# Gender Differences in Intracerebral Hemorrhage

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**KEYWORDS**

• Sex differences • Intracerebral hemorrhage • Intraparenchymal hemorrhage

**KEY POINTS**

- Intracerebral hemorrhage has many potential secondary causes, many of which have gender differences.
- Physiologic differences between men and women play a role, as do differences in risk factors.
- Health care and family bias may influence treatment decisions and outcomes.

## INTRODUCTION

Nontraumatic intracerebral hemorrhages (ICHs) are the second most common type of disabling stroke after ischemic stroke (IS), accounting for around 26% of cases globally.[1] In the United States, recent data suggest an annual incidence of 23 to 25 per 100,000,[2,3] with recently increasing rates in the young and middle age,[2] and higher rates in men (25.67 compared with 19.17 per 100,000 in women).[3] Mortality rates in the United States are 13.96 per 100,000 for men, and slightly lower at 11.35 per 100,000 for women.[2] Although commonly studied and reported as a single disease entity, ICH is best understood as a manifestation of different potential pathophysiologic processes, many of which vary in prevalence between men and women and are discussed further.

Globally, there is variation between countries and populations regarding incidence and mortality. Data reporting validity can vary as well, because some IS and subarachnoid hemorrhage (SAH) cases can be grouped in together with ICHs under the umbrella category of "stroke." Naturally this contributes to the challenging nature of the study of ICH.[1,4] The variation between countries regarding incidence and outcome is to be expected, however, because ICH does not occur in an isolated fashion, but rather in a context of risk factors, which vary between both individuals and regions. Treatment and recovery from ICH likewise both occur in the context of a health care system, and these systems of course vary between and within countries.[5]

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Differences between sexes in epidemiology, along with causes, risk factors, interventions, as well as recovery and outcomes are covered. It is important to keep in mind that there are a variety of interacting variables, contributing to disparate findings in the literature. As stated by Gokhale and colleagues,[4] the relationship between gender and ICH is not straightforward given the interaction of gender with other factors such as age and ethnicity. To add to these, we can include any pertinent factor that may significantly vary between genders and influence ICH epidemiology and outcomes, such as substance use,[6] anticoagulant use, and smoking among many other pertinent factors, which are covered in more detail.

### *Differences in Epidemiology*

Gender differences in epidemiology vary widely based on study geography.[1,4] Little variation in incidence between men and women has been found in European and Australian studies, and higher rates in men in North America, Japan, and China.[4] In addition to geographic variations in health care systems, additional factors that vary between geographic settings such as diet, availability and implementation of primary and secondary ICH prevention, age and related demographics, substance use patterns, as well as potential ethnic and/or racial differences can also potentially play a role.[7] All these interacting factors together can be challenging to account for when attempting to isolate gender-specific differences.[4,8]

In many geographic areas and health care systems, women present with ICH at older ages than men[9] (although this is not the case in all cohorts),[6] so it follows that specific causes associated with lobar ICH in the elderly, such as cerebral amyloid angiopathy, may be more common in women as a result of age differences in presentation as opposed to other sex-specific factors that could in theory predispose women to higher rates of lobar ICH. Conversely, ICH in young people may be more likely to be associated with substance use for a similar reason, and so it follows that ICH could potentially be more closely related to cultural and psychological predispositions to substance abuse in specific cohorts than to inherent biologic differences between men and women.[6]

Overall, the relative risk of ICH seems to be higher in men when compared with women,[10] with a robust meta-analysis of more than 11 epidemiologic data sets demonstrating an odds ratio of 1.6 in men.[4]

### *Differences in Intervention*

The cornerstones of acute management for ICH (which ideally should not differ between men and women) include blood pressure (BP) control, reversal of any anticoagulation, investigation into potential secondary causes, admission to a hospital floor able to provide close neurologic monitoring with trained nursing staff, along with evaluation of cases by neurosurgery.[11,12] Regarding BP control, no sex differences in outcomes using “intense” BP reduction with a systolic BP of less than 140 mm Hg have been found in a posthoc analysis of the Antihypertensive Treatment in Intracerebral Hemorrhage-2 (ATACH-2) trial.[13] However, a pooled analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) trial 1 demonstrated a greater odds of 3-month mortality in men in the intensive arm (odds ratio [OR], 1.22, $P = .022$).[14]

