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Second-Trimester Ultrasound to Detect Fetuses with Down Syndrome

ABSTRACT & COMMENTARY

In february 2001, an article by smith-bindman and colleagues appeared in the *Journal of the American Medical Association* that has generated substantial controversy. Smith-Bindman et al pooled data from 59 prospective, retrospective, nonrandomized studies in which ultrasound markers of Down syndrome (DS) were evaluated. These included choroid plexus cysts (CPC), nuchal skinfold thickness (NSFT), echogenic intracardiac focus (EIF), echogenic bowel, and renal pyelectasis. In addition, both humeral and femur lengths were evaluated as predictors of DS. The meta-analysis involved 1930 pregnancies affected by DS and 130,363 unaffected pregnancies, chosen from studies that met Smith-Bindman et al's seemingly stringent inclusion requirements.

After analyzing the jumble of data, Smith-Bindman et al concluded that isolated markers, with the possible exception of NSFT, had only a "marginal impact on the risk of DS." They even suggested that clustered markers had little screening value since they increased the false-positive rate. Finally, they concluded that a "negative" sonogram did not substantially decrease the risk of DS.

In the discussion section of the paper, Smith-Bindman et al took their findings to an interesting conclusion—that if one were to act on isolated markers, an alarming number of normal fetuses would be lost through unnecessary amniocentesis.

The concept that noninvasive testing combinations that have less than 100% accuracy can be offered as an alternative to an invasive test has not been uniformly embraced by all obstetricians and geneticists. Smith-Bindman et al's conclusions that the genetic sonogram is not only essentially useless, but may be dangerous, is music to the ears of the techniques' naysayers. However, before obstetricians yield to the rallying cry of the "amniocentesis for all" faction, it is important to scrutinize the study data and Smith-Bindman et al's conclusions. (Smith-Bindman R, et al. *JAMA*. 2001;285:1044-1055.)

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INSIDE

COMMENT BY JOHN C. HOBBINS, MD

First, a meta-analysis is designed to boost statistical power by combining data from many "similar" related studies, thus allowing conclusions to be reached that might not be supported by each of the individual studies. This technique has been especially effective in prospective, randomized, clinical trials (RCTs). However, this analysis has occasionally been used effectively in non-randomized observational studies, as long as certain critical assumptions are verified and appropriate analytical safeguards are enforced.

The meta-analysis above contained many studies that were published before 1995, indicating that the data were collected in the late 1980s and early 1990s when investigators were first acquiring experience with the ultrasound techniques, often on vintage equipment. Including these early "learning stage" studies in the meta-analysis could skew the results. In fact, a table in the study demonstrates that the sensitivity is almost uniformly improved as the timing of the study approaches the late 1990s.

Also, rigid standardization of the ultrasound techniques (similar to that used in today's first trimester nuchal translucency trials) is essential in the critical evaluation of the true value of any method. This was not the case in many studies included in the meta-analysis.

Smith-Bindman et al point out that a single ultrasound marker for DS has very little predictive value, but, hopefully, most clinicians are aware that 1 marker in isolation is not a reason to move to amniocentesis, especially in a patient at low risk for fetal DS. However, Smith-Bindman et al's assertion that a "negative" sonogram has no merit is inconceivable since their own data indicate its' substantial value. For example, their data summarized in one table shows that the sensitivity of multiple markers and/or the presence of structural abnormalities is 69% and the specificity is 92%. This results in a negative-likelihood ratio of 0.33 (100-69/92). Therefore, in patients with a negative sonogram, their risk could be adjusted downward from their age-adjusted risk by 66%. This assumption would take the DS risk of a 35-year-old to that of a 31-year-old, and certainly way below the risk of amniocentesis.

Vintzileos has pointed out that the ability to change a patient's risk for DS (from her age-related risk) is based on the accuracy (sensitivity) of the center in which the ultrasound examination is performed. His center's sensitivity is 82% with a specificity of 91%, which translates into a negative likelihood ratio of 0.20 (of a negative genetic sonogram). This, in turn, would drop a patient's risk of fetal DS by 80%. Nyberg has published similar results, which are also similar to data from a large 9-center study soon to be submitted. Interestingly, the RR of a negative sonogram in this *JAMA* meta-analysis is extremely similar to this and other published data.

