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INVITED REVIEW ARTICLE AND CALL FOR ACTION
/ ПРЕГЛЕДНИ РАД ПО ПОЗИВУ И АКЦИОНИ ПЛАН

Women's health in Serbia – past, present, and future

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SUMMARY
Cardiovascular and reproductive health of women have been going hand in hand since the dawn of time, however, their links have been poorly studied and once the basis of their connections started to be established in late 20th century, it depended on local regional abilities and the level of progressive thinking to afford comprehensive women's care beyond the "bikini medicine". Further research identified different associations rendering more conditions sex-specific and launching therefore a slow, yet initial turn around in clinical trials' concept as the majority of global cardiovascular guidelines rely on the results of research conducted on a very modest percentage of women and even less on the women of color.
Currently, the concept of women's heart centers varies depending on the local demographics' guided needs, available logistics driven by budgeting and societal support of a broad-minded thinking environment, free of bias for everyone: from young adults questioning their gender identity, via women of reproductive age both struggling to conceive or keep working part time when healthy and line of work permits it during pregnancy, up to aging and the elderly.
Using "Investigate-Educate-Advocate-Legislate" as the four pillars of advancing cardiovascular care of women, we aimed to summarize standing of women's health in Serbia, present ongoing projects and propose actionable solutions for the future.
Keywords: COVID-19; sex differences; pregnancy; women in cardiology; discrimination; diversity; inclusion

INTRODUCTION

Women's health has traditionally been following the "bikini medicine" concept making women live in a delusion that breast cancer is their biggest enemy, when in fact it is heart disease that claims more lives than all cancers combined. Not only do we see these disparities in cardiovascular care in the United States, the beacon of modern democracy and global leader in technologically savvy healthcare, but worldwide also, where women's access to care and policies vary extensively rendering all implementation of innovative ways more challenging [1, 2]. The ongoing black maternal crisis in the United States, sadly, confirmed that, even in most affluent settings, black mothers suffer more than other women during childbirth and the "fourth and fifth trimester", so care offered to women has to become void of all bias [3, 4]. The bias-free care is taught in medical schools in different forms, however, sex-specific pathologies and racial disparities in a world whose landscape changes due to migrations of all kinds, demand our attention to the most vulnerable to meet the demand of the patients we tend to treat to the best of our knowledges [5]. The women's heart centers (WHC) and programs in Northern America have been established over the past three decades, however, their concept and structure remain a work in progress globally [6, 7].

DEMOGRAPHICS

The 2019 edition of the "Health Statistical Yearbook of the Republic of Serbia", published by the Institute of Public Health of Serbia, "Dr Milan Jovanović Batut", showed a 3.4% population decline from the 2011 census with a total of 3,561,503 women representing 51.3% of the population [8]. Same source reports that the women of childbearing age (15–49 years) make 21.7% of the population, while the aging and the elderly (over 65 years of age) make 20.7%. Steady decline in birth rates was noted over the past decade, while an additional 2.3% drop was registered when comparing January to July of 2020 and 2021, the two COVID-19 pandemic years [9].

SEX-SPECIFIC MORBIDITY AND MORTALITY IN SERBIA

At the primary healthcare level 5731 women over 15 years of age are assigned to one gynecologist, and in 2019, 43% of the visits represented first time ever visits and the prevailing reasons of visits were disease of the genitourinary tract (36%), pregnancy (6%) and tumors (4%) [8].
Currently, approximately half of the women of reproductive age struggle with some fertility issue from dysmenorrhea, polycystic ovary syndrome via infertility [8, 9] necessitating repeated assisted reproductive technology, known to increase cardiovascular risk long term [10, 11], besides a myriad of different acute complications of the procedure.

ACTIONABLE SOLUTIONS

Using the "Investigate-Educate-Advocate-Legislate" as the four pillars of advancing cardiovascular care of women [12], we aimed to summarize both the standing of women's reproductive and cardiovascular health Serbia and actionable solutions

Investigate

Reviewing currently available sex-specific research dedicated to women's health in Serbia, a pattern itself is absent and reported results come mainly from a moderate number of centers and research groups: whether from basic research standpoint [13–16], or clinical ones dedicated to women's cardiometabolic health [17–21], cardio-obstetrics [14, 22, 23, 24], peri-/menopause [25, 26, 27], different cardiovascular outcomes [28, 29], cancer [30, 31, 32] or mental health [33, 34] including the vulnerable and underserved populations [35].

