A 22-year-old female with hypercalcemia in pregnancy

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Endorama, 10/10/24

Learning objectives

1. Review the initial presentation and evaluation of hypercalcemia.
2. Discuss management of hypercalcemia in pregnancy.

Initial presentation to our clinic 9/2023

- The patient is a 22-year-old female G2P0010 at 34 weeks gestation for evaluation of hypercalcemia during this pregnancy
- She is not having polyuria, bone pain, changes in mood or anxiety, or significant constipation and is hydrating well
- She had two recent admissions this pregnancy at two outside hospitals
- She has had fetal growth restriction and abnormal Dopplers on ultrasound at 28 weeks this gestation

First admission in 4/2023

- Presented ~12 weeks gestation with nausea, vomiting, and abdominal pain
- Labs showed:
  - Ca 15.1, PTH 155, albumin 4.0
  - PTHrp 10.8 and 6.5 (both elevated)
  - 25-OH vitamin D 7 and 1,25-OH vitamin D 122 (elevated)
  - TSH was suppressed to 0.009 with free T4 1.4
  - She had urine and serum screening for monoclonal gammopathy including immunofixation, IgA, and IgM levels which were negative
- US thyroid showed “unremarkable appearance of thyroid gland” and “two hypoechoic solid nodules inferior to the left thyroid lobe which may represent lymph nodes or parathyroid adenoma”
- She was given fluids and calcitonin with improvement and discharged

Second admission in 6/2023

- She presented again at 23 weeks gestation with failure to thrive due to dysphagia to solid foods
- Labs showed:
  - Ca 11.0, PTH 93, albumin 3.5
  - 25-OH vitamin D 9
  - TSH 1.63
- She passed a clinical speech evaluation and was discharged with nutritional supplementation
- On discussion of this in our clinic, she continues to have difficulty with solid food but no issues with liquids or soft foods, such as mashed potatoes

Relevant history

PMH

Anemia, failure to thrive

PSH

None

Allergies

NKA

Family

Autoimmune thyroid disease in sister requiring medication

Thyroid surgery in MGM

No hypercalcemia or kidney stones

Social

No tobacco, alcohol, or drug use

Medications

Vitamin D3 1,000 units daily

Cyclobenzaprine 5 mg BID PRN

Docusate 100 mg

Ferrous sulfate 325 mg daily

Magnesium 200 mg daily

Ondansetron 4 mg Q8H PRN

Prenatal multivitamin

Exam

Vitals: T 35.9, HR 57, BP 124/71, weight 52.2 kg, BMI 20.2

- GEN: No acute distress.
- HENT: Moist mucous membranes. Not plethoric. No evident hirsutism or thyromegaly. **Some mild fullness of neck but no palpable nodules or tenderness.** No lymphadenopathy.
- EYES: Extraocular movements intact. No injection or proptosis.
- PULM: Normal work of breathing.
- CV: Normal heart rate.
- ABD: **Gravid.**
- NEURO: Moves upper/lower extremities spontaneously. No tremor.
- PSYCH: Appropriate affect and mood, normal thought process and content.
- EXT: Warm. No lower extremity edema.
- SKIN: No rashes.

