Clinical applications

Women’s health: an introduction

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Women represent more than half the world’s population, have a longer life expectancy than men and consume more healthcare resources. In the USA, for example, women account for two-thirds of the surgical procedures and office visits and approximately 65% of national annual medical bills. Women also make up to 90% of the healthcare decisions for their families [1]. Nevertheless, until relatively recently, the concept of women’s health was primarily related to conditions that occur exclusively or predominantly in women, such as pregnancy, gynecological problems or breast cancer.

However, in 1999, the Society for Women’s Health Research [2] was instrumental in obtaining authorization and funding for a major study conducted by the Institute of Medicine (IOM) of the US National Academy of Sciences. This study was aimed at assessing the state of knowledge on sex-based biology and gender-based medicine, in order to make recommendations for an appropriate agenda for research into women’s health.

In April 2001, the IOM released a report on the study entitled Exploring the Biological Contributions to Human Health: Does Sex Matter? [3]. This was almost certainly the first significant review of the status of sex and gender differences in biomedical research to be published by an independent research organization. It stressed the need for better understanding of the importance of sex differences and how that

Heart Disease – Heart disease kills 500,000 American women each year – over 50,000 more women than men – and strikes women, on average, 10 years later than men. Women are more likely than men to have a second heart attack within a year of the first one.

Depression – Women are two-to-three times more likely than men to suffer from depression, in part because women’s brains make less of the hormone serotonin.

Osteoporosis – Women comprise 80 percent of the population suffering from osteoporosis, which is attributable to a higher rate of lost bone mass.

Smoking – Smoking has a more negative effect on cardiovascular health in women than men. Women are also less successful quitting smoking and have more severe withdrawal symptoms.

STDs – Women are two times more likely than men to contract a sexually transmitted disease, and more likely to experience significant drops in body weight, which can lead to wasting syndrome.

Anesthesia – Women tend to wake up from anesthesia more quickly than men – an average of seven minutes for women and 11 minutes for men.

Drug reactions – Even common drugs like antihistamines and antibiotic drugs can cause different reactions and side effects in women and men.

Autoimmune Disease – Three out of four people suffering from autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and lupus, are women.

Alcohol – Women produce less of the gastric enzyme that breaks down ethanol in the stomach. Therefore, after consuming the same amount of alcohol, women have higher blood alcohol content than men, even allowing for size differences.

Pain – Some pain medications (known as kappa-opiates) are far more effective in relieving pain in women than in men.

Gender differences important to health and disease exist at all levels in the body.

Table 1. Women and men: Ten differences that make a difference. Information by courtesy of the Society for Women’s Health Research, Washington, DC. www.womenshealthresearch.org
knowledge can be applied in medical practice. The report found that gender differences important to health and human disease occur in the womb and throughout the life span. They exist at the system, organ, tissue, cellular, and sub-cellular levels, affecting behavior, perception, general health and response to pharmaceuticals. In addition to the conditions specifically associated with women, the report pinpointed ten significant gender differences (Table 1).

The Women’s Health Care Cycle

Philips Healthcare recognized the benefits of a program focused specifically on women’s health, and established the Women’s Health Care Cycle program in 2007 with the objective of improving the health and quality of women’s lives worldwide. The care cycle encompasses the whole continuum of care from prevention, screening and diagnosis to treatment, management and surveillance (Figure 1).

Following the patient and the caregivers through every step of the care cycle not only gives a valuable insight into their needs, but also helps the industry to create solutions that will best address their needs. Following this approach provides a greater understanding of the clinical pathways for a particular disease in a particular geographical region, and can show where improvements need to be made.

Today, Philips Healthcare’s Women’s Health program focuses on three key areas of disease in women: breast cancer, heart disease, and gynecology. All three represent important global health issues.

Figure 1. The Women’s Health Care Cycle

Figure 2. Merging of diagnosis and treatment.

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Breast cancer is the most frequently diagnosed cancer in women worldwide. Because breast cancer presents in many different ways, a multimodality approach is often required for a comprehensive diagnosis. Philips recognizes this need and offers a portfolio of imaging systems and healthcare informatics solutions. The company is also actively involved in programs that will add value in other points of the breast cancer care cycle.