The clinicians who care for patients with ICH and offer medical, surgical, rehabilitative, and palliative services are human, and despite the best of intentions, are subject to possible practice variation based on unconscious bias.[15,16] Although women may have a slightly lower ICH risk when compared with men when using direct oral anticoagulation medications,[17,18] women may be less likely to be prescribed anticoagulants

in the setting of atrial fibrillation in the first place.[18] In those who are prescribed anticoagulants and suffer ICH, one retrospective study identified that women on oral anticoagulation were nearly *half* as likely as men to receive reversal agents ($P = .007$).[19] A single-center study demonstrated a nearly 3-fold likelihood of external ventricular drain (EVD) utilization in men when compared with women, despite controlling for differences in bleed location, shift, and clinical decline among other reasons for EVD utilization in the management of patients with ICH.[20] Other work has been unable to find clear evidence of bias leading to differences in treatment.[21]

### *Differences in Pathophysiology and Presentation*

There are multiple different potential causes of ICH, along with multiple risk factors that contribute to ICH risk, many of these related to factors that may vary between genders. A portion of these factors are more closely related to inherent physiologic differences between men and women (for example, risks of ICH associated with pregnancy), and others are more closely related to demographic, social, and psychological factors (such as different rates of cocaine and alcohol use between sexes in certain age ranges, socioeconomic status, and geographic areas).[6,22,23] An excellent example of the interaction between age, gender, and risk factors is the work of Umeano and colleagues,[6] who demonstrated a contradictory finding compared with most literature, with a cohort of women presenting with ICH approximately 4 years younger than men (61.1 + 14.5 vs 65.8 + 17.3 years, $P = .03$). This observation was explained by a much greater extent of substance abuse in the women in this North Carolina cohort (35% vs 8.9%, $P < .0001$).[6]

This discussion of risk factors and ICH risk is not to distract from the biologic effects that gender has on ICH. Simplistically, genetic differences lead to differences in the hormonal environment, which has downstream effects on platelet activation, vasomotor reactivity, and endogenous fibrinolytic systems. As a specific example, slit guidance ligand (SLIT3) protein and G protein-coupled receptor 26 (GPR26) are involved in estrogen and serotonin modulation with potential sex-linked effects on ICH occurrence.[24] These differences in the hormonal environment between men and women likely play a role in ICH risk overall[25] and may play a more prominent role in specific secondary causes of ICH such as ICH associated with reversible cerebral vasoconstriction syndrome (RCVS).

Patients with ICH often present with focal neurologic deficits; seizure, headache, and disturbances of consciousness are also at times present, and most are hypertensive. No difference in headache as a presenting symptom among those with primary ICH was reported in a meta-analysis of 5 studies.[26] Hemorrhage location differences between genders seem to vary by region, with some regions and literature reporting no differences in bleed location, and some with an increase in lobar bleeds in women.[4] Other specific gender differences in presentation in the setting of secondary causes of ICH, such as in the setting of RCVS, are discussed further in more detail in association with these specific causes.

Most ICHs in patients younger than 70 years are related pathophysiologically to uncontrolled hypertension, which over time results in lipohyalinosis and the formation of Charcot-Bouchard aneurysms,[27] setting the stage for ICH. These bleeds are classically located in deep gray matter, although a fair number can be lobar in location.[28] Immediately posthemorrhage, blood-brain barrier breakdown contributes to perihematomal edema, which can result in postbleed neurologic deterioration. There is evidence that this so-called secondary injury may be less extensive in women.[29]

ICH in the setting of pregnancy may, in many cases, have a distinct pathophysiologic process, and different risk factors when compared with the nonpregnant

population.[30] Eclampsia, postpartum angiopathy, posterior reversible encephalopathy syndrome (PRES), and RCVS are thought to share a common pathophysiology of increased brain barrier permeability and disordered vasomotor reactivity (likely mediated in part by estrogen) with some common triggering or inciting factors (such as vasoactive medications) along with overlapping clinical and radiographic presentations.[30,31]

Not only RCVS (however, specifically in the setting of tetrahydrocannabinol-mediated RCVS in certain cohorts, males predominate)[32] but also hemorrhagic complications are much more likely in women when compared with men (OR, 2.57; $P = .001$).[33] In the setting of postpartum specifically, the bleed location may be more likely parenchymal as opposed to the subarachnoid space (the opposite pattern is generally found in RCVS outside of pregnancy).[34] Blood in the subarachnoid space or parenchymal hemorrhage may complicate cases of PRES in a minority of cases, and analysis of several data sets suggests this is a risk for poor outcome. Interestingly, analysis of the same data suggested that PRES in the context of pregnancy was more likely to be associated with a favorable outcome.[35] One retrospective study demonstrated that hemorrhagic RCVS was associated with a longer hospital stay but not necessarily worse outcome.[33]