Labs

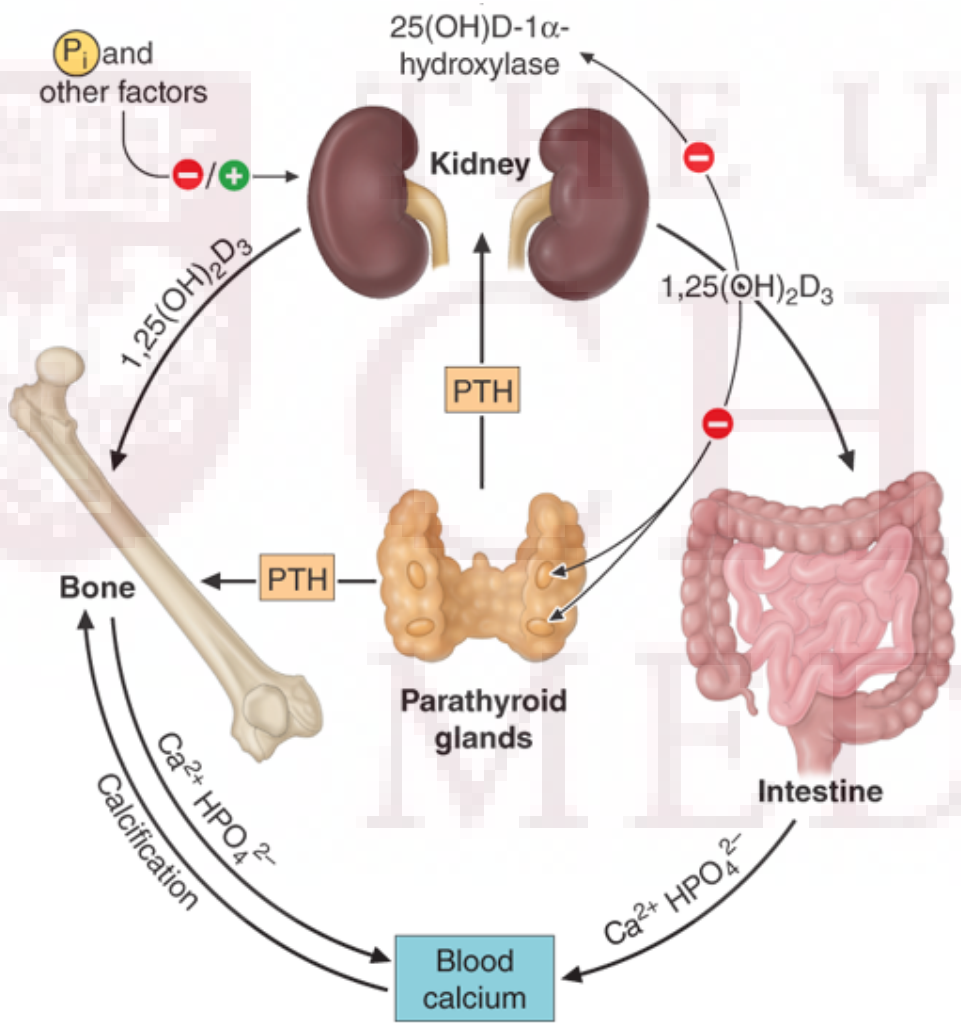
Drawn 2 weeks prior to clinic presentation:

- Na 138 / K 4.0 / Cl 109 / CO2 21 / BUN 6 / Cr 0.76 / Glu 71
- Ca 10.3 / TB 0.2 / AST 13 / ALT 12 / ALP 108 / ALB 3.1 / TP 7.8
- WBC 8.0 / Hgb 10.5 / Plt 463

Outside labs going back to 2014 and 2015 (age ~14-15) showed she had hypercalcemia up to 10.9 and 11.8 with normal albumin or slightly high albumin

What is your differential and next steps for her hypercalcemia?

