Antidepressant-Induced Weight Gain

Sarah Grace Kachur

Christine L. Hannan

See next page for additional authors

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SPECIAL ISSUE: WOMEN'S HEALTH
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GOOD - authentic, honest, just, kind, pleasant, skillful, valid
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BEING “NORMAL”

In certain areas it is easy to define “normal.” In other areas it is challenging or impossible. In general, if given a choice, we prefer normality although we sometimes like to stand out. For things that can be measured we can define normal, assuming that the measurement has a “normal distribution” curve, as being within two standard deviations of the mean. For many things we want to be “better than average”, though, smarter, better looking, faster, stronger, more creative, more musical, more artistic, more clever, nicer, more successful, etc. These are “normal” desires.

We can’t define normal appearance, nor can we define normal behavior. We know what seems “freakish” in appearance and we have a fairly uniform agreement on what behaviors are clearly beyond the normal, and probably to a lesser extent, an agreement on what behaviors are considered “abnormal.” In non-statistical terms, we might consider some behaviors to be “fringe” behaviors, borderline acceptable, perhaps eccentric and “different” but not clearly “abnormal.”

Almost all of us have dreaded “not fitting in.” We are an impressively conforming species. Dress codes, work habits, gender stereotypes, social intercourse are quite strictly defined in the various cultures of the world and deviation is not generally well accepted.

It is this fairly straightforward and banal view of the world, which I think is shared by most people, that is challenged in a recent book, One of Us. The author, a non-physician, reports on the world of Siamese twins. Her thesis is that Siamese twins, sharing a world so close, have a life experience that is so closely shared that no one else can possibly imagine it. This shared life is so special and wonderful that it overcomes the obvious difficulties that having a shared body requires. A point stated repeatedly, that only a single set of Siamese twins who were adults ever decided to undergo a surgical separation. This observation, the author suggests, indicates that Siamese twin adults prefer their life, see themselves as quite special, and cannot see themselves as benefiting from a separation.

This author expands her argument by arguing that people with congenital malformations, such as cleft palate, do not necessarily lead improved lives as a result of early repair. She notes that over the years, with further experience with cleft palate repair, more social behavior supports have been provided to the children and their families, and that some people who did not have this surgery are glad that they didn’t.

I read the review of this book in the New England Journal of Medicine and bought it right away. I love iconoclastic thinking. I love to be intellectually provoked, to have to rethink my basic assumptions on almost anything. One either strengthens old convictions by seeing them survive another attack, or one may have to modify old beliefs and “grow.” Sometimes though, one is disappointed. I recently was shown a mathematical “proof” by my teenage son, purporting to show that $1=2$. The various steps in the proof are self-evident, starting with the “given,” that $a=b$, then progressing through a few simple arithmetic steps, the penultimate one being division by $a-b$. Unfortunately $a-b=0$, and division by zero is not allowed. The proof that $1=2$ founders on an unacceptable step. The book above lacks what psychologists call “face validity.” Asking Siamese twins whether they’d prefer to be separate is almost akin to asking someone if they’d rather never have been born. It is almost unthinkable. I suspect, to imagine a life so totally different than the one you’d led, to imagine two points of view when you’ve always had one, to imagine a freedom unimaginable, to live “on your own” once you’re an adult who never had such an opportunity. The book makes clear that one of the largest preoccupations of the general public is how these twins have sexual relations (some have had families) or even toilet themselves.

On National Public Radio several years ago I heard a program on dwarfism and abortion. The world of the achondroplastic dwarf, the most common form of dwarfism, is, as one would imagine, quite different than the world of larger, “normal” people. The issue being considered was the ethics of an achondroplastic couple having an abortion if the fetus was normal and not affected by dwarfism, since it was reported that achondroplastic dwarf couples prefer to have children like themselves. I have no idea if other groups of people with genetic disorders, for example, people with inherited deafness, feel the same way. Perhaps this could be true for Siamese twins. I suspect that most people, especially doctors, who routinely interact with many more people in much more intimate settings than most people, would find the concept of Siamese twins refusing to be separated as lacking “face validity.”

Currently the operations are dictated by the parents, who, like most of us, see very little of value in maintaining the connection between the two bodies. “Normal” trumps “special,” especially when “special” does not look in any way appealing. How can anyone argue that the surgery should await adult decision-making, when the surgery becomes more dangerous AND the personalities become increasingly formed by the unique circumstances? On the other hand, maybe there’s a power in two twins sharing a life.

Bipolar (manic depressive disorder) disease has been associated with increased creativity. If bipolar disease could be “cured” (not simply controlled), but only in childhood, and this resulted in diminished creativity in adults, would we do it? And would it matter if we knew the child was or was not destined to be “creative?” “Curing” conjoined twins is now often possible. Other life altering “cures” of non-fatal disorders and anomalies lie in the near future. Ethical issues will undoubtedly abound.

Joseph H. Friedman, MD
From bitter, intimate experience, Oscar Wilde once wrote:
I know not whether the laws be right,
Or whether laws be wrong:
All that we know who lie in Gaol
Is that the wall is strong.

Wilde had been imprisoned in Reading Gaol (in the US, spelled jail) from 1895 to 1897; and upon his release, he changed his name to Sebastian Melmoth, fled in haste to France, and within years died an embittered, lonely person. British prisons were probably no worse than those on continental Europe. But it required the literary passions of a Dickens, a Wilde or some of the more contemporary Russian writers, to convey the true dehumanizing horrors of gaols, jails or gulags.

Charles Dickens frequently described the infamous prisons of London. Talking of the wretched Newgate Gaol:

“But, the gaol was a vile place in which most kinds of debauchery and villainy were practiced, and where dire diseases were bred, that came into court with the prisoners, and sometimes rushed straight from the dock at my Lord Chief Justice himself, and pulled him off the bench. It had more than once happened that the judge in the black cap pronounced his own doom as certainly as the prisoner’s, and even died before him.”

Dickens was referring, in general, to what “dire disease” known as gaol fever which was the dreaded pestilence infesting jails, army encampments, concentration camps, refugee centers, orphan asylums, almshouses and the steerage compartments of passenger ships. The disease had been known variously as famine fever, ship fever, Irish ague and Hungarian disease (since, on many occasions, it had decimated the Holy Roman Empire armies during their periodic invasions of Hungary.) Gaol fever is a contagious disorder, caused by Rickettsial germs, and is transmitted from person to person by body lice. It is a communicable disease, now called epidemic typhus, which prospers in desperately inhuman conditions of filth and overcrowding.

But Dickens was referring to something more specific than the disease which had killed far more soldiers than all the battlefield casualties caused by gunfire, and far more English prisoners than all of the sanctioned hangings at Newgate prison.

The year was 1577 and Queen Elizabeth was in the nineteenth year of her lengthy reign. The English realm was relatively quiet, the threat of a Spanish armada would not materialize for another decade, and while smallpox, syphilis and bubonic plague continued to be endemic, this had not been a year of notable epidemic intensity of any of these three pestilences.

In July of 1577, in Oxfordshire, the periodic Assize (a word of Latin origin meaning an official court session) was convened in the Old County Hall on New Road. Presiding over the court was Sir Robert Bell, Lord Chief Baron of the province; and in attendance was Sir Robert D’Oyly, Lord High Sheriff. On trial was a local bookseller from the town of Oxford, one Rowland Jenkes, described in court records as “a saucy, fouled-mouthed bookseller who was imprisoned for scandalous words uttered against the Queen.”

During the trial of Mr. Jenkes, brief though it was, note was made of the nauseating stench issuing from the subterranean caverns beneath the courtroom, where about three hundred prisoners were closely held while awaiting their summary judgments issued by the court then in session. Gaol fever, with its terrible headaches, hectic fevers, blotchy skin rashes, delirium and high mortality rate had spread rapidly through these huddled masses of prisoners. And within forty days, about 300 prisoners had succumbed to the fever. The Lord Chief Baron, the Lord High Sheriff as well as their entourages, had also fallen victim to gaol fever. While they did not share the crowded dungeons beneath the courtroom, the body lice nesting in the prisoners’ clothing had inevitably spread to the velvet robes of those proffering judgment.

By the 18th Century, gaol fever became a known occupational hazard for court attendants—even judges. As long as the English legal system required that prisoners be afforded a day in court, facing the judge, the hazard existed of the prisoner’s lice-infected body contaminating the judge’s robes. And so, periodically, English magistrates learned, through personal encounter, the travails of epidemic typhus. The 1577 trial of Rowland Jenkes, with its spread of gaol fever to the judge, was likely the first to enter the history books. It is now referred to as the Black Assize.

Newgate Prison, one of London’s more notorious gaols, was completely rebuilt in the 19th Century in the hopes of reducing the risk of typhus contagion. But this worldly end was not achieved until hygienic measures were finally undertaken to reduce or eliminate lice infestation.

The draconian laws that imprisoned a Mr. Jenkes for ill-considered words about a ruling monarch or an Oscar Wilde for intemperate verbiage which his trial declared to be libel, have since become more tolerant. Prisons, at least in Western nations, have become less dungeons and more impersonal lockups with relatively sanitary facilities. Typhus, therefore, may not be a looming threat in American prisons, but whenever incarceration conditions sink to barbaric levels, the likelihood will be high of a return to the circumstances which foster epidemic typhus.

An eminent physician-bacteriologist, Hanz Zinser, wrote a book on the history of typhus. This 1934 classic, Rats, Lice and History, offered a comprehensive review of the tragic impact of typhus fever upon the many European armies, including Napoleon’s Grand Army in its ill-considered invasion of Russia, and particularly the destructive role of typhus in devastating the trench-bound troops of World War I, especially the Eastern Front armies struggling to survive under terribly primitive circumstances. Millions died of typhus during that conflict as well as during the civil wars and revolution which overtook Russia after 1917.

Zinser concluded with these prophetic words: “Typhus is not dead. It will live on for centuries, and it will continue to break into the open whenever human stupidity and brutality give it a chance, as most likely they occasionally will.”

STANLEY M. ARONSON, MD
INTRODUCTION: WOMEN’S HEALTH

Sharon Marable, MD, MPH, and Maureen G. Phipps, MD, MPH

This edition of Medicine & Health/Rhode Island represents a partnership between the Rhode Island Department of Health (HEALTH) Office of Women's Health and the Brown University / Women & Infants Hospital National Center for Excellence on Women's Health (CoE). Together, we envision a Rhode Island where all women have the opportunity to achieve an optimal state of health and wellness.

The HEALTH Office of Women's Health works to elevate the health status of women and girls by coordinating internal HEALTH efforts and collaborating statewide with agencies that advocate for women and girls. Since being designated a CoE by the US Department of Health and Human Services in 2003, the mission of the Brown University / Women & Infants Hospital National Center of Excellence in Women’s Health has been to foster participation and contributions from the community to improve health and health care for all women. This mission is accomplished through promoting representation of women from all backgrounds in medical leadership positions, enhancing professional education, expanding innovative women’s health research, educating the community and providing a model of quality clinical care for all women.

This edition highlights the collaborative effort between HEALTH and the CoE to improve women’s health in Rhode Island, by educating practitioners about key clinical issues facing their women patients. Articles focus on the unique psycho-social pressures women experience which impact upon their well-being, and medical conditions that present differently or more commonly in women compared to men. Authors also recognize medical conditions where women do not receive the same level of treatment as men and where clinical trials have not effectively included women to establish appropriate treatment regimens.

Dr. Barbara Roberts in “Gender Specific Aspects of Cardiovascular Disease” points out that women with cardiovascular disease often do not present with classic symptoms of chest pain. She outlines the lack of evidence in the current guidelines for prescribing statins in women for the primary prevention of coronary events. Dr. Rosanna Moura discusses Irritable Bowel Syndrome (IBS), a complex disorder of unknown cause and cure, which affects a higher proportion of women than men. She outlines criteria for the diagnosis of IBS and options physicians can take to alleviate its symptoms. Understanding that many women have concerns around weight gain and incontinence, especially as they bear children or become older, two articles focus on these issues. Drs. Suzanne Phelan and Rena Wing provide recommendations for the promotion of healthy lifestyles and weight control for women, particularly during pregnancy and menopause. Drs. Vivian Sung and Deborah Myers review the economic impact of stress urinary incontinence (SUI) and advances in surgical options.

Many of the columns have a Women’s Health focus. “Images in Medicine,” by Drs. Beth Plante and Troilus Plante, illustrates radiological findings in a woman with abdominal pain. Doctors of Pharmacy Sarah G. Kachur, Christine L. Hannan, and Kristina E. Ward discuss “Antidepressant-Induced Weight Gain” in Advances in Pharmacology.

Dr. Jennifer Gass describes a vision of the future of breast surgery in “Creative Clinician.” Drs. Linsay Madom and Lori Boardman explain the utility of HPV testing in the context of cervical cancer screening in Advances in Laboratory Medicine. Columnists from Quality Partners of RI and the Rhode Island Department of Health focus on women’s health.

In summary, this edition brings together clinicians, researchers, public health officials and health policy experts to discuss issues that face our women patients. Elevating the health status of women is essential to improving the health of the entire community. We hope that you enjoy this special edition and the information gives you new insights regarding the medical care of the women in your office practice.

Correspondence:
Sharon Marable, MD, MPH
RI Department of Health
3 Capitol Hill, Room 408
Providence, RI 02908
Phone: (401) 222-5353
E-mail: sharon.marable@health.ri.gov

Maureen G. Phipps, MD, MPH
Women & Infants Hospital
101 Dudley Street
Providence, RI 02905
Phone (401) 274-1122 x2834
E-mail: mphipps@wihri.org

Sharon Marable, MD, MPH, is Medical Director, Office of Women's Health Rhode Island Department of Health, and Clinical Assistant Professor, Community Health Brown Medical School.

Maureen G. Phipps, MD, MPH, is Director, Brown University/Women & Infants Hospital National Center of Excellence in Women's Health, and Assistant Professor, Departments of Obstetrics and Gynecology and Community Health, Brown Medical School.

Reach Out and Read RI (RORRI) will host a benefit, Salon d'Art, at the Providence Art Club, 5:30 – 8:30 p.m., Friday, November 4, to celebrate artists Mary Jane Begin and Christopher Denise. Their exhibit, “The Art of the Book,” will feature works from the artists’ recent works for children. Reach Out and Read RI partners with pediatric primary care providers so that all children can grow up loving books. All proceeds from Salon d’Art will benefit RORRI. To learn more about Salon d’Art or Reach Out and Read, contact Sarah Gleason, Executive Director: (401) 521-1266, or reachoutandread-ri@cox.net.
Gender-Specific Aspects of Cardiovascular Disease

Barbara H. Roberts, MD

Misconceptions about women and heart disease date back almost 250 years to William Heberden, an eighteenth-century British physician who first described the symptom of angina pectoris in 1768. He noted, “Males are most liable to this disease, especially such as have past their fiftieth year. I have seen nearly a hundred people under this disorder, of which number there have been three women.” James Herrick in 1912 described the symptoms of acute myocardial infarction (MI) and noted that nearly all cases were in men past middle age.11

Only in the last few decades have the medical profession and the public begun to appreciate the magnitude of the problem of cardiac disease in women. Since 1984 more women than men have died of atherosclerotic cardiovascular disease (ASCVD) annually in the United States.42 Despite this, women are diagnosed and treated less aggressively than men,53,4 and are woefully underrepresented in clinical trials.

