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From the guest editors

Dear Colleagues,

We hope you find this special edition of the *Cleveland Clinic Journal of Medicine* devoted to women's health—the second of its kind, following the inaugural edition in 2001—both interesting and pertinent to your clinical practice.

In these pages we have collected a broad array of articles by women's health experts on common, interdisciplinary women's health concerns. The articles, all published in the *Journal* within the past 3 years, range in format from review articles to editorials and from Medical Grand Rounds write-ups to One-Minute Consult columns. They were selected to stimulate discussion on current preventive health guidelines, gender-specific medicine, as well as cultural and ethnic issues that are relevant to your daily practice.

Many of these articles' authors are presenting cutting-edge information on the diagnosis, management, and treatment of women's health concerns in a variety of plenary sessions and workshops at the 1st Annual Women's Health Summit, April 15 and 16, 2005. This course, presented by The Cleveland Clinic Women's Health Center and the National Speaking of Women's Health Foundation, is being held at the InterContinental Hotel and MBNA Conference Center, Cleveland, Ohio. The summit is preceded by a symposium, "Challenging Issues in Obstetrics," on April 14 at HealthSpace Cleveland.

We are part of an exciting time in medicine in which gender and ethnic/cultural differences are increasingly recognized as important to the health of the individual and society. Women's health has emerged as a new interdisciplinary field of collaborative research, education, and practice. We hope this special edition of the *Cleveland Clinic Journal of Medicine* and the historic 1st Annual Women's Health Summit will further your expertise and commitment to women's health and gender-based medicine.

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Recognizing and intervening in intimate partner violence

ABSTRACT

Intimate partner violence is as prevalent as many conditions for which we routinely screen. Yet intimate partner violence remains underdiagnosed and undertreated. Physicians and other health care workers are in a unique position to detect it and intervene. This article reviews what we can do, what we should do, and what we legally and ethically must do.

KEY POINTS

Intimate partner violence occurs in women of all racial, ethnic, and socioeconomic groups—not just in minority or poor women.

Two simple screening questions, *"Do you ever feel unsafe at home?"* and *"Has anyone at home hit you or tried to injure you in any way?"* have a sensitivity of 71% and specificity of almost 85% in detecting violence.

A battered woman may come across as a "difficult" patient with multiple vague complaints.

The risks of serious harm and murder increase when a victim decides to leave an abusive relationship.

Physicians should familiarize themselves with the laws in their own states governing mandatory reporting to police.

Hospitals and practices should establish policies for documentation in cases of suspected intimate partner violence.

MANY CLINICIANS feel uncomfortable addressing the topic of intimate partner violence, perhaps due to a lack of training in medical school and residency, as well as a lack of continuing medical education opportunities.

However, there are several screening tools available that can help clinicians identify patients at risk, even during a short office visit.

The goals of this article are to discuss intimate partner violence in detail and to promote screening for this important public health problem.

DEFINITION

Intimate partner violence is defined as intentional behavior to obtain power and control over a partner in an intimate relationship. The abuse can be physical, sexual, or emotional, and it eventually creates progressive social isolation and economic control. Approximately 95% of victims are women, and 95% of perpetrators are men.[1]

PREVALENCE

The true prevalence of intimate partner violence is unknown, but it is quite common, with estimates of the number of women battered or abused every year in the United States ranging from 1.5 to 4 million.[2,3] Even if we accept a number near the low end of this range, this means that a woman is beaten every 15 seconds. Approximately one of every four women will be abused by a partner in her lifetime.[2]

It is believed that 3% to 4% of adult women are victims of severe violence.[1] And in nearly two thirds of cases of rape, physical

Historical perspective

VIOLENCE has long-standing cultural and historical roots in our society.

English common law allowed husbands to physically chastise their wives for disciplinary purposes, as long as they did not use a stick bigger than their thumb (hence the expression "rule of thumb").[8] The Mississippi State Supreme Court reinforced this idea in *Bradley v State* (1824) by ruling that a husband could physically chastise his wife.[9] The court also made a point that domestic issues should stay within the home and not be subjected to outside intervention.

The marriage contract also subjugated the wife to her husband's authority in that she gave up her name, moved to her husband's home, and became his dependent.[10] The marriage vow required the wife to "love, honor, and obey" her husband, which led to her economic and legal dependency.

The end of the 19th century marked a major change in the legal rights of US women when legal restrictions were eliminated and the right of a husband to chastise his wife was abolished.[9] Interestingly, until the 1970s, abuse against a spouse was considered only a misdemeanor, but the same assault against a stranger was treated as a felony.[11]

assault, or stalking of women, the perpetrator was someone the victim knew—a current or former husband, cohabitating partner, boyfriend, or date.[3]

No universal profile of battered women…

There is no universal profile of battered women. The key point to remember is that intimate partner violence occurs in women of all racial, ethnic, and socioeconomic groups—*not* just in minority or poor women.

Young women (ages 12 to 30 years) are believed to be at the highest risk, but women of any age can be victims.[4] Younger women may be more susceptible since they are more financially vulnerable and may be more likely to suffer from low self-esteem. Other risk factors may include single marital status (or recent separation or divorce), pregnancy, witnessing or experiencing childhood violence, low socioeconomic status, and substance abuse.[5,6]

…or of their abusive partners

One particular profile does not fit all batterers, either.

In general, batterers are more likely than nonbatterers to be unemployed or have a low income level,[5,7] but higher socioeconomic groups are not excluded. They are usually single, divorced, or separated and have a lower education level.[5,7] Many of these men witnessed violence during childhood and use violence to address their own problems.[7] (Violence has long-standing roots in our culture[8–11]—see Historical perspective on this page.) They may abuse drugs or alcohol (it is estimated that drugs, alcohol, or both are involved in half of all cases of intimate partner violence).[1] They also have high levels of insecurity, anger, hostility, and jealousy and may choose to batter for fear of abandonment.

One should be wary of abusers who may be intentionally charming but are really trying to gain the health care provider's trust in order to divert any suspicion from themselves. They may also come across as being overly affectionate and may answer questions for the victim.

Victims try to deny the abuse and rationalize it by blaming themselves

CYCLE OF VIOLENCE

Walker's "cycle of violence"[12] is useful in understanding the complexities of a violent relationship.

The tension-building phase is characterized by verbal abuse and hostility, leading to degradation of the victim's self-esteem. This phase may last hours to days.

The perpetrator may verbally attack the partner for not taking care of the family or for being flirtatious with other men. He may make derogatory comments about her intelligence, appearance, or decision-making. He may also try to isolate her by controlling her contact with family and friends and her access to money and transportation. Minor abuse such as slapping may occur, and tension continues to increase over time.

TABLE 1

Health sequelae of intimate partner violence

Gynecologic
- Chronic pelvic pain
- Sexually transmitted diseases
- Vaginal bleeding
- Vaginitis
- Fibroids
- Dyspareunia
- Urinary tract infections

Central nervous system
- Headaches
- Back pain
- Paresthesias
- Fainting
- Seizures

Gastrointestinal
- Chronic abdominal pain
- Irritable bowel syndrome
- Bloating
- Eating disorders
- Loss of appetite

Psychological
- Post-traumatic stress disorder
- Depression
- Anxiety
- Suicidal ideation
- Insomnia
- Substance abuse

Cardiac
- Chest pain
- Palpitations

The abuser may appear calm and collected, unlike his 'crazy' wife

The woman tries to deny that any abuse is occurring and rationalizes the situation by blaming herself, thereby justifying the abuser's behavior. She may try to please the abuser to prevent further abuse, but the built-up tension eventually erupts into anger and battery occurs.

Acute battering, the second phase, involves explosive physical violence and property destruction that is worse than in the first stage. This is usually the shortest phase, lasting 2 to 24 hours. Sometimes the victim may intentionally provoke the abuser into becoming violent to release tension, knowing that the abuse will end at last, and they will progress to the next phase.

If the police intervene, it is usually during this phase, depending on the severity of the attack and the injuries. The victim may be quite angry and appear hysterical to law enforcement authorities, while the abuser may portray himself as calm and collected while explaining his wife's "crazed" phases. The victim generally does not seek medical attention unless her injuries are severe, wishing to prevent repercussions of revenge, which can lead to further abuse. She may also have loyalty issues with the abuser.

Honeymoon phase. With the release of tension, the third phase is characterized by remorse and kindness by the abuser towards the victim. This phase can last from 1 day to months. The abuser apologizes for his violent behavior and promises to never become violent again. He may shower the victim with gifts and try to convince her to stay in the relationship.

These thoughtful moments and promises strengthen the victim's resolve to forgive the abuser and believe that such violence will not recur. The victim earnestly hopes that the abuser will change, but in most cases, tension starts to build again and the cycle repeats itself.

HEALTH CONSEQUENCES

Most authorities agree that intimate partner violence causes both physical and mental health problems (TABLE 1). These long-term health consequences lead to poor health, decreased quality of life, and increased use of health services.

It is estimated that intimate partner violence leads to a 50% to 70% increase in gynecologic, central nervous system, and stress-related problems.[13] Gynecologic problems can include chronic pelvic pain, sexually transmitted diseases, vaginal bleeding, vaginitis, dyspareunia, fibroids, and urinary tract infections.[14,15] Central nervous system complaints can include headaches, back pain, paresthesias, fainting, or seizures.[15,16]

Intimate partner violence can also cause significant stress, leading to gastrointestinal, cardiac, and psychological manifestations. Gastrointestinal symptoms can present as chronic abdominal pain, irritable bowel syndrome, bloating, eating disorders, or loss of appetite.[13,15,17] Cardiac symptoms can include

chest pain and palpitations.[15]

Not surprisingly, intimate partner violence leads to an increased rate of mental and psychological sequelae. One study reported an incidence of major depression of 60% and of post-traumatic stress disorder of 40% in women who were abused.[18] Victims are also more susceptible to anxiety, suicidal ideation, insomnia, and substance abuse.

The Centers for Disease Control and Prevention reported that the health care costs of intimate partner rape, physical assault, and stalking exceed $5.8 billion each year, with $4.1 billion going towards medical and mental health care services.[19]

CLINICAL FINDINGS

The most common injuries from intimate partner violence include abrasions, minor lacerations, contusions, sprains, fractures, and gunshot or knife wounds to the head, face, neck, chest, breasts, and abdomen.[20,21] These injuries exhibit a central distribution and are usually covered by clothing. Often, multiple sites are involved. On examination, one may find bruises in different stages of healing.[22] The victim may claim to be "accident-prone" when asked about the cause of her injuries.

A battered woman may come across as a "difficult" patient with multiple vague complaints for which investigation has not yielded a diagnosis. Symptoms can include generalized malaise and fatigue; headaches; chronic abdominal, pelvic, back, or chest pain; sexual dysfunction; insomnia; palpitations; depression; anxiety; and irritable bowel.[20,21] Complex problems like these should raise the clinician's suspicion and prompt screening for intimate partner violence.

Other red flags to raise one's suspicion include the partner's insistence on remaining in the examination room, answering questions for the patient, or looking sternly at the patient before she answers anything, as if to remind her not to disclose any information that might incriminate him. The patient may also appear to be uncomfortable (fidgeting, clasping hands, clammy skin) and look towards her partner before answering questions or committing to anything that involves a return visit.

THE CASE FOR SCREENING

Intimate partner violence is at least as prevalent as breast cancer, thyroid dysfunction, hypertension, or colon cancer.[23] Primary care physicians spend a lot of time screening for these other medical conditions, but very few of them screen for violence issues.

As a result, intimate partner violence is underdiagnosed, being detected in only 1 in an estimated 20 battered women.[24] Hamberger et al[24] in 1992 reported that only 6 out of 364 women were even asked about abuse. But when asked about violence, most women are willing to discuss these issues with their physicians.[25]

Criteria for a good screening test

The US Public Health Service's "Put Prevention into Practice" campaign[26] determines the utility of a screening test by analyzing the following principles originally established by Frame and Carlson[27] in 1975.

We believe that intimate partner violence fulfills each of the criteria and merits screening.

- *The condition must be significant enough to affect the quality and quantity of life*. As we have noted, abuse is serious. When a woman is abused, she may sustain injuries that can lead to an untimely death. She is generally isolated from family and friends, leading to diminished self-esteem. Long-standing abuse can also affect multiple organ systems, thereby leading to long-term health consequences.
- *Treatment must be available and acceptable*. Most communities have resources to guide women to seek help from various shelters and organizations.
- *The condition must have an asymptomatic period during which early detection and treatment substantially reduces morbidity and mortality*. By routinely screening all women, clinicians are in a unique position to help prevent injury and death by being alert to abusive patterns and by coming up with ways to get help (see the patient information pages that follow this article.) Early detection of abuse can preserve a woman's self-esteem and help her remain safe. She can also be educated about what to do when she decides to leave and about things she will need to start over.
- *Treatment in the asymptomatic period must provide a result better than that of delaying treatment until symptoms appear*. Unfortunately,

The victim may claim to be "accident-prone" when asked about her injuries

there are no hard data from randomized trials. Indeed, some may argue that screening and intervention may *increase* the victim's risk of serious injury or death, as these events are statistically more probable after the victim decides to leave, and screening may precipitate this chain of events.

However, we believe this argument may not apply. By detecting and intervening in intimate partner violence, we are trying to stop one human being from harming another. The question touches on ethics and the law as much as it does on science. Turning a blind eye is not acceptable.

- *Testing must be available at a reasonable cost to detect the condition during the asymptomatic period*. Most questionnaires are easily administered at a negligible cost.
- *The incidence of the condition must be significant enough to justify screening costs*. As noted, intimate partner violence is much more common than some of the other conditions that are routinely screened for.

Screening tools

Several tools with easy-to-remember acronyms have been created to screen for intimate partner violence. Examples include:

- RADAR,[28] ie:

*R*outinely screen all female patients over 14 years of age
*A*sk direct questions
*D*ocument clinical findings
*A*ssess patient safety and also safety of her children
*R*eview options and referrals.

- SAFE,[29] ie:

*S*afety in one's relationships and ability to return home
*A*buse (physical or sexual)
*F*riend and family awareness of the situation and ability to help
*E*mergency plan (shelter, cash, important documents).

- HITS,[30] ie, *how often has your partner:*

*H*urt you?
*I*nsulted or talked down to you?
*T*hreatened you with harm?
*S*creamed or cursed at you?

- Two simple screening questions, "*Do you ever feel unsafe at home?*" and "*Has anyone at home hit you or tried to injure you in any way?*" have a sensitivity of 71% and specificity of almost 85% in detecting violence.[31]

73% of domestic homicides take place after the victim leaves the perpetrator

Barriers to screening

Screening for intimate partner violence is an important health issue, but multiple barriers prevent universal recognition and identification.

Limited time. Most outpatient visits are only 15 to 20 minutes—not enough time to get into extensive discussions.

Physician discomfort. Fourteen percent of men and 13% of women have a personal experience with violence, which creates a barrier to addressing the topic.[32]

Misconceptions. Most clinicians do not believe intimate partner violence is a common problem, or they may feel that it occurs only in lower socioeconomic groups. They may also be afraid of offending a patient by asking about abuse.

Lack of training. A 1988 survey of US and Canadian medical schools indicated that fewer than half provided formal instruction on violence to their students.[33] In addition, very few residency and continuing medical education programs provide education on this topic.

The patient must be seen alone. The woman must not be accompanied by anyone when this discussion is conducted, as abuse can escalate once they leave the office if the abuser is present with her.

Legal obligations and court testimony. Many clinicians are unaware of their legal responsibilities and are wary of long court battles and testimony.[34]

Lack of confidence. Most clinicians are uncomfortable talking about violence since they feel ill-equipped to offer help. Additionally, male clinicians have lower screening rates than their female colleagues.[35]

Does it help? Currently, there are no studies demonstrating the effectiveness of screening. One recent review[36] suggested that it would be premature to recommend universal screening until more studies outline the benefits and risks to women, the appropriate screening interval, and the training needs of health professionals.

CLINICAL PRACTICE GUIDELINES

Various organizations have developed differing clinical guidelines on intimate partner violence.

Organizations that advocate screening and counseling are:

- The Family Violence Prevention Fund[37] (a national, nonprofit organization)
- The American Academy of Family Physicians[38]
- The American College of Emergency Physicians[39]
- The American College of Obstetricians and Gynecologists[40]
- The American Medical Association Council on Scientific Affairs.[41]

Organizations that recommend neither for nor against screening (due to insufficient evidence) are:

- The US Preventive Services Task Force[42]
- The Canadian Task Force on Preventive Health Care.[43]

STATE REPORTING LAWS

In assessing and intervening in situations of domestic violence, it is important to understand the laws regarding reporting requirements and the resources available to victims and their children in the community. In addition, it is imperative for practitioners to be aware of liability issues associated with intervention and documentation.

Mandatory reporting

There is much controversy regarding mandatory reporting, as many service providers believe that it places a victim at greater risk of physical harm. In addition, states with mandatory reporting often do not have adequate criminal justice resources to follow up on reports or do not have mechanisms in place to protect victims.[44]

In a 2001 statement, the American College of Emergency Physicians opposed mandatory reporting of domestic violence but rather encouraged reporting to community social service and victim agencies, as well as criminal justice agencies or any resource that can provide confidential counseling and assistance to victims. It also stated that referrals should be made with the express permission of the patient.[45]

In the United States, laws regarding when a physician must report a suspected case vary from state to state.

Three states mandate that suspicion of domestic violence be reported to legal authorities: California, Colorado, and Kentucky.[46]

Forty-two states have laws that require physicians to report any injury that results from the use of a firearm, knife, or other weapon.[46] These laws are not specific to the act of domestic violence but rather encompass crimes of domestic violence under the statute. These statutes make it difficult for practitioners to understand their legal obligation and its potential for liability regarding reporting vs not reporting.[44]

Twenty-three states require that injuries resulting from crimes be reported. Seven states have statutes requiring health care providers to report injuries from domestic violence.[46] Ten states have laws addressing domestic violence training. Eight states have required domestic violence protocols. Only three states have laws addressing screening for domestic violence.[37]

Five states (Alabama, New Mexico, South Carolina, Washington, and Wyoming) have no specific requirements that health care providers report patient injuries resulting from assault-related incidents.[46]

FEDERAL LAW

The Violence Against Women Act, enacted as part of the Crime Bill of 1994, empowers the federal Department of Justice to prosecute crimes of domestic violence.[47]

This legislation allows the federal government, which has historically lacked jurisdiction over crimes of domestic violence, to prosecute offenders in certain circumstances that involve interstate travel or activity and the use of firearms.

The United States has for the most part made great strides on the federal and state levels in the fight against domestic violence and in protecting victims. It is important that criminal justice systems learn what works in victim protection and what may put victims at increased risk of harm.[47]

Only California, Colorado, and Kentucky require that suspected domestic violence be reported to police

DOCUMENTATION IS CRITICAL

It is critical for hospitals to adopt procedures for documenting suspected domestic violence. Some states require written policies and procedures regarding documentation of verified and suspected domestic violence. Each health

TABLE 2

Internet resources on intimate partner violence

Family Violence Prevention Fund
http://endabuse.org

State-by-State Report Card on Health Care Laws and Domestic Violence
http://endabuse.org/statereport/list.php3

US Department of Justice
Extent, Nature, and Consequences of Intimate Partner Violence
www.ncjrs.org/pdffiles/nij/181867.pdf

World Health Organization
www.who.int/violence_injury_prevention/violence/global_campaign/en/

American College of Obstetricians and Gynecologists
Violence Against Women
www.acog.org/from_home/departments/dept_web.cfm?recno=17

American Medical Women's Association
www.amwa-doc.org/publications/wchealthbook/violenceamwa-ch10.html

American Medical Association
www.ama-assn.org/ama/pub/category/3242.html

National Institutes of Health
www.nlm.nih.gov/medlineplus/domesticviolence.html

care organization and provider should be knowledgeable regarding his or her individual state's requirements.[48] The personnel directly involved in documentation in the patient record of any suspected abuse are physicians, registered nurses, licensed practical nurses, interns, residents, social workers, counselors, and psychologists.[48]

Hospitals must have procedures for documenting domestic violence

In states with laws regarding documentation of known or suspected abuse, the health care provider must have reasonable cause to believe that a patient has been a victim of domestic violence. Then the health care personnel must record observations, impressions, and the basis of those impressions in the patient's record.[48] Suspicion of domestic violence must be documented in a clear and objective manner. If abuse is suspected but the patient denies it, health care personnel must document the suspicions and validate them with objective observations that the injuries are inconsistent with the explanation of the patient. The patient's general demeanor should be documented, as well as any quotes from the patient. Also, use words such as "stated" and "said."[37]

Documentation should be in detail and in the patient's words. It should contain how the injuries occurred and who committed the abuse, including the abuser's name and any other identifying information. It is helpful to use a body map identifying the injury observed.[37]

A procedure regarding photographing of victims who have been abused must be written and implemented. Photos should be taken whenever possible with the patient's permission.[37] It is optimal that an uninterested party—such as the hospital photographer rather than the nurse or social worker who is involved in the intervention—take the photographs. Multiple photographs, which include a full head and body shot, should be taken, as well as photographs of the injury from different angles. The date and time of the photograph should be included in the actual photo.[49]

Discharge plans should include any referrals and recommendations that were made for the patient's follow-up care, as well as any contacts with outside resources such as police and community agencies.[49]

Health care organizations must have a protocol for interviewing victims and their accompanying family members.[48] A patient should be interviewed privately and separately from any family members, friends, or relatives who may have accompanied the patient to the health care facility. Hospital protocol, which includes written policies and procedures, must link closely with services and resources of com-

munity police departments, the judicial system, and social service agencies.[49]

REFERRAL SOURCES

National referral sources include the National Domestic Violence Hotline at (800) 799-SAFE (7233). National Web sites (TABLE 2) include the National Coalition Against Domestic Violence at www.ncadv.org, the Family Violence Prevention Fund at www.endabuse.org, and the Office on Violence Against Women at www.ojp.usdog.gov/vawo, offering numerous resources to victims and providers of victim services. Information and referrals to batterers' intervention programs are generally made through the criminal justice system in the jurisdiction where the crime was committed.

It is important to note that once referral information is given and a victim decides to leave, her risk is increased. According to statistics, 73% of domestic violence homicides take place after the victim leaves the perpetrator.[50] Identification of and intervention in domestic violence are critical to providing comprehensive patient care. All health care personnel must be knowledgeable in the legal and medical implications of domestic violence and its impact on health care and victim safety.

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REVIEW

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New cervical cancer screening strategy: Combined Pap and HPV testing

ABSTRACT

Our strategy for cervical cancer screeing is being revolutionized by our new understanding of how human papillomavirus (HPV) contributes to carcinogenesis and the natural history of cervical cancer. The American Cancer Society and the American College of Obstetricians and Gynecologists now recommend combined HPV and Papanicolaou (Pap) testing for cervical cancer screening in women age 30 or older. However, although incorporation of HPV DNA testing into primary screening provides clear benefits, it also raises new questions.

KEY POINTS

HPV infection most often is transient in younger women. With increasing age, the likelihood increases that HPV positivity represents persistent disease, and only those who have persistent high-risk HPV infection are at risk of cervical cancer.

Combined HPV DNA testing and Pap testing is now recommended for primary screening in women age 30 or older. If both tests are negative, the screening interval can be extended to every 3 years.

If a woman has a positive result on HPV testing but a negative result on Pap testing, she should repeat both tests in 6 to 12 months.

Eventually, the search for ideal cervical cancer biomarkers will improve risk stratification in screening, while an HPV vaccine will eradicate cervical cancer.

WOMEN AGE 30 and older may undergo combined Papanicolaou (Pap) and human papillomavirus (HPV) testing to screen for cervical cancer, according to new guidelines from several professional societies.[1–3] If both test results are negative, subsequent screening can be at 3-year intervals.

These recommendations came after the US Food and Drug Administration (FDA) approved the HPV test (Hybrid Capture 2; Digene Corporation, Gaithersburg, MD) as an adjunct for primary cervical cytology screening. The United States Preventive Services Task Force (USPSTF),[4] however, finds that there is insufficient evidence to recommend for or against its routine use for this purpose.

Up to now, the HPV test has been recommended and approved only as a follow-up test for women with a Pap test finding of atypical squamous cells of undetermined significance (ASC-US).[5] For women younger than 30 years, screening is still every year with conventional Pap testing or every 2 years with ThinPrep Pap testing (or every 3 years according to the USPSTF).

These are exciting times in the field of cervical cancer detection and prevention, as progress in understanding the role of HPV in carcinogenesis is being applied to clinical practice (TABLE 1).[6–13]

This article briefly reviews contemporary concepts of cervical cancer carcinogenesis, evidence supporting HPV testing in primary screening, current practice guidelines, commonly asked questions, and future directions in screening.

ROLE OF HPV IN CERVICAL CANCER

HPV infection is necessary for cervical cancer to develop but does not suffice by itself.[14–18]

To date, more than 80 HPV types have

TABLE 1

Recent milestones in cervical cancer screening

1996	The FDA approves liquid-based ThinPrep technology, significantly increasing rates of specimen adequacy and cytologic diagnosis of cervical cancer precursors and decreasing ambiguous interpretations[6–8]
2000	The FDA approves HPV DNA test for testing women with an abnormal Pap test to determine if they need colposcopy
2001	The Bethesda terminology for Pap smear reporting is revised, reducing ambiguity and allowing better clinical decisions[9,10]
2001	The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions (ASCUS/LSIL) Triage Study (ALTS trial) validates the clinical effectiveness of HPV testing in women with mildly abnormal cervical cytologic findings[11–13]
2003	The FDA approves the Hybrid Capture 2 HPV DNA test for women of all ages with ASCUS and for women age 30 or older in routine primary screening

been identified, and more than 30 of these can infect the genital tract.[19] Certain genital HPV types (16 and 18) are associated with a substantially higher risk of cervical cancer than other types. HPV types that carry a moderate risk of cervical cancer include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.[20] Types 6 and 11 carry a low risk.

HPV infection precedes the development of cytologic abnormalities

Extensive studies provide compelling evidence that infection of the cervix with one of the 15 high-risk or moderate-risk HPV types is required for the development of virtually all cervical cancers.[21]

A multicenter study from 22 countries found that HPV DNA could be detected in 93% of squamous cell carcinomas of the cervix.[15] Furthermore, HPV DNA can also be isolated from metastatic cervical cancer tissues and from cervical cancer tumor cell lines in vitro.[22,23]

Finally, in vitro studies are shedding light on the mechanism by which HPV infection increases the risk of cancer (Mechanisms of HPV oncogenesis on page 144).[24–33]

WHY HPV-PLUS-PAP TESTING IS THE NEW STANDARD OF CARE

Combining the HPV test with the Pap test in primary cervical cancer screening is the logical extension of the knowledge acquired over the past 2 decades on the natural history of HPV infection and cervical cancer development.

Pap testing lacks sensitivity

For the last 5 decades, annual Pap testing has been the standard of care in screening for cervical cancer. It has decreased both the incidence of cervical cancer and the number of deaths due to cervical cancer by about 75%.[34]

However, in routine screening, the estimated true sensitivity of the conventional Pap test is only 50% to 60%.[35–37] Pap screening is successful, despite this relative insensitivity, because patients undergo repeated testing.

The new liquid-based ThinPrep technology (Cytyc Corporation, Boxborough, MA) has improved the sensitivity of Pap testing. Yet Pap testing may still miss 15% to 35% of cases of cervical intraepithelial neoplasia grade 3 (CIN 3, a precursor of cancer) or cancer itself.[38]

In addition, Pap tests must be interpreted by a pathologist, and results are not very reproducible. And pathologists who, despite their best efforts, failed to detect CIN or cervical cancer on conventional Pap smears have been exposed to increasing numbers of lawsuits.[39–41] Therefore, the conventional Pap smear by itself no longer meets the expectations of clinicians and patients.

HPV testing is more sensitive

In a search for a more sensitive screening test, multiple large-scale studies from many countries evaluated the role of HPV testing in primary screening (TABLE 2).[38,42–45] Important findings from these studies:

- The high-risk HPV DNA test was positive in 80% to 100% of cases of histologically confirmed CIN 2 or cancer.

TABLE 2

Combined HPV and Pap testing in primary screening

STUDY	LOCATION	NO. OF WOMEN	SENSITIVITY (%)*			SPECIFICITY (%)*			NEGATIVE PREDICTIVE VALUE*
			PAP	HPV	PAP+HPV	PAP	HPV	PAP+HPV	
Petry et al[45]	Germany	7,592	34	86	94	99	97	96	0.999
Cuzick et al[1]	United Kingdom	10,358	72	97	100	99	94	93	1.000
Salmeron et al[42]	Mexico	6,115	57	94	98	99	94	94	1.000
Schiffman et al[1]	Costa Rica	6,176	80	86	92	95	94	90	0.998
Belinson et al[43]	China	1,936	94	98	100	78	85	70	1.000
Womack et al[1]	United States	1,040	60	100	100	98	97	96	1.000

*For CIN 2+ = cervical intraepithelial neoplasia grades 2 and 3 or cancer

BASED ON WRIGHT TC JR, SCHIFFMAN M, SOLOMON D, ET AL. INTERIM GUIDANCE FOR THE USE OF HUMAN PAPILLOMAVIRUS DNA TESTING AS AN ADJUNCT TO CERVICAL CYTOLOGY FOR SCREENING. OBSTET GYNECOL 2004; 103:304–309.

- HPV testing was more sensitive in detecting CIN 2, CIN 3, or cancer than a single Pap test. (It was, however, less specific. For this reason, HPV testing cannot replace Pap testing. Combined, the two tests have a specificity of 70% to 96%.)
- When HPV testing was combined with a Pap smear, the sensitivity was even higher than that of HPV testing used alone.
- Most important: the combination of a negative Pap smear and a negative HPV test indicated absence of CIN 3 or cancer to a certainty of almost 100%.

Specificity of HPV testing increases with age

Women who test positive for HPV on more than one occasion do not necessarily have persistent infection with the same type of high-risk HPV, nor will they necessarily go on to develop cervical cancer.

Sherman et al[46] reported that the prevalence of high-risk HPV infection declines with age: only 31.2% among women with ASCUS who were 29 years or older, compared with 65% in those age 28 and younger. HPV infection most often is transient in younger women. With increasing age, the likelihood increases that HPV positivity represents persistent disease, and only those who have persistent high-risk HPV infection are at risk of cervical cancer.

As a result, both the specificity and the positive predictive value of an HPV test increase with the age of the patient. Therefore, combined HPV-plus-Pap testing in women age 30 years or older is the new standard of care in cervical cancer screening.

POTENTIAL HARM FROM HPV TESTING

Adding HPV testing to Pap testing brings clear potential benefits but also poses the risks of overuse and unnecessary invasive treatment.

A negative Pap-plus-HPV test nearly rules out CIN 3 or cancer

HPV infection is very common in women, but few of these women will develop cervical cancer or a high-grade precancerous lesion. Combined HPV-plus-Pap testing will identify 10% to 20% of adult women as having transient, clinically insignificant HPV infection.

It is very important to restrict HPV testing to women age 30 or older, to provide adequate counseling regarding their risk of cervical cancer, and to avoid unnecessary invasive therapy such as the loop electrosurgical excision procedure (LEEP).[1]

CURRENT GUIDELINES FOR SCREENING

In view of recent advances (TABLE 1), the American Cancer Society, the USPSTF, and the American College of Obstetricians and Gynecologists have developed practice guidelines (TABLE 3).[1–4]

The American Cancer Society and American College of Obstetricians and Gynecologists both recommend adding HPV

Mechanisms of HPV oncogenesis

Evidence about the mechanism by which HPV contributes to oncogenesis comes from in vitro studies, in which human epithelial cells that are infected with high-risk types of HPV become immortal.[24,25] Other in vitro studies have identified two HPV viral gene products, the proteins E6 and E7, that are necessary for immortalization.[26–28]

E6 proteins from high-risk HPV types interact with the cellular tumor-suppressor protein p53. In noninfected cells, p53 levels increase in response to cellular or DNA damage or aberrant cell proliferation signals. High levels of p53 cause the cell to stop growing in the G1 phase of the cell cycle and allow it to either repair damaged DNA before the next round of DNA synthesis or be eliminated through programmed cell death (apoptosis).[29]

In HPV-infected cells, the E6 protein binds to p53, resulting in rapid proteolytic degradation of the bound p53 through a ubiquitin-dependent pathway.[30,31] The decreased level of p53 diminishes the cell's ability to control the cell cycle and repair DNA damage and ultimately leads to uncontrolled cell growth.[31]

In contrast, E6 proteins from low-risk HPV types do not bind p53 in detectable levels and have no effect on p53 stability in vitro. This weak affinity for p53 may explain the lesser oncogenic potential of the low-risk HPV types.

Similarly, E7 proteins from high-risk HPV types interact with another cellular tumor-suppressor protein, the retinoblastoma protein (pRB). The binding of E7 proteins to pRB disrupts the complex between the cellular transcription factor E2F-1 and pRB. This results in the release of E2F-1, allowing it to stimulate cellular DNA synthesis and uncontrolled cell growth.[32] Again, the E7 protein from low-risk HPV types 6 and 11 binds pRB with a much weaker affinity.

A recent study also suggests a model whereby HPV-16 E7 protein induces centrosome-related mitotic disturbances that are potentiated by HPV-16 E6 protein.[33]

testing to Pap testing in women 30 years and older in primary screening.

To help provide guidance for physicians when using HPV testing as an adjunct to Pap testing for screening, the National Institutes of Health National Cancer Institute, the American Society of Colposcopy and Cervical Pathology, and the American Cancer Society cosponsored a workshop in 2003. It is the consensus from the workshop that HPV testing may be added to the Pap smear for screening in women age 30 or older.[1] The workshop also provided an interim guideline for management after screening (FIGURE 1).

COMMONLY ASKED QUESTIONS

Incorporating HPV testing into primary screening provides a better risk assessment and an excellent negative predictive value, but also raises some new questions from patients and clinicians.

Why do we need to add HPV testing? Isn't the Pap test effective by itself?

