Features of diseases distinctly differ for women and men
Focus on menopause and women's heart illnesses is needed

Health care professionals, along with society in general… should not regularly tell women, … who go through menopause to accept the misery of the transition and the health troubles that follow (see Nature, Vol. 637, 23 January 2025, page 782 ff)

Controversial aspects of geopolitics were recently turned upside down in the USA. Seventy-seven million against seventy-five million voted for an 180^0 change, among others, to get rid of the LGBTQ+ movement. With an executive order, President Trump declared that the US government would only recognize a person's sex as assigned at birth. As expected, those in the minority camp cried wolf (1). Knowing what will come, a group of Australian researchers, in a lengthy statement in Science, backed the LGBTQ+ movement with the well-known claim that culture and society demand to distinguish between sex and gender (2).

A certain group of people declaring that having culture and society on their side and demanding that everybody follow suit is impertinent, but is not elaborated in this blog. However, health issues going along with the LGBTQ+ ideology were reviewed in length here recently and allow everybody to read it and come up with her or his judgment (3, 4).

<u>The male body should not be the default in science and medicine</u>

Fortunately, despite controversial opinions, there is a general content that women's health in science and medicine was largely neglected 'by an assumption that the male body is the default (2, 5).' A telling example is menopause. Quite recently, it came into the general consciousness that half of the world's population is hampered in the middle of their life, often at the height of their professional life, by a full-blown upheaval in their setting of hormones related to their sex (6, 7). The consequences menopause has for the lives of women are commonly ignored. Even in studies about increasing age, less than 1% deal with menopause as well (8).

<u>Menopause</u>

Menopause changes the fat distribution of many women into androgenic central obesity, followed by metabolic alterations with an increase in adiponectin and leptin and a negative association with resting levels (9). The risk for severe illnesses, particularly for cardiovascular diseases, hypertension, type 2 diabetes mellitus, non-alcoholic fatty liver diseases, and osteoporosis increases (7, 10).

The perimenopause starts with a downturn of reproductive hormones produced by the ovary four to eight years before menopause, which ultimately strikes between the ages of 45 and 55. Highly variable mood changes, sleeplessness, and hot flashes are frequent symptoms (7). To counteract the symptoms, hormone therapy with estrogen and progesterone, common in the past, declined around 2002 due to a report of a randomized control trial indicating increased risks for a variety of severe diseases (11).

The women's health initiative and its randomized trials

The trial against placebo was stopped after about five years because of statistically significant hazard ratios of coronary heart diseases, breast cancer, stroke, and pulmonary embolism. Slightly preventive ratios were calculated for hip fractures, while no significant outcome for colorectal and endometrial cancer and for death to other causes was found. Significant hazard ratios were estimated for composite outcomes for arterial and venous diseases and a decreased risk for fractures. Absolute excess risks for 10.000 person-years revealed 7 more cardiovascular cases, 8 cases each for strokes, pulmonary embolism, and invasive breast cancer. On the other hand, 6 persons were spared from colorectal cancer and 5 from hip fractures.

When combining all events, 19 cases per 10.000 person-years were obtained, and it was concluded that the 'overall health risks exceeded benefits from the use of combined estrogen plus progestin' in postmenopausal healthy US women (11). Besides oral contraceptives and therapies against hot flushes, other remedies for symptomatic treatment, such as antidepressants, vitamin D against memory loss, and changes in lifestyle, especially low-fat food, remained (7, 12).

Estrogen therapy – yes or no?

The conclusion was drawn from one of four clinical trials of a wide-ranging undertaking, named Women's Health Initiative, which included 10.739 women on hormone oral replacement versus placebo (12). The findings were challenged in claiming that the combination of estrogen with progesterone is not advisable, and the age of those participating should have been younger, actuality at the onset of menopause (10, 13). The risk of heart disease in younger women and estrogen therapy alone decreased the risk of breast cancer. Instead of oral treatment, transdermal patches will reduce the risk of blood clots. In addition, the benefit of estrogen therapy for osteoporosis for all age groups was undervalued (7, 12).

