

Internal Medicine

Evidence-based summaries of the
latest research in internal medicine

[ALERT]

ABSTRACT & COMMENTARY

Meat Consumption Associated with Less Anxiety and Depression

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SYNOPSIS: A meta-analysis of 20 studies showed meat consumption resulted in better mental health, with less anxiety and depression vs. meat abstinence.

SOURCE: Dobersek U, Teel K, Altmeyer S, et al. Meat and mental health: A meta-analysis of meat consumption, depression and anxiety. *Crit Rev Food Sci Nutr* 2021:1-18.

What we eat plays a major role in how we feel. Dobersek et al reviewed the literature regarding dietary intake and mental health disorders. The issue they studied was whether meat consumption or avoidance is associated with better mental health.

Twenty studies met the selection criteria, representing 171,802 participants (157,778 meat consumers and 13,259 meat abstainers). Most studies showed meat abstainers recorded higher rates of depression, anxiety, and self-harm, including suicide. Meat abstainers also were more likely to be prescribed medication for mental health problems. Conversely, the authors observed meat consumption was associated with significantly lower rates of depression ($P < 0.001$) and anxiety ($P = 0.02$). Their analysis showed the more rigorous

the study, the more positive and consistent the relation between meat consumption and better mental health.

■ COMMENTARY

Evolutionary biologists have shown ancient *Homo sapiens* were omnivores who ate both animal and plant foods.^{1,2} Our relatively large brains and narrow waistlines reflect this. What proportion of animal and plant foods we ate depended on our local geography as well as our skills as hunters and gatherers. Today, our food choices carry with it certain beliefs. Advocates for a plant-based diet (vegans and vegetarians) focus on data that support these beliefs.³ The same can be said of zealous carnivores.⁴

There was no apparent bias among the authors in their selection of studies. Since depression and anxiety

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are so common in medicine today, asking about diet may be important to give insight into these clinical conditions. People who were vegans for many years have reported a dramatic improvement in their well-being once they varied their diet to include healthy animal products.⁵ ■

REFERENCES

1. Lieberman D. *The Story of the Human Body: Evolution, Health and Disease*. New York: Vintage Books; 2014.
2. Harari YN. *Sapiens: A Brief History of Humankind*. New York: Harper Collins; 2015.
3. Greger M. *How Not to Die: Discover the Foods Scientifically Proven to Prevent and Reverse Disease*. New York: Flatiron Books; 2015.
4. Saladino P. *The Carnivore Code: Unlocking the Secrets to Optimal Health by Returning to Our Ancestral Diet*. Mariner Books; 2020.
5. Keith L. *The Vegetarian Myth: Food, Justice and Sustainability*. Crescent City, CA: Flashpoint Press; 2009.

SPECIAL FEATURE

COVID-19 Vaccination, Pregnancy, Lactation, and Fertility

By Katherine Rivlin, MD, MSc

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Pregnancy is independently associated with severe COVID-19 disease. Yet, with pregnant and lactating women excluded from participation in vaccine trials, the remaining information gap too often is filled with misinformation. With the increasing circulation of the delta variant, it has become critically important for clinicians to discuss COVID-19 vaccination with patients, and, specifically, to address concerns related to pregnancy, lactation, and fertility. The following is a review of the most recent guidance from the American College of Obstetricians and Gynecologists (ACOG), the Society of Maternal-Fetal Medicine (SMFM), and the American Society for Reproductive Medicine (ASRM) on vaccination in reproductive-age individuals.

VACCINE DEVELOPMENT, MECHANISMS OF ACTION, EFFICACY, AND SIDE EFFECTS

Considering the magnitude of the pandemic, the effort to develop vaccines has been rapid. Yet, no safety standards have been relaxed in this process. Instead, additional safety monitoring systems are in place to monitor and track vaccines, including real-time assessments. The FDA has issued an emergency use authorization (EUA) for three vaccines. The Pfizer-BioNTech (Pfizer) mRNA vaccine, for use in individuals age 12 years and older, is a two-dose regimen, given three weeks (or 21 days) apart. The Moderna mRNA vaccine, for use in individuals age 18 years

and older, is a two-dose regimen given one month (or 28 days) apart. The Johnson & Johnson vaccine, for use in individuals age 18 years and older, is a single-dose regimen.