Calcium homeostasis in pregnancy

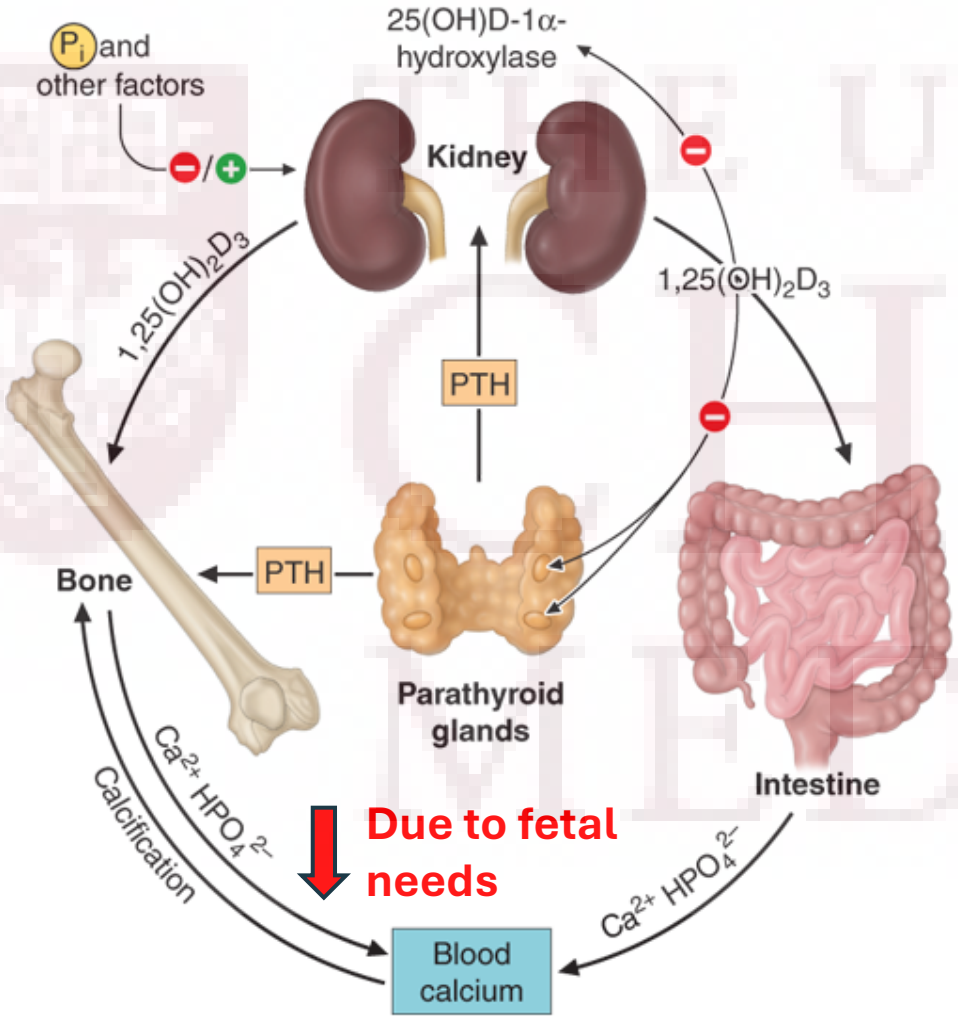


Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e

- Normal calcium homeostasis (left) changes in pregnancy
- Fetal calcium needs are about 30 g per term and are met by hyperplasia of the parathyroid glands and elevated PTHrp and 1,25-OHD from the decidua
- Total maternal calcium reaches a nadir around 28-32 weeks due to low albumin but usually remains normal

Patel et al. The Endocrinology of Pregnancy. In: Gardner and, Shoback eds. Greenspan's Basic & Clinical Endocrinology, 10e. McGraw-Hill Education; 2017.