Under-representation of women in recruitment practices and delayed invasive strategy in Serbia – *per local, in press and unpublished results of ongoing research projects* – are detrimental as anywhere else in the world, however day-to-day re-evaluation of our changes of clinical practices remain of critical importance. The COVID-19 pandemic opened an additional Pandora's box of suboptimal care for women [36] and women frontline healthcare workers in

Figure 1. The first "Dr Nanette Kass Wenger" International Conference on CVD in Women (Dec 2018): Program, snapshot of the article dedicated to the event in the Serbian Medical Chamber's journal "Glasnik" and pictures from the event

particular [36, 37, 38], here proposed Serbian model of a WHC offers also a possible solution to the problem.

Also, more comprehensive registry-oriented and epidemiological research of different population strata should ameliorate long term research and, consequently, improve outcomes for women in Serbia at all levels of care currently offered both in nationally budgeted institutions (primary, secondary and tertiary), as well as privately-owned ones (primary mainly, secondary in a small number of selected procedures).

Educate

The road to providing sex-specific education for medical students is seemingly a long and winding one, even in countries where budgeting is not an issue and multiple sources of funding are available. However, before the new generations of physicians reach the workforce, continuing medical education for sub-specialties beyond endocrinology, gynecology and obstetrics, and urology, is sorely needed together with implicit bias trainings along with recertification. Although dedicated WHC culturally, worldwide, are staffed with women, teaching male doctors that "women are not small men", but that their presentation of the same diseases can be different, as well as that with current migration rates, women of different ethnic [39] carry different burden of disease is of a growing importance.

Furthermore, educating women as patients of their symptoms and risks for different outcomes is equally important.

Advocate

Aiming to promote awareness and advance cardiovascular care of women in Serbia, the "Dr Nanette Kass Wenger" International Conference on Cardiovascular Disease in Women, was born as an idea to help bridge the gaps in available regional knowledges in the least judgmental way and help existing local teams build bonds.

The launch of the conference series started in 2018 supported by the current Presidents of the American Heart Association, Robert A. Harrington and the American College of Cardiology's Michael Valentine and both associations' CEOs, Nancy Brown and Cathy Gates. International speakers: Sandra Lewis, Annabelle Santos Volgman and Martha Gulati were welcomed by the ACC Chapter Governor of Serbia and Republika Srpska Professor Milan Nedeljković, Belgrade University's School of Medicine Dean Academician Nebojša Lalić, the Serbian Medical Chamber's Director Dr Milan Dinić and Academician Vladimir Kanjuh, president of the Serbian Academy's Science and Arts' Board for Cardiovascular Pathology who was one of the co-organizers (**Figure 1**). The newly confirmed Government, led by Ms Ana Brnabić, voiced its support to formation of a WHC under the roof of the leading country's healthcare institution, the University Clinical Center of Serbia, in an appeal sent out to needed medical and scientific entities by the Minister for Population Policy and Demographics Dr Slavica Đukić-Dejanović – a professor of Psychiatry and fervent advocate of equitable healthcare for the underserved populations, besides formal engagement with the national UN's Generation Equality initiative – who stressed the importance of timely management of healthcare issues of women and girls, and the first to confirm support was Academician Vladimir Kostić, President of the Serbian Academy of Sciences and Arts.

The second conference took place in December 2019 where besides sustained local and international support, the launch of the THEMIS foundation announced partnership with American Heart Association's GoRedForWomen for Serbia and additional support from the Royal Medical Board was offered, while Professor Wenger was hosted by the Crowned Princes Alexander and Katherine. During her working visit, Dr Wenger participated in multiple meetings with local opinion leaders in the field, addressed a reunion of national Nursing leadership and also met with the representative of the National's Gender Equity office that reaffirmed Government support in providing equitable care (Figure 2). The existing support of the Minister of Health, Associate Professor Dr Zlatibor Lončar, was confirmed once more and Dr Wenger toured the entire campus of the University Clinical Center of Serbia under heavy reconstruction at the time, while the idea of offering virtual telemedicine visits was emerging already.