### *Cerebral Dural Venous Sinus Thrombosis*

Cerebral dural venous sinus thrombosis (CDVST) involves occlusion of the dural sinuses and draining veins of the central nervous system (CNS), which can subsequently result in ICH after ensuing venous edema and infarction. CDVST can be incidentally found with no immediate pathophysiologic consequence if the occlusion is not complete and/or other veins are able to compensate. Although clinicians generally think of the large cerebral veins when considering this condition, cortical vein thrombosis can occur as well (either in isolation or as an extension of a larger clot). When ICH complicates CDVST, blood may present radiographically on initial head computed tomography (CT) as lobar ICH and/or convexity SAH. States of increased coagulability, such as those associated with oral contraceptive use or physiologic changes of pregnancy, contribute significantly to an increase risk of CDVST in women, with one cohort publication demonstrating 20% of CDVST cases in women occurring in the setting of pregnancy.[36] Female sex is not a risk for poor prognosis after CDVST, although pregnancy may complicate treatment.[37] Unlike other causes of ICH, anticoagulation is used as treatment along with careful neurologic monitoring; this is not always successful and sometimes surgical intervention is required in the event of neurologic decline despite adequate anticoagulation (**Fig. 1**).

### *Vascular Malformations*

ICH related to vascular malformation, such as arteriovenous malformations, dural arteriovenous fistulas, and cerebral cavernous malformations are a more common cause of ICH in the young, up to nearly 50% of ICH cause in one cohort.[38] One Chinese retrospective series found ICH secondary to vascular malformations occurring more commonly in women,[39] and a separate single-center Japanese study demonstrated a nearly 3-fold risk of rebleed among women with ICH due to vascular malformations.[40] Another study examining outcomes in more than 50 centers in China found a nearly 2.5 times likelihood for poor outcome among women with bleeds occurring in association with a vascular malformation.[41] This gender difference has been hypothesized to be partially related to differences in hormonal receptors, but immunohistochemical analysis has not proved this.[42]

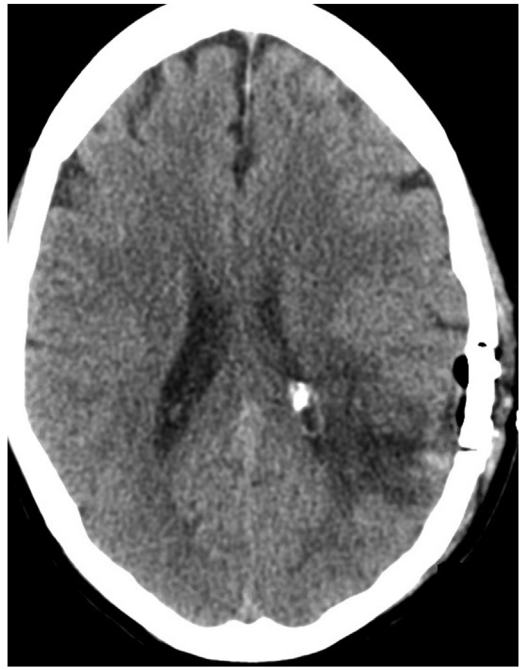

**Fig. 1.** Axial plain head CT of a 56-year-old woman on estrogen-containing oral contraceptives with headache, aphasia, and extensive CDVST, who declined despite therapeutic anticoagulation, requiring decompressive hemicraniectomy.