As more attention has been paid to the problem of ASCVD in women we have learned more about gender differences in clinical presentation which influence the way women are approached and treated. We have known since the early publications of the Framingham Heart Study that women tend to present with angina pectoris and men with either MI or sudden cardiac death. The Framingham Heart Study was among the first to note the increased likelihood of “silent myocardial infarction” in women compared to men.

The classic symptoms of MI are severe, substernal chest pain associated with dyspnea, diaphoresis and a feeling of impending doom. However, these symptoms, while typical in men, may not be experienced as frequently in women. A study reported in 2003 on prodromal and acute symptoms in 515 female survivors of acute MI,35 Prodromal symptoms were present in 95% of women for a month or more pre-infarct and the most frequent were unusual fatigue (70.7%) and sleep disturbance (47.8%). The most frequent acute symptoms were shortness of breath (57.9%), weakness (54.8%), unusual fatigue (42.9%), cold sweat (39%), dizziness (39%), back discomfort (37%) and high chest discomfort (27.7%). 43% of patients in this series experienced no chest discomfort at all, and the authors postulated that lack of significant chest pain may be a major reason that women have more unrecognized MIs.

...THE DATA REVEAL NO EVIDENCE THAT TREATING WOMEN WITHOUT CLINICALLY APPARENT VASCULAR DISEASE WITH STATINS, EVEN THOSE AT HIGH RISK, LOWERS THEIR RISK OF CARDIAC EVENTS.”

The greater mortality rate of women with MIs has been attributed to the fact that they tend to be older than men at the time of presentation. However, a retrospective study of 155,565 women and 229,313 men with acute MI enrolled in the National Registry of Myocardial Infarction 2, found that a higher hospital mortality rate occurred only among younger women.46 Women under age 50 had a 6.1% hospital mortality rate compared to 2.9% for same aged men. The sex difference in mortality rates decreased with increasing age and was not significant after age 74. The authors also found more co-morbid conditions, higher pulse rates and lower systolic blood pressures among younger women than among younger men but not in older women compared to older men. Of interest, despite these findings, younger women were less likely than younger men to present with ST-segment elevation, and while they had similar infarct locations, creatine kinase levels and left ventricular ejection fractions, they had higher rates of hypotension, shock, heart failure and bleeding.

Women undergoing coronary artery bypass grafting (CABG) have also been noted to have a higher mortality than men. This has traditionally been ascribed to their older age. However, just as is the case with MI, an analysis of 51,187 patients (30% women) who had CABG between 1993 and 1999 found that younger women had higher hospital mortality than men (3.4% versus 1.1% for women and men < 50 years of age and 2.6% versus 1.1% for women and men 50 to 59 years of age).57 Among patients 80 years of age or older there was no significant difference in mortality (9.0% in women versus 8.3% in men). Younger women undergoing CABG had more risk factors and comorbid conditions than age-matched men but multivariate analysis found that this explained less than 30% of the mortality difference between younger men and women.

This mortality difference persisted after adjustment for body size and remains largely unexplained. Also, women in this study had angiographically less severe coronary artery disease (CAD) and better left ventricular (LV) function in all age categories.

In contrast, a review of the results of percutaneous coronary intervention (PCI) in 200168 found that the apparent gender difference in outcomes was negated after adjustment for body size. Using data from the National Cardiovascular Network Database on 109,708 patients (33% women) who underwent PCI between 1994 and 1998, researchers found that
women had higher risks for stroke, vascular complications and repeat in-hospital procedures, even after risk-adjustment. They had higher unadjusted hospital mortality rates (1.8% versus 1.0%) but after correction for body size, gender was not found to be an independent predictor of mortality.

Perhaps the most striking gender disparity with regard to cardiovascular disease is the under-representation of women in clinical trials. Physicians are urged to practice “evidence-based medicine” but when it comes to women, the evidence is often lacking, particularly in the area of drug treatment of hyperlipidemia. The guidelines for treatment of hyperlipidemia take no account of gender (except in the different cut points for the normal level of HDL-cholesterol). But there is reason to believe that they should. Over the past few decades several large, randomized, placebo-controlled trials have shown the benefit of statins (and to a lesser extent fibrates) in both primary and secondary prevention of cardiovascular events.

Of the three large primary prevention trials of statin use, two included women: the AFCAPS/TexCAPS trial and ASCOT-LLA trials. (Overall, women made up 12.5% of the 23,505 subjects enrolled in the three large primary prevention trials of statins. The WOSCOPS trial enrolled only men.) The AFCAPS/TexCAPS trial was undertaken to determine if treatment with lovastatin in subjects without clinically evident ASCVD with average total cholesterol (TC) and LDL-cholesterol (LDL-C) levels, but below average HDL-cholesterol (HDL-C), would lead to a reduction in the risk of first major coronary event. This was defined as fatal or non-fatal MI, unstable angina, or sudden cardiac death. AFCAPS/TexCAPS enrolled 997 women (15% of the study population). The ages of participants ranged from 45 to 73 years for the women. Overall, the trial found a statistically significant benefit of treatment with a 37% relative risk reduction in the likelihood of first major coronary event. However, on gender-specific analysis, while 13 primary end point events occurred in women on placebo and 7 events occurred in women on lovastatin, this was not a statistically significant difference, given the small numbers of events. (In contrast there were 170 events in men on placebo compared to 109 events in men on lovastatin.)

The ASCOT-LLA was a trial in hypertensive patients without known ASCVD but with at least three other risk factors who were randomized to either placebo or atorvastatin and followed for the occurrence of the composite primary end point of non-fatal MI or fatal coronary heart disease. Participants’ ages ranged from 40 to 79 years. ASCOT-LLA enrolled 1,942 women (19% of the study population). Overall the trial found a statistically significant 36% relative risk reduction in the likelihood of the primary end point. However, on gender-specific analysis there were 19 primary events in the women on atorvastatin and 17 events in the women on placebo, again, not a statistically significant difference. (In contrast there were 81 primary events in men on atorvastatin and 137 events in men on placebo.) Summarizing the results of these two primary prevention trials of statin use, there were 30 events in 1,461 women on placebo and 26 events in 1,478 women on statins, a difference that is not statistically significant (p = 0.56).

Despite this lack of evidence for the efficacy of statins in the primary prevention of coronary events in women, both the Adult Treatment Panel III and the more recent “Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women” recommend statin use in women with LDL-C levels above a certain value based on level of risk, even in the absence of diagnosed ASCVD. However, the data reveal no evidence that treating women without clinically apparent vascular disease with statins, even those at high risk, lowers their risk of cardiac events.

When it comes to secondary prevention with statins, the data in women are also not as compelling as they are in men. During the past two decades five large secondary prevention trials of statins in coronary heart disease included men and women. Women made up 25% of the 43,957 subjects enrolled in the 4S trial, the Heart Protection Study, the Cholesterol and Recurrent Events Trial, the LIPID Trial and the PROSPER Trial. All of these studies showed a statistically significant decrease in the relative risk of coronary events in statin treated compared to placebo treated men. In contrast, gender-specific analysis did not find a statistically significant decrease in risk of cardiac events in women in two of these five trials (LIPID and PROSPER), while the other three did demonstrate benefit in women.

Why the disparity between the findings with regard to the efficacy of statins in men versus women, at least with respect to primary prevention? It might be due to the small numbers of women in the statin trials. However, there is an alternative explanation. Elevations of LDL-C do not appear to be as potent a risk factor in women as they are in men. Even among kindred with Type II Familial Hyperlipoproteinemia, the onset of coronary artery disease in women lags 10 to 15 years behind that of men with equivalent and very high levels of LDL-C. More than twenty years ago, women were noted to have significantly less cholesterol in small dense LDL and more in large LDL than men. Small dense LDL-C particles are more atherogenic than large fluffy LDL-C particles and since women, at least before the menopause, have more of the latter, it is likely that equivalent levels of LDL-C are less atherogenic in women than men.

In support of this hypothesis, a follow-up study of 2,406 men and 2,056 women enrolled in the Lipid Research Clinics program who were free of vascular disease and aged 40 to 64 years at entry, followed for an average of 19 years, found that only elevated non HDL-C and low HDL-C significantly predicted cardiovascular disease (CVD) mortality in women, whereas TC, LDL-C, non HDL-C and low HDL-C all predicted CVD mortality in men.

More recently, it has been suggested that the LDL-C goal for very high-risk patients be lowered to 70 mg/dl or less, based on the findings of the PROVE-IT trial, which en-
rolled 4162 patients (22% women) with acute coronary syndromes to receive either 40 mg of pravastatin or 80 mg of atorvastatin. The subjects in the atorvastatin group, who achieved a median LDL-C level of 62 mg/dl, had a statistically significant 16% relative risk reduction in the rate of the primary end point compared to the pravastatin treated group who achieved a median LDL-C level of 95 mg/dl. The benefit of intensive therapy with high dose atorvastatin was consistent across all prespecified subgroups, including women.

The preventive guidelines for women also recommend treating non-HDL-C and low HDL-C with a fibrate or niacin if they are abnormal once the LDL-C goal is achieved. There is not only a paucity of data to support this, there are no data. The two controlled trials of fibrates (the Helsinki Heart Study and VA-HIT) that showed benefit in reducing cardiac events enrolled only men.

Where do these studies leave us with respect to primary prevention in women? Unfortunately, we do not have evidence-based answers to this question. For premenopausal women with no other risk factors than an LDL-cholesterol above the current threshold, statins have not been shown to decrease the risk of cardiac events. There is clearly no harm in counseling ALL patients on weight control, regular exercise and heart healthy diet. The use of statins in ostensibly healthy young women should probably be reserved for those with Familial Hypercholesterolemia where LDL-C values are in the range of 300 to 400 mg/dl. In addition, their use is contraindicated during pregnancy and lactation; most package inserts state that: “STATINS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF RISKS, we know little about their long-term effects. If we are proposing to treat healthy, low-risk women for decades it behooves us to be certain that efficacy is beyond doubt and that benefits outweigh the risks. We simply do not know this with regard to statin (or fibrate/niacin) use in young women who do not have vascular disease.

The recently reported results of the trial of aspirin for primary prevention of cardiovascular disease in women demonstrate the fallacy of assuming that results in men can be generalized to women. Among 39,875 healthy women 45 years of age or older who were randomized to either 100 mg of aspirin every other day or placebo there was a 24% reduction in the risk of ischemic stroke but no decrease in the risk of fatal or non-fatal MI or death from cardiovascular causes. (However, in women 65 or older aspirin significantly reduced the risk of both ischemic stroke and MI.) These results in women contrast with those of the Physicians’ Health Study which found that aspirin significantly reduced the risk of MI in that all-male cohort but had no significant effect on the risk of stroke. The accompanying editorial concludes, “…clinical research…needs always to account for the evolutionary biology of sex.”

The Institute of Medicine also noted the importance of taking sex into account: “Sex matters. Sex, that is, being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research.”

In summary there are gender-specific differences in cardiovascular disease including age at presentation, risk factor weighting, response to medicines, symptoms and mortality. More research needs to be done to elucidate gender differences and to determine the safest, most efficacious preventive strategies and treatments in both sexes.

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Barbara H. Roberts, MD, is Director, The Women’s Cardiac Center at The Miriam Hospital, and Associate Clinical Professor of Medicine, Brown Medical School.

Correspondence:
Barbara H. Roberts, MD
The Women’s Cardiac Center
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906
Phone: (401) 793-7870
E-mail: BHRoberts@lifespan.org
IRRITABLE BOWEL SYNDROME

Rossana Moura, MD

Irritable Bowel Syndrome (IBS) affects up to 20% of the US population, with a 2:1 female-to-male ratio. IBS accounts for approximately 3 million physician visits annually, 12% of office visits to primary care physicians, 28% of all referrals to gastroenterologists; and $1.7 billion to $10 billion in direct annual medical costs (excluding medications) and up to $20 billion in indirect costs (e.g., lost work productivity and missed workdays).

The higher prevalence of the disorder in American women might reflect their increased willingness to seek medical advice. Other factors influencing consultation in IBS include access to care, symptom severity, fear of cancer, psychiatric comorbidities and personality factors, including learned illness behavior and recent life events.

Definition

Although first recognized nearly 2 centuries ago, IBS remains widely misunderstood by both patients and physicians. Because it is a functional disorder, no organic or structural abnormality can be identified. The lack of objective findings can be frustrating and the differential diagnosis broad. For that reason, a number of symptom-based criteria have been developed to try to simplify and standardize the diagnostic approach to IBS; in 1978 the Manning criteria were published, and most recently, the Rome II criteria. (Table)

Clinical Symptoms

IBS is a chronic condition and consists of abdominal pain or discomfort, associated with changes in bowel pattern (constipation, diarrhea or alternation of both). Patients with IBS are usually categorized, according to their primary bowel habits, as having IBS-C (less than three bowel movements per week, presence of hard stools, straining and lumpy stools), IBS-D (more than three bowel movements per day, loose watery stools, and urgency), or IBS-A (alternating constipation and diarrhea). Women are more likely to report constipation-predominant bowel habits, while men are more likely to report diarrhea. Women are also more likely than men to complain of bloating.

Symptoms usually begin in late adolescence or early adult life, although the problem may not be diagnosed for years. The peak prevalence of IBS occurs in the third and fourth decades; the prevalence decreases in the sixth and seventh decades of life. Although IBS can be diagnosed at any age, a new diagnosis of IBS should be made cautiously in patients older than 60 because other diseases may present with similar symptoms.

Besides the symptoms in the Rome II criteria, patients with IBS frequently suffer from straining, bloating, urgency, feeling of incomplete evacuation and/or passage of mucus during a bowel movement. In many cases, patients with IBS also complain of tiredness, breathlessness, indigestion, heartburn, back pain, headache, dizziness, urinary frequency, muscle pains, arthritis, palpitations, anorexia, sleeplessness, menorrhagia, dyspareunia, panic attacks, anxiety and depression.

IBS can be associated with significant emotional distress, poor quality of life, disability and increased health care costs. Patients with IBS miss three times as many work days as those without the disorder.
fact, after the common cold, IBS is the second leading cause of work absenteeism.\textsuperscript{13} It is not uncommon for IBS sufferers to limit their social interactions, cancel appointments, stop traveling, avoid sexual intercourse and even stay confined to the house for fear of embarrassment. Patients often state that their symptoms dominate their lives.

