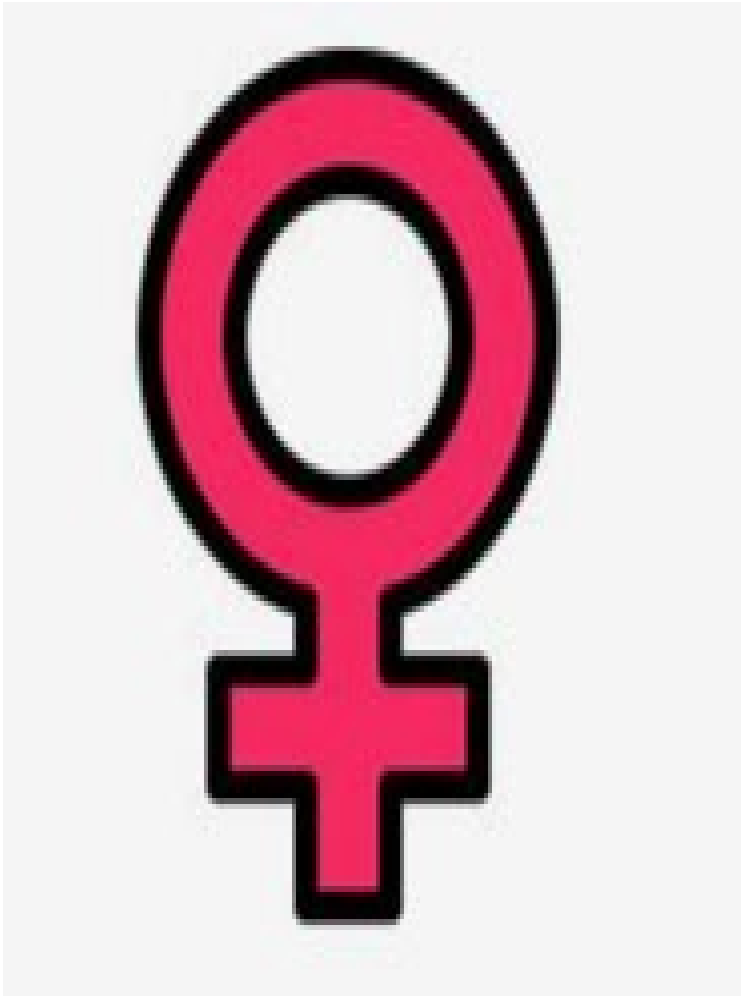
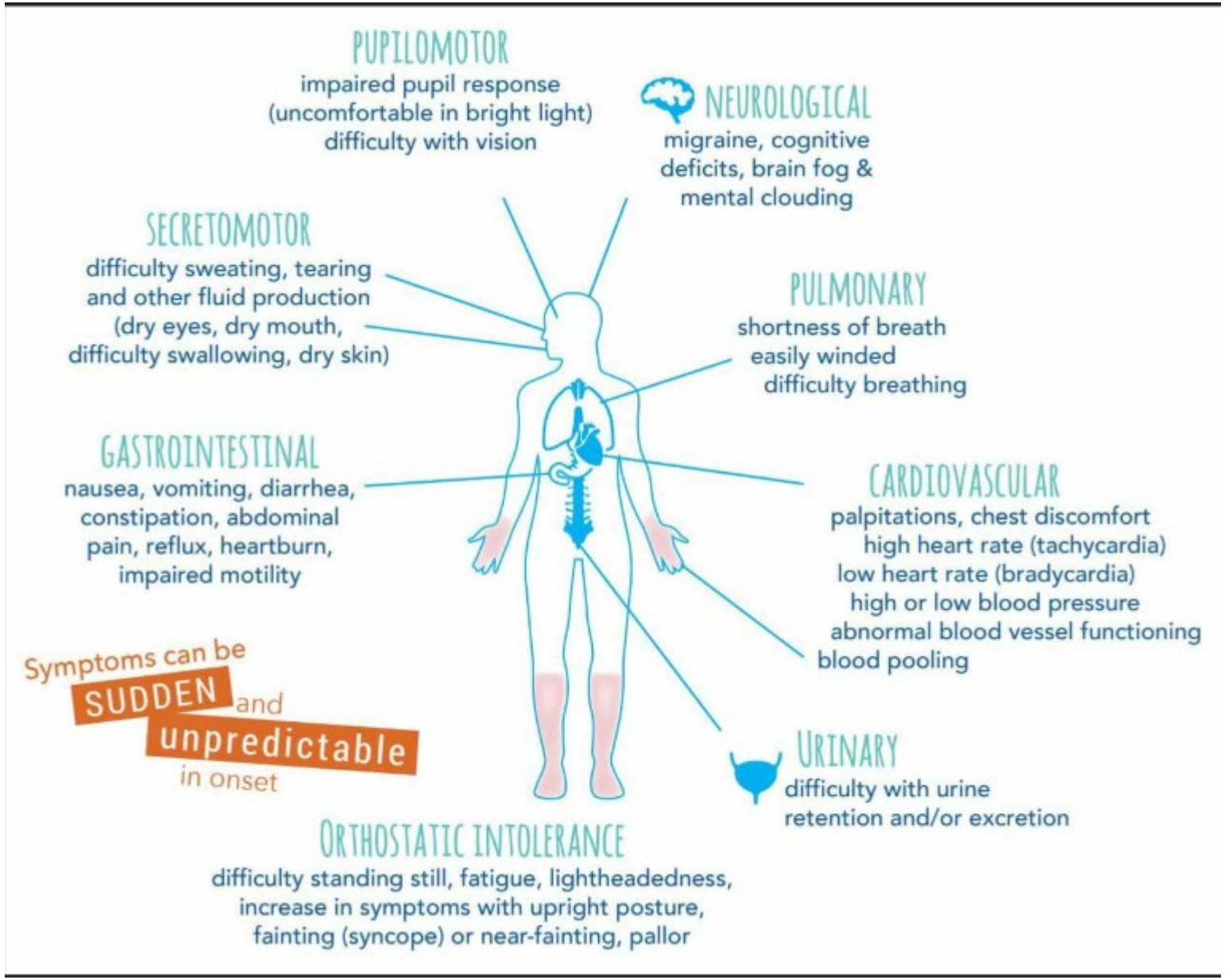


