Update on specificities of stroke in women

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Summary

The majority of strokes occur in women who in crude numbers have poorer outcome including higher mortality from stroke than men. This may, however, to a large degree be explained by the preponderance of women in the older age groups. Nevertheless, incidence of stroke is higher in men than in women. Overall rates of stroke decline, but more in men than in women; consequently the excess number of strokes in women will be on the rise in the years to come. Risk factors differ between men and women: e.g. rates of atrial fibrillation and hypertension are higher in women with stroke, while rates of e.g. smoking or high alcohol consumption are higher in men, while some risk factors including diabetes or smoking carries a higher risk in women than in men. Especially older women are less well represented in many trials, which reduces the generalizability of results to this from a stroke perspective extremely important population, however, in areas of treatment where sufficient data is available, e.g. i.v. thrombolysis or mechanical thrombectomy the benefit is equal between sexes and may even be higher in women due to their longer life expectancy. Access to care varies between regions depending both on cultural factors and the overall access to care; in especially lower income countries though data is very scarce the impression is that women’s access to care is restricted in comparison to men. Specific female risk factors including pregnancy or sex hormone therapy are rare causes of stroke especially in high-income countries, however these stroke events occur early in life and have massive effect of individual families. Evidence on stroke care in these events is extremely limited and more data, also including prospective generalizable observational data is urgently needed to guide clinicians. Further more specific data on women and stroke is needed to identify if gender in some instances should guide treatment and care.

Until recently, focus on specificities of stroke in women has been limited to issues in relation to pregnancy, post-partum period, oral anticonception and hormone replacement therapy. However, there is increasing evidence that gender differences in stroke are not restricted to reproductive issues but may be of a more general nature. Overall, women suffer more stroke events than men and are less likely to recover; women account for 60% of all stroke events.
Gender differences have been reported in epidemiology, in distribution of risk factors, in stroke subtypes as well as in treatment benefit and in outcome. Further, trials are often imbalanced as to sex leaving especially older women highly underrepresented, reducing the generalizability to this group. This is highly problematic due to the high prevalence of stroke in older women. These differences are no doubt to some degree caused by socio-psychological factors, e.g. higher frequency of smoking in men or larger burden of post-stroke depression in women but there is also increasing evidence of influence of biological factors, including effects of sex hormones on the vasculature. Stroke in women related to reproduction remains an issue of major societal importance due to the young age of the victims and the effects on their families.

This review aims at providing an overview of gender issues in stroke with focus on women. The perspective is mainly clinical, though there is little evidence if and when investigation and treatment should differ depending on the patients’ sex and on how to deal with stroke in pregnancy.

Possible biological mechanisms: oestrogens, progesteron and stroke

Sex hormones, including progesterone, oestrogens, and testosterone, influence vessel physiology, including vascular reactivity, CBF, blood-brain barrier, and atherosclerosis [1]. Oestrogen and progesterone have dilatory effects on blood vessels and increase blood flow, whereas testosterone has the opposite effect. The vascular reactivity is affected by oestrogen by at least three mechanisms: increased production of NO, induction of vaso-dilatory prostanoids, and by manipulation of endothelium derived hyperpolarization factor (EDHF). NO levels are higher in females, which affects CBF and autoregulation. NO can be induced by oestrogen in animal models with ovariectomized rats [2] where oestrogen also induces a shift towards more dilatory prostanoids [3]. EDHF has a compensatory role in NO deficiency leading to vasodilatation [4]. It has been hypothesised that this shift towards a vasodilatory state leads to better perfusion and smaller final infarct sized in pre-menopausal women.

Further, oestrogen as well as progesterone reduces formation of atherosclerotic plaques by mechanisms also involving effects on smooth muscle cells and anti-inflammatory effects [5,6]. Consequently, oestrogen has been considered as a possible treatment in prevention of vascular disease in post-menopausal women; however, post-menopausal hormone replacement therapy has not shown any protection against stroke. This is also the case in recently reported trials with early initiation of therapy.

Most preclinical models are based on male rodents, also in stroke models, and no reliable model of menopause has so far been established [7]. This may theoretically reduce generalizability to females in general and more specifically because steroid hormones affect vessel wall dynamics.

