AMERICAN HEALTH CONSULTANTS®

Providing Evidence-Based Clinical Information for 17 Years

OB/GYN CLINICAL ALERT®

A monthly update of developments in female reproductive medicine

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Gene-Expression Profiles in Hereditary Breast Cancer

ABSTRACT & COMMENTARY

It has been well established that mutant brca1 or brca2 genes increase a woman's lifetime risk of breast and ovarian cancer. When a family history of breast cancer is encountered, patients can be tested to determine whether they have normal expression of the BRAC1 and 2 genes. However, it now has become clear that there are histological differences in the tumors of patients with BRCA1 and 2 mutations, and these also differ from sporadic breast cancer cases. Although these differences have been noted, it is not absolutely possible to classify any given tumor based on the pathologic features alone, as there is considerable overlap among the 3 groups. The purpose of this paper was to determine whether distinctive patterns of gene expression could be determined that could differentiate BRCA1 mutant tumors from BRCA2 tumors. In addition, sporadic breast cancer tumors were included.

The material for this study included 7 patients with BRCA1 mutations, 7 patients with BRCA2 mutations, and 7 with sporadic primary breast cancer. Hedenfalk and colleagues used complimentary DNA samples representing 5361 unique genes. Appropriate laboratory handling of the specimens was performed. The statistical analyses were complicated, yet precise. Hedenfalk et al looked for associations between clinical variables and mutation type. Because of the large number of data points examined and the relatively small number of breast cancer samples, Hedenfalk et al used a technique called class-predication to help determine whether their classification was based on fact or chance. Several other complicated methods of analysis were used to help determine that their observed differences were not based on chance association.

Hedenfalk et al determined that it was possible to separate the BRCA1 mutation breast cancers from BRCA2 breast cancers based on significant differences in their gene-expression profiles. While histopathology and receptor analyses were able to grossly separate the lesions into BRCA1 and 2 types, this analysis was not as accurate as the development of the gene-expression profiles.

Hedenfalk et al did encounter 1 case of misclassification of a

Volume 17 • Number 12 • April 2001 • Pages 89-96

INSIDE

BRCA1 mutation. However, on further study of the patient, Hedenfalk et al found that while the BRCA1 was not mutated, the BRCA1 promoter region was abnormal, causing hypermethylation, which inactivates the BRCA1 gene.

Hedenfalk et al conclude that BRCA1 and 2 tumors can be differentiated based on their gene-expression patterns. (Hedenfalk I, et al. *N Engl J Med*. 2001;344:539-548).

COMMENT BY KENNETH L. NOLLER, MD

During the past several weeks, it has been almost impossible to turn on the nightly news without hearing some story about the completion of the "human genome project." According to these news sources, the sequencing of the human genome will now make it possible to wipe out all human disease, all congenital defects, obesity, and bad breath. While it is indeed likely that major breakthroughs in both the diagnosis and treatment of human disease will occur because of an increased knowledge of the human genome, it will occur only as a result of careful, detailed work such as that performed by Hedenfalk et al.

The reason I chose this article for review is that all of us in clinical medicine must now begin to learn an entirely new language. It will be virtually impossible to read the medical literature (and perhaps even to treat some patients) without better understanding the human genome and gene therapy. Unfortunately, to the present time, most of the work in this area has been buried deep in molecular biology journals and is written in some obscure laboratory babble. It was, therefore, refreshing to find an article, in what is perhaps the world's best clinical medical journal, that can serve as an introduction to gene jargon for many of us. I would definitely suggest seeking out the article but would also suggest that it be read in the following sequence: First, read the accompanying editorial, then read the article itself, then reread the editorial. Perhaps by spending a bit of time reading and rereading some of these articles that are presented in clinical journals (and some like this one even have color pictures), we may be able to understand the literature of gene therapy, eventually. It will be hard but necessary work. ❖

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Neill Larmore.
COPY EDITOR: Robert Kimball.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $33. Two to nine additional copies, $179 each; 10 or more additional copies, $159 each. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

Customer Service: 1-800-688-2421
Editorial E-Mail: robert.kimball@ahcpub.com
Customer Service E-Mail: customerservice@ahcpub.com

Subscription Prices
United States
$249 per year
Canada
Add GST and $30 shipping
Elsewhere
Add $30 shipping

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

This program has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of Jan. 1,

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517 or **Robert Kimball**, Copy Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Parke-Davis, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Parke-Davis, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Dr. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Sakombut, Dr. Noller, and Dr. Gabbe report no relationships related to this field of study.

