News and Views

Screen All Women for Breast Cancer Starting 40 Years, Says USPSTF

The United States Preventive Services Task Force (USPSTF) has suggested that all women aged 40 to 74 years should undergo screening for breast cancer biennially, i.e., once every 2 years, according to a new draft recommendation statement on May 9, 2023.[1]

Notably, the Task Force has lowered the age of initiation of screening to 40 years instead of 50 years as had been recommended in the 2016 guideline, which also said that the decision to start screening earlier than 50 years "should be an individual one".

It has been given Grade B recommendation, which according to the Task Force means that this service should be offered or provided as "*there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial*".[2]

These recommendations do not apply to high-risk women – those who have a personal history of breast cancer, presence of genetic markers (*BRCA* gene), those who have received high-dose radiation therapy to their chest when they were young or women who were found to have a high-risk lesion on earlier biopsies.

Additionally, the Task Force has made recommendations for women aged 75 years or older and women with dense breasts. It says that there is inadequate evidence if these women should undergo breast ultrasonography or magnetic resonance imaging (MRI) as screening modalities if their screening mammograms are negative. These statements have been given Grade I recommendation, which means that "*the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality or conflicting, and the balance of benefits and harms cannot be determined*".[2]

The draft recommendation statement is available on USPSTF website for comments till June 5, 2023.

References

1. Breast cancer: screening. May 09, 2023. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/breast-cancer-screening-adults#bcei-recommendation-title-area. Accessed May 10, 2023.
2. Grade definitions. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions. Accessed May 10, 2023.

Factors Increasing Risk of Perinatal Stroke

Smoking during pregnancy, neonatal infection and hypoglycemia are risk factors for perinatal stroke, according to a new study from New South Wales, Australia published in April 2023 issue of *The Journal of Paediatrics and Child Health*.[1]

This study analyzed 60 term infants with perinatal stroke reported between 2017 and 2019. Each infant was matched by gestational age and birth date with 3 healthy controls. There were 60% arterial strokes (neonatal arterial ischemic stroke [NAIS]), 35% venous strokes (neonatal hemorrhagic stroke [NHS] 30%, cerebral sinovenous thrombosis [CSVT] 3% and NHS + CSVT 2%) and 5% mixed strokes (NAIS + NHS 3% and NAIS + CSVT 2%). Out of the 60 cases included in the study, 57 were found to have multiple risk factors for perinatal stroke.

On univariate risk factor analysis, factors significantly associated with higher risk of perinatal stroke were low Apgar score (<7) at 1, 5 and 10 minutes of age; emergency cesarean section, abnormal cord blood gas, neonatal infection or sepsis, congenital heart disease, neonatal hypoglycemia and resuscitation at birth. While factors like multigravida, maternal age more than 35 years, history of miscarriage, stillbirth or neonatal death had lower associated risk of stroke.

On multivariate analysis, in the full multivariable logistic regression model, after adjusting for the other maternal and neonatal risk factors, the risk of perinatal stroke was markedly increased with a 1-minute Apgar score of <7 with odds ratio (OR) of 1.54. Other risk factors that were significantly associated with stroke were smoking during pregnancy with OR 1.48, 10-min Apgar score <7 (OR 1.26) and hypoglycemia (OR 1.49). In the reduced model (after selection of variables), the risk of stroke was increased by 39% with a maternal history of smoking; the risk increased 61% with a 1-min Apgar score <7, 27% with a 10-min Apgar score <7 and 39% with neonatal infection or sepsis.

Diagnosis of perinatal stroke is often challenging because of unknown cause, non-neurological presentation and multiple risk factors. This study has established exposure to smoking during pregnancy, 10-min Apgar score <7, neonatal infection and hypoglycemia as independent risk factors for perinatal stroke suggesting

a multifactorial etiology on account of prenatal, perinatal and neonatal factors.

Reference

1. Roy B, et al. Risk factors for perinatal stroke in term infants: a case-control study in Australia. J Paediatr Child Health. 2023;59(4):673-9.