**Epidemiology**

**Incidence and prevalence of stroke in men and women**

In a global perspective based on Global Burden of Disease data, stroke is reported more frequently in men in comparison to women [8]. Based on 2013 data, ischemic stroke incidence was 132.77 per 100,000 in men vs. 98.85 in women; hemorrhagic stroke incidence was 64.89 in men versus 45.48 in women [8]. Stroke incidence is lower in women in the middle-aged and older – approximately 60 % – and higher in the oldest group with a cut-off at 57–85 years [9–11] in comparison to men. Based on US data, the prevalence of stroke can be estimated at 2.5 % in women and 2.7 % in men [12], this observed difference is markedly smaller than the 41 % higher prevalence in men reported in a global systematic review [13]; this may both come down to demographic differences and insufficient data especially in women from low-income countries. Due to the longer life expectancy in women especially in developed countries, stroke ultimately affects more women than men. When correcting the US data [12] for the preponderance of women at older age, a total of 3.1 million female stroke survivors versus 2.7 male stroke survivors can be estimated.

A decline in stroke incidence has been observed during the last 50 years in high-income country population-based studies; this decline is more marked in men than in women (30.3 % in men vs. 17.8 % in women) [14]. However, a recent worldwide review of stroke incidence, prevalence and mortality in women documented that the development in stroke epidemiology is significantly related to regions’ transition in industrialization and economy. In less developed regions, data was limited due to lack of reliable registries and possibly reduced access to care and treatment for women. In especially Eastern Europe, the burden of stroke in women was on the rise, while in high-income countries, a decrease was observed [15].

Overall, more women than men are admitted with stroke in spite of higher incidence rates in men, due to the longer life expectancy in women. In low-income countries, data is limited, especially in women, while a tendency to increasing levels is observed e.g. in Eastern Europe. In high-income countries, rates are declining in both men and women, but more in men than in women, so even higher numbers of women will be admitted with stroke or living with sequelae from stroke in the years to come.

**Characteristics of women with stroke: age and risk factors of stroke**

Women admitted with stroke are overall older and frailer than men and tend to have accumulated more risk factors at the time of first stroke [13,16]. Reported mean age in men and women
Migraine is also a risk factor, which produces a higher risk of stroke in women in comparison to men. RR for stroke in migraineurs (men and women) is 2.2, in women < 45 years RR is reported at 2.8, and women with migraine on oral anticoagulation have a RR of stroke at 8.7 [25]. It is noteworthy that women on average have more risk factors than men, mainly due to their higher age. This increases the complexity of secondary prevention and it is likely that the absolute risk of recurrent stroke is higher in women due to the larger burden of risk factors. Further, this emphasized the importance of primary prevention e.g. antihypertensive treatment and anticoagulant treatment, which generally are reported at lower rates in women than in men.

**Oral anticonception (OAC)**

Oral anticonception is used very frequently in Denmark (population 5.5 millions) approx. 400,000 women have a prescription for OAC. The risk attributed to OAC is much higher for venous thromboembolism than stroke – however, sinus venous thrombosis is a VTE. There are four generations of OAC with different risk profiles for thromboembolism. In deep venous thrombosis, the age adjusted annual risk in pre-menopausal women was observed higher in 3rd and 4th generation OAC – in comparison to 1st and 2nd generation – based on nationwide registry data [26,27]. This is in contrast to results from meta-analyses of trial data [28,29], which did not find any relations to OAC generations. However, numbers of events are very small, so it is likely that large observational samples are needed to observe a difference. A relation to oestrogen doses has been observed rather consistently [21,28] where doses below 50 μg of oestrogen appear to have no attributable risk.

As to the absolute risk of stroke in OAC users, the background risk for stroke is very low in young healthy women. Use of OAC is associated with up to 2-3-fold increase in the risk of stroke [28-30] corresponding at an incidence in the group of approx. 4/100,000/y, which is of limited clinical relevance. However, additional risk factors including age > 35 years, migraine, hypertension or thrombophilia, and smoking significantly increases the risk up to 20-30 times, a level of certain clinical significance [21].

In an observational study of sinus venous thrombosis in a western population, 54.3 % of women < 50 years used OAC, which is clearly higher than the background population. The majority of women with SVT on OAC had other risk factors, e.g. thrombophilia [31].

No excess risk for stroke [28,32] or VTE [33] has been established with gestagen-only products or low dose topical oestrogens [34].

