12-21-19

Ann Intern Med 2019 Dec 17

Hospital at Home Is Supported by a Randomized Trial

Patients receiving hospital-level care at home had lower healthcare costs and fewer readmissions than did similar inpatients.

Providing hospital-level acute care for select patients at their homes — hospital-at-home (HaH) — has not been studied in randomized, controlled trials. Investigators at Boston's Brigham and Women's Hospital and Faulkner Hospital (a smaller community hospital in the same healthcare system) randomized 91 emergency department (ED) patients slated for non–intensive care unit hospital admission to receive either traditional inpatient hospital care or acute care at home, which included daily nurse and physician visits, intravenous medications, point-of-

care testing, remote monitoring, and video communication. Patients at high risk for clinical deterioration based on validated algorithms were excluded. Approximately 80% of included patients were admitted for infections, heart failure, or chronic obstructive pulmonary disease or asthma exacerbations.

Patients cared for in HaH spent significantly less of their care time sedentary (12% vs. 23%) or lying down (32% vs. 66%), used significantly fewer healthcare resources (e.g., lab orders, radiologic studies, specialty consultations); and were significantly less likely to require readmissions within 30 days (7% vs. 23%). Adjusted cost of HaH — and HaH plus 30-day post–acute care — was about two thirds the cost of traditional hospital care and remained significantly lower even when physician labor costs were incorporated. Length of stay, patient quality and safety measures, and patient satisfaction were similar between the two groups. No HaH patients were transferred back to an acute care hospital.

COMMENT: HaH requires substantial institutional planning, including home monitoring systems and support technology, staffing, ancillary services, and point-of-care testing for homes. Nevertheless, hospitals that run at or near capacity might benefit from systematically integrating an HaH model to relieve crowded EDs and lower hospital readmissions and costs.

CITATION(S): Levine DM et al. Hospital-level care at home for acutely ill adults: A randomized controlled trial. *Ann Intern Med* 2019 Dec 17; [e-pub]. (https://doi.org/10.7326/M19-0600)

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Proc Natl Acad Sci U S A 2019 Nov 19; 116:23505

Gene Therapy Protects Against Major Age-Related Diseases in Mice

Three mouse mo.dels of disease responded to therapy with the same "longevity" genes.

Aging once seemed inscrutable and inevitable. In recent years, however, scientists have identified molecular factors that control aging and have used that information to prolong life in several animal species. Do genes that attenuate aging do anything to protect against "age-related" diseases?

Using a viral vector, investigators introduced three longevity-associated genes into mice and showed that the genes produced their proteins appropriately. This vector-encoded combination gene therapy then was tested in several mouse models of human disease. In mice that develop cardiac hypertrophy and heart failure following aortic constriction, this gene therapy caused heart function to increase by 58%; in mice that develop renal medullary fibrosis and atrophy following ureteral constriction, this gene therapy led to 75% less atrophy. And in an experiment in which mice received a high-fat diet and gained substantial weight, those treated with the combination gene therapy (but not controls that received the viral vector only) had complete reversal of the weight gain and normalization of glucose tolerance, despite continuing high-fat diets. Necropsies revealed no adverse effects of this gene therapy.

COMMENT; Aging is a biological process that can be modified. This study suggests that molecular forces that slow aging might also protect against age-related diseases in mammals. Human studies are unlikely in the near future, but the advancing knowledge about aging biology **CITATION(S):** Davidsohn N et al. A single combination gene therapy treats multiple age-related diseases. *Proc Natl Acad Sci U S A* 2019 Nov 19; 116:23505. (https://doi.org/10.1073/pnas.1910073116)

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Science 2019 Nov 1; 366:628

Neurovascular Process Flushes Toxins from the Brain During Sleep

Interstitial fluid might carry toxins like β-amyloid out of the brain during slow-wave sleep.

