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Prenatal Maternal Anxiety Linked to Hyperactivity in Offspring as Teenagers

Bruce Jancin

Maternal somatic anxiety during pregnancy and early childhood is associated in dose-response fashion with increased hyperactivity symptoms in the offspring's teen years, research suggests. Perhaps most intriguing, the dose-response effect did not apply to the offspring of mothers in the highest quintile of somatic anxiety, as measured during pregnancy and early childhood.

"It's possible that a ceiling effect exists for those children who are exposed to continuous high levels of anxiety from pregnancy up to age 5," according to Blanca Bolea-Alamanac, PhD, from the Department of Psychiatry at the University of Toronto.

At the annual congress of the European College of Neuropsychopharmacology, Dr. Bolea-Alamanac provided an update from the landmark Avon Longitudinal Study of Parents and Offspring. This birth cohort study was conducted in Southwest England and followed women who were pregnant in 1990, and their 14,062 offspring, prospectively for 26 years.

Dr. Bolea-Alamanac offered several possible explanations for the apparent ceiling effect. One is that children continuously exposed to high levels of maternal stress hormones in utero and through breastfeeding become desensitized to the effects of those hormones in ways that affect their future behavior. Another possibility is that children exposed to very high levels of anxiety in early life later develop internalizing-type symptoms rather than externalizing hyperactivity-type symptoms.

Dr. Bolea-Alamanac's analysis included the 8,725 women with maternal anxiety assessments obtained at 18 and 32 weeks of pregnancy, as well as at 8 weeks, 8 months, 2.67 years, and 5 years postpartum. Maternal anxiety was measured using the Crown-Crisp Experiential Index, which provided a specific indicator of somatic anxiety via responses to questions including: Are you troubled by dizziness or shortness of breath?; Do you experience a tingling or prickling sensation in your body, arms, or legs?; Have you felt that you may faint, feel sick, or have indigestion?; and Do you experience extra sweating? Response options were "never," "sometimes," "often," or "very often." Hyperactivity symptoms were assessed in 3,417 of their offspring using the Strengths and Difficulties Questionnaire hyperactivity subscale.

All women experienced increased anxiety during pregnancy, peaking in the weeks shortly prior to delivery. But by examining the totality of data obtained at two timepoints in pregnancy and four points afterward, the psychiatrist was able to construct a model with five distinct quintiles of maternal anxiety.

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A logistic regression analysis adjusted for maternal age, alcohol intake, and education; life events during pregnancy; socioeconomic status; and the child's sex. Class 1, the reference class, was comprised of women with low anxiety during pregnancy and after delivery. In comparison, the women in classes 2, 3, and 4 were at statistically significantly increased risk for having a hyperactive teenager (relative risks, 1.44 for class 2, 1.87 for class 3, and 2.5 for class 4). In contrast, women in class 5—those who scored highest for somatic anxiety both in pregnancy and during the next five years—had only a nonsignificant trend toward an increased risk for having a hyperactive teenager.

This association seen in the Avon study is consistent with Barker's theory, according to Dr. Bolea-Alamanac. Developed by the prominent late British epidemiologist David Barker, MD, PhD, this theory holds that intrauterine influences interact with the environment at birth to produce specific disease risks for the child. Barker's theory has gained considerable traction over the years, as evidenced by the creation of the multidisciplinary International Society for Developmental Origins of Health and Disease.

Disclosures: Dr. Bolea-Alamanac reported having no relevant financial conflicts of interest.

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The Better Mammogram: Experts Explore Sensitivity of New Modalities

Kari Oakes

Is it time to think about "the better mammogram" as the new standard of care? Can nuclear medicine provide a cost-effective workaround for imaging of women with dense breasts? Leading breast-imaging researchers, speaking at a plenary session at the annual meeting of the North American Menopause Society, say it may be time to revisit current screening practices to take best advantage of today's technology.

DIGITAL BREAST TOMOSYNTHESIS

"Digital breast tomosynthesis is the new kid on the block for screening," said Emily F. Conant, MD, Professor of Radiology and Chief of Breast Imaging at the University of Pennsylvania, Philadelphia. "It's becoming the new standard of care in mammography."

