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Gender and Sex Conscious Medicine and the future direction of health care: An invited scientific review by the European Board and College of Obstetrics and Gynaecology (EBCOG)

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ABSTRACT

Gender- and Sex-Conscious Medicine (GSCM) represents a critical and emerging paradigm in clinical practice and biomedical research. Biological sex is defined by chromosomal complement, gonadal structure, reproductive anatomy and circulating sex steroid profiles— In contrast, gender identity—the subjective experience of gender may encompass masculine, feminine, nonbinary, or other identities and is primarily self – defined and a sociocultural construct with considerable variability.

Both sex (biological attributes) and gender (psychosocial context) exert profound effects on the physiology and pathophysiology of organ systems, influencing disease susceptibility, clinical presentation, progression, and outcomes. These factors also modulate pharmacokinetics and pharmacodynamics, such that individuals of different sexes and genders may respond differently to the same diagnostic and therapeutic interventions. Despite this, the majority of preclinical studies and clinical trials historically enrolled predominantly male subjects, resulting in an evidence base that is inadequately sex- and gender-disaggregated.

Consequently, sex- and gender-related disparities in diagnosis, treatment response, adverse events, and health outcomes persist—an inequity that is both an ethical concern and a substantial socioeconomic burden. Estimates suggest that removing this "health gap" could add at least US$1 trillion annually to global GDP by 2040.

In this review, we present physiological, pathophysiological, and clinical examples that illustrate the necessity of integrating sex- and gender-conscious approaches into research, teaching, guideline development, and clinical care. Although we acknowledge the continuum of gender identities, for analytic clarity this review uses binary male and female classifications. The clinical care and health concerns of sexual and gender minorities (LGBTQ +) constitute a distinct field—sexual and gender minority health. A comprehensive treatment of that topic is beyond the scope of the present review and would require a separate focused review.

Background

Gender- and Sex-Conscious Medicine (GSCM), also referred to as "Gender Medicine," focusses on physiological and pathophysiological differences associated with an individual's biological sex and/or gender identity [1–3]. Biological sex, generally categorized as male or female, is determined by genetic factors and is typically considered binary. In contrast, gender identity—the subjective experience of gender—may encompass masculine, feminine, nonbinary, or other identities and is primarily self – defined and a sociocultural construct with considerable variability. Both sex and gender exert significant impact on health status, disease susceptibility, and clinical outcomes.

Functional differences between men and women manifest across almost every bodily system. These distinctions, though occasionally subtle, ca be significant and can influence health and disease outcomes. The prevalence, incidence, symptoms, and treatment efficacy for the

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same conditions often differ between the sexes, as can the severity of side effects to medications [4]. Moreover, hormonal regulation vary between the sexes and across the lifespan, beginning during fetal development and continuing throughout life. Females undergo cyclical hormonal changes associated with menstrual cycles, reproductive processes such as pregnancy and lactation, and menopause—the latter with a male equivalent, albeit with a substantially lower prevalence. Numerous physical and mental health conditions are affected by the menstrual phase [5]; for instance, wound healing may be more optimal during the follicular phase [6].

Gender perspective: Bias and stereotypes in women's health

Gender is both an individual's self-identified identity and a societal construct shaped by sociocultural factors, wherein certain roles are assigned according to societal norms. These gender constructs give rise to stereotypes concerning physical appearance and behavioral expectations related to masculinity and femininity within a specific society.

Gender roles and health risks

The assignment of gender roles may act as a risk factor for health. Schistosomiasis illustrates the impact of gender roles on health outcomes. In endemic regions of sub-Saharan Africa, women are often more exposed to Schistosoma-contaminated water due to culturally defined duties such as fetching water, laundering, and agricultural tasks, which increases their risk of helminthic infections and results in higher prevalence of schistosomiasis rates compared to men. Alternatively, in areas where men are primarily engaged in water-related occupations such as fishing, the incidence among men is higher [7].

Cultural norms or stereotypes can be so pervasive that they prevent lifesaving actions for women, as demonstrated by a report of healthcare workers who refused to touch and assist women trapped in rubble following a recent earthquake in Afghanistan [8].

