Introduction

Jo Ann Rosenfeld, MD

The purpose of this book is to consider the woman and her health needs in her position in her life cycle, her family, and society. Women have historically been “the other” in medical care. Sigmund Freud and Erik Erikson considered women’s development to be deviant from the normal, which was men’s. Although the Greeks Hippocrates and Soranus wrote about women’s medical needs, women’s health concerns have either been considered abnormal, or, traditionally, been condensed to their gynecological functions and disorders, perhaps because these were their only valued functions. Since the 1860s and the organization of medicine, women’s health and those who provided for it were usually considered one of the least important parts of medicine. In the past 20 to 40 years, women’s health concerns have begun to take their place as topics worthy of discussion.

Recognizing that combining “all women” into any classification is fraught with difficulties, this book attempts to distinguish and point out the differences and individualities of women. Women are more likely to be different than all alike, and must be treated as individuals.

Because much of clinical experience and research does not separate or study women independently, this book examines the strength and depth of evidence, using clinical experience and data discovered on studies on women, when available, and on men, when research on women is lacking. Thus, at times, deciding on the best way to help the woman manage health concerns may be difficult.

Finally, realizing that women seek physicians’ care for a variety of purposes, only some of which are medical diseases, this book emphasizes collaborative care between the woman and her physician. Women’s health concerns are not all diseases, nor should all women be considered patients. Contraception, fertility, infertility, cigarette, alcohol and drug abuse, sexuality, life changes, and family problems need collaboration and cooperative care, not disease management. Emphasizing prevention, this book will help practitioners’ daily work with women to promote health.
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Singular health care of women

Jo Ann Rosenfeld, MD

The way women’s health concerns have been handled, examined, and researched by the medical establishment may be different from that of men. Women’s health concerns have been considered different and abnormal when compared with that of men. Yet differences between men and women, noted in medicine and by physicians, may be more creations of society and its expectations than of nature;¹ women are more similar to men than they are different.

Research

Exclusion and extension

1. Researchers have historically assumed that data collected and extended from male subjects, often middle-aged white men, applied to women of all ages (and the elderly) as well.² The American Medical Association (AMA) has said “Medical treatments for women are based on a male model, regardless of the fact that women may react differently to treatments than men or that some diseases manifest themselves differently in women than men. The results of medical research on men are generalized to women without sufficient evidence of applicability to women.”³

2. Exclusion: Women, children, ethnic minorities and the elderly have been excluded from research protocols. The justification given for this “is lack of data, but there is also a belief that health iniquities are a smaller problem for women than men.”⁴

For example, research into the acquired immune deficiency syndrome (AIDS) is almost completely androcentric. Until 1993 the US Centers for Disease Control (CDC) failed to recognize different manifestations of human immunodeficiency virus (HIV) infection in women, such as pelvic inflammatory disease (PID), vaginal infections and cervical cancer. AIDS vaccine trials
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and mandatory screening of pregnant women continue the different treatment of women in research.

Yet, the percentage of women with AIDS is increasing and women are at least twice as susceptible to HIV infection compared with men. The first large AIDS study on women started only in 1994 and is following 2500 women with AIDS.5

3. Marginalization: What research that has been done on women’s problems has emphasized female childbearing concerns. For example, there is extensive research on female contraception while comparable research on men has been neglected.2 Research in this area ignored women, unless it considered increasing, improving or controlling fertility, in which case women shared an unequal and almost exclusive burden.

Medical treatments for women are based on a male model, regardless of the fact that women may react differently to treatments than men.

New guidelines for research

In 1994, realizing these disparities, the National Institutes of Health (NIH) issued new guidelines for research funding. In addition to continuing inclusion of women and members of minority groups in research, the NIH has been tasked with:

1. Ensuring that women and members of minorities are included in all human subject research. “Women of childbearing potential should not be routinely excluded from participation in clinical research.”6

2. For phase III trials, ensuring that women and minorities “must be included such that valid analyses of differences in intervention effect can be accomplished”.6

3. Cost is not an acceptable reason for excluding these groups.

4. The NIH must “initiate programs and support for outreach efforts to recruit these groups into clinical studies.”6

5. “Over the past decade [the 1990s], there has been growing concern that the drug development process does not produce adequate information about the effect of drugs in women . . . . Analyses of published clinical trials in certain therapeutic areas (notably cardiovascular disease) have indicated that there has been little or no participation of women in many of the studies.”7

6. The FDA may even have a requirement that women are included in early studies if disease is serious and affects women.7
Women in population studies

1. Except for the Framingham study, in which 2200 women were included to act as a control group for the study of the development of heart disease in men, most early, large, prospective population studies excluded or did not actively recruit women. In the past two decades, there have been several important long-term women-only studies.