The risks and consequences – both as to health and socio-psychological status – of unwanted pregnancy are well established and must be weighed against the risks of OAC and the individual woman’s risk profile. In women with no risk factors,

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**Figure 1**

Risk factors of stroke in men and women. This is an estimate based on literature. The populations vary in size and characteristics and definitions according to the studies, especially as to definition of smoking and alcohol. The % are simple averages not taking sizes of population, age or any other factor into account [16-18]
the risk of thromboembolic events is acceptably low; however, choice of drug is of importance. In women with risk factors – including age above 35 years and migraine – other options including gestagen-only formulations and barrier methods should be considered to reduce risk of thromboembolism.

This decision process however remains with the GP or gynaecologist; however, it seems reasonable that the neurologist also introduces this topic in relation to e.g. migraine consultations. As OAC is used extremely frequently, while stroke in younger women with no risk factors being very rare, accepting anticonception as a cause of stroke without very thorough work-up cannot be considered good clinical practice in this population. In patients with prior stroke, TIA or venous thromboembolism, stopping oestrogen-containing OAC is reasonable; gestagen-only products can be used; as no excess risk has been documented with these products.

Hormone replacement therapy (HRT)

Average age of menopause is 51 years, a menopause is considered normal if occurring between 40 and 60 years of age [35]. During this period, a 7-10-fold decrease in oestradiol levels occurs [21], together with a relative increase in androgens due to the slower decrease in androgens in comparison to oestrogens after menopause [36]. In relation to normal menopause, the stroke rate doubles from the age of 45 to 55 years in women [37]; some data even suggests that the risk of stroke in women is larger in this age in women than in men, in contrast to other age groups [38].

A number of physiological changes occur in relation to menopause that is related to increased risk of stroke and other vascular events [39]. These include abdominal obesity, increased BMI, increased triglycerides, increased total cholesterol + LDL-cholesterol, decreased HDL, increased fasting blood glucose, and increasing blood pressure levels [40]. Especially early menopause has major impact on risk factors; early menopause is predicted by cigarette smoking, poor nutritional status, and low socio-economic status; however, hereditary factors are most important [37]. A relation between early menopause and incident stroke has been observed, namely that early menopause doubles the risk of stroke [37,41]. However, no relation has been observed between age at menopause and stroke mortality [37].

Hormone replacement therapy is used to ameliorate menopausal discomfort (especially heat flashes and vaginal dryness) and reduced bone loss is an observed benefit. Based on the described biological effects of oestrogens, a positive impact on ischaemic heart disease, stroke and atherosclerosis has been assumed and supported by epidemiological studies [42]. However, this has not been confirmed in large interventional studies, and is now assumed to be a ‘healthy user’ effect: the women using HRT were those following contemporary advice on health issues. Large clinical trials have been performed aiming at reducing the risk of stroke by treatment with HRT. Women’s Health Initiative (WHI) observed a 44 % increase in the risk of stroke in the intervention period [43], this subsequently disappeared during a 10-year follow-up after the intervention period. Heart and Estrogen/Progestin Replacement Study (HERS) concluded that HRT did not reduce the risk of stroke [44], while the Women’s Estrogen for Stroke Trial reported an increase in early stroke in the intervention arm [45]. A meta-analysis also including trials not looking at stroke as primary endpoint, reported a 30 % increase in risk of stroke related to HRT [46]. It is important to note that the substantially higher background risk in this age group makes this increase in risk for stroke clinically highly significant.

Two recent trials have investigated if the timing of HRT introduction in relation to menopause affects the effects of oestrogen on vascular events and atherosclerosis. The KRONOS Early Estrogen Prevention Study (KEEPS) studied the effect of treatment introduction within 3 years of menopause and found no differences [47]. The ELITE study (Early versus Late intervention trial) compared introduction of HRT within 6 years of menopause to later than 10 years after. Less progression in carotid artery intima media thickness was observed in the early group; no effects on measures related to heart CT were observed [48]. The risk does not appear to relate to the route of administration (transdermal, oral), however low dose transdermal oestrogen (≤ 50 μg) appears to carry no excess risk [34], which is clinically relevant as it allows for safe use of topical vaginal oestrogen to reduce dryness and discomfort. There appears to be a dose dependency so that higher doses carry a higher risk of stroke [37] but the age of treatment initiation does not appear to affect the risk.