Gender bias in tool and equipment design

Gender bias is also evident in the design of tools and equipment primarily intended for the male population, including PCR mannequins, spacesuits, car crash dummies, and smartphones [9]. A survey of female surgeons in New Zealand, Australia, Canada, and the USA (n = 480) found that 89 % faced difficulties manipulating surgical instruments due to size. Additionally, 71 % reported challenges related to the grip strength required for instrument usage. The survey identified 112 distinct instruments associated with these difficulties. Impaired usability can increase procedural complexity, extend operative times, and potentially raise the risk of iatrogenic complications. Notably, 6 % of female surgeons attributed surgical complications to difficulties with equipment [10]. These ergonomic issues may furthermore predispose female surgeons to occupational musculoskeletal injuries [11].

Gender disparities in healthcare access

Gender disparities in healthcare access are well-documented and frequently reported. Daher et al. [9] conducted one of the largest telephone-based surveys to date in order to analyze data from over 1,700,300 individuals with atherosclerotic cardiovascular disease in the US. The study revealed that women more often faced delays in healthcare access, appointment scheduling challenges due to costs, and higher rates of cost-related medication non-adherence. Despite having greater healthcare coverage, women underwent fewer diagnostic procedures and exhibited worse clinical outcomes compared to men [12].

Gender biased treatment

Approximately 70 million surgical procedures occur annually in the United States, with 75 % to 80 % of patients experiencing moderate to severe postoperative pain. The odds ratio for severe postoperative pain in women compared to men is 1.16; however, men tend to receive more analgesic medication than women [13].

Pain management decisions are significantly influenced by gender bias. Guzikevits et al. [14] analyzed 21,851 discharge summaries from emergency departments in the USA and Israel, finding that men were consistently more likely to receive analgesics across all pain scores and age groups compared to women.

Naamany et al. [15] reported that in a study from Tel Aviv of 824 patients admitted for renal colic, women waited longer for treatment and received fewer analgesics and opioids than men.

Lee et al. conducted a stepped-wedge, cluster-randomized controlled trial involving 48,282 patients in Scotland presenting with acute coronary syndrome (ACS). By using sex-specific thresholds for troponin measurement (16 ng/L for women and 34 ng/L for men), they identified a fivefold increase in myocardial injury diagnoses among women. Despite this, fewer women received dual antiplatelet therapy or revascularization procedures compared to men.

Gender-biased perception and treatment of pain in women

In a study where laypersons evaluated video clips of female and male patients with chronic shoulder pain, female patients' pain was often underestimated compared to male patients. Moreover. observers more frequently recommended psychotherapy for female patients and analgesics for male patients [17].

The biological perspective

Since the inception of the FDA over a century ago and until the year 2000, around 1,000 distinct New Molecular Entities (NMEs) received approval. An additional 800 NMEs were approved subsequently and until 2020 [18,19]. Remarkably, until the year 2000, there were no mandatory requirements for the inclusion of women in clinical trials, leading to a scenario where approximately two-thirds of approved drugs remain untested in the female population. Consequently, data obtained from male-centred research has become the "gold standard" upon which pharmacological therapies for females have been based. This practice exposes women to potentially inaccurate dosing regimens, including overdosing, with the occurrence of severe adverse drug reactions (ADRs) being almost twice as prevalent in women compared to men [20].

A fundamental challenge in pharmacotherapy is the presence of sex-based differences in drug pharmacokinetics and pharmacodynamics [21]. Females differ from males not only at the genetic and molecular levels but also in anthropometric parameters, such as mean stature, body mass, body surface and the relative distribution of tissue compartments, including adipose tissue, lean muscle mass and total body water.

These physiological variations significantly impact pharmacokinetic processes by altering drug distribution within tissue compartments, as well as affecting hepatic metabolism and renal clearance [22]. As a result, pharmacokinetic parameters—such as volume of distribution (Vd), clearance (Cl), and half-life—may differ markedly between sexes. For instance, drugs such as ethanol (smaller Vd in women), diazepam (larger Vd in women) and propranolol (slower clearing in women) are subject to sex-specific differences in biotransformation, necessitating adjusted dosing regimens. Moreover, functional differences of body system between the sexes also affect pharmacokinetics. For example, the majorities of pharmaceuticals are administered orally and undergo absorption in the gastrointestinal tract. Notably, gastrointestinal transit time is significantly prolonged in females, impacting not merely the digestion of food but also the absorption of medications [23].