Digital breast tomosynthesis (DBT) can involve simultaneous acquisition of a conventional 2D mammogram along with a series of images to create a 3D image. Another protocol, which delivers a lower radiation dose, produces a "synthetic" 2D reconstruction of 3D mammography. In either case, according to Dr. Conant, tomosynthesis is "a digital reformatting of data" that allows the radiologist to "open the book" of the 2D image to flip through the pages, seeing the 1-mm slices that comprise the final product.

In addition to making visible tumors that otherwise might be obscured by the overlay of dense breast tissue, DBT can help reduce the recall rate, with the 3D images providing immediate clarification at the initial appointment. Studies show that the recall rate can go down by as much as 31%, Dr. Conant said.

DBT has been shown to increase detection of invasive cancers, but it does not pick up more ductal carcinoma in situ. This fact helps address the problem of overdiagnosis of small tumors that might regress. Overall, cancer detection is reported to increase by up to 53% with DBT, Dr. Conant said.

When primarily retrospective American studies are taken together with smaller

prospective European studies, "the improvement in outcomes achieved with DBT directly addresses the major concerns regarding screening for breast cancer with mammography," she said.

However, studies to date have not offered DBT routinely to all comers. Since 2011, DBT has been offered to every woman screened at the University of Pennsylvania, at no additional cost. This created "a sort of natural experiment—there was no bias as to who got it." Three consecutive years' worth of outcomes have now been analyzed, Dr. Conant said.

Patient-level data from the University of Pennsylvania show statistically significant reductions in recall rate from diagnostic mammography alone. Also, researchers saw a steady increase in the rate of cancers detected per 1,000 patients, from 4.6 with digital mammography alone, to 6.1 by year three of DBT (*JAMA Oncol.* 2016 Jun 1;2[6]:737-743). This reflected the institutional learning curve with DBT, Dr. Conant said.

The data also showed "a promising trend down in false negatives," with an early reduction in cancers that were missed by DBT. Time is needed for mature cancer registry data to bear out these early trends, Dr. Conant added.

Other recent data show that DBT has promise to improve detection rates in a population of great interest: younger women, in whom there are often too many false positives and not enough cancers found. If the risk-benefit ratio for DBT continues to play out as the data pile up, "I would strongly suggest that we should be doing screening in the 40s," Dr. Conant said.

An important caveat, she noted, is that whether or not tomosynthesis is used, mammography captures anatomy, not physiology. Very dense breast tissue may still obscure a tumor, even when the tomographic slices are peeled back.

Though "DBT is 'the better mammogram,' additional outcome data are needed," Dr. Conant said, particularly studies that compare modalities, include subgroup analyses, and better delineate the effect of cancer biology.

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MOLECULAR BREAST IMAGING

Another imaging modality uses nuclear medicine to capture the physiologic changes that accompany cancer. Molecular breast imaging (MBI), or scintimammography, can help "unveil the reservoir of hidden cancers in dense breasts," said Deborah J. Rhodes, MD, Professor of Medicine at the Mayo Clinic, Rochester, Minnesota.

Dr. Rhodes—and her colleagues Michael O'Connor, PhD, Connie Hruska, PhD, Katie Hunt, MD, and Amy Conners, MD—uses a specialized array of gamma cameras to detect uptake of an injected radionuclide that's preferentially avid for tumor tissue. This technique can unmask smaller tumors not seen on mammography because it's not impeded by having to "see" through dense breast tissue.

The radiation dose for an MBI study is a bit more than for DBT, but less than a coronary calcium score scan. The cost is about one-tenth that of breast MRI, and interpretation is relatively straightforward, said Dr. Rhodes.

"The traditional measure of mammography's performance inflates its effectiveness," especially in dense breast tissue, said Dr. Rhodes. "What is the sensitivity of mammography in the dense breast? It depends

on what you measure it against."

When cancers detected by MRI or MBI are added, the sensitivity of mammography drops from the 86.9% reported by the Breast Cancer Surveillance Consortium to 21% to 31%, according to several published studies.