AUTONOMIC DISORDERS IN WOMEN

Aditi Varma-Doyle, MD

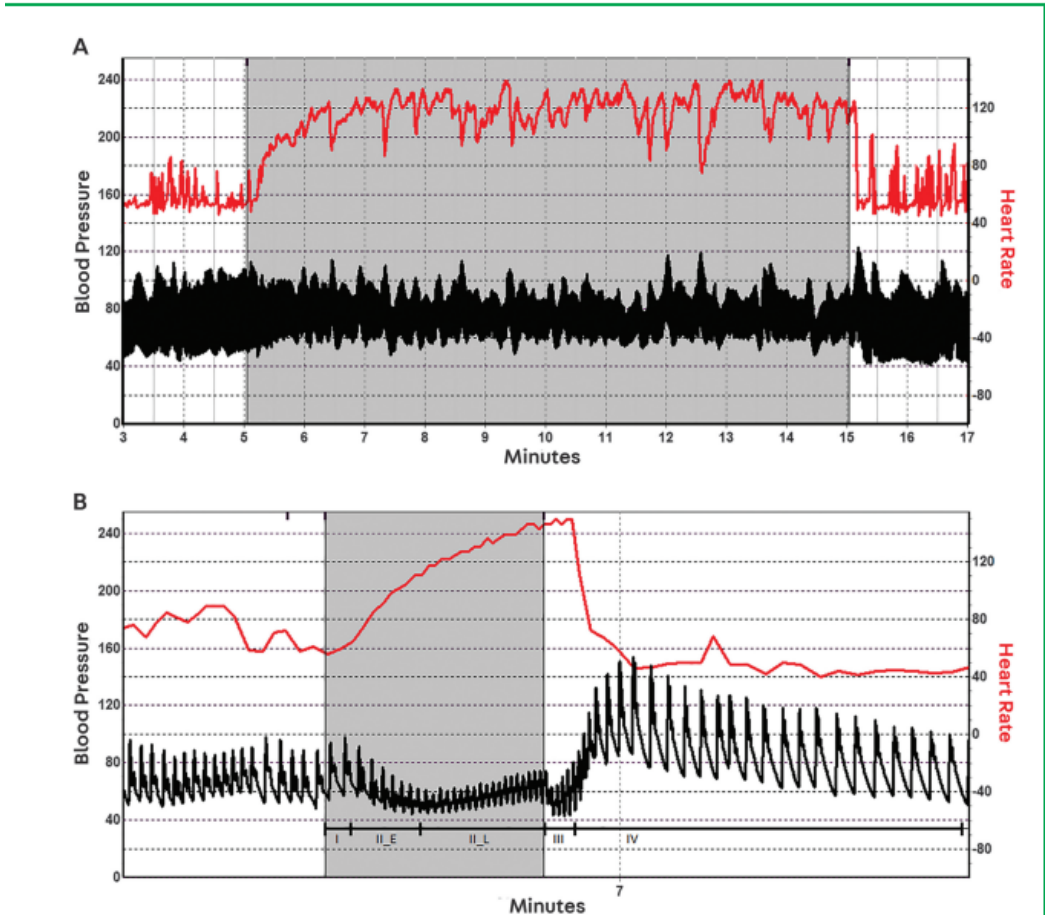
Brigham & Women's Neurology


PUPILOMOTOR
impaired pupil response
(uncomfortable in bright light)
difficulty with vision
NEUROLOGICAL
migraine, cognitive
deficits, brain fog &
mental clouding
SECRETOMOTOR
difficulty sweating, tearing
and other fluid production
(dry eyes, dry mouth,
difficulty swallowing, dry skin)
PULMONARY
shortness of breath
easily winded
difficulty breathing
GASTROINTESTINAL
nausea, vomiting, diarrhea,
constipation, abdominal
pain, reflux, heartburn,
impaired motility
CARDIOVASCULAR
palpitations, chest discomfort
high heart rate (tachycardia)
low heart rate (bradycardia)
high or low blood pressure
abnormal blood vessel functioning
blood pooling
Symptoms can be
SUDDEN and
unpredictable
in onset
URINARY
difficulty with urine
retention and/or excretion
ORTHOSTATIC INTOLERANCE
difficulty standing still, fatigue, lightheadedness,
increase in symptoms with upright posture,
fainting (syncope) or near-fainting, pallor

CASE-1

- A 16-year-old girl was seen in clinic for 6 months of postural
- lightheadedness and sweating.
- She could no longer stand through choir rehearsal
- Spells of palpitations, tremulousness, and sweating
- Neurologic and cardiac examinations were normal.
- General examination revealed cool, clammy hands and hyperextensibility of both little fingers and the right elbow.

Autonomic testing showed excessive and symptomatic heart rate rise during head-up tilt and other evidence of a hyperadrenergic state



- Hyperadrenergic POTS :prominent palpitations, tremulousness, and sweating, even from sleep.
- HTN
- This patient's cool, clammy hands :adrenaline-related peripheral vasoconstriction
- Hyperextensibility of joints indicates an EDS phenotype

THE BEIGHTON SCORING SYSTEM

Measuring joint hypermobility

The Ehlers Danlos Society

A. 5th FINGER / 'PINKIES'

Test **both sides**: Rest palm of the hand and forearm a **flat surface** with palm side down and fingers out straight.

Can the **fifth finger** be bent/lifted upwards at the knuckle to go back **beyond 90 degrees?**

If yes, add **one point** for each hand.

1 POINT FOR EACH HAND

B. THUMBS

Test **both sides**: With the arm out straight, the palm facing down, and the wrist then fully bent downward, can the thumb be pushed back to touch the forearm?

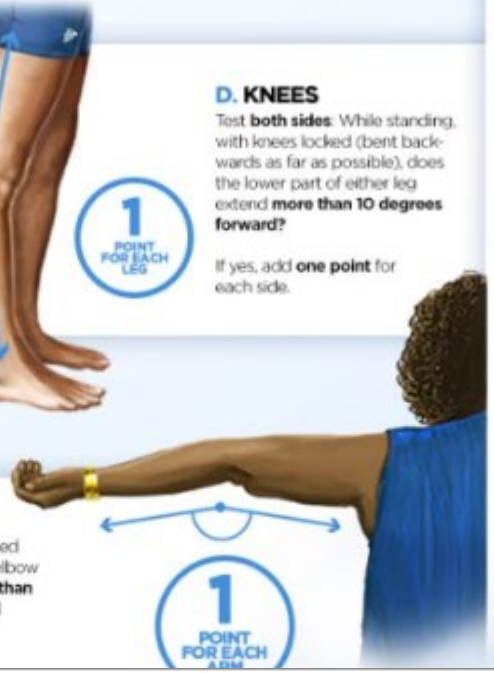
If yes, add **one point** for each thumb.

1 POINT FOR EACH THUMB

C. ELBOWS

Test **both sides**: With arms outstretched and palms facing upwards, does the elbow extend (bend too far) upwards **more than an extra 10 degrees** beyond a normal outstretched position?

