PharmaVOICE

THERAPEUTIC DIGEST

WOMEN'S HEALTH

ADVANCES IN KNOWLEDGE AND UNDERSTANDING

IN COLLABORATION WITH thinkgen

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Defining Women's Health

Women's health is a complex and multifaceted therapeutic area. Thousands, even millions of factors, affect the ways women develop, get sick, get well, interact with others, reproduce, age, and receive healthcare. Women's health includes the study of the whole body; it examines the biological characteristics unique to women, the most obvious being the reproductive organs, but also differences in body structure, childhood development, hormones, genetics, and brain chemistry. Yet, women's health is also concerned with factors that affect both genders, including the common cold, heart disease, depression, and the benefits of regular physical exercise. Women's health includes the study of disease, but it also examines factors that affect a woman's physical and mental well-being. Studies of women's health include the analysis of social and environmental factors that impact the health of women.

The entire spectrum of research and social sciences can provide insight into women's health. A full understanding of women's sexual and reproductive health requires biological, cultural, historical, psychological, and political perspectives. The physical components of the reproductive system influence a woman's sexual response but so do cultural mores and traditions that dictate when and how women are supposed to enjoy and think about their sexuality. Women's health includes reproductive health, defined as the well-being of a person's reproductive system, including their ability to decide if and when to have children[1]. Studying reproductive health requires examining the laws, practices, and cultural beliefs that influence when and where women learn about childbirth, family planning, birth control, and their legal opinions for ending a pregnancy.

Because women's unequal treatment affects their well-being and lives in many ways, feminism is also an important part of women's health. Not all women become mothers, but because all mothers are biologically women, women's health also includes studying pregnancy, fetal development, and mother-infant interactions.

Finally, society and culture also influence women's health. Women's health includes women's ability to obtain and benefit from healthcare. The study of access to healthcare has increased dramatically over the past 20 years. Access to healthcare not only includes whether women can physically get to a doctor or healthcare provider but also whether she trusts that provider, whether she has insurance or some other way to pay for healthcare, and whether she knows if and when something is wrong. Access to healthcare and decision-making are especially important for women's health, because women are more likely than men to make decisions regarding healthcare for their relatives and families.

Women's Health Movement

The past 200 years have seen enormous improvements in women's health, political and economic rights, and place in society. The battle to bring women's healthcare to the forefront of the health industry has resulted in some groundbreaking advances. Although, without a doubt there's more work to be done, exploring how women's healthcare has evolved over the past 200 years can help us understand just how far we've come and how far we still need to go.

Reductions in morbidity and mortality — or injuries and deaths resulting from pregnancy and childbirth — are one of the most important human achievements over the past 200 years. Until the late 1800s, rates of maternal death in the United States and Europe range from 25/1,000 to 85/1,000[2]. This means women had a 2.5% to 8.5% chance of dying every time they gave birth. Without access to family planning, the large family sizes that were often the norm of that era made childbirth a major cause of death for women.

Today, the maternal mortality rate in the United States is about 23.8/100,000, less than half of what it was in the 19th century, but it is slowly increasing among at-risk populations over the last decade[3]. Maternal mortality rates are even lower throughout most of Western Europe. Rates of infant mortality have fallen even more dramatically. In the late 1800s, anywhere between 10% and 25% of infants died either during or shortly after childbirth in Europe and in the United States[4]. Today, just 0.6% of U.S. infants die during or shortly after childbirth, although the rates are significantly higher when looking only at multiples or babies born in other high-risk scenarios[5].

1830s and 1840s: The Health Movement

Many historians believe the women's health movement began in the 1830s and 1840s, when small groups of women began advocating taking an active role in preventing disease and staying healthy rather than relying on formally trained physicians for treatment. This first wave of advocacy focused on eating a proper diet, the elimination of the corset, and periodic sexual abstinence in marriage to control family size. For the first time, a few middle-class women who became interested in their own health sought entry into the medical profession. Elizabeth Blackwell, for example, entered medical school in 1847 and prompted the opening of several medical schools for women. In 1948, the first women's right's convention was held in Seneca Falls, N.Y.; the convention marked the official beginning of the women's rights movement.

1861 — 1865: The Civil War

The Civil War prompted many women to volunteer as doctors and nurses; some women even disguised themselves as men to tend to wounded soldiers on the battlefield. Dorothea Dix and Clara Baron led a national effort to organize corps to care for the war's wounded and sick.

Women's participation in the war led to the opening of the first training schools for nurses in 1873; by 1890, 35 such schools existed. Although this trend represented advancement for women, the relationship between male doctors and female nurses mirrored the domestic sexual division of labor, with males as the authority figures and females as the subordinates.

Mid- to Late 1800s: The Women's Medical Movement

After the Civil War, educational and employment opportunities, although still severely limited increased for women. The women's medical movement emerged from the growing number of women attending medical schools, their struggles to achieve equal status within the profession, and the popularity of challenging historical notions regarding women's fragility.

1890s — 1920s: The Progressive Era

The women's medical movement gave way to the Progressive Era, which advanced the roles of women and women's rights as well as women's health. In 1920, the 19th Amendment to the U.S. constitution, which guaranteed women the right to vote, was ratified. A few years later, the National Women's Party, formed in 1917, proposed the Equal Rights Amendment, which to this day remains unratified.

During this time, Margaret Sanger and other activists pushed to legalize birth control. In 1916, Sanger opened the nation's first birth control clinic in Brooklyn, New York, and was arrested shortly afterward for violating a federal ban on contraception. Sanger was found guilty and was sentenced to 30 days of labor; However, in an appeal, a judge legalized contraception — but only for married couples with a doctor's prescription. Other progressives worked to promote healthy motherhood throughout prenatal and child health services. The Sheppard–Towner Act of 1921 greatly increased the availability of prenatal and child healthcare, especially in rural areas where care was scarce. This legislation provided federal funding for programs that opened clinics for women and children, educated women about pregnancy and childbirth, and trained midwives and physicians about childbirth. The Act lasted until 1929, when a conservative Congress refused to continue its funding.