### *Cerebral Amyloid Angiopathy*

Cerebral amyloid angiopathy (CAA) is a common cause of lobar ICH in the elderly.[43–45] Amyloid protein deposition in the vasculature leading to weakening of the vessel walls along with an inflammatory reaction is thought be the mechanism underlying the pathophysiologic process. This condition can manifest clinically as sudden persistent neurologic deficits with lobar ICH (**Fig. 2**), potentially along with history of memory impairment, and radiographically on MRI the presence of cortical microbleeds along with cortical superficial siderosis and enlarged perivascular spaces.[44] Patchy or confluent T2-hyperintense lesions in the cortex and subcortical white matter can at times be visualized on MRI in association with microbleeds, which can be associated with subacute cognitive changes, headaches, seizures, and stroke-like symptoms suggesting CAA-related inflammation.[44]

Some mouse models of CAA have demonstrated more severe cognitive impairment and higher rates of microbleeds in females,[43,46] potentially mediated by a more aggressive inflammatory response to the amyloid depositions.[47] However, other models have not demonstrated a clear sex-linked difference in microbleeds and cognitive impairment.[48]

### *Moyamoya Disease*

Moyamoya disease (MMD) refers to a progressive occlusive vasculopathy, traditionally associated with gradual narrowing of the terminal portion of the internal carotid arteries with resulting sprouting of the classic “puff of smoke” lenticulostriates, most visible on conventional angiography. Although IS is the more commonly known

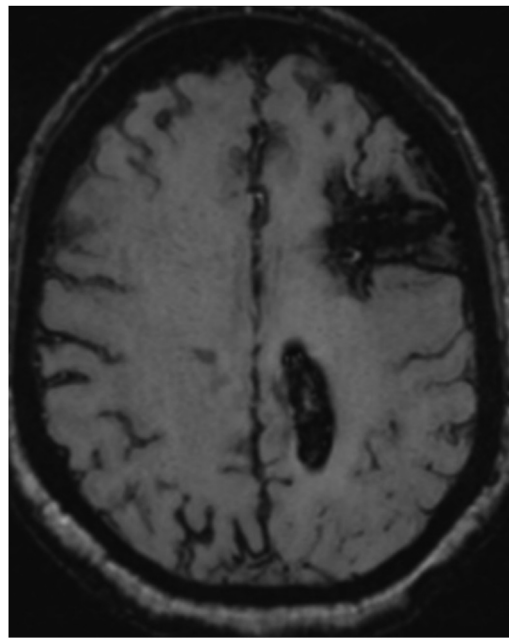

**Fig. 2.** Axial MRI of the brain—susceptibility weighted imaging—of a 63-year-old woman with multiple lobar hemorrhages, with probable diagnosis of CAA.

complication of the disease, ICH can occur as well,[49–51] at times diagnosed during pregnancy,[51] with the highest bleeding risk between 24 weeks and delivery.[52] MMD is also a more common disease in women, with a 2.9 to 1.1 ratio when compared with men depending on the geographic area of the study.[53–55]

Radiographically, women have a greater likelihood of enlarged perivascular spaces on imaging (OR, 2.67; $P = .34$) and are more likely to receive a diagnosis of bilateral MMD (OR, 0.6, $P = .04$).[56,57] Bleeds in the setting of MMD can occur in similar locations to those associated with hypertension, such as the basal ganglia and thalamus[58]; they are more likely to involve blood in the ventricular system,[59] and can be in atypical locations as well such as the corpus callosum,[58] or in multiple simultaneous locations.[60] Female sex trended closely toward being a significant risk factor for rebleeding in one study ($P = .08$).[61]

The disease needs to be differentiated from a moyamoya radiographic pattern (frequently described as a moyamoya syndrome) that can occur as a result of many other secondary causes, some of which have significant sex differences in the underlying disease causing the syndrome. As an example, a moyamoya radiographic pattern in association with autoimmune thyroiditis has a nearly 10 times higher incidence in women when compared with men.[62]

### *Hemorrhagic Transformation of Ischemic Stroke*

Hemorrhagic transformation of an IS is common, ranging from petechial and clinically insignificant (**Fig. 3**), to transformation of most of the stroke bed with associated neurologic decline. Hemorrhagic transformation is a well-known potential complication of IS and associated thrombolytic therapy (**Fig. 4**), in which case the cause of the ICH is not a mystery. There are cases, however, in which a patient