If yes, add



1 POINT FOR EACH ARM

D. KNEES

Test **both sides**: While standing, with knees locked (bent backwards as far as possible), does the lower part of either leg extend **more than 10 degrees forward?**

If yes, add **one point** for each side.

1 POINT FOR EACH LEG

E. SPINE

Bend forward, can you place the palms of your hands **flat on the floor in front of your feet without bending your knees?**

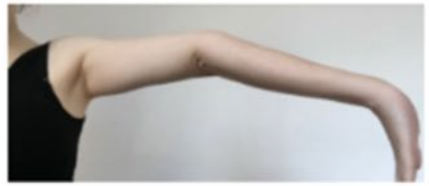
If yes, **add one point.**

1 POINT

BEIGHTON SCORE – Assessment tool for hypermobility

1

2



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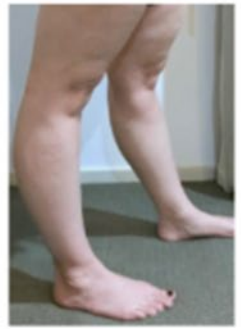

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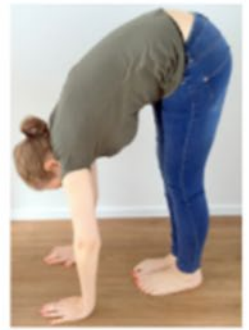


5

1 point for each side for 1-4 and 1 point for 5. Total 9. If ≥ 4/9, hypermobility is present

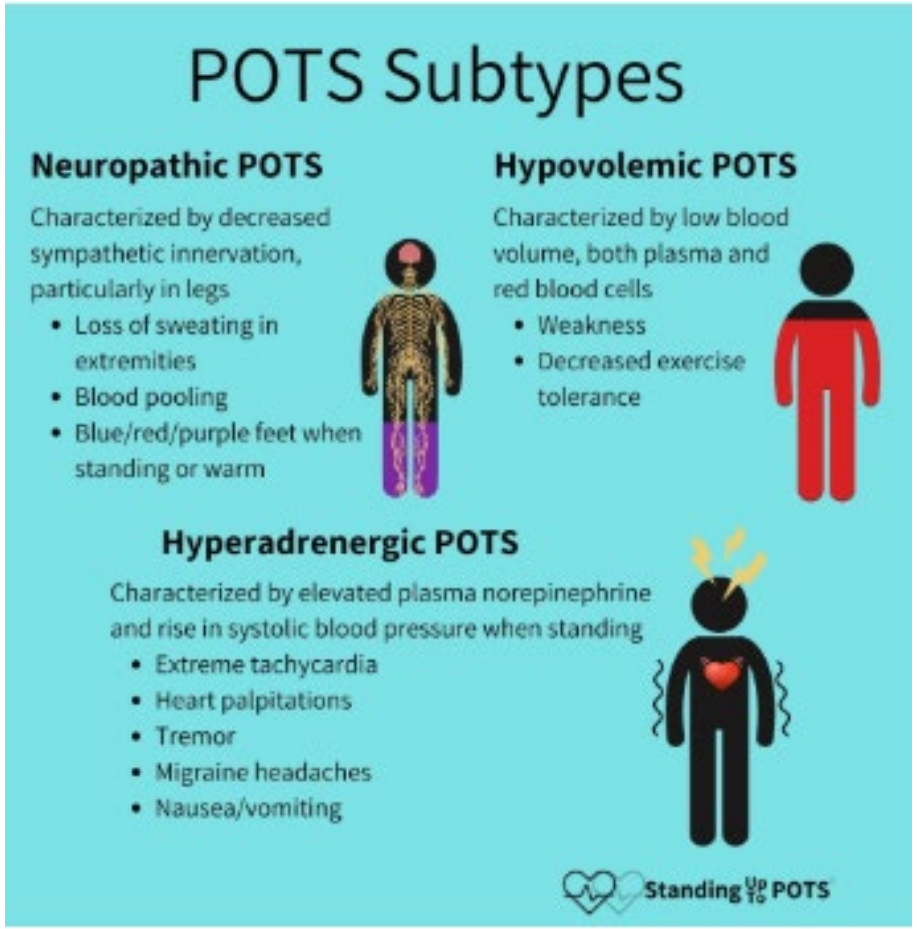
POTS

Reproducible orthostatic tachycardia (HR rise ≥ 30 bpm > age 19 and ≥ 40 bpm age ≤ 19) with symptoms of orthostatic intolerance

1. A clear definition of orthostatic change in position and time in each position
2. Orthostatic tachycardia within 3–10 min of standing and/or on a tilt table test
3. No evidence for orthostatic hypotension at any time with standing
4. A chronic condition present for at least six months / 3 m
5. No other explainable cause for orthostatic tachycardia or tachycardia
6. Symptoms of orthostatic intolerance that include postural chest pain, exertional dyspnea, dependent acrocyanosis, dizziness, lightheadedness with associated heart rate response abnormalities.
7. Orthostatic symptoms disappear when supine
8. Extra orthostatic symptoms - chronic fatigue, "brain fog"
9. Other autonomic symptoms – bloating, constipation, sweating abnormalities
10. Syncope is not a criterion
11. Symptoms alone do not make the diagnosis
12. "Secondary" orthostatic tachycardia is not POTS