mRNA VACCINES (PFIZER AND MODERNA)

mRNA vaccines are a novel vaccine technology. They consist of mRNA encapsulated in lipid nanoparticles for transportation into host cells. The host cells create coronavirus spike proteins, causing immune cells to make COVID-19 antibodies. These vaccines are not live and do not enter the host cell's nucleus or alter DNA. Their mechanism of action, the safety and efficacy data from Phase I and II trials, and the observational data collected since vaccine distribution all indicate mRNA vaccines are safe in pregnancy. The Pfizer vaccine is 95% effective and the Moderna vaccine is 94.1% effective in clinical trials at preventing laboratory-confirmed COVID-19 illness.¹

ADENOVIRUS-VECTOR VACCINES (J&J)

Adenovirus-vector vaccines are monovalent shots made of a recombinant human adenovirus. They encode a stabilized form of a coronavirus spike protein. The vaccine cannot replicate, is not live, and does not contain preservatives. Other adenovirus-vector vaccines studied in pregnancy, such as HIV and Ebola vaccines, have no known pregnancy-related safety concerns. Clinical trials indicate the J&J vaccine is 66.9%

effective at preventing moderate COVID-19 illness, 76.7% effective at preventing severe/critical COVID-19 illness, and 93.1% effective at preventing hospitalization related to COVID-19. Side effects from all three vaccines are common, expected, and indicate development of COVID-19 antibodies. Most people will experience mild flu-like symptoms, and clinicians should discuss this as part of anticipatory guidance. Allergic reactions, such as anaphylaxis, are rare. Clinicians should manage such reactions similarly in both pregnant and nonpregnant patients by notifying emergency medical services, placing the patient in the supine position, giving epinephrine, and monitoring for reoccurrence.¹

THROMBOSIS AND THROMBOCYTOPENIA SYNDROME

The FDA has added a warning and fact sheet to the J&J vaccine about the possibility of thrombosis and thrombocytopenia syndrome (TTS) following vaccination. TTS is rare, occurring in only 8.9 per 1 million doses of the J&J vaccine. Most incidences occurred in women of reproductive age, none of whom were pregnant. The risk of thrombosis increases in pregnancy, postpartum, and in patients using estrogen-containing contraceptives. However, these factors likely do not increase the risk of TTS after using the J&J vaccine. Therefore, ACOG does not recommend stopping estrogen-containing contraceptives after the J&J vaccine. Considering the high risk of serious illness from COVID-19 and the low incidence of TTS, women of reproductive age and pregnant patients still can receive the J&J vaccine.¹

SAFETY OF THE COVID-19 VACCINE IN PREGNANCY

Despite advocacy efforts by ACOG, SMFM, and the National Academy of Medicine to include pregnant and lactating individuals in vaccine trials, none of the COVID-19 vaccines approved under an EUA were tested in pregnant women. Unfortunately, the concept of “protection by exclusion” leads to experimentation on pregnant and lactating women outside of clinical trials, without the protections that clinical trials provide.² Although studies are underway, most of the current data come from post-marketing surveillance. One prospective cohort study showed vaccinated pregnant and lactating patients produced comparable immune responses to nonpregnant controls.³ In Phase II and Phase III trials, some inadvertent pregnancies occurred. Researchers are following these patients for safety outcomes. The CDC is monitoring more than 100,000 pregnancies through the v-safe post-vaccination health checker. Although self-reported, these data do not indicate pregnancy-related safety concerns. To date, the CDC’s v-safe pregnancy registry includes more than 6,000 pregnancies. Vaccine-related adverse events and side effects appear similar in pregnant and nonpregnant women. The post-vaccination miscarriage rate also appears consistent with the background rate, although a risk estimate is unavailable.⁴

SAFETY OF THE COVID-19 VACCINE DURING LACTATION

No biological plausibility exists to support a concern for lactating women and COVID-19 vaccination. ACOG and SMFM recommend vaccination for lactating patients. Although this population was not included in most clinical trials, the potential benefits far outweigh theoretical concerns. Patients can initiate and continue breastfeeding after COVID-19 vaccination. After natural COVID-19 infection, specific antibodies are present in human milk, which may offer protection to the newborn. In a prospective trial, vaccine-generated antibodies also were present in umbilical cord blood and breastmilk after maternal vaccination, which also may confer immunity.⁵