1930s — 1950s: World War II and Postwar Years

The United States dramatically increased its production during World War II while millions of male workers were leaving to join the military. Women made a vital contribution to this effort. Twelve million women were working when the United States entered the war; by the time the war ended 18 million women were employed[6]. Women began receiving more pay and worked in greater variety of positions, although they were rarely, if ever, employed in skilled labor or managerial positions. When the war ended, women were pressured to leave their jobs and return to being housewives.

Although many women were using birth control by the 1950s, popular culture still reinforced the idea that sexuality was simply a means for married couples to produce children. The Kinsey reports on human sexuality, issued in 1953, started to dispel this idea by revealing that, for many men and women, marriage was not a prerequisite for sex.

1960s — 1970s: The Grassroots Movement

During the 1960s and 1970s, grassroots organizations challenged medical authority in the delivery of healthcare to women. These groups believed that the overwhelmingly male medical community excluded women from making decisions about their own healthcare, and they began to address issues such as unnecessary hysterectomies and cesarean sections, postpartum depression, abortion, and childbirth reform from a feminist perspective. The self-help manual Our Bodies, Ourselves epitomized this effort, written and self-published in 1970 by 12 feminist activists selling millions of copies throughout the years.

Legal reforms during this time gave greater rights to women. The U.S. Food and Drug Administration (FDA) approved the birth control pill in 1960. In 1964, Congress passed the Civil Rights Act, including Title VII, which protected women against employment discrimination. In 1972, Congress passed the Equal Rights Amendment, although this amendment fell short of 38 states needed to ratify it and add it to the Constitution.

For decades, the women's health movement has been composed mostly of middle-class white women. During the 1960s and 1970s, this movement began to be more inclusive. Organizations such as the National Black Women's Health Project (now called the Black Women's Health Imperative), the National Latina Women's Health Organization, the National Asian Women's Health Organization, and the Native American Women's Health Education and Resource Center were developed to focus on issues and disease that disproportionately affect women of color.

1980s: Changing Public Policy

In the 1980s, the U.S. Public Health Service's Task Force on Women's Health Issues formed to assess the status of women's health. The task force issues recommendations to increase gender equity in biomedical research and establish guidelines for the inclusion of women in federally sponsored studies. In 1990, the National Institutes of Health (NIH) strengthened its guidelines and established the Office of Research on Women's Health (ORWH). ORWH ensures women's participation in clinical trials, strengthens research on diseases affecting women, and promotes the career advancement of women in science. The Women's Health Equity Act was also passed, allocating money to fund health research in particular areas of concern to women, including contraception, infertility, breast cancer, ovarian cancer, HIV/AIDS, and osteoporosis.

1990s: Women's Health at the Forefront

The 1990s brought together government, healthcare institutions, academia, and advocacy organizations to analyze and promote women's health and well-being. New women's health offices in federal agencies and in regional public health service offices opened throughout the country. Existing centers broadened their scope beyond reproductive issues to take a more comprehensive look at health and disease among women.

In the 1993 NIH Revitalization Act, Congress required women and minorities be included as subjects in all human subject research funded by the NIH. This decision was a bold and innovative step. The inclusion of women in research has broadened the scientific knowledge base necessary for developing sex-specific diagnostic techniques, preventive measures, and effective treatments for diseases and conditions affecting women throughout their life span. The Family and Medical Leave Act, also introduced in 1993, gives employees unpaid medical leave for themselves or for the care of a family member or a newborn or adopted infant. In 1994, the Violence Against Women Act mandated a unified judicial response to sex crimes committed against women.

The 21st Century

The new millennium has brought many contributions to improving the health for the public — for example, the identification of the human genome, improvements in HIV/AIDS medications, public health programs targeting behavior-related health problems, the inclusion of children in clinical trials, and the Patient Protection and Affordable Care Act, which has extended health insurance to millions of women, men, and children. Nevertheless, women still face many difficulties in health care arena. There has been a rollback of many of the advances made in the 1990s. Funding for reproductive health initiatives fell both domestically and internationally for the first decade of the 21st century. In 2018, a record number of women were elected to Congress, with 25 women serving

in the Senate and more than 102 women serving in the House of Representatives. This reflected a national wave of women being elected to political positions around the country, many of whom were women of color and members of the LGBTA community. However, women still remain underrepresented in the national, state, and local governments. Women are living longer but not necessarily with better quality of life; and women across the United States and the world continue to be a victim of individual and societal violence and discrimination.

Women's Health Specialties and Areas of Focus

Women's health has a broad range of specialties and focus areas since it is a branch of medicine that focuses on the treatment and diagnosis of diseases and conditions that affect a woman's physical and emotional well-being. The term "women's health" covers therapy areas from mental health to reproductive health to bone health. The following are just three of the multitude of focus areas that concern women's health.

Birth Control

Contraceptive choices currently available in the United States provide safe, reliable, effective, and affordable birth control for virtually any patient. Products come in a variety of forms — tablet, patch, injection, implant, vaginal, and intrauterine. Current oral contraceptive products also contain novel progestins that have altered the scope of benefits and adverse effects.

The availability of new, effective contraceptive products in the last decade has not generated a significant decrease in the rate of unintended pregnancy. About half of all pregnancies in the U.S. are unintended, and more than one in five U.S. pregnancies end in abortion[7]. A study of more than 10,000 women who requested an abortion found that 46% had not used a contraceptive method during the month they conceived[8].

The No. 1 method of contraception in the U.S. is sterilization[9]. Many women who opt for sterilization before the age of 30 later express regret and report choosing sterilization because they didn't know that equally effective reversible options exist[10]. Combination oral contraceptives (COCs) are the most commonly used reversible form of birth control in the U.S.[11] By the third month, the typical user misses three or more pills each cycle[12]. This data suggests that the contraceptive needs of women are currently unmet.