The thrust of the genetic sonogram has been to diminish the need for amniocentesis, especially in patients who would have been urged to have one a few years ago. What is the alternative? If we were to perform an amniocentesis on every patient who was 35 years old with a second trimester fetal DS risk of 1:300, we would be doing 299 unnecessary amniocentesis to identify 1 DS fetus, losing 2.4 fetuses along the way (using Smith-Bindman et al's 0.8% amnio loss rate).

A genetic sonogram has a similar value to a "triple screen" which can also diminish the need for amniocentesis. As indicated in a previous clinical study, Egan et al calculated from 1997 national statistics that if triple screens were offered to all patients older than age 34, and amniocentesis was performed in only those with a risk of 1:250 or greater, 154,756 fewer amniocentesis would be performed and 733 procedure-related fetal losses would be averted.

It remains to be seen through expanded studies in progress whether the genetic sonogram and the triple

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screen will have greater adjunctive power than either alone, but initial findings suggest benefit when they are used together. A caveat must be added to any statement regarding the value of a genetic sonogram. Through bitter experience, it is clear that the benefit of this type of technique, in contrast to the mechanized triple screen, is dependent upon the skill and diligence of the operator and will suffer if rigid standardization is not pursued during the performance of the examination. In fact, many have suggested that this type of screening program would be best conducted in a high volume, high efficacy setting which would favor large-center screening programs.

In summary, a genetic sonogram should consist of a fetal anatomy survey (as described in the AIUM guidelines for a basic ultrasound examination), a femur and humerus length assessment, and an evaluation of DS markers. This should always include an assessment of the NSFT, which even in the meta-analysis increased the risk of DS by 17-fold, if positive. Every aspect of this exam must be compulsively standardized, and the exam should be performed by sonographers/sonologists with substantial experience. Based on data in the literature, if vigorous safeguards are used, one can diminish a patient's risk of DS by at least 50% from her pre-exam risk. ❖

Suggested Reading

1. Egan JF, et al. *Obstet Gynecol*. 2000;96:979-985.
2. Vintzileos AM, et al. *Am J Obstet Gynecol*. 1999; 181:1045-1048.
3. Nyberg DA, et al. *J Ultrasound Med*. 2000;19(4 suppl): S7-S8.

Uterine Artery Embolization for Leiomyomata

ABSTRACT & COMMENTARY

Synopsis: *Uterine artery embolization is a safe and effective means of treating uterine fibroids.*

Source: Spies JB, et al. *Obstet Gynecol*. 2001;98:29-34.

Spies and colleagues report 200 consecutive patients with uterine fibroids who underwent uterine artery embolization. Prior to treatment all women had symptoms of heavy menstrual bleeding, pelvic pain and pressure, or urinary symptoms. For this study, Spies et al combined pelvic pain and pressure with urinary symptoms into a category called "bulk" symptoms. There were a number of exclusionary criteria, the most important being pregnancy, easily resectable fibroids, and women with a uterus larger than 24 weeks gestational size. Except for the first 14 patients, all others received a magnetic resonance imaging (MRI) study. Repeat MRIs were scheduled at 3 months and 12 months following the procedure. Based on the MRI results, the volume of both the uterus and the dominant fibroid were calculated.

Spies et al performed bilateral embolization with polyvinyl alcohol; both major and minor complications were recorded.

Spies et al mailed symptom questionnaires to all of the patients at 3, 6, and 12 months after treatment.

Only 2 of the 200 patients could not be treated. Ninety-three percent of the patients were admitted to the hospital overnight for observation and pain control. Four patients were readmitted for 1 night for pain control and 3 others were seen in the emergency department. The average number of days required before returning to work was 8. The mean duration of follow-up was 21 months. All patients were followed for at least 12 months following the procedure. A large majority of patients returned the follow-up questionnaires.