Primary hyperparathyroidism in pregnancy



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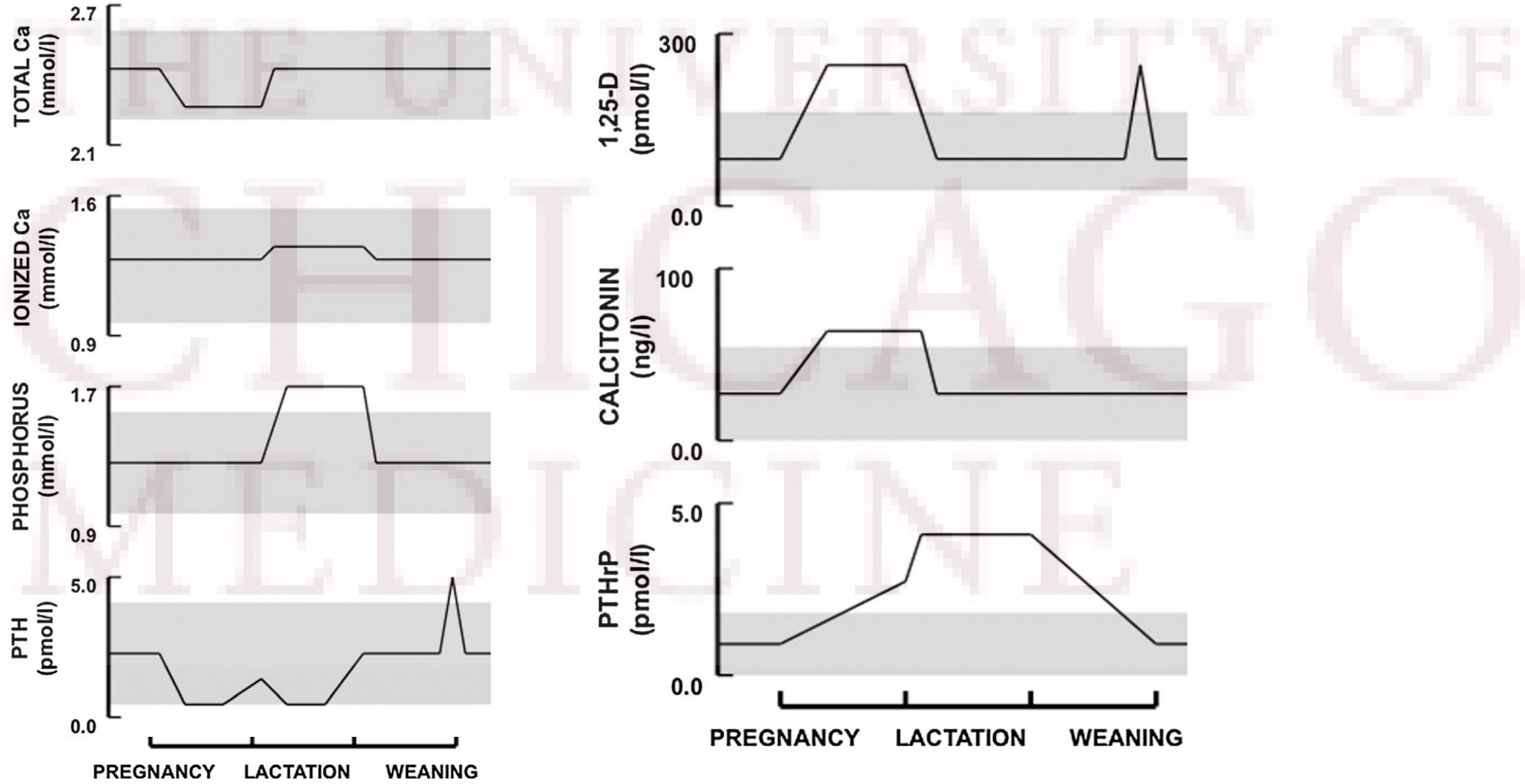
- Patients with primary hyperPTH in pregnancy can experience improvement in symptoms due to fetal calcium requirements
- Maternal complications can include nephrolithiasis, pancreatitis, hyperemesis gravidarum, pre-eclampsia, and hypercalcemic crisis
- Fetal complications >80% and include miscarriage, preterm delivery, IUGR, low birth weight, neonatal hypocalcemia (suppression of PTH secretion)