VACCINE SAFETY AMONG THOSE CONTEMPLATING PREGNANCY

Although fertility outcomes were not studied specifically in vaccine trials, ACOG, SMFM, and ASRM recommend COVID-19 vaccination for women actively trying to become pregnant or contemplating pregnancy. All COVID-19 vaccines available do not replicate and immediately clear from tissue following injection. Yet, misinformation around the COVID-19 vaccine and its effects on fertility is widespread on social media. The proposed mechanism of infertility relies on a presumed similarity between the SARS-CoV-2 spike protein and the syncytin-1, a protein necessary for the formation of the syncytiotrophoblast in a developing embryo. According to this theory, immune cross-reactivity could damage the trophoblast and prevent implantation. Such cross-reactivity not only would occur following vaccination, but also following natural illness. Yet, such cross-reactivity has never been demonstrated in laboratory analysis or in human clinical data, nor have effects on male fertility been shown.^{6,7} Anecdotal post-vaccine menstrual disturbances have been reported, but little evidence exists. Although environmental stresses can affect menses temporarily, no prior vaccines have been associated with changes to menses. The National Institutes of Health put out a special call for research on this issue.¹

CLINICAL CONSIDERATIONS AND CONCLUSIONS

Clinicians should understand vaccine hesitancy exists in all populations, but that historical and current healthcare injustices play an important role. Communities of color have been affected disproportionately by COVID-19, with higher rates of severe illness and death. Yet, Black and Latinx populations generally receive vaccines at lower rates, in part as the result of differential access. Clinicians should listen to and validate patient fears and concerns, while providing accurate information and resources for accessing vaccination.

Should patients decline vaccination, the clinician should continue to provide support and recommend protective measures, such as hand washing, social distancing,

and masking. Providers should discuss vaccination with individuals in future visits if they are amenable.¹ ACOG recommends discussing and documenting vaccination status with everyone. Patients need not undergo pregnancy testing or a conversation with clinicians before vaccination, although discussions can occur as needed. The COVID-19 vaccine can be administered simultaneously with other vaccines, including within 14 days of other shots. The CDC, ACOG, SMFM, and ASRM all recommend vaccination in pregnancy.⁸ Still, vaccination rates are notably low among pregnant women. Clinicians should underscore the safety of vaccination and the risks of natural infection, particularly in pregnancy and in patients with underlying comorbidities. Finally, the notable absence of pregnant and lactating women in vaccination trials and the lack of fertility outcomes all have left a notable gap in available evidence. Misinformation has filled this gap, even as we have relied on the public to accept vaccination to combat the pandemic. ■

REFERENCES

1. American College of Obstetricians and Gynecologists. COVID-19 vaccination considerations for obstetric-gynecologic care. Updated Nov. 3, 2021. <https://bit.ly/3HqU4tU>
2. Costantine MM, Landon MB, Saade GR. Protection by exclusion: Another missed opportunity to include pregnant women in research during the coronavirus disease 2019 (COVID-19) pandemic. *Obstet Gynecol* 2020;136:26-28.
3. Gray KJ, Bordt EA, Atyeo C, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: A cohort study. *Am J Obstet Gynecol* 2021; Mar 26:S0002-9378(21)00187-3. doi: 10.1016/j.ajog.2021.03.023. [Online ahead of print].
4. Centers for Disease Control and Prevention. V-safe COVID-19 Vaccine Pregnancy Registry. Updated Nov. 22, 2021. <https://bit.ly/3oz2RkL>
5. Juncker HG, Mulleners SJ, van Gils MJ, et al. The levels of SARS-CoV-2 specific antibodies in human milk following vaccination. *J Hum Lact* 2021;37:477-484.
6. Morris RS. SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility. *F S Rep* 2021;2:253-255.
7. American Society for Reproductive Medicine. Patient management and clinical recommendations during the coronavirus (COVID-19) pandemic. <https://bit.ly/3nkKvo6>
8. Centers for Disease Control and Prevention. COVID-19 vaccines while pregnant or breastfeeding. Updated Nov. 19, 2021. <https://bit.ly/3DhMzD3>

ABSTRACT & COMMENTARY

Environmental Shedding of MRSA Far Greater Than From Multidrug-Resistant Gram-Negative Bacilli

By *Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC*

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SYNOPSIS: An observational cohort study showed shedding of methicillin-resistant *Staphylococcus aureus* by colonized patients outside hospital rooms or during outpatient clinic visits occurred more often than in those colonized by multidrug-resistant gram-negative bacilli.