Heart disease is the greatest cause of death in women worldwide. The World Health Organization reports that more than 3.4 million women die from heart disease every year [4]. Coronary artery disease in women is often clinically different than in men, and women are more likely to present with atypical symptoms. Philips offers a complete portfolio of solutions to support diagnosis in women, and works closely with leading healthcare organizations to provide solutions that address women’s unique cardiovascular needs and help to improve early detection.

Gynecological conditions include benign conditions such as abnormal uterine bleeding, pelvic floor disorders, and infertility, as well as cancer of the cervix, uterus, and ovaries. There were more than one million new cases of gynecologic cancers worldwide in 2008 [4]. Here, novel technologies for imaging can help to provide earlier diagnosis, at a stage when treatment offers a better chance of success, and novel treatment techniques offer less invasive therapy.

One common trend in all these areas is a blurring of the distinction between diagnosis and treatment (Figure 2).

**Breast cancer**

Globally, breast cancer is the most frequently diagnosed cancer in women, accounting for an estimated 1.3 million new cancer cases and 465,000 deaths in 2007 [2]. It is the leading cause of cancer death among women worldwide. The five-year survival from breast cancer is about 89% in the United States, 76% in Europe, and much lower in developing countries [4]. The favorable survival statistics in the developed world is attributed to the detection of cancers at an earlier stage by screening. For example, the overall five-year relative survival of women with breast cancer if detected at an early stage is 98%. The survival drops to 84% when the disease spreads to regional lymph nodes and 28% when spread to distant organs [4]. It has therefore become critical to combat the disease at an early stage.

Figure 3. Digital mammography provides superior contrast resolution, of particular value in dense breasts. Images by courtesy of G. Newstead.
Recent technological advances have significantly increased the scope of ultrasound in breast imaging [7]. The Philips iU22 system with Vision 2009 offers volumetric acquisition (Figure 4), new interventional and contrast tools, and new approaches to improve workflow efficiency, including the new VL13-5 3D linear array transducer with Tissue Aberration Correction (Figure 5). Tissue Aberration Correction corrects for the different speeds of sound in different tissue types, such as fat and glandular tissue in the breast. The result is sharper images with better spatial resolution and less clutter, making it possible to detect smaller and less conspicuous lesions.

Breast MRI (Figure 6) is a supplementary procedure used for further assessment of findings detected by mammography or ultrasound. Typical applications include:

- identification of early breast cancer, particularly in women with dense breast tissue and those at high risk for the disease
- further assessment of lesions, particularly in women with dense breast tissue and those at high risk for the disease
- assessing multiple tumor locations, especially prior to breast conservation surgery
- distinguishing between scar tissue and recurrent tumors
- determining whether a known cancer has spread further in the breast or into the chest wall
- assessing the effect of chemotherapy
- assessing breast tissue density, cysts, enlarged ducts and hematomas
- helping to distinguish between benign and malignant lesions.

The use of breast MRI has substantially increased in recent years. A recent survey of physician members of the Society of Breast Imaging (SBI) indicated that contrast-enhanced breast MRI was offered at 73.8% of the practices and screening breast MRI was offered at 64.0% of practices in the United States [8]. The American Cancer Society (ACS) and the European Society of Breast Imaging recommend screening MRI as an adjunct to mammography for women with an approximately 20% or greater lifetime risk of breast cancer. The ACS recommends breast MRI screening in addition to mammograms for women who meet at least one of the following conditions:

- they have a BRCA1 or BRCA2 mutation
- they have a first-degree relative (parent, sibling, child) with a BRCA1 or BRCA2 mutation, even if they have yet to be tested themselves
- their lifetime risk of breast cancer has been scored at 20%-25% or greater, based on one of several accepted risk assessment tools that look at family history and other factors
- they had radiation to the chest between the ages of 10 and 30
- they have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalca syndrome, or may have one of these syndromes based on a history in a first-degree relative [9,10].