**Pathophysiology**

IBS is not caused by a single factor; rather, it is a disorder in which a number of physiologic processes are involved. These include abnormalities in intestinal motility, alterations in visceral sensory function, changes in central nervous system (CNS) processing of sensory information, as well as psychosocial and other factors.

**Altered Gut Motility**

Contractile and electrical activities in the distal colon are exaggerated in patients with IBS, and can be demonstrated by increased rectosigmoid contractile activity in response to a meal, injections of cholecystokinin, local infusion of bile acids and distention of the rectum.\textsuperscript{14} Several studies have shown an abnormally high frequency of discrete clusters of contractions in the jejunum and prolonged propagated contractions in the ileum,\textsuperscript{15} but these findings are not specific for IBS. Abnormal intestinal motility does not seem to explain IBS in all patients, and it is unclear whether it is a symptom or cause of the disorder.

**Enhanced Visceral Sensitivity**

Patients with IBS exhibit more symptoms during transit of a standard meal\textsuperscript{16} and during transit of gases\textsuperscript{17} than do normal subjects. There is also greater sensitivity to rectal distention at volumes lower than those that cause pain in normal volunteers.\textsuperscript{18} The observations that IBS patients are more likely than controls to notice intestinal contractions and gas are consistent with the concept of enhanced perception of visceral events. However, IBS patients do not show somatic hypersensitivity to pain and may have elevated somatic pain thresholds.\textsuperscript{19}

**Post Infectious**

There is well-documented relationship between an attack of gastroenteritis and subsequent development of chronic symptoms compatible with the diagnosis of IBS. The precise mechanism for this type of IBS is unknown; but several possibilities exist. An infectious process may transiently or permanently injure the enteric nervous system; or alternatively, an infectious agent may initiate a cycle of chronic mucosal inflammation that eventually alters gut motility and/or sensation. Studies have demonstrated that an increased number of activated immune cells are present within the intestinal mucosa of patients with IBS.\textsuperscript{20} Post infectious IBS patients tend to be women and experience more severe acute illness. Several studies have found that major, sustained stressful live events occurring either before or immediately following the acute infection are the strongest predictors of IBS development.\textsuperscript{21}

**Brain-Gut Interactions**

The motor, sensory and secretory activities of the intestines occur through coordinated bidirectional communications between the CNS, ANS (autonomic nervous system), and ENS (enteric nervous system), forming what is known as the brain-gut axis.\textsuperscript{22} GI symptoms can result not only from a disorder in the gut itself but also from dysregulated interactions at any level among these control mechanisms of the gut.

Using positron emission tomography scanning of the CNS during rectal balloon distention, Silverman et al\textsuperscript{23} demonstrated that IBS patients had increased activity in the prefrontal cortex (an area associated with anxiety and hypervigilance), and reduced activity in the anterior cingulate cortex (an area important for opioid binding), when compared to healthy subjects. Another study that used functional magnetic resonance imaging also reported differences in CNS activity in patients with IBS relative to subjects without IBS.\textsuperscript{24} These findings suggest that patients with IBS may process sensory information from the GI tract differently from patients without IBS. In addition, other stimuli, such as stress, anxiety, and depression, may modulate sensory processing and influence the perception of pain.

**Role of Serotonin**

Serotonin (5-hydroxytryptamine, 5-HT) is a naturally occurring neurotransmitter and signaling molecule. Ninety-five percent of the body’s serotonin is found in the gastrointestinal tract. Serotonin appears to be the common link in GI motility, intestinal secretion, and pain perception and is involved at multiple levels in the bidirectional interactions between the ENS and the CNS. In the GI tract, serotonin acts via intrinsic ENS neurons to initiate motor and secretory reflexes and via extrinsic ENS neurons to initiate bowel-related sensations such as pain and bloating. As many as 14 serotonin-receptor subtypes have been identified. Of these, the 5-HT\textsubscript{1A}, 5-HT\textsubscript{1B}, and 5-HT\textsubscript{3} subtypes are considered the most clinically relevant for lower GI-tract function and regulation.\textsuperscript{25}

**Hormonal Factors**

GI symptoms in women appear to be influenced by female sex hormones, increasing during the late luteal phase and early menses. The effect of menstruation on IBS symptoms is thought to be mediated by ovarian hormones affecting bowel function either centrally or peripherally. This is supported by the finding that during pregnancy (state of high estrogen and progesterone levels), GI symptoms (nausea, constipation, upper GI distress) increase\textsuperscript{26} and that IBS patients on oral contraceptives that mimic naturally fluctuating ovarian hormones will continue to have amplification of their GI symptoms during menses.\textsuperscript{26} In addition to a higher prevalence of visceral pain in women patients during the perimenstrual phase,\textsuperscript{3} the diagnosis of IBS is threefold more common in women with dysmenorrhea than in those without.\textsuperscript{27}

**Food Intolerance**

Although studies of dietary restriction followed by the sequential reintroduction of single foods have suggested that food intolerance exists in up to two thirds of patients
with IBS, true food allergies are uncommon. Instead, in most cases of IBS, it is not what the patient eats that causes symptoms; rather, the simple act of eating precipitates bloating, gas, and abdominal discomfort. A number of foods are known to cause symptoms that can mimic or aggravate IBS; e.g., dairy products, legumes and cruciferous vegetables (broccoli, cauliflower and cabbage), carbonated beverages, caffeine, fatty foods, alcohol, sorbitol and certain spices.

**Psychosocial Factors**

People with IBS who seek medical help are more likely to suffer from coexisting psychosocial stress and dysfunction than those who do not seek medical advice. Psychological disorders are frequently seen concomitantly with IBS, but probably do not cause the symptoms. Depression and anxiety are the most common psychiatric conditions, but phobias, obsessional behavior, sleep disturbance, multiple somatic symptoms, hostile feelings, panic attacks, and alcohol abuse are also more common than in healthy control subjects. A history of major life stress (sexual, physical or verbal abuse, divorce or family death) plays an important role in modulating the illness experience and its clinical outcome. Patients with IBS tend to be more preoccupied with diseases and tend to report more illness not related to IBS. Female patients with IBS are three times as likely to undergo cholecystectomy, twice as likely to have an appendectomy or hysterectomy, and 50% more likely to have back surgery. Such operations may lead to scar pain, adhesions, and further alteration in bowel habit.

**Diagnosis**

Evidence-based consensus recommendations developed by the ACG **Functional Gastrointestinal Disorders (FIDG)** Task Force advocate a stepwise, symptom-based approach to the diagnosis of IBS. This approach involves identifying the patient's primary symptoms, conducting a thorough patient history and physical examination to exclude signs suggestive of other diagnosis and making a decision about diagnostic testing on the basis of the history and physical examination. If alarm features or "red flags" are present, such as severe or nocturnal diarrhea, unintentional weight loss, gastrointestinal bleeding, anemia or family history of colon cancer, directed diagnostic testing should be performed to rule out the possibility of organic disease.

Several intestinal disorders have similar symptoms, such as lactose intolerance, celiac sprue, inflammatory bowel disease and microscopic colitis. The danger of missing a diagnosis needs to be balanced against the cost of performing unnecessary investigations and the risk of reinforcing illness behavior. Many physicians are concerned about diagnosing IBS confidently without performing any objective tests. A complete blood cell count should be obtained, the erythrocyte sedimentation rate (or C-reactive protein level) and the thyroid-stimulating hormone level measured. If diarrhea is the patient's primary complaint, stool samples should be tested. Serologic tests for celiac disease can also be performed in patients with persistent diarrhea. Flexible sigmoidoscopy may be recommended for younger patients with rectal discomfort or bleeding. A colonoscopy is warranted in patients who are 50 years of age or older, have a strong family history of inflammatory bowel disease or colorectal cancer, or show evidence of anemia. In patients with diarrhea, random colon biopsies can be obtained to rule out microscopic colitis.

**Treatment**

Although the cause of IBS is not known and there is no cure, there are several ways to manage this disorder, according to the type and severity of symptoms. The chronic nature of IBS and the challenge of controlling its symptoms can be frustrating for both patients and doctors. An effective physician-patient relationship plays an important part of treatment. Patients need to be educated and reassured about their condition.

The efficacy of drugs in IBS is difficult to demonstrate due to the high placebo response rate. The same applies to dietary restrictions and alternative medicine. Nonetheless, such therapies should not be dismissed simply because they have not been verified in randomized controlled trials. A symptom diary may help pinpoint possible triggers and guide treatment options. Any food that appears to precipitate symptoms should obviously be avoided. Increasing dietary fiber (either by adding foods to the diet or using fiber supplements) can relieve constipation, but may also help in diarrhea since it can improve the consistency of stools. Dietary fiber supplements should be increased to the prescribed dose over several weeks to reduce symptoms of excessive intestinal gas. Gas-producing foods, gum and carbonated drinks should be avoided if the patients suffer from bloating. Lactose intolerance is very common in the general population, and avoidance of dairy products may be helpful in reducing symptoms of IBS.

In patients with abdominal pain, anticholinergic drugs, which have antispasmodic effects, may be prescribed to relieve severe cramping. Drugs in this category include dicyclomine (Bentyl®) and hyoscyamine (Levsin®). Common side-effects include dry mouth and eyes and blurred vision. Antidepressants may also be helpful due to a pain relieving effect that is independent of their depression relieving effect. Tricyclics slow movement of contents through the gastrointestinal tract and may be most helpful in people with diarrhea-predominant IBS. Selective serotonin reuptake inhibitors can be prescribed for IBS with constipation. Magnesium hydroxide, lactulose or polyethylene glycol solutions can also be prescribed for constipation. For diarrhea-predominant IBS, antidiarrheal drugs such as loperamide or diphenoxylate with atropine can help slow bowel transit time. These drugs should only be used as needed, and rarely on a continuous basis. Cholestryamine, bile acid binding agent, can also be used for diarrhea in patients who have undergone prior cholecystectomy.

Drugs affecting serotonin receptors were developed for the treatment of IBS. Women treated with the 5-
HT3 receptor antagonist alosetron (lotronex) experience significant improvements in abdominal pain and stool frequency and consistency compared to placebo. After its initial approval in 2000 by the US Food and Drug Administration (FDA), the drug was withdrawn from the market that same year due to reports of ischemic colitis. In response to patient and public demand, the FDA reinstated the drug in 2002 under restrictive guidelines.

Phase III trials have demonstrated the efficacy of cilansetron, another 5-HT3 receptor antagonist, in women and men with diarrhea-predominant IBS. After the review process, the FDA recently notified the manufacturing company (Solvay Pharmaceuticals) that further clinical trials are needed before cilansetron can be approved.

Tegaserod (Zelnorm) is a partial 5-HT3 agonist. This drug accelerates bowel transit, relieving global IBS symptoms, pain and constipation. Although initially indicated only for female IBS-C patients, it was also recently shown to be effective for the treatment of chronic constipation in men and women and is also approved for this indication. Headache and diarrhea are the most commonly reported adverse events. A recent update on the safety of tegaserod was issued by the manufacturer about rare cases of ischemic colitis in the post-marketing use of this agent.

Non-pharmacological treatment, such as massage, acupuncture, shiatsu, meditation and hypnotherapy, can be considered in IBS patients with moderate to severe symptoms, when patients have failed medical treatments, or when there is evidence of stress or psychological factors contributing to symptom exacerbations.

**Conclusion**

In the United States, up to 70% of patients with IBS symptoms do not seek medical attention. Longitudinal studies have shown that once IBS has been diagnosed, nearly 75% of patients will carry the diagnosis 5 years later. With a careful history and physical examination, it is often possible for the physician to make a positive diagnosis of IBS. It is important in the initial visit that psychosocial factors that may contribute to symptoms are elicited from the patient. It is also important that patients receive an adequate explanation about the nature of their symptoms and the overall good prognosis. Although IBS can produce substantial physical discomfort and emotional distress, the vast majority of patients learn to control their symptoms.

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Rossana Moura, MD, is a gastroenterologist, Program in Women’s Digestive Disorders, Women & Infants’ Hospital, and Clinical Instructor of Medicine, Brown Medical School.

**Correspondence:** Rossana Moura, MD
Women & Infants Hospital
100 Dudley Street, 3rd Floor,
Providence, RI 02905
Phone: (401) 453-7953
E-mail: Rmoura@wihri.org
UPDATE IN SURGICAL MANAGEMENT OF FEMALE STRESS URINARY INCONTINENCE

Vivian W. Sung, MD, and Deborah L. Myers, MD

It is estimated that the rate of stress urinary incontinence (SUI) is approximately 35% in older women and 28% in younger women. As life expectancy among the US population increases, the prevalence of this disorder will increase. It is predicted that by year 2030, the number of women over age 55 will almost double to over 60 million. The predicted shift in demographic makeup of the United States and improved overall health will lead to an increase in the number of women receiving care for SUI.

Although rarely life threatening, SUI may precipitate insecurity, embarrassment, depression, social disengagement, and/or psychological and functional decline. Spousal relationships can be negatively affected and women with urinary incontinence may have poorer sexual functioning. In 1995, the annual direct cost of urinary incontinence in the United States was estimated at $16.3 billion; the majority of these costs went to routine care including laundry and protective garments (70%). Only 1-3% of these costs were attributed to diagnosis and treatment of the disorder.

In the past urinary incontinence was considered to be a natural, and unavoidable, result of aging. Despite treatments, it is estimated that only 13% of women will seek help for this condition. Some women, with mild symptoms do not feel that treatment is needed. Other women are embarrassed to speak with a health care provider about the condition; some women may believe the only treatment is major surgery. Finally, physicians may not feel prepared to discuss treatment options with their patients. The Agency of Health Care Policy and Research estimated that only 20% of physicians routinely discussed urinary incontinence with patients and most physicians felt inadequately prepared to discuss options. As minimally invasive surgical treatments evolve, women who were once considered non-surgical candidates have increased options. This article will review diagnosis, management and surgical treatment options for SUI.

**Diagnosis**

The International Continence Society defines SUI symptoms as “involuntary leakage on effort or exertion, or on sneezing or coughing, in an amount unacceptable to the patient.” SUI can be evaluated and treated at many levels, depending on how bothersome the symptoms are to the patient. It is possible to reach a working diagnosis of SUI based on symptoms alone and the clinician may initiate conservative, non-surgical treatment. Women who have a satisfactory response may not need further testing.