Who gets POTS

- POTS between the ages of 15 and 25 years
- more than 75% are female

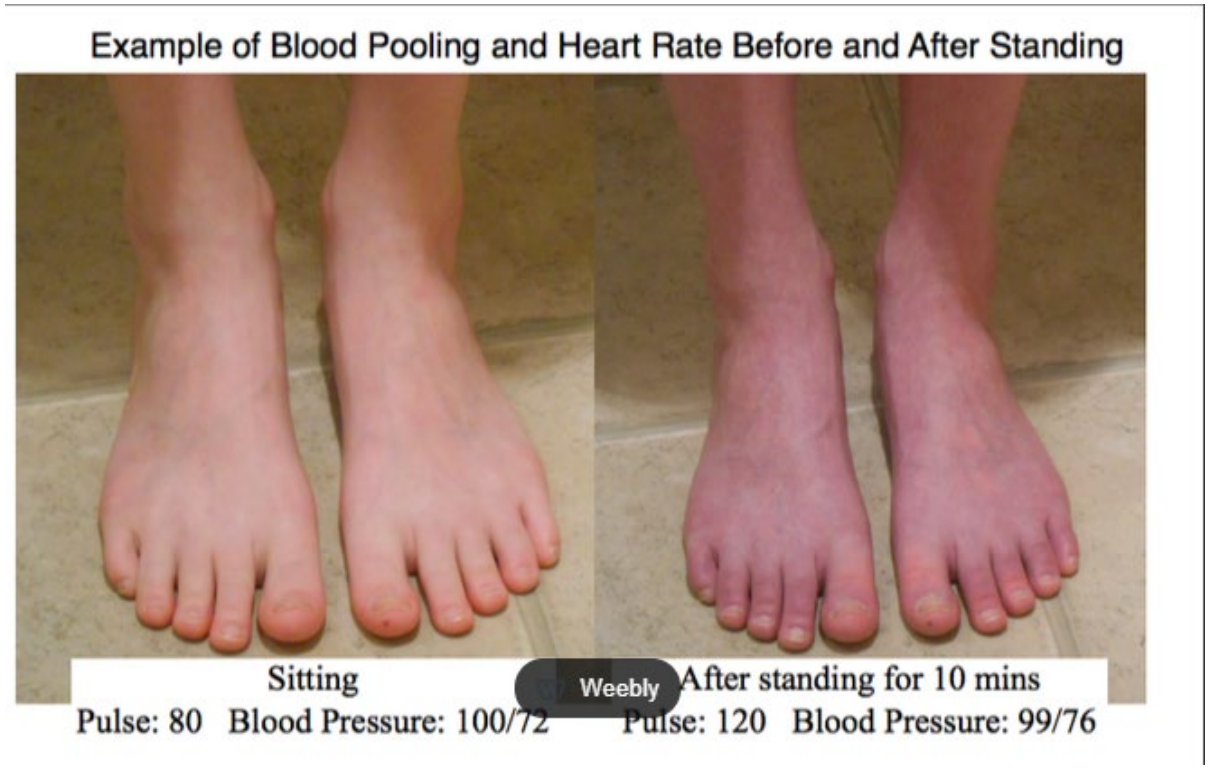


Hyperadrenergic POTS

50%

- **In hyperadrenergic POTS, the sympathetic nervous system is overactivated**
- **Clinical Presentation**: palpitations, anxiety, tachycardia, and tremor.
- Increased blood pressure,
- Elevated levels of plasma norepinephrine levels >600 pg/mL
- AND >10 mmHg rise in systolic blood pressure while standing for 10 min
- **MCAS**
- Treatments : decreasing the activity of the sympathetic nervous system
- Clonidine - central nervous system sympatholytic medication that decreases the central sympathetic tone
- Beta Blockers - block B-adrenergic receptors bound by norepinephrine and prevent sympathetic activity peripherally

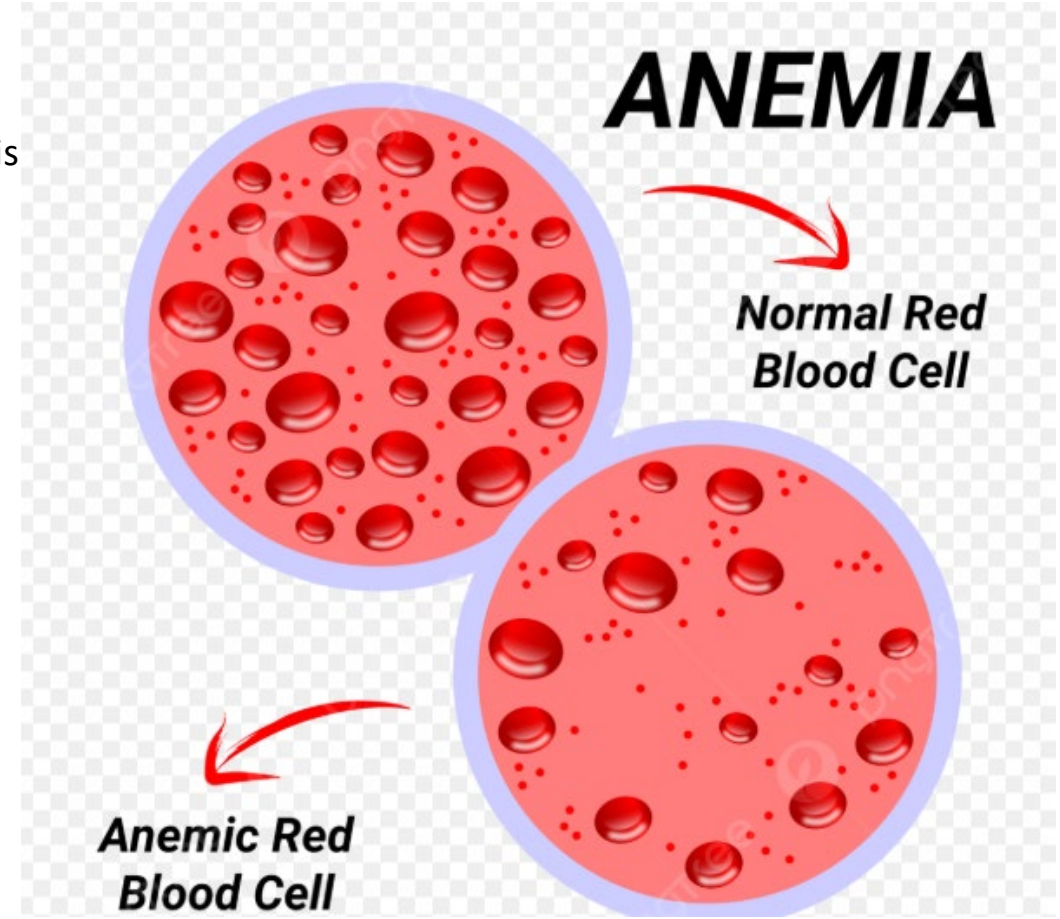
- **Neuropathic POTS**
- **small fiber neuropathy.**
- Damaged small nerves -→less release of norepinephrine.
- Because norepinephrine is a vasoconstrictor: NPOTS a/w Excessive blood pooling in the hands and feet.
- (low venous return) ->HR to increase in order to compensate.
- Etiology: infection, surgery or trauma, autoimmune form
- Loss of sweating in extremities, Blood pooling, Cyanosis



- TREATMENT: Graded compression garments, including abdominal compression of 40 mmHg and leg compression of 20-30 mmHg.
- Midodrine – an alpha 1 adrenergic agonist (binds NE receptors) that causes constriction of the peripheral blood vessels and promotes return of blood to the heart and brain
- Pyridostigmine – an acetylcholinesterase inhibitor that increases the acetylcholine levels in the synapse (increasing parasympathetic activity) of autonomic ganglia which helps to decrease heart rate
- A study of 24 patients with Ehlers-Danlos syndrome (20 with hypermobility type) : SFN, w diffuse neuropathic pain, sensitive skin, and restless legs.