Other diagnostic imaging technologies such as MR/optical hybrid imaging, breast specific gamma imaging (BSGI), positron emission mammography (PEM), tomosynthesis, and dedicated breast CT are discussed as potential methods for early breast cancer detection [11-13].

The utilization of multiple modalities for breast care is creating new challenges for the care giver.

Digital mammography offers superior contrast resolution and better clinical performance.

At present, there is no single modality that can guarantee the early detection of breast cancer, since the manifestation and progression of the disease varies widely. Screen-film X-ray mammography has been by far the most widely used modality to screen for breast cancer, but with the advent of digital mammography (Figure 3), the clinical community is reaping the benefits of superior contrast resolution and better clinical performance compared with traditional screen-film systems, particularly in women with dense breasts [5]. The digital images also serve as the input for centralized reading and digital archiving as well as computer aided detection (CAD). However, the diagnostic accuracy of X-ray mammography is still limited and breast care is rapidly transitioning to a multi-modality solution-driven approach.

Recent results from the ACRIN 6666 clinical trial demonstrated that combining ultrasound with mammography increased the diagnostic accuracy to 91% compared to 78% with mammography alone [6] at the expense of increasing the number of false-positives. Nevertheless, this has stimulated active technological and clinical investigations to broaden the role of ultrasound for breast cancer screening in addition to its valuable benefits in diagnostic imaging.

Major advantages of ultrasound include the absence of ionizing radiation, the widespread availability, and the relative ease of use. Until recently, however, ultrasound examinations suffered from a relatively low resolution and a high degree of operator dependency, resulting in rather poor reproducibility.

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It becomes an arduous task to independently review and report on the imaging data from each modality and becomes even more challenging when the modalities are from different vendors. This is driving the need for integrated workflow solutions that can help the physician view, analyze, and report from a single workstation that can communicate seamlessly with modalities from any vendor (Figure 7).

Imaging is at the forefront of the breast care cycle. However, interventional procedures such as biopsies are a crucial part of breast care, which leads to the final diagnosis. Substantial progress has been made in this field transforming it from a surgical procedure to a minimally invasive office-based method. Vacuum Assisted Biopsy is the more recent form of various biopsy techniques, making it possible to extract large tissue samples with excellent integrity, which improves the overall quality of pathology. It is used under stereotactic X-ray, ultrasound, and MR image guidance.

The improvements in imaging and interventional diagnosis make it possible to detect increasingly smaller lesions. This helps to drive the transition from mastectomy to breast conserving surgery, and the adoption of focal therapies such as Accelerated Partial Breast Irradiation (APBI) instead of conventional whole breast irradiation. Balloon breast brachytherapy is one such APBI technique that enables treatment of the lumpectomy cavity in five days, rather than the five to six weeks needed with external beam
Cardiovascular disease

Cardiovascular disease is the world’s leading cause of death in women, not only in developed nations, but in developing countries as well. Coronary artery disease is responsible for 294,000 deaths in women annually and is the greatest cause of death in women in the USA (38%), Europe (23%), and China (23%) [15-17]. Prevalence of heart disease in women increases after menopause with the decline in serum estrogen levels. Since older women (>60 yrs) are the largest growing population segment, the public health and economic burden of women’s heart disease will increase significantly in the future. This effect will be magnified in developing countries, where the projected increase in the number of older women exceeds that of developed countries for the same period [18].

Although women under age 55 with heart attacks represent a smaller proportion of all patients with heart disease, they account for approximately 40,000 hospitalizations in the USA each year. Young women also have significantly worse outcomes than men of similar age. About 8,000 women under the age of 55 in the USA die of heart disease annually, ranking it among the major causes of death in this age group [19].

Clinical issues in ischemic disease

Differences in the manifestation of heart disease in women and men have been identified in several areas, including etiology, pathophysiology, and clinical presentation. Women have smaller coronary vessels with more diffuse atherosclerosis, microvessels that are more frequently dysfunctional, and less obstructive disease. Ischemic heart disease presents clinical challenges that are not adequately addressed by current techniques developed, tested, and studied in largely male populations. Because women’s ischemic disease often evades detection through traditional diagnostic techniques, it may continue to cause symptoms, but remain undiagnosed until progressing to a critical stage.