We spend one third of our lives sleeping: But to what end? One function of sleep is to consolidate memories and to help with subsequent computational challenges. Studies in rodents have suggested another function: During sleep, increased volumes of interstitial fluid drain through a "glymphatic" system — a recently discovered set of small vessels like lymphatics that carry toxins (like β-amyloid) away from the brain (NEJM JW Gen Med Aug 21 2018; [e-pub] and *Nature* 2018; 560:185). Does this occur in humans?

In a new study, researchers evaluated sleeping humans with prolonged functional magnetic resonance imaging techniques coupled with electroencephalograms and identified a similar phenomenon: Slow-wave sleep leads to reductions in cerebral blood volume, increases in interstitial fluid, and increased flow of cerebrospinal fluid into the ventricles — a flushing of the brain. This study was not designed to demonstrate directly that a glymphatic system exists in the human brain (the concept still is controversial), but, as was seen in the rodent studies, it showed that slow-wave sleep generates increased interstitial fluid that is flushed out of the brain.

COMMENT; The suggestion that sleep might allow the brain to flush away toxins is fascinating and also might have therapeutic implications. People with dementias have shortened slow-wave sleep. Could the shortened slow-wave sleep cause less flushing of toxins, which in turn leads to or exacerbates dementia? If so, drugs that lengthen slow-wave sleep might help prevent or even treat dementia.

CITATION(S): Fultz NE et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* 2019 Nov 1; 366:628. (https://doi.org/10.1126/science.aax5440)

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JAMA Intern Med 2019 Nov 11

Does Testosterone Therapy Confer Risk for Venous Thromboembolism?

In a case-crossover study, testosterone therapy was associated with excess risk.

Testosterone therapy can induce hematologic abnormalities associated with hypercoagulability, but whether it actually confers excess risk for venous thromboembolism (VTE; i.e., deep venous thrombosis or pulmonary embolism) is controversial. In this study, researchers used U.S. national pharmacy and medical claims databases to identify about 40,000 men (mean age, 57) with incident VTE and at least 12 months of data before VTE. Patients with cancer were excluded. About 4% of these men had received testosterone prescriptions during the year before their VTE events.

The design of the study was "case-crossover," in which patients served as their own controls. When use of testosterone during the 6 months immediately preceding VTE (case period) was compared with use of testosterone during months 6 to 12 prior to VTE (the control period), testosterone therapy was associated significantly with development of VTE (odds ratio, ≈2.0). Outcomes were similar in patients with or without coded diagnoses of hypogonadism.

COMMENT; Medical claims and pharmacy data have many potential sources of error, including inaccuracy in capturing all hypogonadism diagnoses. This study emphasizes the proximate nature of testosterone therapy and incident VTE, not necessarily the absolute risk for VTE with or without testosterone therapy.

CITATION(S): Walker RF et al. Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. *JAMA Intern Med* 2019 Nov 11; [e-pub]. (https://doi.org/10.1001/jamainternmed.2019.5135)

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Lancet 2019 Nov 30; 394:1993

Few Effective Treatments Exist for Hand Osteoarthritis

A course of prednisolone might give short-term relief.

We have few effective therapies for people with hand osteoarthritis (OA); nonsteroidal anti-inflammatory drugs, other analgesics, and splints are only modestly effective. Because accumulating evidence points to an inflammatory component in OA, researchers in the Netherlands examined the effectiveness of short-term prednisolone in 92 patients with symptomatic hand OA. All patients had four or more distal and proximal interphalangeal joints involved, with at least one joint having soft tissue swelling and erythema, and an overall pain score ≥30 on a 100-point visual analog scale.

Patients were randomized to receive 10 mg of prednisolone or placebo daily for 6 weeks, followed by a 2-week taper. At 6 weeks (before drug tapering), finger pain had decreased by 21 points in the prednisolone group and by 5 points in the placebo group (a significant difference). At follow-up (6 weeks after tapering), pain had reverted to baseline for most participants. Soft tissue swelling and ultrasound markers were similar and unchanged from baseline in the two groups, and adverse events were similar.