Extended-cycle Oral Contraceptives

Combined oral contraceptives (COC) pill is often just called "the pill," and contains two hormones — an estrogen and a progesterone. Extended-cycle products differ from traditional 21/7 COCs by decreasing or eliminating the hormone-free interval (HFI). Consecutive days of hormone therapy may extend to 84 or 365 days. In add-back regimens, which is the addition of a small amount of progesterone with or without estrogen, the HFI is shortened to zero, two, or four days instead of the typical seven-day interval.

Reasons for switching to an extended-cycle product include the typical menstrual symptoms experienced during the HFI; Improving efficacy in women who forget to restart the pill; And patient preference to decrease the frequency of menstrual-like bleeding. For a number of years, prescribers have utilized continuous administration of monophasic pills to simulate an extended-cycle product. However, patients typically incur additional financial expense with this dosing regimen because insurance companies generally pay for only 13 cycles per year[13].

A randomized clinical trial found that continuous COC regimens were more effective at preventing follicular development and breakthrough ovulation during the HFI[14]. These issues are a concern, particularly in patients who have difficult adhering to the dosing schedule, as low-dose products are the norm[15]. A definitive answer will not be available until long-term studies of extended-cycle products are completed. To date, no studies supporting these concerns have been published.

Economically speaking, eliminating menstrual disorders may improve women's work productivity and decrease healthcare costs. Data collected from 1984 through 1992 found that menstrual disorders were the most commonly reported gynecologic condition[16]. More than 75% of women studied had consulted a doctor about this condition, and nearly 30% had spent one or more days in bed in the previous year[17]. A 2002 study concluded that menstrual bleeding has a significant economic impact for working women, with an estimated annual cost of $1,692 per woman in the workplace[18].

Desogestrel-containing Oral Contraceptives

Desogestrel is a third-generation progestin that is found in a number of COCs, including Cyclessa, Ortho-Cept, Mircette, and Desogen. The third-generation products were developed during 1980s to decrease the androgenic (relating to male hormones like testosterone) effects, including hirsutism (the excessive growth of course hair with male-like effect on women like on the chest, lip, and jaw line) and acne, commonly seen with the earlier generations of oral contraceptives. Two meta-analyses published in 2001 concluded that desogestrel-containing oral contraceptives increase the risk of thromboembolism by a factor of 1.7 over products that contain levonorgestrel[19].

The FDA requires manufacturers of desogestrel-containing products to include a statement in the warnings section of COC labeling that these products are associated with a two-fold increase in the risk of venous thromboembolism, and those at risk should consider switching to a second-generation product[20]. The Public Citizen's Health Research Group (PCHRG) filed a petition with the FDA in February 2007 to remove desogestrel because of the increased risk of developing blood clots[21].

Drospirenone-containing Oral Contraceptives

COCs that contain the antimineralocorticoid drospirenone (Yasmin, Taz; 3mg drospirenone) as the progestin component may decrease the bloating and water retention that commonly occur with COC use. Drospirenone may cause potassium retention, however leading to hyperkalemia. While this is not likely to be a problem in most patients, those who are concurrently taking potassium-sparing drugs, including nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II agonists, and potassium chloride, are at increased risk for hyperkalemia[22]. Pharmacists can monitor for this interaction and educate patients to help them overcome barriers to having their potassium levels monitored.

Chewable Oral Contraceptive and Use of COCs in Older Women

Femcon Fe contains 35 mcg ethinyl estradiol and 0.4mg norethindrone in a spearmint-flavored pill that can be swallowed or chewed. The tablet should be followed immediately by a full 8oz of liquid. The proposed advantage of this product is ease of administration[23].

Perimenopausal women commonly experience hot flashes and dysfunctional uterine bleeding. Hormone replacement therapy can treat vasomotor and menstrual symptoms, but not prevent ovulation. The use of COCs in older women confers both effective birth control and non-contraceptive benefits like increased bone mineral density and reduced risk of ovarian and endometrial cancer[24].

Transdermal Contraceptive Patch

The Ortho Evra contraceptive patch, a matrix system containing 6mg norelgestromin and 0.75mg ethinyl estradiol, was approved in 2001. Proposed advantages include improved adherence to the regimen and better efficacy if errors of up to two days are made in dosing. This dosing method avoids first-pass metabolism or hormones, gastrointestinal enzymatic degradation, and peaks and troughs in drug levels. It is easy to confirm the presence of the patch, which reassures the user of continued protection. Disadvantages are application-site reactions and decreased efficacy in patients weighing more than 198lbs.

The FDA revised the labeling for Ortho Evra in September 2006 and again in January 2008, based on results of an epidemiologic study that found that users of the birth control patch were exposed to 60% more estrogen than users of a typical COC containing 35mcg estrogen and were twice as likely to develop blood clots[25,26].

PCHRG filed a petition with the FDA in May 2008, requesting withdrawal of Ortho Evra from the market due to safety concerns based on the risks[27]. PCHRG suggested that the FDA phase out sale of the patch, allowing users to obtain refills while switching to another contraceptive[28]. Use of the path has decreased in recent years, most likely due to reports of risk of thromboembolism.

Emergency Contraception

In August 2006, Plan B was approved for OTC sale to women aged 18 years and older. Plan B contains two tablets of 0.75mg levonorgestrel. The product labeling states that the tablets are to be taken 12 hours apart starting within 72 hours of unprotected sex. Recent findings suggest that the regimen is equally effective if the tablets are taken as one dose[29]. Additional evidence suggests that Plan B may be effective taken up to five days after intercourse; however, this use is not approved[30].

COCs may be used for emergency contraception also. Two to five tablets of a COC that contains levonorgestrel as the progestin are used in the Yuzpe regimen, which comprises 100mcg to 120mcg ethinyl estrodiol combine with 0.5mg to 0.6mg levonorgestrel. Plan B is preferred to the Yuzpe regimen because it has fewer adverse effects, particularly nausea and vomiting, that may decrease the regimen's effectiveness[31].