Despite considerable advocacy and reform efforts by policy makers and the medical community, the "medication disparity" remains insufficiently resolved and in most published biomedical research women are still underrepresented.

A pivotal positive development in addressing this issue was the 2013 FDA mandate recommending a 50 % dose reduction of zolpidem for women, independent of body weight. Subsequently, in 2014, similar guidelines were issued for flurazepam, another hypnotic agent.

Metabolism

The liver is the primary organ responsible for drug biotransformation. In vitro data indicate that female hepatocytes demonstrate increased susceptibility to hepatotoxicity from medications such as diclofenac, chlorpromazine, and paracetamol compared to male hepatocytes. The initial phase of hepatic biotransformation (phase I oxidation, reduction, hydrolysis, or hydroxylation) is approximately 50 % more efficient in females [24], as exemplified by drugs like haloperidol and erythromycin. Conversely, the subsequent phase of hepatic metabolism (phase II conjugation processes), which also occurs within the liver, tends to be more active in males. For example, drugs such as paracetamol and oxazepam are more effectively metabolized during this phase in males .

Moreover, sex-related differences in renal clearance are evident, with renal function approximately 10 % reduced in females relative to males [25]. Examples include drugs such as digoxin and gabapentin.

GI tract

Functional gastrointestinal disorders are more prevalent in women, with irritable bowel syndrome (IBS) occurring approximately four times more frequently [26]. Additionally, some pharmacological treatments for IBS demonstrate sex-specific efficacy [27]. The composition of digestive secretions also varies by sex; for example, levels of alcohol dehydrogenase are about fivefold higher in men than in women. As a result, women experience greater intoxication from equal alcohol doses, and mortality rates related to heavy alcohol consumption are notably higher among women [28].

Various parts of the gastrointestinal system differ in size, composition of fluids, and enzymes (Table 1).

In females, gallbladder motility shows reduced contractile frequency, leading to delayed bile excretion and a different composition of bile compared to males.

The incidence of cholelithiasis is fourfold higher in women than in men, particularly during periods of elevated estrogen levels, such as pregnancy.

Duodenal ulcers display a twofold higher prevalence in males; however, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are approximately 1.5 times more common in females.

The gut microbiota composition is highly individualized and exhibits sexual dimorphism. This microbial flora plays a critical role in the development, modulation, and regulation of the host immune system [30]. Dysbiosis can disrupt immune homeostasis, contributing to the pathogenesis of autoimmune, inflammatory, and hypersensitivity conditions—all of which show increased prevalence within Western populations and are more prominent among women.

There are strong indications for bidirectional interactions among sex hormones, immune regulation, and microbiota composition. It has been demonstrated in mice that the microbiota can modulate endocrine function, exemplified by increased testosterone levels [31]. Furthermore, testosterone appears to exert immunosuppressive effects.

Sex differences are also evident in colorectal pathologies; for instance, neoplastic polyps and colorectal carcinoma are more frequently diagnosed in males. Females who smoke have a higher risk of developing colorectal cancer compared to male smokers. Fecal occult blood testing (FOBT) for early detection of colorectal neoplasms is less sensitive in women, possibly owing to slower colonic transit times [32]. Prolonged retention of blood within the gastrointestinal lumen may result in increased erythrocyte oxygenation, thereby impairing detection sensitivity of FOBT assays.

Table 1
Some sex differences in various parts of the intestines. M = Male, F = Female Adapted after Freire et al [29].

Stomach	pH	F > M
	Emptying Time	F > M
	Gluthatione Activity	F > M
	Fluid Volume	M > F
	Alcohol Dehydrogenase	M > F
Duodenum	Gluthatione Activity	F > M
	Bicarbonate	F > M
Small Intestine	Motility	F > M
	Length	M > F
Transverse Colon	Length	F > M
Colon	Transit Time	F > M
	Gluthatione Activity	M > F

Brain

As in all cells, the chromosomal basis in brain cells differs genetically between the sexes. Furthermore, during fetal neurodevelopment, the developing male and female brains are exposed to distinctly different hormonal milieus. These differences manifest in variations in brain volume, cytoarchitectural organization, synaptic connectivity, and the functional properties of specific cell groups [33]. Postnatal brain maturation continues under the influence of environmental factors, gender, societal influences, and cultural norms, further contributing to sex-specific cognitive, behavioral, and functional profiles [34,35].