Prior to the procedure, 85% of the patients complained of menorrhagia. This was improved for more than 80% of the patients, with only 3% and 2% reporting worse symptoms 3 months and 12 months following the procedure.

Of the patients, 83% reported pelvic pain and/or pressure and 54% urinary symptoms prior to the procedure. These "bulk" symptoms were improved in more than 90% of the patients with only 3% reporting worse symptoms at 3 months and 2% at 1 year postoperatively. Overall only 3% of the patients were dissatisfied with the procedure 3 months postoperation.

Postprocedure imaging showed that uterine volume was reduced by 27% at 3 months and 38% at 12 months following the procedure. In addition, the dominant fibroid volume was reduced by 44% at 3 months and 58% at 12 months.

Of the patients, 10.5% required some type of gynecologic surgical intervention during the follow-up. This included 9 hysterectomies, none of which were performed to treat complications of the procedure. Seven of the hysterectomies were performed for failure of symptom improvement. Only one major complication occurred, a pulmonary embolism 2 days following the procedure.

COMMENT BY KENNETH L. NOLLER, MD

Leiomyomata are the leading indication for hysterec-

tomy in the United States. In recent years some decrease in symptomatology has been accomplished through medications, though the long-term benefit has been somewhat disappointing. More recently, the use of uterine artery embolization to reduce or eliminate the symptoms of leiomyomata has been gaining popularity.

This article represents the largest single series of patients treated with this procedure. The study is generally well conceived. The 21-month average follow-up is much longer than many of the published series, but we will need to wait for the 5 and 10-year follow-ups to know for certain that the procedure results in true long-term improvement.

I was quite surprised (and impressed) with the low level of complication experienced by these patients. Pain remains the biggest postoperative problem. In my experience, the pain experienced by these patients during the first 24 hours is not trivial. Many/most require substantial amounts of narcotics. However, after 24 hours few continue to have more pain than can be controlled with nonsteroidals.

I hope our profession does not miss its opportunity to evaluate this procedure correctly. So far all of the published studies (including this one) are "show and tell" papers. That is, they are merely case series. What is desperately needed is a prospective, randomized trial comparing uterine artery embolization to hysterectomy for the treatment of uterine leiomyomata. We will have one opportunity—now—to perform such a study. If it is not done soon, uterine artery embolization and hysterectomy will both be done for fibroids without one ever knowing which is better. ❖

A New Option for Contraception—The Patch

ABSTRACT & COMMENTARY

Synopsis: *The contraceptive patch was found comparable to oral contraception in efficacy and cycle control.*

Source: Audet MC, et al. *JAMA.* 2001;285:2347-2354.

Audet and colleagues reported the results from a multicenter trial studying a transdermal contraceptive patch. This trial included 1417 women who were randomized to either the contraceptive patch or an oral contraceptive (Triphasil®), and followed for either 6 cycles or 13 cycles. Although the differences were not statistically significant, the failure rate was lower in the patch group than in the oral contraceptive group. Only 5 pregnancies occurred with the patch (1 user failure and 4 method failures). The breakthrough bleeding incidence and pattern were similar in the 2 groups. Spotting was slightly higher in the first 2 cycles with the patch. Perfect compliance with the patch was achieved in 88.7% of the cycles compared with 79.2% in the oral contraceptive cycles. Also, 4.6% of the patches had to be replaced for either partial or complete detachment. Breast discomfort was slightly higher in the first 2 cycles with the patch. Dysmenorrhea was also more frequent with the patch, but the difference did not achieve statistical significance. The contraceptive patch, therefore, was comparable to oral contraception in efficacy and cycle control.

COMMENT BY LEON SPEROFF, MD

The contraceptive patch is expected to be on the US market in the summer of 2001 from Ortho-McNeil, with the trade name "Ortho Evra®." The 20 cm^2 patch delivers 20 mg ethinyl estradiol and 150 mg norelgestromin (the active metabolite of norgestimate) daily. Each patch provides effective systemic blood levels of the steroid hormones for a little more than 7 days; therefore, treatment consists of a new patch applied weekly for 3 weeks followed by a patch-free week. The patch can be applied to the buttocks, the upper outer arm, the lower abdomen, or upper torso (except for the breasts). The patch has been studied under rigorous conditions (exercising, swimming, and in sauna baths), and patients can be reassured that usual activities need not be limited.