Women who do not respond to conservative therapy will need a more detailed evaluation. A detailed history includes questions about frequency and amount of leakage, precipitating factors, impact of leakage on daily life and pad use pelvic organ prolapse symptoms, urinary urgency, nocturia, incomplete bladder emptying, hematuria, and anal incontinence. A detailed pelvic examination assesses neurologic function, pelvic organ support, and pelvic muscle strength. A cough stress test will help confirm the diagnosis. A postvoid residual will help rule out urinary retention. A urinalysis and culture will help rule out urinary tract infection.

Further assessment of bladder function with urodynamic testing is recommended for women with an unclear diagnosis, women considering surgical treatment, women with an elevated postvoid residual volume or a neurologic condition, significant pelvic organ prolapse, or prior attempts at surgical correction. Urodynamic testing provides a more precise evaluation and includes a combination of tests measuring urethral and bladder function during bladder filling, storage, and emptying.

**Treatment**

The treatment goal for SUI is achieving a cure or minimizing the impact of the condition. Once the diagnosis of stress incontinence is made, a treatment strategy will consider the severity of symptoms, degree of bother, associated pelvic floor conditions, prior surgery, and a patient’s willingness to accept the risks and success rates of different interventions. Many women report satisfaction even if they are not completely dry. Conservative options should always be discussed. These include behavioral modification (fluid intake modification, weight loss for obese patients), pelvic floor exercises with or without biofeedback, and vaginal supportive devices. Pharmacologic therapy includes tricyclic antidepressants (imipramine) which facilitate bladder storage and increase urethral resistance. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is being investigated in the treatment of SUI.

Patients who are dissatisfied with conservative measures may opt for surgical treatment. The choice of procedure is guided in part by severity of SUI, presence of associated pelvic prolapse, voiding function, patient comorbidities and patient preference.

**Retropubic Colposuspensions (MMK or Burch)**

The basic goal of retropubic suspensions is to suspend the anterior vagina and stabilize the bladder neck in a retropubic position, allowing urethral
compression against a stable suburethral support. Trans-abdominal retropubic suspensions involve entering the retropubic space, placing sutures in the periurethral fascia and suspension to nearby structures including the periosteum of the pubic bone or Cooper’s ligament.12-15

In 1997, members of a clinical guidelines panel from the American Urological Association reviewed the literature and outcomes data on surgical treatment of female SUI.16 The panel concluded that retropubic colposuspensions were effective in the treatment of SUI, with median cure rates of 84% (95% CI 79-88%) at 2 years or greater. Postoperative complications of retropubic procedures include voiding dysfunction (10%), prolonged urinary retention (5%), de novo detrusor overactivity (17%), and risk of future enterocoele (7-13%).17-19

A laparoscopic approach may also be used to perform the Burch colposuspension. Advantages of the laparoscopic approach include smaller skin incisions, quicker post-operative recovery and return to work. Disadvantages may include longer operative times, especially during the surgeon training period, and technical difficulty.

There is little level 1 evidence comparing the laparoscopic approach with the traditional abdominal approach. In 2004, the Cochrane Incontinence Group reviewed 8 randomized trials and concluded that the cure rate for laparoscopic colposuspension trended lower compared to the open approach (relative risk 0.91; 95% CI 0.82-1.01).20 However, different techniques and modifications to overcome laparoscopic suturing, and inconsistent numbers of sutures were used between studies, making comparisons difficult and unreliable. The long-term success of laparoscopic colposuspension remains unclear and well-designed randomized trials are required to definitively compare these procedures.

**Bladder Neck Sling**

Suburethral slings are designed to support the bladder neck and urethra. The sling forms a “backboard” to support the urethra while providing a mild component of urethral compression. Due to increased dissection and concern of denervation with traditional slings, these procedures were often reserved for women with recurrent incontinence or intrinsic sphincter deficiency. The American Urological Association determined in 1997 that the sling procedure was an effective treatment for SUI. Median success rate for sling procedures were comparable to retropubic colposuspensions and estimated to be 83% (95% CI 75-88%) at 2 years or greater.

Numerous materials are available for suburethral slings. Autologous rectus fascia and fascia lata are commonly used and require either an abdominal or leg incision to harvest the fascia. There are also a variety of synthetic materials including Gore-Tex, prolene, and Mersilene. Comparative studies of ideal sling materials are lacking.

Similar to retropubic colposuspensions, bladder neck slings have a risk of voiding dysfunction of 12.8%, prolonged urinary retention of 8%, and de novo urge symptoms of 7%. The Urinary Incontinence Treatment Network, a National Institutes of Health-sponsored network including 9 centers, is comparing long-term (24 months) outcomes following Burch colposuspensions and autologous rectus fascia slings in a randomized trial.

**Midurethral Sling**

**Tension free vaginal tape (TVT):**

The search for more minimally invasive sling procedures led to the evolution of the TVT™ (Gynecare, Sommerville, NJ) sling. The TVT aims to restore continence through compensation of the pubourethral ligaments and formation of a firm backboard for the urethral to close against during episodes of increased intra-abdominal pressure.21 The TVT is tension-free, which differs from traditional bladder neck slings that have an obstructive component.

The TVT was introduced in the 1990s; initial success rates were reported through case series from individual institutions. Ulmsten, et al reported that at 2-3 years following the TVT, 86% of women were dry, an additional 13% were improved, and 3% had no improvement.22 Nilsson, et al reported five-year subjective and objective cure rates as 84.7% cure rate, 10.6% improvement rate, and a low 4.5% failure rate.23

The TVT may be performed under local or minimal regional anesthesia and is often performed on an outpatient or overnight stay basis. Operative time is short and in general, postoperative pain and recovery are less severe than traditional slings and retropubic colposuspensions. Two small 0.5-cm suprapubic skin incisions are made, and one 1.5 cm incision is made in the vagina over the midurethra. A thin strip of polypropylene mesh tape is then passed vaginally through the suprapubic incision on either side with 4-mm needles and the mesh is situated at the midurethra, tension free. There is no need to suture the mesh in place. Variations of the TVT include the SPARC ™ (American Medical Systems, Minnetonka, Minn), a “top-down” method of passing the needles.

Complication rates are overall favorable following the TVT. The risk of prolonged urinary retention is 2%, retropubic hematoma is 1.9%, de novo urinary urgency is 5%, and sling erosion is low, <1%.24,25 The most common intraoperative complication is bladder perforation (3.6%), but long-term sequelae following this event are rare. Although rare, there are reports of injury to bowel, iliac vessels and the obturator nerve.

In 2004, Ward and Hilton published results from a large, multi-center randomized trial comparing the TVT to the open Burch colposuspension.26 At 2 years, the authors found no difference in success rates between the two procedures. Depending on how missing data was treated, objective cure ranged from 63-85% for the TVT group and 51-87% for the colposuspension group. Women in the TVT group were less likely to have voiding dysfunction requiring self-catherization and had shorter recovery times.

**Trans-obturator tape (TOT)***

Given the rare but potentially serious complications with the TVT, there has been a search for a safer but equally effective alternative. The TOT
was first described in 1998; based on early case series, the clinical effectiveness was similar to the TVT. The TOT is also a midurethral sling, thus the same principles and mechanisms of the TVT apply. A small incision is made at each groin and a 1.5 cm vaginal incision is made in the anterior vagina over the midurethra. A thin strip of prolene mesh tape is placed under the midurethra which then passes behind the ischiopubic ramus, punctures the obturator membrane and passes through each corresponding groin incision. 

Like the TVT, the TOT is often performed under local or light regional anesthesia on an outpatient basis. Operative time is short, and patients recover quickly. A proposed advantage of the TOT is a decreased risk of bleeding, as there are no needles passed through the retropubic space and the great vessels are not at risk. This also theoretically decreases or eliminates the risk of bowel and bladder injury, although there has been a report of bladder perforation with this approach.27 Another proposed advantage is lower risk of urinary retention and voiding dysfunction, due to less risk of over-correction.

The greatest risk with this approach may be injury to the obturator nerve and vessels. In cadaver studies, the obturator nerve branches and bundle are on average 2.5-cm from the mesh.29 The most medial obturator vessel is on average 1.1-cm from the mesh. The risk of obturator nerve injury with this approach is likely low, and consequences of injury to obturator vessels are unknown. Based on a query of the MAUDE database, (an FDA database that collects physician initiated reports of complications associated with medical devices), the complication rate associated with the TOT is 0.0001%.29 However, this physician-initiated database likely underestimates the true complication rate.

There is very limited data comparing efficacy rates of the TOT with traditional bladder neck slings or the TVT. Based on one small randomized trial, the TOT approach is associated with a significantly shorter operative time compared to the TVT (approximately 15 vs. 30 minutes).30 However, this study was not powered to compare efficacy rates. Although the TOT appears promising, benefits, cure rates, management of nerve and vessel injury remain unclear. The TOT may be reserved for cases where the retropubic space should be avoided (i.e: women with prior retropubic surgery, history of retropubic bleed, history of reconstructive abdominoplasty). Well-designed, controlled and comparative studies are still needed before this approach is routinely used.

**Urethral Bulking Agents**

The goal of bulking agents in the urethra is to improve urethral coaptation during the storage phase and to maintain coaptation during episodes of increased intra-abdominal pressure. Bulking agents may be administered under local anesthesia as an outpatient procedure or performed in the office. The agents may be injected at the bladder neck using a periurethral or a transurethral approach.

Agents include glutaraldehyde cross-linked collagen, a highly purified suspension of bovine collagen (GAX™, CR Bard, GA). The implant does not cause any inflammatory reaction, but does degrade over time. All patients must undergo skin testing with collagen before the procedure to confirm that they are not sensitized to collagen, which may occur through dietary exposure.

Carbon beads are composed of non-absorbable pyrolytic carbon-coated zirconium oxide beads (Durasphere®, Boston Scientific, Natick, MA). Although in theory this agent is permanent and not biodegraded, cure rates have not been shown to be improved compared to collagen.31 There have also been reports of migration of the agent.

The Food and Drug Administration (FDA) recently approved ethylene vinyl alcohol (Tegess™, CR Bard) for transurethral injection. At body temperature, the polymer precipitates into a spongiform, non-absorbable mass; skin testing is not needed.

Other agents include silicone micro-particles, polytetrafluoroethylene paste, calcium hydroxyl apatite, and autologous fat. Overall, bulking agents have a wide range of success rates, from 13%-78%.32 Many women may need multiple injections to reach acceptable improvement. Long-term success and durability are the primary concerns with bulking agents. However, these procedures are very low risk and may be offered to women with multiple comorbidities, or women who are poor surgical candidates.

**Conclusion**

SUI is a common condition, and minimally invasive procedures may improve a woman's symptoms and quality of life. As the population ages, it will be important for health care providers to be familiar with the treatment options.
Urethral bulking agents
Mid-urethral sling
Retropubic colposuspension
Bladder neck sling
Mid-urethral sling
Urethral bulking agents

Table 2
Treatment Options for Stress Urinary Incontinence

Absorptive products
Behavioral therapy/Pelvic floor rehabilitation
Continuous catheterization
Occlusive devices
Pharmacologic therapy
Alpha-adrenergic agonists
Serotonin-norepinephrine reuptake inhibitors
Surgical treatment
Retropubic colposuspension
Bladder neck sling
Mid-urethral sling

References

Vivian W. Sung, MD, is a Fellow, Urogynecology and Reconstructive Pelvic Surgery, and a Fellow, T32 Fellowship in Clinical Trials and Epidemiology, Department of Obstetrics and Gynecology, Brown Medical School.
Deborah L. Myers, MD, is Director, Urogynecology and Reconstructive Pelvic Surgery, and Associate Professor of Obstetrics and Gynecology, Brown Medical School.

Correspondence:
Vivian W. Sung, MD
Women & Infants’ Hospital of RI
Division of Urogynecology and Reconstructive Pelvic Surgery
Center for Women’s Surgery
695 Eddy Street
Providence RI 02903
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E-mail: vsung@wihri.org

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Good things start here.
Obesity rates are reaching epidemic proportions in the United States and other industrialized nations. In the United States, 34.1% of the population is overweight (defined as a BMI of 25-29.9 kg/m²), while 31.1% are obese (BMI > 30 kg/m²). Obesity affects 34.0% of women and 28.1% of men. Non-Hispanic black women have the highest rates of obesity: nearly half are obese. (Table 1) Obesity is six times more prevalent among women of low as compared with high socioeconomic status.

Obesity causes, exacerbates, and predisposes to many diseases affecting women, including heart disease, breast and endometrial cancers, diabetes, urinary incontinence, and arthritis. Weight gain in women during adult life is associated with increased risk of heart disease and death. Even modest weight gains after age 18 dramatically increase the risk for the development of diabetes.

Fortunately, modest weight losses of 5%-10% of body weight are sufficient to control, or at least improve, most complications of obesity. Improvements in blood pressure, serum triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, blood glucose levels, sleep apnea, osteoarthritis, and gout are observed. In a recent large-scale study, increased physical activity and loss of 7 kg prevented or delayed the onset of type 2 diabetes in individuals with impaired glucose tolerance. Participants who were assigned to lifestyle intervention reduced their risk of developing type 2 diabetes by 58%. Participants receiving standard care plus pharmacotherapy (metformin) reduced their risk of type 2 diabetes by 31%; lifestyle intervention was twice as effective as medication.

**Key Components of Successful Weight Control**

Much of what we know about lifestyle change to promote successful weight loss is derived from the National Weight Control Registry (NWCR) data. The NWCR is a registry of individuals who have successfully maintained a loss of at least 13.6 kg for at least 1 year. However, the 5,000 participants in the NWCR have far exceeded these minimum criteria; on average, they have lost almost 70 lb and kept it off for 6 years. Research from the NWCR and randomized controlled trials have identified several key lifestyle changes for long-term successful weight control. (Table 2) These include consumption of a low calorie, low fat diet, engaging in high levels of physical activity, and self-monitoring.

Consumption of a low calorie, low fat diet. Although the optimal degree of caloric restriction remains unclear, typically diets of approximately 1200-1500 kcal/day for women and 1500-1800 for men are recommended, with fat intake <30% of calories. Data from the NWCR support these low calorie, low fat recommendations. In addition, 78% of registry members reported eating breakfast every day of the week. Maintaining consistency in the diet also appears to be a key characteristic of NWCR participants; most participants reported that their eating was the same on weekends and weekdays and on holidays/vacations and the rest of the year.

Recently, there has been renewed interest in diets that severely restrict carbohydrate intake, like the Atkins' and South Beach diets. Such diets are only beginning to be formally evaluated in weight loss trials. Short-term evaluations have found significantly greater weight losses with low carbohydrate regimens relative to low fat, low calorie regimens. Two long-term evaluations of low carbohydrate diets found no significant differences relative to low-fat diet controls at 1 year. Although low-carbohydrate dieters are often allowed to eat as much protein and fat as they desire, the average intake on these regimens is approximately 1500 kcal/day; this reduced calorie intake is responsible for the weight loss seen on these regimens.