Key neuroendocrine structures such as the hypothalamus regulate essential physiological processes, including alimentation, sleep-wake cycles, and gonadal functions. In females, gonadotropic hormonal secretion is cyclic, underpinning the menstrual cycle, whereas in males, gonadotropin release remains relatively constant, supporting continuous spermatogenesis. Morphologically comparable hypothalamic regions may appear similar, and circulating hormone may be qualitatively identical but quantitatively very different with different secretion patterns leading to significant functional distinctions in reproductive endocrine regulation and target organ responses.

Cardio-vascular system

Cardiovascular pathology can present with sex-specific clinical symptoms. While the classic symptomatology of myocardial infarction is widely recognized, approximately 20 % of females experiencing acute coronary syndromes present with "atypical" symptoms, such as abdominal, epigastric or chest discomfort with insidious onset, and pain radiating to the neck and chin rather than the shoulder and left arm. Failure to recognize these manifestations as indicative of myocardial ischemia may result in diagnostic delays, both by patients and healthcare providers, leading to underdiagnosis or delayed intervention, with the potential for increased mortality [36]. This disparity may be attributable to gender bias within medical practice and healthcare systems.

Pain

To receive appropriate and unbiased treatment for pain is a basic human right (Table 2) and must be founded on an evidence based definition of pain (Table 3).

Yet, there is still a gender bias, based on stereotypes which results in underestimation of pain in women with resulting undertreatment [17,37].

Pain perception and response demonstrate clinically significant sex differences mediated by interacting biological, psychological, and sociocultural determinants, with parallel effects on analgesic efficacy and adverse-effect profiles. Biologic contributors include sex hormone–dependent modulation of nociceptive processing, differences in

Table 2
Declaration of Montreal 2010 by the International Association for the Study of Pain (Abbreviated) [38].

Human rights that must be recognized throughout the world:
1. The right of all people to have access to pain management without discrimination on the basis of age, sex, gender…….,
2. The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals…..
3. The obligation of all health care professionals in a treatment relationship with a patient…. to offer to a patient in pain [appropriate] management… Failure to offer such management is a breach of the patient's human rights.

Table 3
Revised definition of pain by the International Association for the Study of Pain, (ISAP) 2020 (abbreviated) [39]:

1. Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage
2. Pain is always a personal experience, influenced by biological, psychological and social factors
3. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
4. Pain is usually adaptive, may have adverse effects on function and social and psychological well-being.

peripheral and central sensitization, and sex-specific variations in pharmacokinetics and pharmacodynamics. Clinically, females often present with lower nociceptive thresholds, distinct pain phenotypes (including greater prevalence of diffuse and centralized pain syndromes), and amplified affective–motivational responses to pain (increased pain-related anxiety and catastrophizing). Females also exhibit different pain expression and reporting patterns compared with males.

Psychosocial and gender-related factors—such as socially mediated expectations about pain expression and clinician interpretation of symptoms—further modulate outcomes. These dynamics contribute to documented disparities in analgesic management: postoperative and acute pain studies report consistent undertreatment among women, racial/ethnic minorities, and individuals of lower socioeconomic status [37]. Recognition of sex- and gender-based differences in pain biology, communication, and health-care bias is therefore essential for individualized assessment and equitable analgesic planning.

Chronic pain is defined clinically as pain persisting for $\geq$ 3 months and is associated with significant functional limitation and reduced health-related quality of life. Epidemiologic data indicate a higher burden of chronic pain syndromes in females versus males [40] (e.g., migraine disorders: ~17 % of females vs ~ 6 % of males; fibromyalgia prevalence approximately ninefold greater in females). Investigations in mice implicate sexually dimorphic immune mechanisms in chronic pain pathogenesis: microglia-dependent pathways predominate in male nociceptive modulation, whereas adaptive immune cells (notably T lymphocytes) have been shown to contribute critically to pain processing in females [41]. By contrast to acute pain, which serves an adaptive, protective role and is critical for survival, chronic pain is not protective and represents one of the most frequent reasons for presentation to primary care and emergency departments. Despite its high prevalence and morbidity, chronic pain remains largely without objective biomarkers or physiologic diagnostic tests, necessitating reliance on patient-reported outcome measures (e.g., numeric rating scale, visual analog scale, pain inventories) and clinician observation of pain behaviors (facial expression, posture, activity). These assessment limitations are particularly problematic in pediatric and geriatric populations and in patients with language barriers or cognitive impairment.