Although the cycle control data indicated that breakthrough bleeding and spotting were similar with the 2 methods studied, note that the oral contraceptive was Triphasil®, a product that delivers more estrogen per day than the patch. Thus, this patch that delivers 20 mg ethinyl estradiol per day performed better than what we would expect with a 20 mg oral product.

The most obvious advantage for this contraceptive patch is the improvement in compliance with the once-a-week administration. The better failure rate with the patch in this study did not achieve statistical significance, but the difference promises to be an important one when the product is in general use, most likely due to better compliance. Although the patch won't be acceptable for all women—2.6% of the participants in this study withdrew because of application site reactions—the option should be presented to any patient considering oral contraception. The potential for greater efficacy because of better compliance makes the patch a good choice for all women, and especially teenagers. ❖

Association Between the T29fiC Polymorphism in the Transforming Growth Factor b1 (TGF-b1) Gene and Breast Cancer Among Elderly White Women

ABSTRACT & COMMENTARY

Synopsis: *TGF-b1 genotype is associated with risk of breast cancer in white women aged 65 years and older. Because the T allele is common and confers risk, it may be associated with a large proportion of breast cancer cases.*

Source: Ziv E, et al. *JAMA*. 2001;285:2859-2863.

Tgf-b1 has been shown to inhibit cellular proliferation, suppress inflammatory response, stimulate angiogenesis, and increase production of the extracellular matrix. In vitro studies have shown that increased activity in the TGF-b1 pathway is a potent inhibitor of most mammary cells lines. Transgenic mice with single gene deletion of TGF-b1 are more susceptible to lung, breast, and liver cancers induced by carcinogens. Since the activities of TGF-b1 play a role in the development and progression of cancer, Ziv and colleagues sought to determine if common allelic variants conferred risk for, or protection from, breast cancer. The answer is apparently "yes" for the population studied. The study group consisted of 3075 white women older than age 65. The allelic variant that was most common was T/C at 48.6%. The allelic variant that conferred protection was least common at 14.9%. The allelic variant T/T, present in 36.7%, did not give more risk than the T/C variant. Adjusting for age, age at menarche, age at menopause, parity, hormone use, body mass index, and bone mass did not change the associations. Ziv et al note that roughly 60% of women carry either the T/T or T/C genotype, so if this association holds, then this genotype might be responsible for far more excess risk for breast cancer than high-penetrance genotypes such as BRCA1. A limitation of the study is that so few women in any category developed breast cancer when followed for almost 10 years. In the T/C group, the rate was 5.8 per 1000 person-years and 80 cases of breast cancer. In the T/T group, the rate was 5.4 per 1000 person-years and 56 cases. In the C/C group, the rate was only 2.3 per 1000 person-years and only 10 cases of breast cancer. Therefore, Ziv et al consider their findings preliminary. Of note, there was no difference in stage or estrogen receptor status in those who did develop breast cancer.

COMMENT BY SARAH L. BERGA, MD

It is commonplace to attribute causality to things we can control. It gives us a sense of order. However, to the extent that we are mislead by our attributions, then we stand to pay a price for this longing. This is what I worry about when we blame breast cancer on postmenopausal hormone use. On the other hand, we often wink at habits that we know are unhealthy, such as tobacco smoking, because we know the behavior is difficult to stop. It is obviously our job, as physicians, to help patients distinguish between behaviors that are unhealthy and those that are not. Do we really think that estrogen causes breast cancer? What if it does not? My greatest fear is that many women will be denied the benefits of hormone use because we cannot provide an unequivocal answer that it is largely safe. Our hesitation results from the constant trickle of studies purporting to find an association. But what if breast cancer is generally NOT related to a personal behavior such as hormone use or vitamin intake, but, instead, due to some kind of bad luck, such as a genetic factor? Enter the present study.