The copper IUD can be used in women who want emergency as well as regular contraception. The proposed mechanism of action MOA is to impair fertilization, alter sperm motility, and impede implantation[32]. The IUD may be inserted up to five days after unprotected sex. IUD use is contraindicated in cases of sexual assault where there is a high risk of sexually transmitted disease[33].

Mifepristone, used in the U.S as an abortifacient since 2000, has been examined for emergency contraception. It has multiple MOA, depending on when in the menstrual cycle it is administered. A single dose of 10mg to 50mg has been shown to be highly effective for preventing pregnancy[34]. The dose is effective up to five days after unprotected sex. Prescriber availability is limited to physicians who have registered with the FDA to obtain access; and the drug is likely to delay the onset of menstrual bleeding versus other methods of emergency contraception[35].

Osteoporosis

Osteoporosis is a worldwide epidemic characterized by low bone mass and weakened microarchitecture, which predispose affected patients to fragility fractures. It is projected that ~40% of women and ~14% of men over age 50 will suffer an osteoporotic fracture in their remaining lifetime. These figures are alarming because fractures, particularly of the hip, are associated with significant morbidity and mortality. This translates into overwhelming financial burden for society; The medical cost of osteoporotic fractures in 2005 was estimated at about $17 billion and will only continue to rise as the population ages[36].

Substantial progress has been made toward developing drugs that treat osteoporosis. Early studies focused on drugs that target bone resorption, including bisphosphonates, calcitonin, selective estrogen response modulators (SERMs), and estrogen. The potent antiresorptive agent denosumab was developed more recently. All of these agents inhibit bone resorption, but due to the coupling between resorption and formation, they secondarily reduce formation. Concomitant efforts focused on strategies to enhance bone cell anabolic activity. The first approved agent to accomplish this was teriparatide. Teriparatide (recombinant human parathyroid hormone, PTH(1–434) stimulates bone formation, but it eventually also increases bone resorption because the two processes remain coupled. Bone resorption is due to the well-known ability of PTH to stimulate production of RANKL (receptor activator of nuclear factor kappa B ligand) by cells of the osteoblast lineage[37].

A major concern with prolonged use of potent antiresorptive agents such as the bisphosphonates and denosumab is the rare incidence of osteonecrosis of the jaw and atypical femoral fracture. These occurrences have restrained the use of these agents for the long term. Considering these limitations and the need for more potent agents capable of restoring skeletal structure and integrity, efforts have been directed toward developing therapies that target anabolic pathways in bone and therapies that restore a population of bone-forming cells, osteoblasts and their precursors, capable of enhancing bone mass and/or healing fractures.

▶ Current Osteoporosis Therapies

Antiresorptive drugs are the most common therapies for treating osteoporosis[38]. These agents are from several classes, including estrogen, SERMs, bisphosphonates, and monoclonal antibodies such as the RANKL inhibitor denosumab. While these medications inhabit bone resorption, they subsequently inhibit bone formation because the processes are coupled. Thus, effects on both aspects of bone remodeling will be the final outcome of antiresorptive therapy. Bisphosphonates are taken up by osteoclasts, induce apoptosis of mature osteoclasts, and inhibit the formation of the

ruffled border, thus halting bone resorption. Denosumab neutralizes RANKL, a molecule produced by osteoblasts that interact with RANK, a receptor expressed on the surface of cells of the osteoclast lineage[39]. Blockade of the RANKL-RANK interaction inhibits key steps in osteoclast-mediated bone resorption.

Currently available anabolic agents improve bone mass and reduce fractures through intermittent stimulation of the PTH receptor-1 on osteoblasts and their precursors by either PTH (i.e. teriparatide) or the PTH-related peptide analog abaloparatide[40]. These agents produce greater bone anabolic versus catabolic activity. Teriparatide is the best-studied anabolic agent. Abaloparatide exerts its anabolic actions through the same receptor as PTH. Treatment with abaloparatide for 18 months in ACTIVE (the Abaloparatide Comparator Trial in Vertebral Endpoints) was shown to reduce fractures compared to placebo.

The recently completed ACTIVExtend trial built upon data from the ACTIVE trial[41]. In ACTIVExtend, patients who had been randomized to either placebo or abaloparatide for 18 months were subsequently treated with oral alendronate for an additional 24 months. Incident rates for other osteoporotic fractures were also significantly lower in the abaloparatide/alendronate group compared in animal studies to the placebo/alendronate group[42]. The concern of possible osteosarcoma, observed in animal studies with teriparatide and abaloparatide, restricts their use to two years in a patient's lifetime.

New Osteoporosis Agents and Combination Therapies

- ***Wnt Pathway Activation:***
  Agents that stimulate signaling through the Wnt pathway are a new direction in anabolic therapy for osteoporosis. One such medication recently approved by the FDA is romosozumab, a neutralizing antibody to sclerostin. Sclerostin is an endogenous inhibitor of the canonical Wnt pathway and is critically important in regulating osteoblast activity and bone formation[43]. The notion that sclerostin inhibition might be a successful pathway to bone formation was supported by reports that inactivating mutations of SOST, the gene encoding sclerostin, manifested as high-bone-mass phenotypes. Disorders causes by SOST inactivation include the rare genetic bone disorders sclerosteosis and Van Buchem disease[44]. A detailed investigation of sclerostin's actions by numerous laboratories led to the development of two antisclerostin antibodies, romosozumab and blosozumab. Both have been tested in clinical trials, and while blosozumab produced favorable skeletal findings in Phase I and II trials, only romosozumab progressed to phase III trials and is approved at this time[45,46].

Several trials have shown that romosozumab is highly effective at increasing BMD and reducing new vertebral fractures, such as the FRAME (Fracture Study in Post-Menopausal Women with Osteoporosis) trial. The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) trial reported that fracture risk was reduced at vertebral and nonvertebral sites[47,48]. After completion of phase III trials, romosozumab was approved in 2019 for the treatment of osteoporosis with high risk of fracture. The recommended duration of therapy is 12 months, and there is a boxed warning of possibly increased cardiovascular and cerebrovascular risk, which must be factored into choosing candidates for this new therapy[49].