HYPOVOLEMIC POTS

- Abnormally low blood levels, including both red blood cells and plasma.
- may be related to low levels of circulating renin and aldosterone which typically help to increase blood volume and blood pressure.
- Their kidneys excreting too much sodium and water, which contributes to this low blood level.
- a low-flow subtype with inappropriately high angiotensin II levels
- Low blood volume leads to less blood return to the heart, which causes an increased heart rate and force of contraction : homeostasis



- SYMPTOMS: Weakness, Decreased tolerance for exercise
- **TREATMENT**
- Increased salt (6-8 g) and fluids (2-3 L) to increase blood volume
- Compression garments with at least 20-30 mm Hg pressure,
- Raise head of bed 4-6 inches. Mild orthostatic stress shifts fluid to the lower body which activates the renin-angiotensin-aldosterone system
- Fludrocortisone: enhances sodium and water retention ->⇑blood volume
- Desmopressin: synthetic ADH that increases water reabsorption without increasing sodium reabsorption to increase blood plasma levels
- Erythropoietin: stimulates red blood cell production and increases overall blood volume
- IV fluids can be helpful.

DECONDITIONING

- Reduced left ventricular mass, stroke volume,
- Stroke volume decreases in POTS, with impaired cardiac filling when standing.

ANXIETY, HYPERVIGILANCE, PTSD

- Anxiety and somatic vigilance are significantly higher in patients with POTS, which raises the issue of the role of
- somatic hypervigilance in the source of the symptoms.

Associated comorbidities

- INAPPROPRIATE SINUS TACHYCARDIA: sinus heart rate higher than 100 bpm at rest, mean 24-hour heart rate higher than 90 bpm, palpitations
- HEADACHE. Migraines, sometimes postural headache), CSF leak (postural)
- VISCERAL PAIN AND DYSMOTILITY. Nausea, bloating, diarrhea, constipation, functional motility disorders

POTS does not necessarily suggest a widespread autonomic neuropathy because these are disorders of visceral sensitivity mediated by visceral afferents and central processing circuits and not of the enteric nervous system

- MAST CELL ACTIVATION DISORDER. flushing, diarrhea, nausea, and vomiting.
- elevated serum tryptase and urinary leukotriene E4, N-methylhistamine, and prostaglandin F2α.
- MEDIAN ARCUATE LIGAMENT SYNDROME. The celiac artery and associated nervous structures can be compressed by the median arcuate ligament as they traverse the diaphragm.
- prominent weight loss, nausea, vomiting, and abdominal pain worsened by eating.
- Diagnosis is by duplex ultrasonography, CT angiography, or magnetic resonance angiography (MRA).
- Treatment if pursued, should be directed toward the abdominal symptoms, not toward POTS.

- CHRONIC FATIGUE, INSOMNIA, AND FIBROMYALGIA. Chronic fatigue, sleep disturbances, and fibromyalgia

Covid-19

- Significant percentage of COVID-19 survivors develop POTS within 6 to 8 months of infection.
- Autoantibody production against autonomic nerve fibers, direct toxic effects of SARS-CoV-2, or sympathetic nervous system stimulation secondary to infection.

Vaccines…. HPV vaccine

- At this time, the American Autonomic Society finds that there are no data to support a causal relationship between HPV vaccination and postural tachycardia syndrome to other forms of dysautonomia.

- Certain conditions are prevalent in the same populations that are vaccinated with the HPV vaccine (peri-pubertal males and females). This association, however, is an insufficient proof of causality.

Autoimmunity

- 78% of autoimmune patients = female
- low level of g-AChR antibodies
- G-protein coupled receptor autoantibodies bound and activated alpha 1 and/or beta adrenergic receptors
- Reduce the effectiveness of peripheral norepinephrine ->increased sympathetic response to posture
- Lower standing blood pressure in POTS: The angiotensin II antibody appears to cause an inhibitory effect on the angiotensin II type I receptor
- Increased presence of muscarinic receptor 1, 2, 3 antibodies
- +ANA

IV IG for POTS..?

- Immunomodulatory therapies are not recommended unless a systemic autoimmune disorder is confirmed.

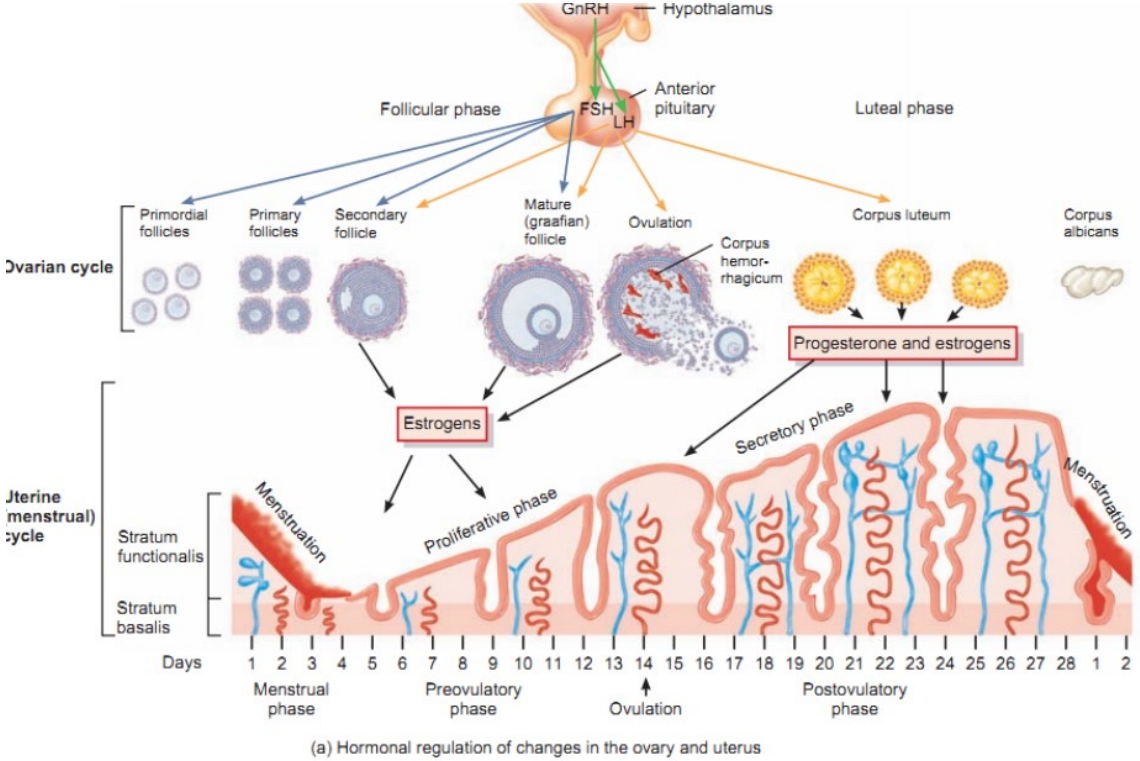
Other therapies

- Vagus nerve stimulation that harness the cholinergic anti-inflammatory reflex
- regular exercise
- anti-inflammatory diet rich in omega-3 fatty acids
- Gluten free diet
- acupuncture, meditation, music therapy, and biofeedback