SOURCE: Alhmidi H, Cadnum JL, Koganti S, et al. Shedding of methicillin-resistant *Staphylococcus aureus* and multidrug-resistant gram-negative bacilli during outpatient appointments and procedures outside hospital rooms. *Am J Infect Control* 2021;49:991-994.

Patients colonized with pathogenic bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant gram-negative bacilli (MDR-GNB), are known to shed these organisms in their hospital rooms and during procedures. This leads to contamination of other people, environmental surfaces, and medical equipment. However, less is known about bacterial shedding outside patient rooms, such as at outpatient clinics, during physical therapy appointments, and in the radiology department. Alhmidi et al examined environmental shedding of MRSA and MDR-GNB by colonized patients in settings outside hospital rooms.

This was an observational cohort study that included patients in contact precautions for MDR-GNB or MRSA. MDR-GNB were defined as an extended-

spectrum beta-lactamase (ESBL)-producing GNB or a carbapenem-resistant GNB. A control group of 10 patients with no history of MRSA or MDR-GNB colonization and with negative baseline cultures also was included. Culture swabs were obtained of the anterior nares to determine MRSA colonization and from the skin and perirectal area for patients with MDR-GNB. Environmental shedding was assessed outside patient rooms for inpatients and during outpatient clinic visits within three months of hospital discharge. Investigators cleaned and disinfected environmental surfaces. Immediately after appointments, they used culture plates to recover MRSA or MDR-GNB from a standardized group of high-touch surfaces. For the first 10 appointments, they collected cultures before patients entered the room to ensure no MRSA

or MDR-GNB were recoverable. For patients known to be colonized with MRSA, spa typing was performed on environmental isolates. These were considered to be concordant with nares isolates if the spa type was the same. In those with MDR-GNB colonization, environmental isolates were considered concordant if the perirectal or skin isolates had the same species identification and susceptibility pattern.

There were 39 patients with MRSA colonization and 11 with MDR-GNB included in the study. The frequency of environmental shedding was significantly greater for MRSA (38%) vs. MDR-GNB (0%; $P = 0.02$). No MRSA or MDR-GNB were recovered from the 10 control patients. Following two outpatient appointments with MRSA-colonized patients, contamination was detected in the provider work area after a provider's hands contacted a patient without wearing gloves and did not perform hand hygiene. Spa typing was performed on 10 MRSA carriers, of whom eight had the same nasal and environmental isolates identified. Finally, the presence of a wound that was culture-positive for MRSA was the only significant characteristic associated with shedding.

■ COMMENTARY

The study by Alhmidi et al demonstrates the high frequency of MRSA shedding into the environment by colonized patients, particularly those with MRSA in their wounds. This provides strong evidence of the need for effective environmental decontamination in outpatient clinics and other sites where inpatient appointments occur, such as physical therapy, to reduce MRSA transmission. It also supports implementing other methods that might lead to less MRSA shedding.

such as chlorhexidine bathing, patient hand hygiene, and the use of intranasal mupirocin.

Of equal importance was the finding that MDR-GNB colonization did not lead to similar environmental shedding. This calls into question the appropriateness of contact isolation for patients colonized with MDR-GNB. Contact precautions carry several potential downsides, including patient dissatisfaction caused by less interaction with hospital staff, higher hospital costs (e.g., isolation gowns and gloves), and restricted visitation. These must be weighed against the potential of transmission of pathogenic bacteria to vulnerable patients, staff, and objects in the environment, such as medical equipment. Although the results of the study are reassuring in terms of the low risk of MDR-GNB shedding, further research is necessary to replicate this finding. There were a few limitations. First, the study was conducted at a single Veterans Affairs hospital, so the population almost entirely was older men. Thus, the results might not be generalizable to other groups. Second, there was a relatively small number ($n = 11$) of patients colonized with MDR-GNB. Third, 20% of the MRSA isolates featured spa types different from concurrent nasal isolates, which raises the possibility some MRSA isolates originated from healthcare workers or another source. Finally, healthcare workers were aware they were under observation. MRSA shedding can occur in other areas besides inpatient rooms. This has important policy ramifications for infection control personnel in their efforts to reduce the transmission of MRSA in healthcare facilities. Fortunately, the risk of transmission of MDR-GNB by colonized patients shedding into the environment appears to be much lower. ■

BRIEF REPORT

Intensive Blood Pressure Lowering Does Not Affect Small Vessel Disease Progression

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor and Chair, Department of Neurology; Associate Dean for Clinical Affairs, New York Presbyterian/Weill Cornell Medical College

SOURCE: Markus HS, Egle M, Croall ID, et al. PRESERVE: Randomized trial of intensive versus standard blood pressure control in small vessel disease. *Stroke* 2021;52:2484-2493.