Angina is more common in women than men [20,21], but is more often due to microvascular disease with normal non-obstructed coronary arteries. The landmark National Heart Lung Blood Institute (NHLBI) Women’s Ischemic Syndrome Evaluation (WISE) II study showed 60% of women referred to cardiology practices for suspected ischemia did not exhibit obstructive CAD by angiography despite persistent or worsening symptoms [22].

When patients are evaluated for chest pain, cardiologists typically look for an obstructive lesion, i.e. plaque that is blocking an artery; however, in many women, two areas of dysfunction (one in the cells lining coronary arteries and another in the smaller vessels branching within the heart) combine to deprive the heart muscle of oxygen. “Functional”, rather than structural abnormalities of the coronary circulation may provide evidence of ischemic disease in women. Although the diffuse atherosclerosis that many women experience is not seen on coronary angiography, it results in abnormal resistance that limits flow to the heart tissue but without angiographic evidence of blocked artery [22].

The results of the WISE study were summarized as follows: “Ischemic heart disease in women represents an important problem that is difficult to identify early... A heightened awareness of women at risk of IHD and a different approach than that used in men is necessary to allow for diagnosis before late stages develop... But women also are likely to have nonendothelial-dependent microvascular dysfunction, particularly in the early stages of IHD. Limitations to the prevailing diagnostic evaluation of women are now more clearly defined”.

Women have comprised only 25% of participants in heart-related research studies to date. There is a clear need for validated diagnostic methods to provide unequivocal test results in women who are symptomatic for IHD. The WISE results have generated interest in refocusing the diagnostic work-up in women to emphasize functional, rather than structural, abnormalities. Functional capacity, global ventricular function, regional wall motion, and coronary flow reserve show promise of increased effectiveness in the diagnosis of women’s IHD [23].
Imaging modalities

In addition to the tried and tested cath lab techniques, increased understanding of asymptomatic and symptomatic cardiovascular disease in women has created a need for non-invasive techniques to diagnose non-obstructive coronary artery disease (CAD). Stress echocardiography is a widely accepted technique, while SPECT imaging provides valuable metabolic information on existing or incipient ischemia.

Cardiac magnetic resonance offers a complete spectrum of tools to assess cardiac morphology, function, perfusion, viability and coronary vascular dysfunction in a single clinical study [24].

The DXL algorithm

Philips Healthcare has a long-term commitment to developing technologies and solutions for women's heart health. Beginning in the 1970’s, Philips has used gender and age-specific criteria in diagnostic electrocardiograph algorithms. The latest DXL Algorithm applies new gender, age and lead-specific STEMI (ST-segment Elevation Myocardial Infarction) criteria to detect acute myocardial infarction in women as well as men. A widespread pattern of ST depression often reflects global ischemia due to left main coronary obstruction, multi-vessel obstructions, or microvascular disease, which is more prevalent in women. The DXL Algorithm incorporates new criteria for these conditions and provides a critical value of “Global Ischemia” to highlight that prompt intervention may be needed.

Gynecology

Gynecological conditions include benign conditions such as abnormal uterine bleeding, pelvic floor disorders, and infertility, as well as cancer of the cervix, uterus, and ovaries.

New therapies for abnormal uterine bleeding

Menorrhagia, including heavy or prolonged menstruation or bleeding between menstrual cycles, affects a significant population of women between the ages of 35 and 54. While the majority of menorrhagia cases are benign in origin, 10% are due to premalignancies or cancer. In the USA alone, over 9 million women suffer from this condition and, in India, it is estimated that 25 million women have fibroid tumors, a primary cause of menorrhagia [25]. At least one-third of menorrhagia cases are caused by uterine fibroids, which can also lead to infertility.

Ultrasound has proven to be a very useful tool for identifying the cause of abnormal uterine bleeding and can help exclude endometrial carcinoma [26]. Transvaginal ultrasound with saline infusion sonohysterography is particularly valuable in triaging certain menorrhagia patients to:

- no further evaluation
- blind endometrial sampling
- visually directed endometrial sampling for focal pathology.