COMMENT: This study confirms that low-dose prednisolone therapy can give temporary relief to patients with hand osteoarthritis, without affecting objective signs of inflammation. This raises a question about mechanism of action: Are steroids working locally as anti-inflammatories or centrally as pain modulators? Because relief is transient and repetitive courses might be needed, steroid courses for hand OA should be used only when immediate, short-term respite is necessary. I would not recommend steroids as a routine therapy. However, these results suggest that a search for a safer anti-inflammatory therapy or analgesic would be worthwhile.

CITATION(S): Kroon FPB et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): A double-blind, randomised, placebo-controlled trial. *Lancet* 2019 Nov 30; 394:1993. (https://doi.org/10.1016/S0140-6736(19)32489-4**)**

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Neurology 2019 Dec 3; 93:e2157

Does Physical Activity Affect Early Prodromal Parkinson Symptoms?

A long-term study suggests so.

Researchers sought to uncover a potential relationship between physical activity and prodromal features of Parkinson disease (PD) — features that precede the clinical diagnosis — using the Nurses' Health Study and the Health Professionals Follow-Up Study. Participants were followed from 1986 through 2012, with assessments at baseline and longitudinally at many consecutive 24-month periods thereafter.

The odds of manifesting three or more prodromal features associated with later emergence of PD were approximately 35% lower in the cohort of patients classified at the study baseline in the highest quintile of physical activity compared with the lowest quintile. These prodromal features were constipation, probable REM sleep behavior disorder, excessive

daytime sleepiness, depression, and pain. Certain prodromal features — hyposmia and impaired color vision — were not associated with physical activity.

COMMENT: The authors note previous research showing that more physical activity is associated with a decreased risk for later Parkinson disease. The current findings add to the literature by examining the effects on prodromal symptoms. An important weakness of this study was that prodromal features were not present at baseline. Additionally, early loss of dopamine in these patients may have contributed to less exercise. However, the authors highlight similar odds in a recent meta-analysis on physical activity and risk for PD, which showed a 34% lower risk with the highest rate of activity versus the lowest. Collectively, the evidence suggests that exercise is a reasonable recommendation for those at risk or worried about their risk for Parkinson disease.

CITATION(S): Hughes KC et al. Physical activity and prodromal features of Parkinson disease. *Neurology* 2019 Dec 3; 93:e2157. (https://doi.org/10.1212/WNL.0000000000008567)

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JAMA 2019 Dec 10; 322:2203

Do Children Conceived by Fertility Treatment Have Excess Risk for Cancer?

Cryopreserved embryo transfer, but not fresh embryo transfer, was associated with modestly increased risk.

To clarify whether children conceived as a result of fertility treatment are at excess risk for cancer, investigators linked the Danish health registry with the infertility cohort, resulting in 12.2 million person-years of follow-up (mean, 11.3 years) and identifying 2217 cases of cancer among >1,000,000 children from 1996 through 2012.

Incidence rates of childhood cancer were 17.5 per 100,000 children-years in those born to fertile women, 17.1 following fresh embryo in vitro fertilization (IVF), and 23.1 following intracytoplasmic sperm injection (ICSI). In contrast, the incidence rate was 44.4 among children conceived using cryopreserved embryos (hazard ratio, 2.4). Although the total number of cancer cases was small, children conceived using cryopreserved embryos appeared to have excess risk for leukemia and sympathetic nervous system tumors. Overall, children conceived after use of any fertility hormone were not at excess risk for childhood cancer.

COMMENT: This retrospective cohort study spanning 17 years in the Danish population provides reassurance that use of fertility hormones and fresh embryo transfer (IVF and ICSI) are not associated with increased risk for childhood cancer. However, the detection of a small excess risk following use of cryopreserved embryos is a new and worrisome finding. In clinical practice, embryo cryopreservation is most often used to facilitate single embryo transfer, thereby reducing the likelihood of multiple gestation — an important public health goal. Given the substantial risk for premature birth among children born from multiple gestations, it's unlikely that these new findings will diminish the use of embryo cryopreservation in fertility care.