Small vessel disease of the brain accounts for 20% to 25% of all ischemic strokes and is a common cause of vascular cognitive impairments. The major risk factor for small vessel disease is hypertension. The precise target blood pressure that is optimal to prevent stroke or long-term cognitive impairment in these patients is undetermined. To prevent other cardiovascular events, researchers have recommended targeting a systolic blood

pressure of 120 mmHg to 125 mmHg, but this has not been confirmed as effective in preventing stroke or long-term cognitive impairment. Because cerebral autoregulation is impaired in these patients, lowering the blood pressure too much runs the risk of accelerating white matter damage and making outcomes worse. Markus et al performed a randomized, multicenter, controlled, and blinded-to-outcomes clinical trial with 111 patients

who had MRI-confirmed symptomatic lacunar infarcts and extensive white matter hyperintensities. They were randomized into one of two groups: targeting a systolic blood pressure of 130 mmHg to 140 mmHg or intensive blood pressure lowering, targeting systolic blood pressure of < 125 mmHg. The primary endpoint was a change in diffusion tensor imaging of white matter mean diffusivity between baseline evaluation and 24 months of treatment. Secondary endpoints were imaging markers of recurrent stroke, progression of white matter abnormalities, and cognitive impairments. The mean age

of the patients was 60 years, and 60% were men. The mean blood pressure reduction was 15.3 mmHg and 23.1 mmHg in the standard and intensive groups, respectively ($P < 0.001$). There was no difference between the treatment groups in the primary endpoint, and no significant difference between white matter hyperintensities or a decrease in cognition over the 24 months of follow-up. The investigators concluded intensive blood pressure lowering was not associated with worsening but did not demonstrate any benefit in this population over standard blood pressure management. ■

PHARMACOLOGY UPDATE

Varenicline Nasal Spray (Tyrvaya)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

The FDA has approved a nasal spray to treat dry eyes using the nasolacrimal reflex pathway. The active ingredient, varenicline (a selective partial agonist of the alpha-4 beta-2 nicotine acetylcholine receptor) has been used as pharmacotherapy for smoking cessation since 2006. The nasal spray is marketed as Tyrvaya.

INDICATIONS

Varenicline nasal spray (NS) is indicated to treat the signs and symptoms of dry eye disease.¹

DOSAGE

The recommended dose is one spray in each nostril twice daily, approximately 12 hours apart.¹ Varenicline NS is available in a device that delivers 0.03 mg with each actuation. Each bottle is expected to last 15 days based on the recommended dose.

POTENTIAL ADVANTAGES

Varenicline NS provides a drug with a different mode of action to treat dry eye disease and is an option for patients who struggle with eye drops.

POTENTIAL DISADVANTAGES

Frequently reported adverse reactions were sneezing (82%), cough (16%), throat irritation (13%), and nose irritation (8%).¹ Some patients may find these adverse reactions bothersome. Long-term safety, tolerability, and effectiveness have not been established. In clinical trials, the maximum exposure was 105 days.¹

COMMENTS

Varenicline increases production of basal tear film and is believed to cause chemical activation of the trigeminal parasympathetic nasolacrimal reflex pathway.^{1,2} Afferent (sensory) pathways, including

ophthalmic and maxillary branches, are found in nasal mucosa. Its efficacy was supported by two randomized, double-masked, vehicle-controlled studies (ONSET-1 [n = 91] and ONSET-2 [n = 512]).¹ Subjects had a baseline anesthetized Schirmer score of about 5 mm. This test involves applying a sterile paper strip into the inferior-temporal aspect of the conjunctival sac of each eye. The wetted length (in millimeters) is used to quantify basal tear secretion.³ At the recommended dose, 52% of subjects achieved 10 mm or better improvement from baseline at day 28 vs. 14% with the vehicle in ONSET-1, and 47% and 28%, respectively, for ONSET-2. The mean change was 11.7 mm and 11.3 mm vs. 3.2 mm and 6.3 mm, respectively. A Schirmer score > 15 mm is normal basal tear secretion, and mildly dry is between 10 mm and 15 mm. The systemic exposure following one spray in each nostril at twice the recommended dose (0.06 mg) is approximately 7.5% of a 1 mg oral dose of varenicline (half the dose for smoking cessation).¹