As the world came to a standstill that delayed all care to all other patients with the emerging SARS-CoV2 pandemic in Europe in late 2019 and early 2020 in Serbia, the physical opening of the WHC planned for later that year suffered

Figure 2. The second "Dr Nanette Kass Wenger" International Conference on CVD in Women (Dec 2019):
(a) Professor Gordana Teofilovski-Parapid (Member of the Board for cardiovascular pathology of the Serbian Academy of Sciences and Arts), together with Academician Professor Dragan Micić and Professor Snežana Polovina hosting Professor Wenger at the Serbian Academy of Sciences and Arts
(b) Program of the event
(c) Professor Wenger with the Crown Princes' Alexander and Katherine and Ms Danijela Šegan, representative of the Gender equity office of the Serbian government (sitting) with Professor Gordana Teofilovski-Parapid, Dr Biljana Parapid and Professor Lukas Rasulić (standing) during the THEMIS Foundation launch and presentation of the GRFW program for Serbia

Figure 3. The third "Dr Nanette Kass Wenger" International Conference on CVD in Women (Dec 2020): Program and invite, while link of the event is available in the references

a delay, as well. However, the pilot telemedicine projects with the one of the oldest Belgrade's Primary Healthcare Physician's Office Centers, led by Dr Branka Lazić in collaboration with Dr Parapid, went as planned with minimal modifications for the benefit of the patients. So, the third conference amidst pandemic was held in December 2020 and hosted virtually [40] courtesy of the International Society of Telemedicine and eHealth, Working Group for Telecardiology President Dr Alexandru Mischie and Co-Chaired by ESC's Board Member Professor Dan Gaita, Professor Aleksandar Nešković as Cardiology Fellowship Program Director of the University of Belgrade, Faculty of Medicine and Dr Parapid as founder of the Conference series and WHC. Faculty of previous two conferences were joined by Dean Emeritus of the Georgetown University School of Medicine Professor S.Ray Mitchell that couldn't be hosted live for the Belgrade University's 100th birthday as planned and also by growing number of global allies of the "Dr Nanette Kass Wenger" WHC in Belgrade who together confirming the toll of the SARS-CoV2 pandemic and its influence on women's health on both sides of the frontline that was noted earlier [36] and that later reconfirmed in Serbia as well [37] only increased the need of such Center. Also, the 2020 conference gained another important global ally in the *Women As One* think tank whose team helped promote the event and committed to further partnership

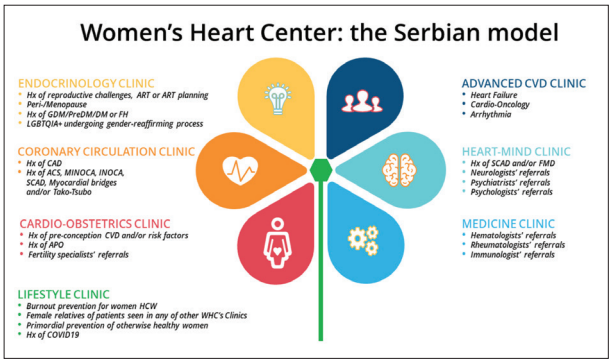

Figure 4. The "Dr Nanette Kass Wenger" Women's Heart Program and Women's Heart Center (Belgrade, Serbia) outline; Hx – history; GDM – gestational diabetes mellitus; DM – diabetes mellitus; FH – family hypercholesterolemia; LGBTQIA+ – lesbian, gay, bisexual, transgender, queer/questioning (one's sexual or gender identity), intersex, asexual/aromantic/agender and allies; CAD – coronary artery disease; ACS – acute coronary syndrome; MINOCA – myocardial infarction with non-obstructive coronary arteries; INOCA – ischemia and no obstructive coronary artery disease; SCAD – spontaneous coronary artery dissection; CVD – cardiovascular disease; APO – adverse pregnancy outcomes; HCW – healthcare workers; WHC – Women's Heart Center; FMD – fibromuscular dysplasia

in all equity-dedicated endeavors of the conference and "Dr Nanette Kass Wenger" WHC team (Figure 3).