CITATION(S): Hargreave M et al. Association between fertility treatment and cancer risk in children. *JAMA* 2019 Dec 10; 322:2203. (https://doi.org/10.1001/jama.2019.18037)

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JAMA Pediatr 2019 Dec 2

Autism Spectrum Disorder and Comorbid Mood and Anxiety Disorders

1+1=3: Autism significantly increases risks for both mood and anxiety disorders.

When Kanner described autistic disturbances of affective contact in 1943, he observed that one of the hallmark clinical features was an "anxiously obsessive desire for the maintenance of sameness." Many studies since have documented the prevalence of co-occurring psychiatric disorders in patients with autism spectrum disorder (ASD). In this population-based study, investigators leveraged a cohort of 31,220 individuals born from 1976 to 2000 in Olmsted County, Minnesota, to ascertain the prevalence of bipolar disorder, depression, and anxiety disorders in 1014 individuals with ASD, compared with 2028 age- and sex-matched controls.

Incident rates of these disorders by age 30 were as follows:

- Bipolar disorder: 7.3% in individuals with ASD and just 0.9% in controls
- Depression: 54.1% and 28.9%, respectively
- Anxiety disorder: 50.0% and 22.2%, respectively

Thus, patients with ASD were fully nine times more likely than controls to have clinically diagnosed bipolar disorder (hazard ratio, 9.34) and roughly three times more likely to be diagnosed with depression (HR, 2.81) or anxiety (HR, 3.45). Of people with one psychiatric diagnosis, those with ASD were significantly more likely than controls to meet criteria for a diagnosis in two or three categories (318 of 574 [55.3%] vs. 202 of 457 [44.2%]).

COMMENT; An ASD diagnosis can cast a large shadow that obscures the comorbid presence of treatable psychiatric illnesses. Indeed, the diagnostic tally might well exceed two additional conditions. While this study focused on mood and anxiety disorders, risk in people with ASD is also elevated for attention-deficit/hyperactivity disorder, suicide, and psychotic disorders. The growing appreciation for this psychiatric complexity underscores the importance of ongoing surveillance and appropriate mental-health supports for individuals with ASD.

CITATION(S): Kirsch AC et al. Association of comorbid mood and anxiety disorders with autism spectrum disorder. *JAMA Pediatr* 2019 Dec 2; [e-pub]. (https://doi.org/10.1001/jamapediatrics.2019.4368)

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JAMA 2019 Nov 26; 322:2020

Holiday Warning: Aspiration of Toy Parts Continues to Kill Children

During the past 50 years, pediatric aspiration deaths from small toy objects have decreased by 75% but remain a considerable cause of mortality.

The 1969 Child Protection and Toy Safety Act led to a series of efforts to reduce aspiration of small objects by children. Safety measures have since included the introduction of a small parts test cylinder in 1979, a recommendation regarding first aid for choking by the American Academy of Pediatrics (AAP) in 1988, and a requirement for choking hazard warnings on toys by the Child Safety Protection Act in 1994. Additional measures regarding recalls and manufacturer accountability were instituted by the Consumer Product Safety Improvement Act in 2008, and new guidelines on choking prevention were issued by the AAP in 2010.

To examine the effect of these efforts, investigators reviewed aspiration deaths from nonfood objects in children 0 to 17 years of age in the National Vital Statistics System from 1968 through 2017.

Results were as follows:

- Since 1969, 20,629 deaths occurred from aspiration of small objects.
- The annual rate of mortality from object aspiration fell from 1.02 per 100,000 children in 1968 (719 deaths) to 0.25 per 100,000 in 2017 (184 deaths).
- Among children <3 years of age, the annual rate of mortality fell by 2.8% from 1968 to 1991, 8.4% from 1991 to 1999, and 2.4% from 1999 to 2017.
- Among children ≥3 years of age, mortality rates were much lower than among younger children; the annual rate of mortality was unchanged from 1968 to 1976, and it fell by 2.1% from 1976 to 1992 and by 4.5% from 1992 to 2017.