Inhibition of Postmenopausal Atherosclerosis Progression

ABSTRACT & COMMENTARY

Synopsis: *Monkeys fed a diet containing soy phytoestrogens showed a better lipid and lipoprotein profile than those fed an otherwise equivalent diet in which conjugated equine estrogens replaced the soy phytoestrogens. However, atherosclerosis was inhibited more in the monkeys whose diet contained CEE.*

Source: Clarkson TB, et al. *J Clin Endocrinol Metab.* 2001;86:41-47.

In this study, 189 cynomolgus monkeys were randomized to 1 of 3 arms for 36 months. In 1 arm, monkeys were fed soy protein devoid of phytoestrogens; in another soy protein with phytoestrogens, and in the other soy protein with conjugated equine estrogens (CEE) given at a dose that approximates the standard 0.625 mg dose given to postmenopausal women. Outcome variables included measurement of plasma lipids and lipoproteins and extent of atherosclerosis. The groups that received phytoestrogen and CEE had comparable reductions in total cholesterol. The group that was given phytoestrogens had higher HDL levels, but the group that received CEE did not differ from the con-

trol group. Both the phytoestrogen and CEE groups had lower LDL levels than the control group. The group given CEE had higher triglyceride levels than the other 2 groups. Atherosclerosis progressed in the iliac arteries in 63% of the control group, 39% of the phytoestrogen group, and 35% of the CEE group. In the coronary arteries, CEE-treated monkeys had significantly less plaque than phytoestrogen-treated animals. In the carotid arteries, CEE was slightly more protective than phytoestrogens.

COMMENT BY SARAH L. BERGA, MD

Last month in *OB/GYN Clinical Alert*, I reviewed a study that reported the localization of estrogen receptor (ER) subtypes α and β in various human reproductive tissues.[1] A key finding was that both estrogen receptor subtypes displayed similar distribution patterns in breast tissue, while vaginal tissues expressed only ERα. Granted, both ER subtypes may not initiate the same activities in breast tissue, but they are both there. Of course, the main rationale for wanting to know the distribution pattern of ERs is that we hope that this knowledge will help us to design a "smarter" selective estrogen receptor modulator (SERM). However, as the distribution of ER subtypes shows, the hope of finding a perfect SERM based on selective expression of ER subtypes in key tissues is unwarranted.

This month's article concerns the cardiovascular actions in a cynomolgus monkey model of so-called "natural" SERMs, phytoestrogens. Phytoestrogens are isoflavones. They are primarily antioxidants, but they also bind to ERβ with 80% of the affinity of 17b-estradiol while binding only weakly to ERα. It is hoped that phytoestrogens will behave as estrogen agonists in brain, heart, vagina, pelvic floor, and bone, but as estrogen antagonists in uterus and breast, thus making them the "perfect" SERM. The present study is intended to determine to what extent phytoestrogens mimic estrogen's actions in the cardiovascular tree. However, we already know from last month's study that phytoestrogens are unlikely to be the perfect SERM, because they bind mostly to ERβ and the vagina does not express ERβ. Therefore, phytoestrogens are not predicted to maintain the urogenital tract in postmenopausal women. In tissues that express both ERα and ERβ, the consequences of only occupying ERβ are not predictable. Perhaps some of the dissociation between the strongly beneficial change in lipoprotein profiles and the weakly beneficial change in atherosclerosis progression observed in the group given phytoestrogens relates to the downstream consequences of just occupying ERβ. In some tissues such as breast, ERβ is thought to inhibit ERα action, and in breast both subtypes are localized similarly. However, the localization study did not determine ERα and ERβ distribution in the cardiovascular tree of humans. In the brain, the regions that express ERα differ markedly from those that express ERβ. Thus, ERβ occupancy alone may not be fully (or even partially) neuroprotective. In summary, one should be extremely cautious in advocating the use of phytoestrogens as a substitute for conventional estrogen preparations.