The fourth conference planned for December 2021 should be a hybrid one: local limited seating event aiming to support the fully vaccinated COVID-19 pandemic healthcare workforce that is attempting to re-prioritize care of all patients beyond the SARS-CoV2 and virtual involvement of all interested, but mainly foreign faculty with travel restrictions.

As shown in Figure 4, we propose a model of a women's heart center most suiting the needs of a country on the road of financial recovery, encompassing multiple clinics:

Endocrinology clinic

Endocrinology and Reproductive Endocrinology play an important role in cardiovascular risk factors' management of women of different ages and life stages [41]: from safe peri-conception counselling of apparently healthy women, via assisted reproductive techniques (ART) management [42], menopause/hormone replacement therapy [43] and in sex-reaffirming process due to described risks for accelerated development of heart disease [44]. Existing teams of the Division of endocrinology, diabetes and metabolic disorders of the University Clinical Center of Serbia would continue its collaboration with the WHC's team.

Medicine Clinic

Hematologists', rheumatologists', immunologists' and geriatrics' referrals locally constitute the second largest group of women patients necessitating cardiologists' follow up at least during a short period of the treatment received in respective sub-specialty clinics or as hospitalized patients whose management is beyond the usual interdepartmental cardiology consult offered by the Division of Cardiology. Formalization of existing collaboration between research groups of other teaching hospitals of the University of Belgrade, Faculty of Medicine was delayed due to COVID-19 pandemic, but is on the way.

Coronary Circulation Clinic

It is well established [45] that non-obstructive coronary disease is more common in women, including myocardial infarction with no obstructed coronary arteries (MINOCA) [46], ischaemia without obstructed coronaries (INOCA) [47], spontaneous coronary artery dissection (SCAD) [48], fibromuscular dysplasia [49, 50], myocardial bridges [51, 52] and Takotsubo (stress-induced) cardiomyopathy [53]. Eventually, when hospitalized [54, 55], women receive far less invasive treatment strategies [56], guidelines directed medical therapy and physical rehabilitation post-discharge with almost immediate return to full activities of daily life in sharp contrast to male patients. Well known gaps in diagnostics [57, 58], care [59] and treatment short- and long-term, need to be bridged [60] and become the standard of care to avoid women being denied timely management for chest pain syndromes.

Heart-Mind Clinic

Diagnoses such as SCAD and FMD are under-diagnosed in Serbia, and when migraine and mental health issues as risk factors for heart disease are added, all remain under-studied and consequently, patients under-treated. The Clinic would offer an umbrella for nation-wide programs with pre-existing partners, as the relationship of these clinical entities remains subject of ongoing research worldwide [61–66].

Cardio-Obstetrics Clinic

Cardio-Obstetrics as a new field, aims to join Cardiologists and Gynecology & Obstetrics specialists in a collaborative care for women, particularly important where Maternal-Fetal Medicine specialists as such do not exist and where Neonatologists and Pediatricians help the best they can. The clinic is dedicated to women with pre-existing heart disease pre-conception and women who developed an adverse pregnancy outcome (APO) (post-partum cardiomyopathy, preeclampsia, gestational diabetes, premature delivery or infant of low birth weight) during a previous or ongoing pregnancy, but can accept other referrals (Figure 4), in particular from pediatricians aware of the risks children conceived via ART carry, once they reach adolescence [10, 11, 67] and harnessing power of the digital world should become an everyday tool for both children and young adults [68].

Advanced Cardiovascular Disease Clinic

The clinic should see patients of all age groups who present with refractory heart failure of various origins (including non-recovered peri-partum cardiomyopathy, ischemic cardiomyopathy, cancer patients *en lieu* of a separate Cardio-Oncology clinic (if regional needs demand it, an independent one should be opened, taking in consideration overall risks for cancer patient post-procedurally, in general [69]), arrhythmia patients and aging and elderly patients whose pharmacotherapy needs more caution [70–73].