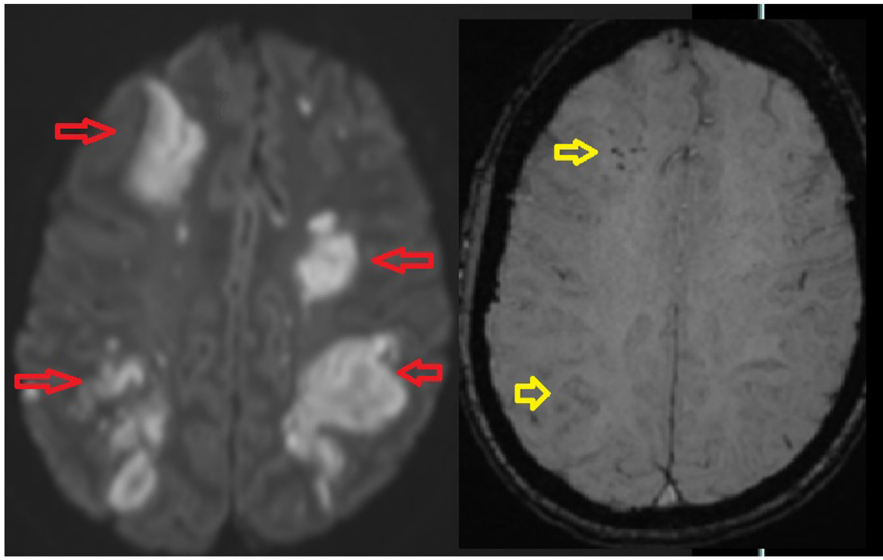

**Fig. 3.** Axial diffusion-weighted (*A*) and susceptibility-weighted (*B*) MRI of the brain of a 52-year-old woman with multiple infarctions secondary to RCVS (*red arrows*) with petechial hemorrhagic changes (*yellow arrows*) on susceptibility-weighted sequence.

may present to the emergency room with an apparently acute ICH on initial head CT that is the result of a transformed IS. A careful history in combination with MRI can be very useful in ferreting out a transformed IS as the cause in such situations.

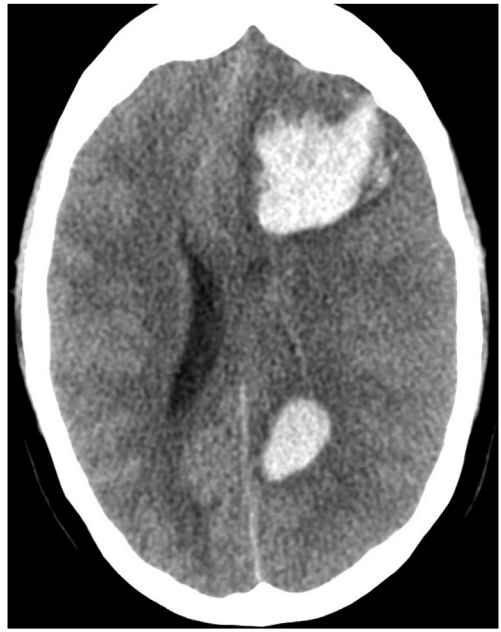

**Fig. 4.** Axial plain head CT of a 50-year-old woman with hemorrhagic complications after receiving lytic therapy for suspected ischemic stroke.

### *Infection and Malignancy*

ICH can be a complication of infectious CNS encephalitis. Among the most common of viral CNS infections is herpes simplex encephalitis, which has a special predilection for the temporal lobes, resulting in both ischemic and hemorrhagic complications. Cardiac and CNS infections can result in mycotic aneurysms with subsequent rupture and resultant ICH. Meta-analyses have not demonstrated a difference in functional outcome between men and women with infectious encephalitis.[63] Recently, ICH has been reported in association with infection in the setting of coronavirus disease 2019 (COVID-19), more commonly in men (64%–74%).[64–66] Many patients hospitalized with COVID-19 were exposed to treatment doses of anticoagulation, which may have complicated the process of determining the ICH mechanism.[65]

Either primary CNS tumors or solid metastases from systemic malignancy can present initially with ICH. Although hemorrhagic changes within a primary CNS malignancy are easily detected, metastatic hemorrhagic lesions that are most commonly encountered in the gray-white junction may require elaborate workup. Hematologic malignancies and chemotherapy-induced thrombocytopenia are both associated with increased risk of ICH.[67].