Let's consider phytoestrogens in another light, that is, as food. Here, I think that the evidence in aggregate supports the notion that the best diet is one that is replete with vegetables and fruits. The current recommendation is for 5 servings of vegetables and 5 servings of fruit daily. While the average "western" vegetable may not contain the same amount of phytoestrogen as soy on a weight basis, most, if not all, vegetables do contain phytoestrogens. Still, the benefits of fruits and vegetables may not parallel phytoestrogen content. Fruits and vegetables contain many wondrous ingredients, many of which remain unnamed. What makes sense to me, given the state of our knowledge, is to recommend a diet rich in fruits and vegetable (such as the DASH diet) and HRT for most postmenopausal women. ❖

Reference

1. Pelletier G, El-Alfy. *J Clin Endocrinol Metab*. 2000;85: 4835-4840.

Pattern of Lymph Node Metastases in Stage I Invasive Epithelial Ovarian Carcinomas

ABSTRACT & COMMENTARY

Synopsis: *Fifteen percent of patients with apparent stage I unilateral ovarian carcinoma have microscopic lymph node metastases, with contralateral nodal involvement seen in half the cases.*

Source: Cass I, et al. *Gynecol Oncol*. 2001;80:56-61.

Cass and colleagues identified 96 patients with stage I ovarian cancer visibly confined to 1 ovary. Pathology reports were reviewed to identify metastatic lymph node involvement, number of involved nodes, and their locations. Patients with gross disease in the pelvis or abdomen or those who had

grossly positive lymph nodes removed for debulking were excluded from this review. Fourteen of 96 patients (15%) had microscopically positive lymph nodes on pathologic review. All of these patients had grade 3 tumors. Grade 3 tumors were more commonly seen in lymph node-positive vs. lymph node-negative patients ($P < .001$). Pelvic nodes were positive in 7 patients (50%), paraaortic nodes in 5 patients (36%), and both in 2 patients (14%). Forty-two patients had lymph node sampling only on the side ipsilateral to the neoplastic ovary, 4 of whom (10%) had lymph node metastases. Fifty-four patients had bilateral sampling performed, 10 of whom (19%) had lymph node metastases. Of these 10 patients, isolated ipsilateral lymph node metastases were seen in 5 (50%) cases. Isolated contralateral lymph node metastases were seen in 3 (30%) cases, and bilateral metastases were seen in 2 (20%). Cass et al concluded that in this cohort of patients with clinical stage I ovarian cancer with disease limited to one ovary, bilateral lymph node sampling increased the identification of nodal metastases. Ipsilateral sampling may result in the understaging of patients. Bilateral pelvic and paraaortic lymph node sampling is recommended to accurately stage ovarian cancer.

COMMENT BY DAVID M. GERSHENSON, MD

Lymphatic drainage of the ovary is an understudied area. Available information, based on studies of the past 2 decades, suggests that lymph node involvement in ovarian cancer is common—as high as 75% in apparent stage III disease based on peritoneal assessment. The incidence of occult lymph node metastases in apparent stage I ovarian cancer in unknown, but existing studies estimate the rate to be between 5-25%. Thus, the results of this study are consistent with previous studies. A number of important points can be made about this study. First, studies of apparent early-stage ovarian cancer are difficult because stage I disease is relatively uncommon. This study is retrospective and comes from 2 large institutions. Second, the question addressed in this study is extremely difficult to study because of the low incidence of lymph node involvement in apparent stage I disease. Only 14 of 96 patients had positive findings; when one begins to subdivide patients, the numbers become small. Third, the prevailing thought is that apparent stage I ovarian cancer confined to one ovary only metastasizes to ipsilateral lymph nodes; this study demonstrates that this is a myth. Even at these two academic institutions, 42 of the 96 patients had only unilateral nodal sampling. And finally, as in endometrial cancer, there is no standard regarding the extent of lymph node sampling. The findings of this study would suggest that complete bilateral paraaortic and pelvic lymphadenectomy should be the standard in apparent stage I ovarian cancer. Ideally, the results of this study should be confirmed by a large, prospective, clinical trial. ❖