In one study, Dr. Rhodes and her colleagues found that the diagnostic yield per 1,000 patients with dense breasts by mammogram alone was 1.9 cancers. When MBI was added, that figure jumped to 8.8 cancers per 1,000 patients, an incremental gain of 363%.

"Tumor size matters profoundly," she added. "If a tumor is detected above 2 cm, long-term survival drops below 50%."

That contrasts with the better-than-80% long-term survival rate seen for those with subcentimeter tumors, even in node-positive disease. "Only a third of tumors are detected when they are less than 1 cm" with regular screening mammography, Dr. Rhodes said.

However, in 2016, the US Preventive Services Task Force concluded that the current evidence was insufficient to assess whether adjunctive screening for breast cancer using breast ultrasonography, MRI, DBT, or other methods should be used in women with dense breasts. The USPSTF noted that there weren't studies that addressed the effect of supplemental screening on breast cancer morbidity or mortality.

The problem is that it can take 20 years or more to demonstrate mortality reduction, meaning that "no other imaging modality can compete" with mammography when this yardstick is used, Dr. Rhodes said. "This insistence on a mortality endpoint before we change practice" is impeding progress in screening.

The American College of Obstetricians and Gynecologists "does not recommend adjunctive tests to screening mammography in women with dense breasts who are asymptomatic and have no additional risk factors." However, the organization "strongly supports additional research to identify more effective screening methods" that will improve outcomes and minimize false positives in women with dense breasts.

Though DBT is becoming more widely available, MBI is still primarily used in research centers. Both Dr. Conant and Dr. Rhodes acknowledged that since these techniques are not required to be covered by insurance, payment—and patient access—may vary. Both physicians said their home institutions have worked hard to keep costs down for their studies.

Disclosures: Dr. Conant is a consultant or advisory board member for Hologic. Dr. Rhodes reported having no conflicts of interest.

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Large Database Analysis Suggests Safety of Bariatric Surgery in Seniors

Ted Bosworth

Gastric bypass and sleeve gastrectomy procedures for weight loss should not be denied to patients older than 60, despite a slight increase in unadjusted mortality rates, according to an analysis of data from the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP).

Based on data that was collected in 2015 and submitted to MBSAQIP, "bariatric surgery is safe in the elderly, even in those 70 and older," reported Tallal Zeni, MD, Director of the Michigan Bariatric Institute in Livonia.

Although the analysis was drawn from one of the largest datasets to evaluate the safety of bariatric surgery in the elderly, it is not the first to conclude that morbidity and mortality rates are acceptably low, according to Dr. Zeni. This may explain why the proportion of bariatric procedures performed in patients ages 60 and older has been increasing. In figures provided by Dr. Zeni, that proportion rose from 2.7% during 1999-2005 to 10.1% during 2009-2013.

There were 16,568 patients older than 60 entered into the MBSAQIP database in 2015. When those were compared with the 117,443 younger patients, the unadjusted rates of morbidity (6.5% vs 6.0%) and mortality (0.3% v. 0.1%) were higher for the older patients, but "they are close," according to Dr. Zeni. Both rates reached significance by the conventional definition ($P < .05$), but he suggested that they are lower in this study than those in prior studies of MBSAQIP datasets and that they are acceptable relative to the anticipated health benefits.

Beyond age 60, no correlation could be made between increasing age and increasing risk for morbidity, mortality, or reoperation, according to Dr. Zeni.

Why should bariatric surgery be considered in older patients? He cited data from a study that showed life expectancy in a 70-year-old without functional limitations is 13 years. As a result, he added, "it behooves us to provide them with the best quality of life we can."

Relative to prior MBSAQIP evaluations of bariatric surgery in the elderly, the proportion of patients undergoing sleeve gastrectomy versus gastric bypass has been increasing, Dr. Zeni reported. In the analysis, approximately two-thirds of the bariatric procedures were performed with sleeve gastrectomy, which is higher than in previous analyses.