The Pap smear is relatively insensitive and has to be repeated frequently to detect the disease in the general population. The problem with frequent testing is that it detects many cases of transient and minimal abnormalities that would not progress to cervical cancer. As a result, many women with abnormal Pap tests but no significant underlying pathology will undergo an invasive procedure to ensure that they do not have precancerous lesions.

Studies have also shown that almost one third of women with invasive cervical cancer have had one or more normal Pap tests or no abnormal Pap test during the previous 3 years.[47] The ALTS trial demonstrated that HPV testing can predict who really is at risk for CIN 2, CIN 3, or cancer and who is not. Most recent large clinical screening trials clearly demonstrated that combined HPV-plus-Pap testing has greater sensitivity for detecting these lesions than does Pap testing by itself.

Furthermore, if both the Pap and HPV tests are negative, then the probability that CIN 3 or cancer is absent (the negative predictive value) is almost 100%.

Therefore, combined HPV-plus-Pap testing allows us to better identify women at risk of developing cervical cancer and to reassure

TABLE 3

Recommendations for cervical cancer screening

HPV DNA testing for primary screening
- **ACS:** Yes, in combination with the Papanicolaou (Pap) test in women 30 years and older
- **ACOG:** Same as ACS recommendation
- **USPSTF:** Insufficient evidence to recommend for or against routine use

When to start screening
- **ACS:** Approximately 3 years after the onset of vaginal intercourse; no later than age 21
- **ACOG:** Same as ACS
- **USPSTF:** Same as ACS

Screening interval
- **ACS:** Annual with conventional Pap test or every 2 years using liquid-based ThinPrep until age 30. At or after age 30, Pap combined with HPV testing; if both negative, every 3 years
- **ACOG:** Annually in women < 30 years old; in women > 30 years old, same as ACS
- **USPSTF:** Every 3 years

When to stop screening
- **ACS:** Age 70 and older who have had three or more consecutive normal Pap tests
- **ACOG:** Individual basis
- **USPSTF:** Age 65 if she had adequate recent screening with normal Pap smears

Screening after hysterectomy
- **ACS:** If hysterectomy for a benign condition: no more screening; if hysterectomy was for precancer: continue screening for 10 years to achieve three consecutive negative Pap tests; if hysterectomy was for cancer, continue screening as long as the patient is in reasonably good health
- **ACOG:** If hysterectomy was for grade 2 or 3 cervical intraepithelial neoplasia, continue annual screening until three consecutive Pap smears are negative
- **USPSTF:** Same as ACS

ACS = American Cancer Society, ACOG = American College of Obstetricians and Gynecologists, USPSTF = United States Preventive Services Task Force

Many women acquire HPV, but few develop cancer

women that "negative is negative" with a high degree of certainty.

Is it safe to screen women every 3 years?

Some clinicians are concerned that even if a woman tests negative on both the HPV and Pap tests, she could subsequently acquire HPV from a new sexual partner and might be at risk of developing invasive cancer before her next screening in 3 years.

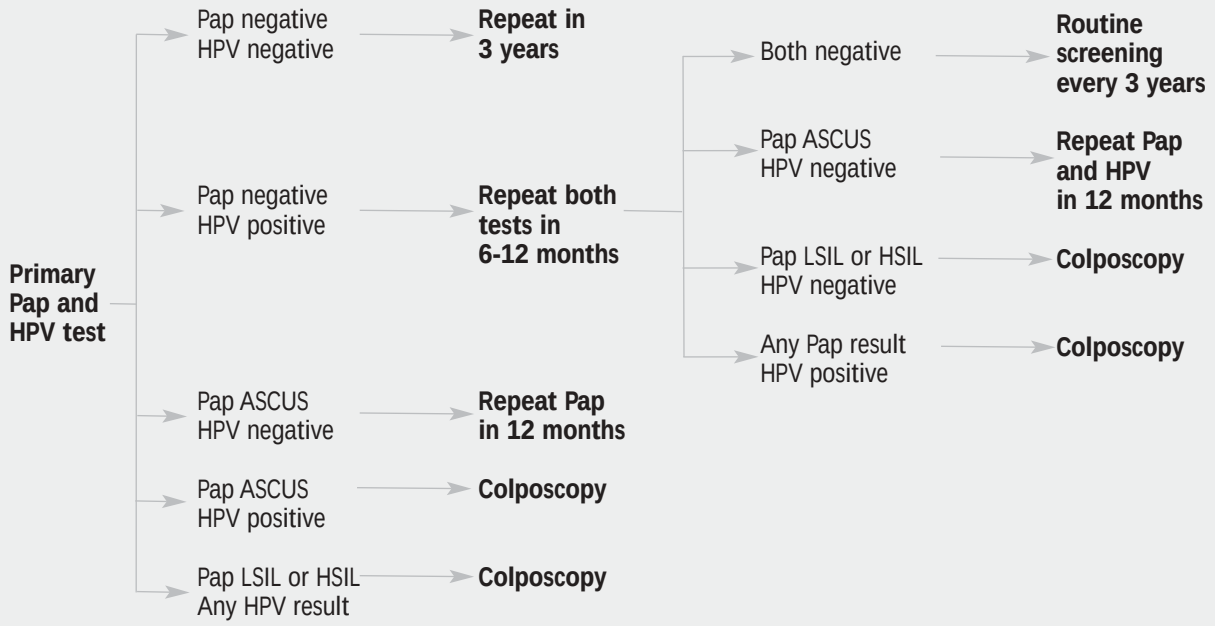
It is true that a woman can have a double-negative test today, acquire high-risk HPV tomorrow, and develop high-grade CIN within a few weeks or months. However, the transit time—the time from initial infection to the development of cervical cancer—usually exceeds 10 years.[48] Her high-grade CIN will be detected at her next screening, long before 10 years.

We have a similar screening model in clinical practice: colonoscopy. A negative colonoscopy at age 50 indicates a very low risk of colon cancer in the next 10 years, since the transit time is long. Therefore, clinicians should have a high level of comfort in promoting a longer screening interval in women over 30 who test negative on both the HPV and the Pap test.

Pap-negative but HPV-positive: Is it a 'false-positive'?

The combination of a positive HPV test plus a negative Pap test should not be considered a false-positive result, since HPV infection precedes the development of cytologic abnormalities.[49] If the HPV infection persists, the woman is at high risk of developing cervical cytologic abnormalities that will be detected

Management algorithm after combined Pap and HPV testing



ASCUS = atypical squamous cells of undetermined significance, HPV = human papillomavirus (testing by Hybrid Capture 2), HSIL = high-grade squamous intraepithelial lesion, LSIL = low-grade squamous intraepithelial lesion, Pap = Papanicolaou smear

FIGURE 1

BASED ON WRIGHT TC JR, SCHIFFMAN M, SOLOMON D, ET AL. INTERIM GUIDANCE FOR THE USE OF HUMAN PAPILLOMAVIRUS DNA TESTING AS AN ADJUNCT TO CERVICAL CYTOLOGY FOR SCREENING. OBSTET GYNECOL 2004; 103:304–309.

on a subsequent Pap test.[50,51] Such patients should be followed closely.

'I am HPV-positive. How did I get it? Who gave it to me and when?'

HPV infection is indeed transmitted by sexual contact. Most likely, a woman with HPV infection acquired it from her sexual partner.[52,53] However, due to the latency of HPV infection, it is almost impossible to determine *when* she acquired it or from which partner. HPV infection certainly does not suggest infidelity or promiscuity.

Physicians need to provide appropriate counseling to women who test positive for HPV to avoid unnecessary anxiety and negative implications in personal relationships.

Should we test the male partners of women testing positive for HPV?

Screening male partners is not recommended at present.

Overall, little is known about the natural history of penile HPV infection.[54] Although men are believed to be vectors for HPV transmission, HPV DNA testing does not accurately reflect a man's HPV infection status or lifetime exposure to HPV even using highly sensitive methods.[55]

Only about one fifth of men whose wives are positive for CIN 3 test positive for penile HPV. Furthermore, the same HPV types are rarely identified in husbands and wives.[56]

FUTURE DIRECTIONS IN SCREENING AND PREVENTION

Biomarkers of cancer

Despite the value of HPV testing in women with ASCUS, only 77 of 611 women with ASCUS and HPV in the ALTS trial were subsequently found to have CIN 3. Clearly, many women underwent unnecessary colposcopy and biopsy.

Similarly, in routine primary screening, a positive HPV test does not predict the subsequent development of CIN 3 or cancer. The positive predictive value of HPV testing is poor.

Therefore, research is under way to identify markers that can be used to predict which lesion will regress and which will progress.

One of the most promising biomarkers for cervical cancer is $p16^{INK4A}$, a cyclin-dependent kinase inhibitor[57] that is strongly expressed in almost all cervical cancers. However, it is still not clear whether $p16^{INK4A}$ positivity can be used to distinguish which lesion will progress.[58]

HPV vaccine

To eliminate cervical cancer we will need not only effective screening, but also preventive strategies such as an HPV vaccine.

Recently, Koutsky et al[59] elegantly demonstrated the efficacy of HPV-16 vaccine in a clinical trial in 1,194 women. At 17 months, the incidence of persistent HPV-16 infection was 0 per 100 woman-years in vaccinated women, compared with 3.8 in a placebo group. No cases of HPV-16-related CIN occurred in the vaccinated group, vs 9 in the placebo group. This is a remarkable advance in cervical cancer prevention and a very powerful demonstration that cervical HPV infection and cervical cancer can be prevented by vaccination.

Ultimately, a vaccine against all oncogenic HPV strains will allow us to eradicate cervical cancer.[60]

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Cardiovascular problems and pregnancy: An approach to management

ABSTRACT

Women with some congenital or acquired heart lesions are at increased risk for a number of maternal and neonatal complications during pregnancy. Knowing what constitutes high risk and when to refer to a specialty clinic are key to successfully managing such patients.

KEY POINTS

Cardiac output increases 50% in pregnancy while peripheral vascular resistance and blood pressure decrease. These changes can exacerbate certain pre-existing cardiac conditions.

Pregnant women with congenital heart lesions are at risk for heart failure, arrhythmia, stroke, neonatal complications, and even death in some conditions.

Women of reproductive age with congenital heart lesions should be counseled as to whether pregnancy is advisable and whether their problem can be corrected or palliated before pregnancy.

Women at intermediate or high risk for maternal or fetal complications should be referred for specialty care.

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IS IT SAFE for a woman with a heart problem to have a baby? What should we advise her and how should her pregnancy be managed?

The answers depend on the problem and on the woman's heart status. With some types of heart disease, outcomes are excellent without any special management in women with good function. With other types, pregnancy poses a reasonable risk if the problem is corrected first, and still other types should rule out pregnancy altogether.

This article reviews the impact of pregnancy on a number of congenital and acquired heart diseases (and vice versa) and offers recommendations for their management. It also provides a method to assess risk to help in deciding whether to refer a patient for specialty care.

CARDIOVASCULAR CHANGES DURING PREGNANCY

During pregnancy, intravascular volume and cardiac output increase by 50%, peaking during the second trimester and remaining high through the rest of pregnancy. This "physiologic" high-output state is accompanied by decreases in peripheral vascular resistance and blood pressure. The hemodynamic changes of pregnancy may not fully resolve until 6 months after delivery.

Owing to these normal changes, many healthy pregnant women have symptoms mimicking those of cardiac disease, including fatigue, dyspnea, and light-headedness, and a number of "abnormal" findings on physical examination, electrocardiography, and echocardiography (TABLE 1).

TABLE 1

Common cardiac findings in normal pregnancy

Symptoms
- Fatigue
- Dyspnea
- Light-headedness

Physical findings
- Displaced apical impulse
- Prominent jugular venous pulsations
- Widely split first and second heart sounds
- Soft ejection systolic murmur

Electrocardiographic findings
- Sinus tachycardia
- Premature atrial or ventricular ectopic beats
- Right or left axis deviation
- ST-segment depression
- T-wave changes

Echocardiographic findings
- Mild increase in left ventricular diastolic dimension with preservation of ejection fraction
- Functional tricuspid and mitral regurgitation
- Small pericardial effusion

OUTCOMES VARY WITH DIFFERENT CARDIAC LESIONS

In Marfan syndrome, aortic root replacement does not eliminate the risk of dissection

Few women with heart disease actually die during pregnancy; the high-risk exceptions are women with Eisenmenger syndrome, pulmonary vascular obstructive disease, or Marfan syndrome with aortopathy. However, pregnant women with heart disease are at risk for other complications such as heart failure, arrhythmias, and stroke.[1–6] Their babies are also at risk of complications such as birth weight that is low for the gestational age, premature birth, and death.[1,2,7]

Congenital heart disease is now the most common heart problem in pregnant women seen at referral centers in North America.[5] Peripartum cardiomyopathy is infrequent. Isolated mitral valve prolapse is probably the most common cardiac lesion in pregnant women, but it has an excellent prognosis in pregnancy, and patients with it may not need to be referred to a cardiovascular specialist.[8]

CONGENITAL HEART LESIONS

Left-to-right cardiac shunts

In patients with an atrial septal defect, ventricular septal defect, or patent ductus arteriosus, blood can shunt from the high-pressure left side of the heart to the lower-pressure right side. During pregnancy, as cardiac output increases, one would expect this left-to-right shunting to increase. However, this effect may be attenuated by the decrease in peripheral vascular resistance.

If there is no pulmonary hypertension, then pregnancy, labor, and delivery are well tolerated.[2,4,5,9] However, during labor and delivery, a risk of paradoxical embolism exists (ie, a venous thromboembolism passing from the right side of the heart to the left), particularly with an atrial shunt such as a patent foramen ovale.

Aortic stenosis, left ventricular outflow tract obstruction

The most common cause of aortic stenosis in pregnant women is a congenital bicuspid aortic valve, but fixed subvalvular and supravalvular aortic stenoses have similar hemodynamic implications.

If the stenosis is severe, the heart must strain to increase its output during pregnancy, and heart failure or ischemia may develop. The left ventricle can become hypertrophied and noncompliant, and in this condition, any condition that decreases preload—such as compression of the inferior vena cava in late pregnancy, anesthetic agents with

vasodilatory effects, peripartum blood loss, and bearing-down maneuvers—can lead to an exaggerated drop in cardiac output and to hypotension.

In a 1993 overview of 106 pregnancies in women with congenital aortic stenosis, the maternal mortality rate was 11% and the perinatal mortality rate was 4%.[10] However, in a more recent series of 49 pregnancies (59% in women with severe stenosis), no women died.[11] Adverse maternal cardiac events occurred in 3 women (6%), all of whom had severe stenosis, defined as an aortic valve area of 1 cm^2 or smaller or a transvalvular pressure gradient of 64 mm Hg or greater.

Aortic dissection has been reported in pregnant women with a bicuspid aortic valve and ascending aortopathy,[12] although this risk is probably lower than for women with Marfan syndrome with aortopathy.

Recommendations. Women with symptomatic aortic stenosis should delay getting pregnant until the stenosis is surgically corrected.[13] However, absence of symptoms does not guarantee that pregnancy will be well tolerated. Balloon valvuloplasty during labor and delivery may be palliative in certain cases.

Coarctation of the aorta

Coarctation of the aorta is commonly associated with a bicuspid aortic valve; other associations include aneurysms of the circle of Willis, ventricular septal defects, and Turner syndrome.

The coarctation often is corrected before a woman becomes pregnant; if it is not, aortic rupture is a risk in the third trimester and during labor. In early series of uncorrected cases, the maternal mortality rate was 3% to 4%, or higher if there were associated cardiac defects, aortopathy, or long-standing hypertension.

Even if the coarctation is corrected before pregnancy, pregnancy-induced hypertension can occur,[4,5,14] probably due to residual abnormalities in aortic compliance.

Maternal death is rare. Recent studies in patients with both corrected and uncorrected aortas have been encouraging, with only one maternal death reported in 182 pregnancies.[14]

Pulmonary valve stenosis

Pulmonary valve stenosis can be classified by echocardiographic estimates of the peak pressure gradient across the valve:

- Mild (< 50 mm Hg)
- Moderate (50–79 mm Hg)
- Severe (≥ 80 mm Hg).

The gradient increases with cardiac output during pregnancy, so the severity may be overestimated if no antenatal study is available.

Pulmonary valve stenosis that is mild or that has been treated by valvuloplasty or surgery is well tolerated during pregnancy.[4,5] Fetal outcome is also favorable.[4,5]

Severe stenosis, even if asymptomatic before pregnancy, may lead to right-sided heart failure or atrial arrhythmias owing to the increased hemodynamic load of pregnancy.

Recommendations. Patients with severe pulmonary valve stenosis should be considered for correction before pregnancy. Balloon valvuloplasty may be feasible during pregnancy if symptoms progress.

Cyanotic heart disease: Unrepaired and repaired

The most common form of cyanotic congenital heart disease is the tetralogy of Fallot, the essential features of which are right ventricular outflow tract obstruction and a large, nonrestrictive ventricular septal defect.

If the problem is not corrected or palliated, the pregnancy-associated fall in systemic vascular resistance and rise in cardiac output exacerbate right-to-left shunting, leading to increased maternal hypoxemia and cyanosis. The fetal loss rate may be as high as 30%, and the maternal mortality rate is 4% to 15%.[15]

Women with Eisenmenger syndrome should be offered sterilization or pregnancy termination

In a series of 96 pregnancies in 44 women with a variety of cyanotic congenital heart defects, there were high rates of maternal cardiac events (32%, including 1 death) and prematurity (37%), and a low live birth rate (43%).[16] The lowest live birth rate (12%) was in mothers with arterial oxygen saturation of 85% or lower.

Risk is low in women in whom the tetralogy has been successfully corrected.[2,4,5]

Marfan syndrome

Marfan syndrome is a connective tissue disorder inherited in an autosomal-dominant pattern. Life-threatening aortic complications are due to medial aortopathy, resulting in dilatation, dissection, and valvular regurgitation.

The aortopathy is a generalized process. Therefore, in patients with aortic root dilatation, prophylactically replacing the root before pregnancy may not fully eliminate the risk of dissection of the residual native aorta.

Risk is increased in pregnancy, owing to hemodynamic stress and perhaps hormonal effects. Although the mortality rate was very high (around 30%) in older case reports, more recent data suggest an overall maternal mortality rate of 1% and a fetal mortality rate of 22%.[17]

In a prospective study of 45 pregnancies in 21 patients, most patients had no obstetric complications or significant change in aortic root size. However, in 8 patients with a dilated aortic root (> 40 mm) or prior aortic root surgery, 3 of 9 pregnancies were complicated by either aortic dissection or rapid aortic dilatation.[18]

Recommendations. Patients with aortic root involvement should receive preconception counseling emphasizing their risk. If the patient is seen in early pregnancy, she should be offered the option to terminate the pregnancy.

In contrast, women with little cardiovascular involvement and an aortic root diameter smaller than 40 mm by echocardiography tolerate pregnancy well. Serial echocardiography should be done to monitor for progressive aortic root dilatation, and beta-blockers should be given prophylactically.[19] The possibility of dissection even with a normal aortic root should be acknowledged to the patient.

Maternal cardiac status is an important predictor of pregnancy outcome

Eisenmenger syndrome and pulmonary vascular obstructive disease

Eisenmenger syndrome involves pulmonary vascular obstructive disease resulting from a pre-existing left-to-right shunt. Over time, pulmonary pressures rise to systemic levels, changing the shunt flow to right-to-left.

Most complications during pregnancy occur at term and during the first postpartum week. Spontaneous abortion, intrauterine growth restriction, and preterm labor are frequent. Perinatal mortality is due mainly to prematurity.

Maternal and neonatal mortality rates are high in patients with pulmonary hypertension. A 1998 review of 125 pregnancies found the maternal mortality rate to be 30% in those with primary pulmonary hypertension, 36% in those with Eisenmenger syndrome, and 56% in those with secondary vascular pulmonary hypertension. The overall neonatal mortality rate was 12%.[20]

Recommendations. Preconception counseling should stress the extreme risks from pregnancy. Patients with Eisenmenger syndrome should always be offered sterilization or pregnancy termination.

RHEUMATIC HEART DISEASE

Mitral stenosis

Mitral stenosis is the most common rheumatic valvular lesion of pregnancy. The hypervolemia and tachycardia associated with pregnancy exacerbate the transmitral gradient.

Atrial fibrillation may result from the elevated left atrial pressure. This can precipitate heart failure, primarily due to an uncontrolled ventricular rate; equivalent tachycardia from any cause may be equally detrimental. Even patients with only mild to moderate mitral stenosis (who have no symptoms before pregnancy) may develop atrial fibrillation and heart failure during the antepartum and peripartum periods.

Recent studies found no mortality but substantial morbidity from heart failure and arrhythmia.[4,5,21,22] The risk of complications is higher in women with a history of cardiac events (arrhythmias, stroke, or pulmonary edema) and with moderate or severe mitral stenosis.

The risk of adverse fetal or neonatal outcomes also increases with increasing severity of mitral stenosis.[22]

Percutaneous mitral valvuloplasty during pregnancy should be considered in patients who, despite optimal medical therapy, are in New York Heart Association (NYHA) functional class III or IV (markedly limited ability or inability to engage in any physical activity without symptoms).[23]

Other rheumatic lesions

Rheumatic aortic stenosis poses a risk during pregnancy similar to that of congenital aortic stenosis.

Aortic or mitral regurgitation, even if severe, is generally well tolerated during pregnancy, although function may deteriorate as measured by the NYHA classification.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy, an idiopathic dilated cardiomyopathy, involves ventricular systolic dysfunction that develops during the last month of pregnancy or in the first 5 months after delivery in patients with no known underlying disease.[24]

Heart failure is the most common manifestation, although arrhythmias and embolic events also occur. Many women improve in NYHA functional status and ventricular function postpartum, but others have persisting problems or even worsen.

The relapse rate during subsequent pregnancies is substantial in women with evidence of persisting cardiac enlargement or left ventricular dysfunction. However, pregnancy may not be risk-free even in those who recover systolic function, as subclinical abnormalities may persist.[25]

A multicenter survey examined the outcomes of 60 pregnancies in women with peripartum cardiomyopathy diagnosed during a prior pregnancy. Of those with a poor left ventricular ejection fraction (< 0.50), 44% developed symptoms of congestive heart failure and 19% died. Of those with better heart function (ejection fraction ≥ 0.50), 21% developed symptoms of congestive heart failure and none died.[26]

MANAGEMENT

The following five areas should be considered in the clinical approach to the woman with heart disease who is pregnant or considering pregnancy: 1) risk stratification, 2) antepartum management, 3) peripartum management, 4) recurrence of congenital lesion in the neonate, and 5) site of antepartum and peripartum care.

Assess risk before pregnancy

Risk should ideally be assessed before a patient becomes pregnant. The data needed for risk assessment can be acquired from:

- A thorough cardiovascular history and examination
- A 12-lead electrocardiogram
- A transthoracic echocardiogram
- An arterial oxygen saturation measurement by percutaneous oximetry (in patients with cyanosis).

The underlying cardiac lesion should be defined, and ventricular function, pulmonary pressure, severity of obstructive lesions, persistence of shunts, and presence of hypoxemia should be assessed.

When possible, surgery to correct cyanosis should be done before conception to improve maternal and fetal outcomes,[2] and symptomatic obstructive lesions should be corrected.[13] During pregnancy, cardiovascular surgery is more dangerous, involving a 6% risk of maternal mortality and a 30% risk of fetal mortality.[27]

Risk can be stratified according to the nature of the cardiac lesion, maternal factors (functional class or cyanosis), and the use of a risk index.

Low-risk patients include those with small left-to-right shunts, repaired lesions without residual cardiac dysfunction, isolated mitral valve prolapse without significant regurgitation, bicuspid aortic valve without stenosis, mild-moderate pulmonary stenosis, or valvular regurgitation with normal ventricular systolic function. Those at high risk include patients with significant pulmonary hypertension, Marfan syndrome with aortic root or major valvular involvement, and peripartum cardiomyopathy with residual left ventricular systolic dysfunction. The remaining cardiac lesions are considered to be in the intermediate-risk group.

If possible, avoid antiarrhythmic drugs in the first trimester

Maternal functional class is an important predictor of outcome. A 1982 study of 482 pregnancies in women with congenital heart disease found that those in NYHA functional class I (ie, without limitation of physical activity) have lower cardiovascular morbidity and higher live birth rates.[1] Similarly, NYHA classes III (markedly limited activity) and IV (unable to be active without symptoms) predict adverse maternal cardiac events.[5,6]

In a prospective, multicenter study of 599 completed pregnancies,[5] four risk factors were identified that predicted a cardiac event (cardiac death, stroke, pulmonary edema, or arrhythmia) in pregnancy:

- Poor functional status (NYHA class III or IV) or cyanosis
- Left ventricular systolic dysfunction (ejection fraction < 0.40)
- Left heart obstruction (mitral valve area < 2.0 cm^2, aortic valve area < 1.5 cm^2, or

TABLE 2

Determining cardiovascular risk in pregnancy

Low-risk features
- Small left-to-right shunt
- Repaired lesion without residual cardiac dysfunction
- Isolated mitral valve prolapse without significant regurgitation
- Bicuspid aortic valve without stenosis
- Mild-to-moderate pulmonary stenosis
- Valvular regurgitation with normal ventricular systolic function

Intermediate-risk features
- Unrepaired or palliated cyanotic congenital heart disease
- Large left-to-right shunt
- Uncorrected coarctation of the aorta
- Mitral stenosis
- Moderate aortic stenosis
- Prosthetic valve
- Severe pulmonary stenosis
- Moderate-to-severe systemic ventricular dysfunction

High-risk features
- New York Heart Association class III or IV symptoms (markedly limited physical activity or unable to perform any physical activity without symptoms)
- Significant pulmonary hypertension
- Marfan syndrome with aortic root or major valvular involvement
- Eisenmenger syndrome
- Severe aortic stenosis

peak left ventricular outflow tract gradient > 30 mm Hg)

- A cardiac event (arrhythmia, stroke, transient ischemic attack, or pulmonary edema) before pregnancy but since a prior cardiac surgical procedure.

The authors developed a risk index incorporating these factors. In a woman with heart disease and no other risk factors, the likelihood of a cardiac event during pregnancy is about 5%, increasing to 25% with one risk factor and 75% with more than one risk factor.[5]

This index should be used in conjunction with lesion-specific risk estimates, if available, to predict a low (risk index of zero without high-risk lesion), intermediate (risk index of 1 without high-risk lesion), or high risk (risk index > 1 or high-risk lesion). Women at highest risk (eg, those with Eisenmenger syndrome or Marfan syndrome with a dilated aortic root) are less likely to undergo pregnancy and so were underrepresented in contemporary studies (see TABLE 2.)

Neonatal risk. Maternal heart disease also increases the risk of neonatal complications,[1–5,7] especially if the mother also has noncardiac risk factors for neonatal complications (TABLE 3).[7]

Antepartum management

Limiting activity is helpful in severely affected women with ventricular dysfunction, left heart obstruction, or class III or IV symptoms. Hospital admission by mid-second trimester may be advisable for some.

Problems should be identified early and treated aggressively, especially pregnancy-induced hypertension, hyperthyroidism, infection, and anemia.

Beta-blockers rather than digoxin should be used to control the heart rate for patients with functionally significant mitral stenosis. Empiric therapy with beta-blockers is offered to patients with coarctation, Marfan syndrome, and ascending aortopathy for other reasons (eg, a bicuspid aortic valve).

Arrhythmias should be treated if warranted. Premature atrial or ventricular beats are common in normal pregnancy, and in patients with preexisting arrhythmias, pregnancy may exacerbate their frequency and hemodynamic severity. These usually are not treated.

Pharmacologic treatment is usually reserved for patients with severe symptoms or when sustained episodes are poorly tolerated in the presence of structural cardiac abnormalities. Sustained tachyarrhythmias, such as atrial flutter or atrial fibrillation, should be treated promptly.

If possible, all antiarrhythmic drugs should be avoided during the first trimester, and those known to be teratogenic should be avoided throughout pregnancy.

Because of their safety profiles, preferred drugs include digoxin, beta-blockers (possibly excluding atenolol), and adenosine.[28] One can also consider quinidine, sotalol, lidocaine, flecainide, and propafenone, but published data on their use in pregnancy are more limited.[29]

Amiodarone is generally regarded as contraindicated in pregnancy, although case reports describe its successful use. It is not teratogenic, but may impair neonatal thyroid function.[30,31]

Electrical cardioversion is safe. A report of 44 pregnancies in women with implantable cardioverter-defibrillators reported favorable maternal and fetal outcomes.[32]

Anticoagulation therapy. No current strategy is equally safe for both mother and fetus.

Oral therapy with warfarin is effective and logistically easy. However, it can affect embryonic organ development, although some evidence shows that a dosage of 5 mg per day may not be teratogenic.[33] Fetal intracranial bleeding is a risk throughout pregnancy, particularly during vaginal delivery, unless warfarin is stopped before labor.

Heparin in adjusted subcutaneous doses does not cross the placenta and so has no teratogenic effects. However, it may cause maternal thrombocytopenia and osteoporosis and is less effective in preventing thrombosis in patients with prosthetic valves.

In an overview of anticoagulation and pregnancy outcomes in women with prosthetic heart valves, the overall maternal mortality rate was 3%. Oral anticoagulation throughout pregnancy was associated with the lowest rate of valve thrombosis or systemic embolism (4%), while unfractionated heparin between 6 weeks and 12 weeks gestational age was associated with an increased risk of valve thrombosis (9%).[34]

Previous practice guidelines from 1998 recommended using either warfarin plus low-dose aspirin or heparin during the first 35 weeks of pregnancy and then heparin from the 36th gestational week onwards.[13]

The warfarin/aspirin strategy may be most appropriate if therapeutic anticoagulation can be achieved with a warfarin dosage of 5 mg per day.[33]

More recent guidelines recommend either (1) adjusted-dose heparin during the entire pregnancy or (2) adjusted-dose heparin until the 13th week of gestation, warfarin from the 14th week to the middle of the third trimester, and then resumption of adjusted-dose heparin.[35]

Low-molecular-weight heparin in adjusted doses is easier to administer and has been suggested as an alternative to adjusted-dose unfractionated heparin.[35] We currently utilize adjusted-dose low-molecular-weight heparin when heparin will be part of the antithrombotic regimen during pregnancy.

TABLE 3

Risk factors for neonatal complications

Maternal risk factors
- Cardiac
  - Poor functional class or cyanosis
  - Left heart obstruction
- Other
  - Age < 20 or > 35
  - Multiple gestation
  - Smoking
  - Anticoagulant therapy
  - History of premature delivery
  - Membrane rupture
  - Incompetent cervix
  - Cesarean section
  - Intrauterine growth retardation
  - Antepartum bleeding after 12 weeks' gestation
  - Febrile illness
  - Uterine or placental abnormalities

Neonatal complications
- Premature birth
- Low birth weight for gestational age
- Respiratory distress syndrome
- Intraventricular hemorrhage
- Fetal or neonatal death

In women with prosthetic valves at high risk of thromboembolic complications, adding low-dose aspirin should also be considered.[35] Although high-dose aspirin may promote premature duct closure, low-dose aspirin is safe for the fetus, even at term.[36]

Peripartum management

Cesarean section is indicated only for the following conditions:

- Aortic dissection
- Marfan syndrome with dilated aortic root
- Taking warfarin within 2 weeks of labor.

Preterm induction is uncommon. However, once fetal lung maturity is assured, a planned induction and delivery may be warranted for high-risk patients to ensure that appropriate staff and equipment are available.

Hemodynamic monitoring. No consensus exists on using invasive hemodynamic monitoring during labor and delivery. We commonly use intra-arterial monitoring and may also

use central venous pressure monitoring if interpreting a sudden drop in systemic blood pressure is of concern. A pulmonary artery catheter is rarely indicated.

Heparin anticoagulation should be discontinued at least 12 hours before induction, or reversed with protamine if spontaneous labor develops. It can usually be resumed 6 to 12 hours postpartum.

Antibiotic prophylaxis for endocarditis is not routine. American Heart Association guidelines do not recommend routine endocarditis prophylaxis for cesarean section delivery or for uncomplicated vaginal delivery without infection.[37]

However, some centers do administer endocarditis prophylaxis for vaginal delivery in women with structural heart disease, as an uncomplicated delivery cannot always be anticipated.

Pain control should be offered with epidural anesthesia and adequate volume preloading. Epidural fentanyl does not lower peripheral vascular resistance, making it particularly advantageous for cyanotic patients with shunt lesions or significant aortic stenosis. Air-and-particulate filters should be placed in all intravenous lines for patients with a shunt.

Positioning the patient on her left side lessens the hemodynamic fluctuations associated with contractions when the patient is supine.

Forceps or vacuum extraction should be considered at the end of the second stage of labor to shorten and ease delivery.

Postpartum monitoring. Because hemodynamics do not return to baseline for many days after delivery, patients at intermediate or high risk may require monitoring for at least 72 hours postpartum.

Patients with Eisenmenger syndrome are at risk of death for up to 7 days postpartum, and so require close observation longer.

Lying on the left side decreases hemodynamic fluctuations during contractions

RISK OF CONGENITAL HEART DISEASE IN OFFSPRING

The risk of congenital heart disease is 0.4% to 0.6% in the general population; this risk increases about 10-fold if a first-degree relative is affected.[38]

Left-sided heart obstructive lesions have a higher rate of transmission to offspring. Certain conditions, such as Marfan syndrome and the 22q11 deletion syndromes, are autosomal-dominant, conferring a 50% risk of transmission.[38]

Patients of reproductive age with congenital heart disease should be offered genetic assessment and counseling so that they are fully informed of the transmission risk and of the options for prenatal diagnosis. Strategies to decrease the incidence of congenital defects, including taking multivitamins preconception, should also be discussed.[39]

HIGH-RISK PREGNANCY UNITS

Women at intermediate or high risk should be managed in a high-risk pregnancy unit by a multidisciplinary team staffed by obstetricians, cardiologists, anesthesiologists, and pediatricians. Candidates for this care include:

- Those with at least one risk factor according to the risk index (TABLE 2)
- Those with lesion-specific risks in the high-risk category
- Those at risk for neonatal complications (TABLE 3).[4,5]

The multidisciplinary team should meet with patients early in pregnancy and write a management plan for most contingencies.