Present guidelines suggest initiation of HRT only after individual consideration of the patient’s menopausal symptoms and risk of vascular events. Low dose oestrogen (≤ 50 μg) appears to be the safest choice if HRT is required. Other treatment options include topical vaginal oestrogen, if vaginal dryness is the main problem and clonodin if the major problem is heat flashes. Physical activity is also assumed to ameliorate post-menopausal discomfort.

It is considered good clinical practice to stop HRT in case of stroke or TIA. It is relevant for the neurologist to inform and guide women on HRT with vascular events of other options of ameliorative treatment when stopping HRT as menopausal symptoms, especially heat flashes and vaginal dryness leading to termination of vita sexualis may have substantial negative consequences on quality of life.

Stroke subtypes

Based on 17,370 patients from the International Stroke Trial, it was reported that severe stroke was more frequent in women (total anterior circulation stroke [TAC] women 27.4 % versus men 20.9 %; partial anterior circulation stroke [PAC] women
40.5 % versus men 39.8 %; lacunar syndrome [LACI] women 22.5 % versus men 25.8 %). Further posterior circulation stroke (POCI) was more frequent in men (13.5 % versus 9.6 % in women) [49]. This is in concordance with cardioembolic stroke being more frequent in women than in men (34.1 % versus 20.9 %) [16] as well as the higher frequency of atrial fibrillation (figure 1).

**Stroke severity and neurological findings**

Women suffer more severe strokes than men, rates of patients presenting with NIHSS > 7 have been reported at 44 % in women versus 36 % in men [50]; this trend has been confirmed by others [13]. Women more often present with cortical symptoms and unusual symptoms, including pain, changes in consciousness or headaches [51]. Women less often present with symptoms, including dysarthria, ataxia, and paraesthesia [50] while more frequent with symptoms, such as coma, urinary incontinence, loss of consciousness, and dysphasia [17]. Drowsiness and unconsciousness was also reported more frequent in women (26.7 %) than in men (19.7 %) based on data from the International Stroke Trial [49]. Studies based on smaller cohorts have not been able to detect any gender differences [52]. There is some evidence that women may have a slightly different profile in clinical presentation than men and that unusual presentations are more common in women.

As to severity, this implies longer hospital stay and large morbidity and mortality but is unlikely to reduce diagnostic certainty or standard of care. However, it is important to note that women are more prone to unusual presentation, which will inevitably increase the risk of late or absent diagnosis, which may lead to withholding investigations and treatment thereby reducing the chance of good outcome. More research is needed to document if this is a clinically significant problem and identify red flags.

**Pregnancy and post-partum period**

The thrombotic risk increases during pregnancy due to haemostatic changes leading to increase in clotting factors and decrease in anticoagulants and fibrinolytic factors [53]. Incidence of stroke during pregnancy and the post-partum period ranges from 9-34/100,000 deliveries worldwide [54]. In the USA the incidence has been established at 34.2/100,000 deliveries in comparison to 11/100,000 age-matched non-pregnant women [55]. The risk of any presentations of stroke is increased in pregnancy, but in ICH the most important increase in frequency occurs; the period of highest risk is the peri-partum period [56].

Recently, estimates of incidence based on large high quality registries of stroke (haemorrhagic and ischaemic) during pregnancy and the post-partum period have been published. The study was based on data from the Get on with the Guidelines Registry (2008-2013) [57]. It was reported that 388 ischaemic stroke incidents occurred during pregnancy or in the 6-week post-partum period in women aged 18-44 years during the observation period, in comparison to 24,303 stroke events in non-pregnant women in the same age group. Of those strokes, 44.8 % occurred ante-partum, 2.8 % during delivery, and 52.4 % post-partum. In general, pregnant women with stroke had fewer risk factors for stroke than the age-matched stroke population. This was significant as to age (pregnant mean 31 years versus 39 years in non-pregnant), prior stroke or TIA (7.4 % versus 20.5 %), ischemic heart disease (1.2 % versus 5.6 %), DM (6.5 % versus 21.5 %), and hypertension (17.5 % versus 42 %). As to haemorrhagic stroke (ICH and SAH) [58], these events occurred in 330 pregnant and 10,625 non-pregnant women. Pregnant women presented fewer risk factors, were less impaired on arrival and had a lower in-hospital mortality in comparison to non-pregnant women (ICH: OR 0.57 [0.35–0.45]; SAH OR 0.17 [0.06–0.45]). The chance of discharge to home was higher in pregnant versus non-pregnant women (OR 2.6 [1.67–4.06]) as well as the chance of independent ambulation at discharge (OR 2.4 [1.56–3.7]).