Self-monitoring of body weight, food intake, and physical activity. Self-
Table 2. Key Strategies for Long Term Successful Weight Loss

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consume a low calorie diet</td>
<td>1200-1500 kcal/day for women 1500-1800 kcal/day for men</td>
</tr>
<tr>
<td>Consume a low fat diet</td>
<td>&lt;30% kcal/day from fat</td>
</tr>
<tr>
<td>Consume breakfast</td>
<td>Eat breakfast daily</td>
</tr>
<tr>
<td>Increase physical activity</td>
<td>Goal of 60 minutes/day</td>
</tr>
<tr>
<td>Self-monitor weight, intake, and exercise</td>
<td>Record daily</td>
</tr>
</tbody>
</table>

Monitoring appears to be another important ongoing strategy for successful weight loss. Seventy-five percent of members in the NWCR weighed themselves at least once per week, and 44% weighed themselves daily. Additionally, 50% of registry members reported that they still occasionally counted calories, fat grams, or both. Other treatment studies have confirmed the role of self-monitoring in successful weight management. Notably, self-monitoring is often not totally accurate; in fact, estimates of dietary intake obtained from such recording underestimate actual intake by 30% on average. Therefore, this technique should be viewed more as a behavior change tool than as an assessment technique.

Engaging in High Levels of Physical Activity. Correlational studies, as well as controlled trials, show consistently that persons who engage in regular physical activity are the ones most likely to maintain a reduced weight. Almost all participants (91%) in the NWCR reported engaging in regular physical activity. On average, women in the registry reported that they engaged in 2545 kcal/week of physical activity and men engaged in an average of 3293 kcal/week in physical activity. This amount of physical activity is comparable to walking about 28 miles/week or about an hour per day of moderate intensity physical activity. This amount of physical activity is also consistent with the United States Department of Agriculture’s (USDA) recommendations for the general public. The USDA recommends that adults engage in 60 to 90 minutes/day of moderate intensity physical activity and exercise equipment may also enhance exercise adherence and improve the maintenance of weight loss.

Treatments Specific for Women

Several treatments have been tailored to address weight concerns of women. Although the basic elements of treatment are consistent with standard weight control practices (i.e., modifying diet, physical activity, and self-monitoring), the timing and structure of treatment may be tailored to address the needs of women.

Pregnancy. One period when obesity prevention efforts may be particularly effective for women is the period surrounding pregnancy. Although studies of the general population have reported average weight gains of only 0.4 to 3.8 kg more than aging, approximately 25% of women experience a weight gain of 4.5 kg or more with pregnancy. Moreover, weight changes during pregnancy are strongly related to subsequent weight change and future obesity.
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The single strongest predictor of weight gain from pre-to 1-year post-pregnancy is the magnitude of weight gained during pregnancy. The National Academy of Science Institute of Medicine (IOM) has formulated recommendations for healthy weight gain during pregnancy. However, in a recent study of 500 pregnancies in Rhode Island, we found that more than one-third of normal weight women and two thirds of overweight women exceeded these recommended levels; similar findings have been observed elsewhere.

Women with excessive weight gains during pregnancy are at increased risk of retaining significant degrees of weight postpartum. Moreover, weight gains that exceed the recommended levels have been connected to hypertension, diabetes, pre-eclampsia, cesarean sections, and babies that are large for gestational age. Helping women gain the recommended amount during pregnancy through healthy eating, physical activity, and self-monitoring, could prevent excessive weight retention and its associated complications. The years preceding and/or following pregnancy may provide other opportunities (“teachable moments”) for practitioners to help women achieve and maintain a healthy body weight. Breastfeeding for one-year post-partum may slightly reduce one-year weight retention, but has other benefits for maternal and infant health. Our clinic is seeking to determine whether the incidence of pregnancy-associated weight retention and obesity can be reduced through behavioral lifestyle interventions that target the pre-pregnancy, pregnancy, and/or the postpartum periods.

Menopause Another high-risk time for weight gain in women is the period surrounding menopause. In a longitudinal study of 541 healthy pre-menopausal women, aged 42 – 50 at study entry, the average weight gain was 5 pounds over 3 years and 12 pounds over 8 years. This gain was associated primarily with aging, rather than with the hormonal changes of menopause per se. Moreover, decreased physical activity was the most consistent behavioral factor associated with this gain.

The menopausal transition is associated with a worsening in cholesterol levels, an effect which is particularly pronounced in women who gain weight at this time. Therefore, lifestyle intervention aimed at modifying dietary and physical activity behaviors might help prevent both the weight gain and the worsening in cardiovascular risk factors. The Women’s Healthy Lifestyle Project was a 5-year randomized clinical trial testing the hypothesis that lifestyle intervention could reduce the magnitude of weight gain and the increase in LDL-cholesterol seen in women during the time of the menopause. The 535 participants were aged 44 – 50, had a BMI of 20 – 34, fasting cholesterol of 140 – 260 mg/dl and a fasting LDL-C of 80 – 160 mg/dl. These women were randomly assigned to lifestyle intervention or an assessment only control group.

All women, including those who were normal weight, were encouraged to lose weight initially to offset the anticipated weight gain. Women who were normal weight (BMI ≤ 24 mg/dl) were encouraged to lose 5 lbs; those with a BMI of 25 – 26 were encouraged to lose 10 lbs; those with a BMI of 27 – 34 were encouraged to lose 15 lbs. Women consumed a low calorie/low fat diet and increased physical activity to a goal of 1000 – 1500 kcal/week. Intervention activities included 6 months of group meetings followed by periodic individual and group sessions throughout the 4 years. Follow-up assessments were held at 6, 18, 30, 42, and 54 months.

The intervention was effective in blunting the anticipated gain; the intervention group lost 10.8 lb during the first 6 months. Although these women gradually regained weight over the course of the trial, they maintained a weight loss of -0.2 lb at 54 months. This contrasted with a 5.2 lb weight gain in the control group. At the end of the study, 55% of the intervention participants were at or below their baseline weight, compared with 26% of controls (p < .001). Weight loss was strongly associated with adherence to both physical activity and the dietary prescriptions.

The intervention also produced significant effects on lipids, blood pressure, insulin, and glucose. At month 54, LDL cholesterol in the intervention group had increased by 3.5 mg/dl, whereas the control group had increased by 8.9 mg/dl (p <.009). Waist circumference decreased 2.9 cm in the intervention group compared with .5 cm in the control. Thus, intervention at this time period may have multiple benefits for women.

Urinary incontinence Urinary incontinence may be alleviated by weight loss. An estimated 13+ million women in the US have urinary incontinence; including approximately 25% of reproductive age women and 50% of postmenopausal women. Epidemiological studies show that obesity is a strong risk factor for incontinence; each 5-unit increase in BMI leads to 60% increase in risk of daily incontinence. Among older women with incontinence, 65 – 75% are overweight.

Several studies have suggested that weight loss may improve incontinence. Subak et al. reported results of a small randomized trial with 42 overweight or obese incontinent women: 22 were randomized to an immediate weight loss condition, 20 to a delayed treatment control. The weight loss intervention included a very low calorie diet, exercise, and behavior modification. The intervention-group women lost 14 kg compared to a 0 kg in the control group. This weight loss resulted in a 60% reduction in weekly incontinence episodes compared to a 15% reduction in the control group. In the intervention group, 16% of women had 100% improvement in incontinence, 37% were at least 75% improved, and 58% were at least 50% improved. Stress and urge incontinence both decreased in the treatment group vs. the wait-list.

The NIH (NIDDK) recently funded a multi-center clinical trial, PRIDE (Program to Reduce Incontinence through Diet and Exercise), testing the effectiveness of weight loss for women with urinary
incontinence. Researchers at the Weight Control & Diabetes Research Center, The Miriam Hospital, are one of the Centers participating in this trial. A total of 165 women will be studied at The Miriam Hospital. (Table 3)

**Concerns about Weight Loss in Women**

In the past, dieting was criticized for limited effectiveness, causing adverse emotional responses or precipitating binge eating. However, recent studies and a review by the National Task Force on the Prevention and Treatment have put these concerns to rest. The review concluded that dieting in overweight and obese women is not associated with adverse psychosocial or behavioral effects. On the contrary, dieting and weight loss are associated with numerous psychosocial and physical benefits. In particular, weight loss regimens including very low calorie diets have not been shown to increase binge eating.

Dietary-induced weight loss may result in a loss of bone mass in overweight women. In a randomized study, women in the weight loss intervention who lost 3.2 kg over 18 months experienced a 2-fold increase in rate of hip bone mineral density (BMD) loss compared to the control group, which gained 1.5 kg. A similar pattern was seen for BMD change at the spine, although the difference was non-significant. Large increases in physical activity helped reduce the amount of spine BMD loss, but not hip loss. Since osteoporosis is an important health concern for women, further research is needed to determine whether the effect of weight loss on BMD can be attenuated by aerobic or resistance training.

**Conclusion**

Obesity affects the health of millions of women nationwide. Successful weight loss typically involves a combination of consuming a low calorie, low fat diet, engaging in high levels of physical activity, and frequent self-monitoring. Promoting such lifestyle changes during critical life junctures for women, such as during pregnancy and menopause, may be effective in treating and preventing obesity-related diseases in women.

**References**


Suzanne Phelan, PhD, is Assistant Professor, Department of Psychiatry and Human Behavior, Brown Medical School.

Rena R. Wing, PhD, is Professor, Department of Psychiatry and Human Behavior, Brown Medical School.

**Correspondence:**

Suzanne Phelan, PhD
Brown Medical School
The Miriam Hospital
196 Richmond Street
Providence, RI 02903
Phone: (401) 793-8968
E-mail: sphelan@lifespan.org

**Table 3.**

<table>
<thead>
<tr>
<th>NIH-funded Studies Currently Recruiting at the Weight Control and Diabetes Research Center (401-793-8940)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIDE:</strong> Program to Reduce Urinary Incontinence by Diet and Exercise. This study provides an 18-month weight loss program for overweight women aged ≥30 years with ≥ 10 incontinent episodes/week.</td>
</tr>
<tr>
<td><strong>LEAP:</strong> Lifestyle, Eating and Activity Program. This 18-month program is recruiting pairs of overweight individuals who live together (e.g., spouses) to examine the effects of modifying the home environment.</td>
</tr>
<tr>
<td><strong>LITE:</strong> Living Lean in a Toxic Environment. Individuals who are normal weight or have successfully reduced from obese to normal weight are provided information about their current eating and exercise habits.</td>
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A 28-year-old woman presented with one month of abdominal pain. The CT scan and ultrasound images displayed are consistent with a large simple-appearing cystic structure in the abdomen and pelvis measuring 20 x 17 x 8 cm, arising from the right ovary. The CT scan revealed no free fluid, lymphadenopathy, or suspicious lesions in the abdomen and pelvis. The ultrasound characteristics were highly suggestive of a benign process. The mass had no malignant features, such as internal septations, solid components, papillary projections, or internal echoes. The literature suggests that the sensitivity of transvaginal ultrasound for the detection of a malignant adnexal mass ranges from 85 to 97%, and the specificity varies between 56 and 95%. The sensitivity and specificity may improve when color Doppler is used in addition to standard morphologic analysis with transvaginal ultrasound. In light of the patient’s age and reassuring radiographic findings, it was felt that there was a very high likelihood that the mass was benign. This patient underwent a CT-guided drainage of the cyst to facilitate a laparoscopic surgical resection. Approximately 1400 cc of straw-colored fluid was obtained. Intraoperatively, the patient was found to have a large collapsed right ovarian cyst with no evidence of ovarian torsion. The cyst wall was excised laparoscopically. Final pathology was consistent with a benign serous cystadenoma. Serous tumors, including benign, borderline, and malignant subtypes, account for approximately 30% of all ovarian tumors.

REFERENCES

CORRESPONDENCE:
Beth Plante, MD
Phone: (401)270-3616
E-mail: bplante@wihri.org

Beth Plante, MD, is a PGY-4 OB/GYN Resident, Women & Infants’ Hospital, and Assistant Instructor in Obstetrics and Gynecology, Brown Medical School.
Troilus Plante, MD, is a PGY-4 Emergency Medicine Resident, Rhode Island Hospital, and Assistant Instructor in Emergency Medicine, Brown Medical School.
A 57 year old woman presents to your office with a 1.2 cm moderately differentiated infiltrating ductal carcinoma, highly ER/PR positive, detected on screening mammography and biopsied under ultrasound guidance with good correlation of size. She has a clinically negative axilla and no significant medical co-morbidities. After presentation at a prospective multidisciplinary tumor board, consensus recommendation is for needle localized wide local excision and sentinel node biopsy - the textbook response. Yet could there be a better approach?

The Evolution of Breast Surgery

The universe is in a constant state of flux. Medicine like nature advances through what sometimes feels like a random process of evolution, and while when evaluated in short-term segments it can seem unclear whether true advances are made, over centuries it seems certain that we do. In breast cancer therapy, a similar process governs change. Looking back to the first recognized pioneer in breast cancer therapy William Halsted, who developed the first standardized approach; radical resection of the breast, chest wall and nodal basins, it is easy to see how far we have come. In Halsted’s era, it was uncontrolled local disease that ravaged the patient and seemed to cause death. With the diagnosis of early staged, surgically controllable disease, Fisher and colleagues turned the world’s attention to addressing distant failure; ushering in the era of systemic chemotherapy. The seminal NSABP B-04 and B-06 trials have reached maturity with over 20 years of follow-up still showing no survival difference between breast conservation and more radical resection. Venturing even further into therapeutic minimalism, surgeons have practically abandoned axillary dissection in favor of sentinel node biopsy for the clinically negative axilla. The more precise surgical intervention is permitted by an earlier diagnosed breast cancer, afforded by the standardized screening of women over fifty years of age since the 1978 NIH recommendation. Since that time we have seen a progressive decrease in breast cancer size, with the mean diameter of breast cancer decreasing by 10% every five years. For Rhode Island, with the most successful statewide mammographic screening program, the median size of breast cancer has decreased from 2.0 cm in 1987 to 1.5 cm in 2001. As cancers are identified below the limits of tactile discretion; excision guided by palpation is replaced by image-directed surgery. Yet the standard approach of excision remains. Is this the best we have to offer? Or is there, in the current milieu of minimal invasive-ism, an opportunity to revolutionize the approach to breast cancer surgery.

Contemporary Strategies

The goals of breast cancer surgery are to surgically remove the index cancer from the body, eliminating its potential for future metastasis, and to stage the axilla. Subsequent radiotherapy completes the local control. While excising the cancer is way to achieve this endpoint, other options are numerous. While more contemporary modalities in-situ ablation were not available, Hippocrates described the concept of thermal destruction as 460 BC and in the first century another Greek physician, Leonides, described a process of incision and cauterization. Alas what is old is new again, this time centuries later. Contemporary literature is replete with reports of the successful use of thermal ablation of lung, liver, bone, adrenal, kidney, and prostate in both the metastatic and primary settings. Advances

Figure 1 A. Ultrasound demonstrating Cryoprobe placement within target lesion.