DKK1 is another endogenous inhibitor of LRP5/6 binding to Wnt ligands, similar to sclerostin. High levels of DKK1 block Wnt signaling, stimulate β-catenin phosphorylation and degradation, and suppress osteoblastic activity[50]. DKK1 differs from sclerostin in important ways. DKK1 binds to different domains of LRP5/6 and produces broader inhibition of Wnt signaling. DKK1 is expressed in multiple tissues, in contrast to the largely bone-specific expression of sclerostin, which underlies concerns about possible off-target effects of agents directed against DKK1[51].

- ***Combination and Sequential Therapies***

  Combining or sequencing treatments with anabolic and resorptive agents have been studied for some time, in an effort to achieve synergism by capitalizing on distinct modes of action of different agents. Two clinical trials studying the combination of an oral bisphosphonate with PTH (1-84) — namely the PaTH (Parathyroid Hormone and Alendronate)[52] study and PICS (PTH and Ibandronate Combination Study)[53] — failed to demonstrate superior benefit of the combination treatments for bone mineral density (BMD). Concomitant administration of zoledronic acid with teriparatide for 52 weeks did show enhanced lumbar spine (LS) BMD gains versus zoledronic acid along and greater total hip (TH) BMD gains versus teriparatide alone suggesting site-specific differences in responsiveness to combination therapy. The study, however, was short-term and not powered for fracture reduction endpoints[54].

  The most recent combination study in postmenopausal osteoporosis was the DATA (Denosumab and Teriparatide Administration) trial, which compared BMD responses to combine treatment with both denosumab and teriparatide to either drug as monotherapy over 24 months[55]. Significantly greater gains in LS, TH, and FN BMD were seen in the combination arm than in the denosumab alone or teriparatide alone treatment arms. At the one-third distal radius sire, BMD responses to combination therapy and to denosumab alone were greater than those due to teriparatide over 24 months.

The DATA-Switch trial extended this study for an additional 24 months[56]. Subjects were switched from both the combination and teriparatide monotherapy arms to denosumab, and subjects in the denosumab arm switched to teriparatide. At 48 months, all three treatment groups showed continued increases in LS BMD compared to baseline, and there were no significant differences among the three groups. However, there were modest differences in BMD responses at the hip and radius. At the TH, BMD responses were significantly greater in combination to denosumab treatment group compared to either two other treatment groups.

- ***New Approaches and Targets to Treat Osteoporosis***
    - **Stem Cell Therapies**

      Osteoporosis is thought to be caused in part by decreased numbers of MSCs and their preferential differentiation into adipocytes rather than osteoblasts in the aging skeleton. This could lead to decreased number and quality of osteoblasts in the bone of aging women and men and increased bone marrow fat[57]. Age-related dysfunction of MSCs may result in decreased bone formation and compromised bone microarchitecture. These consequences could lead to increased fractures and reduced fracture healing. Thus, if aging MSCs could be augmented to increase their osteoblastic potential, or if health MSCs could be transplanted into osteoporotic bone and stimulated to differentiate into osteoblasts and synthesize new bone, such cell replacement could potentially be used to treat osteoporosis.

    - **Targeting Senescent Cells in Bone**

      Cellular senescence occurs in nearly all tissues and is characterized by irreversible cell cycle arrest without loss of cell viability. Senescent cells accumulate and secrete various factors that have both autocrine and paracrine effects on the microenvironment. This is referred to as the senescence-associated secretory phenotype (SASP)[58]. Cellular senescence is thought to be the consequence of multiple stressors including telomere loss, oxidative damage, oncogene activation, and direct DNA damage[59]. Cells in the bone microenvironment become senescent, which leads to decreased bone mass, increased bone marrow fat, and increased bone turnover. Since osteoporosis typically accompanies advancing age, it is hypothesized that the attendant bone loss might be arrested if these senescent cells and their secretory phenotype could be pharmacologically targeted.

Breast Cancer

Breast cancer remains one of the most common types of cancer in the world, according to the World Health Organization. It's the fifth-leading cause of cancer-related deaths annually. And more than 265,000 people will be diagnosed with it in the United States alone, during any given year.

But there is reason for hope. Research has yielded a number of exciting developments in breast cancer diagnosis and treatment that will improve the lives of breast cancer patients for years to come.

Node Preservation Reduces Lymphedema Cases

Axillary lymph nodes used to be removed from armpit routinely during breast cancer surgery to test for metastasis. This caused chronic pain, numbness, and lymphedema in about 1 in 5 patients. But studies have shown that many of those nodes can be preserved — without compromising long-term survival rates. Sentinel node mapping lets surgeons identify which lymph nodes are most likely to be affected by a tumor[60]. Targeted axillary dissection allows surgeons to potentially preserve nodes that once tested positive for cancer but reverted to negative status after chemotherapy or another treatment. In both cases, if tests come back negative for cancer on the first few nodes taken out, the remaining nodes can be left alone. That means fewer complications, and fewer side effects for our breast cancer patients.

Genomic Testing Minimizes Chemotherapy Exposure

For years, many patients also got chemotherapy as part of their breast cancer treatment. But a July 2018 study in the New England Journal of Medicine showed that chemotherapy wouldn't benefit up to 85% of patients over age 50 whose breast cancer was HR+, HER- and had not spread to any lymph nodes. The study involved a genomic assay (or OncotypeDX test) that looked at the expression of 21 different genes in a patient's primary tumor[61]. A tumor's gene expression pattern shows whether or not it will be responsive to chemotherapy, or whether endocrine therapy alone (such as tamoxifen) would be a better choice. The study showed that patients scoring in the low-to-mid-risk range could safely skip chemotherapy, avoiding the hair loss, neuropathy, weight loss, and other side effects that often come with it.