Based on rates of morbidity for those two surgical approaches, the trend makes sense. While the higher 30-day mortality for gastric bypass, compared with sleeve gastrectomy, was not significant (0.38% vs 0.26%), all-cause morbidity was almost two times greater for those undergoing gastric bypass than it was for those undergoing sleeve gastrectomy (10.61% vs 5.81%), Dr. Zeni reported.

Credit: Sergey Furtaev / Shutterstock

However, some of that difference may be explained by baseline disparities between the two groups. In the gastric bypass group, there were higher rates of preoperative diabetes (54% vs 40%), sleep apnea (57% vs 50%) and hyperlipidemia (59% vs 54%). Also, gastric bypass patients were more likely to have a history of a previous bariatric procedure (11% vs 8.5%) and to have an American Society of Anesthesiologists Physical Status score of 3 (84% vs 80%), according to Dr. Zeni.

The specific complications more common in the gastric bypass group than the sleeve gastrectomy group included anastomotic leak (0.56% vs 0.3%), surgical site infection (1.74% vs 0.61%), pneumonia (0.87% vs 0.32%), and bleeding (1.14% vs 0.5%). Al-

though the average operating time was 40 minutes longer in the bypass group, there were no significant differences in thromboembolic complications.

Overall, despite a modest increase in the risk for complications of bariatric surgery in elderly patients, that risk can be considered acceptable in relation to the potential health benefits, according to Dr. Zeni. He suggested that the data might encourage further growth in the rates of bariatric procedures among patients older than 60.

Disclosures: Dr. Zeni reports no relevant financial relationships.

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Salivary Biomarker for Huntington Disease Identified

M. Alexander Otto

Huntingtin protein—the key biomarker for Huntington disease (HD)—can be detected in saliva, which might prove to be an easy and inexpensive way to diagnose and monitor HD, and perhaps even predict clinical onset, according to investigators at the University of California, San Diego.

In a study of 178 subjects, they found that salivary total huntingtin protein (Htt) was significantly increased in saliva from individuals with HD, compared with controls without HD (mean, 0.775 ng/mL vs 0.359 ng/mL). Levels remained consistent throughout the day and from day to day, and were not affected by age or sex.

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Salivary Htt level also correlated with motor scores on the Unified Huntington's Disease Rating Scale (Spearman's rho = 0.264) and total functional capacity scores (Spearman's rho = –0.283).

Meanwhile, salivary mutant Htt levels were higher in gene-positive, premanifest HD subjects than in normal controls. Salivary C-reactive protein level was also significantly elevated in premanifest HD subjects (9,548 pg/mL vs 3,399 pg/mL), indicating a pathologic inflammatory or metabolic state. When considered together, the two measurements might herald the onset of symptoms.

There's an acute need for a convenient, inexpensive HD biomarker. Htt isn't often measured in clinical practice, and when it is, it's assessed from blood or cerebrospinal fluid. With salivary Htt, "you don't need any specialized personnel, [and samples] are easy to obtain and process," said lead investigator Jody Corey-Bloom, MD, PhD, Professor Emeritus of Neurosciences at the university. "They keep well and are very stable. We don't have to rush to get them somewhere."

"We are really excited about the potential of salivary Htt," she said at the annual meeting of the American Neurological Association. "We think this is going to be an easy way to follow patients."

The next step is to see how salivary Htt correlates with cerebrospinal fluid and blood levels. The team will also investigate it as a diagnostic tool; perhaps there's a cut point that diagnoses HD. "It's an intriguing idea," Dr. Corey-Bloom said.

Perhaps the greatest potential is for predicting disease onset so treatments can be started before symptoms emerge. There's nothing on the market yet that can delay or prevent progression, but trials are in the works for therapeutics that lower levels of mutant Htt in the brain. "If we can use something simple like salivary Htt [to start preemptive treatment] that would be phenomenal," she said. "That's the hope."

Subjects refrained from smoking, eating, drinking, and brushing their teeth for at least an hour before saliva samples were taken. Testing was done by Western blot and enzyme-linked immunosorbent assay.

Disclosures: The work was funded by the University of California, San Diego. Dr. Corey-Bloom said she had no relevant disclosures. **CR**

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