Women with heart disease deemed to be at low risk can be managed in a community hospital. If the mother's status or her risk profile is in doubt, a consultation at a regional referral center should be arranged. ■

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Treatment options for menopausal hot flashes

ABSTRACT

Although alternatives exist, hormone therapy remains the most effective treatment for menopausal symptoms such as hot flashes, and it is the only treatment approved by the US Food and Drug Administration (FDA) for this indication. The FDA recommends using the lowest effective dose of hormones. New low-dose preparations and new dosage forms of hormone therapy are available.

KEY POINTS

Lifestyle modifications should be the first-line approach for women with menopausal symptoms.

Nonapproved alternative agents include venlafaxine, fluoxetine, paroxetine, gabapentin, soy products, and herbs such as black cohosh.

New estrogen products include lower-dose Prempro (conjugated equine estrogen 0.3 mg and medroxyprogesterone 1.5 mg), transdermal patches, estrogen lotion, and an intravaginal ring.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

WOMEN are looking for alternatives to estrogen to treat menopausal symptoms, after hearing about possible risks of hormone therapy.

Alternatives exist, but none is as effective as hormone therapy, and none is approved by the US Food and Drug Administration (FDA) for this purpose. Moreover, the risks associated with hormone therapy may not be as great as many people imagine, especially when used as currently recommended, ie, in the lowest effective dose for the shortest possible time consistent with the indication for therapy.

This paper discusses the current recommendations for hormone therapy, the alternative therapies, and the newer hormonal products—information we hope will be helpful when weighing the risks and benefits of therapy for menopausal symptoms.

WHAT CAUSES HOT FLASHES?

Most perimenopausal women experience some vasomotor symptoms such as classic hot flashes (a feeling of intense heat) and hot flushes, felt and seen as redness of the upper neck, face, and torso. These symptoms can range in severity from a minor irritation to a major disruption in the quality of life.[1]

The etiology of hot flashes is not completely understood but involves some destabilization of the thermoregulatory zone in the hypothalamus related to estrogen withdrawal.

Not all hot flashes are due to menopause; the differential diagnosis includes:

- Thyrotoxicosis
- Carcinoid
- Diabetes
- Hyperhidrosis
- Panic disorder
- Obesity (in which the extra adipose tissue

acts as insulation, causing a chronic feeling of warmth)
- Pheochromocytoma.

Some medications can also cause or exacerbate hot flashes, eg, the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene and the gonadotropin analogues leuprolide, goserelin, and nafarelin. Furthermore, some men who undergo androgen ablation for prostate cancer experience hot flashes.

HOW RISKY IS HORMONE THERAPY?

Concerns about hormone therapy come from the Women's Health Initiative,[2–4] a large prospective randomized study designed to determine if hormone therapy would reduce the incidence of cardiovascular disease and other adverse outcomes.

Of note: this study was not designed to evaluate the efficacy of hormone therapy in treating menopausal symptoms. In fact, all perimenopausal women were excluded, as were young castrated women and women with premature ovarian insufficiency.[3] Thus, the study population was not similar to most patients seeking help for menopausal symptoms.

Hormone therapy did not decrease the incidence of cardiovascular disease. In fact, at 5.2 years of follow-up, compared with women receiving placebo, the relative risk of nonfatal myocardial infarction or death due to coronary heart disease among participants receiving conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day was 1.24, although the difference did not quite reach statistical significance (nominal 95% confidence interval 1.00–1.54). In view of these findings, the estrogen-progestin arm of the study was stopped early.

Expert opinion[5] is now that hormone therapy should not be prescribed to prevent cardiovascular disease. The known risks of hormonal therapy remain:
- A twofold to threefold increased risk of venous thromboembolism
- A small but definite increased risk of breast cancer with estrogen-progestin use[6,7]
- An increased risk of stroke and gall bladder disease.

These risks must be balanced against the benefits of hormonal therapy: excellent menopausal symptom control, control of genitourinary atrophy, and bone preservation.

Absolute contraindications for hormone therapy include undiagnosed vaginal bleeding, active thromboembolic disease, and active breast cancer.

Recently the FDA announced its cautious support of hormone therapy for menopausal symptoms. A consumer-supported program, MenoPAUSE, has been launched nationwide to inform women about menopause, its symptoms, how to communicate with health care providers, and the treatment options.[8]

Weaning off hormone therapy

Women who have tried to wean off hormone therapy and are unable to do so can continue on it but need periodic clinical reevaluation; the North American Menopause Society consensus conference recommends at least yearly reevaluation of the indications, risks, benefits, and alternatives.

There are no evidence-based strategies for weaning off hormone therapy, but there are several low-dose formulations to choose from for vasomotor symptom control (see below).

ALTERNATIVE TREATMENTS

While hormone therapy remains the gold standard for menopause-related vasomotor symptoms, a number of women cannot or will not take it in spite of significant menopausal symptoms.

Women on hormone therapy need reevaluation at least yearly

Nonpharmacologic treatments

First-line treatments for hot flashes include nonpharmacologic lifestyle adjustments, such as:
- Avoiding triggers such as warm environments, alcohol, and caffeine
- Wearing layered cotton clothing[9]
- Practicing deep, slow diaphragmatic breathing and relaxation therapy.

Exercise, although important for a number of health benefits, has not specifically been shown to reduce vasomotor symptoms.[9] Alternative and integrative strategies such as acupuncture, nutraceuticals, and herbal products have not been studied enough to assess their risks and benefits.[10]

Antidepressants

Venlafaxine is our first-line nonhormonal alternative in symptomatic menopausal

TABLE 1

Vasomotor symptom reduction with various therapies

THERAPY	% REDUCTION
Hormone therapy	≥ 90%
Venlafaxine	60%–75%
Gabapentin	50%–60%
Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline)	50%
Vitamin E/soy	25%
Placebo	20%–30%

women. Norepinephrine is thought to be integral for controlling the thermoregulatory set point[11]; therefore, serotonin-norepinephrine reuptake inhibitors such as venlafaxine are prime candidate drugs for nonhormonal treatment.

In a study in breast cancer survivors, venlafaxine reduced vasomotor symptoms by 60% to 75%.[12,13] The most effective doses, as reflected in diminished hot flash scores and improved quality-of-life indicators, were 37.5 to 75 mg/day.

Side effects include dry mouth, nausea, anorexia, and constipation at higher doses.[12]

Studies of antidepressants for hot flashes were not as rigorous as studies of hormone therapy

Selective serotonin reuptake inhibitors (SSRIs). Fluoxetine and paroxetine have been studied in women with and without breast cancer.[14–16]

In a recent study that received wide attention,[15] controlled-release paroxetine 25 mg/day was compared with placebo. At 6 weeks, the paroxetine group reported a 64.6% reduction in hot flashes vs 37.8% with placebo.

Dry mouth was the predominant side effect noted in these studies. Other adverse effects common to SSRIs include nausea, diarrhea, headache, insomnia, jitteriness, fatigue, and sexual dysfunction.[16]

Of note, the studies were not as rigorous (requiring at least seven to eight hot flashes per day) as the studies of estrogens seeking FDA approval for vasomotor symptom control.[9] Furthermore, studies of hot flash reduction generally show a significant placebo effect, so all studies need to have a placebo group.

A recent study in women with the CYP2D6 genotype who were receiving tamoxifen for breast cancer demonstrated that paroxetine reduces the active metabolite of tamoxifen.[17] Thus, drug interactions should be considered in women on tamoxifen and SSRIs. Pending further study, we do not recommend the concurrent use of paroxetine in women requiring tamoxifen therapy.

Other agents

Gabapentin has undergone investigation for treating hot flashes, after patients taking it for other indications incidentally noted improvement of hot flashes.

Although it is an analogue of gamma-aminobutyric acid (GABA) and is used to treat neurologic disorders such as seizures and neuropathic pain, gabapentin does not affect GABA receptors directly, and its mechanism of action remains unclear. Proposed mechanisms include modification of adrenergic and serotonergic pathways in the pituitary-hypothalamic areas.[11]

A randomized trial showed gabapentin in doses of 200 to 1,600 mg/day to reduce hot flashes by 50% to 60%.[18] Side effects included dizziness and fatigue, which tended to dissipate over time, and, less often, peripheral edema.

Clonidine is a centrally acting alpha adrenergic agonist. Various doses and delivery routes have been tested, and several small randomized controlled trials showed statistically significant reductions in hot flashes; in one study, at 8 weeks the frequency of hot flashes had declined by 38% with clonidine vs 24% with placebo.

Clonidine's side effects of dry mouth, drowsiness, postural hypotension, and constipation, together with its modest effect on vasomotor symptoms, have limited its use.[19]

Cetirizine. A recent abstract described a double-blind, randomized, placebo-controlled trial in 50 symptomatic postmenopausal women not already on hormonal therapy. At 4 weeks, those given cetirizine 10 mg/day had a reduction in hot flash scores of 39.7%, vs 8.8% with placebo.[20]

Vitamins. Vitamin C and vitamin B complex have been advocated but not shown in any rigorous studies to reduce hot flashes. Vitamin E 800 IU is frequently recommended; however, it is not much more likely than

placebo to reduce vasomotor symptoms.[5]

Megestrol acetate, a synthetic progestin, reduced hot flashes in a study in breast cancer survivors.[21] Its association with weight gain limits its use in many menopausal women.

Other options available in Europe but not in the United States include tibolone (an agent associated with an apparent increased risk of breast cancer)[22] and veralipride.

Soy products

Phytoestrogens and isoflavones are naturally occurring plant-derived estrogens that are thought to have mixed estrogen agonism and antagonism to certain estrogen receptors.

Studies of the effects of soy on hot flashes have yielded conflicting results.[5,23]

Soy is available in a variety of forms. Doses of isoflavones in multiple studies ranged from 50 to 150 mg/day.[24] Red clover (Promensil) contains isoflavones similar to soy protein isoflavones. This product has not been clearly demonstrated to be effective in reducing menopausal signs or in the prevention of osteoporosis and is therefore not recommended.[25]

The long-term safety of isoflavone or soy supplement use has not been studied in women with breast cancer. In theory, these products could pose a risk in patients with contraindications to estrogens due to their potential estrogenic agonist activity in some tissues.

However, all women can be encouraged to adopt a healthy diet, which may include 25 grams of soy protein, primarily for possible cholesterol reduction, as per American Heart Association recommendations.

Herbs

Herbs, particularly black cohosh (*Cimicifuga racemosa*), have been used for centuries to reduce hot flashes. Their mechanism of action remains unknown. The German Commission E (similar to the US FDA) approves the use of black cohosh for only up to 6 months (based on study length) for hot flash reduction.[5]

Women should be warned that some herbal products may contain other agents, including kava kava, which recently was linked to hepatotoxicity.[26]

Dong quai, a Chinese herb, was tested in a large randomized trial and was found not to reduce hot flashes; furthermore, it can increase the international normalized ratio in patients on warfarin.[27]

Wild yam contains diosgenin, used in the manufacture of steroids and progesterone. It is not, however, converted to active progesterone in the human body and has not been studied adequately to prove its efficacy in treating hot flashes.[10]

Bellergal not recommended

Bellergal-S remains available by prescription and has been used to treat hot flashes. It contains phenobarbital and belladonna and works primarily by sedation. We and others[11] discourage Bellergal-S use in view of its adverse effects, limited efficacy, and addictive potential.

NEWER ESTROGEN OPTIONS

Low-dose estrogen therapy

Because the risks and benefits of alternative agents are not fully known, and they may be much less effective than hormone therapy, attention has turned to using lower doses of hormone therapy in the hopes of maintaining the same efficacy while reducing the side effects and risks.

Of note, the results of the estrogen-only arm of the Women's Health Initiative were recently released and showed no increased risk of breast cancer in women using conjugated equine estrogen 0.625 mg. The only reported increased risk in older women with hysterectomy taking estrogen was an increased risk of stroke.[28]

Some herbal products contain other agents

Low-dose Prempro (conjugated equine estrogen 0.45 mg plus medroxyprogesterone 1.5 mg) was released in the summer of 2003, after the Women's HOPE (Health, Osteoporosis, Progestin, Estrogen) trial showed it was as effective as usual-dose Prempro in hot flash control, with improved bleeding patterns and less mastalgia compared with prior standard doses of Prempro 0.625/2.5 mg.[29] An even lower dose of Prempro (0.3/1.5 mg) is now available. Lower doses of estrogen are thought to confer similar benefit with less risk.

Ultra-low doses of estrogen (estradiol 0.025 mg/day by mouth or via a transdermal patch, changed weekly) have been shown to preserve bone status.[30]

Newer estrogen delivery systems

Femring is an intravaginal ring that is changed every 3 months and provides both

local and systemic estrogen. It is approved to treat vasomotor symptoms in women who have had a hysterectomy. (In contrast, the Estring is only for early local genitourinary effects.)

Estrasorb estrogen lotion is available for topical application on the thighs and arms daily and has systemic estrogenic effects. It may be an effective option for symptom control for women who do not want to take an oral estrogen, who do not like the adhesive of transdermal estrogen systems, and who do not want to use a vaginal ring. However, the FDA has not approved it for preventing or managing osteoporosis.

Of importance: any woman with a uterus who is using systemic estrogen—transdermally, orally, or topically with systemic effects—needs progestin opposition. ■

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Shared medical appointments: Increasing patient access without increasing physician hours

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ABSTRACT

Shared medical visits are a new concept in patient care. Doctors perform a series of one-on-one patient encounters in a group setting during a 90-minute visit and manage and advise each patient in front of the others. Patients benefit from improved access to their physician and significantly increased education, while providers can boost their access and productivity without increasing hours. Such group visits are voluntary and for established patients only.

YOU'RE IN A BUSY PRACTICE—so busy that the next available appointment for a physical examination is 6 months away. Your established patients complain about the difficulty in getting to see you. Despite the busy practice, the budget is stretched thin, and you and your colleagues often put in extra hours. What can be done to help patients gain access and keep physicians from burning out?

An increasing number of medical practices are looking to a new concept: shared medical appointments. We will describe The Cleveland Clinic's efforts in this area, how appointments are conducted, and who the best patient and physician candidates are for them to work well. We will also review the literature and discuss the impacts on office backlog, productivity, finances, patient care, and access.

Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

ACCESS IS THE PROBLEM

When resources are readily available, the best way for a full and busy practice to improve patient access is to add another physician. But this necessitates finding the right physician, extra support staff, more office space, and associated expenses. Solutions such as advanced access scheduling (also known as "open access scheduling": same-day access for every patient) can help doctors see their patients on a more timely basis but do not improve productivity or efficiency. Advanced access assumes a fixed "panel size" of patients, an approach to practice that is not always practical.

Practice costs are rising while reimbursement is falling

SHARED APPOINTMENTS ARE INCREASINGLY OFFERED NATIONWIDE

Shared medical visits, in which multiple patients meet simultaneously with their provider, may be a practical way to improve patient access and physician productivity. It may also offer enhanced patient satisfaction and better health outcomes. The concept was originally developed by health psychologist Dr. Edward Noffsinger at Kaiser of Northern California and was designed to improve both access and the quality of care through enhanced patient education and support. At first, the approach was designed for "drop-in" care, but most encounters are now scheduled.

This approach is being used at many centers. Stanford Health Partners at Stanford University reports a shared-appointment program that they promote as a model for chronic disease care.[1] They assert that with the increasing number of people living with chronic disease, the patient-provider model as it now exists

is unrealistic in today's health care environment.

Other organizations using or exploring the role of shared appointments include Palo Alto Medical Foundation, Dartmouth Hitchcock Medical Center, University of Virginia, Christus Medical Group, University of Michigan, Massachusetts General Hospital, and the US Department of Defense.

The Cleveland Clinic began experimenting with group visits on October 15, 2002. As of February 29, 2004, 19 physicians have seen a total of 3,123 patients in 385 shared medical appointments: 501 patients in 85 shared medical appointments for physical examinations, and 2,622 patients in 300 shared appointments for follow-ups.

MODELS OF GROUP CARE

Some practitioners avoid the term "group visits," which may connote impersonal care and a lecture-style format. Instead these are truly shared medical visits, in which each patient has an individual appointment in which other patients are also present in the room as observers. These visits must be done correctly so that they provide the appropriate standard of medical care; otherwise they become simply a class. The enhanced learning as well as the increased efficiency occur because each patient benefits from hearing the doctor's advice and management of the other patients. More time can be spent by the physician educating about a specific topic (eg, hyperlipidemia) because it may be an issue for several participants.

Shared visits may improve access, productivity, satisfaction, and outcomes

There are two models for shared medical appointments. Both last for 90 minutes and are led by a physician, a behaviorist (eg, a social worker, nurse practitioner, nurse, or health psychologist), and occasionally a person dedicated only to documentation. Both types of groups are voluntary and for established patients only.

Shared appointments for follow-up care

Shared medical appointments are designed for follow-up visits for a variety of medical conditions. Any physical examination needed takes place in the group setting, within the limits of patient comfort and privacy. We are presently using the model for such problems as cardiac risk factor follow-up, hypertension, diabetes, weight loss and lifestyle management, movement disorders, asthma, fibromyalgia and chronic pain management, hematology (leukemia, lymphoma, and chronic anemia), women's health care, and bariatric surgery patients.

Ten to 16 patients form a group with the physician, behaviorist, and possibly a documentation specialist. Their responsibilities differ.

The physician:

- Evaluates, examines, and treats patients just as in an individual appointment
- Documents medical information if no documentation specialist is present.

The behaviorist:

- Manages confidentiality, reminding patients of rules and collecting confidentiality forms
- Runs the discussion when the physician is documenting or performing private examinations
- Makes sure patients leave with referrals, prescriptions, and appointments for follow-up visits
- Keeps the group on schedule so all patients have their needs met
- Makes sure no one dominates the conversation.

A sample session

Here's how a shared follow-up appointment might run: Patients check in for their appointment and are immediately escorted to the group room. As each patient arrives, vital signs are taken by a nurse in a nearby examination room (this can continue after the discussion begins, as necessary). Refreshments may be served to promote a relaxed atmosphere, and patients wear name tags with their first names. Patients sign confidentiality waiver forms, write down medical concerns that they want to cover, and turn in their papers to the behaviorist.

The patients, doctor, and behaviorist sit in a circle or semicircle as the group visit begins. There are a few introductory remarks of welcome. Then the provider concentrates on the first patient:

Doctor: "Mrs. Maxwell, let's talk about your hypertension. I notice you are having sleep problems, and wonder if sleep apnea may have something to do with your poorly controlled hypertension."

After a brief discussion with Mrs. Maxwell about the nature of her sleep problems, the physician states: "Let's order a sleep study while you continue on your medications. Do you have any other questions?" The doctor documents information and writes referrals and prescriptions.

Behaviorist: "Do any of the rest of you have sleep problems? Let's talk about how to deal

with them."

The behaviorist discusses typical contributors to poor sleep such as caffeine and lack of exercise.

When the doctor finishes documenting the first patient, the discussion winds down and the doctor focuses on the needs of the second patient. By the end of the 90-minute session, each patient's problems have been managed, a variety of health topics have been discussed, and all documentation is complete.

If shared medical appointment groups are large enough, they can afford to add an extra staff member devoted to documentation, freeing up the provider to participate more in the discussion. Whichever method of documentation is used, it is important to fully document patients within the 90-minute session. If the physician must spend another hour charting, the model becomes much less efficient.

Shared appointments for physical exams

Shared medical appointments for physical examinations are similar to those for follow-up, but the physical examinations occur privately. Discussion and medical management still take place in the group. These appointments are designed for complete yearly physical examinations, although they may also be used for other health conditions that require a private physical examination.

The groups are usually about half the size of those for follow-up appointments: women are typically seen in groups of 6, and men in groups of 8 or 9. Same-gender patients of a similar age are seen together so that common issues can be discussed. For example, a group with men over 50 years might include a discussion of cardiac risk factors, prostate-specific antigen levels, and colonoscopy. Women either under or over 45 years are typically seen together, but in large practices, groups may be broken up further for women less than 45 years, 45 to 60 years, and over 60 years old.

Running a shared appointment for physical exams

Half the group is brought into the group room, while the others are taken to individual examination rooms. The physician examines each patient individually without detailed medical discussion.

The documentation specialist may follow the physician to facilitate an efficient physical examination, documenting all pertinent information that the physician says aloud (eg, tympanic membrane normal, throat clear). Many physicians are able to document during the physical exam, but occasionally employ documentation support for the evaluation and management discussion.

While the physical examinations are taking place, the behaviorist elicits the health concerns of the remaining patients that will need discussion when the physician returns. Patients who have been receiving physical examinations move into the group room as their examinations are finished, and the other patients move out to have their examinations. The behaviorist, frequently an advanced-practice nurse, also reviews lab results, determines need for prescription refills, and initiates group discussion of common health concerns.

After another 45 minutes, the group comes together in the discussion room along with the physician. Then the physician spends time with each patient in turn, managing individual problems in front of the others. There is no more general discussion from the behaviorist between managing patients. As groups mature, behaviorists frequently take over documentation, making staffing more efficient.

When the model was first developed, the group discussions were run before the private physical examinations. This led to problems: some patients would "save up" their real concerns until they were alone with the doctor, diminishing the effectiveness of the group process.

If you repeat the same information many times a day, group visits may work for you

THE NUTS AND BOLTS OF GROUP VISITS

For group appointments to work well, the model should be adhered to as closely as possible. You need:

- A designated room to accommodate a minimum of 15 people
- Designated staff available for the 90-minute time slot
- A regular location, day, and time each week for groups to meet.

Bill for level of care

Shared medical visits are billed as an individual appointment and are coded according to the level of care. It's important not to bill for time spent: even though the patients are in the group for 90 minutes, each one has the

individual attention of the doctor for perhaps only 7 or 8 minutes. In addition, there is no billing for the time of the behaviorist. To bill for the service, the appropriate level of care must be provided and documented.

Don't skimp on personnel

Both models require extra personnel, but enough patients are seen to cover this extra cost. For example, normally an adult physical is allotted 30 to 45 minutes; with the shared medical appointment, 6 to 9 people are seen during 90 minutes.

Insist on confidentiality

All patients and support staff sign a shared medical visit waiver form before the group begins. Patients consent to discuss their personal medical information in front of the group and agree not to disclose personal information of the others. This message is contained in the letter of invitation from the physician and in the scripts for schedulers, and is reinforced by behaviorists.

GOOD PHYSICIAN CANDIDATES

Heavily backlogged schedule

The group models work well for physicians with patients who must wait weeks or longer to be seen. The physician should feel "hopelessly backlogged." A full but not overwhelmed practice will quickly reduce any backlog, often to the point of leaving open slots in the schedule.

For group visits, you need staff and a regular location, day, and time

Repetitive advice

Physicians who find themselves repeating the same information many times a day to different patients are also good candidates. In group visits, the key information can be more effectively delivered because more time is available and other important issues can then be covered.

PATIENT BENEFITS

Chronic disease management may be enhanced

This is a new approach and there are few published studies about its effectiveness. The early research has had encouraging results, showing no harm and sometimes modest gains for patients in group care.

One 24-month trial involved 707 patients with type 2 diabetes, on oral medications or insulin, who were randomly assigned to either shared visits or usual care.[2] The patients who participated in shared visits had fewer emergency room visits, fewer disability days, and better general health status. There was no difference between groups in glucose control as measured by hemoglobin A_1c.

A similar randomized controlled study[3] of 112 patients with type 2 diabetes not treated by insulin compared shared visits to usual care for 4 years. The mean hemoglobin A_1c level was 7.4% at baseline: it decreased to 7.0% in the shared-visit cohort and increased to 8.6% with usual care, a statistically significant difference. Weight decreased in the shared-visit patients by an average of 2.6 kg compared to only a 0.9-kg decrease in the control group. The patients who had shared visits were able to decrease their dosages of hypoglycemic medications and had more slowly progressing retinopathy than the usual-care patients.

Prompt access

Patients can see their physician much sooner by joining a group than by waiting for an individual appointment. One of our physicians does 14 physicals a week, and before starting shared visits, his third available appointment for a physical exam was 5 months out. Within 3 months, he reduced his third available private appointment from 150 days to 66 days out, and patients could get an upcoming group appointment within a week.

A second physician went from a third-appointment availability of 105 days to 30 days out, and patients could be seen in a group within 1-1/2 weeks. The physician began group visits in October with an 8-week backlog, and his backlog was gone by Christmas.

Greater patient satisfaction

We have been pleasantly surprised by our patients' satisfaction with group visits. All patients are given the option of an individual appointment or group appointment for their next visit. For shared follow-up medical appointments, 85% of patients seen in groups opted for another shared visit for their next visit, and 79% of patients in shared medical appointments marked "excellent" for overall visit satisfaction on a survey.

Even though patients may only get 7 or 8 minutes of individual attention from the physician, most patients gain greatly through the

extended time spent listening to similar issues discussed by and with other patients. Patients in groups also often bond to one another: one group of women patients decided to coordinate their subsequent annual physicals so that they could stay together.

Patients typically report feeling more relaxed than during a regular appointment. It's surprising how willing they are to discuss personal health problems in front of a group.

More education

Patients learn from the management of others in the room. Much more information can be covered in 90 minutes than during a short visit. If a patient forgets to ask about a specific concern, chances are someone else will bring it up. Patients frequently support and advise one another based on personal experience. It is very powerful to be held accountable by a peer group for efforts to improve lifestyle and adherence to recommended treatment programs.

PHYSICIAN BENEFITS

Improved productivity

Productivity is difficult to assess: it should not be measured only in more patient visits per month because some physicians have used their extra time for administrative, teaching, research, or personal responsibilities. Nevertheless, productivity has increased by as much as 31%, with corresponding financial results.

Increased satisfaction

Physicians who run groups have typically reported that they are a great "break" in their day: it is a very different, effective, and enjoyable form of patient care.

PITFALLS

Low census

The key to continued effectiveness of the program is in maintaining a full census for the sessions. Shared medical appointments with a low census are less efficient and can be more costly than routine care. The key to having successfully full shared medical appointments lies in effective promotion by the physician and the physician's staff. These visits should be viewed as enhanced care, not less care.

Running a class

Physicians need to remember that these are regular medical encounters with individual patients done in a group setting. Avoid the temptation to turn these into a "class."

Patient selection

Care must be taken to ensure that the right patients are seen in the group. There are always a few patients for whom this setting may not be appropriate, especially those who cannot or will not maintain confidentiality, the hearing impaired, patients with cognitive impairment, and those who require an interpreter.

Low levels of support

Having a behaviorist and dedicated administrative help in ensuring adequate space and scheduling support will keep the shared medical visits within the 90-minute time frame. Having less help will lead to less efficiency and inadequate documentation. The support of the practice's administrative leadership is essential.

SUMMARY

Shared medical appointments are an effective way to ensure patients' access to the busiest physicians and enhance overall productivity. Both patient and physician satisfaction have been high with these encounters, and we continue to expand their use at the Cleveland Clinic. The key to success is to follow the requirements of the process carefully and ensure that each patient receives the most appropriate care for his or her individual medical issues.

85% of patients seen in groups opted for another shared visit

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Premenstrual dysphoric disorder: A review for the treating practitioner

ABSTRACT

Premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome (PMS), is characterized by physical and behavioral symptoms that cause marked social impairment during the last half of the menstrual cycle. Symptoms are believed to result from the interaction of central neurotransmitters and normal menstrual hormonal changes. Treatment usually begins with lifestyle changes, over-the-counter medications, and, if needed, selective serotonin reuptake inhibitors. Physicians should be aware of the risks of many of the alternative therapies commonly touted in the popular press.

KEY POINTS

PMDD is diagnosed by prospective recording of symptoms for two menstrual cycles and by laboratory testing to rule out thyroid disorders, anemia, and electrolyte disturbances.

The symptoms of PMDD are likely caused by low levels of serotonin, gamma-aminobutyric acid, and beta-endorphins.

Selective serotonin reuptake inhibitors are the first-line medications. Anxiolytics, ovulation suppressants, and diuretics are recommended for specific symptoms.

Patients should be warned of potential risks of herbal products and of large doses of vitamins and food supplements.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

WHILE MOST WOMEN of reproductive age suffer from some degree of premenstrual syndrome (PMS), usually involving mood changes and somatic symptoms, only a small percentage have the more severe form, known as premenstrual dysphoric disorder (PMDD), which causes marked impairment.

This review will help the clinician recognize, understand, and treat this disorder. We also provide an overview of alternative therapies that patients may be using on their own to treat the condition.

CONSTELLATION OF SYMPTOMS DURING LUTEAL PHASE

PMDD was first defined in 1987 in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) and revised in the following edition in 1994.[1] Its constellation of somatic and behavioral symptoms occur only in the 10 to 14 days before menstrual bleeding, corresponding to the luteal phase of the cycle.

Symptoms are similar to those of PMS, a condition that affects as many as 75% of women of menstruating age. Only 3% to 8% of women[2] have symptoms severe enough to be diagnosed with PMDD (TABLE 1).

RISK FACTORS

Some women are more prone to PMDD. Risk factors include:

- Age—PMDD is most likely to occur in a woman's late 20s to mid 30s[3]
- Psychiatric disorders—As many as 70% of women with PMDD have a history of mood disorders (including major depression), anxiety disorders, personality disorders, or substance abuse[4–6]
- Genetics—Twin studies suggest a genetic

component is present[4,7,8]

- Low parity—Women with fewer pregnancies have a higher incidence of PMDD. Additional exposure to changing levels of estrogen and progesterone from more menstrual cycles may predispose women to the disorder[9,10]
- Psychosocial factors—Studies suggest that the incidence of PMDD increases after major life events and stressors[4,9,11]
- Menstrual cycle length—Data conflict on the association of menstrual cycle length and symptom severity.[4,12,13]

WHAT CAUSES PMDD?

A number of theories have been proposed to explain PMDD, but the exact cause is unknown.

An abnormal response to normal hormone cycles

The current theory is that premenstrual symptoms are caused by normal cyclic changes in ovarian steroids.[4] In 1984, Muse et al[14] studied the effects of eliminating the hormonal changes of menstrual cycles in eight patients over a 6-month period using the gonadotropin-releasing hormone (GnRH) agonist leuprolide (Lupron). Symptoms resolved with GnRH treatment, then recurred when the medication was withdrawn.

Cyclic changes of ovarian steroids may not be the only explanation for symptoms. Estrogen and progesterone levels of women with premenstrual symptoms are about the same as those of control subjects, suggesting that behavioral disturbances in affected women may be due to an abnormal response of central neurotransmitters to normal ovarian function.[4,15]

Low levels of neurotransmitters

Serotonin is the most widely studied neurotransmitter in women with PMDD: central serotonin levels tend to be low,[16,17] and symptoms are aggravated by depletion of the serotonin precursor tryptophan.[18] In addition, many patients with PMDD improve with treatment using selective serotonin reuptake inhibitors (SSRIs).[19–21]

Gamma-aminobutyric acid (GABA) and beta-endorphin probably also play a role.

TABLE 1

Differences between premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)

	PMS	PMDD
Prevalence	75%	3%–8%
Symptoms required	1	5 of 11 (see TABLE 2)
Diagnosis	ICD-10*	DSM-IV†
Social impairment	Not required	Required
Prospective charting	Not required	Required

**International Statistical Classification of Diseases and Related Health Problems*, 10th revision.
†*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

Premenstrual women have reduced GABA receptor sensitivity and abnormal levels of allopregnanolone, a progesterone metabolite.[22] Differences in beta-endorphin levels between the periovulatory and premenstrual phases have been suggested but remain unconfirmed.[23–25]

Vitamin and mineral deficiencies unproven

Attempts to link vitamin and mineral deficiencies with PMDD have been inconclusive. No differences in levels of vitamin A,[26] vitamin E,[27] or vitamin B_6[28,29] have been observed. Initial studies suggested that women with PMDD may have lower levels of magnesium,[30,31] but subsequent studies have not confirmed this finding.[32,33] Calcium levels may also be low in the premenstrual phase.[34,35]

Central serotonin levels tend to be low in women with PMDD

A DIAGNOSIS OF EXCLUSION

PMDD is diagnosed with a thorough history and physical examination and by excluding other causes. No objective diagnostic tests exist.

Record symptoms daily

Symptoms should be recorded as they occur daily for at least two consecutive symptomatic menstrual cycles. Common tools include the Calendar of Premenstrual Experiences (COPE),[36] the Moos Menstrual Distress Questionnaire (MDQ),[37] the Premenstrual Assessment Form (PAF),[38] and the Prospective Record of the Impact and Severity

TABLE 2

Criteria for diagnosis of premenstrual dysphoric disorder

Symptoms occur 1 week before menses and resolve in the first few days after menses begins (over most menstrual cycles during the past year)

Five or more of the following (one must be among the first four):
- Markedly depressed mood with feelings of hopelessness
- Marked anxiety or tension
- Marked affective lability
- Irritability and anger
- Decreased interest in usual activities and social withdrawal
- Lack of energy
- Appetite change (overeating or undereating)
- Change in sleep pattern (hypersomnia or insomnia)
- Feeling out of control or overwhelmed
- Difficulty with concentration
- Somatic symptoms such as abdominal bloating, breast tenderness, headaches, or joint pain

Symptoms are severe enough to interfere with work, school, usual activities, or interpersonal relationships

Symptoms may be superimposed upon an underlying psychiatric disorder but may not be an exacerbation of another condition

These criteria must be confirmed by prospective daily charting for a minimum of two consecutive symptomatic menstrual cycles

of Menstruation (PRISM).[39] These questionnaires are similar, and all have proven useful in gathering objective and quantified data about PMDD symptoms.

Symptoms of PMDD typically include mood disturbances and somatic symptoms, and are severe enough to markedly impair day-to-day functioning (TABLE 2). Symptoms occur during the last half of the menstrual cycle (the luteal phase) and are absent in the follicular phase, which begins from the first day of menstruation and lasts about 14 days until ovulation.