Better Identification of Hereditary Cancer Syndromes

A number of genetic mutations — such as BRCA1 and BRCA2 — are already known to increase a person's risk of developing certain cancers, including breast cancer. But now, next-generation gene sequencing techniques are helping researchers identify other hereditary cancer syndromes that can put people at risk.

An Oral Option for Targeted Therapy

Until recently, PARP inhibitors were used primarily to treat ovarian cancer. They work by preventing damaged cancer cells with specific genetic mutations from repairing themselves. Today, this targeted therapy is being used to treat breast cancer successfully, too. Breast cancer is linked to fewer mutations than ovarian cancers, Litton notes, but PARP inhibitors can still exploit them. Two Phase III clinical trials are currently underway comparing PARP inhibitors to standard-of-care chemotherapy. The OlympiAD trial evaluated olaparib and the EMBRACA trial, led by Litton, evaluated talazoparib. Both trials showed improvements in progression-free survival for patients with an inherited BRCA gene mutation and metastatic breast cancer. Both studies also showed overall improvements in quality of life in patients who received these oral drugs, as opposed to those patients who received chemotherapy.

New Drug Combination Makes Estrogen-Blocking Agents More Effective

Patients with HR+ — or hormone receptor-positive — breast cancers are often prescribed estrogen-reducing agents such as letrozole and anastrozole to starve the tumors. Now, studies show that those patients do even better when hormone therapy is combined with CDK4/6 inhibitors, which prevent cancer cells from dividing.

The Next Generation of Monoclonal Antibodies

Trastuzimab (Herceptin) is a monoclonal antibody that has been used to treat HER2+ breast cancer patients since the 1990s. It works by targeting the HER2 receptor, preventing cancer growth. Some breast cancers express too much HER2 protein, triggering the cells to multiply very rapidly. Other monoclonal antibodies (such as pertruzimab/Perjeta) have since been developed. Today, this targeted therapy has gotten even more advanced. T-DM1 (Kadycla), an antibody-drug combination, has been approved for use in the treatment of HER2+ breast cancers. Antibody-drug combinations work like a "smart bomb," delivering chemotherapy directly to cancer cells by attaching to their HER2+ receptors.

CONCLUSION

For those conditions where substantial progress has been made in improving women's health — birth control, cardiovascular disease, and breast cancer — there is a large and diverse body of research from the last 20 years, including basic research at the molecular, cellular and organ level; animal studies; observational studies; and small and large randomized controlled clinical trials. That research led to advances in the understanding of the underlying biology and pathophysiology of the disease, which in turn led to advances in the prevention and diagnosis of and treatment for those conditions in women. Research has resulted in improved diagnostic tests and screening for diseases such as breast and cervical cancer; vaccines against a virus that causes cervical cancer, making prevention of cervical cancer possible; new treatments for cardiovascular disease; and targeted therapies for breast cancer. Even when great progress has been made through scientific advances, other factors in or determinants of health can present barriers to improving women's health, such as the effects of societal beliefs or morals on the use of the vaccine for cervical cancer, social acceptance of and stigmas attached to depression, and use of and compliance with use of contraceptives to prevent unintended pregnancy. Although much work remains and the incidence and mortality for some of those diseases remains high, those advances have led to decreases in prevalence (for example, of cervical cancer) or in mortality (for example, from breast cancer and cardiovascular disease). Knowledge about differences in the manifestation of diseases is crucial for further studies to identify the underlying biology of disease in women vs men and to develop appropriate prevention, diagnosis, and treatment strategies for women.

NOTES:

[1] World Health Organization. External evaluation 2008-2012: Advancing sexual and reproductive health. 2013.

[2] Chamberlain G. "British maternal mortality in the early 20th centuries." Journal of the Royal Society o Medicine. 2006.

[3] MacDorman M, et al. "Is the United States maternal mortality rate increasing? Disentangling trends from measurement issues Short title: US Maternal mortality trends." Obstetrics & Gynecology. 2016.

[4] Corsini C and Viazzo P. "The decline of infant mortality in Europe, 1800-1950: Four national case studies." UNICEF Innocenti Research Centre. 1993.

[5] UNICEF, WHO, the World Bank, UN DESA Population Division "Estimates developed by the UN Interagency Group for Child Mortality Estimation. www.childmortality.org

[6] Sorensen A. "Rosie the riveter: women working during world war II." National Park Service. 2004.

[7] Finer LB, Hensaw SK. "Disparaties in rates of unintended pregnancy in the United States, 1994 and 2001." Perspectives on Sex and Reproductive Health. 2006.

[8] Jones RK, et al. "Contraceptive use among US women having abortions in 2000-2001. Perspectives on Sex and Reproductive Health. 2002.

[9] Chandra A, et al. "Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth." Vital Health Statistics. 2005.

[10] Hillis SD, et al. "Poststerilization regret: findings from the United States Collaborative Review of Sterilization. Obstetrics & Gynecology. 1999.

[11] Chandra A, et al. "Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth." Vital Health Statistics. 2005.

[12] Potter L, et al. "Measuring compliance among oral contraceptive users." Family Planning Perspectives. 1996.

[13] AHRP Clinical Proceedings. "Extended and Continuous Use of Contraceptives to Reduce Menstruation." Washington DC; Association of Reproductive Health Professionals. 2004.

[14] AHRP Clinical Proceedings. "Extended and Continuous Use of Contraceptives to Reduce Menstruation." Washington DC; Association of Reproductive Health Professionals. 2004.

[15] Birtch RL, et al. "Ovarian follicular dynamics during conventional vs continuous oral contraceptive use." Contraception. 2006.

[16] Kjerulff KH, et al. "Chronic hynecological conditions reported by US women: findings from the National Health Interview Survey, 1984 to 1992. American Journal of Public Health. 1996.

[17] Kjerulff KH, et al. "Chronic hynecological conditions reported by US women: findings from the National Health Interview Survey, 1984 to 1992. American Journal of Public Health. 1996.