2. The Nurses’ Health Study (NHS) enrolled 120 000 women aged between age 30 and 55 years; participants, now aged 50 to 75, have been followed for more than 20 years. Every two years, this cohort fills out extensive questionnaires about their health and lifestyles and the questions are periodically changed, allowing examination of the relationship between different lifestyle factors and medical outcomes.  

3. Other large population studies that involved women are listed in Table 1.1. Realizing some of these research deficits, recently the Women’s Health Initiative (WHI) was started. It is a large-scale multicenter randomized trial, evaluating 163 000 postmenopausal women, and examining preventative therapies including hormone replacement treatment (HRT), heart disease, osteoporosis and breast cancer, and the first results cannot be expected until approximately 2006.

Societal differences between men and women that affect health

Men and women may live different lives within society and the way they live affects their health.

Caregiving

1. Women are more likely to be caregivers to children, spouses, and the elderly family members, putting themselves at risk of increased stress and role stresses. Women are more likely to perform duties at home and work. Twenty five percent of women working full time also care for a relative.

2. Long-term care for relatives is a familial responsibility that usually devolves upon women. Lower income women bear a disproportionate burden in caring for elderly relatives.

3. Caregivers are more likely to suffer anxiety, depression and role stress, and accompanying medical problems.

Insurance

Women are more likely to be uninsured and underinsured. They may work parttime or in professions or jobs that do not provide insurance, and, if
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Table 1.1. Population studies that examined the health of many women

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Colditz, Stampf and others</td>
<td>Nurses’ Health Study</td>
<td>Prospective cohort of 121 701 female registered nurses (98% white) 30–55 years old when started in 1976. Followed 12 or more years</td>
</tr>
<tr>
<td>Buring</td>
<td>Women’s Health Study</td>
<td>1992: &gt; 38 000 health care professional women, looking at effect of aspirin on heart attacks</td>
</tr>
<tr>
<td></td>
<td>Women’s Health Initiative</td>
<td>Prospective study of more than 163 000 postmenopausal women testing impact of low fat diets, estrogen, and calcium and vitamin D on breast cancer, osteoporosis, hip fractures and cardiovascular disease</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>2200 women used to study cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>PEPI Trial</td>
<td>Postmenopausal Estrogen/Progestin Intervention Trial 1987 from National Heart Lung and Blood Institute found that orally administered estrogen alone or in combination with progesterone increased levels of HDL cholesterol in 875 postmenopausal women over 3 years of follow-up</td>
<td></td>
</tr>
<tr>
<td>Clay</td>
<td>Royal College of General Practitioners Oral Contraception Study 1993 NIAID Women’s Interagency HIV study</td>
<td>1400 general practitioners looking at 46 000 women half of whom used OCPs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2500 women with AIDS</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein.

Divorced or single, may not be eligible for spouse’s or family insurance. By 2025, only 37 percent of women in the USA aged 65 to 69 years will still be in their first marriage. This makes it less likely for these women to receive preventive and continuing health services.

Living circumstances

Within each disease process, the circumstances for women may be different from those of men and these circumstances must be taken into account in the care of women with health problems.
1. For example, men with chronic obstructive lung disease (COPD) are very likely to be in their 60s, be insured (at least by Medicare in the USA) be married, and have a wife to help with their care and activities of daily living (ADLs). Women with COPD are more likely to be in their 50s, living alone, and uninsured. If they need help, family members or community groups may be needed.

2. Similarly, women with severe drug abuse problems (see Chapter 27) are more likely than men to be multiply addicted, homeless, and with children. In caring for the woman with addiction, dealing with her individual circumstances is very important.

Elderly women

1. Among the elderly, more men are married, and many more women are living alone (two-thirds of women versus one-half of men). Dietary recommendations may be easier to suggest to, and will be followed by, a married man whose wife does the cooking, than to a single woman.

