***J Neurol Neurosurg Psychiatry*** 2004; 75: 984-987.
35. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, et al. Migraine as a risk factor for subclinical brain lesions. ***JAMA*** 2004; 291: 427-434.
36. Ho J, Sibbald WJ, Chin-Yee IH. Effects of storage on efficacy of red cell transfusion: when is it not safe? ***Crit Care Med*** 2003; 31: 687-697.
37. Witlin AG, Mattar F, Sibai BM. Postpartum stroke: a twenty-year experience. ***Am J Obstet Gynecol*** 2000; 183: 83-88.
38. Lindenstrom E, Boysen G, Nyboe J. Influence of systolic and diastolic blood pressure on stroke risk: a prospective observational study. ***Am J Epidemiol*** 1995; 142: 1279-1290.
39. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. ***Am J Obstet Gynecol*** 2000; 183: 1-22.
40. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GDV, et al, editors. Williams Obstetrics. 20th ed. Stamford (CT): Appleton & Lange; 1997. p. 727.
41. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GDV, et al, editors. Williams Obstetrics. 20th ed. Stamford (CT): Appleton & Lange; 1997. p. 603.
42. Chesley LC. Management of preeclampsia and eclampsia. In: Chesley LC, editor. Hypertensive disorders of pregnancy. New York (NY): Appleton-Century-Crofts; 1978. p. 341.
43. Simolke GA, Cox SM, Cunningham FG. Cerebrovascular accidents complicating pregnancy and the puerperium. ***Obstet Gynecol*** 1991; 78: 37-42.

STATISTICS

Excerpts from the Uniform Requirements for Manuscripts Submitted to Biomedical Journals updated November 2003.
Available from www.icmje.org

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.