In this article, Ziv et al find that a common genetic allele for the protein TGF-b1 confers risk for breast cancer. What is an allelic variant? It just means that for any one gene, there are variations in the coding sequence that show up as minor variations in the resulting gene product. In this study there is a single change, so instead of being cytosine, there is thymine at the 29th nucleotide of the coding sequence. The apparent effect of this change is to increase the amount of TGF-b1 that is made and released into the circulation. Is an allelic variant a mutation? This is a matter of perspective, I suppose. In this study, the excess risk is conferred by the 2 most common variants. It is difficult to call them mutations when they are so prevalent. The effect size if one has either the T/T or T/C variant is about a tripling of risk for breast cancer, far more than has ever been suggested for ERT or HRT use. Not addressed by this study is whether there might be an interaction between this genetic risk factor and behavioral risk factors, such as alcohol intake or tobacco use. Should we screen for this allelic variant? Ziv et al say that more work is needed to confirm this association, but their hope is that work of this type will make prediction of breast cancer risk more accurate.

While there is clearly much work to be done in identifying and understanding how various cellular products regulate cell growth and risk for cancer, it is becoming

much easier to do genotyping. Let's say that there are 200 genes that appear to confer a moderate to high risk for breast cancer. Can we easily screen for these? The answer is yes. This is what gene microassay technology promises. The polymorphisms in the genes are found, the associations are found, and then a "gene chip" is developed for easily detecting in one assay all of these 200 high-risk polymorphisms for breast cancer. Instead of literally chipping away at an individual's genotype one gene at a time, if we know what we are looking for, then we can make the chip for the "worst" genes. Using the "gene chip," we can find out how many of the 200 or so genes that might confer risk a given individual has. Screening for gene polymorphisms with microassay technology gets increasingly easier. Figuring out which ones to screen for is still hard, but increasingly feasible with molecular epidemiology. So don't forget to donate your blood to the next molecular epidemiologist who asks. We will need large numbers, and lots of public good will, to figure out these associations. Once found, then we will need to figure out how to explain this to our patients. I have 2 hopes about this process of discovery. First, I hope that we learn what is and what is not high-risk behavior so that we can wisely advise our patients. Second, since it is likely that we will all have some high-risk genes, I hope that we as a society will learn to be a lot less judgmental and stop blaming patients for illnesses that are linked to genes. ❖

Special Feature

The Meaning of Mammographic Breast Density

By Leon Speroff, MD

High breast density on mammography is associated with a 4 to 6-fold increased risk of breast cancer.[1,2] A review of 8 cohort studies concluded that women with the highest breast density compared with the lowest density have a relative risk of 5.2 (CI = 3.6-7.5) for breast cancer.[3] Increased density is also a problem because it impairs the detection of breast masses (microcalcifications are less obscured by surrounding dense tissue than masses). A failure to detect masses because of high density would cause an increase in interval cancers (cancers that present between mammographic screenings). Difficulties in reading high-density mammograms also produce false-positive recalls (patients who are recalled for assessment and found not to have cancer). Being recalled for reassessment after an initial mammogram is a cause of significant psychological stress.[4] In addition, at least 25% of the overall cost of mammographic screening in 1 US program was attributed to investigations of false-positive readings.[5]

These 2 problems, an increase in interval cancers (a decrease in mammographic sensitivity) and an increase in false-positive recalls (a decrease in mammographic specificity), are consistent with a decrease in the detection of cancer. Thus, the concern with dense breasts in postmenopausal women is a reduced quality of mammograms with a decrease in the ability to detect early breast cancers. Factors that are associated with greater breast density are nulliparity, older age at first birth, and current use of hormone therapy.[6] Mammographically dense breasts reflect a high proportion of stromal, ductal, and glandular tissue. The likelihood of dense breasts decreases with advancing age and increasing body weight as glandular tissue is replaced by fat. The link with nulliparity supports the contention that a full-term pregnancy early in life produces a change in structure in the breast that persists throughout life and is associated with resistance to proliferation.

Summary

1. High density on mammography is associated with an increased risk of breast cancer.
2. High breast density can reduce mammographic sensitivity and specificity.