Steiner et al[40,41] proposed that there must be at least a 30% worsening of symptoms between the follicular and luteal phases within each cycle, regardless of the assessment tool used.

Exclude other problems

Other diagnoses need to be excluded (TABLE 3). Blood should be tested if clinically indicated:
- A chemistry profile to assess electrolyte disturbances
- A complete blood cell count to rule out anemia
- A thyroid-stimulating hormone (TSH) level to rule out thyroid disorders.

Clinicians should be careful to differentiate PMDD from premenstrual exacerbations of chronic psychiatric disorders. A referral to a psychiatrist may be indicated to evaluate for a mood or anxiety disorder if the patient has no symptom-free period.

TREATMENT OPTIONS

No single intervention has proven effective for all patients with PMDD, but many options are available.

Start with lifestyle changes

Treatment should begin with a 2- to 3-month trial of lifestyle changes while the patient records her symptoms.[9]

Reducing intake of salt, sugar, caffeine, dairy products, and alcohol often helps

Reducing intake of salt, sugar, caffeine, dairy products, and alcohol[9] often helps decrease fluid retention, irritability, and bloating. Lactose intolerance commonly causes bloating in women and may be alleviated by lactase enzymes such as Lactaid. Eating frequent and smaller portions of foods high in complex carbohydrates may also improve mood symptoms, possibly by raising levels of

tryptophan, a precursor in serotonin biosynthesis.[9,42,43]

Contemporary women fulfill multiple social roles, including wife, mother, caregiver to the elderly, and wage-earner, and often experience considerable emotional strain. Exercise, yoga, relaxation, and stress management may enhance general well-being. If possible, scheduling more challenging and stressful tasks during the first half of menstrual cycles may also help.

Medications

Nonsteroidal anti-inflammatory drugs are effective treatments for dysmenorrhea[44]; ibuprofen and naproxen are available over the counter. Acetaminophen (Tylenol) may also alleviate pain. Prescription medications should be used if lifestyle changes and over-the-counter medications do not adequately alleviate symptoms (TABLE 4).

Selective serotonin reuptake inhibitors (SSRIs)[45–58] are the first-line drugs for PMDD and have been shown to be effective in more than 60% of treated patients.[45,46] Treatment only during the luteal phase (10–14 days before menses begins) works as well as full-cycle dosing, with fewer adverse effects.[47–51]

SSRIs have a faster onset of action (1–2 days) when used for PMDD than for depression and other psychiatric disorders, possibly due to their ability to alter allopregnanolone levels.[56–58] Examples include fluoxetine (Sarafem), sertraline (Zoloft), paroxetine (Paxil), and citalopram (Celexa).

Common SSRI side effects include sexual dysfunction, insomnia, fatigue, nervousness, headache, and nausea.

Other serotonergic agents used to treat PMDD inhibit the serotonin transporter as well as the uptake of norepinephrine. Examples include venlafaxine (Effexor)[59] and clomipramine (Anafranil).[60–62]

Alprazolam (Xanax) is a GABA agonist with anxiolytic properties. It has proven effective in double-blind, placebo-controlled crossover studies against premenstrual symptoms, especially tension, anxiety, irritability, and hostility.[63,64] The addictive potential of this medication makes it a second-line treatment.

Buspirone (BuSpar), a partial agonist of serotonin receptors, is also effective because of its anxiolytic properties. It is not addictive.[65,66]

TABLE 3

Differential diagnosis of premenstrual dysphoric disorder

Thyroid disorders
Migraine
Chronic fatigue syndrome
Irritable bowel syndrome
Seizures
Anemia
Endometriosis
Psychiatric disorders (especially bipolar disorder, depression, or anxiety)
Drug or alcohol abuse

Gonadotropin-releasing hormone (GnRH) agonists down-regulate GnRH receptors, which reduce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.[67] This subsequently inhibits ovulation, thereby decreasing estrogen and progesterone levels, creating a pharmacologic menopause.[67]

GnRH agonists are reserved mainly for patients with severe symptoms that do not respond to other treatments. They are expensive and have menopause-like side effects: hot flashes, headaches, muscle aches, vaginal dryness, and irritability. The low-estrogen state also raises concern about development of osteoporosis,[68] so treatment should be limited to 6 months. If extended treatment is required, patients should be given supplemental estrogen and progesterone.[69]

Danazol (Danocrine) is a weak synthetic androgen that inhibits FSH and LH secretion, thus suppressing ovarian steroid production.[70] Its use is limited due to multiple androgenic and antiestrogenic side effects such as amenorrhea, weight gain, acne, fluid retention, hirsutism, hot flashes, vaginal dryness, and emotional lability.

Bromocriptine (Parlodel), a dopamine agonist, lowers prolactin levels and is useful in decreasing breast tenderness.[71,72] Side effects may include dizziness and nausea.

Spironolactone (Aldactone) is the diuretic most studied due to its antimineralocorticoid and antiandrogenic properties. Benefits have not consistently been found.[73–75] Symptoms

Routinely ask your patients about use of vitamins, herbs, and supplements

TABLE 4

Medications for premenstrual dysphoric disorder

Selective serotonin reuptake inhibitors
- Fluoxetine (Prozac, Sarafem) 10–20 mg/day[52] or 90 mg once a week for 2 weeks in the luteal phase[53]*
- Sertraline (Zoloft) 10–150 mg/day[54]*
- Paroxetine (Paxil) 10–30 mg/day[55]*
- Citalopram (Cipramil, Celexa) 5–20 mg/day[48]

Other serotonergic antidepressants
- Venlafaxine (Effexor) 50–150 mg/day[59]
- Clomipramine (Anafranil) 25–75 mg/day[60–62]

Other agents
- Alprazolam (Xanax) 0.25 mg 3–4 times daily in the luteal phase, taper at the onset of menses
- Buspirone (BuSpar) 5–10 mg 3 times daily during luteal phase
- Gonadotropin-releasing hormone agonists (nasal spray, daily or depot injection, and subcutaneous forms available)
- Leuprolide (Lupron) depot 3.75 mg IM/month
- Danazol (Danocrine) 600–800 mg/day in divided doses
- Bromocriptine (Parlodel) 2.5 mg once daily just before ovulation until the onset of menses[72]
- Spironolactone (Aldactone) 50–100 mg/day for 7–10 days during the luteal phase[75]
- Drospirenone (Yasmin)
- Meclofenamate (Meclomen) 100 mg twice a day

*Approved by the US Food and Drug Administration for this indication

most likely to improve include bloating, swelling, breast tenderness, and acne. Side effects of lethargy, headache, and irregular menses are more common during continuous dosing, so administration only during the luteal phase is recommended. Serum potassium levels should be monitored because spironolactone can cause hyperkalemia.

Oral contraceptives. Studies of oral contraceptives have been conflicting.[76,77] In 2001, Freeman et al[78] showed that ethinyl estradiol 30 mg plus drospirenone 3 mg (Yasmin) alleviated bloating, breast tenderness, and swelling. The drospirenone component has antiandrogenic properties and may also reduce acne and hirsutism.

Meclofenamate (Meclomen) reduces menstrual flow and cramps.

Progesterone. Some believe that women with premenstrual symptoms have a deficiency of progesterone in the luteal phase of the menstrual cycle.[79] Dennerstein et al,[80] in a double-blind, randomized, crossover trial, treated women with micronized progesterone in the luteal phase and found progesterone was more effective than placebo for helping mood and some physical symptoms. However, Wyatt et al[81] conducted a systematic review on the use of progesterone in premenstrual women and found no benefit.

SURGERY

In severe, refractory cases of PMDD, ovariectomy may be considered if medical treatment fails. Two studies showed complete relief of symptoms.[82,83] In women of childbearing age, the risk of cardiovascular disease and osteoporosis may increase with the lack of estrogen.

INTEGRATIVE THERAPIES

Physicians should routinely ask patients about their use of vitamins, herbs, and supplements. Although none of these alternative therapies is FDA-approved, they are widely publicized in the popular press, and many patients report relief of symptoms with their use.

Some clinicians may choose to recommend a few of these therapies to certain patients. Most importantly, physicians should be aware of the adverse effects that may occur with self-prescribed supplements and should counsel their patients accordingly.

Vitamins, minerals, and other nutrients

Calcium. Okey et al[34] reported that plasma calcium levels are lower before menstruation, and Thys-Jacobs et al[35] demonstrated in a large trial that 1,200 mg of elemental calcium daily alleviates tension, anxiety, fluid retention, pain, and food cravings in women with PMS. Calcium is inexpensive, is safe during pregnancy, and helps maintain bone health. The typical American diet provides less than half of the recommended 1,200 mg of calcium daily. Intake should not exceed 2,000 mg daily.[84]

Magnesium. Women with PMS have lower levels of magnesium in erythrocytes and leukocytes despite normal plasma magnesium levels.[30–33] Intracellular magnesium is likely a better indicator of true levels, since magnesium is mostly found within cells. Magnesium

is a cofactor in many enzymatic reactions, and some believe that supplementation may alleviate some PMS symptoms by correcting any existing deficiency.

Replacing magnesium in doses of 200 mg to 400 mg once daily reduces fluid retention.[85,86] Magnesium occasionally causes a mild osmotic diarrhea but is usually well tolerated.

Vitamin B_6 is a cofactor in neurotransmitter synthesis, so it may, in theory, play a role in relieving premenstrual mood symptoms. However, studies using vitamin B_6 supplementation have shown inconsistent results.[28,29] The Institute of Medicine of the National Academy of Sciences recommends that women should limit vitamin B_6 intake to no more than 100 mg daily because of the risk of peripheral neuropathy.[87]

Vitamin E may relieve some mood and physical symptoms, including anxiety and breast tenderness.[88] It may exert its effect through prostaglandin synthesis or regulation of central neurotransmitters.[88] Dosage: 400 IU daily.

Manganese levels vary throughout the menstrual cycle. One small study reported that women with low intake of dietary manganese have more premenstrual symptoms of bad mood and pain.[89] Further studies are warranted. Women should be advised that the recommended dose of 6 mg per day to prevent symptoms is higher than the recommended daily allowance of 1.8 mg.[90]

L-tryptophan is an essential amino acid precursor in the serotonin pathway. It has been shown to reduce hostility and cravings in premenstrual women,[91] but more studies are needed to demonstrate its efficacy. Foods rich in tryptophan include milk and turkey. Treatment in supplement form is not recommended because it has been associated with eosinophilia myalgia syndrome (EMS). It is believed that EMS was caused by a contaminant, but it was difficult to implicate one specific substance.

Herbals

Evening primrose oil, derived from the American wildflower *Oenothera biennis*, is a rich source of gamma linolenic acid. This essential omega-6 fatty acid is a prostaglandin precursor. Some believe that women in the premenstrual phase of their cycle are deficient in gamma linolenic acid, leading to symptoms attributable to abnormal prostaglandin synthesis.[92]

Evening primrose oil 3 to 6 g daily has been used to treat breast tenderness; other putative uses are for irritability and ankle swelling. Studies, however, have shown no advantage of evening primrose oil over placebo.[93,94]

Black currant oil and borage seed oil contain a higher content of gamma linolenic acid; however, borage seed oil may contain toxic alkaloids and is not recommended.[95]

Chaste tree extract is obtained from a shrub (*Vitex agnus-castus*) native to southern Europe and the Mediterranean. Prolactin levels are believed to be high premenstrually; chaste tree extract binds to dopamine receptors, inhibiting prolactin release,[95,96] and thereby perhaps relieving irritability and breast tenderness.[97]

Chaste tree extract is not safe during pregnancy[98] on the basis of case reports of uterine stimulation and should not be taken by sexually active women who are not using reliable contraception. The dose is 20 mg to 40 mg per day (aqueous extract). Side effects include gastrointestinal upset, rash, and headache.

Black cohosh stimulates estrogen receptors and is used to treat premenstrual anxiety and breast pain.[95] Currently, no controlled trials exist to support its efficacy. No toxicity has been reported with its use, but experts do not recommend using it longer than 6 months since the long-term safety is unknown.[98]

The typical diet provides < half of the recommended 1,200 mg of calcium daily

Wild yam root contains diosgenin, a compound used in steroid hormone synthesis.[95] Diosgenin converts to progesterone in vitro,[95] and some believe that it should therefore alleviate premenstrual symptoms. However, not much is known about its effects in premenstrual women.

Dong quai is a Chinese herb used for PMS and other gynecological conditions, but no controlled studies support its efficacy.[95] Dong quai is not safe in pregnancy and should not be used by sexually active women who are not using contraception.[95] Since dong quai contains a coumarin derivative, it may increase the prothrombin time and the international normalized ratio, and should not be used by women on warfarin (Coumadin).

Kava kava is used by some women to treat premenstrual anxiety. However, it should not be recommended, as there have been reports of hepatotoxicity.[99] It also may interact with

alprazolam.[100]

St. John's wort (*Hypericum perforatum*) is used to treat mild to moderate depression. A pilot study[101] over two cycles showed improvement in premenstrual mood symptoms, but long-term effects are unknown. St. John's wort interacts with SSRIs, transplant medications, and anti-HIV drugs.

Other alternative therapies

Acupressure and acupuncture are traditional Chinese forms of medicine thought to restore the body's normal flow of energy.[102]

Vaginal biofeedback. Patients can learn to increase their vaginal temperature, warming the pelvic and vaginal tissue. This emulates the thermogenic effects of progesterone and may relieve symptoms.[103]

Homeopathic remedies may have a role in the treatment of premenstrual symptoms as demonstrated by one study,[104] showing the powerful effects of placebo. More studies are needed. Homeopathy has been used successfully at a London clinic.[105]

Chiropractic and massage therapy. Women may benefit from high-velocity, low-amplitude spinal manipulation and soft-tissue kneading two or three times a week premenstrually.[106] Massage therapy has also been shown to decrease anxiety, depressed mood, and pain immediately after massage sessions.[107] Effects over a 5-week period include reduced pain, menstrual distress, and fluid retention.[107]

Reflexology involves applying manual pressure to reflex points (ears, hands, and feet) that correspond to specific areas of the body. Oleson and Flocco[108] found a reduction in premenstrual symptoms in patients treated with reflexology compared with a placebo form of the practice.

Light therapy. Three studies[109–111] found that bright white light used during the luteal phase of the menstrual cycle helps women with PMDD. Women with depressive and physical symptoms are most likely to benefit.

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REVIEW

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Update on contraception: Benefits and risks of the new formulations

ABSTRACT

Several new contraceptives have become available to women in recent years. These new agents include ultra-low-dose oral contraceptives as well as vaginal and patch formulations. We review these, with emphasis on the Yasmin pill (which contains a new progestin), the Ortho Evra patch, the NuvaRing vaginal ring, the Mirena intrauterine device, and emergency contraceptive kits. Patient education regarding these options is essential for patient compliance and satisfaction.

KEY POINTS

Contraception is used both for protection against unwanted pregnancy and for a variety of noncontraceptive health benefits, including improvements in dysmenorrhea, anemia, acne, and others.

Various drugs, including some antibiotics, anticonvulsants, anti-HIV protease inhibitors, and herbal products, can affect the metabolism of oral contraceptives.

Blood pressure should be closely monitored for several months after a women starts taking oral contraceptives, and followed yearly thereafter.

If an Ortho Evra contraceptive patch becomes partially or completely detached, the patient should replace it immediately, but if it has been off for more than 1 day she may not be protected against pregnancy.

This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

WOMEN OFTEN STOP using contraception because of adverse effects, inconvenience, and cost. Improper use alone leads to about 1 million unplanned pregnancies in the United States each year; half end in abortion.[1]

New contraceptives afford women more options. Many of the newer agents have fewer adverse effects, which may ultimately improve compliance and patient satisfaction. Health care providers need to be well informed about these options so that patients can make sound decisions about contraception.

This article reviews the newest developments in contraception, including:

- Low and ultra-low dosing of estrogen
- New progestins
- Risks and benefits of oral contraceptives including drug interactions, health benefits, and potential adverse effects
- New options, including an extended-cycle oral contraceptive regimen, a new progestin, a patch, a vaginal ring, emergency contraception, and an experimental device for surgery-free sterilization.

OVERVIEW OF ORAL CONTRACEPTIVES

Oral contraceptives have been used for more than 40 years in the United States and are the second most popular contraceptive choice for women (after sterilization).[2]

About 35 million women in the United States use some form of contraception, and 95% of all sexually active women have used it at some point.[3,4] Contraception is used both for protection against unwanted pregnancy and, in the case of oral contraceptives, for

TABLE 1

Monophasic oral contraceptives

PRODUCTS	ESTROGEN	PROGESTIN
Necon 1/50, Nelova 1/50 M, Norinyl 1+50, Ortho-Novum 1/50	Mestranol 50 µg	Norethindrone 1.0 mg
Demulen 1/50, Zovia 1/50	Ethinyl estradiol 50 µg	Ethynodiol diacetate 1.0 mg
Ovral, Ogestrel	Ethinyl estradiol 50 µg	Norgestrel 0.5 mg
Ovcon-50	Ethinyl estradiol 50 µg	Norethindrone 1.0 mg
LOW-DOSE		
Demulen 1/35, Zovia 1/35	Ethinyl estradiol 35 µg	Ethynodiol diacetate 1.0 mg
Necon 1/35, Nelova 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/3	Ethinyl estradiol 35 µg	Norethindrone 1.0 mg
Brevicon, Modicon, Necon 0.5/35, Nelova 0.5/35, Nortrel 0.5/35	Ethinyl estradiol 35 µg	Norethindrone 0.5 mg
Ovcon-35	Ethinyl estradiol 35 µg	Norethindrone 0.4 mg
Ortho-Cyclen	Ethinyl estradiol 35 µg	Norgestimate 0.25 mg
Apri, Desogen, Ortho-Cept	Ethinyl estradiol 30 µg	Desogestrel 0.15 mg
Yasmin	Ethinyl estradiol 30 µg	Drospirenone 3.0 mg
Levlen, Levora, Nordette	Ethinyl estradiol 30 µg	Levonorgestrel 0.15 mg
Loestrin 1.5/30	Ethinyl estradiol 30 µg	Norethindrone acetate 1.5 mg
Lo/Ovral, Low-Ogesterel	Ethinyl estradiol 30 µg	Norgestrel 0.3 mg
ULTRA-LOW-DOSE		
Alesse, Aviane, Levlite	Ethinyl estradiol 20 µg	Levonorgestrel 0.1 mg
Loestrin 21 1/20	Ethinyl estradiol 20 µg	Norethindrone acetate 1.0 mg
PROGESTIN-ONLY		
Ovrette	—	Norgestrel 0.075 mg
Ortho Micronor, Nor-Q.D.	—	Norethindrone 0.35 mg

The true failure rate of oral contraceptives is 3%

their noncontraceptive health benefits.

Most oral agents contain both estrogen and progestin, which suppress gonadotropins, inhibit ovulation, and alter cervical mucus to make sperm entry difficult.

In theory, the failure rate is 0.1%, but the true failure rate is 3% due to incorrect use.

Estrogen dosing: Low or ultra low

The two estrogen compounds available in the United States are ethinyl estradiol and mestranol. Ethinyl estradiol is the most commonly used; mestranol is a prodrug that is converted to ethinyl estradiol by the liver. Products containing mestranol do not contain less than 50 µg because lower doses are less effective.

Although early oral contraceptives containing ethinyl estradiol had up to 100 µg, current pills contain an average of 30 to 35 µg. Pills containing less than 50 µg of ethinyl estradiol are called "low-dose."

New "ultra-low-dose" pills contain ethinyl estradiol 20 to 25 µg (TABLE 1, TABLE 2). They are used mainly during the menopausal transition to control symptoms and for contraception, but they also can be used in patients who have adverse effects with higher doses.

The new progestins

In the 1940s, chemists made structural changes

TABLE 2

Multiphasic oral contraceptives

PRODUCT	DAY	ESTROGEN	DOSE	PROGESTIN	DOSE
BIPHASIC					
Mircette	1–21 22–26	Ethinyl estradiol	20 µg 10 µg	Desogestrel	0.15 mg 0.0 mg
Jenest	1–7 8–21	Ethinyl estradiol	35 µg 35 µg	Norethindrone	0.5 mg 1.0 mg
Necon 10/11, Nelova 10/11, Ortho-Novum 10/11	1–10 11–21	Ethinyl estradiol	35 µg 35 µg	Norethindrone	0.5 mg 1.0 mg
TRIPHASIC					
Tri-Levlen, Trivora, Triphasil	1–6 7–11 12–21	Ethinyl estradiol	30 µg 40 µg 30 µg	Levonorgestrel	0.05 mg 0.075 mg 0.125 mg
Ortho Tri-Cyclen	1–7 8–14 15–21	Ethinyl estradiol	35 µg 35 µg 35 µg	Norgestimate	0.18 mg 0.215 mg 0.25 mg
Ortho-Novum 7/7/7	1–7 8–14 15–21	Ethinyl estradiol	35 µg 35 µg 35 µg	Norethindrone	0.5 mg 0.75 mg 0.125 mg
Tri-Norinyl	1–7 8–14 15–21	Ethinyl estradiol	35 µg 35 µg 35 µg	Norethindrone	0.5 mg 1.0 mg 0.5 mg
Cyclessa	1–7 8–14 15–21	Ethinyl estradiol	25 µg 25 µg 25 µg	Desogestrel	1.1 mg 0.125 mg 0.150 mg
Estrostep	1–5 6–12 13–21	Ethinyl estradiol	20 µg 30 µg 35 µg	Norethindrone	1.0 mg 1.0 mg 1.0 mg

to testosterone that altered its activity from an androgen to a progestin. Testosterone-derived progestins bind to the androgen receptor and have varying degrees of androgenic activity.

Adverse metabolic effects of highly androgenic progestins (eg, levonorgestrel) include reductions in serum high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), and glucose intolerance. More-selective, third-generation progestins were developed with structural modifications to lower their androgen activity; examples are norgestimate and desogestrel.

The efficacy of oral contraceptives that contain the new progestins is similar to that of the older formulations. Compared with levonorgestrel-containing pills, which are the most androgenic of the second-generation oral contraceptives, the third-generation pills have less of an effect on carbohydrate and lipid metabolism and are more effective in reducing acne and hirsutism in hyperandrogenic women (TABLE 3).

Unfortunately, data are limited comparing the third-generation progestins with second-generation progestins such as norethindrone and ethynodiol diacetate (which are less androgenic than levonorgestrel).[5] Furthermore, controversy has arisen because of reports of increased risk of deep venous thrombosis with third-generation pills compared with second-generation pills.[6]

Given this debate, our approach is to prescribe pills containing norethindrone, a less androgenic second-generation progestin, when starting a patient on an oral contraceptive for the first time. However, women doing

TABLE 3

Available progestins for oral contraceptives

First-generation
- No longer used

Second-generation*
- Norgestrel
- Ethynodiol diacetate
- Norethindrone
- Levonorgestrel

Third-generation
- Norgestimate
- Desogestrel

Spironolactone-derived
- Drospirenone

*Second-generation progestins are thought to be more androgenic than third-generation progestins.

well on a third-generation progestin do not need to change preparations.

Third-generation oral contraceptives are more effective in reducing acne and hirsutism

Monophasic or multiphasic?

To further lower the total steroid dose, in the late 1970s pharmaceutical companies introduced multiphasic preparations—pill packs that vary the dose at different times in the menstrual cycle (TABLE 2). Trials have not consistently shown significant differences between monophasic, biphasic, and triphasic oral contraceptives regarding bleeding pattern, symptoms, or efficacy, however.[7]

Because most clinical experience and available studies are with the monophasic formulations, these are often preferred. However, as for patient satisfaction, our clinical observation is that the choice of progestin is probably more important than whether the regimen is monophasic or multiphasic.

Progestin-only contraceptives

Progestin-only oral contraceptives, otherwise known as "mini-pills," are available for women who cannot tolerate estrogen (eg, due to a history of heart disease or thromboembolism). These pills, however, are associated with more breakthrough bleeding and lower contraceptive efficacy than combination pills, and they are used mainly in lactating women. In fact, a backup contraceptive method must be used for 2 days if a woman is more than 3 hours late taking a dose. A backup method also is recommended each month at midcycle to improve efficacy.

In addition, progestin-only contraceptives, such as injectable medroxyprogesterone acetate (Depo-Provera), have recently been linked to reversible decreases in bone density.[8,9] The potential role of these agents in osteoporosis risk is still being defined. For this reason, women taking progestin-only agents should be sure to take in at least 1,200 mg of calcium daily.

Drug interactions

Various drugs can influence the metabolism of oral contraceptives. Unintended pregnancy or breakthrough bleeding can result when oral contraceptives are taken with:

- Antimicrobials (eg, penicillins, tetracyclines, griseofulvin, rifampin)
- Anticonvulsants (eg, phenytoin, carbamazepine, felbamate, topiramate)
- Anti-HIV protease inhibitors
- Herbal products. For example, in women taking oral contraceptives and St. John's wort (*Hypericum perforatum*), bleeding irregularities may occur 1 week after starting St. John's wort, with regular cycles returning when the herb is stopped.[10]

The incidence of accidental pregnancy in women taking these medications with oral contraceptives is unknown, but women using the lowest-dose preparations may be at highest risk. This is an important consideration, given the large number of ultra-low-dose regimens on the market (TABLE 1).[11]

Safety of oral contraceptives

The safety profile of oral contraceptives has been demonstrated in millions of women, and taking them is considered safer than pregnancy.[12] A recent study[13] found similar mortality rates in 23,000 users and nonusers of oral contraceptives.

Noncontraceptive benefits of oral contraceptives

Most women are unaware of the many noncontraceptive benefits of oral contraceptives, which include improvements in or decreased risk of:

- Dysmenorrhea
- Anemia
- Acne
- Hirsutism

- Ectopic pregnancy
- Benign breast disease
- Endometrial cancer
- Ovarian cysts[14]
- Ovarian cancer (newly recognized: a 50% decrease in ovarian cancer risk, including cases associated with mutations in the *BRCA* genes[15,16])
- Colorectal cancer (an 18% to 40% reduction[17,18])
- Pelvic inflammatory disease (a 10% to 70% lower incidence)
- Osteopenia, osteoporosis. Because oral contraceptives provide a consistent dose of estrogen, they may increase bone mineral density by promoting higher peak bone mass.[19] This benefit has been reported with ultra-low-dose formulations, and the positive effect increases with higher doses and longer use. A 25% reduction in hip fractures has been demonstrated.[20]
- Dyslipidemia. Oral contraceptives that contain third-generation progestins improve serum lipoprotein profiles by increasing HDL and decreasing LDL, although the clinical significance of these changes is not clear.[21]

Risks of oral contraceptive use

The benefits of oral contraceptives must be weighed against the potential risks.

Coronary artery disease. Low-dose oral contraceptives were developed in response to increased cardiovascular events associated with higher-dose oral contraceptives. Studies of oral contraceptives with less than 50 µg estrogen have found no increased risk of myocardial infarction (MI) among healthy, nonsmoking women.[22]

In oral contraceptive users over age 35, smoking 15 or more cigarettes per day increases the risk of MI.[23] Studies have not defined how other cardiovascular risk factors affect the incidence of MI in oral contraceptive users. Concomitant hypertension, dyslipidemia, diabetes, or obesity may further increase the risk.

Venous thromboembolism. Studies consistently show that the risk of venous thromboembolism (VTE) is two to six times higher in oral contraceptive users than in nonusers.[24] However, the incidence of VTE in otherwise healthy women is low, at about 1 or 2 persons in 1,000 to 10,000, depending on age. The primary factor contributing to VTE is estrogen; however, there are conflicting reports about the potentially additive risk with the third-generation progestins.[25,26]

Risk factors for VTE include increasing age, obesity, family history of VTE, surgery, and the factor V Leiden mutation. Patients with this mutation have six to seven times the risk of VTE, which increases up to 35 times with oral contraceptive use. Women with a documented history of VTE that is unexplained or associated with pregnancy should avoid oral contraceptives.

Hypertension. Many women have an increase in blood pressure with oral contraceptive use, although readings usually remain within the normal range. The risks of pregnancy in women with hypertension should be weighed against the risks of oral contraceptive use.

Low-dose oral contraceptives are not contraindicated in otherwise healthy women with well-controlled hypertension, but women over age 35 who have hypertension and who smoke or have end-organ vascular disease should not use oral contraceptives.

Blood pressure should be closely monitored for several months after starting oral contraceptives and followed yearly thereafter.

Stroke. Studies evaluating oral contraceptives and stroke are difficult to interpret. Most studies were small, did not differentiate between hemorrhagic and thromboembolic stroke, and did not control for major risk factors. Most evidence suggests that there is no increased risk in oral contraceptive users, except in those who smoke.[27,28]

Oral contraceptives may increase bone mineral density

The risk of stroke from use of these agents in migraine patients also is controversial. Studies of older, high-dose oral contraceptives showed an increased risk of stroke, whereas studies of low-dose formulations have not.[29]

Breast cancer. Evidence of a possible link between breast cancer and hormone exposure has been inconsistent.

A meta-analysis[30] of 54 studies that included a total of 53,000 women with breast cancer and 100,000 controls found that the relative risk of breast cancer in current users of oral contraceptives was 1.24. After the oral contraceptive was stopped, this risk decreased and was absent after 10 years. Breast cancers that were diagnosed while the patient was taking an oral contraceptive tended to be less advanced.

On the other hand, a recent case-control study[31] found that, in women aged 35 to 64 years, current or former oral contraceptive use was not associated with a significantly

increased risk of breast cancer.

In women with a family history of breast cancer in a first-degree relative, high-dose formulations (used before 1975) may further increase this risk, although the newer low-dose formulations have not been shown to carry this increased risk.[32]

In patients with a *BRCA1* or *BRCA2* mutation, the potential increased risk of breast cancer needs to be weighed against the decreased risk of ovarian cancer. These patients should consider discussing the safety of oral contraceptives with a consultant, such as a geneticist or a specialist in women's health or breast health.

Cervical cancer. For every 100,000 women who use oral contraceptives for longer than 8 years, 30 to 125 additional cases of cervical cancer may occur. However, oral contraceptive users may have more unprotected sexual encounters and an increased exposure to the human papillomavirus, a known risk factor for cervical cancer.

The slightly increased risk of cervical cancer needs to be weighed against the roughly 50% reduction in the risks of ovarian and endometrial cancers. One model estimated that for every 100,000 women, 44 fewer reproductive cancers would occur in users than in nonusers.[33]

Women with a history of venous thromboembolism should avoid oral contraceptives

NEW CONTRACEPTIVE OPTIONS

Seasonale: The first 'continuous' pill

Seasonale is a low-dose, extended-cycle, monophasic oral contraceptive containing 30 µg of ethinyl estradiol and 0.15 mg of levonorgestrel. Active tablets are taken consecutively for 84 days, followed by inactive tablets for 7 days, which allows for withdrawal bleeding only 4 times a year in contrast to 13 times a year with traditional oral contraceptives. Unanticipated bleeding or spotting may be more common initially as compared with other oral contraceptives, but Seasonale is just as effective in preventing pregnancy. Long-term risks and benefits with extra hormonal exposure remain to be established.

The Yasmin pill: Ethinyl estradiol plus a spironolactone analogue

Yasmin is a low-dose, monophasic oral contraceptive containing ethinyl estradiol and drospirenone, a progestin analogue of spironolactone.[34] Drospirenone is the only progestin with both antimineralocorticoid and antiandrogenic properties that is approved by the US Food and Drug Administration (FDA).

Effectiveness. Yasmin is 99% effective, which is similar to other oral contraceptives.[35]

Advantages. Due to its antiandrogenic diuretic properties, Yasmin has the added benefit of improving acne, seborrhea, and hirsutism as well as providing good weight stability—or even slight weight loss—from decreased water retention.

An 8-month study[36] compared weight gain in 80 women taking either Yasmin or ethinyl estradiol and levonorgestrel (0.15 mg). Women taking Yasmin lost an average of 1.8 lb (0.8 kg), while women taking ethinyl estradiol and levonorgestrel gained an average of 1.5 lb (0.7 kg).

Yasmin may benefit women with premenstrual symptoms such as bloating.[37,38]

Practical considerations. The 3 mg of drospirenone in each pill is equivalent to 25 mg of spironolactone, a potassium-sparing diuretic. Therefore, the serum potassium level should be checked during the first month of therapy.

Yasmin should be used with caution in women taking medications that can lead to hyperkalemia, such as other potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, aldosterone antagonists, and nonsteroidal anti-inflammatory drugs. It is contraindicated in women with renal, hepatic, or adrenal insufficiency.

Ortho Evra: 'The patch'

In 2001, the FDA approved the first transdermal contraceptive patch, Ortho Evra (20 µg ethinyl estradiol and 150 µg norelgestromin per 24 hours).[39] Norelgestromin is a metabolite of norgestimate, the progestin in the third-generation pills Ortho-Cyclen and Ortho Tri-Cyclen.

Effectiveness and advantages. Three clinical trials have been conducted worldwide involving 4,578 women, 3,319 of whom used Ortho Evra. Compared with daily oral contraceptives, the patch offered similar safety, contraceptive efficacy, and menstrual cycle control and had the added benefit of improved compliance.[40] It is hoped that improved compliance will lead to decreased failure rates.

Practical considerations. In clinical trials, most unintended pregnancies were in women weighing more than 198 lb (90 kg), suggesting that Ortho Evra may be less effective in women heavier than this weight. Therefore, Ortho Evra

should be used with caution in these women.

The most common adverse effects in clinical trials were, in decreasing order, breast tenderness, headache, skin irritation, and nausea. It is unknown if the risk of VTE with Ortho Evra is different than with oral contraceptives.

The patient should start Ortho Evra on the first day of her menstrual period (or first day of withdrawal bleeding in oral contraceptive users). A new patch is applied weekly, on the same day each week, for 3 weeks. Week 4 is patch-free, and withdrawal bleeding is expected during this time. As with the oral contraceptives, there should not be more than a 7-day hormone-free interval between dosing cycles.