Polycystic Ovaries and the Obstetrician

ABSTRACT & COMMENTARY

Synopsis: *Women with polycystic ovaries had nearly a 3-fold increase in gestational diabetes compared to normal women.*

Source: Mikola M, et al. *Hum Reprod*. 2001;16: 226-229.

Mikola and colleagues from helsinki evaluated the obstetrical outcome in 99 women with polycystic ovaries compared with 712 normal women. Women with polycystic ovaries were heavier and older, hyperandrogenic, and had more multiple births because of ovulation induction. Comparing singleton pregnancies, there were no differences in birth weight. However, the c-section rate was 2-fold higher in the women with polycystic ovaries. The most important observed difference was nearly a 3-fold increase in gestational diabetes in the polycystic ovary group that was still a significant 2-fold increase after adjustment for weight, age, nulliparity, and multiple pregnancy. There was no difference in the incidence of preeclampsia.

COMMENT BY LEON SPEROFF, MD

Obstetricians-gynecologists now recognize two common conditions associated with an increase in insulin resistance resulting in hyperinsulinemia: 1) the hormonal changes associated with pregnancy; and 2) anovulation with polycystic ovaries, especially in overweight women. Combining the two produces a challenge to the pancreas of sufficient degree to make gestational diabetes a likely consequence. However, reports in the literature have not been uniform. An early report indicated that obesity was the major risk factor, not the polycystic state, and another found no increase in gestational diabetes.[1,2] One small study did report an increase in gestational diabetes.[3] The reason for these differences, it seems to me, is that the studies have been retrospective in nature, and most important, screening for gestational diabetes was not uniformly applied to the subjects. I would expect that a careful, prospective study with glu-

cose challenge screening applied to every patient would reveal an increased incidence of gestational diabetes in women with polycystic ovaries, although largely concentrated in overweight women. Until then, the combination of significant hyperinsulinemia and the high risk of developing adult onset diabetes mellitus at an early age makes it reasonable (indeed, mandatory) to provide appropriate screening and surveillance for gestational diabetes in every overweight pregnant woman who previously displayed all the characteristics of anovulation and polycystic ovaries.

Clinicians have rapidly learned that women with polycystic ovaries (especially overweight women) who are resistant to induction of ovulation with clomiphene successfully achieve pregnancy at a high rate with the use of metformin, either alone or in combination with clomiphene. This raises the question of whether it is appropriate to treat these pregnant women with an oral hypoglycemic agent. Sulfonylurea drugs have not been recommended because of their potential to produce hypoglycemia in the fetus and the possibility of teratogencity. Glyburide (a sulfonylurea drug), however, has been demonstrated in laboratory studies to cross the human placenta in insignificant amounts. A clinical trial randomized 404 women with gestational diabetes to glyburide or insulin, and the outcomes (birth weight, macrosomia, respiratory distress, hypoglycemia, fetal anomalies) were the same.[4] Glyburide was not detected in the cord serum.