Characterization of Knee Pain in Children

Very few children with the main complaint of knee pain referred to pediatric rheumatologist are likely to be diagnosed as juvenile idiopathic arthritis (JIA), according to a study published in the March 2023 issue of *The Journal of Paediatrics and Child Health*.[1] The presence of limping and elevated laboratory markers of acute inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were strongly associated with the diagnosis of JIA.

In this single-center study, researchers retrospectively analyzed medical records of 262 children with a complaint of knee pain. These children had been referred for pediatric rheumatological evaluation between October 2012 and June 2019. They were categorized into four groups: 32 children (12.2%) had confirmed JIA, 46 (17.6%) had inflammatory knee pain other than JIA, 57 (21.7%) had non-inflammatory knee pain, while in 127 children (48.5%), no musculoskeletal disorders were diagnosed. Infection-related arthritis and Lyme arthritis were the most frequent types of arthritis in children with inflammatory pain.

Compared to the other three groups, limping was more common in children who were diagnosed with JIA (84.4%); they were also found more often to have joint swelling (65.6%), decreased range of motion of the knee joint, both passive (71.0%) and active (77.4%). More than half (54.4%) of patients with non-inflammatory pain had significantly increased pain after physical activity versus the JIA and no disorders diagnosed groups. Patients with inflammatory knee pain had significantly less difficulty in climbing stairs than those with JIA or non-inflammatory pain.

On multivariate analysis, patients with inflammatory pain had pain in multiple joints and a positive family history of autoimmune diseases (39.1% vs. ~22% in JIA vs. 14% in non-inflammatory pain). Limping was absent in patients with non-inflammatory pain; pain in joints was limited to the knee and pain increased in intensity after physical activity in this group. Limping and ESR ≥10 were the risk factors in the JIA group.

Among children in the no disorders diagnosed group, the indicators were CRP <5 mg/L, no increase in pain after physical activity and ultrasound showed no musculoskeletal abnormalities.

Children with JIA were significantly younger than those in other groups with a mean age of 5.1 years versus 13.7 in inflammatory pain, 14.4 in non-inflammatory pain and 11.8 years in children with no disorders diagnosed. The JIA group also had leukocytosis, thrombocytosis, decreased hemoglobin and hematocrit levels and increased ESR and CRP levels.

"There is a need to identify specific factors that may indicate JIA as opposed to other causes of knee pain", note the authors. This study has attempted to characterize knee pain in children and provides "clinical clues", which can help the primary care physician to decide if these children need a rheumatological consultation. Seventy percent of children with knee pain, in this study, either had non-inflammatory pain suggestive of a mechanical pathology or had an indeterminate etiology. Only little more than 10% children, who were among the youngest, had a confirmed diagnosis of JIA in this study indicating that "knee pain alone, as a chief complaint, rarely leads to a final JIA diagnosis". It highlights the significance of a "well-documented medical history and detailed clinical examination" when examining a patient with knee pain.

Reference

1. Gorczyca D, et al. Knee pain as a reason for referral to a paediatric rheumatologist: a retrospective study. J Paediatr Child Health. 2023;59(3):439-44.

Advantages of Continuous Glucose Monitoring in Type 1 Diabetes

Young patients with type 1 diabetes who use continuous glucose monitoring (CGM) have lower rates of severe hypoglycemia and diabetic ketoacidosis (DKA) compared to those who self-monitor their blood glucose levels suggests a study published in *The Lancet Diabetes & Endocrinology*.[1]

A total of 32,117 type 1 diabetes patients with duration of diabetes of more than 1 year were selected for this study with an objective to compare the outcomes of CGM in 10,883 patients and blood glucose monitoring in 21,234 patients. Researchers also aimed to identify factors predicting risk of acute diabetes complications in these patients. The median age of the patients was 16.8 years and they had received treatment between January 2014 and June 2021.

The rate of severe hypoglycemia was significantly lower in patients on CGM compared to those who self-monitored their blood glucose levels; 6.74 per

100 patient-years versus 8.84 per 100 patient-years with an incidence rate ratio of 0.76. The rates of DKA were also lower in the CGM group; 3.72 per 100 patient-years versus 7.29 per 100 patient-years with an incidence rate ratio of 0.51. On a similar note, patients using CGM had statistically significant lower rates of hypoglycemic coma (1.01 vs. 1.96) and severe ketoacidosis (0.44 vs. 0.93).