The patch should be applied to clean, dry skin on the buttocks, upper outer arm, lower abdomen, or upper torso (excluding breasts). Ortho Evra should not be placed on skin that is red or irritated or where it will be rubbed by tight clothing. Oils, creams, or cosmetics should not be applied near the patch. The patient should be encouraged to participate in her usual physical activities (eg, sauna, whirlpool, swimming).

If the patch comes off. Of more than 70,000 Ortho Evra patches worn, 4.7% were replaced because they either fell off (1.8%) or were partly detached (2.9%).

If the patch is detached, a new one should be applied immediately. Supplemental adhesives or wraps should not be used.

If a patch is partially or completely detached for less than 1 day, the patient should replace it with a new patch immediately. No back-up contraception is needed.

If a patch is detached for more than 1 day or if the woman is unsure how long it has been detached, she may not be protected from pregnancy. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch.

Packages of single replacement patches are available. Used patches still contain active hormones, so they should be folded in half before they are discarded.

NuvaRing: A once-a-month vaginal ring

NuvaRing is a contraceptive vaginal ring that releases 120 µg of etonogestrel and 15 µg of ethinyl estradiol daily. It is colorless and odorless and measures 2 inches in diameter, with a cross-sectional diameter of 4 mm.

The ring is easy for patients to insert and is left in place for 3 weeks. Withdrawal bleeding occurs during the fourth, ring-free week.

Efficacy. NuvaRing is comparable to oral contraceptives in efficacy.

Advantages. NuvaRing is an excellent choice for most women, although it is not recommended if a cystocele, rectocele, or uterine prolapse is present.[41] One of its main advantages is convenience.

A recent study of 247 women[42] compared cycle control and tolerability of NuvaRing vs a standard combined oral contraceptive containing ethinyl estradiol 30 µg and levonorgestrel 150 µg. Both groups experienced withdrawal bleeding; however, the incidence of irregular bleeding in the NuvaRing group was significantly less than in the oral contraceptive group. In addition, NuvaRing users had a higher incidence of normal intended bleeding patterns compared with the oral contraceptive group. The tolerability of both contraceptives was good, although the NuvaRing users had a higher incidence of vaginal discomfort and vaginitis.

Practical considerations. If the ring is out of the vagina for more than 3 hours during the first 3 weeks of the cycle, effective contraception cannot be guaranteed. The ring should be rinsed with warm water and reinserted within 3 hours to maintain efficacy.

If a woman forgets to remove the ring after 3 weeks, it will continue to inhibit ovulation for up to 5 weeks.

Hypertensive women over age 35 who smoke should not use oral contraceptives

Mirena: The progestin IUD

Mirena, an intrauterine device (IUD), has been used since the early 1980s in other countries for contraceptive and noncontraceptive purposes. It recently was approved for contraceptive use in the United States.

Mirena is a levonorgestrel-releasing system that is effective for up to 5 years. It acts locally on the endometrium with progestogenic effects and may also thicken cervical mucus and inhibit sperm capacitation and survival.

Effectiveness. Mirena is 99% effective. A study in 1,169 women[43] found that pregnancy rates over 1 year and 5 years were less than 1%. Of the unwanted pregnancies, half were ectopic. This translates into an annual incidence of one ectopic pregnancy per 1,000 users, which is not significantly different than the rate of ectopic pregnancies in sexually active women not using any contraception.

Advantages. Mirena's delivery of progesterone to the endometrium results in less bleeding than with copper IUDs.[44] Some women, however, may have irregular bleeding during the first 3 to 6 months. After that, bleeding usually declines, and 20% of women have amenorrhea by the end of the first year.

The decreased bleeding profile and 5-year efficacy of Mirena make it an attractive option, especially for women with menorrhagia or those who desire long-term contraception.

EMERGENCY CONTRACEPTION

Postcoital (emergency) contraception is defined as the prevention of pregnancy within 72 hours of unprotected intercourse or failure of a contraceptive method (eg, a broken condom).

Even though emergency contraception is known to be effective and has a low potential for adverse effects, many patients are not prescribed it because their physicians either do not know about it or are not comfortable with its use. Until recently, the most commonly prescribed regimens included:

- Ethinyl estradiol 2.5 mg twice a day for 5 days
- Ethinyl estradiol 100 µg and levonorgestrel 0.5 mg, repeated in 12 hours
- Levonorgestrel 0.75 mg, repeated in 12 hours.

Drospirenone may benefit women with premenstrual symptoms such as bloating

Recently, the FDA approved two emergency contraceptive kits. The **Preven** kit contains a pregnancy test to exclude pregnancy before taking the pills, which each contain ethinyl estradiol 50 µg and levonorgestrel 0.25 mg. The patient takes two pills and another two in 12 hours.

The **Plan B** kit is similar, but contains progestin only, thus causing less nausea and vomiting than regimens that also contain estrogen.[45] One tablet of Plan B should be followed by a second dose within 12 hours.

These regimens have similar efficacy, reducing the number of pregnancies by 89%; however, if Plan B is taken in the first 24 hours, it can prevent 95% of expected pregnancies.

The most significant side effect of these regimens is nausea; therefore, an antiemetic can be prescribed concomitantly.

Mifepristone (Mifeprex; RU-486), in a single 600-mg dose, has higher efficacy than the previously mentioned regimens, as well as a lower incidence of adverse effects.[46] However, it is not FDA-approved for emergency contraceptive use in the United States.

A copper IUD also can be used as emergency contraception if placed within 120 hours of unprotected intercourse, although this is not commonly done in the clinical setting.

ESSURE: AN EXPERIMENTAL DEVICE FOR SURGERY-FREE STERILIZATION

Currently, the only option for women who want permanent birth control is tubal ligation, a surgical procedure that requires anesthesia and several days of recovery.

The Essure device is a mesh embedded in coils that causes scar tissue and stricture of the fallopian tubes. It is inserted through a hysteroscope and requires no incision and minimal anesthesia. This device was approved by the FDA in late 2002. Long-term data are unavailable.

THE WOMAN SHOULD CHOOSE THE RIGHT OPTION FOR HER LIFESTYLE

Many effective contraceptive methods offer both contraceptive and noncontraceptive benefits. Low-dose oral contraceptives are safe, effective, and popular. Implantable and transdermal formulations are available for women who have difficulties with compliance. Progestin-only contraceptive options are alternatives, especially for women who cannot take or tolerate estrogens.

The best contraceptive choice for each woman is the method that she feels the most comfortable with and that suits her lifestyle. Women should be educated about the various forms of contraception and encouraged to choose one that best meets their needs and desires. This, in turn, will improve patient satisfaction and compliance. ■

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DXA scanning to diagnose osteoporosis: Do you know what the results mean?

ABSTRACT

Dual-energy x-ray absorptiometry (DXA) provides useful information about osteoporosis and fracture risk that, combined with other risk factors for osteoporosis, helps guide therapy. However, DXA is operator-dependent, making it imperative to refer patients to sites where the operators are experienced in this technology.

KEY POINTS

The T score is the number of standard deviations above or below the mean value for young adult reference data (considered to represent peak bone mass); the Z score is the number of standard deviations below the mean for an age-matched population.

Bone density measurements can vary, depending on the machine, size and placement of the region of interest, overlying material in the region measured, and absence of normal structures (eg, laminectomy).

The National Osteoporosis Foundation recommends drug therapy for osteoporosis in patients with T scores of –1.5 or lower who have other risk factors, and in patients with T scores of –2 or lower without other risk factors.

The DXA report should not just provide precise measurements: it should add value to the decision of how to treat the patient, conveying information the referring physician can use when talking to the patient.

The author has indicated that he serves as a consultant for and is on the speakers' bureaus of the Merck and Procter & Gamble corporations.

WHEN YOU SEND a patient for measurement of his or her bone mineral density, do you know what you are getting?

In experienced hands, dual-energy x-ray absorptiometry (DXA) provides accurate, reproducible measurements of bone mineral density and therefore allows the diagnosis of osteoporosis in people without symptoms. But behind the seemingly precise numbers on the report lurk many opportunities for error, and although DXA is high-tech and computerized, the results depend on the operator and specific scanner used.

Moreover, since the bottom-line numbers you need—the T score and the Z score—are indexed to mean values from a database derived from multicenter studies, these can change as new demographic data become available. Further, different interpreters of DXA scans supply different data on their reports, which can either help or confuse the primary care physician.

This article looks at the information DXA provides, what a physician should expect from a DXA report, and how to use this information, along with the patient's age and risk factor profile, to predict risk and guide therapy.

WHY MEASURE BONE MINERAL DENSITY?

Osteoporosis affects approximately 28 million people in the United States[1] and causes 1.5 million fractures each year,[2] posing a major public health problem in terms of morbidity, associated mortality, and economic costs.

In osteoporosis, once a fracture occurs, the risk of a subsequent fracture is high.[3] Therefore, the diagnosis of osteoporosis should be made *before* the first fracture occurs, so that the patient can undertake lifestyle changes

DXA of the hip:
Good scan **"Problem" scans**

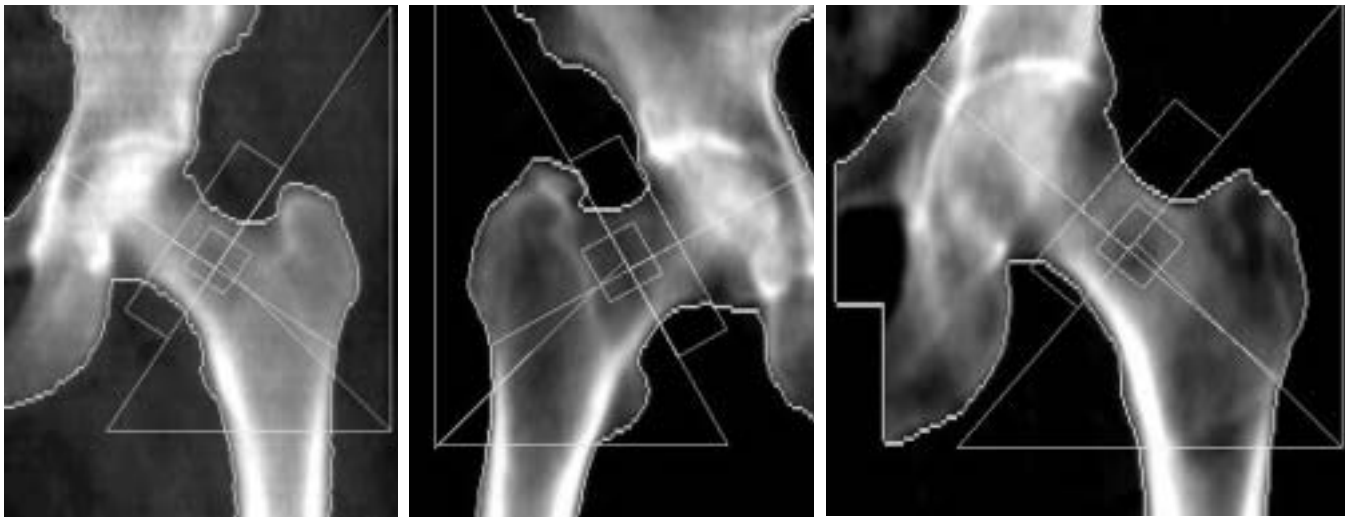

FIGURE 1. **Left,** normal positioning for DXA of the hip. The lesser trochanter is minimally visualized or not visualized; the diaphysis is parallel to the table edge. The hip is not abducted.
Center, external rotation results in visualization of the lesser trochanter, shortening the femoral neck. The hip is also abducted. Improper positioning results in poor precision on follow-up studies because it is difficult to reproduce the positioning. The exam data are also less reliable since the reference database was presumably collected with proper positioning.
Right, loss of joint space from degenerative joint disease results in cortical thickening of the medial femoral neck region, falsely increasing bone mineral density measurement. Eccentric placement of the femoral neck region of interest does not affect bone mineral density analysis. Reproducibility on subsequent scans is difficult, especially as degenerative changes progress.

IMAGES COURTESY OF GE LUNAR MEDICAL SYSTEMS

and undergo treatment to prevent fractures.

The only way to do this is to measure bone mineral density. Low measurements on DXA predict the risk of fractures of the spine[4] and hip,[5] analogous to the relationship between high serum cholesterol and the risk of myocardial infarction, or between high blood pressure and the risk of stroke.[6]

Driving the demand for DXA is the availability of proven, FDA-approved therapies for osteoporosis, ie, alendronate (Fosamax), risedronate (Actonel), calcitonin (Miacalcin), raloxifene (Evista),[7] estrogen replacement therapy,[8,9] and parathyroid hormone (Forteo).[10]

HOW DXA WORKS, HOW IT CAN GO WRONG

DXA uses x-rays at two energy levels to determine the bone mineral content. This is accomplished by subtracting the difference of absorption of x-rays between soft tissue and calcium bone.

The scanner software calculates the bone mineral density, dividing the bone mineral content by the area of the region of interest. The bone mineral density is compared to reference data specific to the scanner, and the results are expressed as the *T score* and the *Z score* (see below).

Although DXA could be used to measure bone density at many skeletal sites, two sites are typically measured: the first four vertebrae of the lumbar spine posteroanteriorly, and the proximal femur ("hip"), including the femoral neck and the trochanteric areas and total hip measurement (FIGURE 1).

Opportunities for error

Several aspects of the bone density measurements should be evaluated before a study is accepted as accurate.

Placement and sizing of the "regions of interest." Changes in placement can significantly affect accuracy. For example, including more of the femoral shaft, where the bone is

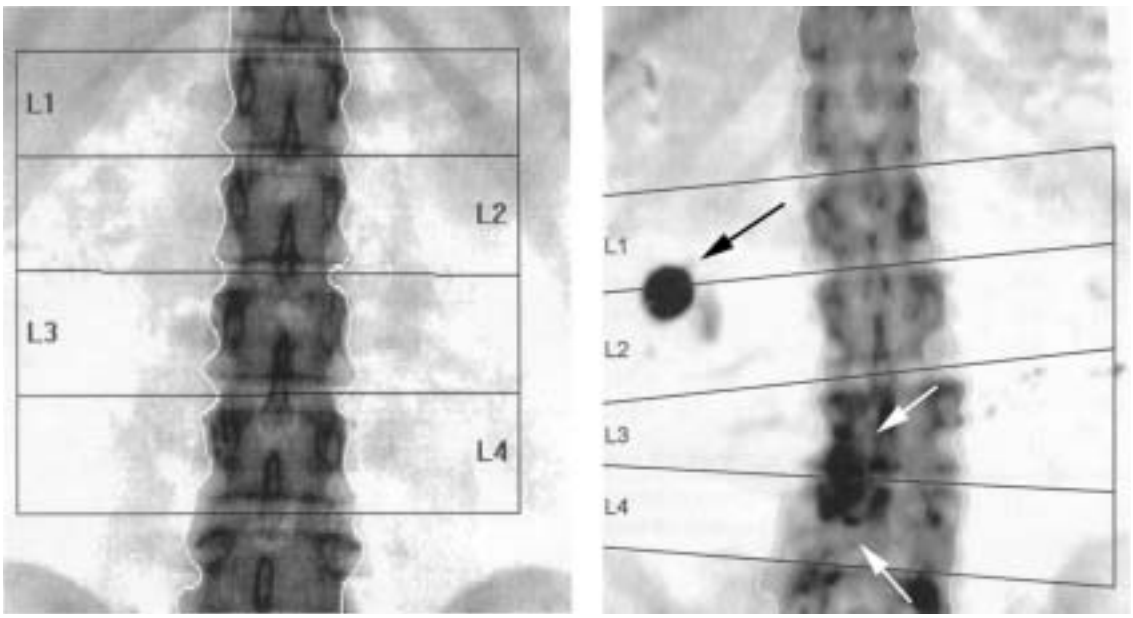

FIGURE 2. **Left,** normal positioning for dual-energy x-ray absorptiometry (DXA) of the lumbar spine. T12 ribs are visualized, and both iliac crests are identified. The numbering of vertebral levels should be consistent, with the first vertebral body after the last ribs most commonly L1.
Right, DXA scan of the lumbar spine in a patient with scoliosis with degenerative changes (white arrows), which falsely elevate the bone mineral density. Black arrow indicates a renal calculus in the soft tissue region of interest of L1 and L2, which may result in a falsely decreased bone mineral density at these levels.

The aim is to prevent a first fracture

normally denser, could result in a falsely high measurement.

Also, since bone mineral density is calculated by dividing the bone mineral content by the area measured, if the area is too small the measured bone mineral density will be falsely high; if it is too big the density will be falsely low.

On follow-up studies the area must be consistent: within 2% of that of the original scan. If the region of interest is not placed correctly each time, no valid comparison can be made.

Overlying material in the region of interest and degenerative changes of the spine add density,[11] as do soft tissue calcifications and any overlying radiodense object. On the other hand, densities adjacent to the area measured can artificially decrease the bone mineral density if they are big enough (FIGURE 2).

Absence of normal structures (eg, after laminectomy) can also affect bone mineral density, since the reference data are based on normal anatomy (intact posterior elements). The person providing the report should be aware of these factors and should note the possible complicating factors in the report.

What is the T score?

The T score compares the patient's bone mineral density with the mean value in young adult white women and is expressed in standard deviations above or below this mean. Male databases are now available on a limited basis.

The World Health Organization (WHO) criteria[12] (TABLE 1) list four diagnostic categories on the basis of the T score:

- Normal: 0 to –0.99
- Osteopenia: –1 to –2.49
- Osteoporosis: ≤ –2.5 (eg, –3.0, –4.0; remember that these are negative numbers)
- Severe or established osteoporosis: ≤ –2.5, with a fragility fracture.

These criteria were based on studies in elderly white women, which presents a problem for nonwhite patients, for men, and for children, in whom this classification system has not been fully evaluated. Reference data-

bases for nonwhite populations exist on some DXA scanners, though the largest database available is still for white women.

The International Society for Clinical Densitometry[13] has recently published position papers stating that a uniform white database should be used to determine T scores in nonwhite women. Male databases, when available, should be used for men. No statement was made concerning Z scores and ethnicity. Manufacturers who currently have ethnic databases will address this issue in the near future.

Another problem: the osteopenic range is quite broad.

The National Osteoporosis Foundation recommends drug therapy for osteoporosis in patients with T scores of –1.5 or lower who have other risk factors for osteoporosis (see below), and in patients with T scores of –2 or lower but no other risk factors. These recommendations emphasize that a patient may experience fragility fractures with a T score in the osteopenic *or* in the osteoporotic range.

Assessing fracture risk with the T score

We can use the T score to estimate the risk of fractures on the basis of two lines of evidence: biomechanical studies of bone strength and prospective epidemiologic studies in specific populations.

Studies in postmenopausal white women found that bone mineral density is associated with an increased risk of fracture that is equal to approximately 1.5 to 3.0 to the power of the decreased standard deviation of the T score.[14]

What is the Z score?

The Z score compares the patient's bone mineral density with the mean value in a population of similar age, sex, and height. This information is useful in determining the likelihood of secondary osteoporosis due to causes such as primary or secondary metabolic bone disease, infiltrating malignancies such as myeloma, and drug-induced decreased bone mass.

If the Z score is –1.5 to –2.0 standard deviations below the mean for age, the patient should undergo an evaluation for secondary osteoporosis.

T score vs Z score in African Americans

Sometimes the Z score is more useful in assessing fracture risk. For example, GE-Lunar scanners (Madison, Wis) use a reference database for calculating the T score that is not ethnically matched for African Americans. Therefore, when using this type of scanner in African American patients, the Z score better reflects the bone mineral density, since it is matched for ethnicity. (Scanner type is usually indicated on the scanning report.)

African Americans have approximately a 10% greater bone mineral density than whites and are believed to have a lower fracture rate. The new position papers from the International Society for Clinical Densitometry recommend that African American women be compared with white databases for these reasons. African American men should be compared with a male database.[13]

TABLE 1

WHO T score criteria for osteopenia and osteoporosis

T SCORE	DIAGNOSIS
0 to –0.99	Normal
–1 to –2.499	Osteopenia
≤ –2.5	Osteoporosis
≤ –2.5 with fracture	Severe or established osteoporosis

OTHER RISK FACTORS

Low bone mineral density is not the only risk factor for osteoporosis and fractures.

Unmodifiable risk factors for osteoporosis include female gender, advancing age, white or Asian ethnicity, family history of osteoporosis, previous fractures, and frail health.

Modifiable risk factors for osteoporosis include estrogen deficiency, calcium deficiency, vitamin D deficiency, low body weight, alcoholism, medications (especially steroids), and smoking.

Risk factors for fractures unrelated to bone mineral density include propensity to fall (especially in patients with low bone mineral density), poor physical function, impaired vision, impaired cognition, and environmental hazards.

All of these factors must be considered in

Refer patients only to a center with certified DXA technologists and interpreters

a patient's overall assessment. For example, a patient with steroid-induced osteoporosis would benefit most from stopping the steroid treatment.

To elicit these additional risk factors more fully, we use a questionnaire. This information allows us to create a more complete clinical picture, to which we can add bone density information. The net product is more useful for the treating physician when selecting the most appropriate therapy.

COMPONENTS OF A DXA REPORT

The reports that radiologists send the primary care physician vary widely. Some simply provide the DXA scan data. At our institution, we provide a more complete report that includes:

- The patient's risk factors for low bone mass and fractures
- The DXA scan data, including the T score and the Z score
- A diagnosis, based on World Health Organization (WHO) criteria (TABLE 1)
- The patient's relative risk for fracture
- Follow-up recommendations
- The patient's current treatment for osteopenia and osteoporosis
- Treatment recommendations, based on the National Osteoporosis Foundation guidelines, eg, weight-bearing and muscle-strengthening exercise, calcium and vitamin D supplementation, moderate alcohol consumption, smoking cessation, and, in postmenopausal women, consideration of hormone therapy unless contraindicated. Drug treatments are recommended based on the reporting physician's experience, relationship with and expectations of the referring physician, knowledge of the patient, and knowledge of the medications. Recommending treatment in the DXA report is an individual decision by the reporting physician.
- Exclusion of secondary causes of low bone mass. A diagnosis of osteoporosis or osteopenia can only be made clinically after all potential secondary causes are excluded. Metabolic disorders, malignancies, medications (especially steroids), alcohol abuse, smoking, and other factors too numerous to mention here can cause low bone mass.[1]

Follow-up scans should be done at the same site as the first

The bone density report should reflect, to the best knowledge of the reporting physician, the patient's relevant history, diagnosis, change on follow-up examinations, and fracture risk, and should include recommendations about current treatments and factors that might have affected the scan.

A complete DXA report should add value to the decision of how to treat the patient. It should convey information the referring physician can use when talking to the patient about the patient's bone health status and about possible treatment options.[15]

Preset report generators

Most DXA scanners can generate preset, standardized reports. Some of these are good and useful, some less so.

Helpful reports include data from the patient's previous DXA scans, making it easier to track trends. They also include the demographic data on which the patient's T score and Z score are based. A report may also include reminders to assess for adequate intake of calcium and vitamin D and to watch for lifestyle-related risk factors for fracture, such as alcohol intake and smoking. A thorough report should also include the reporting physician's overall impression of the patient's diagnosis and any recommendations for follow-up measurements.

On the other hand, preset generated reports must be used with caution. They may be poorly structured and confusing, providing more technical data than is relevant. They may not be tailored to the individual patient. Such reports tend to simply report numbers and remove the cognitive aspects of diagnosis.

CHOOSING A REFERRAL SITE

Some questions to consider when deciding where to refer a patient for DXA scanning:

- Does the physician who will interpret and report the scan have ample experience with DXA? Has he or she attended a symposium or course regarding bone mineral density studies and the reporting of DXA scans? Is he or she certified by the International Society for Clinical Densitometry?
- Are the technologists trained by the

equipment manufacturer, experienced in the use of the equipment, and certified by the International Society for Clinical Densitometry?

- Does the site have a quality-assurance program and proof that the DXA measurements are reproducible? Do the physician and staff know the precision ratings of the scanner and the technicians?
- Are the costs for the examination reasonable? Unless you specify that you desire only the bone mineral density report, referring a patient to a clinical specialist may result in an additional consultation fee.
- What type of report will you receive?

WHO SHOULD UNDERGO DXA?

Clinical indications for bone densitometry include:

- Estrogen deficiency (the Bone Mass Measurement Act of 1998 provides Medicare reimbursement for bone densitometry if it is used to decide whether to give hormone therapy in women with estrogen deficiency[16])
- Prolonged glucocorticoid therapy
- Osteopenia
- Fracture
- Primary hyperparathyroidism
- Monitoring antiresorptive therapy.

The use of bone densitometry to screen populations at high risk is controversial, but the National Osteoporosis Foundation recommends bone densitometry in all white postmenopausal women under age 65 who have at least one risk factor in addition to menopause, and in all white women after age 65 regardless of other risk factors.

Men also can have osteoporosis.[17–20] The most frequent causes of low bone mineral density in men are idiopathic (35% to 50% of cases), alcoholism, steroid therapy, and low testosterone levels. Smoking decreases bone mass in both men and women.

FOLLOW-UP SCANS

Follow-up scans are recommended on the basis of the cause and severity of the patient's bone loss.

The Bone Mass Measurement Act provides for a follow-up DXA scan every 23 months in Medicare patients. Exceptions are allowed, especially in the case of steroid-induced osteoporosis. However, the physician must write a letter explaining the need for the exception.

Medicare will also pay for a quantitative ultrasound of the heel to assess the risk for fracture during the same 23-month period. However, an ultrasound should only be used initially to identify patients at risk for fracture. Follow-up should be by DXA.

Most experts believe that a patient with a T score of –1.5 standard deviations or lower should have a follow-up study in 2 years (if he or she is treated) to determine the efficacy of treatment.[21,22]

More frequent scans (ie, more often than 6 months to 1 year apart) are generally indicated in patients with drug-induced bone loss and metabolic bone disease. These conditions can generally be treated effectively in a shorter period and may demonstrate a more rapid increase in bone mineral density.

What is a significant change?

Most treatments do not result in a significant increase in bone mineral density during the first year. To be considered significant, the percent change in bone mineral density must exceed the precision (or reproducibility) of the study itself—ie, the precision of the scanner and the operator. A typical precision range is a 1% to 3% change in bone density for measurements of the spine and a 3% to 5% change in bone density for measurements of the hip. These precision ranges may be slightly higher in the elderly population.

The osteopenia range is quite broad

This concept is called the *least significant change* and reflects the error of the scanner and the technologist. To ensure a real increase or decrease in bone density, the least significant change must be exceeded on subsequent scans.

A change in T score does not reflect bone loss or gain: it is relevant only to the specific scan it is calculated for. Changes in bone density related to disease or treatment are reflected by the bone density itself, expressed in grams per centimeter squared, considering least significant change, not the T score.

If the bone density does not change over

two to three follow-up scans with therapy, we can conclude that bone loss has stopped. A follow-up scan would then be appropriate to determine if an increase in bone mineral density will follow. The expected increase in bone mineral density for each treatment regimen is beyond the scope of this article.

Use the same scanner for follow-up

Bone mineral density should be measured using the same scanner each time. Attempting to determine change is fraught with problems when using different scanners, even from the same manufacturer. These problems include different reference databases, different precision coefficients of variation among scanners, different measurement techniques, and unfamiliarity with the quality assurance of scanners. Different manufacturers also use different methods of generating the x-rays and different energy levels. In addition, the third National Health and Nutrition Examination Survey introduced a correction factor for hip data when calculating the T score, which some DXA centers use and some do not.

When do you stop following up patients?

An important question is when to stop following patients. Generally, if the patient demonstrates a true increase in bone mineral density after two follow-up examinations, either no more follow-up is necessary or the interval can be increased unless the patient's status or medications change.

For example, if a patient on hormone therapy has a reasonable bone mineral density but decides to stop treatment, she should have a scan within 2 years, during which time her bone mass may decrease to levels that would have existed if she had never started hormonal treatment.[23,24] Patients with multiple risk factors in addition to low bone mineral density may benefit from follow-up scans every 2 years.

BONE DENSITY IN CHILDREN

Measuring bone density in children poses several problems. There are some data for normal values in children, but the T score has little meaning, since T scores are calculated for a peak bone mass that occurs between the ages of 20 to 30 years. Z scores may be helpful in these patients. However, children have different rates of growth. The reporting physician should report the first bone mineral density as baseline, provide information regarding the Z score if it is available, and advise the referring physician that the scan should be considered a baseline to follow the patient to ensure that bone mineral density increases.

How long to follow pediatric patients is more difficult to determine. While we have evidence for effectiveness of various treatments for low bone mass in children, few drugs are approved for pediatric use. Each case should be evaluated independently for expected results.

PERIPHERAL DENSITOMETRY: NOT YET

Peripheral densitometry scans are becoming more common. Perhaps most well known is quantitative ultrasonography of the heel, but other studies include peripheral DXA, peripheral quantitative computed tomography, and radiogammetry. Each reflects a different way of assessing fracture risk.[25–27]

However, these studies have no role in the follow-up management of patients already being treated for osteoporosis. Instead, they should be used to determine fracture risk and who should undergo a central measurement to fully determine bone density status. Further, since ultrasonographic measurement may have false-negative test results,[10] risk factors for low bone mass should always be considered in patients who have a normal ultrasound test, in order to determine the need for central measurement.

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Culture, race, and disparities in health care

CULTURAL COMPETENCE in health care isn't about "political correctness." It's about people's health.

In this issue of the *Journal* (see following article in this special issue), Dr. Misra-Hebert[1] defines cultural competence—basically, the ability to communicate effectively with people different from oneself—and why it is important for physicians.

The concept is germane for two reasons. First, despite talk about "united we stand," we remain a country divided by race and culture, and the percentage of "minority" (read nonwhite, non-English-speaking) people is on the rise.

To be a member of a minority is to be at risk

Second and more important, to be a member of a minority in America is to be at risk of a host of adverse outcomes, at least some of which are due to suboptimal care. And at least some of the suboptimal care may be due to poor communication.

MINORITIES INCREASING IN NUMBER

In 1970, all minorities (African American, Hispanic, Asian, and Native American) comprised 12.3% of the US population; now they account for 25%. These demographic changes are predicted to continue. By 2050, one in every two Americans will be African American, Hispanic, Asian American, Pacific Islander, or Native American.

DISPARITIES IN HEALTH

Despite advances in medicine, minority Americans face pervasive disparities in health—measurable differences in disease incidence, morbidity, and mortality—and in the care they receive.

I could cite examples of disparities for many American minorities. Consider these for African Americans:

- Infant mortality is higher in black people than in white people. The disparity has been attributed to differences in birth weight, age of mothers, income, and education.
- Strokes. Black people have a higher incidence of stroke, but are less likely than white people to receive the invasive procedures that are used to diagnose and treat cerebrovascular disease.[2]
- Acute coronary syndromes. African Americans wait longer before seeking care for acute coronary syndromes than do whites. They are also significantly less likely to receive a revascularization procedure after coronary angiography, with an adjusted odds ratio 78% higher for whites than for blacks,[3] raising the suspicion of hospital or physician bias.
- Mental health. African Americans with a diagnosis of schizophrenia are significantly less likely than white patients to report having past or current treatment for depression, manic depression, or anxiety disorder,[4] suggesting that the US mental health system unequally serves the minority population.
- Renal transplantation. Among appropriate candidates for transplantation, blacks are less likely to be referred for evaluation, to be placed on a waiting list, or to receive a transplant.[5] And they wait two to four times longer on the transplant waiting list.

Many feel that the current system for organ allocation is unfair to African Americans in that it is weighted according to HLA (human lymphocyte antigen) matching, which favors white patients, who have more HLA antigen matches with prospective

cadaver donors. Confounding the problem, there are fewer black cadaver and living donors.

Clearly, there needs to be more organ donation within the black community, but also the system by which organs are allocated should seriously be reexamined to eliminate racial disparity in the distribution of organs.

In addition, after transplantation African Americans suffer higher rates of rejection and diminished allograft survival, suggesting that African Americans should have tailored immunosuppressive regimens, reflecting the higher risk for acute rejection.[6]

- Prostate cancer. Black men have a higher incidence of prostate cancer and a higher mortality rate from it than do white men, stage for stage. This underscores the need for both earlier prostate cancer screening in African American men and more research into the epidemiology of this disease.
- Cervical cancer. A recent study of African American women with cervical carcinoma demonstrated that equal care ensures equal survival for African American women compared with their nonminority counterparts.[7] However, racial differences in cervical screening persist. Disconcerting are reports that even with a diagnosis of a high-grade abnormality on a Papanicolaou smear, black women are less likely to receive a workup.[8]

REASONS FOR THE DISPARITIES

Reasons for these disparities are multifactorial and include economics and lack of health insurance for minorities, but undoubtedly also relate to a lack of understanding by health care providers of the importance of cultural competency.

Suffice it to say that ethnic and minority populations demonstrate patterns of disease occurrence, health care utilization, and mortality that differ from the majority population. Social and cultural influences due to historical, political, environmental, hereditary, and economic factors shape these differences.

CORRECTING THE DISPARITIES

The first step to correcting these disparities is to recognize that they exist.

Several national agencies are aware of the crisis that health disparities pose to our national health and have launched initiatives to eliminate them. An example is the Healthy People 2010 Initiative.

The National Institutes of Health (NIH) in 1994 mandated that all biomedical and behavioral research that it funds include plans to recruit and retain minorities as subjects. Further, NIH-funded clinical trials must be designed to measure differences in intervention effects in subpopulations when warranted.

The NIH also recently created the National Center for Minority Health and Health Disparities, with the express purpose of promoting and supporting research in eliminating health disparities.

Training in cultural competency

To break down barriers in communication between health care providers and patients of different cultures, all health care workers need to become sensitive to the traditions, values, and attitudes of all ethnic groups. To this end, cultural competency training should become mandatory for all health care providers.

Health care providers must also be sensitive to the fact that historically an important barrier to health care for minorities has been a distrust and skepticism of white health care providers and researchers. Researchers and health care providers must make a concerted effort to gain knowledge of and respect for communities whose culture, values, and beliefs may differ from their own.

