

What is the gender of thrombosis? A natural model of precision medicine

It is more important to know what kind of person has a disease than to know what kind of disease a person has
(Hippocrates of Kos, 460-377 BC)

Dear Editor,

We have undoubtedly and definitely entered the season of *personalized* or *precision medicine*. Thrombosis offers a *natural* field of application of this approach. We are talking about a pathogenic mechanism in which the cause of the diseases most represented in the Western world (and rapidly growing in emerging countries) is recognized.

The mechanisms that regulate the activation of platelets and coagulation leading to the inappropriate formation of a clot at a venous or arterial level are responsible for several diseases ranging from venous thromboembolism to myocardial infarction, the so-called *atherothrombotic* diseases. In each of these clinical manifestations, it is possible to recognize a prevalence of the female sex, even in those diseases – such as ischemic heart disease – in which, historically, men were the main protagonists.

Therefore, studying and recognizing in detail how much gender affects the pathophysiological mechanisms allows us to better treat patients and truly apply the principles of precision medicine.

Let's start with venous thromboembolism: exposure to the risk of this disease is peculiar to women and accompanies them in all moments of their life. From adolescence – a stage in life in which they often come into contact with *estro-progestinic* therapy – to pregnancy, natural or induced by assisted procreation techniques, to the possible use of hormone replacement therapy in menopause. Different risks, in relation to different ages and procedures, but always peculiar to being a woman.

The clinical setting of arterial thrombosis, historically a prerogative of the male sex, is also showing and confirming the affinity of thrombosis for the female sex. Women affected by heart attack or stroke die more than men: partially due to a delay in diagnosis and therefore in treatment, linked to the widespread and erroneous belief that these diseases are less likely to occur in women. In Europe, 55 out of 100 women die from vascular diseases, against the 40 out of 100 men: stroke is the third leading cause of death in men, the second in women.

Sex-based disparities in the evaluation and management of acute coronary syndrome are also pervasive. Women with ST-elevation myocardial infarction tend to request medical intervention later after symptom onset than men. Among patients who have sought medical attention for symptoms before acute coronary syndrome, it's more likely for women to have been reassured that the symptoms were not cardiac in nature. For these reasons, women with acute coronary syndrome are less likely than men to undergo revascularization. When percutaneous coronary intervention is performed for acute coronary syndrome, radial access is less commonly used in women, and older women have higher rates of significant post-procedural bleeding than older men. In terms of secondary prevention, women are less likely to receive statins, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers at the time of discharge than men.

These differences in secondary prevention regimens might contribute to the lesser observed reductions in recurrent myocardial infarction rates over time in women than in men.

Finally, antithrombotic therapies have different safety and efficacy profiles among women: this is clear even if the data we acquire from drug intervention trials mostly involve men. Several data show higher platelet reactivity in females and a higher prevalence of high platelet reactivity on aspirin and clopidogrel therapy. In primary prevention, the use of aspirin is associated with a higher reduction of risk for ischemic stroke in females and for myocardial infarction in males. In the context of acute coronary syndrome, females have a significantly higher risk of bleeding.

From now on, prevention is becoming the watchword.

And prevention must be accompanied by the concept of risk awareness and by the perception of one's health. Even in this context, the female sex shows important differences. Only 13 out of 100 women consider thrombosis diseases as an enemy to fight.

But thrombosis is the most serious threat to the quality and duration of their future life. By believing they are protected, women do less physical activity, do not control their level of cholesterol (40% of women over 55 have hypercholesterolemia), nor do they keep their blood pressure in check (only 50% of women over 45 have acceptable blood pressure values), they smoke and they do not want to quit, they are overweight, they have diabetes and are unaware of it.

Women are traditionally caregivers in our society, and as such they tend to underestimate their own thrombotic risk and neglect healthy lifestyles more than men. Not to mention the exposure to thrombotic risk factors – such as smoking – which is dangerously increasing in young women, consequences of which will only emerge in the next decades.

All this considered, it is necessary to commit ourselves on several fronts:

- i. *clinically*, we must apply tailored gender diagnosis and therapy schemes. We can imagine dedicated treatment settings or different modules according to gender, in order to recognize the peculiar elements of women and allow a more appropriate diagnosis and treatment.
- ii. *scientifically*, we must promote all efforts aimed at analyzing pathophysiological mechanisms from a gender perspective.
- iii. *institutionally*, we must organize programs suitable to reach the female population and modeled on gender.

Scientific societies, such as the *Italian Society for the Study of Haemostasis and Thrombosis*, will have to promote the culture of gender difference in the field of thrombosis: a culture that must train, in their own context, all younger generations of doctors (increasingly women), each of whom must act as a spokesperson of this modern reading of medicine.

Medicine should be *precise* not only in curing the patient, but also in how it is studied and taught.

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