In a cross-sectional study (1994-2011), it was estimated that the rate of stroke with hypertensive disease during pregnancy was increased with 103 % during the time period from 0.8–1.6/10,000, a higher increase than what was observed as to stroke with hypertensive disease in non-pregnant women (2.2–3.2/10,000). Women with hypertensive disease in pregnancy had a 5.2-fold higher risk of stroke during pregnancy. As to other risk factors congenital coagulation deficits (OR 2.7), congenital heart disease (OR 13.1), atrial fibrillation (OR 8.1), migraine (OR 4.5), SLE (OR 2.9), valve disease (2.8) and post-partum haemorrhage (OR 1.3) increased the risk of stroke, while no effect was observed from diabetes [59]. Peri-partum migraine has also been identified as a major predictor of stroke in pregnancy [60,61].

Stroke aetiology in pregnancy differs in some cases from the general stroke population. Causes of stroke unique to pregnancy include pre-eclampsia/eclampsia, post-partum angiopathy, amniotic fluid embolism and post-partum cardiomyopathy. Other causes include hypertension, diabetes, aneurisms, A-V malformations and vasculitis [54,62]. Pre-eclampsia/eclampsia predisposes for a number of further vascular complications, including ICH (especially in case of co-existing malformations), PRES (posterior reversible leuкоencephalopathic syndrome), RCVS (reversible cerebral vasoconstriction syndrome) as well as ischaemic heart disease and cerebrovascular disease later in life [54,62]. Post-partum angiopathy is closely related to RCVS. It occurs within days after delivery, most often normal pregnancy and delivery. It is characterized by thunderclap headache, vomiting, altered mental status and/or focal deficits. CTA – or DSA – shows multi-focal narrowing of large and middle-sized arteries [54]. A recent cross-sectional study concluded that RCVS or post-partum angiopathy was the most common cause of cerebrovascular events post-partum, being the cause in app 35 % of cases [63].
Sinus venous thrombosis in pregnancy

In a large series of patients with sinus venous thrombosis, 75% were women and 17% of women were pregnant or in the postpartum period [64]; female gender specific factors – including pregnancy and post-partum period – predicted good outcome. Women had better outcome than men, but only if gender specific risk factors were present. A shift in gender distribution over time leading to an increasing proportion of women with SVT in comparison to men have been observed over time; some have suggested that this might be a consequence of the increasing use of OAC [65]. Symptomatology of SVT in pregnancy does not differ from non-pregnant women; women tend to present with isolated headache more often than men [64]. Especially the risk of sinus venous thrombosis in the post-partum period is very much depending on the woman’s health and social factors, and the risk is much higher in developing countries than in developed countries. In developing countries, infections, dehydration, and electrolyte disturbances remain the most common causes [66].

A recent systematic review has looked into the risk of SVT and other venous thromboembolism during pregnancy after previous SVT [67]. The risk of recurrent SVT was estimated at 9/1000 pregnancies, while non-cerebral VTE occurred in 27/1000; the risk of spontaneous abortion in the observed pregnancies was 18%. Consequently the risk of SVT is acceptably low not to advice against future pregnancies; however, the risk of any VTE is of clinical significance and will require close follow-up during a future pregnancy and in some cases preventive measures; experts should care for this group of patients. The risk of stroke is very low in healthy pregnant women with access to sufficient obstetric care. Pregnant women presenting with possible vascular symptoms should receive adequate work-up but risks of e.g. ionizing investigations should be weighted against the clinical presentation and possible benefits as the vast majority in clinical experience have their symptoms from other causes, including psychological stress. However, this is challenging because this may also increase the risk of overlooking actual vascular pathology.