Dr. Misra-Hebert has researched and outlined a variety of methods, mechanisms, and models in which cultural competency may be achieved.[1]

We must begin to 'think outside the box' to overcome barriers to care

Reaching out to minorities

We must begin to "think outside the box" and devise innovative strategies to overcome barriers to health in minority communities. For example:

- We at tertiary care centers should link up with primary care providers in the communities where minorities live and work, to help provide state-of-the art health care to minorities.
- We must encourage corporate America to help solve this problem by providing employees with opportunities for health education and health screening.

• Health promotion strategies must be designed and implemented in a variety of settings, starting with elementary schools, to address the priority health needs of minorities.
• Health care institutions could have a considerable impact on solving this crisis by developing dedicated minority health initiatives to focus their financial and academic resources (research initiatives) on this health disparity crisis.
• Researchers should be encouraged to look into the epidemiology of diseases that disproportionately afflict minorities to gain insight into more effective treatments and prevention.

The Council on Ethical and Judicial Affairs of the American Medical Association has emphasized the need for greater access to necessary health care for black Americans, greater awareness among physicians of existing and potential disparities in treatment, and the continued development of practice parameters, including criteria that would preclude or diminish racial disparities in health care decisions.[9]

More minority health care workers

More African Americans and members of other minorities should be trained and incorporated into health care professions as primary health care providers, specialists, and leaders. This would go a long way toward facilitating the elimination of disparities in care because minority physicians, nurses, and social workers have historically been the health providers treating minority patients in minority communities.

I applaud Dr. Misra-Hebert for bringing the issue of cultural competence to the forefront of discussion.

The first step to correcting disparities is to recognize they exist

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Physician cultural competence: Cross-cultural communication improves care

ABSTRACT

Cross-cultural communication is a skill worth learning. For the busy clinician, using this skill during the patient encounter will enhance the quality of care by improving the doctor-patient relationship, and will perhaps even increase the efficiency of the encounter.

KEY POINTS

When translation is needed, professional interpreters should be used; friends or family may be reluctant to discuss certain issues and may inadvertently distort information.

Several cultural issues may cause problems in cross-cultural encounters: authority, physical contact, communication styles, gender, sexuality, and family.

Physicians should try to understand how the patient understands his or her illness, using skills in interpreting both verbal and nonverbal cues.

The role of family in decision-making in many cultures should be acknowledged when discussing a treatment plan, and specifically in the context of end-of-life issues.

We should be aware of our own culture, values, and belief system, as our own biases may affect our interactions with patients.

Training programs should aim at enhancing the cultural competence of health care providers by teaching and developing cross-cultural communication skills.

YOUR PATIENT'S CULTURE makes a difference in his or her care—and so does your own. As the demographics of this country change, our ability to provide optimal care will increasingly rely on our skills in communicating with patients from diverse backgrounds. And to communicate successfully across cultural barriers we need to understand what culture is and to raise our own cultural self-awareness.

Cross-cultural communication is a skill worth learning. For the busy clinician, using this skill during the patient encounter will enhance both the quality of care and the doctor-patient relationship, and perhaps even increase the efficiency of the encounter.

This paper defines and discusses cultural competence, with specific emphasis on the relevance of culture to communication skills and the doctor-patient relationship. The role of culture-specific information, cultural issues at the end of life, and the relevance of racial concordance in the doctor-patient interaction will also be discussed.

US MINORITY POPULATION IS INCREASING

Data from the US census of 2000 show that the percentages of ethnic minorities in the United States are increasing. The white population now accounts for 75.1% of the total population (down from 80.3% in the census of 1990), black or African American 12.3%, Hispanic or Latino 12.%, and American Indian and Alaska native 0.9%.[1]

WHAT IS CULTURE?

Culture has been defined as "beliefs and behaviors that are learned and shared by members of a group,"[2] with the distinction that it "encompasses more than ethnic, racial, national, and gender designations."[3]

The American Medical Association's *Cultural Competence Compendium*[4] defines a culture as "any group of people who share experiences, language, and values that permit them to communicate knowledge not shared by those outside the culture."

This definition applies to us physicians too: "physicians reflect many individual cultural attributes, but they also participate to some extent in the culture of medicine."[4] Thus, when a patient without any medical background enters the examination room, one type of cultural barrier is already present. The increasing use of complementary medical therapies makes those of us in the "culture of medicine" question our own attitudes toward those nontraditional treatments that our patients may find extremely beneficial.

CULTURE AFFECTS HEALTH CARE

A culture gap exists between doctors and lay people

Cultural differences may have many effects on care. Cultural differences between the physician and patient may create communication barriers so significant that our patients leave the office not knowing what we are telling them.

Recent publications on disparities in health care[5,6] raise thought-provoking questions as to why such disparities may exist and to what extent cultural bias, on the part of both the physician and the patient, plays a role. For example, why are there substantial racial differences in access to renal transplantation?[6] Or why is the rate of surgical treatment lower among blacks with early-stage, non–small-cell lung cancer as compared with white patients?[5]

WHAT IS A CULTURALLY COMPETENT PHYSICIAN?

The American Medical Association[3] defines culturally competent physicians as those who can provide patient-centered care by adjusting their attitudes and behaviors to the needs and desires of different patients and account for the impact of emotional, cultural, social, and psychological issues on the main biomedical ailment.

Medical schools recognize the need for skills in cultural competence. In the 1999–2000 academic year, 87% of medical schools included content on cultural competence, and 67% included information regarding cultural practices related to death and dying as part of a required course or clerkship.[7]

Federal initiatives such as the Healthy People 2010 plan[8] and the Culturally and Linguistically Appropriate Services (CLAS) Standards Project,[9] created by the Office of Minority Health Center for Linguistic and Cultural Competence in Health Care, have identified cultural competence in health care as an issue of national significance. The former has the goal of eliminating health care disparities in six different areas by the year 2010, while the latter proposes 14 national standards to facilitate culturally competent care in health care organizations.

RAISING SELF-AWARENESS

Gardenswartz and Rowe,[10] in their book *Managing Diversity in Health Care*, define six "realities of cultural programming":

- Culture is not overt, and "cultural rules are not discussed unless a rule is broken." Even more importantly, it may not be obvious just by looking at someone what his or her "culture" may be.
- We are all essentially ethnocentric, feeling that our own culture is best.
- We observe, interpret, then act; we often misinterpret the actions of others by not understanding their cultural norms.
- We may not know when we are offending others.
- Awareness and knowledge increase our choices; by becoming more aware of our differences and possible barriers in relating to people of diverse backgrounds, we will have greater opportunity for successful interactions.
- Understanding one's own "software" is a first step; raising self-awareness regarding our own value systems and potential for bias is a crucial step in becoming a culturally competent health care provider.[10]

Thoughtful reflection upon these concepts is helpful in creating a framework for increasing one's own cultural competence.

CULTURE AND THE DOCTOR-PATIENT RELATIONSHIP

Effective communication is essential in establishing a diagnosis and treatment plan. Cultural competence as it relates specifically to the medical interview refers to the skills required for a health care provider to conduct an effective interview and to create an acceptable plan of care when working with patients from different cultural backgrounds.

Carrillo et al[11] identified several cultural issues that may cause problems in cross-cultural encounters: authority, physical contact, communication styles, gender, sexuality, and family.

A THREE-FUNCTION MODEL

Cole and Bird[12] created a "three-function model" of the medical interview:

- Function 1: building the relationship
- Function 2: assessing the patient's problems
- Function 3: managing the patient's problems.

This model is extremely valuable in teaching about doctor-patient communication and can be applied in the setting of cross-cultural communication. Communication across cultural barriers may present specific problems at each stage of the interview.

The following discusses specific aspects of the doctor-patient encounter that may be affected by cross-cultural barriers, following the general order of the three-function model.

BUILDING THE RELATIONSHIP: VERBAL AND NONVERBAL COMMUNICATION

At the beginning of the interaction, when the focus is on building rapport with the patient, issues of both verbal and nonverbal communication need to be considered.

Verbal communication

If a language barrier exists, a trained interpreter is needed.

Although it is often more convenient to ask an accompanying family member or friend to interpret during the encounter, one should use a professional interpreter whenever possible, as family members or friends are frequently not comfortable with relaying the patient's personal information or may inadvertently reflect the patient's story in their own context. I recall a situation when a patient's friend was serving as an interpreter and was describing the patient's complaint of headache, but then added in a comment, without input from the patient, that she thought the patient was really suffering from depression.

Other key points to remember when interviewing a patient in the presence of an interpreter:

- Speak to the patient directly, using a normal tone of voice
- Avoid slang or technical terms
- Ask one question at a time.

Subtleties of nonverbal communication

Understanding the subtleties of nonverbal communication is also crucial when providing care across cultural barriers.

Gestures are not universal, and their use may cause unnecessary miscommunication.

Personal space. Different cultures have different concepts about personal space. In Western culture, which includes the mainstream United States, personal space (the space between individuals during a one-on-one private conversation) is considered to be 18 inches to 4 feet, whereas social space (the space between individuals in a social setting) is 4 to 12 feet.[13] In many cultures, such as Latin American or Middle Eastern, personal space is much closer, which may lead the physician to misinterpret a patient's behavior or emotional state when interacting with patients from these backgrounds.

Eye contact can also be misinterpreted. In the mainstream US culture, we often assume that a person who does not maintain eye contact is not being truthful or may be suffering from depression. In many other cultures, direct or prolonged eye contact with the physician may be thought to signify disrespect on the part of the patient; thus, eye contact may be avoided.

Due to cultural differences, some patients leave the office not knowing what we are telling them

HOW DOES THE PATIENT UNDERSTAND DISEASE AND ILLNESS?

In the second part of the encounter, when gathering data and assessing the patient's problems, the "disease-illness concept"

becomes significant.

Kleinman et al[14,15] describe diseases as "abnormalities in the structure and function of body organs and systems," while illnesses are "experiences of disvalued changes in states of being and in social function: the human experience of sickness." They further comment that "illness behavior is a normative experience governed by cultural rules."[14]

The way a patient experiences his or her biomedical ailment is influenced by specific cultural norms, or personal health belief systems. Certain diseases may be "acceptable," such as intermittent abdominal discomfort diagnosed as irritable bowel syndrome, and others are not, such as the same symptom attributed to an underlying anxiety disorder.

ELICIT THE PATIENT'S EXPLANATORY MODEL

A culturally competent health care provider should not only focus on the diagnosis of disease, but also attempt to understand the illness behavior, which may be based on cultural beliefs as well. To this end, the physician should elicit the patient's *explanatory model of illness*,[14,15] which is a basic tenet of doctor-patient communication, but is even more crucial with cross-cultural communication.

Confirm the patient's understanding by asking him or her to repeat your instructions

The patient's explanatory model is his or her own interpretation of what is wrong, why it is wrong, and what could (or should) be done about it. Kleinman et al[14] refer to the "cultural construction of clinical reality." For example, if a patient believes in the hot/cold theory of illness, common in many nonmainstream US cultures, with the belief that ailments are caused by "extreme shifts from hot to cold" and vice versa,[16] their belief in prescription medications as a cure to the problem may be limited and thus not accepted. Instead, the patient may place more value on a folk remedy that "corrects" the hot/cold balance.

Specific questions suggested by Kleinman et al[14] that may be helpful when trying to elicit the explanatory model are:

- What do you think has caused your problem?
- Why do you think it started when it did?
- What do you think your sickness does to you? How does it work?
- How severe is your sickness? Will it have a short or long course?
- What kind of treatment do you think you should receive?
- What are the most important results you hope to receive from this treatment?
- What are the chief problems your sickness has caused for you?
- What do you fear most about your sickness?

MANAGING THE PATIENT'S PROBLEMS

In the final part of the encounter, with the focus on managing the patient's problems, the art of negotiation is crucial in cross-cultural communication. Some tips:

- Acknowledge and respect the role of the family in medical decision-making when discussing diagnosis and treatment options.
- Inquire about the use of alternative or complementary treatments, many of which are culture-specific (ie, Chinese herbal remedies, Eastern Indian ayurvedic medicine).
- Provide patient education materials, with consideration of language barriers and illiteracy.
- Confirm the patient's understanding by asking him or her to repeat your instructions.

Finally, as stated by Platt and Gordon in their *Field Guide to the Difficult Patient Interview*,[17] "Tell the patient what he/she wants to know before explaining what he/she needs to know." For example, if you find during the course of the interview that the patient's greatest fear is that his or her constellation of symptoms represents an underlying malignancy, make sure to address how likely or unlikely you feel this possibility may be, in addition to discussing your other diagnostic considerations.

CULTURE-SPECIFIC INFORMATION: IS IT NEEDED?

Is cultural competence merely excellent doctor-patient communication, or is culture-specific or ethnicity-specific information useful?

The ideal scenario would be of a combination of communication skills on a background of familiarity with ethnicity-specific information when dealing with cross-cultural encounters. However, even while attempting to learn about specific cultural norms, the dangers of stereotyping need to be acknowledged, realiz-

ing that factors such as socioeconomic status, educational level, occupation, and family values and belief systems may have as important a role in determining culture as does ethnicity.

First recognize your own culture

As stated above, an important step towards increasing cultural competence in communicating with patients is to first become aware of one's own cultural belief system and preferences. Consider the following "key cultural values" in the mainstream US culture, as identified by Gardenswartz and Rowe,[10] which may be quite different in other cultures and thus may present barriers to cross-cultural communication:

- Status is usually based on accomplishments in the mainstream US culture; in other cultures the role in the family or gender may be the more important determinants
- Privacy may be given greater emphasis in other cultures, with issues of modesty and shame being more prominent
- Fatalism, or a sense of an external locus of control, is more common in other cultures, while the mainstream US culture focuses on a feeling of an internal locus of control, with the attitude of "you control your own destiny"
- A greater emphasis on the individual vs the group is seen in the mainstream US culture
- Telling the patient both good and bad news is expected in the US culture, while withholding bad news from patients is common in other cultures.

These concepts are most relevant regarding cultural components of end-of-life issues, as discussed below.

END-OF-LIFE ISSUES

Issues of cross-cultural communication become especially important when dealing with end-of-life issues.

For example, end-of-life decision-making may be very difficult for a patient who believes in an external locus of control and thus feels that he or she may not be powerful enough to make decisions about issues such as withholding resuscitation efforts, should the situation arise.

For another example, in many cultures the decision-making power would be given to the family member of highest status, which may be the eldest male in the family.

Kagawa-Singer and Blackhall[18] identified six issues related to end-of-life care that may be influenced by cultural beliefs:

- Responses to inequities in care
- Communication and language barriers
- Religion and spirituality
- Truth-telling
- Family involvement in decision-making
- Hospice care.

Concern about historical occurrences of inequities in health care may create an increased desire for futile care at the end of life, and possibly a lack of interest in hospice services,[18] because of an underlying concern that not all the best options are being offered.

Religion and spirituality should be acknowledged and respected, and the practice of withholding terminal diagnoses should be recognized, realizing that an acceptable agreement needs to be reached between the physician, the patient, and the patient's family regarding this issue. People in many cultures believe that informing the patient of a terminal diagnosis may hasten death. Suggested questions to ask a patient in this situation may include "How much would you like to know about your illness?" or "Would you prefer I discuss your diagnosis with you, or with your family?"

Tell patients what they *want* to know before what they *need* to know

Different forms of grief expression also need to be understood; for example, loud wailing at the death of a loved one may be common in some Middle Eastern cultures.[2]

Finally, beliefs regarding postmortem testing may be significantly shaped by cultural norms.[2] For example, both orthodox Jewish and Muslim family members may not be willing to consent to an autopsy.[2]

RACIAL CONCORDANCE

Is the doctor-patient relationship better if the doctor is the same race as the patient?

Saha et al[19] analyzed data from the 1994 Commonwealth Fund's Minority Health Survey of 2,201 white, black, and Hispanic respondents who reported seeing a physician regularly. Compared with black respondents with nonblack physicians, black respondents with black physicians were more likely to rate their physicians as excellent overall, and as treating them with respect. They were also more likely to state

that they received preventive care and all the care they needed. Hispanic patients with Hispanic physicians in this study were more likely to be satisfied with health care overall, but not necessarily with their physicians.

It is difficult to make conclusions about whether racial concordance itself significantly contributes to the quality of the doctor-patient relationship, but increasing the level of cultural competence of the health care provider to the level where the patient feels that his or her values and preferences are understood and treated with respect would likely have a great impact on cross-cultural communication, even in racially discordant doctor-patient interactions.

In this regard, the concept of the "cultural blind spot syndrome" also deserves mention.[20] This refers to the sometimes erroneous assumption that no barriers exist if the patient seems to be similar to the physician.[13] A racially concordant physician-patient relationship may not be successful at all if there is discordance in other determinants of culture, such as education level, socioeconomic status, or degree of assimilation into the mainstream culture.

First become aware of your own cultural belief system and preferences

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Q: What are the key issues women face when ending hormone therapy?

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A: The Women's Health Initiative[1] has thrown physicians and patients into a quandary about hormone therapy (HT).

On one hand, this landmark study laid to rest the question of whether continuous combined estrogen-progestin therapy prevents cardiovascular disease (it doesn't) and delineated the potential risks. On the other hand, it provided no answers to some key issues women face if they choose to stop HT.

The following comments mostly apply to continuous combined estrogen-progestin therapy, since it was this arm of the Women's Health Initiative that was terminated early due to increased rates of coronary artery disease, breast cancer, stroke, and pulmonary embolism. The estrogen-only arm, in women without a uterus, is continuing without evidence of excess risk at this time.

WHY IS THE PATIENT ON HT?

A logical approach is to review why the patient is on HT and to consider alternatives.

If she has no indication for HT

Surprisingly many women have been on estrogen-progestin therapy for long periods of time, but are uncertain as to why they are on it. In this situation, it is logical to stop the HT.

If she has vasomotor symptoms

Most women on HT started because of vasomotor symptoms, and more than 75% stop within 24 months.[2] Those who stop and then start again invariably do so because of a recurrence of severe symptoms.

These patients who wish to stop HT can be advised to try alternatives such as clonidine, selective serotonin reuptake inhibitors, or beta-blockers, but none of these therapies provide the level of effect of HT, and most carry their own set of potential side effects.

Many women try over-the-counter herbal products. These are essentially no more effective than placebo, which can actually be of short-term benefit in up to 40% of women.

In practice, women with severe recurrent symptoms are the most difficult to advise. The strategy should be to carefully explain the known level of risk and to give the patient the option of restarting on a low-dose regimen under continuous scrutiny.

Review why the patient is on HT, and consider alternatives

If she is on HT to prevent osteoporosis

If the patient is on HT to prevent osteoporosis, alternatives are available, including the selective estrogen receptor modulator raloxifene and the bisphosphonates alendronate and risedronate.

Remember that women who stop HT are likely to experience the rapid bone loss that is typical of postmenopause.[3] It is therefore wise to obtain dual-energy x-ray absorptiometry (DEXA) scans of the hip and spine when stopping HT and to repeat them at least 1 year later unless alternative bone-sparing therapy is started immediately.

The real dilemma is how to advise a woman who entered menopause early (ie, at age 40 to 50 years) or prematurely (ie, younger than age 40). In this situation I am less confident about ultra-long-term treatment with bisphosphonates and would prefer raloxifene

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or HT, at least until the usual expected age of menopause around age 50.

If she is on HT for quality-of-life issues

The Women's Health Initiative did not address a variety of conditions that estrogen-progestin therapy may or may not improve, such as vaginal atrophy and problems with the skin, teeth, and gums, cognitive function, mood, sleep, sexuality, and quality of life (appropriately measured by a validated instrument such as the Utian Quality of Life Scale).[4]

Many women experience subjective negative feelings when they stop HT and state they "feel better" on hormones. These responses are difficult to quantify, but women often weigh them heavily in favor of continuing HT when they consider risk and benefit issues.

Unfortunately, there is no one alternative therapy to address each of these issues. Vaginal atrophy is easily corrected by use of low-dose vaginal estrogen cream or vaginal tablets and rings. This certainly benefits women suffering discomfort with intercourse, but will not enhance libido. While androgens are sometimes considered, there are few data on long-term safety or efficacy. Cognitive function and mood are best approached through counselling or selective use of psychopharmacotherapeutic agents. Overall quality of life is best enhanced by counselling, exercise, healthy diet, and lifestyle changes.

Order a DEXA scan when a patient stops HT, and repeat 1 year later

HT to prevent cardiovascular disease

Postmenopausal women should clearly stop taking estrogen-progestin therapy if they have no symptoms and are taking it only for cardiovascular protection. It is essential, however, to define their cardiovascular risk factors and treat these accordingly, for example with antihypertensive or lipid-lowering drugs.

IMMEDIATE BENEFIT VS FUTURE RISK

Women thus face the dilemma of balancing the mostly immediate benefits of HT against its future risks.

Breast cancer risk, the principal concern, increases with duration of HT.[5] In contrast, the risks of cardiovascular disease, stroke, and venous thromboembolism appear to reach a plateau in the first 1 to 2 years of HT but go no higher with long-term use.[1,6] Indeed, alternate routes of administration or lower doses of HT may not demonstrate any early increase in risk of cardic events or stroke.[7] Because coronary heart disease, stroke, venous thromboembolism, and osteoporotic fractures are less common in younger women, the absolute risks and benefits will be lower in the short term in younger women.[8]

The challenge to the health care provider is to identify women at risk of complications before they start HT, so that these women can be advised of appropriate alternatives to HT.

TAPERING VS COLD TURKEY

Women who stop HT need practical advice on how to stop taking the medication, but there is no guidance from the existing medical literature. One can either stop abruptly ("cold turkey") or taper off therapy by either skipping progressively more days between doses or lowering doses every 4 to 6 weeks. A past history of severe symptoms may favor tapering.

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REVIEW

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Vertebral compression fractures: Manage aggressively to prevent sequelae

ABSTRACT

New drugs to treat osteoporosis, along with two new minimally invasive surgical procedures, are important options for preventing vertebral compression fractures and treating severe back pain and disability. However, the mainstay treatments remain cautious use of analgesics, limited bed rest, and physical rehabilitation.

KEY POINTS

Although most vertebral compression fractures are asymptomatic, they are often painful and nearly always associated with a significant increase in mortality and functional and psychological impairment.

Magnetic resonance imaging can help determine whether a compression fracture is old or recent, and whether it is due to osteoporosis or malignancy.

Bracing is commonly used in the nonsurgical management of acute fractures. Spinal orthoses help control pain and promote healing by stabilizing the spine.

Two new minimally invasive surgical procedures may provide immediate pain relief and improve fracture-related spinal deformity. Further study is needed to define the indications for these procedures and to determine their long-term safety.

This paper discusses therapies that are not approved by the US Food and Drug Administration for the use under discussion.

RECENT ADVANCES IN PREVENTING and managing acute vertebral compression fractures offer clinicians an opportunity to reduce its devastating impact, even in the face of an expanding aging population.

Although management generally consists of analgesics, bracing, physical therapy, and treatment of the underlying cause of the fracture, two new minimally invasive surgical procedures may provide immediate pain relief and improve fracture-related spinal deformity.

CLINICAL PRESENTATION

Vertebral compression fractures are common and serious. Each year, about 700,000 occur in the United States, with a prevalence of up to 25% in women over the age of 50.[1–4] Although only about a third are acutely symptomatic, nearly all are associated with a significant increase in mortality and functional and psychological impairment.[5]

A compression fracture is radiographically defined as a reduction in vertebral body height of more than 15%, typically seen on standing anteroposterior and lateral radiographs of the thoracolumbar spine (FIGURE 1).[2] The most common sites are in the thoracolumbar region, specifically T8, T12, L1, and the lower lumbar region (frequently L4).[6]

In most cases, patients do not recall any significant antecedent trauma, although they sometimes describe activities that increase the load on the vertebral column, such as raising a window, carrying a small child or a bag of groceries, or lifting in the forward flexed posture. High-energy trauma is more typically identified in younger patients, particularly men, with normal bone density.

Only about one third of vertebral compres-

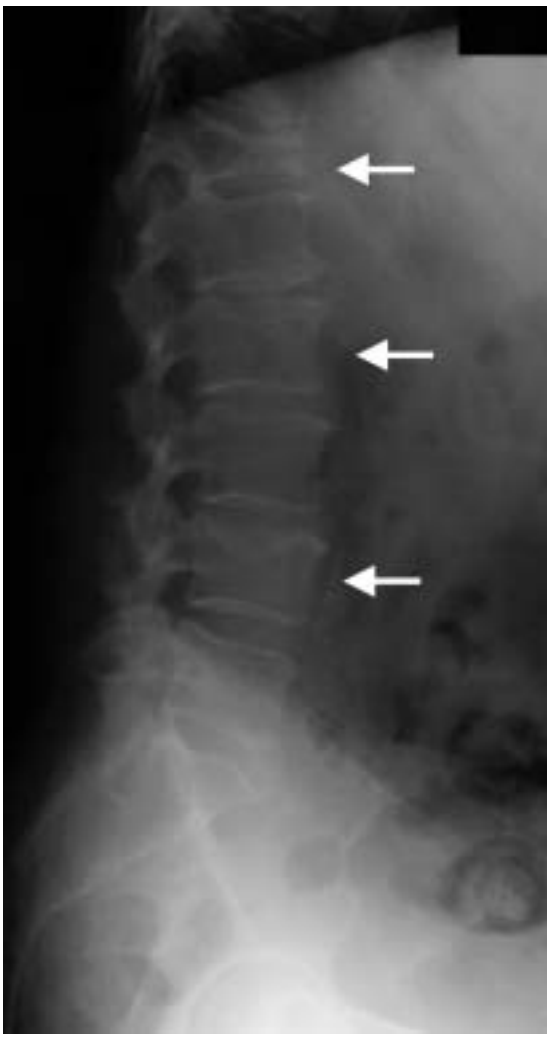


FIGURE 1. Plain lateral radiograph of the lumbar spine depicts vertebral compression fractures at T12, L2, and L4 (arrows).

In an acute fracture, the patient is most comfortable when motionless

sion fractures are symptomatic. If an acute fracture causes pain, it is usually felt deeply at the fracture site. Rarely, it may produce cord compression, presenting clinically with myelopathic features or with true radicular signs and symptoms.[7–10]

Since the pain of an acute fracture is aggravated by any movement, the patient is most comfortable when motionless. Physical examination may reveal tenderness to deep palpation or percussion over the affected vertebra, and paraspinal muscle spasm.[2,6,11]

The acute pain typically resolves after 4 to 12 weeks of limited activity. If the pain persists or gets worse after a period of relative improvement, this suggests additional compression or collapse.

In most patients, the acute incapacitating fracture pain subsides, but mechanical pain persists, due to altered spinal biomechanics and myofascial fatigue.[2,12,13]

CAUSES OF VERTEBRAL COMPRESSION FRACTURES

Trauma is the most common cause in patients under age 50, and because of this, fractures are actually more prevalent in men than in women up until age 60.

Postmenopausal osteoporosis is the most common cause after age 60.

Malignancy. Advancing age also increases the risk of pathologic fracture due to malignancy, and multiple myeloma, avascular necrosis, lymphoma, or other metastatic malignancies or infection must always be considered.[14,15] Vertebral compression fractures occur in 55% to 70% of patients with multiple myeloma and is the initial clinical sign in 34% to 64% of these patients.[16,17]

Secondary osteoporosis. Some patients are found to have bone density measurements well below age-expected values. In these cases, a secondary cause of bone loss should be considered, such as exogenous glucocorticosteroid therapy, excessive alcohol intake, hypogonadism, and endocrinopathies such as hyperthyroidism, Cushing disease, hyperparathyroidism, and diabetes mellitus.[18]

CONSEQUENCES OF VERTEBRAL COMPRESSION FRACTURES

Whether compression fractures are acutely symptomatic or not, their long-term sequelae are significant. They can be categorized as biomechanical, functional, or psychosocial, although they are interdependent. Ultimately, compression fracture is associated with a significant decrease in survival.

Biomechanical consequences

Persistent back pain is due to mechanical factors and to muscle fatigue due to progressive spinal kyphosis.

Abdominal symptoms. Progressive kyphosis, particularly with multiple compression fractures, shortens the thoracic spine and compresses the abdominal contents, which can lead to gastrointestinal symptoms such as

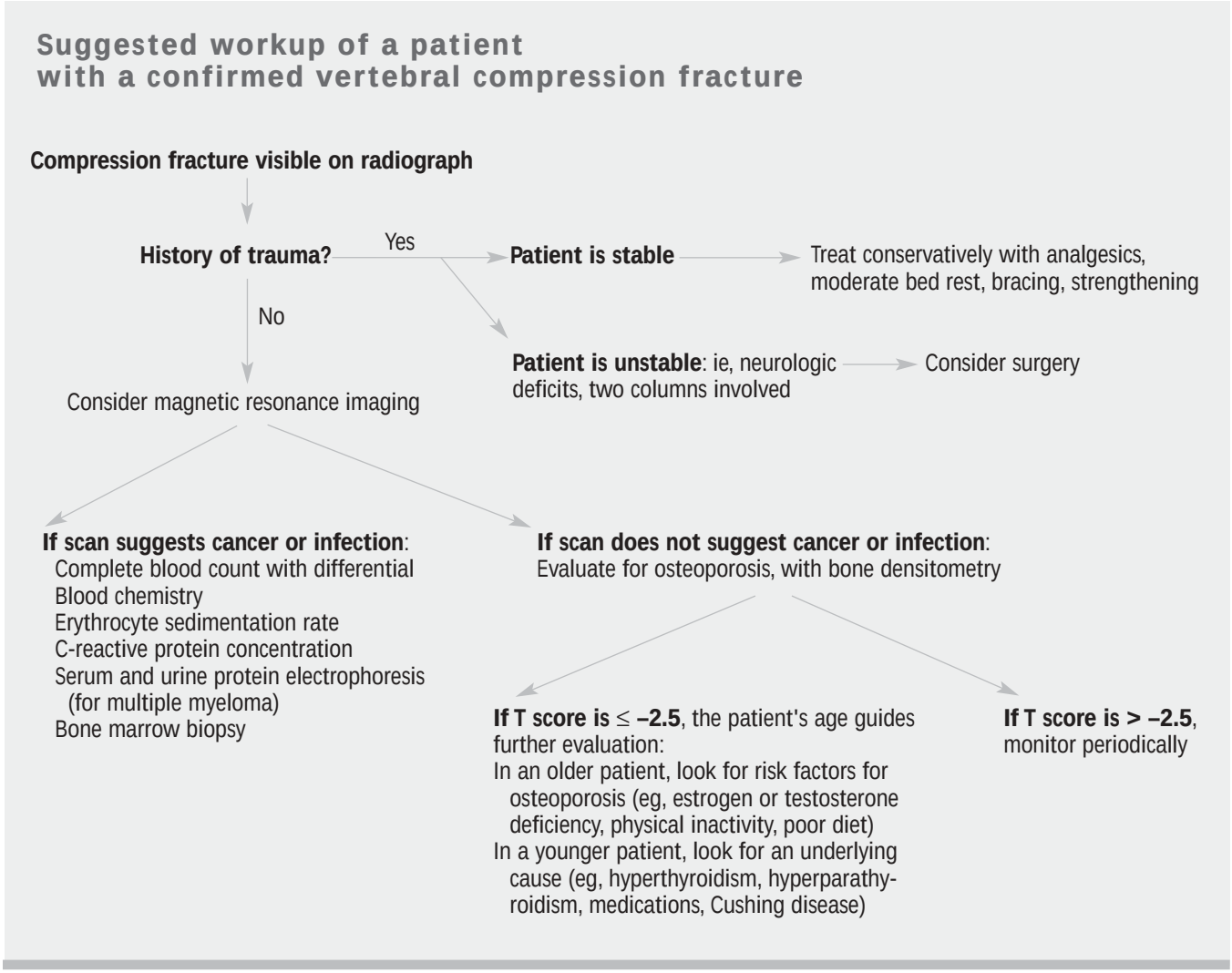


FIGURE 2. Suggested approach to diagnosis in patients with a new vertebral compression fracture

early satiety and abdominal bloating. In some patients with significant thoracolumbar shortening, the lower ribs rest on the pelvic brim, producing lower abdominal discomfort. These abdominal symptoms may result in anorexia and subsequent weight loss, a particular concern in elderly patients who are already frail.[2]

Pulmonary compromise due to vertebral compression fracture and kyphosis typically consists of restrictive lung disease with reduced vital capacity. On the average, each fracture reduces vital capacity by 9%.[19,20]

Increased fracture risk. As kyphosis develops, more force is transmitted to adjacent, already osteoporotic vertebrae, increasing the risk of additional fractures.[21] The presence of one or more vertebral compression fractures increases the risk of an additional fracture fivefold during the following year.[2,22]

Functional consequences

Patients with compression fractures have lower levels of functional performance compared with controls,[2,23] need more assistance, experience more pain with activity, and have more difficulty with activities of daily living. A recent study[24,25] found that these patients had lower scores on a health-related quality of life index with respect to physical function, emotional status, clinical symptoms, and overall functional performance. A fracture in the lumbar spine was most predictive of poor

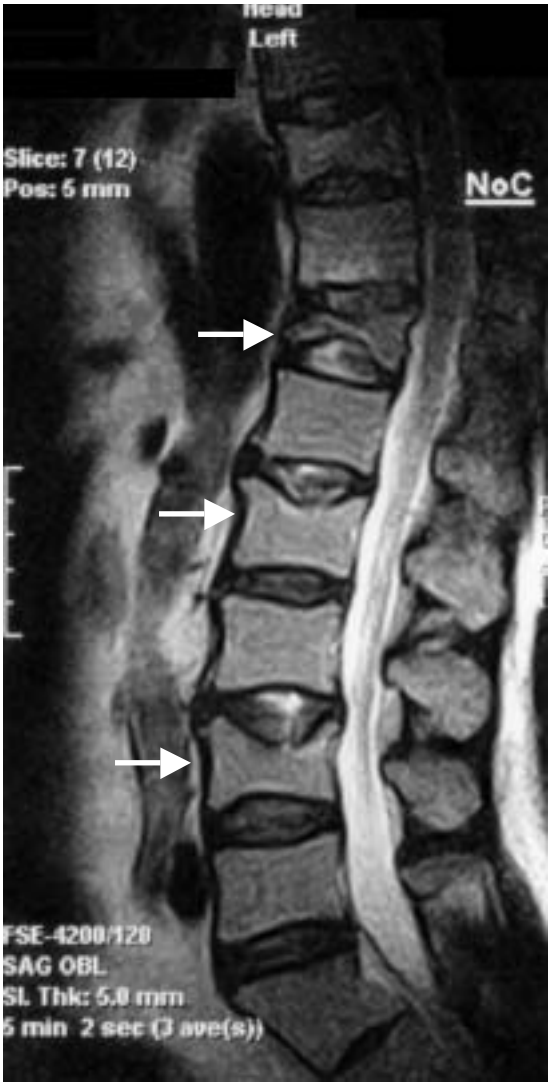


FIGURE 3. T2-weighted magnetic resonance image of the lumbar spine depicts compression fractures at T12, L2, and L4 (arrows).