CLINICAL IMPLICATIONS

Dry eye disease is a multifactorial condition (e.g., tear film instability and ocular surface inflammation) and is estimated to occur in 9.3% of adults.^{3,4} Risk factors include age, female gender, use of contact lens, low humidity environment, and autoimmune disease. Currently, there are two FDA-approved pharmacotherapies with anti-inflammatory properties: topical cyclosporine and topical lifitegrast. A Cochrane Review showed the evidence of effect for cyclosporine to be inconsistent and may not be different from vehicle or artificial tears.⁵ In addition, it may take three months to show clinical efficacy.³ Lifitegrast significantly improved symptoms as assessed by eye dryness score as early as day 14.⁶ A neurostimulator (iTear100) received FDA approval in May 2020.⁷

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This device stimulates the trigeminal nerve through application to the skin of the external nasal region for up to 30 seconds. An earlier intranasal neurostimulator (TrueTear) was discontinued because of prohibitive cost.⁸ There are no direct comparisons between varenicline NS and topical cyclosporine, lifitegrast, or the neurostimulators. Varenicline offers another option with a different mode of action. The cost for a 30-day supply (two bottles) is \$492.29. ■

REFERENCES

1. Oyster Point Pharma. Tyrvaya prescribing information. October 2021. <https://bit.ly/3FKarQJ>
2. O'Neil EC, Henderson M, Massaro-Giordano M, Bunya VY. Advances in dry eye disease. *Curr Opin Ophthalmol* 2019;30:166-178.

3. Science Direct. Schirmer test. <https://bit.ly/3oY2aBY>
4. Baiula M, Spampinato S. Experimental pharmacotherapy for dry eye disease: A review. *J Exp Pharmacol* 2021;13:345-358.
5. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine: A therapy for dry eye syndrome. *Cochrane Database Syst Rev* 2019;9:CD010051.
6. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: Results of a Phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). *Ophthalmology* 2017;124:53-60.
7. Olympic Ophthalmics. Olympic Ophthalmics receives FDA clearance for iTEAR100 neurostimulator. May 14, 2020. <https://prn.to/3CBMuZO>
8. Yu MD, Park JK, Kossler AL. Stimulating tear production: Spotlight on neurostimulation. *Clin Ophthalmol* 2021;15:4219-4226.

CME QUESTIONS

- Which statement is true regarding fertility and the COVID-19 vaccine?
a. The COVID-19 vaccine has been associated with a higher miscarriage rate than the background rate.
b. Cross-reactivity between the SARS-CoV-2 spike protein and the syncytin-1 protein have been shown to affect implantation in animal models.
c. Fertility and menstrual disorder outcomes were studied specifically in vaccine trials.
d. The American College of Obstetricians and Gynecologists, the Society of Maternal-Fetal Medicine, and the American Society for Reproductive Medicine all recommend COVID-19 vaccination for women actively trying for or contemplating pregnancy.
- In a meta-analysis, Dobersek et al observed meat consumption was associated with:
a. higher rates of depression.
b. more anxiety.
c. more episodes of self-harm.
d. better mental health.
- Which is correct regarding shedding of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant gram-negative bacilli (MDR-GNB) by colonized patients?
a. MDR-GNB and MRSA are shed with equal frequency.
b. MRSA is shed with greater frequency than MDR-GNB.
c. MDR-GNB is shed with greater frequency than MRSA.
d. Neither MRSA nor MDR-GNB are shed.
- Intensive lowering of blood pressure to systolic < 125 mmHg results in a lower risk of recurrent stroke and dementia.
a. True
b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