Outcome after stroke: mortality

Reports on possible gender differences in stroke mortality vary significantly. Based on a multicentre-multinational hospital-based registry [17], higher mortality was reported in women at all times of observation: in-hospital 15.3% versus 12.5%; at 28 days 14.5% versus 12.1% and at 3 months 30.9% versus 26.1%. In the International Stroke Trial, 6 months mortality in women was 24.5% in contrast to 19.3% in men [49]. A global systematic review reported a 1-month crude fatality rate of 24.7% in women versus 19.7% in men [13]; generally a difference in crude fatality rates are reported in the range of 5–10%, it is however likely that this is mainly due to higher age, more severe stroke, stroke subtypes and risk factors as adjustment for these factors makes the difference disappear [68,69]. Further, it has been suggested that this effect may be more due to effects of decreasing testosterone in men than protective mechanisms in women [70]; this however remains to be confirmed.

There are also significant age related differences in mortality between genders. There are no differences in mortality between men and women affected by stroke up to the age of 45 years; from 45 to 75 years, mortality is about 20% higher in men than in women and after the age of 75 years, mortality is higher in women by 12–14% [71]. Based on data from the US Census Bureau in 2000 in USA [71], there was an estimated 80,000 stroke deaths in women versus 48,000 in men. These 32,000 excess stroke deaths in women were expected to increase to 68,000 excess stroke deaths in 2050.

Functional outcome

Female sex has been identified as an independent predictor of disability and handicap after stroke, and loss of independent function was reported higher in women measured as ΔmRS at 3 months (1.8 in women versus 1.6 in men) [17]. At 3–6 months after the stroke incident, women are more frequently disabled, single or institutionalized in comparison to men [10,19]. It has been suggested that the larger proportion of women being institutionalized after stroke was due to more severe strokes but better survival in women [70]. In the International Stroke Trial, 26.7% of men versus 22.7% of women were fully recovered at 6 months [49].

Women tend to have a lower quality of life after stroke especially as to physical function and mental health. Post-stroke depression rates are reported higher in women both in-hospital [72] and after discharge [19,73]. This has however not been confirmed by all [51]. Also anxiety disorders are more frequent in women after stroke than in men after stroke [74]. Risk of suicide has been reported increased in the first 5 years after stroke, and more in women than in men [75]. Overall, outcome after stroke is poorer in women than in men. This is the case both as to the frequency of complications, functional outcome, mortality and rates of institutionalization after stroke. This is at least to some degree explained by socio-demographic factors; especially the higher average age of women and the higher degree of social isolation in older women may also contribute.

Access to work-up and treatment

The access to paraclinical examinations, including brain imaging, carotid duplex, ECG and angiography was reported more restricted in women, and consequently the rate of unspecified stroke as final diagnosis higher [17]. A Swedish nationwide cohort reported equal access to stroke unit care but lower rates of antithrombotics in women both as primary and secondary
prevention, also as to anticoagulation in atrial fibrillation [19]; others have reported lower rates of only platelet inhibitors in women [76]. In an observational study, women were less likely to undergo carotid surgery, 1.5 % of men versus 0.3 % of women underwent this procedure in a multicentre hospital-based registry; this may be associated to lower rates of Duplex of carotids and angiography in women as observed in the same study [17]. Equal access to physiotherapy, occupational therapy, and speech therapy as well as stroke unit care has been reported [17,19].

**Treatment**

Women are generally underrepresented in RTC’s limiting the generalizability to women. This is the case in both most acute trials and most trials in secondary prevention, where men account for at least 2/3 of patients, and the average age remains below 70 years. This may reflect barriers in inclusion of women including the need to exclude pregnancy in younger women and those older women are more often alone in life without relative who can contribute with anamnestic information or to giving consent. However, exclusion criteria may also limit the access to trials of older and more frail individuals – who in a stroke population are more frequently female than male, and psychological factors in both patients, relatives and health care professionals may also have some impact.

As to thrombolytic therapy, there are no indications of gender differences as to benefit and risk. Conflicting reports are found indicating more benefit in either sex, as well as no differences [51,77,78]. As to endovascular treatment, a meta-analysis of five trials found no gender differences regarding the adjusted treatment effect on modified Rankin Scale at 90 days [79]. Equal benefit as well as access to stroke unit care and rehabilitation is reported from a large number of studies; there is a trend towards shorter length of stay in men [51]. This may be due to the younger age and less severe stroke presentation attributed to men. Stroke unit care reduces the risk of death or dependency (OR 0.79 [0.68–0.9]) independent of sex [80] as well as age. In carotid artery interventions (carotid endarterectomy [CEA] and carotid artery stenting [CAS]) significant gender differences have consistently been reported. Female sex is regarded a surgical risk with CEA leading to a higher frequency of peri-procedural stroke/death. In comparing CEA to CAS, rates of peri-procedural events were higher with CAS than CEA in women (HR 1.89 [1.01–3.37]), this was driven by peri-procedural stroke events. Overall, the benefit is smaller in woman than in men both as to primary and secondary prevention, leading to minimal absolute risk reductions in women.