COMMENT; These data demonstrate that policy changes have successfully reduced the number of childhood deaths from aspiration of toy parts, but also that too many children continue to die from object aspiration. Pediatricians should remind patients of this danger, perhaps by having informative literature available in the office or on websites, especially around the holiday season.

CITATION(S): Cramer JD et al. Object-related aspiration deaths in children and adolescents in the United States, 1968 to 2017. *JAMA* 2019 Nov 26; 322:2020. (https://doi.org/10.1001/jama.2019.15375)

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Lancet 2019 Dec 7; 394:2073

Another Case Series of Patients with Vaping-Associated Lung Injury

Most of the 60 patients felt better at 2 weeks but had persistently abnormal lung function.

Cases of acute e-cigarette, or vaping, product use–associated lung injury (EVALI) continue to be reported across the U.S., with ongoing investigation about etiology. Investigators prospectively studied 60 patients with EVALI who were cared for at 24 hospitals and 160 clinics in Utah. Average age of EVALI patients was 27; 80% were men; and all had vaped nicotine, tetrahydrocannabinol, or both. As noted in previous reports, a constellation of respiratory, constitutional, and gastrointestinal symptoms was virtually universal. More than half of patients were admitted to intensive care, although fewer than 20% received mechanical ventilation. A minority of patients underwent bronchoscopy, but in those who did, lipid laden macrophages were common.

Most patients received antibiotics, steroids, and oxygen; clinicians perceived that steroids usually led to rapid improvement. Barotrauma occurred in nearly one fifth of patients. Of 26 patients seen at 2-week follow-up, all felt better, but more than half had persistent dyspnea and cough. Follow-up chest radiographs were abnormal in most patients; the same was true for follow-up pulmonary function testing, with reduced diffusing capacity of the lung for carbon monoxide (DLCO) most commonly still abnormal.

COMMENT; Our understanding of EVALI continues to evolve. These findings highlight that not all patients with EVALI are critically ill, which elevates the importance of collecting vaping history in all clinical settings. In this series, most patients' symptoms improved significantly, but they still had persistent lung function abnormality at short-term follow-up.

CITATION(S): Blagev DP et al. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: A prospective observational cohort study. *Lancet* 2019 Dec 7; 394:2073. (https://doi.org/10.1016/S0140-6736(19)32679-0)

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Pediatrics 2019 Dec 11

Trampoline-Related Fractures Are on the Rise

The proportion of pediatric fractures related to trampoline use nearly doubled from 2008 to 2017, and these fractures are increasingly occurring at sports and recreational parks.

Trampolines have been a source of home entertainment and exercise for decades. Recently, however, trampoline parks have increased in popularity. In 2012, the American Academy of Pediatrics (AAP) recommended against recreational trampoline use due to injury risk but noted there was insufficient data regarding trampoline parks (*Pediatrics* 2012; 130:774).

These researchers used a nationwide injury surveillance database to characterize the nearly 1 million pediatric trampoline-related emergency department (ED) visits from 2008 to 2017. Fractures accounted for 27% of these ED visits, and the proportion of all pediatric fractures related to trampoline use nearly doubled over the study period (3.6% to 6.2%), with the steepest rise occurring after the AAP issued recommendations against trampoline use. Although most occurred at home, the odds of trampoline-related fractures occurring at places of sports or recreation increased by an estimated 32% per year.

COMMENT: Recreational trampoline use by children and adolescents, either at home or at recreational facilities, is dangerous. Although trampoline-related fractures comprised only 6% of all pediatric fractures in 2018, trampoline use is a completely modifiable risk factor. Further, this study only examined fractures, but the morbidity is much higher given that sprains, head injuries, lacerations, and contusions make up the other three-quarters of trampoline-related ED visits (*Pediatrics* 2016; 138: e20161236). All recreational activities carry some degree of risk; however, based on the cumulative data, my children will not be using trampolines — at home, at friends' houses, or at trampoline parks — and I continue to recommend the same for others' children as well.