What information is available for metformin? Coetzee and colleagues in South Africa have advocated for more than 20 years the use of metformin during pregnancy, even in the first trimester, reporting no evidence of teratogenicity or neonatal hypoglycemia.[5] A report from Copenhagen, however, indicated that women treated with metformin had a higher prevalence of preeclampsia and perinatal mortality compared with women treated with sufonylurea or insulin.[6] It is not clear to me, however, whether this was due to metformin or the influence of other risk factors; only a randomized trial would give the answer. In the laboratory, metformin does not affect human placental glucose uptake or transport.[7] In a small study of 19 women, metformin treatment continued through the first trimester reduced the rate of early spontaneous abortion, and there was no evidence of teratogenicity.[8]

Therefore, there is a growing story that treatment of pregnant women who were previously anovulatory and hyperinsulinemic with polycystic ovaries is worthwhile. At this point in time, it seems to me that treatment should not be initiated before 28 weeks of pregnancy, both because of the lingering concern of teratogenicity and because hypoglycemic treatment is not necessary any earlier. In an anovulatory, hyperinsulinemic woman with repetitive early pregnancy losses, I would offer the option of metformin treatment without interruption after pregnancy is achieved. ❖

References

1. Gjonnaess H. *Br J Obstet Gynaecol*. 1989;96:714-719.
2. Wortsman J, et al. *J Reprod Med*. 1991;36:659-661.
3. Radon PA, et al. *Obstet Gynecol*. 1999;94:194-197.
4. Langer O, et al. *N Engl J Med*. 2000;343:1134-1138.
5. Coetzee EJ. *S Afr Med J*. 1984;65:635-637.
6. Hellmuth E, et al. *Diabet Med*. 2000;17:507-511.
7. Elliott BD, et al. *Am J Obstet Gynecol*. 1997;176: 527-530.
8. Glueck CJ, et al. *Fertil Steril*. 2001;75:46-52.

Oligohydramnios

ABSTRACT & COMMENTARY

Synopsis: *Does oligohydramnios with intact membranes in a high-risk pregnancy represent a reason to deliver?*

Source: Magann EF, et al. *Obstet Gynecol*. 2000;96: 640-642.

Ultrasound assessment of amniotic fluid "adequacy" has been a component of fetal assessment ever since the introduction of the biophysical profile. The amniotic fluid index (AFI) represented an attempt to further refine the quantification of amniotic fluid. The "modified biophysical profile" that involved only 2 variables, nonstress test and assessment of amniotic fluid, emerged as a substitute for those clinicians not keen on spending the time and effort to observe fetal behavior (breathing, movement, and tone).

The obsession over the amount of amniotic fluid stems from the fact that conditions in which oligohydramnios occurs, such as intrauterine growth restriction (IUGR) and postmaturity, are associated with higher perinatal mortality and morbidity.

Over the last few years, a few reports have surfaced that question the concept that oligohydramnios, as such, is a reason to deliver. In one of these studies, Magann and colleagues evaluated 79 high-risk patients at 34 weeks or greater who had AFIs of less than 5 cm. These patients were empirically induced as part of a management protocol. Each patient's perinatal outcome was then compared with that of the next patient who had a similar high-risk

condition but had an AFI of 6 cm or more.

There was no significant difference in any outcome variable they analyzed, which included meconium-stained amniotic fluid, variable fetal heart rate decelerations, emergency cesarean section, Apgar scores, cord gases, and admissions to neonatal intensive care. Magann et al concluded that "high risk pregnancies with AFIs less than 5 cm appear to carry intrapartum complication rates similar to those of high risk pregnancies with an AFI greater than 5 cm."

COMMENT BY JOHN C. HOBBINS, MD

Oligohydramnios seems to have gotten a "bum rap." In many cases, its presence, in the absence of ruptured membranes, simply represents an adaptive maneuver of the fetus to shift blood away from organs such as the kidneys in favor of the brain, heart, and adrenals. Although this mechanism is put into action when the fetus is demanding more than the placenta can deliver, oligohydramnios is an early, rather than late, sign of fetal compromise, and by itself certainly is only a symptom rather than the culprit in a "supply line" problem.

In IUGR, oligohydramnios will precede a nonreassuring fetal heart rate tracing and/or metabolic acidemia (the best correlate of neurological morbidity) by many weeks.