A recent review overseeing all of the four trials still doesn't 'support' hormone therapy to prevent cardiovascular diseases or 'other chronic diseases.' Recommendations are vague for hormonal therapy against 'vasomotor' heart symptoms in early menopause, provided to those who are 'interested in taking hormone therapy.' According to the authors, routine calcium and vitamin D supplementation is not recommended to prevent fracture. Whether a low-fat diet works against colon and breast cancer, further investigations are necessary (12).

It appears that recommendations are contradictory, and 'expert' opinions don't allow a safe and overall strategy for primary health care for women in menopause. The vision for therapies and even transplantations for prolonging the life of the ovaries are interesting to follow but still without concrete benefit for women suffering from menopause (7).

Risk for cardiovascular disease increases

After losing the protection of estrogen, the risk for women for cardiovascular diseases increases to the same level as for men, just only, somehow, 7 to 10 years later (14-16). At the same time, fat distribution accumulates also for women in the abdominal area and results in an increase in risk for acute coronary syndrome (17, 18). Compared to men, therapy and prevention for heart

diseases seems to be deficient for women, at least in the US, if not also elsewhere. From 1979 (2522) to 1998 (2541), cumulative mortality of coronary heart disease for men declined to about 50%, while for white women to about 30% and for black females to 20% (19).

The difference between men and women in the mortality of coronary heart diseases cannot be explained by arguing that females generally live longer, so higher fatality is due to the generally higher longevity of women. Not breast cancer, but heart diseases are still the leading cause of death in all age groups of women, but with particular different features in the pathological and clinical picture of heart diseases compared to males and are of disadvantage for women because of delayed diagnosis and inadequate therapy (20).

Risk and type of heart diseases differ between men and women

Traditional cardiac risk factors differ between sexes in that in females, triglycerides, diabetes, and central obesity with a BMI over 35 are present while smoking and hypertension are not so often found in female patients (20). Larger waist circumference, signs of the metabolic syndrome, being less active, and having a history of polycystic ovary syndrome are features of the women's risk pattern (20). Since disease displays between sexes differ, angiography often doesn't show, as expected, indications of coronary artery disease in women. Instead, heart failure might be finally diagnosed (21).

Heart failure with preserved ejection fraction (HFpEF)

Heart failure is often due to what formerly was called 'diastolic heart failure' or 'failure of the right heart' (in case you studied medicine in Germany). The correct expression is 'heart failure with preserved ejection fraction (HFpEF).' It is estimated that 50% of heart failure cases are due to HFeEF, and cases seem to increase at least in the US and various European countries (22, 23).

Diagnostic tools, including biomarkers

The symptoms of diastolic dysfunction of the left heart ventricle vary, but often dyspnoea and being quickly tired, even after light physical exertion is observed. As diagnostic tools, echocardiography and cardiac magnetic resonance imaging are applied. The former often failed to indicate the disease, while with the noninvasive magnetic resonance technique, extracellular systolic and diastolic deformation of the left ventricle can be diagnosed (24, 25). Nuclear imaging, called single photon emission tomography, detects insufficient blood and oxygen delivery to the heart muscle, a mechanism called perfusion, a rather sophisticated and expensive procedure.

Biomarkers use the two main elements of the heart muscle: a non-cellular component, the matrix, and the heart tissue cells. Instead of imaging methods to investigate heart failure, a well-known biomarker calculates the ratio of metalloproteinases of the matrix with those of the tissue (MMP-1/TimP-1) (26). Since traditional risk factors underestimate the risk for heart disease in women, additional risk markers should be tested. Suggested are inflammatory markers, here the high sensitivity C-reactive protein. Additional risk markers in women are narrowing the retinal artery and coronary calcification. The lack of correlation between low-density lipoprotein cholesterol

(LDL) and the above-mentioned high sensitivity of C-reactive protein also could indicate heart disease in women (20).