Lifestyle Clinic

Lifestyle intervention for apparently healthy women is a growing global demand irrelevant of patients' age group [70, 74–77], while shift work – even before COVID-19 pandemic – has been confirmed as a risk factor for both cardiovascular disease and infertility [78], however, besides existing [79], specific regional guidance is lacking, while the stratifying cardiovascular risk landscape keeps evolving [80], especially in light of cardiovascular damage post-COVID [81]. The female workforce has additionally faced burnout during the ongoing SARS-CoV2 pandemic [36, 38, 79, 82, 83, 84] emphasizing a rising global need for the institution of a Diversity, Inclusion & Wellbeing Officers or Vice-Deans existing in North America, chiefly. With local governmental efforts and participation in #GenerationEquality initiative of the United Nations – both by former Minister Dr. Slavica Đukić-Dejanović

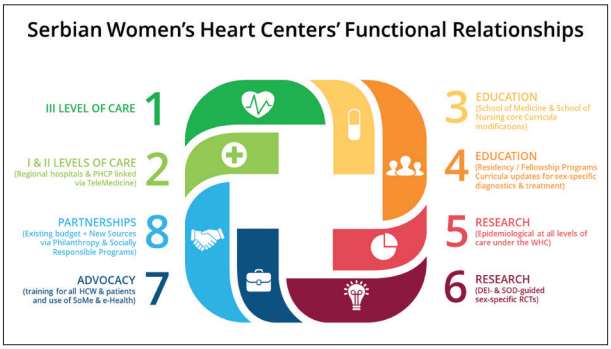

Figure 5. The "Dr Nanette Kass Wenger" Women's Heart Program and Women's Heart Center (Belgrade, Serbia) and its collaborative network outline; PHCP – primary healthcare physician; HCW – healthcare workers; SoMe – social media; WHC – Women's Heart Center; DEI – Diversity, Equity and Inclusion; SOD – social determinants of health; RCT – randomized clinical trial

and current Minister Ms. Zorana Mihajlović – only being amplified, while aforementioned position still not devised, the Lifestyle Clinic may provide women healthcare workers i.e., doctors, nurses and allied professions, a safe haven to seek medical and self-care advice in collaboration with the existing Safety at Work & Occupational Medicine Department of the University Clinical Center of Serbia.

As any WHC worldwide isn't and shouldn't be a solitary formation lacking interactions, for it can only perpetuate the existing stigma of a "female cult"-like self-sufficient formation, that it genuinely is not, aiming to summarize our proposal for its relationships, we have created the Figure 5.

In a country as Serbia, where allocation of national resources must be highly cost-effective, the WHC is advised to be based in a tertiary University hospital setting and represent an umbrella for all proposed activities.

Besides care offered at the Tertiary level – on both in hospital and face to face clinic-based manner – it should be linked to regional Secondary and Primary healthcare centers via telemedicine [85] that turned to be the "silver lining" of the SARS-CoV2 pandemic and its gaining of momentum should be compliant in forms acceptable for each country and local regulatory settings (including reimbursement options for services rendered).

From an educational perspective, WHC should help bridge the gaps in both core teaching curricula of Schools of Medicine and Nursing, as well as residency and fellowship programs, raising awareness in new generations of healthcare providers on sex-specific diagnostics and therapy beyond the traditional concept.

Research following clinical care provided to women in Primary, Secondary and Tertiary healthcare levels should be adopted. Epidemiological research and registries conducted on all three levels of care, while randomized control clinical trials guided by racial and social determinants of health criteria should be designed and conducted at the tertiary level and offered to all interested to participate both nationally and internationally.

Advocacy as a tool for both patients and doctors has been growing worldwide and as such a WHC should offer advocacy tools tailored to needs of any patient within their reach: from in-person guidance by MDs and allied professions on site (Research Nurse are not widespread globally and may take another decade to be utilized more widely), *via* use of simple brochures/pamphlets/themed pad notes or more epidemiological measures-friendly downloading from a website or an app.