B. Ultrasound during creation of iceball. Note clear delineation of treatment field.
in the understanding of thermal biology and advances in both the delivery systems and tumor imaging systems have extended this therapeutic option to other tumor sites, including breast cancer.

The initial reports of ablative techniques in breast cancer therapy focused on radiofrequency ablation. However, this technique suffered from two serious flaws. First, thermal heating is associated with intense discomfort and secondly with RFA under ultrasound guidance, visualization of the treatment zone is severely compromised. Although other modalities such as focused microwave, laser and ultrasound ablation have been described, the remaining literature focuses on cryoablation. Cryoablation is ideally suited to breast cancer therapy for many reasons. First, the majority of invasive breast cancers found today are identified by mammography but characterized and biopsied under ultrasound guidance. The small powerful hand-held ultrasound probe makes ultrasound the ideal modality to guide breast therapeutic interventions as well. Furthermore, during cryoablation, frozen tissue becomes imminently visible under ultrasound, in direct contradiction to thermally heated tissue (Figure 1A,B). Additionally, the freezing process has an anesthetic, anti-inflammatory effect on the treated tissue.

Cryo technology has advanced as well. While once bulky, unwieldy and slow, relying on liquid nitrogen, the new device includes a small lap-top sized console and a 2.7 mm probe through which the cooling argon is delivered. (Figure 2) The entire process involves a freeze-thaw-freeze-thaw cycle that results in tissue destruction through intracellular ice formation, causing cellular wall disruption, subsequent osmotic injury and delayed micro vascular disruption leading to tissue ischemia. The usual treatment for sub four centimeter lesions takes 30 minutes.

Future Directions

In the pioneering study by Sabel and colleagues, cryoablation was 100% effective in tumors of any histology < 1.0 cm, and in tumors 1.0 – 1.5 cm with pure invasive ductal or medullary features without extensive intraductal component.2 The Achilles’ heel is the “image occult” disease, specifically lobular and in situ carcinomas that do not reveal their full extent on imaging. Magnetic Resonance Imaging (MRI) has emerged as the premier imaging modality to document extent of disease in breast cancer. To this end, the American College of Surgeons Oncology Group is evaluating the sensitivity of MRI to detect residual disease after a course of therapeutic cryoablation for sub 1.5 cm infiltrating ductal carcinomas. While today we may not be able to offer our case presentation cryoablation for therapy, she is a candidate for the Cryo-Assisted Lumpectomy Trial, which uses the creation of the ice ball intra-operatively to allow for palpated excision of a non-palpable cancer. The study endpoints are percent of patients achieving negative margin at index operation. With final results are yet to be realized, the interim analysis is promising.

In summary, as we look to the future of breast cancer therapy we have reason to expect that detected tumor size will continue to drop, and therefore the proportion of patients presenting with disease localized to the breast will rise. We must find new modalities to eliminate the disease with a minimum of morbidity to the patient. As we have abandoned axillary dissection for sentinel node, so we may in a select group of patients abandon wide local excision for in-situ ablation.

References

Jennifer S. Gass, MD, FACS, is Clinical Assistant Professor of Surgery, Brown Medical School, and Chief of Surgery, Women & Infants Hospital.

Correspondence:
Jennifer S. Gass, MD, FACS
Breast Health Center
Women & Infants Hospital
101 Dudley Street
Providence, RI 02905
Phone: (401) 453-7540
E-mail: jgass@wihri.org

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Weight gain is a common concern when treating patients with antidepressant medications. The actual effects of antidepressant medications on weight are difficult to quantify because depression is often characterized by changes in appetite, energy and physical activity. The propensity of an antidepressant medication to induce weight gain may be due in part to its neuropharmacologic effects; however, the mechanism for weight gain caused by antidepressants cannot be fully explained. Changes in weight vary between classes of antidepressants, and between agents within each class.

Weight gain is a frequent adverse effect of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The antidepressant action of MAOIs results from the irreversible inhibition of two monoamine oxidase enzyme isoforms, MAO-A and MAO-B. Serotonin and epinephrine have a high affinity for the MAO-A isoenzyme, while dopamine, norepinephrine, and epinephrine have a high affinity for the MAO-B isoenzyme. Of the MAOIs, phenelzine has been most associated with weight gain; however, this conclusion is based primarily on case reports. Another MAOI, tranylcypromine, may cause weight loss due to structural similarities to amphetamines.

TCAs inhibit neurotransmitter re-uptake at several sites, including serotonin, adrenergic and histamine receptors. The nonselective pharmacologic actions of TCAs are the likely cause of carbohydrate cravings, increased appetite, and alterations in the regulation of body fat stores. Although all TCAs are associated with weight gain, amitriptyline is associated with a higher likelihood of weight gain than other agents within the class. 

Selective serotonin reuptake inhibitors (SSRIs) have a more selective and potent effect on serotonin than the less selective activity of TCAs. However, the mechanism of antidepressant action is not entirely understood and is due to effects other than the reuptake of serotonin at the synapse. An increase in serotonin availability should decrease carbohydrate intake and reduce cravings, but this effect is unpredictable and poorly documented. Slight pharmacological differences between SSRIs result in varying affinities for serotonin, histamine and dopamine receptors, further complicating the association between SSRIs and weight. In clinical trials, SSRIs have been associated with both weight gain and weight loss.

...PATIENTS WITH APPETITE SUPPRESSION OR ALTERED EATING HABITS CAUSED BY DEPRESSION ARE MORE LIKELY TO EXPERIENCE WEIGHT CHANGE UPON TREATMENT."

Comparative Weight Changes Between SSRIs

The largest trial prospectively comparing the metabolic effects of SSRIs was conducted by Maina et al. Patients with obsessive-compulsive disorder were randomized to treatment with clomipramine, citalopram, fluoxetine, fluvoxamine, paroxetine or sertraline for 2.5 years. Over the course of the trial, mean body weight increased by 1.58 kg (2.5%) compared to baseline, with 14.5% of patients experiencing significant weight gain (increase of 7% or more from baseline). Patients in the clomipramine group experienced the highest mean percentage weight increase (4.86%) and the highest proportion of significant weight gain (34.8%); this is consistent with the known adverse effects of TCAs. Fluoxetine patients experienced initial weight loss, and were the only treatment group to not experience significant weight gain over the course of the trial. The lowest proportions of patients experiencing significant weight gain were 8.7% and 4.5%, in the fluoxetine and sertraline groups, respectively. Trial results are summarized in the table below.

In another prospective trial evaluating long-term weight change, depressed patients were randomized to fluoxetine, sertraline, or paroxetine for 26 to 32 weeks. There was a small mean decrease in weight (0.2%) among fluoxetine patients and...
a small mean increase in weight (1.0%) among sertraline patients; neither change was statistically significant. Paroxetine-treated patients experienced a significant increase in weight compared with baseline (3.6%). From baseline to endpoint, 25.5%, 6.8% and 4.2% of paroxetine, fluoxetine and sertraline patients, respectively, experienced 7% or greater weight gain (*P* = 0.016 paroxetine vs fluoxetine, *P* = 0.003 paroxetine vs sertraline).

When fluoxetine was compared to placebo for the prevention of relapse after acute treatment of depression, fluoxetine was associated with significantly more weight gain than placebo over one year. After twelve weeks of acute treatment, fluoxetine was associated with slight weight loss (mean −0.35 kg, *P* < 0.01) from baseline weight. After completion of the acute treatment phase, patients were randomized to 14, 26 or 38 weeks of continuation fluoxetine therapy or placebo for relapse prevention. Among patients who completed the second phase of the trial, fluoxetine was associated with significant weight increase over placebo after 14 (mean 1.1 kg, *P* < 0.001), 26 (mean 2.2 kg, *P* < 0.001), and 38 (mean 3.1 kg, *P* < 0.001) weeks of continuation treatment. Both fluoxetine and placebo patients regained the weight lost during the initial 12-week treatment phase, and mean weight at the end of trial was significantly higher than baseline in both groups (mean 3.0 kg, *P* < 0.001).

Newer, non-SSRI antidepressants have variable effects on weight. A pooled analysis of trials comparing nefazodone to SSRIs demonstrated that nefazodone is associated with fewer instances of significant (≥7%) weight loss in the acute phase (6–8 weeks) of treatment. During the long-term treatment phase (16–44 weeks), fewer nefazodone than SSRI patients experienced significant (≥7%) weight gain (8.3% vs. 17.9%, *P* = 0.003 for any point during treatment and 6.9% vs. 13.8%, *P* = 0.007 at endpoint). There was no difference between groups in the incidence of significant weight loss (≥7%) during long-term treatment. Fewer instances of weight loss during the acute phase and weight gain during long-term therapy suggest that nefazodone causes less weight variability than SSRIs.

The weight gain associated with mirtazapine may be due to its activity at histamine receptors. In a long-term continuation of a trial of acute treatment, patients continued treatment with mirtazapine, amitriptyline, or placebo for up to two years. Weight gain was more common with amitriptyline (22%) than mirtazapine (13%) patients, but significantly more mirtazapine than placebo patients experienced weight gain. In a four-week study of healthy subjects, those treated with mirtazapine experienced a significant increase in body weight from baseline (mean increase 3.64 lb.), suggesting that the weight gain caused by mirtazapine is independent of the weight changes associated with recovering depression. This trial also quantified the changes in total cholesterol, LDL and triglycerides associated with mirtazapine treatment. After four weeks of therapy, mirtazapine-treated subjects experienced a significant increase in total cholesterol (mean increase 7.6 mg/dL) and nonsignificant increases in LDL and triglyceride levels compared to baseline, while no significant changes were noted in placebo-treated patients. Among treated patients, weight increase was linearly associated with increasing total cholesterol. The results of this short-term trial suggest that weight and cholesterol changes associated with mirtazapine occur independent of depression recovery.

A small, open-label trial compared the effects of mirtazapine and venlafaxine on weight. During the four weeks of treatment, mirtazapine-treated patients experienced a mean weight gain of 2.4 kg while venlafaxine-treated patients had a mean loss of 0.4 kg. A twelve-week trial did not detect weight change with either venlafaxine- or fluoxetine-treated patients. In another trial, weight changes in elderly patients treated with venlafaxine or citalopram for six months were not clinically significant. More research is needed to clarify the effects of venlafaxine on weight, although the agent is most likely not associated with significant weight gain or loss.

Bupropion is generally associated with weight loss. In an eight-week trial comparing sustained release (SR) bupropion 150–400 mg/day to sertraline 50–200 mg/day, bupropion patients experienced a mean 1.06 kg decrease in weight from baseline to endpoint compared with 0.79 kg decrease for sertraline and a 0.21 kg increase for placebo; these differences were not statistically significant. During an eight-week placebo-controlled trial, bupropion SR 300 mg/day and 400 mg/day caused weight loss greater than 5 pounds in 14% and 19% of patients, respectively, compared with 6% of placebo patients. Weight loss of greater than 10 pounds occurred in 2%, 6% and 2% of bupropion 300 mg, 400 mg and placebo patients.

**Discussion**

Because of the difficulty separating the effects of antidepressant medications from the effects of depression, the true effects of SSRI and non-SSRI antidepressants on weight have yet to be completely understood. In general, SSRIs and other newer antidepressants have a more favorable metabolic profile than TCAs or MAOIs. Among SSRIs, paroxetine is associated with weight gain early in therapy but the long-term effects are unclear. Fluoxetine may cause short-term weight loss that resolves with continued treatment. Other SSRIs are either weight-neutral or the effects have yet to be determined. Nefazodone appears less likely to cause weight gain than SSRIs. Bupropion is often associated with weight loss while mirtazapine is associated with weight gain and the effects of venlafaxine remain unclear.

Several factors predict the development of weight gain with antidepressants. Combination therapy with multiple antidepressants or an antidepressant and concomitant antipsychotic may increase the risk of weight gain, but the adverse effects may counter each other (e.g., bupropion and an SSRI). Patients with appetite suppression or altered eating habits caused by depression are more likely to experience weight change upon treatment. The relationship between higher daily dose and risk of weight gain has not been evaluated.

When selecting an antidepressant, the clinician must balance the risk of weight change with the potential benefits of treatment. Slight increases
in weight upon initial treatment may resolve with continued therapy, but significant weight change may decrease medication compliance.

References

At time of writing, Sarah Grace Kachur and Christine Hanman were Doctor of Pharmacy students at the University of Rhode Island College of Pharmacy.
Sarah Grace Kachur, PharmD, is a clinical pharmacist at Advanced Pharmacy Concepts in North Kingstown, RI.
Christine Hanman, PharmD, is a pharmacy practice resident at Palmetto Health Richland in Columbia, SC.
Kristina E. Ward, PharmD, is Director, Drug Information Services and Clinical Assistant Professor at the University of Rhode Island College of Pharmacy.

Correspondence:
Sarah G. Kachur, PharmD
Advanced Pharmacy Concepts
1130 Ten Rod Rd.
Bldg D Suite 206
North Kingstown, RI 02852
E-mail: skachur@apc-rx.com

A Physician’s Lexicon

The Art and Words of the Apothecary

Shakespeare’s Romeo, referring to the lethal potion that he is about to consume, exclaims: “O, true apothecary, Thy drugs are quick.” The old-fashioned neighborhood drugstore has long since been superseded by national chains of markets selling all manner of health-related products; and in the back of these emporia, typically, are teams of apothecaries (now called registered pharmacists), dispensing a diversity of pills and solutions, although probably not the rapidly-acting poisons of Shakespeare’s Veronese apothecary.

The word “apothecary” is derived from the Greek root theca-, meaning storeroom and the Greek prefix, apo-, meaning from or away from. Thus the word originally signified the contents of any treasure-house or store. The word apotocery, over the centuries, was modified to the Spanish word, bodega (or sometimes bodetta) meaning a storage place, or shop, for wines. In Latin America, bodega has come to mean a neighborhood grocery store. Yet another derivative of apothecary was the old French word, botica, which has evolved into the English word, boutique.

The word pharmacopoeia, a registry or published compendium of accepted medications, is derived from the Greek, pharmicon, meaning drugs or the dispenser of drugs, and a root, poit, meaning to make or produce. This latter root is found in the words poet and poetry. The word “drug” (as in drugstore) is Germanic in origin. An older word, droge, was used to describe any commercial products which came in cases or barrels.