Precision medicine (PM) versus Gender and Sex Conscious Medicine (GSCM)

Accessibility and affordability

GSCM and PM are often contrasted with under the misconception that the former merely serves as a stepping stone towards the latter. This is a misunderstanding. The impetus for developing both PM and GSCM arises from the observation that patients diagnosed with identical medical conditions and undergoing the same therapeutic regimens can exhibit markedly divergent responses. This variability is attributed to influences such as sex, gender, and differences in genomics, epigenomics, transcriptomics, proteomics, and metabolomics. Consequently, there is a significant shift from the "one-size-fits-all" paradigm. However, the focal points diverge; GSCM addresses the variables of sex and gender, while PM focuses on the 'omics' factors, utilizing big data analytics and cellular and molecular biology to develop more individualized therapeutic strategies tailored to the unique profiles of patients or patient cohorts. This approach presents challenges such as high costs, the need for sophisticated equipment and managing extensive databases containing sensitive genomic data, making genomic privacy a critical issue. Ideally, PM advancements in healthcare would allow each patient to receive cost-effective treatment tailored to their genomic and epigenomic profiles, with therapeutic interventions, whether medical devices, pharmacotherapy, or procedures, precisely based on these molecular datasets and administered appropriately. In such scenarios, patient demographics like sex, age, ethnicity, and medical history would be less important for treatment decisions and render GSCM obsolete. However, in real world conditions, even with the availability of advanced PM technologies, the accessibility and affordability of these innovations remain pressing challenges.

The global vaccination campaign during the COVID-19 pandemic illustrates disparities in healthcare access and affordability. While vaccination rates in high- and upper-middle-income countries exceed 82 %, only about 26 % of populations in low-income countries have received at least one vaccine dose [42]. Over 80 % of the world's population resides in low- and middle-income countries, where many essential medications remain inaccessible. For instance, antibiotics have been available for almost hundred years, but while a complete course of antibiotics in Malawi costs under $10, this equates to a week's income for many residents [43]. Despite the availability of insulin since 1921, around 50 % of patients with insulin-dependent diabetes still lack access to this critical therapy [44]. Currently, 19 countries have introduced malaria vaccines recommended by the WHO. Artemisinin-based combination therapies, the standard malaria treatment for over fifty years, have an annual cost of under $3 per individual, yet over 600,000 people, including a child dying every two minutes, succumb to malaria annually—highlighting the persistent mortality caused by this preventable disease [45].

These disparities in accessibility and affordability of essential medical treatments raise profound ethical concerns by underscoring systemic inequities that impede equitable healthcare delivery, especially where advanced technologies like precision medicine, advanced cancer therapies, and other sophisticated treatments are concerned. While PM represents one of the most significant technological advancement in contemporary medicine, it cannot supplant the clinician-patient relationship, medical professionalism, or clinical judgment. Traditional clinical assessments—encompassing simple demographics such as age, body size, race, sex, and gender—will remain crucial in clinical decision-

making. GSCM, not reliant on advanced technologies, will continue to play a vital role in enhancing the quality of medical care for many years to come.

The cost of gender/sex disparity

Over the past two centuries, global life expectancy has more than doubled, increasing from approximately 29 years in 1800 to around 71 years in 2015 [46] with a wide discrepancy between developed and developing countries. Although women have, on average generally a longer "lifespan" than men, they tend to spend more years in poor health and experience a higher morbidity—what is referred to as the "health span". On average, women spend about nine years in poor health, with this difference being measured in disability-adjusted life years (DALYs). Moreover, there is a clear correlation between the socioeconomic status of an individual and her or his access to health care services. As low socioeconomic strata include a disproportionally high prevalence of women, the health care disadvantage for women is obvious [47].

Addressing women's health span would not only improve their quality of life but would have an enormous impact on society in general, positively affecting healthy ageing and improve the health of future generations.