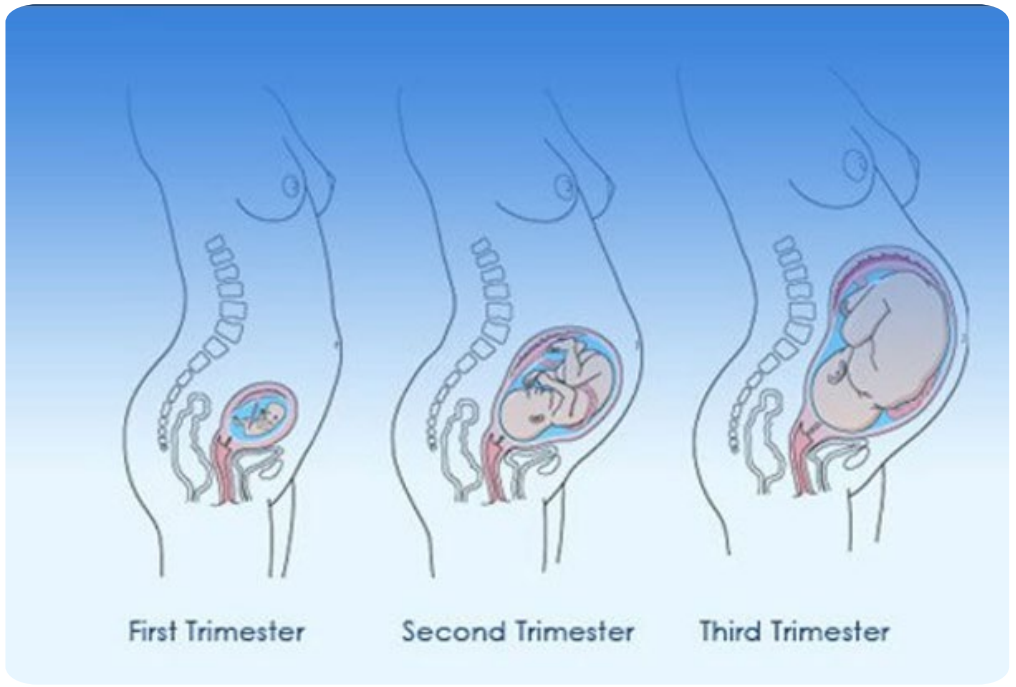
Menstrual cycle

- greatest lightheadedness during menses
- higher estrogen levels can allow for more fluid retention -> increased angiotensin II
- decrease in lightheadedness during the follicular phase.
- The high estrogen and progesterone in the MLP are associated with greater increases in renal-adrenal hormones ->more volume retention

- When the body realizes that the egg is not fertilized, the sex hormones estrogen and progesterone begin to drop quite quickly and significantly.
- The decrease in progesterone stimulates the release of enzymes that leads to the breakdown of cells, releasing prostaglandins.



pregnancy



- Normal physiological changes in pregnancy may mimic or exacerbate the symptoms of POTS
- In the first trimester, POTS symptoms were often exacerbated, but in the second trimester, there was an overall improvement in POTS symptoms.-The third trimester was variable
- increase in blood and plasma volumes during pregnancy, which increases blood pressure and cardiac output
- My experience: Gravid uterus→ syncope

Non-pharmacological management of POTS during pregnancy

- Increased fluid intake of at least 2.5L per day and salt (sodium chloride) intake of at least 7 grams per day is recommended,
- may worsen nausea, vomiting or hyperemesis gravidarum
- IV normal saline can be employed on an as-needed basis (peripheral IV)
- Waist-high maternity compression stockings
- Light exercise, such as swimming or recumbent bike
- NO Supine exercise in the 2nd and 3rd trimester while lying flat on the back: growing uterus that can compress both the inferior vena cava and aorta.

Pharmacological management of POTS during pregnancy

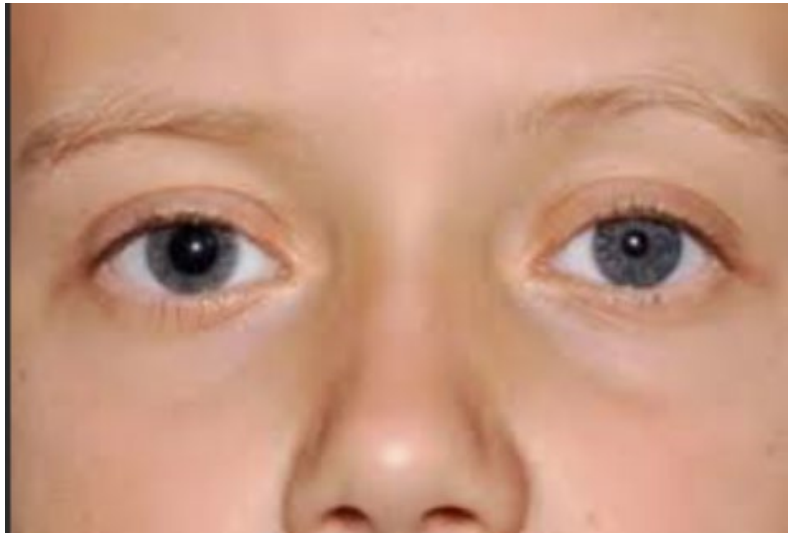
- category B or C
- one medication at the lowest possible dose should be used
- low dose of metoprolol 12.5 mg to 25 mg daily or twice a day, propranolol 5 mg twice a day,
- fludrocortisone 0.05 mg to 0.1 mg daily,
- midodrine 2.5 mg to 5 mg three times a day.
- pyridostigmine 30 mg twice a day is recommended, can be increased
- systemic autoimmune disorder or small fiber neuropathy, may be managed via immunotherapy, such as intravenous or subcutaneous immunoglobulin.