2. Women are more likely to be widowed and live widowed a longer time than men. As well, many men are less prepared to experience loss, and women have more years to adapt to their loss. Men are less accepting of relocation.

3. Many more elderly men have an adequate income and perceive their health status as excellent. Fewer men have activity restrictions and very few men have impairments in ADLs. Women are more likely to be disabled. Older women, in the USA are two times more likely to be living below the poverty level. Women may be less likely to follow exercise recommendations or obtain prescription medications that are not covered by Medicare.

4. Women are more likely to smoke at home, while men smoke during breaks at work. Women are less likely to use smoking cessation programs, especially work-related programs, and are less likely to quit.

5. More women are elderly, and the older the population the greater the percentage who are women. More women (38 percent) live to 85 years than men (18 percent). From age 65 to 69 years there are 81 men per 100 women, but over age 85 there are only 39 men per 100 women.

6. Drug use: The average elderly woman takes eight drugs daily. Women and the elderly are more likely to have comorbid disease processes and to be taking more medications that affect the drug investigated. Other drug use may affect a particular drug’s pharmacokinetics.

7. Pharmacokinetics: Older women have a lower blood volume, decreased gastric acid and reduced intestinal motility. Older women are more likely to suffer central nervous system (CNS) side effects such as confusion, disorientation, delirium, and hallucinations.
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Table 1.2. Percentage of participants in drug studies by gender

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</thead>
<tbody>
<tr>
<td>Antinflammatory</td>
<td>32-36</td>
<td>60-68</td>
<td>31</td>
<td>69</td>
<td>35-40</td>
<td>60-65</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>64-72</td>
<td>27-36</td>
<td>36-59</td>
<td>33-64</td>
<td>31-85</td>
<td>15-70</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>48-57</td>
<td>43-52</td>
<td>67</td>
<td>33</td>
<td>33-89</td>
<td>11-67</td>
</tr>
<tr>
<td>Antiulcer</td>
<td>77</td>
<td>23</td>
<td>69-72</td>
<td>28-31</td>
<td>40-67</td>
<td>33-60</td>
</tr>
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</table>

GAO, General Accounting Office figures.

8. Older women are more likely to use outpatient services and less likely to be hospitalized than older men.\(^{14}\)

The average elderly woman takes eight drugs daily.

Inherent physical and medical differences between women and men

Immunology

Women are immunologically stronger – less susceptible to infection and more likely to contract autoimmune diseases.

Drug use and metabolism

1. Drug studies, especially phase III trials, historically were performed on white middle-aged and adult men (Table 1.2). Some drug studies, such as those of heart disease and antibiotic medications, used primarily men, although these problems are just as important in women. On the other hand, antiarthritis and antiinflammation drugs were tested primarily in women. The percentages given in Table 1.2 have not changed much in the past 20 years.

2. Recent requirements have added ethnic minorities, children, the elderly, and women as populations on which all drugs must be studied. Many of the elderly are women. Drug use, distribution, and toxicity may be fundamentally different in women and the elderly than in men.

3. Women are more likely to receive prescriptions during a physician’s visit, receive a prescription for psychotropic medications, and spend more money on prescription and nonprescription drugs.\(^{15}\)

4. Variations in drug pharmacokinetics can arise from many factors.
J. A. Rosenfeld

Women metabolize some common substances, such as alcohol, differently from men.

a. Women have longer gastric emptying time and less gastric acid. They have slower intestinal transit time and these differences are independent of hormone use and menstrual status. Women metabolize some common substances, such as alcohol, differently from men, and women have an increased and quicker bioavailability with the same amount of alcohol ingested.

b. Women have a larger percentage of fat and a lower total body water value, except when they are pregnant. Antidepressant levels are dependent on body size and fat levels; side effects and therapeutic levels may occur at lower doses than they do in men.

c. Age affects pharmacokinetics. Older people have decreased renal function. For example, younger people metabolize theophylline more quickly.

d. Men have different renal function with higher serum urinary creatinine levels and higher creatinine clearance values, affecting the clearance of drugs, such as antibiotics, metabolized and eliminated by the kidneys. Nonpregnant women may need lower doses of renally eliminated drugs than men.