Up to 40% of patients with compression fractures develop depression

functional status.

Furthermore, many patients with multiple vertebral compression fractures become progressively inactive and sedentary, for a number of reasons, such as relief of mechanical pain in the supine position, fear of falling and additional fractures, and restrictive pulmonary disease. Inactivity, in turn, promotes deconditioning, progressive deterioration in the ability to perform activities of daily living, and further bone loss.[26]

Pain and inactivity may disturb sleep patterns, promoting development of fibromyalgia-like myofascial pain.

Psychological consequences

Depression develops in up to 40% of patients with compression fractures, due to chronic pain, changes in body image, deterioration in the ability to perform self-care, and prolonged bed rest. Patients more likely to develop depression have more than one fracture and tend to be older and more socially isolated.[24]

Decreased survival

In a recent prospective cohort study of almost 10,000 women age 65 or older,[24,27] those with a compression fracture had a 23% higher rate of age-adjusted mortality. The rate was strikingly higher in women who had five or more of these fractures.

Vertebral compression fracture was related to an increased risk of pulmonary death, particularly in the presence of severe kyphosis. For unclear reasons, it was also associated with an increased risk of cancer death.[27]

IS TRAUMA THE CAUSE?

In general, once a vertebral compression fracture is observed on a plain film, the next step depends on whether the fracture is related to trauma (FIGURE 2). If trauma is the cause and the patient is stable, conservative management with analgesics, supportive care, and monitoring is appropriate. If the patient is not stable (eg, has a neurologic deficit on clinical examination or radiologic evidence of spinal fracture involving two columns), then surgery should be considered.

If no history of trauma is evident, magnetic resonance imaging (MRI) may identify malignancy or infection as the cause, in which case blood work, cultures, and bone biopsy may be in order. If MRI is normal, a workup for osteoporosis is recommended, with a focus on secondary osteoporosis in younger patients and primary osteoporosis in older patients.

IS THE FRACTURE OLD OR RECENT?

Although compression fractures are typically discovered on plain anteroposterior and lateral radiographs, these films do not provide information about the age of the fracture.

MRI (FIGURE 3) can help determine whether the fracture is old or recent, and whether it is due to osteoporosis or to malignancy, both of which may affect decision-making regarding treatment.

When evaluating the age of a compression fracture, T2 sagittal short inversion-time inversion-recovery (STIR) sequence MRI may be the most sensitive for assessing water content.[28] Acute fracture is identified by "bone edema."

Bone scanning, especially single-photon emission computed tomography (SPECT) limited to the spine, may also help determine the acuity of the fracture.[29] In a retrospective study, Maynard et al[30] found that increased activity on a bone scan strongly predicted a positive clinical response (ie, relief of pain) to percutaneous vertebroplasty in osteoporotic vertebral compression fractures.[30]

OSTEOPOROSIS OR MALIGNANCY?

MRI also helps identify pathologic causes of vertebral compression fractures, such as malignancy.[17,31,32]

Baur et al[31] showed that in diffusion-weighted MRI scans, benign compression fractures have a negative bone marrow contrast ratio, whereas pathologic fractures have a positive ratio.

In another study, Rupp et al[32] concluded that signal changes on T1-weighted and T2-weighted MRI scans are not sufficiently specific to distinguish osteopenia from collapse due to metastasis, whereas pedicle involvement or an accompanying soft tissue mass was specific for a tumor-related vertebral fracture or lesion.[32]

In patients with multiple myeloma, the MRI scan may appear benign (band-like areas of low signal intensity underlying the fractured endplates), as in osteoporotic compression fractures.[33] Therefore, an apparently normal MRI scan does not rule out multiple myeloma.[16,33]

MANAGEMENT PRINCIPLES

Management may require addressing one or all of the following:

- Acute fracture pain
- Chronic mechanical sequelae
- Prevention of additional compression fractures, including assessing and treating underlying osteoporosis.[34]

MANAGEMENT OF ACUTE FRACTURE PAIN

If the patient is neurologically stable, medical treatment of an acute fracture should emphasize pain relief, with limited bed rest, appropriate analgesics, bracing, and physical strengthening.[18,34]

Avoid prolonged bed rest

The hazards of prolonged bed rest in the elderly include deconditioning, accelerated bone loss, deep venous thrombosis, pneumonia, decubitus ulcers, disorientation, and depression.

Analgesics

Analgesics, in addition to relieving pain, may permit earlier ambulation and avoidance of the complications of prolonged bed rest.[2,24,26]

Calcitonin, given subcutaneously, intranasally, or rectally, has an analgesic effect in compression fractures due to osteoporosis[35–40] and in patients with metastatic bone pain.[41–45]

The analgesic activity of calcitonin may be related to increased levels of plasma endorphins.[44,46] Recently, Yoshimura[47] and Lyritis and Trovas[48] demonstrated that calcitonin may exert its action via serotonergic receptors in the spinal cord.

In osteoporotic vertebral compression fractures, calcitonin also inhibits osteoclast function, thereby preventing bone resorption.[49,50]

Opioid analgesics may be necessary in some patients to relieve pain adequately. However, in older, immobilized patients, opioid-associated constipation and cognitive impairment are significant concerns,[18,34] and a prophylactic laxative program should be started at the same time the opioid is prescribed.

In older patients, prescribe a laxative when starting opioids

When prescribing an opioid, caution the spouse or caregiver to observe the patient carefully for cognitive impairment and to provide a protected environment to reduce the risk of falling.

Avoid nonsteroidal anti-inflammatory drugs (NSAIDs). In general, pure analgesics, opioid or non-opioid, are preferable to NSAIDs, particularly in older patients with

vertebral compression fracture. The risk of NSAID-related gastropathy, renal insufficiency, and congestive heart failure is significantly increased in the elderly.[18,51–55]

Bracing

Bracing is commonly used in acute nonsurgical management. Spinal orthoses help control pain and promote healing by stabilizing the spine. By restraining forward flexion, they reduce the load on the anterior column and the vertebral body.

Definitive studies comparing different types of orthoses are lacking, but in general, all spine orthoses, whether made of cloth, metal, or plastic, or whether rigid or flexible, use a three-point pressure system. If possible, the orthosis should be lightweight and easy for the patient to use.

For lower thoracic and lumbar fractures, a Jewett hyperextension orthosis or cruciform anterior spinal hyperextension (CASH) orthosis is typically used.

The optimal duration of bracing is not well studied. Two to 3 months is adequate for most patients. Excessively prolonged bracing may lead to weakening of trunk muscles, skin breakdown, increased segmental motion at the upper and lower end of the orthosis, and diminished pulmonary capacity.[56–58]

Avoid excessive use of braces; 2 – 3 months is enough for most patients

Strengthening program

As the acute fracture pain subsides, a walking program can begin, with gentle strengthening exercises focusing on spinal extensor muscles.[45] In some patients, a home physical therapist can encourage and assist with early ambulation and mobilization.

A carefully supervised rehabilitation program should be started after 3 to 4 months to more aggressively strengthen the spinal extensor and abdominal muscles.[34,59]

VERTEBROPLASTY AND KYPHOPLASTY

Two new, minimally invasive surgical techniques are used to treat vertebral compression fractures: percutaneous vertebroplasty and kyphoplasty.

Percutaneous vertebroplasty

Percutaneous vertebroplasty[60] involves placing a bone marrow biopsy needle into the compressed vertebra via a posterior approach, guided by fluoroscopy or computed tomography. Methylmethacrylate cement is then injected.

The procedure stabilizes the fracture, and it provides nearly immediate pain relief in 90% to 100% of patients. It does not, however, improve the deformity.[61–64]

Complications occur in fewer than 10% of patients and include radiculopathy, infection, and cord compression. Since the cement is injected under relatively high pressure, leakage outside of the vertebrae is relatively common, occurring in 50% to 67% of patients.[61,63,65–67] Leakage of methylmethacrylate cement into the epidural space may cause neurologic deficit. Other complications include cement leakage from a vertebra to the paravertebral muscles (ie, psoas muscle), causing severe pain due to a localized thermal reaction. In addition, leakage of cement into the venous circulation can produce a generalized toxic reaction. If the cement enters the inferior vena cava, pulmonary embolism can develop.[63–65] However, these complications can be minimized by the use of venography prior to the injection of cement and by using a smaller dose of cement.[68]

Kyphoplasty

Kyphoplasty was introduced in 1998 for treatment of compression fracture. This procedure involves percutaneous insertion of a needle with an inflatable bone tamp into the fractured vertebra (FIGURE 4). Inflation of the bone tamp creates a cavity and re-expands the compressed vertebra. The cavity is then filled with a thick methylmethacrylate mixture under low pressure.

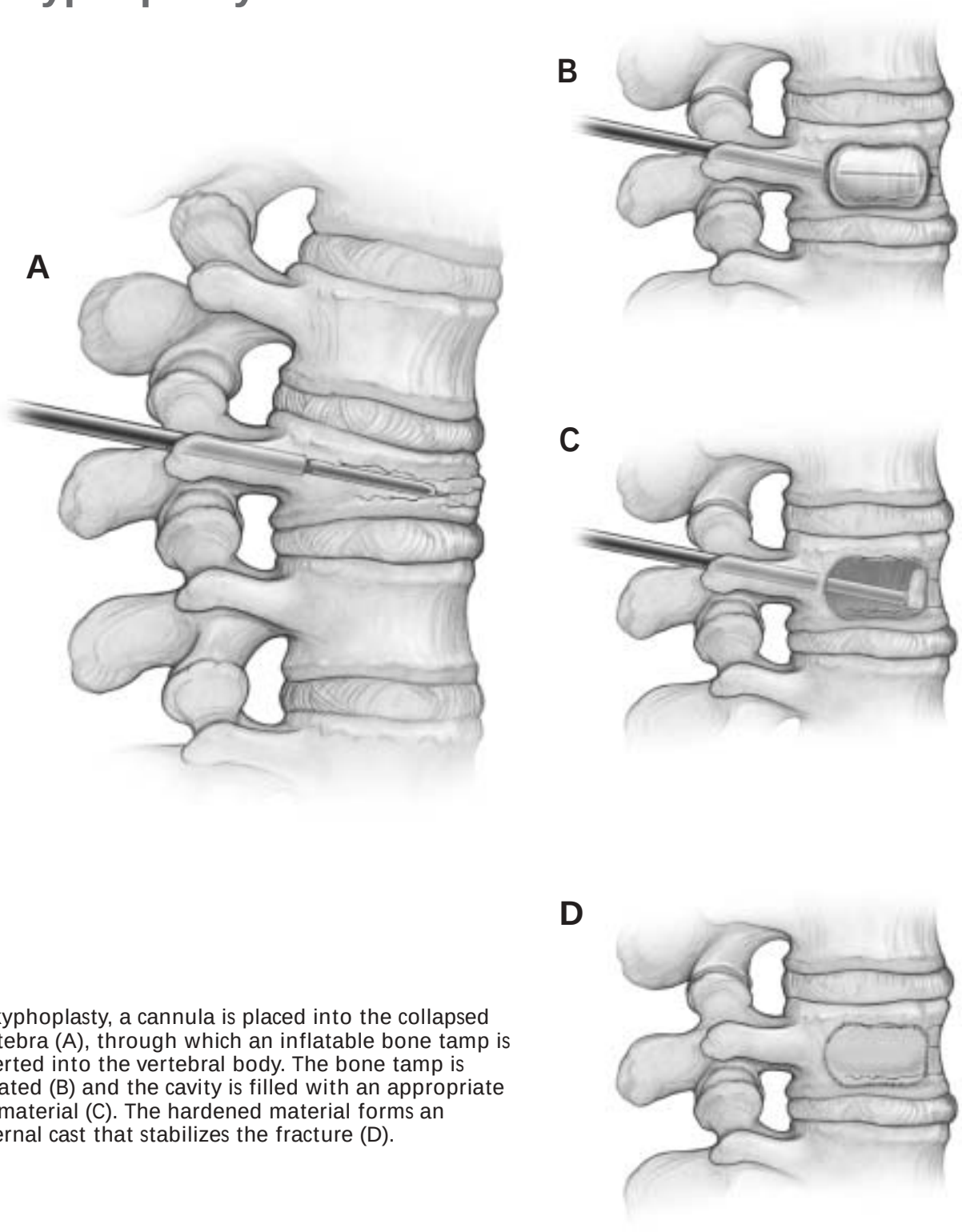
Early experience suggests that more than 90% of patients experience pain relief and prompt functional improvement with this procedure, similar to the results with percutaneous vertebroplasty.[69,70] In addition, kyphoplasty restores vertebral height by almost 50% in approximately 70% of patients. In the other 30% of patients, however, typically those with older fractures, height restoration is not possible.

Complications are uncommon, and cement leakage is less frequent than with vertebroplasty.[61,67,69,70]

Long-term effectiveness

We do not know yet whether kyphoplasty reduces the frequency of serious sequelae of ver-

Kyphoplasty



In kyphoplasty, a cannula is placed into the collapsed vertebra (A), through which an inflatable bone tamp is inserted into the vertebral body. The bone tamp is inflated (B) and the cavity is filled with an appropriate biomaterial (C). The hardened material forms an internal cast that stabilizes the fracture (D).

FIGURE 4

tebral compression fracture, nor do we know the long-term consequences of cement in a vertebral body. In addition, the specific indications for kyphoplasty vs vertebroplasty in patients with acute fracture are yet to be determined.

But this much is certain: both vertebroplasty and kyphoplasty can provide prompt relief of incapacitating pain due to vertebral compression fracture,[71] and kyphoplasty may provide the additional significant benefit of restoring vertebral body height, thus avoiding the progressive kyphosis seen with osteoporotic compression fracture. Clearly, patients with acute compression fracture and incapacitating pain that does not respond to good medical treatment should be considered for one of these procedures. If restoration of vertebral body height is an objective, earlier intervention with kyphoplasty seems more likely to be successful.

LONG-TERM MANAGEMENT

Chronic pain

Some patients experience complete resolution of acute fracture symptoms within 8 to 12 weeks. Others, however, continue to experience mechanical or myofascial back pain, particularly with prolonged standing or walking. Chronic pain is generally more common in patients with multiple fractures, loss of height, and low bone density. In these patients, it is paramount to continue an active extensor muscle strengthening and stretching program, as well as a low-impact aerobic conditioning program such as walking or swimming.

Vertebroplasty and kyphoplasty can relieve severe pain promptly

In addition to analgesics, nonpharmacologic measures such as transcutaneous electrical nerve stimulation, heat or cold applications, or intermittent bracing may provide temporary relief. The psychological aspects of chronic pain and functional loss should be addressed with counseling and, if indicated, antidepressants.[2,23,34]

Fracture prevention

Evaluation and management of osteoporosis is an integral part of the management of vertebral compression fracture. Most patients with an acute osteoporotic fracture should be considered for aggressive osteoporosis therapy.[18,72]

Bone densitometry should be performed in patients presenting with compression fractures and previously unsuspected bone loss.[72–75] The National Osteoporosis Foundation recommends that all women with a spinal fracture and a bone mineral density T score less than – 1.5 should be treated for osteoporosis.[76]

Dietary calcium and vitamin D supplementation should be optimized.

Bisphosphonates (alendronate, risedronate) reduce the incidence of new vertebral fractures by almost 50%,[77–80] and significantly reduce the risk of hip fracture as well.[77] Raloxifene, a selective estrogen receptor modulator, has been shown to reduce new vertebral fractures by about 68% at 1 year and by about 50% at 3 years.[81,82]

Calcitonin has recently been shown to reduce risk of new vertebral fracture by about one third in women with prevalent vertebral fractures.[72]

Teriparatide (Forteo) is a preparation of recombinant parathyroid hormone given by subcutaneous injection. It has been shown to lower the risk of vertebral fractures and increase bone mineral density in postmenopausal women with osteoporosis,[83] and was recently approved by the US Food and Drug Administration. It acts on osteoblasts to stimulate new bone formation. ■

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THE HIP TRIAL

Risedronate prevents hip fractures, but who should get therapy?

ABSTRACT

The Hip Intervention Program (HIP) trial establishes that risedronate (Actonel) prevents hip fracture in elderly women with osteoporosis. However, the drug had no statistically significant effect on hip fracture risk in elderly women in whom bone density status was not known. Patients should be selected for bisphosphonate therapy on the basis of low bone density. A history of vertebral fractures increases the risk for hip fractures.

KEY POINTS

In women age 70 to 79 with low bone density, risedronate had a statistically significant effect in reducing hip fractures. Patients with a history of vertebral fractures are a subset most likely to benefit.

Although women age 80 and older who did not necessarily have low bone density saw no effect of risedronate, it is possible that a properly selected subgroup of older patients with multiple risk factors may benefit from bisphosphonate therapy.

The HIP study did not rigorously evaluate or systematically record risk factors other than bone density. Thus the effect of these factors, singly or in combination, cannot be analyzed.

The contribution of low bone mass to hip fracture risk may actually decline with age as other skeletal and nonskeletal factors, such as the increased risk of falls, become more important.

BISPHOSPHONATES increase bone density and reduce vertebral and nonvertebral fractures, but, until recently, no randomized controlled trial of bisphosphonates has had hip fracture as the primary outcome measured. The Hip Intervention Program (HIP) is the first randomized controlled trial of a bisphosphonate with hip fracture incidence as the primary outcome.

The HIP trial results[1] show that the bisphosphonate risedronate (Actonel) reduced the risk of hip fracture in women age 70 to 79 with osteoporosis; the effect appeared most significant in those women who had a history of vertebral fractures.

Although no effect was found in older women in whom bone density was not measured, the HIP study did not evaluate or record risk factors for hip fractures in a systematic manner.

At the end of this article, I discuss my recommendations for treatment strategies for different patients.

HIP FRACTURE AS A PUBLIC HEALTH ISSUE

Preventing hip fracture is an important public health issue as the American population ages. In 1991, there were 300,000 hip fractures in the United States, a number expected to double by the year 2025.[2]

Aging has a marked effect on risk of falls; yearly risk increases from 1 in 5 in the 60-to-64 age bracket to 1 in 3 in the 80-to-84 bracket.[3] At age 50, a white woman has a 17% lifetime risk of hip fracture.[4]

Up to 50% of hip fracture patients will have permanent functional disability, and hip

TABLE 1

Clinical risk factors for hip fractures in the HIP trial

Difficulty standing from a seated position
Poor tandem gait
Fall-related injury in the previous year
Psychomotor score ≤ 5 on the Clifton modified spiral maze test
Smoking within the past 5 years
Maternal history of hip fracture
Previous hip fracture
Hip axis length ≥ 11.1 cm

fracture raises the risk of death by 12% to 20%.[5,6] In addition, the costs of hip fractures account for approximately 55% of the $17 billion per year spent on osteoporosis.

THE HIP STUDY DESIGN

The HIP study was a randomized controlled trial comparing risedronate with placebo in 9,331 elderly women at high risk of hip fracture.

Hip fracture increases the risk of death by up to 20%

Inclusion criteria

The researchers chose two groups of women at high risk of hip fracture: a relatively younger group and an older group.

The younger group (age 70–79; n = 5,445) was chosen on the basis of confirmed osteoporosis. They had either extremely low bone density (a T score < –4.0), or low bone density (a T score < –3.0) plus at least one additional clinical risk factor for hip fracture (TABLE 1).

The bone density T scores were later recalculated in light of a discrepancy between the densitometer's reference database and the data from the Third National Health Assessment and Nutrition Examination Survey (NHANES III). After recalculation, the T scores in the younger group were between –2.7 and –2.9.

The older group (age 80 and older; n = 3,886) was chosen primarily on the basis of clinical risk factors. These women had to have at least one clinical risk factor (TABLE 1). If no risk factors were present the patient could be enrolled if bone densitometry revealed a T score lower than –4.0, or a T score lower than –3.0 with a hip axis length of 11.1 cm or more (this represented 16% of the 3,886 women).

Treatment

All women took calcium 1,000 mg daily. Vitamin D (up to 500 IU daily) was prescribed if the serum 25-hydroxyvitamin D level at baseline was less than 16 ng/mL.

The trial was designed to have three treatment groups, with patients randomly assigned to receive placebo, risedronate 2.5 mg/day, or risedronate 5.0 mg/day. However, data from the two risedronate groups were pooled in the primary analysis. Previous risedronate trials[7,8] had shown that the 2.5-mg and 5.0-mg doses were equally effective in reducing the frequency of vertebral compression fractures. In addition, pooling increased the study's power because there were relatively few hip fractures in the cohort.

The mean duration of therapy was 2.0 years, and the mean follow-up was 2.3 years. Complete follow-up data were available on only 64% of the patients. Only about half of the women took the study medication for the entire prespecified 3-year study period.

The *New England Journal of Medicine* reviewers requested that the study be analyzed as an intent-to-treat trial, meaning that data from patients who took *any* risedronate or placebo were analyzed as if they had taken the entire course of medication. To comply with the request, the investigators obtained data from about half of the patients who had dropped out or discontinued therapy.

The value of intent-to-treat analysis

Intent-to-treat analysis helps reduce any bias that would occur if the proportion of dropouts were not the same in both treatment groups (for example, if side effects made patients taking the active drug more likely to drop out than patients taking placebo).

Intent-to-treat analysis is also a statistically conservative strategy. Patients who dropped out of the risedronate group were analyzed as part of the treatment group even if they didn't take the drug long enough to produce any effect. This strategy makes the average effect in the treatment group smaller than it would be if everybody in the treatment group had

TABLE 2

The HIP study: Risedronate reduces hip fractures…

	% WITH HIP FRACTURES*		RELATIVE RISK	*P* VALUE
	PLACEBO	RISEDRONATE		
Overall group	3.9	2.8	0.7	.02
Younger group†	3.2	1.9	0.6	.009
With vertebral fractures	5.7	2.3	0.4	.003
Without vertebral fractures	1.6	1.0	0.6	.14
Older group‡	5.1	4.2	0.8	.35

…and all nonvertebral fractures

	% WITH NONVERTEBRAL FRACTURES*		RELATIVE RISK	*P* VALUE
	PLACEBO	RISEDRONATE		
Overall group	11.2	9.4	0.8	.03
T score < –2.5	10.7	8.4	0.8	.03
Younger group† **with vertebral fractures**	16.1	10.3	0.7	.01

*Mean 2.0 years of therapy; risedronate 2.5 mg or 5.0 mg
†Women 70 to 79 years old at baseline with a T score lower than –4.0 or a T score lower than –3.0 with at least one clinical risk factor (TABLE 1)
‡Women 80 years and older at baseline with at least one clinical risk factor (TABLE 1), or a T score lower than –4.0, or a T score lower than –3.0 with a hip axis length ≥ 11.1 cm

ADAPTED FROM MCCLUNG MR, GEUSENS P, MILLER PD, ET AL. EFFECT OF RISEDRONATE ON THE RISK OF HIP FRACTURE IN ELDERLY WOMEN. THE HIP INTERVENTION PROGRAM STUDY GROUP. N ENGL J MED 2001; 344:333–340.

taken the full course of the drug. If this attenuated effect size is statistically significant, the researchers can be confident that the true effect size is also significant.

RESULTS OF THE HIP STUDY

Effect on hip fractures significant, but history of vertebral fractures important

Hip fractures occurred in 232 of the 9,311 women who received at least one dose of study medication: 3.9% of those taking placebo vs 2.8% of those taking risedronate (TABLE 2). There was a statistically significant reduction in the younger patients with osteoporosis, but not in the older, at-risk group.

A post hoc analysis was done in the younger age cohort, based on presence or absence of vertebral fractures. The relative risk of hip fracture in risedronate-treated women with vertebral fractures was 0.4 (P = .003), while in those without vertebral fractures the relative risk was 0.6 (P = .14).

The 2.5-mg and 5-mg treatment groups were pooled because of the lower-than-expected number of hip fractures. A post hoc analysis revealed a relative risk for hip fracture of 0.5 (95% confidence interval 0.3–0.9) for the 2.5-mg dose and 0.7 (0.3–1.1) for the 5-mg dose. Since these confidence intervals overlap there is no statistically significant difference between the two groups.

Effect on all nonvertebral fractures

The primary end point was hip fractures alone, but a secondary analysis of all nonvertebral fractures grouped together showed that risedronate protected against this end point as well (TABLE 2).

CONCLUSIONS FROM HIP: DO NOT TREAT BY AGE ALONE

On the basis of the HIP study, we can conclude that risedronate reduces the frequency

< 1/2 of 80-to-84-year-old women have osteoporosis (hip T score < –2.5)

TABLE 3

Comparing the FIT and HIP trials

	FIT*	HIP (YOUNGER GROUP WITH VERTEBRAL FRACTURES)†
Number of patients	2,027	1,703
Mean age	71 years	74 years
Mean hip T score	–2.1	–2.7 to –2.9
Patients who completed the study	94%	69%
No. of hip fractures	33	47
Hip fractures in the placebo group	2.2%	5.7%
Reduction in hip fractures with therapy	50%	60%
Reduction in nonvertebral fractures	19%	36%‡

*FIT = Fracture Intervention Trials[10]
†HIP = Hip Intervention Program[1]; group with vertebral fractures determined in post hoc analysis
‡16% in the entire cohort (younger and older groups combined)

of hip fracture in elderly women with confirmed osteoporosis, but not in women over age 80 in whom bone density was not measured.

This study suggests that treating women on the basis of their age alone is not an effective therapeutic strategy. It is more effective to target therapy to older women with low bone density.

Combinations of clinical risk factors and low bone density may elevate fracture risk

Comparing HIP's conclusions with other trials

The conclusions from HIP are compatible with those from many of the other trials of interventions for osteoporosis. Nevertheless, direct comparisons should be made cautiously, because the trials differed in design and in study populations.

The Fracture Intervention Trials evaluated the effect of alendronate (Fosamax) in postmenopausal women with low bone mass, with vertebral fractures (FIT 1) or without vertebral fractures (FIT 2).[9,10] Alendronate was associated with a 50% reduction in risk for hip fractures among women with vertebral fracture (mean hip T score of –2.1) and a smaller (19%–27%) reduction in all nonvertebral fractures. FIT 2 did not show a reduction in hip fracture; however, a post hoc analysis of women with T scores lower than –2.5 did show a reduction in hip fractures, and alendronate reduced hip fractures in women with T scores higher than –2.5 who had vertebral fractures.

Although the FIT and HIP trials will inevitably be compared (TABLE 3), any apparent differences or similarities must be viewed with caution because of important differences in the study samples. Nevertheless, both studies suggest a significant reduction in hip fracture risk with bisphosphonates in women with low bone mass and vertebral fractures.

Unfortunately, the HIP study did not rigorously evaluate or systematically record risk factors other than bone density. Thus the effect of single or multiple risk factors on fracture risk and bisphosphonate efficacy cannot be analyzed.

In the Study of Osteoporotic Fractures (SOF),[11] risk factors such as family history of osteoporosis, low body weight, current smoking, previous fracture, and increased risk of falling contributed to the risk of fracture independently of bone density and in an additive fashion. In the SOF cohort, patients in the lowest tertile for bone density with 0, 1, or 2 additional risk factors had a risk of hip fracture of 0.26% per year. However, subjects in the lowest tertile for bone density with 5 or more risk factors had a hip fracture rate of 2.7% per year, a rate of fracture 10 times greater despite similar bone density.

The importance of bone density

Bisphosphonates require low bone mass to exert their antifracture effect. If an increase in fracture risk is caused by increased tendency to fall rather than by decreased bone mass,[12] bisphosphonates are not likely to be effective.

The commonly held notion that all women over the age of 80 are osteoporotic is not true. The Third National Health and Nutrition Examination Survey (NHANES III) found that only 42% of women age 80 to 84 have a T score lower than –2.5 in the femoral neck (TABLE 4).[13]

Although age is a significant risk factor for fractures, since many patients over age 80 do not have osteoporosis, measurement of bone density is necessary to choose subjects who will benefit from bisphosphonate treatment.

TABLE 4

Prevalence of osteoporosis in women: Two studies

AGE, YEARS	PERCENT WITH HIP T SCORE ≤ –2.5	
	NHANES III*	EPIDOS*
80–84	42%	46%
85–89	51%	56%
≥ 90	57%	60%

*NHANES = National Health and Nutrition Examination Survey; EPIDOS = *Epidémiologie de l'ostéoporose* (Epidemiology of Osteoporosis)

DATA FROM LOOKER AC, JOHNSTON CC JR, WAHNER HW, ET AL. PREVALENCE OF LOW FEMORAL BONE DENSITY IN OLDER U.S. WOMEN FROM NHANES III. J BONE MINER RES 1995; 10:796–802; AND SCHOTT AM, CORMIER C, HANS D, ET AL. HOW HIP AND WHOLE-BODY BONE MINERAL DENSITY PREDICT HIP FRACTURE IN ELDERLY WOMEN: THE EPIDOS PROSPECTIVE STUDY. OSTEOPOROS INT 1998; 8: 247–254.

Falls increase in importance in older patients

The contribution of low bone mass to hip fracture risk may actually decline with age as other skeletal and nonskeletal factors become more important. This can be inferred from analysis of the Rotterdam study,[14] which followed a large European cohort for hip fracture and risk factors for fracture. A 58-year-old patient with a femoral neck bone density of 0.5 g/cm^2 has a 1-year risk for hip fracture of 0.5%, but a similar patient at age 90 with the same bone density has a 5% 1-year risk for hip fracture. This 10-fold increase is caused by factors related to aging and not by a decline in bone density.

In a study that demonstrated the declining importance of bone density in older patients, Cooper et al[15] examined Singh lines, which are radiologically evaluated stress lines in the upper femur that are surrogates for bone density. In patients younger than 65 years, the risk of hip fracture in the most osteoporotic subjects (those in the lowest quartile of Singh grade) was 33 times the risk in the least osteoporotic subjects. However, in the over-85 age group, the risk of fracture in the most osteoporotic patients was only five times the risk in the least osteoporotic ones. Thus, in elderly patients, osteoporosis is a relatively less important risk factor for fracture.

Further evidence that skeletal factors are not the sole risk factors comes from a study by Beck et al,[16] which showed that the elastic modulus, a measure of the bending and torsional strength of the femoral neck, does not decline after age 50 in men. Even though bone density decreases, the decrease is mechanically offset by expansion of a bone's subperiosteal diameter.

An increased tendency to fall, and to experience more damaging falls, is a significant cause of the increase in fracture risk. Laboratory tests show that falls can generate a force 10 times that needed to fracture a femur.[17] An 80-year-old is more likely to fall to the side on the greater trochanter and transmit all the force to the hip, and is less likely to cushion the fall with his or her arm.

Increased hip fracture risk with age may be due to more falls, as well as lower bone density

The implication is that bisphosphonates can reduce the risk for fracture when the primary reason for fracture is low bone mass, but not when the reason is falling per se.

WHEN ARE BISPHOSPHONATES COST-EFFECTIVE?

Determining the cost-effectiveness of bisphosphonate therapy requires a complex calculation.

The number needed to treat

If the absolute reduction in risk is divided into 1, the result is the *number needed to treat* (NNT), the number of patients that need to

TABLE 5

Number needed to treat (NNT) and cost to prevent one hip fracture

INTERVENTION	GROUP	NNT*	COST
Risedronate	HIP study (entire cohort)[1]	91	$229,000
	HIP study (younger group)	77	$194,000
	HIP study (younger group with vertebral fracture)	29.4	$74,000
Alendronate	FIT 1[10]	91	$229,000
	FIT 2 (T score ≤ –2.5)[9]	81	$204,000
Hip protectors	Kannus et al[21]	13.6	$3,672
Fall prevention	Tinetti et al[19,20]	NA	$194,700†

*NNT = number needed to treat for 3 years to prevent one hip fracture, NA = not applicable
†Assuming 1% of all falls result in hip fracture; if 2% of falls result in hip fracture, the cost would be $97,350

be treated with a drug to prevent an event. For example, if the absolute risk reduction is 5% or 0.05, the NNT is 20. The total cost to prevent an event is the NNT times the cost of the drug.

The NNT depends on the baseline rate of events. Consider a study subgroup in which 10% of the patients receiving placebo had a fracture, vs 5% of the treated patients. In this case, the relative risk reduction is 50%, the absolute risk reduction is 5 percentage points, and the NNT is 1 ÷ 0.05 = 20.

Hip protectors are cheap and effective but patients don't like them

In contrast, consider a second subgroup in which the risk of fracture in the placebo recipients was 5%, and the risk in the treated patients fell to 2.5%. The relative risk is still halved, but the absolute risk reduction is only 2.5 percentage points, so the NNT would be 1 ÷ 0.025 = 40. Twice as many patients would have to be treated to prevent a single event—at twice the cost.

Thus, a cost-effective strategy requires selecting patients at high risk for fracture. The HIP trial found that the osteoporotic patients ages 70 to 79 without vertebral fractures had hip fractures too rarely for risedronate to show a statistically significant effect. Similarly, patients in the placebo group in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial had a low rate of hip fracture. The frequency was only 0.7% over 3 years, even though they had a mean hip T score of –2.6.[18]

Bisphosphonate therapy

Preventing hip fractures with medication is costly because these medications cost about $70 per month, or $840 per year. The NNT for the HIP patients ages 70 to 79 who had vertebral fractures was 29.4; the 3-year cost to prevent a hip fracture would be 29.4 × $840 × 3 = $74,088. However, the NNT for similar patients without vertebral fracture was 77; the 3-year cost would thus be $194,040 (TABLE 5).