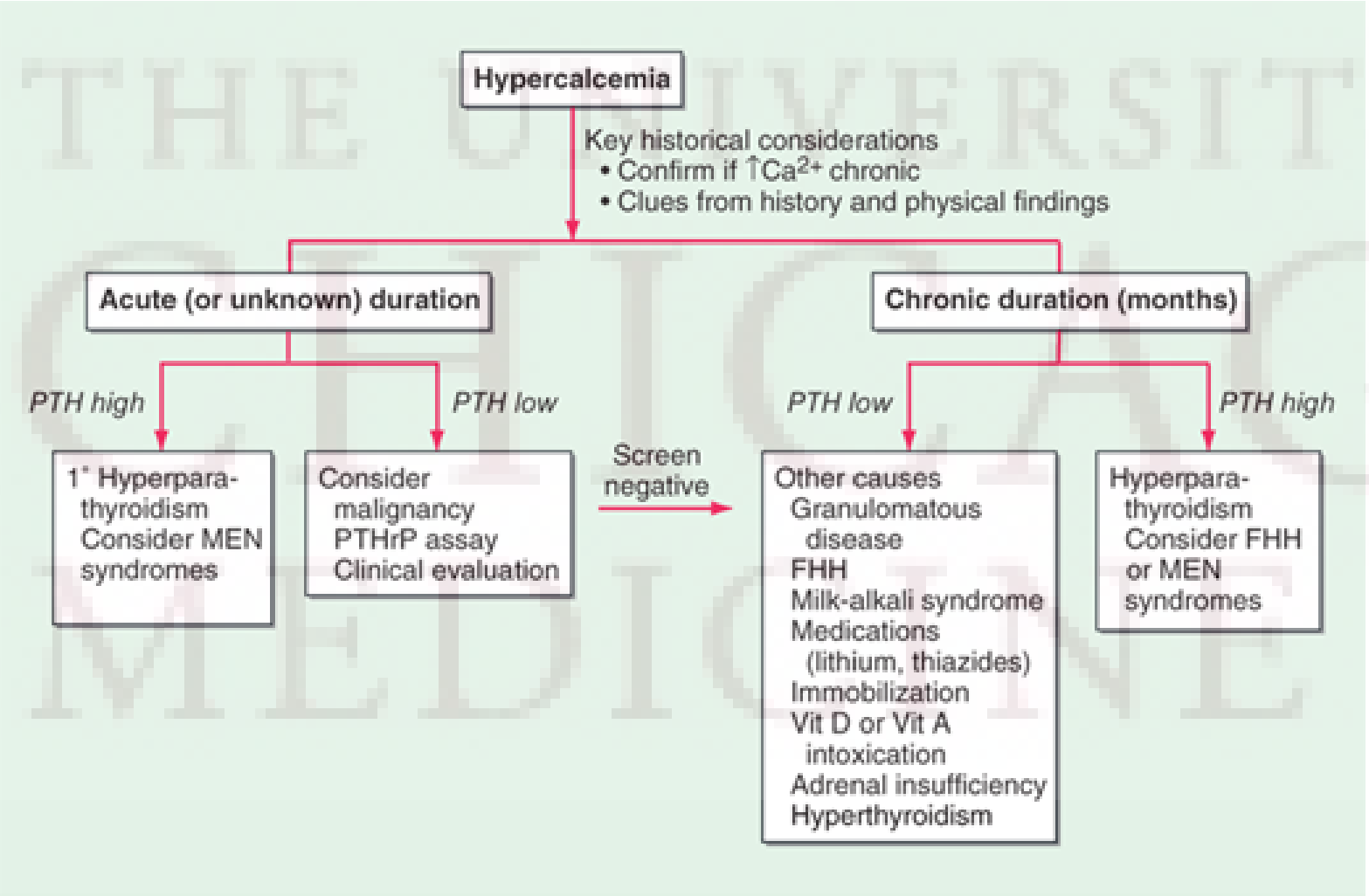
Patel et al. The Endocrinology of Pregnancy. In: Gardner and, Shoback eds. Greenspan's Basic & Clinical Endocrinology, 10e. McGraw-Hill Education; 2017.