The rates of severe hypoglycemia were found to correlate significantly with the time below the target glucose range (70-180 mg/dL). The incidence rate ratio was 1.69 for time ranging between 4.0% to 7.9% versus <4%. For time of ≥8%, the incidence rate ratio was 2.38 compared to time <4%. Glycemic variability also influenced the rates of severe hypoglycemia.

Factors affecting risk of DKA included glycemic variability and average sensor glucose, time in target glucose range and time above the target range. The incidence rate ratio for DKA was 1.77 for mean sensor glucose ranging between 150 to 178 mg/dL versus <150 mg/dL, which jumped to 8.66 for mean sensor glucose ≥210 mg/dL versus <150 mg/dL.

These findings indicate that use of CGM can reduce the incidence of acute diabetes-related complications in children, adolescents and young adults with type 1 diabetes on insulin. CGM, more than self-monitoring of blood glucose, was better able to identify at-risk patients. These patients should be followed-up on priority with adjustment of treatment if required.

Reference

1. Karges B, et al. Continuous glucose monitoring versus blood glucose monitoring for risk of severe hypoglycaemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a population-based study. Lancet Diabetes Endocrinol. 2023;11(5):314-23.

The First FDA-approved Treatment for Agitation in Alzheimer's Disease Dementia

Brexpiprazole, the atypical antipsychotic, has been accorded US Food and Drug Administration (FDA) approval for the treatment of agitation associated with Alzheimer's disease dementia.[1] The drug is available as oral tablets and is already approved for use in schizophrenia in adults and children aged 13 years and older and major depressive disorder in adults. However, it is not approved for the treatment of patients with dementia-related psychosis.

Management of agitation in persons with Alzheimer's disease is challenging. Symptoms of agitation include restlessness, pacing back and forth and even aggression, both physical and verbal.

Dose: The starting dose is 0.5 mg once daily for the first week; increase to 1 mg once daily for the next week and to 2 mg once daily on day 15. The maximum daily dose is 3 mg, which can be given after a minimum of 14 days depending upon clinical response and tolerability.

Side effects: Headache, dizziness, urinary tract infection, nasopharyngitis and sleep disturbances (somnolence and insomnia).

Warning: Brexpiprazole carries a Boxed Warning about risk of increased mortality in elderly patients with dementia-related psychosis and suicidal thoughts and behaviors.

Reference

1. FDA news release. FDA approves first drug to treat agitation symptoms associated with dementia due to Alzheimer's disease. May 11, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-agitation-symptoms-associated-dementia-due-alzheimers-disease. Accessed May 12, 2023.

Lung Manifestations in Psoriasis

Psoriasis is a chronic inflammatory skin disease and is now known to be a systemic disease, instead of just being a cutaneous condition as it was considered earlier. Its association with heart disease and gastrointestinal disease such as inflammatory bowel disease is now recognized. A new study published in the journal *Respiratory Medicine* conducted a study with the aim to describe the features of lung involvement in patients with psoriasis with varying severity of the skin disease.[1]

A team of researchers from Jordan, Qatar and USA recruited 59 patients with psoriasis with no history of respiratory symptoms or active lung disease. They underwent high-resolution computed tomography (HRCT) scans of the chest to screen for subclinical pulmonary manifestations and changes in the lung parenchyma.

Nearly 80% (47/59) of the study participants were found to have abnormal findings on the HRCT scan. The most frequently reported lesions in the lungs were micronodules (66.1%), followed by nonspecific interstitial changes (32.2%), including scarring, focal ground-glass opacities and pleural-parenchymal band or atelectasis. Emphysematous changes and calcified granulomas were also found. Older patients and those with long-standing psoriasis were more likely to have these lung abnormalities. However, no correlation was noted for severity of the cutaneous manifestations.