Researchers have found a strong correlation between oligohydramnios and increased resistance (and decreased blood flow) in the fetal kidneys. We have noticed that oligohydramnios associated with IUGR is accompanied in virtually all cases with increased end diastolic flow in the middle cerebral arteries (MCA), suggesting simply an adaptive maneuver of the fetus to "spare" his/her brain in the face of adversity. However, the message that the fetus is sending us, especially in the premature fetus, is "don't deliver me unless there is other evidence of fetal compromise such as worrisome umbilical artery dopplers (or more recently, ductus venosus wave form abnormalities), or a nonreassuring fetal heart rate pattern." These are far more precise indicators of fetal condition than an ultrasound finding that is difficult to quantify, has a wide inter- and intra-patient day-to-day variation, and is so nonspecific.

Severe oligohydramnios should represent a reason to deliver a post-term patient, but isolated oligohydramnios is an undergrown fetus with otherwise normal testing may well be subjecting many fetuses to the unnecessary complications of prematurity and their mothers to injudicious inductions and unnecessary cesarean sections. ❖

Suggested Reading

1. Magann EF, et al. *Am J Obstet Gynecol*. 1999;180: 1354-1359.
2. Manning FA, et al. *Am J Obstet Gynecol.* 1980;136: 787-795.
3. Phelan JP, et al. *Am J Obstet Gynecol.* 1985;151: 304-308.
4. Arduini D, Rizzo G. *Obset Gynecol.* 1991;77:370-373.
5. Mari G, et al. *Obstet Gynecol.* 1993;81:560-564.
6. Veille JC, Kanaan C. *Am J Obstet Gynecol*. 1989;161: 1502-1507.
7. Hecher K. *Circulation*. 1995;91:129-138.
8. Selam B, et al. *Ultrasound Obstet Gynecol.* 2000;15: 403-406.

Special Feature

The Importance of Recognizing Hypothyroidism

By Sarah L. Berga, MD

We have all been taught various heuristics for when to screen for hypothyroidism, but most of us wonder if we are doing so correctly. Several lines of converging evidence suggest that the untoward consequences of subclinical hypothyroidism pose a serious threat to long-term health, especially for fetuses. Therefore, I thought a brief review of the topic would be timely.

First, I would like to offer some background. Hypothyroidism comes in 2 main flavors. Primary hypothyroidism occurs when the thyroid gland cannot adequately respond to adequate or increased thyroid-stimulating hormone (TSH) stimulation. In contrast, secondary hypothyroidism occurs when the thyroid-releasing hormone (TRH) or TSH message is too low to adequately stimulate the thyroid. In primary hypothyroidism, the TSH signal is generally modestly to greatly elevated. This is the type of hypothyroidism that can often be detected by obtaining a serum TSH. However, as we will review, occult primary hypothyroidism can exist when the TSH is at the upper limit of normal and thyroxine (T4) is at the lower limit of normal. This condition is often referred to as subclinical hypothyroidism or hypothyroxinemia. The major cause of hypothyroxinemia worldwide is iodine deficiency. Another common cause is autoimmune thyroiditis. The most common cause of secondary hypothyroidism is stress, either psychogenic and/or metabolic, such as is induced by

poor nutrition, chronic or severe acute illness, surgical procedures, and excessive exercise. In secondary hypothyroidism, the circulating TSH signal does not rise because there is decreased hypothalamic TRH drive. Thus, secondary hypothyroidism cannot be detected by measuring TSH alone. Given the above considerations, it should be obvious that to adequately screen for hypothyroidism, one must measure both TSH and free thyroxine. The question is not so much how to detect hypothyroidism, but when or in whom to look for it.