CITATION(S): Hadley-Miller N et al. Trends in trampoline fractures: 2008–2017. *Pediatrics* 2019 Dec 11; [e-pub]. (https://doi.org/10.1542/peds.2019-0889)

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Obstet Gynecol 2020 Jan; 135:106

Urinary Tract Dysfunction: Another Consequence of Interpersonal Trauma

Urinary symptoms are common in midlife and older women — are they caused in part by intimate partner violence?

To elucidate the relation between interpersonal trauma and subsequent urinary dysfunction, investigators conducted a cross-sectional study of data from an observational, multiethnic cohort study of risk factors for urinary symptoms in women seen at an integrated healthcare system in northern California. Analysis adjusted for age, race and ethnicity, education, body-mass index, parity, menopausal status, prior hysterectomy, hormone therapy, and diuretic use was used to examine associations between urinary dysfunction and intimate partner violence (IPV), sexual assault, and symptoms of post-traumatic stress disorder (PTSD) in some 2000 women (age range, 40–80).

In all, 21% of women reported lifetime emotional IPV, 16% physical IPV, and 20% sexual assault; 23% met criteria for current PTSD. Forty-five percent of women reported weekly urinary incontinence of any type, with 23% reporting stress incontinence and 23% noting urge incontinence. Nocturia at least twice nightly was reported by 34% of participants. Emotional IPV was associated with increased incidence of all urinary symptoms. Physical IPV was not associated with incontinence but was associated with increased odds of frequent nocturia. Sexual assault was associated with increased odds of incontinence reported as bothersome. Women with a history of PTSD had increased odds of reporting all urinary symptoms assessed. Odds ratios for all these associations were <2.0 (and most were <1.5).

COMMENT: This study documents just how common urinary symptoms and history of IPV are among midlife and older women. While cross-sectional studies cannot confirm causality (and the associations here were not especially pronounced), the data reinforce the need to assess older women with urinary symptoms for any history of IPV. Interpersonal trauma may well be among the factors contributing to urinary symptoms later in life.

CITATION(S): Boyd BAJ et al. Interpersonal trauma as a marker of risk for urinary tract dysfunction in midlife and older women. *Obstet Gynecol* 2020 Jan; 135:106. (https://doi.org/10.1097/AOG.0000000000003586)

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Obstet Gynecol 2019 Nov; 134:1087

Are Childhood Experiences of Violence Linked to Pelvic Pain in Adulthood?

Women with chronic pelvic pain were more likely to have had adverse childhood experiences than women without the condition.

Adverse childhood experiences (ACEs) are associated with serious health issues (e.g., heart and lung diseases, cancer, substance use disorders). Might chronic pelvic pain also be linked to ACEs? To examine the association, investigators age-matched 60 women recruited at an initial visit to a chronic pelvic pain treatment clinic (mean age, 40; 52% Hispanic) with 60 women without pain who presented for initial annual gynecologic examinations at the same institution (mean age, 40; 35% Hispanic). ACEs (defined as experienced or witnessed emotional, physical, and sexual abuse) were assessed with a validated questionnaire.

Women with chronic pelvic pain were less educated, had more medical comorbidities, and were more likely to have other pain syndromes (e.g., fibromyalgia, chronic fatigue), recent opioid use, and depression and anxiety than those in the comparison group. They also reported significantly more ACEs (mean, 4; interquartile range, 2–6) than comparison women (mean, 1; range, 0–4), were significantly less likely to report 0 ACEs, and were more likely to have ≥4 ACEs. Adjusted for educational status, women with pelvic pain were nearly twice as likely to report ≥4 ACEs. Women with pelvic pain were more likely to have experienced all three types of abuse as well as to have witnessed domestic violence.

COMMENT: Although these results may have been affected by recall bias in the chronic pelvic pain group, they are consistent with the documented association between ACEs and other types of chronic pain. Furthermore, cultural differences are known to affect the expression of pain. A team approach to chronic pelvic pain that offers counseling and behavior modification could help address trauma history as well as pain.