Further, no benefit has been observed in surgery later than 2 weeks after the event in symptomatic carotid artery stenosis in women [81,82]. Evidence of benefit of carotid interventions is more limited in women. Scientifically, trials focusing on women with large vessel disease are needed; in clinical practice, focus on prompt surgery, risk factor control and optimised medical secondary prevention is continuously needed.

Differences in benefit of antithrombotic therapy has also been suggested: men seem in some reports to benefit more from platelet inhibiting, which may be explained by vascular effects of sex hormones, however, this is not well documented as to clinical impact [51]. In atrial fibrillation, higher risks of stroke in women have consistently been reported [83–87]. A meta-analysis on gender differences in safety and efficacy of VKA and NOACs [88] reported a tendency towards less protection from thromboembolism from VKA in women and lower risk of bleeding from NOAC in women; time in therapeutic interval for VKA was not included in the analysis.

As women with stroke are older than men, complications in relation to polypharmacy are more likely to occur; the significance of this in a gender perspective has not yet been described.

**Medical and interventional treatment during pregnancy**

Randomized controlled data from pregnant women is non-existing, guidelines rest on experience and reported cases. Twenty-eight cases of thrombolytic treatment for any indication during pregnancy have been reported; maternal death occurred in 7 % and loss of foetus in 24 % [89]. Six reported cases of thrombolysis for stroke resulted in one maternal death, a minor haemorrhagic transformation of the infarct in one case, one intrauterine haematoma and three pregnancies lost or terminated [90], however, these data are not likely to be generalizable. Few reports exist on i.a. thrombolysis or use of mechanical thrombectomy, in some cases with a good result [91–93]. One case of successful treatment with i.v. thrombolysis plus modern mechanical thrombectomy has been reported [94].

It is in no way possible to form a general opinion on acute stroke treatment during pregnancy based on these reports; the only option presently remains swift evaluation by an expert team and treatment according to their best opinion after consultation with the patient and her family. In case of significant symptoms where the spontaneous course is unlikely to be beneficial, it is probably after individual consideration reasonable to accept the excess risk of complications related to the pregnant conditions. There are no trials in prevention (e.g. antiplatelets) during pregnancy; if the risk is considered high – e.g. protein S/C deficiency – low molecular heparin is suggested; in case of stroke during pregnancy, antiplatelets may be a reasonable choice depending on the mechanism and ASA can be used until week 36. However, this should be based on a consultation with an expert in the field. In general, obstetricians have more practical experience in women on low molecular weight heparin than other antithrombotics, which in some cases will guide the choice.
Conclusions – clinical implications
Epidemiology and presentations of stroke vary between sexes to some degree and with a significant covariance with age. Much may be explained by lifestyle but it is plausible that biology also has a say e.g. through the effects of sex hormones. Some differences in treatment response are well documented; this calls for focus on possible sex-differences in designing clinical trials both to ensure statistical power to look for sex-differences but also to ensure recruitment of women, especially older women.

Stroke events related to oestrogen therapy and pregnancy are very rare events, however, devastating to the victims and families. Complete reporting of possible side effects is crucial to establish the incidence of thromboembolism related to oestrogen products, especially as to variation in risk between generations. Further, there is very little data on treatment of stroke during pregnancy, and the lack of knowledge and experience is likely to case uncertainty in doctors and nurses when one of the very rare cases are admitted, often leading to doing nothing at all or waiting too long. Randomised controlled trials or large series are unlikely to appear, however, registry work and case reports will be helpful in sharing experiences.

If no data specifically on women exist or data is very limited, it is only reasonable to rely on data based on men but high quality guidelines on prevention of stroke in women is available [95], and a European Stroke Organisation GRADE-based guideline on Stroke in Women is being prepared.

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