It is well recognized that primary hypothyroidism is associated with altered menstrual patterns.[6] Less well known is that functional forms of hypothalamic hypogonadism ranging from amenorrhea to luteal insufficiency have as a concomitant a spectrum of hypothalamic hypothyroidism.[1] Several mechanisms may be operant, but the most obvious is that the increased cortisol characteristic of functional hypothalamic hypogonadism blunts the thyroidal response to TSH and the pituitary response to TRH. Further, metabolic deficits induced by excess energy expenditure or inadequate or imbalanced energy intake may suppress TRH drive by mechanisms independent of cortisol. The combination of psychogenic and metabolic stress suppresses hypothalamic TRH drive maximally. This form of secondary hypothyroidism presents with TSH levels that are in the lower range of normal and thyroxine levels that are at or below the lower limit of normal. It represents an adaptive mechanism for ensuring survival in the face of challenge. Firm epidemiological data are not available to tell us how often menstrual disturbances are due to primary hypothyroidism or primary hyperthyroidism. However, the most common cause of amenorrhea in reproductive- age women is functional forms of hypothalamic hypogonadism. Further, nearly 50% of recreational runners had a mild form of hypothalamic hypogonadism, even when the menstrual interval was preserved.[3] Thus, there is good reason to recommend that all women with altered menstrual patterns be screened for hypothyroidism (and hyperthyroidism) by obtaining a TSH and free T4.

Another circumstance when thyroidal function is assessed is in the evaluation of infertility. It seems to be an almost universal practice to obtain a TSH level on the female partner even when ovulatory function is adequate. In the past, I have not felt that there was a sufficiently strong rationale for this practice. However, as I will review later in this article, based on emerging concepts, the main rationale for assessing thyroidal function in the female partner (with a TSH and free T4) is to detect occult hypothyroxinemia before pregnancy ensues.

The main reason for screening for hypothyroidism in perimenopausal and menopausal women seems clearer. The prevalence of primary forms of hypothyroidism increases with age and is sufficiently common in women 40 years of age so as to make screening worthwhile. Further, hypothyroidism can mimic many of the symptoms often attributed to the altered ovarian secretion that is the hallmark of the perimenopause and menopause. Since decreased T4 alters the clearance of sex steroids, failure to recognize hypothyroidism in this population may make hormone therapy problematic. For instance, delayed clearance of sex steroids may increase the risk menometrorrhagia or may alter (blunt or exaggerate) the response to customary estrogen doses. In my experience, hypothyroidism is more often a concomitant of menopause rather than the only cause of menopausal symptoms. It is also a cause of altered lipoprotein profiles that are often seen in this age group. Milder forms of hypothyroidism are common in women and deleterious to long-term health. Thus, screening for hypothyroidism in asymptomatic women at 5 year-intervals starting at 35 years of age has been shown to be cost effective.[2]

My main purpose in bringing this topic to your attention has to do with the terrible fetal consequences of maternal hypothyroxinemia.[5] In their review article, Morrelae de Escobar and colleagues offer a wealth of valuable information. Their article, in turn, was inspired by the recently published study by Haddow and colleagues.[4] This study demonstrated that clinically occult maternal thyroid deficiency due to autoimmune thyroiditis during pregnancy resulted in impaired neuropsychological development in the offspring. However, the study by Haddow et al heralds just the tip of the iceberg. As the article by Morreale de Escobar et al documents in detail, motor and cognitive impairment of progeny correlates with degree of maternal hypothyroxinemia, not circulating thyronine (T3) or TSH levels. The dependence upon T4 reflects the expression of nuclear thyroid receptors in the brain by the 10th week of human gestation, a period of active cortical neurogenesis. Since the fetal thyroid does not begin to function until 18-22 weeks of gestation, the maternal supply is the only fetal source until midgestation. Although T3 is the active hormone for the nuclear receptors, the developing brain must synthesize T3 in situ by converting T4 to T3. Thus, T4 is the critical substrate for cortical neurogenesis, not T3. The clinical consequences of maternal hypothyroxinemia can result in a spectrum that ranges from severe mental retardation to milder forms of impaired neuropsychological development. Further, the most common reason for subclinical hypothyroxinemia is not

autoimmune thyroiditis but iodine deficiency, an entity that is simply prevented by increasing dietary iodine. Apparently, 15% of North American women have outright iodine deficiency. While iodine deficiency is easy to treat, one must make certain that sufficient iodine is supplied before pregnancy, or failing that, as early in pregnancy as possible. The recommended intake is 200-300 mg daily, and it can be taken as potassium iodine or as part of a multivitamin. I checked the various multivitamin preparations at home in my cupboard and found that most did not contain iodine. The only one that did was the children's formulation.