Fall prevention programs

Fall prevention programs are also costly, and the 3-year cost to prevent one fracture has been estimated at $194,700.[19,20]

Hip protectors

Hip protectors are much less expensive, but are unlikely to be used by ambulatory patients who do not live in a nursing home. Kannus et al[21] estimated that the NNT to prevent a hip fracture using the hip protector was 13.6. The cost of the device is $90. If the hip protector is replaced yearly, the cost spent over 3 years to prevent one fracture is thus 13.6 × $270 = $3,672.

Calcium and vitamin D

All patients should receive calcium and vitamin D, which have been shown to reduce nonvertebral fracture risk in randomized controlled trials.[22,23]

Fall protection in patients at high risk of falling

In patients at high risk for falls, fall prevention using physical therapy, balance programs, or tai chi can reduce the fall risk. Those who fall frequently should consider a hip protector.

Therapy in women with a history of vertebral fractures

In addition to calcium and vitamin D, bisphosphonates are indicated in patients with low bone mass and are especially effective in patients with vertebral fractures. In the FIT 1 study, a bisphosphonate reduced the risk of hip fracture for patients with a mean T score of –2.1 and a vertebral fracture. In addition, it is possible that patients with T scores between –1.5 and –2.1 with vertebral fracture and other risk factors would benefit from treatment.

Therapy in women without vertebral fractures

For patients without vertebral fractures, a lower bone density is needed to result in effective hip fracture reduction, as demonstrated in the FIT 2 and HIP studies.

Women with other risk factors

The presence of other risk factors (TABLE 1), especially multiple risk factors, should probably lower the effective threshold for treatment, but important questions remain about how these risk factors interact with bone density and affect treatment efficacy.

Recent studies show that only about half of all hip fractures occur in patients with T scores lower than –2.5. Using SOF data, Wainwright et al[24] estimated that 54% of all hip and spine fractures occur in patients with a T score lower than –2.5. An analysis of data from the Rotterdam study estimated that only 22% of nonvertebral fractures would be targeted using a T score cut point of –2.5.[25]

Thus, to make a large reduction in the number of hip fractures, patients with so-called osteopenic T scores (scores between –1.0 and –2.5) would have to be treated. However, using bone density as the sole criterion would select a large number of low-risk women and thus would be expensive. Bone density, age, and other clinical risk factors should all be considered in developing cost-effective strategies for hip fracture prevention.

PREVENTING HIP FRACTURES: MY RECOMMENDATIONS

What can we conclude from the HIP study and prior studies?

- We now have two bisphosphonates demonstrated in randomized controlled trials to reduce the risk of hip fracture: alendronate and risedronate.
- The most significant reduction in hip fracture with risedronate treatment occurred in patients with low bone mass and vertebral fracture.
- Treatment of women based on older age without measurement of bone density is not an effective strategy to reduce hip fractures, since fewer than 50% of women 80 to 84 years old have a hip T score lower than –2.5. ■

Prescribe calcium and vitamin D for all patients at risk of hip fracture

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Discussing breast cancer and hormone therapy with women

ABSTRACT

Although the results of the Women's Health Initiative showed an increased risk of breast cancer in women taking hormone therapy, the absolute risk is very low. We discuss limitations of the study, questions that remain, and how to discuss the study with women at average risk and high risk for breast cancer.

KEY POINTS

The Women's Health Initiative evaluated only one hormone therapy regimen and did not study lower-dose estrogens or newer progestins.

Clinicians must be able to summarize the cumulative body of evidence—not just the results of one trial—when talking to patients about the effects of hormone therapy.

Misinterpreting or magnifying the already well-established risks of hormone therapy may deprive women of an improved quality of life and potential long-term health benefits.

Individualized risk assessment puts breast cancer risk into a more personal perspective for the individual woman.

This paper discusses therapies that are not approved by the US Food and Drug Administration for some of the uses under discussion.

WHAT DO YOU TELL a woman who asks if hormone therapy will give her breast cancer?

Until recently, no randomized controlled trials had addressed this question. Thus, women often found themselves overwhelmed with conflicting information.

Now, the Women's Health Initiative[1] has found an estrogen-progestin regimen to be associated with an increased risk of breast cancer (and heart disease and thromboembolism), leading many clinicians to discourage patients from taking hormone therapy, and causing widespread distress among patients.

Actually, we should be telling patients that, for an individual patient taking hormone therapy, the risk of breast cancer remains low, and we need to relay the true magnitude of the risks and the benefits of hormone therapy in simple language.

In this article, we discuss the findings of the Women's Health Initiative in the context of current clinical practice and 60 years of epidemiologic data on exogenous hormone therapy.

THE WOMEN'S HEALTH INITIATIVE

The Women's Health Initiative[1] is a large, multicenter trial evaluating the effects of hormone therapy on the cardiovascular system, breast, bones, and other organ systems.

Women with an intact uterus were randomly assigned to receive either combined hormone therapy (Prempro—conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg) or placebo; women without a uterus were assigned to receive either conjugated equine estrogens alone or placebo.

The study began in 1991, with results expected by 2006. However, the combination hormone therapy arm was stopped early, after a

TABLE 1

Quantitative reviews of hormone therapy and risk of breast cancer

AUTHORS	YEAR	NO. OF STUDIES	CONCLUSIONS
Dupont et al[8]	1991	28	No increased risk
Steinberg et al[4]	1991	16	No increased risk until 5 years; 30% increase after 15 years
Sillero-Arenas et al[5]	1992	37	6% increased risk
Colditz et al[6]	1993	31	23% increased risk after 10 years
Collaborative Group[3]	1997	51	35% increased risk after 5 years
Bush et al[7]	2001	65	No increased risk

mean follow-up of 5.2 years because the "global index" (the combination of the total increased rates of harm compared with the combination of the benefits) exceeded a predetermined cutpoint. On the harm side, the hormone therapy group had higher rates of:

- Coronary artery disease (hazard ratio 1.29, 95% CI 1.02–1.63)
- Breast cancer (hazard ratio 1.26, 95% CI 1.00–1.59)
- Stroke (hazard ratio 1.41, 95% CI 1.07–1.85)
- Pulmonary embolism (hazard ratio 2.13, 95% CI 1.39–3.25).

We should not overstate the risks of hormone therapy

On the other hand, the risks of colorectal cancer and hip fracture were significantly lower in the hormone therapy group than in the placebo group. Overall, there was no increase in cancer deaths or total mortality in the hormone therapy group compared with the placebo group.

Further, in absolute numbers, the risks were small—there were 38 cases of invasive breast cancer per 10,000 woman-years in the hormone therapy group vs 30 in the placebo group.

LIMITATIONS OF THE STUDY

The Women's Health Initiative was the first randomized controlled trial to evaluate the effect of combined hormone therapy on multiple disease outcomes, but it had several limitations:

- During the trial, physicians were allowed to adjust the doses of both the estrogen and progestin to manage symptoms.
- The analysis was by "intention to treat"; women who had a hysterectomy during the trial and thus changed from combined hormone therapy to estrogen therapy alone or stopped hormone therapy were still included in the combined hormone therapy group for analysis.
- About 40% of patients in the combined hormone therapy group did not adhere to the regimen, and 10% of the women in the placebo group started hormone therapy through their own clinicians.
- The median age was 63, which is about 10 years older than the average menopausal woman considering hormone therapy. Since age is the greatest risk factor for breast cancer in women, the population studied may have been at greater risk than the average woman considering hormone therapy.
- Although the women in the study were considered at low risk for breast cancer, more than 20% had a 5-year risk greater than 2%, as estimated by the Gail model (see below). This is the level at which women are considered at high risk and tamoxifen chemoprophylaxis is considered.
- One of the criteria for diagnosis of silent myocardial infarction was evaluation by serial electrocardiography, but the diagnosis of heart disease on the basis of electrocardiograms has been shown to be inaccurate in women.[2]
- Women in the study were not at high risk for osteoporosis, although the greatest expected benefit of estrogen in this group would be the prevention of osteoporosis. Baseline radiographs were not obtained to look for subclinical vertebral fractures, even though about two thirds of vertebral fractures are asymptomatic and are

diagnosed as an incidental finding on a chest or abdominal radiograph. Despite this, all types of fractures were reduced, including hip fractures.

- The trial did not study the newer low-dose estrogen (0.45-mg, 0.3-mg) or alternate progestin regimens. Furthermore, the arm of the Women's Health Initiative that is studying the net risks and benefits of unopposed estrogen therapy is still under way; these findings will be of significance to women with a hysterectomy.

DIVERGENT FINDINGS IN EPIDEMIOLOGIC STUDIES

The results of the Women's Health Initiative are consistent with the findings of several epidemiologic studies, in which the overall relative risk of breast cancer in hormone therapy users was variously estimated at between 1.06 and 1.40 (TABLE 1).[3–8] The magnitude of risk was similar to other risk factors discussed below.

On the other hand, other epidemiologic studies found no increased risk with hormone therapy. These data are not false but rather are part of the greater picture.

Bush et al[7] reviewed 65 epidemiologic studies performed between 1975 and 2000, including 45 studies of estrogen-only hormone therapy and 20 studies of combined hormone therapy. In about 80% of the studies the relative risk of breast cancer in hormone therapy users was 1.0, ie, hormone therapy was not associated with breast cancer. The authors concluded that there was no consensus in the literature regarding breast cancer risk from hormone therapy use, and that the variability in results could be due to sampling error from multiple repeated studies.

As for mortality, the Nurses' Health Study[9] followed 91,523 women for 17 years and found that current hormone therapy users had a 37% lower risk of death than women who had never taken hormone therapy. The risk was still 20% lower even in those using hormone therapy for more than 10 years. Among women with a first-degree relative with breast cancer (a group that tends to be concerned about their cancer risk), the risk of death was 35% lower in hormone therapy users than in nonusers.

ALL HORMONES MAY NOT BE THE SAME

One explanation for the discrepancies may be that the various endogenous and exogenous hormones differ in their effects.

Estrogens vary

Conjugated estrogen is made up of different estrogens, all with varying degrees of potency, making their interplay and the effect of each component estrogen at the tissue level very complex.[10]

To answer the question of whether hormone therapy increases breast cancer risk, it would seem intuitive to measure estrogen levels in women and to compare the incidence of breast cancer in women who have low vs high estrogen levels. Unfortunately, this is difficult, given the variety of endogenous estrogens, the variability in levels among individuals, and the great variability in the assays used. Furthermore, the protein-bound serum hormone levels measured in standard assays reflect neither the activity of estrogen at the receptor level nor estrogen's intracellular genomic effects.

Nevertheless, a review of six prospective studies evaluating estrogen concentrations and breast cancer risk[11] showed that women who developed breast cancer had 15% higher estradiol concentrations in their blood compared with women who did not develop cancer. Subsequently, a similar association between breast cancer and higher levels of estrone, estrone sulfate, and dehydroepiandrosterone sulfate was shown.[12] We do not yet know, however, which of these hormones, if any, has the greatest effect on breast cancer risk.

Discuss the issues in terms patients can understand

A woman's menstrual history, such as the age at menarche and menopause, is an indirect measure of her lifetime exposure to endogenous estrogen (early menses and late menopause denote longer estrogen exposure). These factors and their relation to breast cancer diagnosis were evaluated in a case-control study of 16,417 women by Titus-Ernstoff et al[13]: they showed that early menopause, whether surgical or natural, was associated with a lower risk of breast cancer, with the greatest protection when menopause occurred before age 40. Breast cancer incidence was also lower in premenopausal women who underwent menarche at age 15 compared with age 13 (odds ratio 0.72).[13]

Do progestins matter?

The effect of progestins on the breast and other organ systems is even less certain.

The Postmenopausal Estrogen/Progestin

TABLE 2

Factors affecting risk of breast cancer: The Gail model risk-assessment tool

Race
Age
Age at menarche
Age at first live birth
Number of first-degree relatives (mother, sisters, daughters) with breast cancer
Number and findings of previous breast biopsies

Interventions (PEPI) trial,[14] which evaluated the effects of hormones on breast density on mammography, revealed that patients on combined hormone therapy regimens were seven to 13 times more likely to have increased density on screening mammography compared with those taking estrogen alone.

Increased breast density is not necessarily an independent risk factor for breast cancer, but it may make mammograms more difficult to interpret, potentially limiting their diagnostic sensitivity. Other studies found no significant difference in the risk of cancer between women taking estrogen-only and combined hormone therapy.[3]

This is an area of ongoing research, so final conclusions cannot yet be drawn. With the expanding use of newer progestins, more information will be needed about the various combinations now available to patients and how they differ from the traditional combinations that contain medroxyprogesterone acetate.

Average 5-year risk of breast cancer:
- **No hormone therapy, 1.1%**
- **With hormone therapy, 1.4%**

SUMMARIZING THE RESULTS OF THESE STUDIES FOR PATIENTS

How can we put all of these findings into perspective for our patients? When discussing hormone therapy with patients, we recommend the following:

- Admit to patients that there is controversy and concern, especially since many women come to the physician's office with their own opinions on this issue, often sculpted by media coverage, the Internet, and the experience of family or friends.
- Discuss with them the results of the recent comprehensive review by Bush et al,[7] pointing out that some well-designed reviews do not show an association between hormone therapy and breast cancer, which patients may find reassuring.
- Point out that, despite the uncertainties, we cannot disregard the modest increase in breast cancer risk with long-term use of standard-dose combination hormone therapy, as observed in the Women's Health Initiative.
- Make sure patients understand that, despite a possible increase in the risk of breast cancer, we have no evidence that hormone therapy increases mortality.
- Calculate your patient's actual risk (see below).

EXPLAINING BREAST CANCER RISK TO PATIENTS

The Gail model risk-assessment tool[15] (TABLE 2) can be used to predict the 5-year and lifetime percentage likelihood that a woman will develop breast cancer, taking into account family history and several external risk factors. This instrument can be used online at the National Cancer Institute web site (http://bcra.nci.nih.gov/brc). Versions that can be downloaded to handheld organizer devices can be found at http://www.pdacortex.com/BreastCa_Download.htm and http://www.stanford.edu/~pmcheng/breastca.

Calculating the individual 5-year risk

After you calculate your patient's risk of breast cancer, multiply by 1.26 to find her risk with hormone therapy.

For example, using the Gail risk-assessment tool, an average menopausal woman has an approximately 1.1% 5-year risk of developing cancer, with average defined as follows: age 51, white, menarche at age 12, first live birth at age 26, no family history of breast cancer, no breast biopsies.

Using the Women's Health Initiative data, such a patient has a 26% relative increase in risk if she takes hormone therapy. Thus, this woman's 5-year risk of breast cancer diagnosis increases from 1.1% to approximately 1.4% (1.1% × 1.26). Conversely, without hormone therapy, she has a 98.9% chance of *not* being diagnosed with breast cancer in 5 years, compared with a 98.6% chance of not being diagnosed with breast cancer if she takes hormone therapy.

Other, less-appreciated risk factors for

breast cancer include first pregnancy after age 30 (relative risk 1.48), body mass index greater than 29 (relative risk 1.48), alcohol use more than 5 g/day (relative risk 1.16), and, oddly, a college degree (relative risk 1.36).[3]

Many patients overestimate their risk

The Gail model helps women to estimate their personal risk of breast cancer more realistically. If a patient has an estimate of her baseline breast cancer risk and understands the potential contribution of hormone therapy to this calculated risk, she may be able to make a more educated decision about whether hormone therapy is right for her.

This is important, since women overestimate their risk of breast cancer morbidity and mortality. In fact, in both Europe and the United States, women rank breast cancer as the leading cause of death among women, although cardiovascular disease is the most common cause of death and disability on both continents. After age 65, one out of three women develops symptoms of cardiovascular disease.

We have found that our patients are often relieved to hear about the low 5-year and lifetime risks of breast cancer, compared with what they would have predicted.

Conversely, women at higher risk of breast cancer may underestimate their actual risk. The Gail model can help select the women who may benefit from genetic testing, intensive screening with ductal lavage, or chemoprevention with tamoxifen.

Limitations of the Gail model

It is crucial, however, to ensure that women are aware of the limitations of this model and that they understand that this is a mathematical model designed for assessments of population risk in women undergoing annual mammography. In women with a family history of breast cancer in a second-degree or third-degree relative (such as the father's side of the family) or early-onset breast cancer in family members, the Gail model may underestimate the risk because it does not include these factors in its calculations.

Despite its limitations, however, the Gail model can be useful when discussing the complex subject of risk with patients, and it should be part of an annual risk reevaluation, since both risk factors and indications for hormone therapy may change.

Discussing absolute risk with patients

Patients often find estimates of absolute risk more useful and easier to understand than relative risk. Recall that in the Women's Health Initiative, there were 38 cases of breast cancer per 10,000 hormone therapy users per year, compared with 30 cases without hormone therapy—an absolute difference of 8 cases.[1] Many patients find the risk associated with hormone therapy much more acceptable when put in these terms instead of a "26% increased risk of developing breast cancer."

Prognosis, duration of therapy

Other issues to discuss with patients include the prognosis of breast cancer that occurs with hormone therapy use and the optimal length of therapy.

Interestingly, the Iowa Women's Health Study[16] showed that cancers diagnosed in women who had used hormone therapy were less advanced. Exposure to hormone therapy was associated most strongly with breast cancer that had a favorable histology and prognosis.

Furthermore, short-term treatment for menopausal symptoms has not been shown to significantly increase breast cancer risk. Women who wish to start hormone therapy for menopausal symptoms such as vasomotor instability, urogenital atrophy, and mood or sleep changes can begin treatment and decide later if they want to take hormone therapy long-term to protect against osteoporosis, colon cancer, and other conditions.[17,18]

The Gail model helps put risk in a personal perspective

Finally, the data regarding breast cancer risk beyond 10 years of hormone therapy are insufficient to draw absolute conclusions at this time.

HORMONE THERAPY IN HIGH-RISK PATIENTS

Women who have previously been diagnosed with breast cancer are at highest risk of new or recurrent breast cancer with hormone therapy use.

The number of breast cancer survivors in the United States now approaches 2.5 million and is on the rise. In view of their numbers, their nononcologic health problems become a prominent health concern.

A major side effect of current chemotherapy regimens is menopausal symptoms due to premature ovarian failure. These symptoms can

be so bothersome that some breast cancer survivors are willing to accept a modest increase in the risk of breast cancer recurrence to alleviate their symptoms and thus improve their quality of life. Hormone therapy is sometimes offered to breast cancer survivors to relieve these symptoms, with the patient's informed consent.

Although women with a history of breast cancer are at higher risk for new breast cancer, a greater concern is the possibility of developing distant breast cancer metastasis, which is incurable. A recent controlled cohort study of 174 women with breast cancer[19] who were subsequently treated with hormone therapy showed that there was actually a lower risk of cancer recurrence and mortality in the group on hormone therapy compared with those not on hormone therapy.

In another recent study,[20] Cheek et al showed that women on hormone therapy at the time of diagnosis with breast cancer had a much more favorable outcome than postmenopausal women diagnosed with breast cancer who were not on hormone therapy. A history of hormone therapy use in this retrospective case series of 292 women did not show any discernible adverse effects on either breast cancer detection or outcomes.

While potential bias in cohort studies must be acknowledged, it is now clear that more research is needed in this area. Thus far, no study has shown an increased recurrence rate or increased mortality in women with a history of breast cancer who choose to take hormones after their diagnosis.

FINAL RECOMMENDATIONS

We should avoid overemphasizing the risks from hormone therapy, as this may deprive women of its benefits. These include improved quality of life and beneficial effects on the bones, genitourinary tract, skin, colon (cancer prevention), and, possibly, cognitive function.

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The case for hormone therapy: New studies that should inform the debate

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ABSTRACT

The Women's Health Initiative found that the risks of hormone therapy exceeded its benefits in a large group of older postmenopausal women, but did not consider the efficacy of hormone therapy in relieving vasomotor symptoms. Another recent study found that low-dose hormone therapy was as effective as standard-dose hormone therapy while causing fewer side effects. Smaller studies suggest that hormone therapy may improve depression. Hormone therapy is not to be used for cardiovascular risk reduction. Genetic testing may point the way to more rational use of hormone therapy.

MANY WOMEN who might benefit from hormone therapy may decide to forgo it after hearing about the recent report of the Women's Health Initiative,[1] a large randomized trial that found that the risks of taking hormone therapy exceeded the benefits.

Nevertheless, hormone therapy is still the best therapy available for menopausal symptoms, and the case is far from closed on its effects on the vasculature and other conditions. Furthermore, lower doses of hormones may well provide the same benefits while reducing side effects.

THE WOMEN'S HEALTH INITIATIVE: EXCESS RISK IN OLDER WOMEN

The Women's Health Initiative[1] compared the use of conjugated equine estrogens (CEE; 0.625 mg) combined with medroxyprogesterone acetate (MPA; 2.5 mg)—the same combination used in the popular hormone therapy formulation Prempro 2.5—vs placebo in 16,608 postmenopausal women, all of whom had a uterus at baseline.

This arm of the trial was stopped early when the data and safety monitoring board detected an excess of cases of invasive breast cancer in the hormone therapy group. The investigators calculated that, per 10,000 woman-years, the attributable risk for invasive breast cancer diagnosis was 38 cases among hormone therapy users vs 30 cases among placebo users, for coronary events 37 vs 30 cases, and for venous thromboembolism 34 vs 16 cases. On the benefit side, per 10,000 women-years, the rates of colon cancer were 10 vs 16 cases and of hip fracture 10 vs 15 cases.

The hormone therapy debate is far from over

Comments. What do these findings mean for a woman with symptoms of early menopause who is contemplating going on hormone therapy, or someone already on hormone therapy? Several observations:

The women in the study were older: the mean age was 63. Thus, they were past the age of menopausal symptoms, and were willing to be randomized to a 50% chance of receiving placebo. The study was not an efficacy trial, but rather a prevention trial. It did not examine the benefit of relieving vasomotor symptoms or halting genitourinary atrophy; rather,

*The author has indicated that she serves on the speakers' bureaus of the Pfizer, Wyeth-Ayerst, Eli Lilly, and Merck corporations. This paper discusses therapies that are not approved by the US Food and Drug Administration for the use under discussion.

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it was designed to examine the risks of cardiovascular disease, breast cancer, hip fracture, colon cancer, and overall mortality. Thus the bar for adverse effects was set very low.

Furthermore, the risks of serious adverse effects were fairly low in both absolute and relative numbers. For example, at 4 years of therapy, the hazard ratio for breast cancer in the hormone therapy group was 1.26 (95% confidence interval 1.00–1.59). There was no overall difference in total mortality in the 0.625/2.5 mg hormone therapy users vs placebo users.

Thus, for the indications for using hormone therapy previously approved by the US Food and Drug Administration—relieving vasomotor symptoms, halting genitourinary atrophy, and preventing osteoporosis—the benefits of hormone therapy may still outweigh the risks for many women.

WOMEN'S HOPE STUDY: LOW DOSES ARE EFFECTIVE, BETTER TOLERATED

Many women stop taking hormone therapy because of side effects. Would lower doses be better tolerated than standard doses? And would they be as effective?

Low-dose hormone therapy was as effective as standard-dose hormone therapy, and better tolerated

The study. The Women's HOPE (Health, Osteoporosis, Progestin, Estrogen) study[2–5] enrolled more than 2,600 healthy but symptomatic postmenopausal women who had an intact uterus and randomly assigned them to receive one of eight regimens:

- CEE 0.3 mg alone
- CEE 0.3 mg plus MPA 1.5 mg
- CEE 0.45 mg alone
- CEE 0.45 mg plus MPA 1.5 mg
- CEE 0.45 mg plus MPA 2.5 mg
- CEE 0.625 mg alone
- CEE 0.625 mg plus MPA 2.5 mg (the same combination used in the Women's Health Initiative)
- Placebo.

Outcomes measured were vasomotor symptoms, vaginal atrophy, metabolic profiles, and endometrial hyperplasia. At 2 years, bone density and metabolic profiles were reassessed.

Findings. Vasomotor symptoms improved with all of the CEE regimens compared with placebo within the first 3 weeks. Data suggested that the addition of MPA to the lower doses of CEE was actually beneficial in relieving vasomotor symptoms. Complaints of adverse effects such as breast tenderness were less frequent in the low-dose groups.

Importantly, no increase in venous thromboembolism was seen in this large group of relatively healthy postmenopausal women.

The lower doses of continuous combined CEE/MPA regimens provided endometrial protection similar to that of standard doses. Also, subjects in the lower-dose CEE/MPA groups had higher rates of amenorrhea than those in the standard-dose group.

Lipid profiles were similar in the CEE 0.45/MPA 1.5 mg group compared with the CEE 0.625/2.5 mg group. There were improvements in measures of coagulation and fibrinolysis in all the active-treatment groups.

Findings show that the lower-dose regimens maintained skeletal health among early postmenopausal women.[5]

Comment. Lower doses of CEE/MPA appear effective for relieving vasomotor symptoms and for protecting the endometrium. The lower dose favorably affects the lipid profile, does not adversely affect carbohydrate metabolism, and appears to maintain skeletal health. The hope is that these lower doses will lead to higher rates of initiation and continuation of hormone therapy and, especially, less risk.

DOES HORMONE THERAPY PROTECT THE HEART?

One would expect hormone therapy to prevent coronary artery disease after observational studies such as the Nurses' Health study[6] showed a lower incidence of heart disease in women who took hormone therapy, and other studies found that hormone therapy favorably affects lipid levels.[7]

However, in the Heart and Estrogen/progestin Replacement Study (HERS),[8,9] postmenopausal women with coronary artery disease at baseline did not have a lower rate of cardiac events if they took hormone therapy; in fact, in the first year the event rate was higher in the hormone therapy group than in the placebo group.

In 2001, the American Heart Association[10,11] issued guidelines stating that hormone therapy is not to be used as secondary cardiovascular prevention; however, women with coronary artery disease who are taking

hormone therapy for other reasons can continue taking it. Statin therapy is the first choice for treating hyperlipidemia in women at risk for heart disease or who already have coronary artery disease. Based on the findings of the Women's Health Initiative,[1] estrogen-progestin will not be recommended for primary cardiovascular prevention either.

Comments. I agree with the guidelines. Nevertheless, I would point out that the women in the HERS had coronary disease to begin with, and we should not jump to the conclusion that hormone therapy *causes* atherogenesis, although we know that it increases the risk of clots in some women.

Furthermore, the National Registry of Myocardial Infarction recently reported data from 114,724 women age 55 or older with myocardial infarction (MI). Women with MI who had used postmenopausal hormone therapy had a lower mortality rate: 7.4% vs 16.2% in nonusers. After adjustment for prior clinical history, clinical characteristics, and treatment, hormone therapy remained associated with improved survival, with an odds ratio of 0.65 (95% confidence interval 0.59–0.72).[12]

These observations may be related to therapeutic effects of hormone therapy, selection or adherence bias, or both.

Hormone therapy and blood pressure

Scuteri et al[13] examined data from 226 healthy, normotensive postmenopausal women in the Baltimore Longitudinal Study of Aging to look at the relationship between hormone therapy and blood pressure.

Seventy-seven women used hormone therapy; 149 did not. Lifestyle variables, blood pressure, and traditional cardiovascular risk factors were measured at baseline and approximately every 2 years thereafter. Systolic blood pressure at baseline was similar in hormone therapy users and nonusers.

Findings. Over time, the average systolic blood pressure increased in both groups, but increased less in hormone therapy users than nonusers, independent of other cardiovascular risk factors, physical activity, and alcohol use. The lesser increase in systolic blood pressure in hormone therapy users was more evident at an older age, when it is potentially more important.

Comment. The mechanisms of this finding may be related to arterial stiffness and nitric oxide production. Structural changes in the endothelial wall may be a mechanism through which hormone therapy exerts a beneficial effect.[14,15]

DOES HORMONE THERAPY IMPROVE DEPRESSION?

Previous studies suggested that estrogen improves somatic and mild depressive symptoms in women. Three new studies, although small, were elegantly done and examined the question further.

Soares et al,[16] in a study in Brazil, randomized 50 perimenopausal women to wear a 100-μg estradiol patch vs a placebo patch for 12 weeks. Depression improved dramatically within 1 week in the estradiol group, and the mean Montgomery-Asberg Depression Rating Scale (MADRS) score dropped from 40 to 11 by the end of the study. Remission of depression was observed in 17 (68%) of the women treated with estradiol compared with 5 (20%) in the placebo group ($P \leq .001$).

The study was limited by brevity, self-selection from a menopause clinic, and no assessment of the endometrium.

Ahokas et al[17] looked at 23 women with postpartum depression in a study using sublingual 1-mg estradiol tablets. MADRS scores were obtained at baseline and each week through 8 weeks. All subjects started with low serum estradiol levels; it took some women 3 to 8 weeks to reach a follicular level. The results were significant, with remission of depression in more than 80% of these women.

Schmidt et al[18] observed a full or partial therapeutic response in 80% of 34 women who received estradiol for 3 weeks in a placebo-controlled crossover study, compared with 22% of those receiving placebo.

Comment. Estrogen seems to influence neuronal function via serotonergic, noradrenergic, dopaminergic, and GABA-mediated systems, but we still don't know the exact mechanism of the antidepressant effect.

Of interest, estradiol appears to reduce the symptoms of depression in perimenopausal women who do not have hot flashes, reinforcing the concept that the effects of estrogen on mood may be independent of vasomotor

Hormone therapy should not be used for primary or secondary cardiovascular prevention

symptom relief. The vasomotor symptoms returned when the hormone therapy ended, but the depression did not.

DOES HORMONE THERAPY PRESERVE COGNITIVE FUNCTION?

Controversy continues regarding whether hormone therapy preserves cognitive function, and, if so, by how much. Small studies in women with existing dementia showed no benefit in cognitive scores. On the other hand, epidemiologic studies[19] show a lower risk of dementia and better cognitive function in long-term users of hormone therapy than in nonusers.

CAN BREAST CANCER SURVIVORS USE HORMONE THERAPY?

Standard dogma holds that women with a history of breast cancer must not take hormone therapy, which might increase the risk of recurrence.[20] However, short-term use of hormone therapy (< 4 years for menopausal symptom control) is not associated with any increase in breast cancer diagnosis risk.

Hormone therapy seems to improve depression independent of its effect on vasomotor symptoms

O'Meara et al,[21] in a 17-year observational cohort study, evaluated data from 2,755 breast cancer survivors, of whom 174 had used hormone therapy after diagnosis.

Fewer women died who used hormone therapy than who did not. The adjusted relative risk of death for users compared with nonusers was 0.5 (95% confidence interval 0.3–0.85). The total mortality rates were 16 per 1,000 woman-years in hormone therapy users and 30 per 1,000 woman-years in the nonusers.

The results suggest that hormone therapy use in self-selected breast cancer survivors has no adverse impact on breast cancer recurrence or mortality.

CAN WE PREDICT WHO WILL BENEFIT OR BE HARMED BY HORMONE THERAPY?

We expect that in the future we will be able to use genetic testing to determine who would most benefit from long-term hormone therapy and, conversely, identify the small but significant subset of women who may be harmed by it.

Predicting fracture risk. A genetic study examining *COLIA1* genotyping in both sexes was able to predict fractures independently of bone mass.[22] The genotyping results, coupled with the data from bone mineral density, helped identify women who were at high risk and low risk for osteoporotic fractures.

Tamoxifen reduces breast cancer risk among *BRCA2* carriers. Tamoxifen has been shown to reduce the incidence of breast cancer by half in women at high risk. Until recently, it was not known whether women who were carriers of the *BRCA1* or *BRCA2* mutation genes had the same benefit with tamoxifen chemoprevention.

Recently, King et al[23] found that tamoxifen reduced breast cancer incidence among healthy *BRCA2* carriers by 62%, similar to the reduction in incidence among all the women in the Breast Cancer Prevention Trial. However, tamoxifen use beginning at age 35 or later did not reduce breast cancer incidence among healthy women with inherited *BRCA1* mutations.

Breast ductoscopy and ductal lavage are emerging procedures that may further help to risk-stratify women who are at increased risk for breast cancer and monitor those on chemoprevention.

Predicting thrombotic and cardiovascular risk. The factor V Leiden mutation substantially increases the risk of thromboembolism. On the other hand, it is relatively rare; an estimated 188 women would need to be screened for the factor V Leiden mutation for one case of venous thromboembolism to be prevented by withholding hormone therapy.[24]

The prothrombin *G20210A* mutation, carried by approximately 5% of people, also increases the risk of thromboembolism. Psaty et al[25] performed a case-control study to investigate the interaction between the prothrombin *G20210A* mutation and myocardial infarction in hormone therapy users with hypertension. The investigators estimated that women who carry the *G20210A* mutation and use hormone therapy have a nearly 11-fold increased risk of MI if they are 80% compliant with their hormone therapy regimen, and a 20-fold increased risk if they are 100% compliant.

Elevated HDL is not always good. Generally, the serum level of high-density lipoprotein (HDL) is inversely related to the risk of ischemic heart disease. However,

Agerholm-Larsen et al[26] recently found that women who were heterozygous or homozygous for the Ile404Val mutation in the cholesteryl ester transfer protein gene had both elevated HDL levels and a 1.4-fold to 2.1-fold increased risk of ischemic heart disease.

Comment. Such studies may point the way to more rational use of long-term hormone therapy. The use of short-term hormone therapy (≤ 4 years) should not change based on the Women's Health Initiative study. Conceivably, women should avoid long-term hormone therapy use if they carry a mutation that increases their risk of thrombosis, cancer, or ischemic heart disease with hormone therapy. Conversely, they might be good candidates for utilizing tailored hormone therapy if they carry a mutation that increases their risk of osteoporosis or derive skin benefits, neuropsychological benefits, or genitourinary benefits from hormone therapy.

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