The addition of saline infusion to a standard transvaginal sonogram has also aided diagnosis.
High-intensity focused ultrasound (HIFU) heats and coagulates tissue deep within the body.

Novel non-surgical treatments for menorrhagia offer new options for women.

of intracavitary polyps and fibroids within the endometrium. Three-dimensional (3D) volumetric imaging may be helpful in detecting polyps and fibroids when the 2D image is not well defined, and can be useful for monitoring the effects of therapy [27].

Many women delay seeking treatment in order to avoid a major surgical procedure with general anesthesia, such as hysterectomy; however, three million women in the U.S. and Europe are treated for menorrhagia each year. Novel non-surgical treatments for menorrhagia offer new options for women. These procedures, which offer less discomfort and faster recovery time, are prompting more women to seek therapy. The choice of therapy depends on factors such as the cause of bleeding and its severity, and patient’s age and preferences. Non-surgical therapies that can be performed under local anesthesia or conscious sedation include:

**Global endometrial ablation**
Endometrium is treated with thermal ablation, using various energy sources, such as circulating heated saline, cryoablation, hot water balloon, laser energy, microwave ablation, and radiofrequency (RF) ablation.

**Uterine artery embolization (fibroids)**
Particles, such as polyvinyl alcohol, are injected via a catheter into the uterine arteries, resulting in thrombosis and occlusion.

**High-intensity focused ultrasound (fibroids)**
High-intensity focused ultrasound (HIFU) is an emerging therapy technique using focused ultrasound to heat and coagulate tissue deep within the body, without damaging intervening tissue.

In this technique, a specially designed transducer is used to focus a beam of ultrasound energy into a small volume at specific target locations within the body. The focused beam causes localized high temperatures (55 to 90°C) in a region as small as 1 x 1 x 5 mm. The high temperature, maintained for a few seconds, produces a well-defined region of necrosis. This procedure is referred to as ultrasound ablation.

The tight focusing properties of the transducer limit the ablation to the target location. Accurate positioning requires high-resolution images, while effective therapy requires real-time temperature monitoring and adequate post-treatment lesion assessment. To meet these requirements, Philips Healthcare is currently developing a dedicated MRI-guided HIFU system. Increasingly, significant issues in women’s health are emerging in developing countries. Care cycles in these regions can be dramatically different from those in developed countries. For example, factors such as lack of infrastructure, including technology and trained resources, cultural customs and stigmas, and economic issues can have a negative impact on women’s gynecological health. In many areas, a critical need exists for low-cost/high-value, patient-accessible solutions that fit the demands and particular constraints of a given country.

Another dynamic in countries such as China and India is the emerging middle class. There are a growing number of women entering the workforce in middle tier and smaller cities, as well as major urban centers. These women have raised expectations for health care and they need to minimize time away from the workplace due to health issues. As a result, they demand non-surgical, faster recovery therapies for their gynecological conditions.

**Cervical cancer in developing countries**
Cervical cancer continues to be a leading cause of cancer-related death among women in developing countries. It was a major contributor to the one million new cases of gynecological cancers worldwide in 2007. Each year, 80% of the approximately 500,000 new cases and over 250,000 deaths from cervical cancer occur in developing countries [28].

In developed countries, the Pap test and, more recently, HPV testing have been very successful in reducing the incidence of cervical cancer. It is well-established that screening models which work well in the developed world have not been successful in developing countries, due in part to the reliance on laboratory-based screening tests, and to poor patient compliance with a care cycle that requires multiple repeat visits for screening, diagnosis, and therapy. New care models that support screening, diagnosis, and therapy in one visit have shown some promise in overcoming these obstacles.

An important tool for diagnosing and guiding therapy for cervical neoplasias is colposcopy. In colposcopy, magnified visualization of the cervical tissue is used to evaluate abnormal vascular changes that indicate the presence of dysplasia. Digital colposcopes, such as Philips/Goldway SLC-series, can be especially useful for enhancing workflow and quality control in high patient volume settings. In resource-limited settings, digital colposcopy systems support telecolposcopy for improved, timely clinician training and access to center-of-excellence experts from remote sites.
References


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