There is no doubt that postmenopausal hormone therapy can affect breast density, but because hormone use has reached a relatively high prevalence only in recent years, studies are just now documenting the effect on mammographic screening. More current users of hormone therapy have dense breasts than nonusers.[7-10] In the Seattle area, 49% of current users had dense breasts compared with 33% of nonusers, and the effect was greater with increasing age.[6] Indeed, in women younger than age 55, it is difficult to find any differences between hormone users and nonusers.[11] But how large is the effect on older than age 55? In one study, breast density increased in only 8% of hormone users older than age 55 (two-thirds of the patients used estrogen alone, one-third used estrogen and progestin); in the large majority of the patients, the breasts remained the same.[11]

The effect of hormone therapy occurs rapidly; thus, duration of use has no effect.[11] In the PEPI 3-year randomized trial, almost all increases occurred within the first year, with an increase in breast density observed in 8% of estrogen users and 19-24% of estrogen-progestin

users, and only 2% in the placebo group.[12] The users of estrogen and progestin-combined regimens had a greater risk of developing denser breasts compared with estrogen alone treatment (7-13-fold greater in the PEPI trial with no differences observed comparing medroxyprogesterone acetate to micronized progesterone).[12] In careful studies, the daily, continuous combined estrogen-progestin regimens have been reported to have a greater effect than sequential regimens, with an increase in density occurring within the first months of treatment and then maintained with no change.[13,14] Therefore, hormone therapy increases breast density mainly in older postmenopausal women, more women respond to combined estrogen-progestin regimens (especially the daily, continuous programs), and the effect occurs within the first months of use and remains stable with no changes with increasing duration of use. But this effect is only seen in about 20% more users compared to nonusers; indeed, not all women respond in this fashion (in fact, most do not). And most importantly, in those women who respond with an increase in breast density, discontinuation of treatment is followed by a decrease in density.[10,15,16]

Summary

1. Postmenopausal hormone therapy increases breast density in about 10% of estrogen users and about 20% of estrogen-progestin users, an effect that occurs within the first months of treatment.
2. An increase in breast density is observed most often in women receiving a daily, continuous combination of estrogen-progestin.
3. In those women who have an increase in breast density with hormone therapy, cessation of treatment is followed by a decrease in density.

Does this hormonal effect on breast density impair mammographic screening? In other words, is there an increase in interval cancers and false-positive recalls in postmenopausal hormone users? In a review of 7 studies, there were relatively few interval cancers in the user groups (from 1 to 46), nevertheless, 6 of the 7 studies reported decreased mammographic sensitivity in hormone users with increases in interval cancers in users compared with nonusers.[17] Excluding women younger than age 50, the relative risk for an interval cancer was summarized as 1.7 (1.2-2.4). The risk of false-positive recall (mammographic specificity) was investigated in 5 studies. The rate of false-positive recall in nonusers ranges from 2.1% in the United Kingdom to as high as 14.7% in an American program; 3 of the 5 studies found a slight increase in the risk of false-positive recalls. In a French study, mammographic sensitivity was reduced from 92% to 71% in users because of an incidence of interval cancers that was 3.5 times that of nonusers within the first year of the initial exam, and 1.7 times greater during the following 2 years.[18] Most of the hormone users were on combined estrogen-progestin regimens. The false-positive recall rate was only slightly higher, 3.3% in users and 2.8% in nonusers. A Finnish study concluded that women with the most dense breasts and using hormones had the highest relative risk of breast cancer, but this conclusion was based on only 4 cases of cancer in women with dense breasts.[19] American, Scottish, and Australian studies have indicated a 15-20% decrease in mammographic sensitivity in hormone users who have dense breasts.[20-23] Recent retrospective and prospective studies from Massachusetts General Hospital concluded that recall rates were essentially the same comparing hormone users and nonusers.[24]

Summary

1. The sensitivity of mammography is slightly decreased in women who develop high breast density on hormone therapy; the magnitude and consequences are still uncertain.
2. Postmenopausal hormone therapy does not have a major effect on mammographic specificity.