Legislate

Legislation pertaining to new modalities of promotion of healthcare and healthy lifestyle is still somewhat vague, as the healthcare providing part of the private sector has flourished immensely over the past two decades and advertising depends mainly on the core ethical values of the owner. Fortunately, among the oldest ones, "VIZIM" primary healthcare physicians' office as the oldest private system of the kind is a good example of appropriate health-related messages both on their walls nation-wide and on their website and both in caring for patients and for their employees.

Currently, global legislative efforts in providing adequate and timely healthcare for women are still meek [2, 86] and although Serbia's laws provides generous paid maternity and paternity leaves, cover ART for couples struggling with infertility and the entire country's population enjoys universal coverage employed or not, access to care due to cultural habits and logistical management, render the fine line between health and social issues, rather blurry, hence hard to help advance healthcare where needed the most.

In Serbia nowadays, the role of progressive, bias-free and equity-promoting experts' groups, East-West Bridge [87] in particular, has been shown effective in working with all stakeholders aiming to implement global initiatives that can also help re-establish Serbia as a leader in region. A country that never knew slavery even in the XIV century (per Dušan's Code, Constitution written by Serbia's mediaval Emperor Stefan Dušan in 1349) and formally banned all feudal relationships as such in the XIX century (the Candlemas Constitution of 1835), should at least live up to the expectations of its broad-minded ancestors who granted freedom to any slave stepping on medieval Serbia's soil. In that regard, the core team of the "Dr Nanette Kass Wenger" WHC takes special pride in the fact that the initiative has gained multi-partisan support despite all societal complexities where #HeForShe advocacy [88, 89, 90] is usually encountered where you least expect it.

CONCLUSION

Growing popularity of women's cardiovascular and reproductive health, created a flood of reports on outcomes of women derived from protocols designed with other aims, but targeted sex-specific research that endorses substantial changes in local practices and legislation is still pending – not only in Serbia, but worldwide, which emphasizes need for equitable care for all. The concept of WHC's remains sorely needed wherever healthcare provided for women is in any way unsatisfactory, while the proposed Serbian model is adaptable to local, country-specific needs

and should be tailored accordingly. As the "Dr Nanette Kass Wenger" WHC awaits its opening in function of the COVID-19 pandemic that keeps derailing all endeavors, despite stellar home team ones, as long as there remains a will a way shall be made for advancing healthcare of the most fragile.

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САЖЕТАК

Кардиоваскуларно и репродуктивно здравље жена су нераздвојни кроз историју. Међутим, њихова повезаност је била мало проучавана и тек када су основи њихових веза утврђени крајем 20. века, пружање свеобухватног лечења и неге жена даље од „бикини медицине" зависило је од регионалних могућности и степена прогресивног размишљања. Даља истраживања су идентификовала различите удружености које су различита медицинска стања учинила полноспецифичним, чиме је започет спор, али ипак заокрет у концепцији клиничких студија, што је од посебног значаја имајући у виду да се већина светских кардиоваскуларних препорука базира на резултатима истраживања спроведеним на јако мало броју жена и, још мање процентуално, на женама различитих етничких група.

Тренутно, концепт центара за женско срце зависи од локалних демографских потреба, доступне логистике условљене како финансијском, тако и друштвеном подршком окружења лишеног предрасуда према целом спектруму могућих пацијенткиња: од младих који преиспитују свој родни идентитет, преко жена репродуктивног узраста које покушавају да реализују своју жељу за потомством или су пак здраве, али желе током трудноће да наставе да раде скраћено радно време ако то природа њиховог посла дозвољава, до старијих и оних позног животног доба.

Користећи принцип „Истражите-Образујте-Заступајте-Озаконите" као четири стуба напретка кардиоваскуларног лечења и неге жена, настојали смо да пружимо пресек здравственог стања жена у Србији, да представимо текуће пројекте и пружимо предлоге за даља, одржива и изводљива решења за будућност.

Кључне речи: ковид 19; сексуалне разлике; трудноћа; жене у кардиологији; дискриминација; инклузија