Apothecaries had once sold preparations called philters, or love potions. The word is a modification of the Greek philo-,- to love (as in words such as Anglophile or philos). The categories of medications include the febrifuges, drugs to fight fever (from the Latin febris, meaning fever, and fugo, meaning to flee); the anodynes, drugs to allay pain (the Greek privative prefix, ano- and dino, meaning pain), the emollients, softening agents (Latin, mollis, meaning soft), the cathartics (from a Greek word meaning to cleanse, to purify, leading to such English words as catharsis and Cathartist), the emetics (from a Greek word meaning to vomit), and of course, the aphrodisiacs, named to honor Aphrodite, the Greek goddess of love (the Greek root, aphros, meaning sea-foam, is a reminder that Aphrodite was said to have arisen from the foam of the sea.)

Stanley M. Aronson, MD
In several surveys of cervical cancer screening practices among obstetricians and gynecologists in the United States, discrepancies between published guidelines and actual patient management have emerged. For example, in 1998, Suh-Burgmann found that the majority of practitioners surveyed were performing repeat smears at more frequent intervals than recommended either by the American College of Obstetricians and Gynecologists (ACOG) or the National Cancer Institute (NCI). As recently as 2005, Saint found that most gynecologists screen low-risk women often and indefinitely and that nearly three-quarters would begin screening virginal girls at age 18, despite national guidelines to the contrary. This review summarizes recent recommendations for cervical cancer screening and discusses the role of high-risk or oncogenic human papillomavirus (HPV) testing as an adjunct to screening and in the management of women with cytologic abnormalities.

Screening Guidelines: Recent Changes

Although adolescents have a higher prevalence of abnormal screening Pap smear results than adult females, they are much more likely to experience regression of such abnormalities. As a result, the American Cancer Society (ACS) and ACOG recommend that cervical cancer screening should begin three years following the onset of vaginal intercourse, but no later than 21 years of age. Discontinuation of screening, on the other hand, should occur for the majority of women undergoing total hysterectomy. In 1996, the US Preventive Services Task Force recommended that routine cytologic screening was unnecessary for women who had undergone a complete hysterectomy for benign disease. Yet, in 2002, of the 22 million US women who had undergone hysterectomy, nearly half continued to undergo Pap smear screening unnecessarily.

... DATA SUGGEST THAT COMBINED TESTING WITH BOTH CYTOLOGY AND HIGH-RISK HPV TYPING IS SUPERIOR TO CYTOLeGIC SURVEILLANCE ALONE.

High-risk or oncogenic HPV is a necessary cause of nearly all high-grade cervical neoplasia and squamous cell cancer of the cervix. However, only a fraction of the women with evidence of high-risk HPV infection in the US will develop cancer. While repeatedly negative cervical cytologic results are reassuring, particularly in women aged 30 and over for whom screening intervals may then be increased, data suggest that combined testing with both cytology and high-risk HPV typing is superior to cytologic surveillance alone in this population. In a number of studies, combined HPV testing with cervical cytology resulted in negative predictive values for CIN 2 and CIN 3 of 99-100%. Specificity, however, of the combined tests remained lower than that for cytology alone.

Based on such evidence, the NCI, the American Society for Colposcopy and Cervical Pathology and the ACS issued interim guidelines recommending the use of a combination of cervical cytology and HPV DNA screening in women aged 30 and over, a recommendation ACOG endorsed in 2005. Today’s commercial probes, designed to identify 13 oncogenic HPV subtypes, are sandwich capture molecular hybridization assays that utilize chemiluminescent detection.

ADVANCES IN LABORATORY MEDICINE

HPV TESTING AND CERVICAL CANCER SCREENING: RECOMMENDATIONS AND PRACTICE PATTERNS

LINDSAY M. MADOM, MD, AND LORI A. BOARDMAN, MD, ScM

MEDICINE AND HEALTH / RHODE ISLAND
be HPV positive, she should undergo colposcopy as well. The most difficult clinical issue that arises, however, has been the triage of a woman with negative cytology, but a positive high-risk HPV test. Because the risk of CIN 2 or worse is low, both tests should be repeated in 6 to 12 months. For those with evidence of persistent HPV infection but negative cytology, colposcopy is warranted. Clearly, questions arise regarding further management, including the possible need for treatment of persistent HPV infection coupled with negative cytology and no evidence of neoplasia on colposcopic examination. At present, however, the rationale for treatment is unjustified.

**HPV Typing in Management of Cytologic Abnormalities**

Oncogenic HPV testing is used in two other clinical situations: as a triage method for ASC-US and as a test of cure for women following therapy for CIN 2 or CIN 3. Although HPV DNA testing was not found to be helpful in the management of LSIL, investigators have demonstrated that among women with ASC-US, reflex HPV typing, compared to a single repeat cervical cytology at 4-6 months, was significantly more sensitive for the detection of histologically diagnosed CIN 3 or worse. Although the traditional scheme of two repeat cytologic evaluations was subsequently reported to be similar in sensitivity to reflex HPV testing, the latter is preferred in settings where liquid-based cytology is used due to its cost-effectiveness. If HPV testing is found to be positive, the patient is referred to colposcopy, while a negative HPV allows for return to annual cytologic screening. Of note, adjunct HPV typing is not recommended for ASC-H, LSIL or worse or any glandular abnormality, as such patients require colposcopy.

Finally, in a meta-analysis of 11 studies evaluating oncogenic HPV typing in monitoring women treated for CIN 3, combined testing with high-risk HPV and cytology at 6 months following therapy proved more effective in predicting persistent CIN than either test alone or resection margin status. From studies to date, 70% of women treated for CIN 3 will test negative on both HPV testing and cytology at 6 months follow up, and further monitoring may be less intensive.

**Summary**

In summary, guidelines for cervical cancer screening continue to evolve, as knowledge of the pathogenesis of the disease as well as the role of HPV expands. Oncogenic HPV typing has proven effective in cancer screening and follow-up in certain situations, and its uses will undoubtedly increase. Patients and providers may be reassured with negative HPV testing, but long term management of positive HPV testing (especially in conjunction with negative cytology) is unclear. At present, however, numerous worldwide, prospective studies involving HPV testing and cervical cancer screening will, we hope, provide some of the answers regarding optimal management of women who remain persistently HPV positive.

**References**


**Correspondence:**

Lori A. Boardman, MD, ScM, is Associate Professor of Obstetrics and Gynecology, Brown Medical School, and Director of Colposcopy, Women & Infants’ Hospital.

Lindsay M. Madom, MD, is a Resident Physician in Obstetrics and Gynecology, Women & Infants’ Hospital.

**Acknowledgement:**

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Reducing the proportion of Rhode Island adults who are obese and reducing the proportion of Rhode Island youth who are overweight and obese are Healthy Rhode Islanders 2010 (HRI2010) objectives. HRI2010 strategies promote increased physical activity and increased fruit and vegetable consumption.

This paper presents data for Rhode Island girls and women on overweight/obesity, weight control strategies, physical activity, and fruit and vegetable consumption based on two Rhode Island surveys performed in 2003 -- the Behavioral Risk Factor Surveillance System (BRFSS) and the Youth Risk Behavior Survey (YRBS).

**Methods**

The BRFSS is a telephone survey of randomly selected non-institutionalized adults ages 18 and older. It is administered in all 50 states and 4 US territories with funding and methodological specifications provided by the federal Centers for Disease Control and Prevention (CDC). In 2003, RI's BRFSS interviewed 4,053 RI adults.

The YRBS is an anonymous and voluntary survey conducted in alternate years among randomly selected high schools and students. The CDC sponsors the YRBS in states and localities nationwide. In spring 2003 the Rhode Island Departments of Education and Health administered the YRBS to 1,814 Rhode Island public school students in grades 9 through 12.

In 2003 both the Rhode Island BRFSS and YRBS collected information about height and weight, which are used to calculate body mass index (BMI); participation in physical activity; fruit and vegetable consumption; and weight control efforts.

The two surveys asked similar questions about weight control efforts -- Are you now trying to lose weight? Are you now trying to keep from gaining weight? Are you eating fewer calories or less fat to lose or maintain weight? Are you exercising to lose or maintain weight? In addition, the YRBS asked about several high-risk weight loss behaviors that adolescents may use.

For both surveys CDC derives two variables for physical activity and one measure for fruit and vegetable consumption. For physical activity the variables are: "meets guidelines for recommended level of moderate or vigorous physical activity" (30 minutes a day five or more days a week; or 20 minutes or more of vigorous physical activity 3 or more days a week); and "engages in no physical activity." The dietary measure is "meets guidelines for fruit and vegetable consumption" (five or more servings of fruits and vegetables a day). Prevalence estimates for all variables were calculated for high school girls (YRBS), and for women in four age groups (BRFSS).

**Results**

The proportion of females who are overweight increases with age, from 21% of adolescents who are at risk for overweight or overweight, to 32% of women ages 18 – 24 who are overweight or obese, up to 56% of women ages 65 and older. While 21% of girls are at risk for or overweight, 35% describe themselves as slightly or very overweight. (Table 1)

Eighty percent or more of girls and women up to age 64 and 75% of those 65 and older are either trying to lose weight or keep from gaining weight. Sixty-one percent of girls and nearly half of all women are trying to lose weight. (Table 2) Three times as many girls are trying to lose weight as are at risk or overweight, and 50% more women ages 18 – 24 are trying to lose weight than are overweight or obese.

Half or more of girls and women up to age 64 and one-third of women ages 65 and older are using both calorie restriction and physical activity to lose or maintain weight. The proportion using dieting alone increases with age from 7% of girls to 36% of women ages 65 and older, while the proportion using exercise alone decreases from 23% of girls to 9% of women ages 65 and older. (Table 2)

The YRBS also asked girls about high risks behaviors to lose or maintain weight; e.g., fasting for 24 hours or more (17%); using diet pills, powders or liquids without a doctor's advice (8%); and vomiting or using laxatives (6%). (Table 2)

High school girls and women ages 18 – 24 have the lowest proportion (26%) meeting the recommended fruit and vegetable guidelines. Women 65 and older have the highest percentage meeting this guideline (41%). (Table 3)

---

**Table 1. Overweight and Obesity among High School Girls and Women Ages 18 and Older, Rhode Island 2003**

<table>
<thead>
<tr>
<th>Weight Measure</th>
<th>Girls Grades 9–12 Ages 18-24</th>
<th>Ages 25-44</th>
<th>Ages 45-64</th>
<th>Ages 65+</th>
<th>Ages 18+</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk of overweight*</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight**</td>
<td>21%</td>
<td>25%</td>
<td>31%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Overweight***</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese****</td>
<td>11%</td>
<td>18%</td>
<td>23%</td>
<td>16%</td>
<td>18%</td>
</tr>
<tr>
<td>Self–perceived overweight</td>
<td>35%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* At or above the 85th percentile but below the 95th percentile for BMI for age and sex based on data from the National Health and Nutrition Examination Survey I (NHANES I);
** BMI >25 and <30
*** At or above the 95th percentile for BMI for age and sex based on NHANES I
**** BMI >30

Edited by Jay S. Buechner, PhD
Girls (60%) and women ages 18–24 (57%) have the highest proportion meeting the recommended guidelines for moderate or vigorous physical activity. The proportion declines with age, to 28% for women ages 65 and older. Only 10% of girls do not participate in any moderate or vigorous physical activity while the proportion of women who do not participate in any leisure time physical activity increases from 21% of those ages 18–24 to 40% of women ages 65 and older. (Table 3)

**Discussion**

Addressing the epidemic of overweight and obesity in the US requires, in part, the individual intention to manage weight. Three quarters or more of Rhode Island girls and women surveyed in 2003 were trying to lose or maintain their weight, which may suggest a healthy intent. However, with the exception of women over age 65, a higher percentage of females, especially girls, are trying to lose weight than are actually estimated to be overweight, which signals a potential health risk.

Close to 90% of girls and women trying to lose or maintain their weight report doing so by restricting calories or fat, by exercising, or both. While a high percentage report that they exercise to control weight, a lower percentage report participation in the recommended level of either moderate or vigorous physical activity. A difference of about 20 percentage points between the two estimates is consistent across all age groups.

Likewise, the low proportion of girls and women eating the recommended 5 or more servings of fruits and vegetables is discrepant with the high proportion saying they are eating fewer calories or less fat to manage their weight.

Several observations from this analysis can inform public health interventions designed to address the obesity “epidemic.” First, the discrepancy between the high level of weight management actions of girls and women and their reported physical activity and fruit and vegetable intake practices suggests greater effort is needed to help the public recognize the amount of exercise and types of food that can be most effective for weight management. Second, the use of some risky weight loss practices by high school girls may indicate a low salience of health concerns in their choice of weight reduction and maintenance strategies. There is need to reinforce public health messages about the health-related risks of overweight and obesity and about healthy exercise and dietary weight loss strategies. Given the large proportion of girls and women trying to lose weight who may not actually be overweight, efforts must also address when it is appropriate and healthy to engage in weight loss strategies.

### References

3. CDC BRFSS website: http://www.cdc.gov/brfss
4. CDC YRBS website: http://www.cdc.gov/HealthyYouth/yrbs/index.htm

### Acknowledgements:

The 2003 RI BRFSS was supported in part by the CDC Cooperative Agreement U58/CCU122791. The 2003 RI YRBS was supported in part by the CDC Cooperative Agreement U87/CCU109023.

### Table 2. Strategies and Objectives for Losing or Maintaining Weight among High School Girls and Women Ages 18 and Older, Rhode Island 2003.

<table>
<thead>
<tr>
<th>Weight Control</th>
<th>Girls Grades 9–12</th>
<th>Ages 18–24</th>
<th>Ages 25–44</th>
<th>Ages 45–64</th>
<th>Ages 65+</th>
<th>Ages 18+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lose weight</td>
<td>61%</td>
<td>48%</td>
<td>49%</td>
<td>56%</td>
<td>40%</td>
<td>49%</td>
</tr>
<tr>
<td>Maintain weight</td>
<td>19%</td>
<td>37%</td>
<td>38%</td>
<td>32%</td>
<td>35%</td>
<td>36%</td>
</tr>
<tr>
<td>Weight loss strategy (for those trying to lose or maintain weight):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Just fewer calories/less fat</td>
<td>7%</td>
<td>13%</td>
<td>17%</td>
<td>26%</td>
<td>36%</td>
<td>23%</td>
</tr>
<tr>
<td>Just exercise</td>
<td>23%</td>
<td>22%</td>
<td>16%</td>
<td>8%</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Both fewer calories and exercise</td>
<td>58%</td>
<td>52%</td>
<td>55%</td>
<td>58%</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Fasted 24 + hours</td>
<td>17%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Took diet meds*</td>
<td>8%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vomited/took laxatives</td>
<td>6%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Without doctor’s advice

### Table 3. Weight-Related Health Behaviors among High School Girls and Women Ages 18 and Older, Rhode Island 2003.

<table>
<thead>
<tr>
<th>Weight-Related Health Behavior</th>
<th>Girls Grades 9–12</th>
<th>Ages 18–24</th>
<th>Ages 25–44</th>
<th>Ages 45–64</th>
<th>Ages 65+</th>
<th>Ages 18+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meet guidelines of 5 or more servings of fruits and vegetables per day</td>
<td>26%</td>
<td>26%</td>
<td>31%</td>
<td>30%</td>
<td>41%</td>
<td>32%</td>
</tr>
<tr>
<td>Physical Activity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meet guidelines for recommended moderate or vigorous physical activity</td>
<td>60%</td>
<td>57%</td>
<td>55%</td>
<td>48%</td>
<td>28%</td>
<td>53%</td>
</tr>
<tr>
<td>Does not participate in physical activity</td>
<td>10%</td>
<td>21%</td>
<td>25%</td>
<td>28%</td>
<td>40%</td>
<td>28%</td>
</tr>
</tbody>
</table>
The concept of women's health, traditionally, has focused on reproductive health and breast and cervical cancer. This view has changed in the last decade to encompass the physical, mental, social, and economic factors that influence women's health status across their lifespan.