[18] Cote I, et al. "Work loss associated with increased menstrual loss in the United States. Obstetrics & Gynecology. 2002.

[19] Hennessy S, et al. "Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonogestrel: a meta-analysis and formal sensitivity analysis." Contraception. 2001.

[20] Kemmeren JM, et al. "Third generation oral contraceptives and risk of venous thrombosis: meta-analysis." British Medical Journal. 2001.

[21] Public Citizen Health Research Group. "Petition to the FDA to Ban Third Generation Oral Contraceptives Containing Desogestrel due to Increased Risk of Venous Thrombosis. 2008.

[22] McAdams M, et al. "The concomitant prescribing of ethinyl estradiol/drospirenone and potentially interacting drug." Contraception. 2007.

[23] www.femconfe.com/more.jsp

[24] Kaunitz AM. "Clinicaly practice. Hormonal contraception in women of older reproductive age." NEJM. 2008.

[25] Ortho Evra (norelgestromin/ ethinyl estradiol transdermal system) package insert. Raritan NJ. Ortho-McNeil-Janssen Pharmaceuticals.

[26] Cole JA, et al. "Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users." Obstetrics & Gynecology. 2007.

[27] Public Citizen Health Research Group. Petition to the FDA to Ban Ortho-Evra (HRG Publication #1840). www.citizen.org/publications/release.cfm?ID=7582

[28] Public Citizen Health Research Group. Petition to the FDA to Ban Ortho-Evra (HRG Publication #1840). www.citizen.org/publications/release.cfm?ID=7582

[29] Von Hertzen H, et al. "Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial." Lancet. 2002.

[30] Rodrigues I, et al. "Effectiveness of emergency contraceptive pills between 72 and 120 hours after unprotected sexual intercourse." American Journal of Obstetrics and Gynecology. 2001.

[31] LaValleur J. "Emergency Contraception." Obstetrics & Gynecology Clinics of North America. 2000.

[32] LaValleur J. "Emergency Contraception." Obstetrics & Gynecology Clinics of North America. 2000.

[33] LaValleur J. "Emergency Contraception." Obstetrics & Gynecology Clinics of North America. 2000.

[34] LaValleur J. "Emergency Contraception." Obstetrics & Gynecology Clinics of North America. 2000.

[35] Von Hertzen H, et al. "Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial." Lancet. 2002.

[36] Burge R, et al. "Incidence and economic burden of osteoporosis-related fractures in the United States. 2005-2025." Journal of Bone and Mineral Research. 2007.

[37] Cheloha RW, et al. "PTH receptor-1 signaling- mechanistic insights and therapeutic prospects." National Review of Endocrinology. 2015.

[38] Chapurlat RD, Genant HK. "Osteoporosis: treatment." NIH. 2016.

[39] Chapurlat RD, Genant HK. "Osteoporosis: treatment." NIH. 2016.

[40] Chapurlat RD, Genant HK. "Osteoporosis: treatment." NIH. 2016.

[41] Bone HG, et al. "ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis." Journal of Clinical Endocrinology and Metabolism. 2018.

[42] Bone HG, et al. "ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis." Journal of Clinical Endocrinology and Metabolism. 2018.

[43] Whyte MJ. "Hereditary disorders of the skeleton: sclerosing bone disorders." NIH. 2016.

[44] Whyte MJ. "Hereditary disorders of the skeleton: sclerosing bone disorders." NIH. 2016

[45] McColm J, et al. "Single- and multiple-dose randomized studies of blosozumab, a monoclonal antibody against sclerostin, in healthy postmenopausal women." Journal of Bone and Mineral Research. 2014.

[46] Recker R, et al. "A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density." Journal of Bone and Mineral Research. 2015.

[47] Cosman F, et al. "Romosozumab treatment in postmenopausal women with osteoporosis. New England Journal of Medicine. 2016.

[48] Saag KG, et al. "Romosozumab or alendronate for fracture prevention in women with osteoporosis." New England Journal of Medicine. 2017.

[49] Evenity (romosozumab) package insert. Thousand Oaks, CA. Amgen. 2019.

[50] Ke HZ, et, al. "Sclerostin and dickkopf-1 as therapeutic targets in bone diseases." Endocrinology Review. 2012.

[51] Ke HZ, et, al. "Sclerostin and dickkopf-1 as therapeutic targets in bone diseases." Endocrinology Review. 2012.

[52] Black DM, et al. "The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis." New England Journal of Medicine. 2003.

[53] Schafer AL, et al. "Six months of parathyroid hormone (I-84) administered concurrently versus sequentially with monthly ibandronate over two years: the PTH and Ibandronate Combination Study (PICS) randomized trial." Journal of Clinical Endocrinology and Metabolism. 2012.

[54] Cosman F, et al. "Effects of intravenous zoledronic acid plus subcutaneous teriparatide in postmenopausal osteoporosis." Journal of Bone and Mineral Research. 2011.

[55] Tsai JN, et al. "Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis." Journal of Bone and Mineral Research. 2013.

[56] Leder BZ, et al. "Two years of denosumab and teriparatide administration in postmenopausal osteoporosis: a randomized controlled trial." Journal of Clinical Endocrinology. 2014.

[57] Hu L, et al. "Mesechymal stem cells: cell fate decision to osteoblast or adipocyte and application in osteoporosis treatment." International Journal of Molecular Sciences. 2018.

[58] Pignolo RJ, et al. "Targeting cell senescence for the treatment of age-related bone loss. Current Osteoporosis Reports. 2019.

[59] Pignolo RJ, et al. "Targeting cell senescence for the treatment of age-related bone loss. Current Osteoporosis Reports. 2019.

[60] Blackburn K. "Sentinel lymph node biopsy: What cancer patients should know." MD Anderson Cancer Center. 2019.

[61] Sparano J, et al. "Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer." New England Journal of Medicine. 2018.