These findings illustrate a link between lung pathology and psoriasis. Hence, physicians should screen patients

with psoriasis for possible pulmonary involvement and address them accordingly, as needed. The authors have however called for "larger multicenter studies" to verify these findings.

Reference

1. Samrah SM, et al. Subclinical high-resolution chest CT scan features in psoriasis. Respir Med. 2023;212:107226.

A New Drug to Treat Menopausal Hot Flashes

The US FDA has approved a new drug to treat moderate to severe hot flashes associated with menopause. Fezolinetant, is a neurokinin 3 (NK3) receptor antagonist and is the first in this class of drugs.[1] The NK3 receptor is involved in the regulation of the body temperature by the brain. By binding to the receptor, fezolinetant binds to this receptor and inhibits its action.

Contraindications: Co-administration with CYP1A2 inhibitors (such as carbamazepine, fluvoxamine, ciprofloxacin), patients with known cirrhosis, severe renal damage or end-stage renal disease (ESRD).

Dose: 45 mg once daily orally; may be taken with meals or without meals. However, there is a caveat regarding administration. The drug has to be taken at the same time every day. If the dose is missed or delayed, it should be taken at the earliest. However, the same schedule should be followed the next day.

Side effects: Abdominal pain, diarrhea, back pain, insomnia, hot flush and raised hepatic enzymes.

Warning and precautions: Liver function tests should be done before starting the treatment and every 3 months for the initial 9 months of the treatment. Treatment should be discontinued if signs of liver damage such as nausea, vomiting, jaundice appear.

Reference

1. FDA news release. FDA approves novel drug to treat moderate to severe hot flashes caused by menopause. May 12, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-drug-treatmoderate-severe-hot-flashes-caused-menopause. Accessed May 13, 2023.

Microvascular Complications of Type 2 Diabetes and Risk of Heart Disease

To investigate the impact of microvascular diseases on the risks of macrovascular complications in patients with type 2 diabetes, Taiwanese patients with type 2 diabetes diagnosed within 1 year were identified from the National Health Insurance Research Database between January 2008 and December 2019. Patients with microvascular diseases were categorized as having diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, diabetic kidney disease and retinopathy, diabetic kidney disease and neuropathy, diabetic retinopathy and neuropathy and diabetic kidney disease, retinopathy and neuropathy.

Results published in the journal *Cardiovascular Diabetology* showed that patient who had diabetic retinopathy or diabetic kidney disease or diabetic neuropathy were at higher risk of cardiovascular disease (CVD) (such as coronary artery disease, stroke, heart failure) and related mortality versus patients who did not have a microvascular disease.

Based on propensity-score matching, three pairs of patients were defined: patients with diabetic kidney disease and retinopathy, patients with diabetic kidney disease and neuropathy and patients with diabetic retinopathy and neuropathy.

The risk of incident coronary artery disease was higher among patients with diabetic neuropathy compared to those with diabetic kidney disease with adjusted hazard ratio (aHR) of 1.07. Patients with diabetic retinopathy were more likely to suffer a stroke versus those with diabetic kidney disease with aHR of 1.11. Compared to diabetic kidney disease and diabetic retinopathy, the risk of stroke was significantly higher with diabetic neuropathy with aHR of 1.17 and 1.12, respectively. The odds of new-onset heart failure were higher with diabetic retinopathy versus diabetic kidney disease (aHR 1.43), while the risk of incident heart failure was considerably lower with diabetic neuropathy versus diabetic retinopathy (aHR 0.79).

This study has demonstrated the higher risk of CVD and related mortality in type 2 diabetes patients with early development of microvascular disease. The risk was further enhanced among those who had more than one microvascular disease. While all the three microvascular diseases investigated in this study were associated with heart disease, the risk of stroke was significant with diabetic neuropathy, while diabetic retinopathy was linked to greater risk of heart failure. "Further research may be needed to elucidate whether there are causal relationships and plausible mechanisms between retinopathy and heart failure, neuropathy and stroke" concluded the authors.

Reference

1. Yen FS, et al. Impact of individual microvascular disease on the risks of macrovascular complications in type 2 diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol. 2023;22(1):109.