A very small proportion of women's health burden is related to female specific diseases and sexual and reproductive health but the majority of health conditions leading to morbidity have a higher prevalence or different symptomatology in women [48].

Westergaard et al. [49] reported, based on nationwide systematic research that diagnosis of over the majority of assessed diseases was typically delayed in women as compared to men. For example, cancer diagnosis and diabetes diagnoses occurred 2.5 years and 4.5 later for women than for men, respectively.

Addressing sex-based disparities and their intersections with health outcomes and gender equity, as outlined in the United Nations Sustainable Development Goals, is a vital yet underrecognized strategy for strengthening social protection systems and advancing toward universal health coverage [50].

Investing more in women's health increase their quality of life which is not only a moral duty but will also lead to greater participation in the workforce with resulting economic independence. The potential economic benefits for society as a result clearly surpass the costs of such investments by far, with a global ratio of approximately $3 in benefits for every $1 spent. This investment estimates include the costs for development and implementation of cost-effective strategies and intervention in different settings aimed to close the women's health gap.The highest return on investment is projected in higher-income countries in which much of the requested infrastructure is already in place and where roughly $3.50 can be gained for every dollar invested. In low-income countries, additional investment may be required to create the necessary health infrastructure needed to deliver affordable, quality healthcare and to create more economic opportunities for women. Nonetheless, analyses suggest that the overall benefits in these regions would still outweigh the costs, at an approximate rate of $2 in reurn for every dollar spent [51].

Overall, closing the health gap between women and men may improve health and quality of life for 3.9 billion women, adding more than 500 days over a woman's lifetime thereby opening the workforce market for them. This would potentially add at least one trillion US Dollar annually to the GDP by 2040 [51].

Inequalities in the provision of sexual and reproductive health in Europe

Unfortunately, there is a huge unmet need for the provision of essential sexual and reproductive health care services globally due to multiple factors such as financial, political and restrictive practices. These are well documented by various publications by the WHO reporting a higher incidence of untimed pregnancies, associated with maternal deaths due to septic abortion, obstetric hemorrhage, puerperal sepsis, hypertensive disorders and mental illness. All these deaths are avoidable in 21st century if only the society and the healthcare planners start recognizing that "life of every woman is worth saving". The European Board and College of Obstetrics and Gynaecologists (EBCOG) as part of its advocacy campaign, has been working very closely with the United Nations Population Fund Eastern Europe and Central Asia region (UNFPA-EECA Region) to raise awareness about these unmet needs and inequalities for the past ten years [52,53].

Women's right groups and sexual and health care providers globally were stunned following the announcement of United States Supreme Court's ruling on restricting access to safe abortion care. EBCOG issued its position statement expressing its concern on the wider implications of this ruling for women's health not only in the United States but globally as well. Our concern about this aspect of women' sexual and reproductive rights has turned out to be very genuine with the recent changes in US government aid policy globally for the under resourced countries which unfortunately would hit the women and their families the hardest in these countries [54].

EBCOG has long recognised that inequalities in the provision of women's health care services even persist widely within Europe. These disparities have further deepened due to global geo political changes. The Standing Committee of standards of care and position statements have published research papers describing inequalities in access to essential reproductive health services within Europe even specifically access to antenatal care and contraception [55–57].

Armed conflicts within Europe and elsewhere have clearly shown that women and children who bear the major brunt of these conflicts not only within the theatre of conflict, but are forced to emigrate, have poor access to health, are at increased vulnerability to sexual exploitation and face much higher morbidity and mortality [58].

Now recognizing these inequalities, we need to define solutions:

Ensuring equitable access to healthcare is vital, especially in addressing significant global health disparities. Investment in women's health, through research, data, and targeted healthcare strategies, is not only a moral obligation but also an economic opportunity, with potential returns far exceeding the initial investments. Addressing the women's health gap involves improving research, access to gender-specific treatments, and supporting innovations and policy changes to support women's health effectively.

EBCOG is committed to work closely with international partners (FIGO, WHO and UNFPA) national societies at the country level, patient interest groups, and national and global health care policy makers and healthcare providers to define and implement solutions to address inequalities in healthcare for women and their children as envisaged in the United Nations Sustainable Development Goal [59].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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