The pathophysiology of the HFpEF still needs to be explored in more detail and might be multifactorial. Comorbidities such as pulmonary emphysema, anemia, or renal diseases finally also result in heart failure. Death of the functional cells of the heart, called cardiomyocytes, due to a heart attack, or inflammation and increased matrix stiffness, involves the heart function, leading to morbidity and mortality (25, 26).

Coronary microvascular dysfunction

The two review publications about the epidemiology of HFpEF largely ignored sex differences. Coronary microvascular dysfunction is another heard disease, often failing to be diagnosed in women, while those suffering from the disease account for 60% up to 70%, often of younger age (27). The vascular system of the heart consists of epicardial arteries (>400 μm), small arteries (<400 μm), arterioles (<100 μm) and capillaries (<10 μm). Under microvascular dysfunction, spasms, particularly of the heart capillaries, are understood to cause pain, known as angina, without having obstructive coronary artery disease (CAD) (28). Expecting CAD, not realizing that the underlying reason for the disturbing and threatening symptoms is caused by microvascular angina, results in time-consuming, expensive diagnostic procedures, and the patient worries for weeks and months before the reason for the pain is known and adequately treated (29). The reasons for the disorder are manifold, including neurohumoral disturbances, inflammation, oxidative stress, disorders in vasodilatation, and sex-specific influences (27, 30).

Although coronary microvascular dysfunction is defined as a condition in the absence of obstructive coronary arteria diseases, the prevalence of arteriosclerosis has been observed in patients during diagnostic intravascular ultrasound analysis (31). This indicates a possible pathophysiological link to heart failure due to HPeHF (32). To complicate the situation even more, another coronary vasomotor disorder must be considered as well. I

Vasospastic angina, formerly called Prinzmetal angina

Vasospastic angina, formerly called Prinzmetal angina, named after the first author of a publication in 1959, described a very often overlooked episode of vasospastic angina (33). The disease is characterized by ‘spontaneous episodes’ of ‘nitrate-responsive rest angina with associated transient ischemic electrocardiogram (ECG) changes (34).’ The chest pain might wake the patient in the early morning. Strong physical movements do not aggravate the pain. Some patients even control the attacks by strenuous physical exercise and, given the simultaneous presence of an arteriosclerotic cardiovascular disease, can differentiate between the pain caused by either of the two conditions by exercising and observing a decrease or increase in pain. Some patients claim to have difficulties resting, trying to relax, and being hit by a spontaneous spasm attack.

Attacks also might happen at any time during the day. Patients are usually younger than those suffering from coronary heart disease but might develop coronary heart disease as they grow

older. Ethnicity might play a role in that in Japan, 80% of the diseases are men, but in Italy, 70% are female. Calcium channel blockers and nitrate are drugs of choice during an attack (34).

Suspected reasons for the condition are localized hyperreactivity of the coronary artery, influenced by the autonomic nervous system, and aggravated by mental stress. Smoking, drugs, such as cocaine and ecstasy, and alcohol can be underlying reasons. A general condition prone to allergic reactions or diseases is also a precipitating factor. A recent investigation among Japanese patients in a longitudinal study revealed that under certain conditions, the vasospastic anginal could develop into coronary microvascular dysfunction or even into what is called a 'major adverse cardiovascular event (MACE) (35).

Outline:

The third entry into this blog reflects the need to observe the health and well-being of women separately from men in science, public health, and curative medicine. It draws attention to menopause and the integrated risk of heart diseases often overlooked. The quality of life of half the world's population in the middle of life and into the following decades needs to be improved, and the confusing interwoven spectrum of heart diseases must be sorted out for effective prevention and treatment. The task requires the combined effort of all health specialties. Notably, public health and curative medicine must work together, starting within the population in the field and extending into the hospitals. What began with a presidential order from the outgoing president of the US and was taken up frequently by publications in respected journals such as Science and Nature is not only a challenge for North America and Western Europe but an even more urgent confrontation for the health authorities in countries of Africa and Asia and including Thailand. It was mentioned and repeated here that Thailand faired exceptionally well during the primary health care initiative to improve mother and child health. Similarly, it can be expected that Thailand will also turn towards the particular needs of females again in the second half of their lives.

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