e. Individual differences, such as size or muscle mass, may affect pharmacokinetics or health. While not all women are the same size, more women are likely to be smaller and have smaller muscle mass than most men. For example, women were found to have a greater mortality with coronary artery angioplasty. When studies compared body size and size of coronary arteries, it was found that the variable was not ‘‘women’’ but ‘‘size of the arteries’’. Those women and men with smaller arteries do less well with angioplasty.

f. There are particularly ‘‘female’’ concerns involved in pharmacokinetics of some drugs in women. These include the influence of the cycling menstrual status on drug pharmacokinetics, the effect of menopausal status, the influence of concomitant supplementary estrogen administration, both oral contraceptive pills (OCPs) and HRT, on drugs and whether the drug clearance and use is affected by the phase of the menstrual cycle.7,16

Women are more likely to receive prescriptions during a physician’s visit.
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**Table 1.3. Interaction of OCPs with some other drugs**

- Cause decreased clearance
  - Imipramine
  - Diazepam
  - Chlordiazepoxide
  - Phenytoin
  - Caffeine
  - Cyclosporine
- Increase clearances by inducing drug metabolism
  - Acetaminophen
  - Aspirin
  - Morphine
  - Lorazepam
  - Temazepam
  - Ibuprofen
- Reduce the effectiveness of OCPs
  - Carbamazepine
  - Phenytoin
  - Antibiotics rifampin, ampicillin


**Pregnancy**

Pregnant women have larger volumes of distribution and total body water and fat levels. They may need higher doses of drugs such as antibiotics to reach therapeutic levels. Pregnancy induces a decrease in pepsin activity and gastric acid secretion, with a slower gastric emptying time in later trimesters, although intestinal motility is greater. High steroid levels affect hepatic metabolism of drugs.\(^\text{15}\)

**Specific examples**

1. Drug differences: Drugs, especially those that are metabolized or used in the liver, in the cytochrome P450 system, which is also affected by estrogen, OCPs, HRT, and other female hormones may act differently in women (Table 1.3).
2. Seizure medications:
   a. Most drugs for seizures are metabolized in the liver. Estrogen-containing
      OCPs and other hormones are known to affect the metabolism of most of
      these drugs; the drugs also reduce the effectiveness of OCPs.
   b. Women on antiseizure medication often have reduced fertility, menstrual
      cycles, and hormone levels, including disturbances in luteinizing hormone
      (LH), growth hormone, prolactin, and androgen levels. Women with
      epilepsy were only 37 percent as likely to have ever had a pregnancy, in one
      study.
   c. Epileptic women are more likely to have poorer bone health and failure of
      hormonal contraception. The failure rate of OCPs in epileptic women is
      more than four times that in nonepileptic women.
   d. Most of the older antiseizure drugs including hydantoin are fetal terato-
      gens, while the newer drugs such as gabapentin, oxcarbazepine, tiagabine,
      and topiramate have not been well studied in pregnant women. Steroid
      hormones, including estrogen and progesterone, affect the seizure thresh-
      old.
   e. In double blind randomized controlled trials, women have responded
      better to gabapentin than men, both as a first-line and as an additional
      drug for seizures.
   f. Antiepileptic drugs, especially phenytoin, phenobarbital and carbamezine,
      have been known to affect bone metabolism and induce hypocalcemia and
      these effects occur more often in women.

3. Antidepressants: Studies have suggested that antidepressant levels vary
during the menstrual cycle and a constant level of drug may require varying
the dose.

4. Antipsychotic drugs: Antipsychotic drugs are more often prescribed for
women. Side effects of sexual dysfunction including anorgasmia, menstrual
abnormalities and changes in libido occur in women. Levels of lithium excreted
by the kidney may be different in women given the same doses as men
and should be monitored carefully.

5. Cardiovascular drugs: Although more women than men use antihypertensive
medications, most recommendations have been made from studies performed
on men under age 65 years. Calcium channel blockers and nitrates may be better
choices for angina in women because women usually have smaller coronary arteries in
which artery tone is a more important determinant of flow. High blood pressure levels in
women may be more responsive to calcium channel blockers and diuretics.

Side effect profiles may be different. Women who use beta-blockers may
have more side effects, including Raynaud’s phenomenon and alterations of