Morreale de Escobar et al recommend that all pregnant women be screened early in pregnancy (no later than the 12th week) by obtaining TSH, free T4, thyroid peroxidase (TPO) antibodies, and possibly antithyroglobulin antibodies. When the manuscript by Haddow et al was published, the Endocrine Society issued a similar alert but did not call for testing of free T4 or antibodies. For the general Ob/Gyn, the critical take-home point is to screen early in pregnancy and to make sure that pregnant women or those who could become pregnant have sufficient iodine intake. For those of us involved in infertility care, the take-home message is to delay infertility treatment in hypothyroxinemic women until it is corrected. One must have a diagnosis first. Thus, rather than screening with a TSH, one must obtain also free T4 and possibly also antithyroid antibodies. For women with functional forms of hypothalamic hypogonadism, the optimal course of action is to initiate lifestyle changes that permit restoration of ovulatory adequacy. Ovulation induction is relatively contraindicated in recognition of the fact that women with functional hypothalamic hypogonadism also have functional hypothalamic hypothyroidism of the same magnitude as that found with subclinical autoimmune thyroiditis. Functional hypothalamic hypothyroidism corrects when ovulatory function resumes but persists if ovulation induction is undertaken in the absence of lifestyle and attitudinal adjustments. In the case of organic thyroidal disturbances, replacement with exogenous thyroxine or increasing iodine intake should correct the problem. It is not clear that thyroxine will have the same beneficial effects in the face of hypothalamic forms of hypothyroidism. ❖

References

1. Berga SL, et al. *J Clin Endocrinol Metab*. 1989;68: 301-308.
2. Danese MD, et al. *JAMA*. 1996;276:285-292.
3. De Souza MJ, et al. *J Clin Endocrinol Metab*. 1998;83:4220-4232.
4. Haddow JE, et al. *N Engl J Med*. 1999;341:549-555.
5. Morreale de Escobar G, et al. *J Clin Endocrinol Metab*. 2000;85:3975-3987.
6. Winters SJ, Berga SL. *The Endocrinologist*. 1997;7: 167-173.

CME Questions

10. According to the article by Hedenfalk et al, breast cancer tissue may be used to determine whether the patient has a BRCA1 or BRCA2 mutation with greatest accuracy using which of the following techniques?

a. Cytopathology
b. Histological evaluation
c. Tissue receptor analysis
d. Tumor gene-expression analysis

11. Which statement about phytoestrogens is true?

a. For postmenopausal women, a diet high in phytoestrogens provides equal cardiovascular protection as taking conjugated equine estrogens.
b. Phytoestrogens are likely to be devoid of any estrogenic action in breast tissue.
c. Phytoestrogens bind mostly to ERb and, therefore, do not have the same biological actions as conjugated equine estrogens.
d. Phytoestrogen use by postmenopausal women is likely to protect against the atrophic vaginitis.
e. Phytoestrogen use by postmenopausal women protects against dementia.

12. Based on available information, the incidence of occult lymph node metastases in apparent stage I ovarian cancer confined to 1 ovary is:

a. 5-10%.
b. 10-15%.
c. 5-25%.
d. 20-40%.
e. 40-50%.

13. The following statements regarding pregnancy and polycystic ovaries are true *except*:

a. Hyperinsulinemia increases the risk of gestational diabetes.
b. All anovulatory women who get pregnant should be screened for gestational diabetes.
c. Thus far, there is no evidence that metformin used in the first trimester is associated with teratogenicity.
d. Metformin treatment may be associated with an increased risk of pre-eclampsia.

In Future Issues:

Intravenous Cisplatin vs. Carboplatin in Ovarian Carcinoma