### *Differences in Modifiable Contributing Risk Factors*

Hypertension is a well-known risk factor for ICH. In general, men have higher mean arterial pressure readings than women, but this is influenced by both age and race (among other factors as well, such as diet and salt sensitivity).[68] On the other hand, women may be less likely to be adherent to recommended antihypertensive regimens, with a recent large meta-analysis demonstrating lower self-reports of compliance with antihypertensives among women older than 65 years (OR, 0.84; $P = .02$).[69]

Heavy alcohol intake has been associated with an increased risk for ICH.[70] Although in general men have higher rates of harmful alcohol use, this gap has recently been closing.[23–71] In addition, men may have a stronger pathophysiologic association between high BP in response to alcohol than women.[72] Smoking is a risk factor for ICH in both genders, and although there are wide regional variations in smoking rates between men and women, worldwide there are more men who smoke than women.[73] Obstructive sleep apnea (OSA) is also a risk factor for ICH, with one study demonstrating a trend toward a statistically significant interaction between women with OSA and ICH risk (OR, 1.12; $P = .057$).[74]

The association between statin use and ICH risk continues to be an area of active investigation with conflicting data. Recently published data from the Danish Stroke Registry found that both current statin and longer duration of statin use may be associated with reduced risk of ICH in both men and women.[75] It is of note that historically women are less likely than men to receive aggressive lipid management and to be prescribed statins for primary and secondary prevention of cardiovascular conditions including myocardial infarction (67.0% vs 78.4%, $P < .001$). Women are also more likely to discontinue statin therapy (10.9% vs 6.1%; $P < .001$),[76] with similar results found in other studies that also account for the interaction of racial and socioeconomic variables in addition to gender.[77–79]

### *Differences in Outcome*

Although there may be underlying genetic or hormonal factors contributing to differences in outcome in ICH between men and women, it is important to keep in mind that such disparities may potentially vary between sexes given differences in age, associated comorbidities, mediating factors such as treating clinical/hospital practice

variations, and family preferences regarding aggressiveness of interventions. It should therefore be no surprise that sex differences in the outcome of patients with ICH has been somewhat conflicting, with some studies demonstrating increased risk of mortality in men,[1,2,9,14,80,81] and some with increased risk in women.[82,83] Part of this discrepancy may be related to challenges associated with accounting for differences in potentially confounding variables listed earlier; after controlling for age, one study found higher rates of death or discharge to hospice in women with ICH (OR, 1.304; $P < .0001$).[83] As an example of the effect that age differences may have in outcome, it can be assumed that conditions associated with increased age such as atrial fibrillation (AF) may be more likely to co-occur in an old cohort of patients, independent of sex.[84] Patients with a lobar bleed along with a diagnosis of AF can be challenging to optimally manage, given the need for anticoagulation, and this could in part explain why females may be more likely to experience poor outcomes caused by a subsequent IS after ICH (OR, 1.3; $P = .004$).[85]

A prognostic marker for worse outcome in the setting of ICH is hemorrhage expansion.[86] Male sex has been associated with higher rates of expansion (OR, 1.7; $P = .007$) in some studies but not in others.[14–87] Assuming patients survive the initial bleed, mortality in ICH survivors is still significantly increased compared with age-matched cohorts without ICH. EVD insertion in ICH-related hydrocephalus was less common in women when compared with men ($P = .016$), raising concerns about sex biases and social factors limitations. Mortality has been largely attributed to superimposed infections, cardiac causes, and recurrent ICH among other less common causes. Regarding specific post-ICH complications, men overall are at higher risk for pneumonia and sepsis (21.9 vs 15.5%, $P < .001$ and 3.4 vs 1.6%, $P = .009$, respectively),[88] whereas women who survive ICH may be less likely to die from infection (OR 0.9, $P = .001$). A Japanese cohort detected nearly seven times higher rates of post-ICH deep vein thrombosis detection in women when compared with men.[89] Very early implementation of "Do not resuscitate" orders have been found to occur at nearly 3 times the rate in women with ICH when compared with men[90]; this has been shown in a separate work to be related to poor outcome, but it is unclear to what extent this may be a causal relationship.[91,92]

Differences between sexes in ICH are in part attributable to physiologic differences and demographic and social/behavioral risk factors, along with patient interface with the health care system as well as the interaction effects between all these factors. Some current work on sex differences in ICH may be limited in examining all potential factors involved in sex differences, which likely contributes to discordant findings in the literature. Further epidemiologic work should continue to incorporate ICH cause, associated contributing risk factors, and detailed demographics to the extent possible. Potential clinician, family, and health care system bias in treatment and interventions can be challenging to study but must continue to be addressed.

## CLINICS CARE POINTS

- Blood pressure control and reversal of anticoagulation are cornerstones of acute management.
- Caution needs to be utilized with early DNR orders so that a self fulfiling prophecy does not occur.
- A higher index of suspicion for less common eitiologies of ICH is especailly important in the setting of pregnancy.

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