It seems to me that there are several reasons to suspect that the increase in breast density reported with postmenopausal hormone therapy may not be identical to the high breast density associated with an increased risk of breast cancer.

Overall, studies have suggested a decrease in mammographic sensitivity with little effect on specificity (false recall rates). The studies are based on small numbers of interval cancers, and it is uncertain how real or how large this effect is because of the difficulty in controlling for confounding factors (eg, age, age of menopause, and time since menopause). If the effectiveness of breast cancer screening is reduced by postmenopausal hormone therapy, one would expect an adverse impact on breast cancer mortality. Instead, a study that indicated a reduction in mammographic sensitivity also reported smaller, more differentiated (Grade I) tumors among the users compared with the nonusers,[18] and most of the studies that have examined the breast cancer mortality rates of women who had used postmenopausal hormone therapy have documented improved survival rates.[25-34] Evidence indicates that estrogen users develop smaller, better-differentiated (lower grade) tumors, and that surveillance/detection bias is not the only explanation for better survival.[35-40] Lower grade tumors are present even when there is no

difference in the prevalence of mammography comparing hormone users and nonusers, or when the data are adjusted for the method of detection.[32,34,40]

The mammographic pattern of breast density and the risk of breast cancer do not always go together. For example, women with increasing body weight have a decreasing prevalence of high-risk patterns, yet overweight postmenopausal women have an increased risk of breast cancer.

Another reason to believe that the increase in breast density associated with postmenopausal hormone therapy is different than that associated with an increased risk of breast cancer is that it is a transient, reversible change. After discontinuing hormone therapy, breast density rapidly decreases.[10,15,16] Rather than epithelial proliferation, this change in response to hormone therapy could be a combination of edema and vasodilatation. In a retrospective analysis, regression of hormone-induced abnormalities was found to occur within 2 weeks of cessation of treatment.[16] In the 12 patients who exhibited no change after discontinuing therapy, 8 were biopsied after ultrasonography, revealing one cancer and one case of atypical hyperplasia. Bigger and better studies of this approach are needed, but it suggests a clinical recommendation.

Clinical Summary

The older a patient is, the greater the risk of developing an increase in breast density with hormone therapy. Therefore, there is a good reason to recommend the discontinuation of hormone therapy for 2 weeks prior to mammography in women older than age 65 who have dense breasts. In younger women who are recalled for a suspicious or difficult-to-read mammogram, it would be worthwhile to discontinue hormone treatment for 2 weeks prior to the repeat evaluation. ❖

Attention Readers

Due to the large amount of references contained within this issue's special feature, Dr. Speroff and the staff at *OB/GYN Clinical Alert* will provide copies of the references by request only. If you would like to receive the references, please contact Rob Kimball, Senior Copy Editor, at 404-262-5413, or e-mail at robert.kimball@ahcpub.com. ❖

CME Questions

5. **In the series of uterine artery embolization patients reported by Spies et al, the only major complication among the 198 treated patients was:**
   a. pelvic abscess.
   b. uterine hemorrhage.
   c. pulmonary embolism.
   d. cardiac arrest.

6. **Which of the following statements regarding the contraceptive patch is *false*?**
   a. ORTHO-EVRA delivers blood levels of contraceptive steroids equivalent to a 20 mg estrogen-progestin oral contraceptive.
   b. The contraceptive patch has fewer side effects compared with an oral contraceptive.
   c. In clinical trials, compliance with the patch is better than with oral contraceptives.
   d. Better compliance with the patch should yield fewer unwanted pregnancies due to user failures.

7. **Which one of the following is true?**
   a. Screening for genetic factors that increase the risk of cancer is technically feasible.
   b. The allelic variant for TGF-b1 known as C/C specifies an abnormal gene product.
   c. High levels of TGF-b1 cause breast cancer.
   d. It is highly unlikely that we will be able to understand the gene-environment interactions that cause breast cancer.
   e. Allelic variants are not gene mutations.

Attention Readers

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com.

We look forward to hearing from you. ❖

In Future Issues:

Neoadjuvant Chemotherapy for Unresectable Ovarian Cancer