Women's health is devoted to facilitating the preservation of wellness and the prevention of illness in women and includes screening, diagnosis, and management of conditions which are unique to women; are more common in women; are more serious in women; and have manifestations, risk factors or interventions which are different in women.  

**Health Status of Rhode Island Women**

The Office of Women's Health was created in 2001 to provide a gender-informed approach to programs and services within the Rhode Island Department of Health to eliminate health disparities and improve the health status of Rhode Island women and girls.

Health disparities for Rhode Island women are not solely a factor of gender. In addition to gender differences in health status, there are also substantial differences between women in Rhode Island compared to women nationally, in Rhode Island women as they age, and among different racial or ethnic groups.

Tobacco use in Rhode Island among adolescent girls, for example, is higher than among adolescent boys. About one in four women smoke and rates are similar for female high school students. A higher proportion of female students smoke than male students, with the greatest difference occurring in the 9th grade.

Rhode Island women self-report a higher rate (11%) of asthma than Rhode Island men (6%), and the rate for RI women is higher than the median for US women (9%).

Physical activity decreases as women age. Regular physical activity has been shown to reduce the risk of death from heart disease, lower the risk of developing diabetes, help prevent high blood pressures, and is associated with a decreased risk of colon cancer. Yet fewer than one woman in four (at any age) gets the minimum recommended amount of physical activity and the percent of Rhode Island women who are active decreases with age. Overweight and obesity are associated with 54 co-morbid diseases. Although all women may be at risk, minority women are disproportionately affected. State data show that more than half of all Rhode Island women are overweight or obese. Hispanic and Black non-Hispanic women are more likely to be overweight than White non-Hispanic women, and minority women are more than twice as likely to be obese.

**Office of Women's Health**

The health status of men and women differ in many areas. Gender-neutral policies assume that everyone is affected by programs in the same way. The same interventions, however, do not necessarily yield equal results; different treatments may sometimes be required to achieve similar results, and the Office works with programs to identify areas where targeted efforts are needed.

Among its responsibilities, the Office hosts an annual statewide conference on women's health. Past conferences have focused on women 65 years of age and older, women in midlife from 45 – 64 years of age, and women of reproductive age between 18 – 44 years. This year the conference will focus on adolescent girls aged 11 – 17. “The Face of Health: Risk and Resiliency in Adolescent Girls” will be held at the Holiday Inn in Providence on November 15, 2005. Co-sponsors include the Health Department's Division of Family Health, Brown University/Women & Infants Hospital Centers of Excellence in Women's Health, and the Rhode Island Department of Education. Pre-registration is required; the cost is $25.

The Office is assisted by an Internal Work Group comprised of representatives from all of the Department's Divisions. This group improves internal coordination among program areas, provides information, and addresses areas where there are significant disparities in the health of RI women.

For more information about the Office of Women's Health visit:
http://www.health.ri.gov/disease/owh/index.php

**Osteoporosis Program**

The Office of Women's Health is primarily a policy office, but it does have overall responsibility for the Department's Osteoporosis Program. In Rhode Island, the prevalence of osteoporosis and low bone mass for those over 50 years of age is 129,100 women and 53,500 men.

The Osteoporosis Program Manager works closely with and staffs the RI Osteoporosis Coalition. The Department of Health and the Coalition share the goal of reducing osteoporosis in Rhode Island. Collaboratively they implement public awareness campaigns to educate people about the risks of osteoporosis and encourage them to talk with their doctor about this disease. Campaigns include osteoporosis education classes, bone density screenings, and distribution of educational materials at community health fairs.

A goal of the program is to reduce the number of undiagnosed cases of osteoporosis and increase treatment. Professional education efforts include articles about osteoporosis in Medicine & Health/Rhode Island and grand rounds at local hospitals. On October 1, 2005, the Coalition held the Osteoporosis Workshop for Physicians at the Marriott Hotel in Providence.

The Osteoporosis Program routinely assesses the status of osteoporosis...
sis in Rhode Island by means of the state’s annual Behavioral Risk Factor Surveillance System (BRFSS), a random telephone health survey of Rhode Island adults. Some of the questions ask about the information these individuals receive from their doctor or health care professional. The practice of doctors and health care providers is evaluated by asking survey participants questions pertaining to any discussion they recall with their doctor about the risks of osteoporosis, the need for calcium and vitamin D, and the recommendation for a bone mineral density test. In 2005 questions were included to estimate the prevalence of osteoporosis in Rhode Island.

Information about the Osteoporosis Program can be found on the Department’s website: http://www.health.ri.gov/disease/osteo/index.php

**Women’s Health Advisory Committee**

The Office of Women’s Health is guided by the Women’s Health Advisory Committee whose members are appointed by the Director of Health and represent women from diverse areas of the state, ages, professions, ethnic and racial groups, and abilities. The Advisory Committee provides leadership in setting priorities, makes recommendations to the Director of Health, advises on policies and programs that impact women, and increases the visibility of women’s health issues. In its efforts to develop a coordinated, comprehensive health system for women in Rhode Island, it has enlisted the input of women throughout the state in their work, collaborated with other organizations and agencies, conducted public forums, and targeted areas of concern.

An Advisory Committee priority is health literacy. Health literacy seems to affect women more than men. Women who live in poverty or have less than a high school education have shorter life spans, higher rates of illness, injury, disability and death, and more limited access to high quality health care services. There is a high correlation between lower literacy levels, poverty and poorer health status. This creates an even greater burden since women, in addition to caring for their health needs, often function as gatekeepers for the health care of their families.

**References**

1. National Academy on Women’s Health Medical Education.

Nancy Libby-Fisher, MMHS, is Program Manager, Women’s Health Program, Rhode Island Department of Health.
Recent data from the 2004 national Behavioral Risk Factor Surveillance Survey (BRFSS), a population-based telephone survey conducted by the Centers for Disease Control and Prevention (CDC), show that Rhode Island women over the age of 40 tied with women in Massachusetts and Delaware for the highest rate of self-reported biennial mammography screening in the country, at 82.4%.\(^1\) The national average rate was 74.6%. Achieving the nation’s highest percentage of women 40+ obtaining screening mammograms is a tremendous accomplishment for Rhode Island. Clearly, the Rhode Island medical and public health communities are doing a great job at promoting mammography screening.

These self-reported data contrast sharply with the rates seen when examining actual claims for mammography. (Figure 1) As part of its work as the Quality Improvement Organization for the state, Quality Partners of Rhode Island tracks Medicare claims for screening mammography in women aged 50-69. Over a similar time frame, Rhode Island women with Medicare, aged 50-69, have a much lower screening rate when claims are used as a data source. Of the 8,686 female Medicare beneficiaries aged 50-69, only 5,124 (59%) had a claim filed for a mammogram from 2002-2004. Further, this rate is a decline from the 61.1% who had a mammography claim in the 1999-2001 timeframe. In contrast, the self-reported rate in BRFSS for women 65 and over was 84.7%, and for women aged 60-64 was 87.8%.

Literature demonstrates that Medicare claims data may underestimate the number of mammography screenings through a combination of lost claims, self-pay or use of alternate payers, and free programs.\(^2\),\(^3\),\(^4\) One study in Colorado found that Medicare claims data underestimated true screenings by 15%.\(^4\) With Rhode Island claims rates at only around 60%, one might assume that a true mammography screening rate for this population hovers somewhere around 75%, indicating that one in four women in this high-risk group is not seeking or receiving a screening mammography.

In contrast, there is some suggestion that BRFSS may over-report mammography screening due to “social desirability bias” which leads women to over-report having a test that they recognize as recommended. The magnitude of this potential bias, and its accompanying over-reporting in BRFSS, is unclear. Further, self-report of “ever having a mammogram” is probably more accurate than rates which pertain to a particular time period, as women may state that a mammogram has occurred in the last two years when in fact it occurred outside of that time frame.\(^5\) While Medicare claims may under-report the actual screening rate, and BRFSS possibly over reports that rate, one can conclude that there is still a substantial portion of the Medicare population in Rhode Island, somewhere between 15-25%, who are not receiving the appropriate screening for breast cancer.

According to claims data Rhode Island has achieved little success in increasing the percentage of women on Medicare who obtain screening mammograms since 1991-2004, despite the fact that mammograms are fully covered by Medicare. National claims-based rates also declined, from 59.7% to 59.1% in the same period. Intensive interventions targeting this age group in Rhode Island have yielded little improvement. A three-year, multi-pronged intervention implemented by Quality Partners included direct mail and incentives, physician referral and follow-up assistance, outreach to senior centers, media advertisements, and a facility wait time survey/physician awareness effort.

According to National Cancer Institute Surveillance and the American Cancer Society, breast cancer risk increases with age. Not only is the incidence of breast cancer higher in older women, but older women are more likely to present with advanced breast cancer at diagnosis than younger women.\(^6\),\(^7\) Screening mammography has been shown to reduce mortality from breast cancer by 20% to 39% among women aged 50 and older.\(^8\) Rhode Island women on Medicare are fully covered for mammography screenings (although they must pay a small co-pay), face increased risk according to age, and yet a substantial number do not get screened. What are the root causes for this gap, and what are the local challenges for helping to improve these rates?
Studies have repeatedly demonstrated that physician referral is the primary catalyst motivating women to seek mammograms. As part of a mammography screening campaign Quality Partners developed a physician referral and follow-up tool consisting of a two-part form to assist providers in monitoring and following-up when a patient fails to obtain a mammogram after referral. We have found that few offices have systems which allow them to track patients who are due or overdue for screening, few offices notify women who are overdue for the test, and many do not have systems to follow-up after a screening mammogram has been ordered to be sure that it has occurred. With the growing emphasis on electronic medical records and disease registries, more and more practices should be able to develop these capabilities.

Our survey of Rhode Island mammography screening facilities found that screening appointment wait times ranged from 1 day to 150 days, with few facilities sending reminder cards or letters to women who are due for a mammogram. Women referred by their doctors to a specific facility, and discovering a wait time of several weeks or months, may be failing to make an appointment or keep the appointment that is scheduled too far in advance. Quality Partners received positive feedback from Rhode Island physicians who, upon receiving the wait time survey results, were made aware of the delays for the first time and, equally important, learned of the existence of other facilities with little or no wait time that were equally convenient for their patients. Scheduling appointments for screenings is an important component of patient compliance, especially since Rhode Island lacks mobile facilities which allow for on-site visits to senior centers, elderly housing sites, etc.

Women on Medicare may face unique challenges that impact on their likelihood to seek screening mammograms. Some women still are not aware of their need to be screened. Women under age 65 on Medicare face co-existing morbidities that qualify them for the program at a younger age. These health conditions may limit their independence and/or mobility. Additionally, the day-to-day demands of managing competing morbidities, including physician visits, treatments, medications, and tests, can push preventive screenings into low priority and even cause patients to question the utility of “looking for more problems.” These patients require additional encouragement and explanation by their physicians to raise the issue of mammography screening to a more compelling level.

Women over age 65 still need to receive annual screening mammography. Clinical practice guidelines for mammography recommend annual screenings for women age 50-69. There is currently no evidence citing an age at which women fail to benefit from screening mammography. Most guidelines recommend that physicians evaluate such factors as competing morbidity, life expectancy and ability to undergo treatment in determining whether to refer female patients over 70 for mammography screenings. The Rhode Island medical and public health community has a proud record of promoting and facilitating annual mammography screenings for women over 40. Yet the data continue to point to a significant proportion of those on Medicare who have not shared in the improved mammography screening rates despite full coverage for mammography screening and increased risk for breast cancer. Special attention must be paid to the needs, barriers, and challenges faced by women in this group in order for the state to truly meet its mammography screening goals in the next two-year period and beyond.

References

Correspondence:
Johanna Bell Butler, MPH
Quality Partners of Rhode Island
235 Promenade Street, Suite 500
Providence, RI 02908
E-mail: JohannaBButler@aol.com

7SOW-RI-MAMM-05-10
Ninety Years Ago, October 1915

An Editorial urged physicians to take vacations, even though patients may object to the physician's absence: “When we find a patient tired out from overwork or protracted work, we appreciate the futility of our medical armamentarium, and we advise him to take a vacation, and it is the good doctor who prescribes a vacation for himself as well as for his patient.” The same Editorial laments the ungrateful patient: “The time was when we could show with pride a silver loving cup, a gold watch…but these instances are now so rare that they are to be regarded as a curiosity of medical pride...”

W.H. Peters, MD, discussed “Carelessness in Physical Examinations for Life Insurance.” Dr. Peters confessed: “I have witnessed life insurance examinations for good-sized policies...” The reason for the laxity: salesmen were paid on over in their reports a heart a little wobbly or a little sugar in the urine, and so on.” The likelihood of significant reactions depend upon the specific immunological mechanisms involved.

Twenty-Five Years Ago, October 1980

Guy A. Settipane, MD, discussed “Anaphylactic Reactions in Asthmatic Patients.” The “likelihood of significant reactions depend upon the specific immunological mechanisms involved.”

Vital Statistics

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

<table>
<thead>
<tr>
<th>Underlying Cause of Death</th>
<th>October 2004</th>
<th>12 Months Ending with October 2004</th>
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<tbody>
<tr>
<td></td>
<td>Number (a)</td>
<td>Number (a)</td>
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<tr>
<td>Diseases of the Heart</td>
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<td>Malignant Neoplasms</td>
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<td>Cerebrovascular Diseases</td>
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<td>Injuries (Accident/Suicide)</td>
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<tr>
<td>COPD</td>
<td>31</td>
<td>461</td>
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</tbody>
</table>

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population # Rates per 1,000 live births

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