RESOURCES:

AHRP Clinical Proceedings. "Extended and Continuous Use of Contraceptives to Reduce Menstruation." Washington DC; Association of Reproductive Health Professionals. 2004.

Alexander LL, et al. "New Dimensions in Women's Health." Jones & Bartlett Learning. 2020.

Birtch RL, et al. "Ovarian follicular dynamics during conventional vs continuous oral contraceptive use." Contraception. 2006.

Black DM, et al. "The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis." New England Journal of Medicine. 2003.

Blackburn K. "Sentinel lymph node biopsy: What cancer patients should know." MD Anderson Cancer Center. 2019.

Bone HG, et al. "ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis." Journal of Clinical Endocrinology and Metabolism. 2018.

Burge R, et al. "Incidence and economic burden of osteoporosis-related fractures in the United States. 2005-2025." Journal of Bone and Mineral Research. 2007.

Chamberlain G. "British maternal mortality in the early 20th centuries." Journal of the Royal Society o Medicine. 2006.

Chapurlat RD, Genant HK. "Osteoporosis: treatment." NIH. 2016.

Cheloha RW, et al. "PTH receptor-1 signaling- mechanistic insights and therapeutic prospects." National Review of Endocrinology. 2015.

Cheng C, et al. "New Frontiers in Osteoporosis Therapy." Annual Review of Medicine. September 2019.

Cole JA, et al. "Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users." Obstetrics & Gynecology. 2007.

Corsini C, Viazzo P. "The decline of infant mortality in Europe, 1800-1950: Four national case studies." UNICEF Innocenti Research Centre. 1993.

Cosman F, et al. "Effects of intravenous zoledronic acid plus subcutaneous teriparatide in postmenopausal osteoporosis." Journal of Bone and Mineral Research. 2011.

Cosman F, et al. "Romosozumab treatment in postmenopausal women with osteoporosis. New England Journal of Medicine. 2016.

Cote I, et al. "Work loss associated with increased menstrual loss in the United States. Obstetrics & Gynecology. 2002.

Demarco C. "Six advances in breast cancer diagnosis and treatment." MD Anderson Cancer Center. 2019.

Hennessy S, et al. "Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonogestrel: a meta-analysis and formal sensitivity analysis." Contraception. 2001.

Hu L, et al. "Mesechymal stem cells: cell fate decision to osteoblast or adipocyte and application in osteoporosis treatment." International Journal of Molecular Sciences. 2018.

Kaunitz AM. "Clinicaly practice. Hormonal contraception in women of older reproductive age." NEJM. 2008.

Ke HZ, et, al. "Sclerostin and dickkopf-1 as therapeutic targets in bone diseases." Endocrinology Review. 2012.

Kemmeren JM, et al. "Third generation oral contraceptives and risk of venous thrombosis: meta-analysis." British Medical Journal. 2001.

Kjerulff KH, et al. "Chronic hynecological conditions reported by US women: findings from the National Health Interview Survey, 1984 to 1992. American Journal of Public Health. 1996.

Koblinsky M, et al. "The Health of Women: A Global Perspective." Westview Press. 2018.

LaValleur J. "Emergency Contraception." Obstetrics & Gynecology Clinics of North America. 2000.

Leder BZ, et al. "Two years of denosumab and teriparatide administration in postmenopausal osteoporosis: a randomized controlled trial." Journal of Clinical Endocrinology. 2014.

MacDorman M, et al. "Is the United States maternal mortality rate increasing? Disentangling trends from measurement issues Short title: US Maternal mortality trends." Obstetrics & Gynecology. 2016.

McAdams M, et al. "The concomitant prescribing of ethinyl estradiol/drospirenone and potentially interacting drug." Contraception. 2007.

McColm J, et al. "Single- and multiple-dose randomized studies of blosozumab, a monoclonal antibody against sclerostin, in healthy postmenopausal women." Journal of Bone and Mineral Research. 2014.

Paik JE. "The Feminization of Medicine." MS JAMA. 2000.

Piascik P. "Recent Advances in Oral and Transdermal Contraception." U.S. Pharmacist. 2008.

Pignolo RJ, et al. "Targeting cell senescence for the treatment of age-related bone loss. Current Osteoporosis Reports. 2019.

Public Citizen Health Research Group. "Petition to the FDA to Ban Third Generation Oral Contraceptives Containing Desogestrel due to Increased Risk of Venous Thrombosis. 2008.

Public Citizen Health Research Group. Petition to the FDA to Ban Ortho-Evra (HRG Publication #1840). www.citizen.org/publications/release.cfm?ID=7582

Recker R, et al. "A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density." Journal of Bone and Mineral Research. 2015.

Rodrigues I, et al. "Effectiveness of emergency contraceptive pills between 72 and 120 hours after unprotected sexual intercourse." American Journal of Obstetrics and Gynecology. 2001.

Saag KG, et al. "Romosozumab or alendronate for fracture prevention in women with osteoporosis." New England Journal of Medicine. 2017.

Schafer AL, et al. "Six months of parathyroid hormone (I-84) administered concurrently versus sequentially with monthly ibandronate over two years: the PTH and Ibandronate Combination Study (PICS) randomized trial." Journal of Clinical Endocrinology and Metabolism. 2012.

Sorensen A. "Rosie the riveter: women working during world war II." National Park Service. 2004.

Sparano J, et al. "Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer." New England Journal of Medicine. 2018.

Tsai JN, et al. "Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis." Journal of Bone and Mineral Research. 2013.

UNICEF, WHO, the World Bank, UN DESA Population Division "Estimates developed by the UN Interagency Group for Child Mortality Estimation. www.childmortality.org

Von Hertzen H, et al. "Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicenter randomized trial." Lancet. 2002.

Whyte MJ. "Hereditary disorders of the skeleton: sclerosing bone disorders." NIH. 2016.

"Women's Health Research: Progress, Pitfalls, and Promise." Committee on Women's Health Research. Institute of Medicine. 2010.

World Health Organization. External evaluation 2008-2012: Advancing sexual and reproductive health. 2013.

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