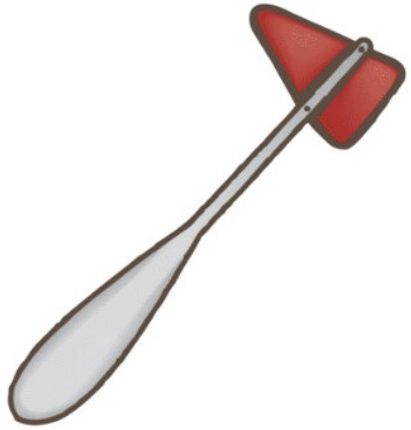
Labor and delivery

- .Early utilization of anesthetic management during labor is recommended
- Pain is a major trigger of the autonomic instability.
- Natural birth without pain control is not recommended
- Vaginal delivery: safe for the majority of women with POTS, preferred mode of delivery
- Breastfeeding is safe, reducing symptoms due to the antidiuresis effect caused by the release of oxytocin in the bloodstream

Pupils

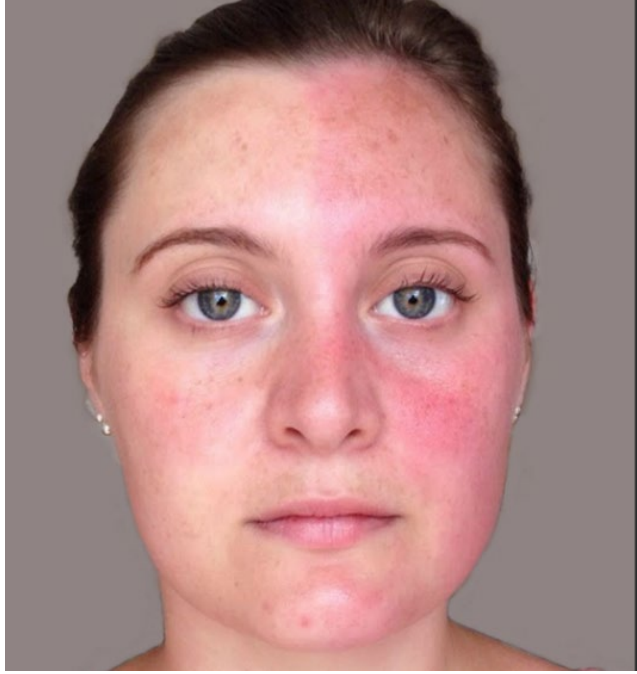
- Adie syndrome, or Holmes-Adie syndrome
- Pupil is dilated and slow to react in response to direct light.
- Absent or diminished tendon reflexes
- Cause is mostly unknown (idiopathic), VS due to trauma, surgery, ischemia or infection.
- Non-progressive and limited damage to the autonomic nervous system
- Inflammation or damage to the ciliary ganglion
- The loss of deep tendon reflexes is believed to be caused by damage to the dorsal root ganglions.





- Diagnosis Pilocarpine, eye drops, causes the pupils to constrict.
- In individuals with Adie syndrome, the affected pupil, which does not constrict in response to light, will constrict in response to dilute pilocarpine (0.05 – 0.1%)
- In most instances, treatment will not be necessary. Glasses may be prescribed to correct blurred vision; sunglasses can help individuals with sensitivity to light.
- Therapy using dilute pilocarpine may improve poor depth perception and relieve glare in some patients. The loss of deep tendon reflexes is permanent.

- Ross syndrome is a variant of Adie: anhidrosis + Holmes-Adie syndrome
- Compensatory hyperhidrosis
- The differential diagnoses to be considered
- Horner syndrome (miosis with anhidrosis, deep tendon reflexes are normal)
- Harlequin syndrome: unilateral blockade of the T2-T3 sympathetic fibers carrying sudomotor and vasomotor supply to the face.
- It results in hemifacial discoloration with half of the flushed hyperemic face sharply differentiated in the midline from the other pale half. Idiopathic vs injury, compression, following many surgical and anesthetic procedures.
- Hereditary sensory and autonomic neuropathy,
- Diabetes mellitus, leprosy and other polyneuropathies
- If hyperhidrosis: botulinum toxin, aluminum chloride, 0.5% glycopyrrolate, sympathetic thoracotomy, and systemic anticholinergics
- Hypohidrosis: avoidance of hot environment and wearing wet clothes during strenuous activities.
- Intravenous immunoglobulin therapy +/-: when likely autoimmune causation.