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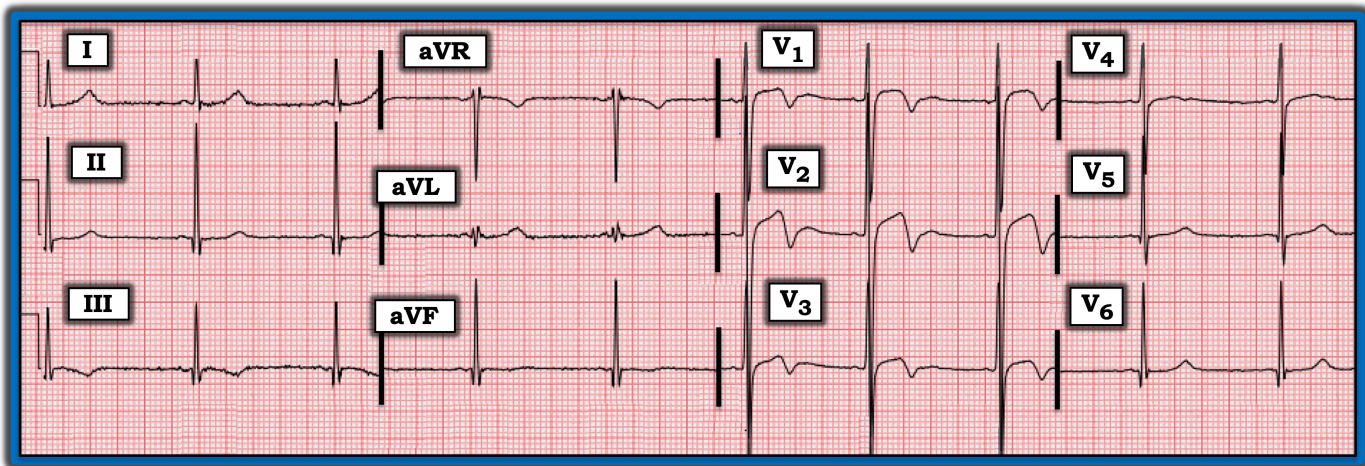
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Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Is This Wellens' Syndrome?

The ECG in the figure below is from a young adult man known to have a bicuspid aortic valve. He presented to the ED following a presyncopal episode. The patient has not experienced chest pain recently. Does this patient have Wellens' syndrome?



There is sinus arrhythmia at a fairly slow rate. The PR interval is a little short (0.11 to 0.12 seconds in duration), although this is not necessarily an abnormal finding for a young adult. QRS duration, the QTc interval, and the frontal plane axis all are normal.

QRS amplitude often is increased in younger adults. Voltage criteria for left ventricular hypertrophy probably are satisfied nonetheless, considering the tall R waves in leads II and V5, and especially considering the extremely deep anterior S waves (well over 20 mm in lead V2, and so deep that S waves are cut off in lead V3).

Deeper-than-usual Q waves are seen in each inferior lead, as well as in lateral chest lead V6 (with a tiny q wave in lead V5). In addition, there are prominent anterior forces (an R wave in lead V1 of ~9 mm, followed by a huge R wave measuring 24 mm in anterior lead V2). These two features should suggest the possibility of hypertrophic cardiomyopathy.

That said, the most remarkable ECG finding is anterior ST-segment coving with slight elevation, followed by a steep downsloping of the T wave (especially in lead V2) that ends in terminal T wave inversion. The ST-T wave picture in the anterior leads of this tracing resembles the changes seen with Wellens' syndrome, in which there is a high-grade stenosis of

the proximal left anterior descending coronary artery. Nevertheless, there are several clinical and ECG features in this case that suggest this patient does not have Wellens' syndrome.

The patient is a younger adult; therefore, he is likely to be in a lower prevalence group for coronary disease. A history of recent chest pain that has resolved by the time the ECG is obtained is expected with Wellens' syndrome, yet there was no history of chest pain in this case. The QTc interval is normal here, but, typically, it is prolonged with Wellens' syndrome. There is early transition, with extremely prominent anterior R waves in this case, whereas there usually is loss of anterior forces with Wellens' syndrome. Finally, there is markedly increased QRS amplitude, which often makes recognition of Wellens' syndrome problematic.

Further evaluation of this patient suggested no underlying coronary disease. Echo ruled out chamber enlargement and hypertrophic cardiomyopathy. By exclusion, clinicians believed this patient was living with a repolarization variant, which can (especially in a young adult) produce the ECG pattern of increased voltage, early transition, and ST-T wave changes similar to those seen in the figure.

For more information about and further discussion of this case, please visit: <https://bit.ly/2Yqmp1d>.