CITATION(S): Krantz TE et al. Adverse childhood experiences among gynecology patients with chronic pelvic pain. *Obstet Gynecol* 2019 Nov; 134:1087. (https://doi.org/10.1097/AOG.0000000000003533)

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Obstet Gynecol 2019 Dec 5; 35:100

How Often Should Office Visits for Pessary Care Happen?

In a randomized trial, a 24-week visit interval was noninferior to a 12-week interval.

Vaginal pessaries represent a common, effective therapy for pelvic organ prolapse and stress urinary incontinence; however, vaginal mucosal erosions can complicate pessary use — and risk for erosions is likely affected by frequency with which the pessary is removed, cleaned, and reinserted. Investigators at a single U.S. hospital conducted a randomized trial involving women who were ongoing users of ring, incontinence dish, or Gelhorn pessaries; did not change their pessaries by themselves; and had no vaginal mucosal abnormalities. In all, 130 participants (mean age, 79; 91% white, 5%

black, 4% Hispanic; 74% using vaginal estrogen) were assigned to routine care (office visits for pessary changes every 12 weeks) or extended care (every 24 weeks).

At 48 weeks' follow-up, rates of vaginal epithelial erosion were 7.4% (routine care) and 1.7% (extended care), meeting the prespecified criteria for noninferiority of the extended interval for pessary care. Women in each group reported similar degrees of bothersome vaginal discharge (reported on a 5-point scale with higher numbers indicating greater degree of bother; mean scores, 1.4 [routine] and 1.3 [extended]).

COMMENT: Many women change their pessaries at home as often as daily or weekly; however, for those who rely on office visits for pessary care, this trial provides good-quality evidence that, among ongoing users, pessaries can be changed as seldom as every 24 weeks without compromising outcomes. An important study limitation is that, as most participants used vaginal estrogen, the findings may not apply to pessary use among women not using this form of hormone therapy.

CITATION(S): Propst K et al. Timing of office-based pessary care: A randomized controlled trial. *Obstet Gynecol* 2019 Dec 5; 35:100. (https://doi.org/10.1097/AOG.0000000000003580)

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Nature 2019 Oct; 574:264

One Fungal Genus Is Linked Strongly to Pancreatic Cancer

Malassezia-*triggered tumor growth involves activation of the C3 complement cascade*.

A meticulous series of experiments links one particular fungal genus to pancreatic cancer. Researchers showed that fungi from the genus *Malassezia* (particularly, *M. globosa*) travel from the gut through the sphincter of Oddi to the pancreas. Both in human pancreatic cancer and in a genetically engineered mouse model that develops pancreatic cancer, this fungal species is present in concentrations 3000 times higher than its concentrations in normal or benignly inflamed pancreatic tissue — an association not seen with any other gut fungi. Is this fungus an opportunistic colonizer of tumor tissue, or does the fungus encourage growth of the tumor?

In the mouse model, eliminating the fungus from the gut early in life slowed development of pancreatic cancer, and repopulating the mice with *Malassezia* (but not with other fungi) triggered tumor growth. The mechanism by which the fungus triggered tumor growth involved inflammation, particularly activation of the C3 complement cascade. The investigators think pancreatic tumors somehow encourage growth of *Malassezia* in the gut and the fungus then homes to the tumor and enhances tumor growth.

COMMENT: This intriguing study incriminates the fungal genus *Malassezia*, and particularly *M. globosa*, as a factor in pancreatic cancer. Interestingly, *M. globosa* is a cause of dandruff and previously has not been considered to be a gut pathogen. By linking pancreatic cancer to a particular organism, and by identifying the molecular mechanism by which the organism stimulates tumor growth, this research suggests new targets for attacking this malignancy.

CITATION(S): Aykut B et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature* 2019 Oct; 574:264. (https://doi.org/10.1038/s41586-019-1608-2)

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