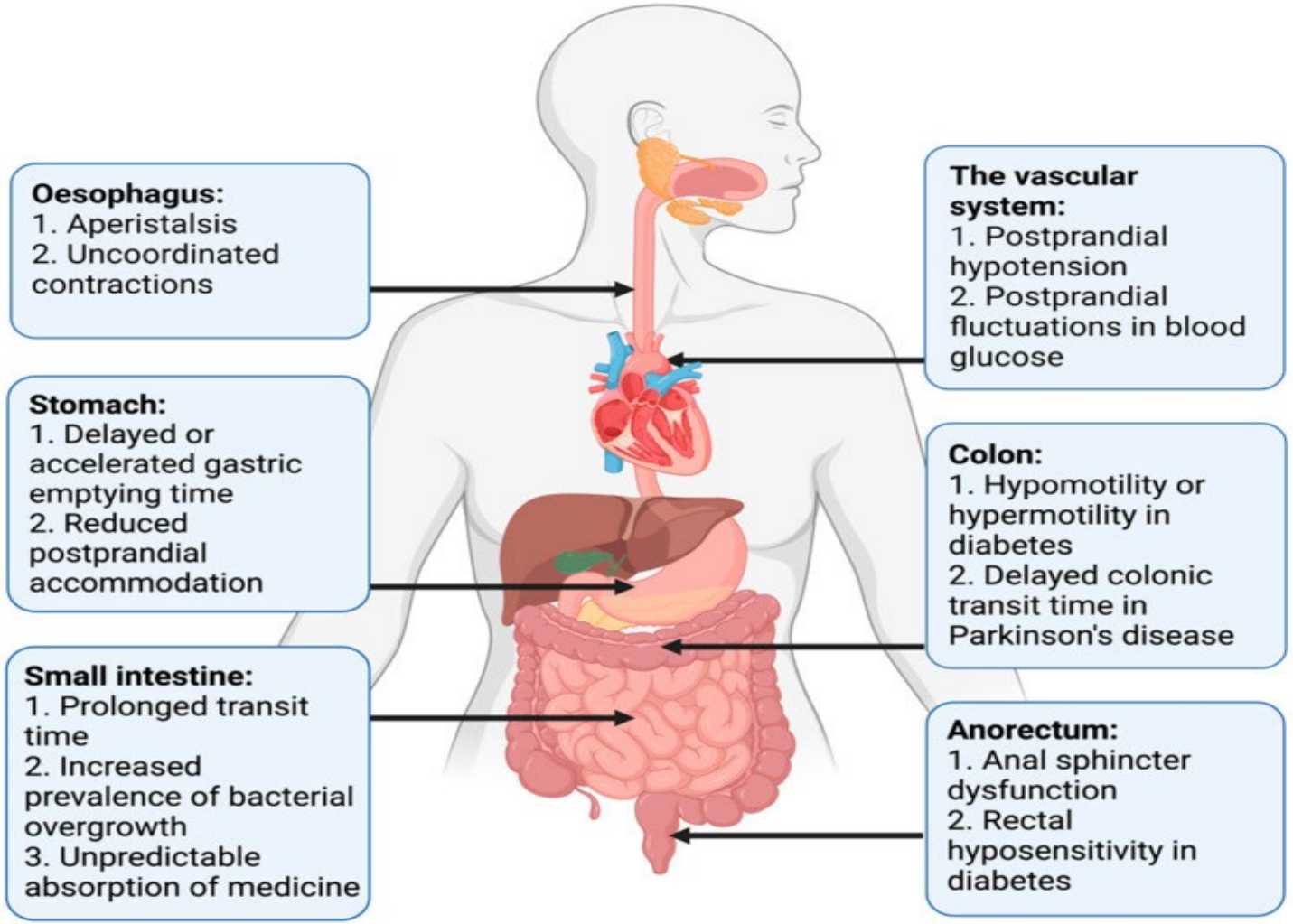


Fowler’s syndrome.

- A 37-year-old nurse was first seen at age 22 after she had undergone an ear, nose, and throat procedure under general anesthetic.
- Following this she was unable to urinate. She had some feeling of pressure when her bladder was full but had lost normal sensation. In addition, she was complaining of vague sensory symptoms in her left leg.
- Clinical examination was essentially normal except for some inconsistent sensory disturbance on the left.
- Neurologic investigations, including a myelogram, MRI of the brain, and visual evoked potentials, were normal.
- A neurologist suggested her urinary retention might have been of psychogenic origin.
- Outpatient, urethral sphincter EMG was highly abnormal. Profuse complex repetitive discharges and decelerating bursts were recorded
- She remained in complete urinary retention and for 7 years managed to empty her bladder by intermittent self-catheterization.
- SNS was implanted, and she was able to urinate spontaneously for the first time in many years. She no longer needs to self-catheterize.

- Fowler’s syndrome: Neural axis imaging, CSF exam normal
- painless urinary retention
- Abdominal straining does not help voiding.
- Absent sense bladder fullness, large bladder capacities, decrease in bladder sensation.
- Hormonally sensitive striated sphincter -> local muscle membrane instability→ inappropriate and involuntary sustained contraction of the sphincter
- Animal studies indicate that contraction of the striated sphincter has an inhibitory effect on detrusor contraction and on bladder afferent activity
- Etiology: surgical procedure under general anesthesia, a urinary tract infection, or childbirth
- In younger women in particular, the onset is often apparently spontaneous
- Can recur

Bowel Dysautonomia in women



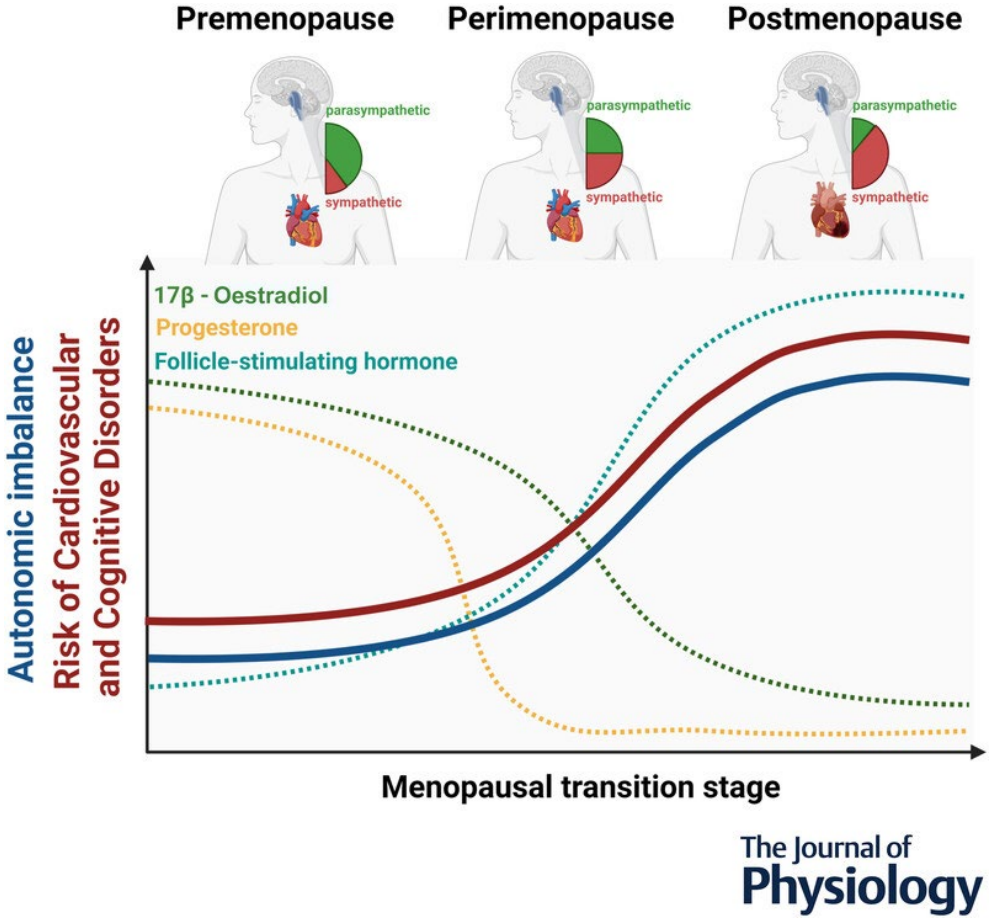
Post menopausal women

- Dizzy

- -check vestibular system
- Estrogen supplementation, vit D

Menopause

- Cardiovascular diseases (CVD) are highly prevalent conditions in middle-aged women
- The autonomic nervous system, the main heart-brain axis physiological orchestrator, has been suggested to play a role
- Decreases in estrogen-related signalling: Estrogen appears to be able to increase the vagal influence on the heart and reduce the cardiovascular sympathetic drive



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The Dysautonomia Project.org

Ligamentous hyperlaxity - OsteoMag.ca

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