PTHrp in pregnancy and postpartum



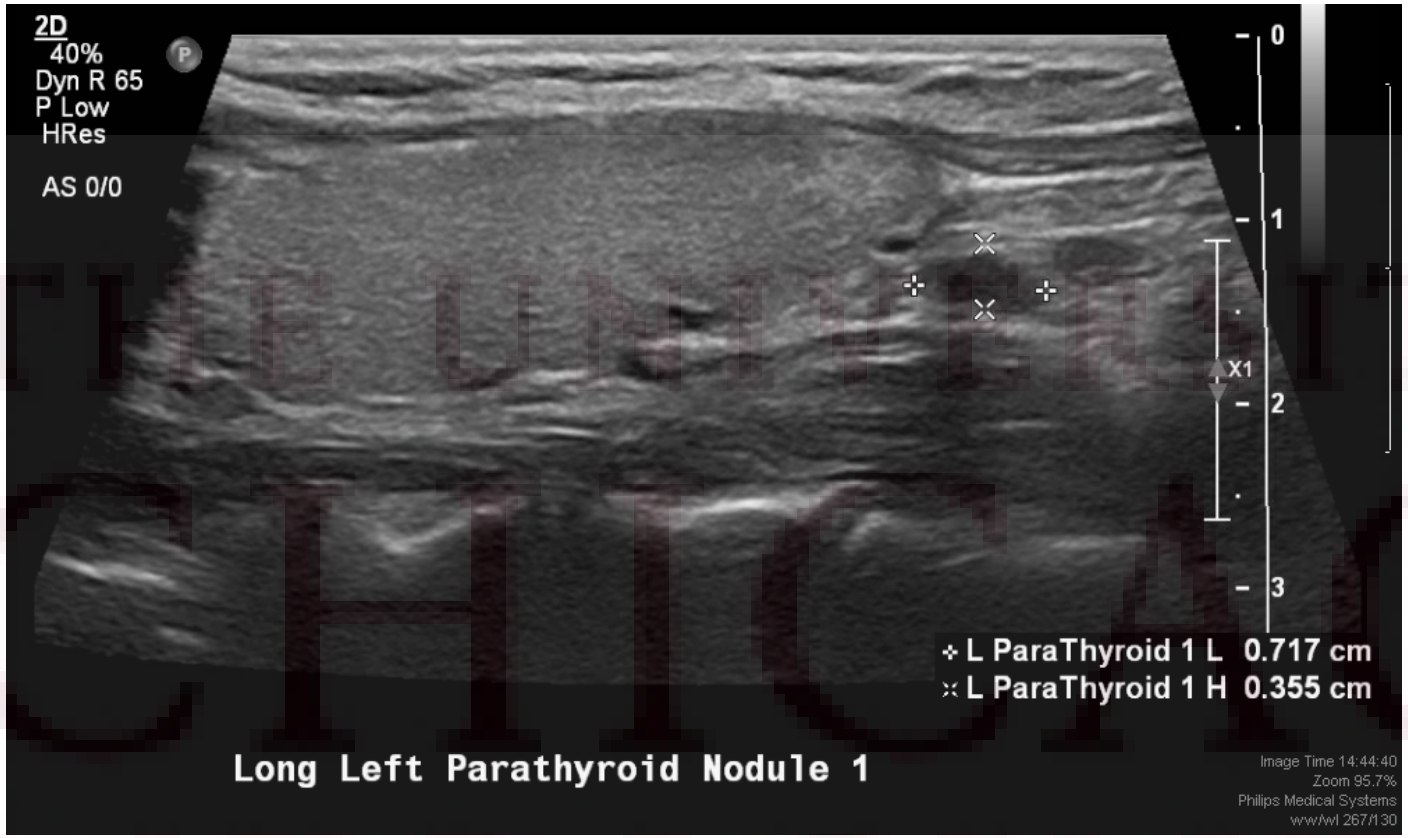
Kovacs et al. Clinic Rev Bone Miner Metab. 2014 Sep 1;12(3):142–64.

Diagnosis and evaluation of hypercalcemia



Labs after pregnancy

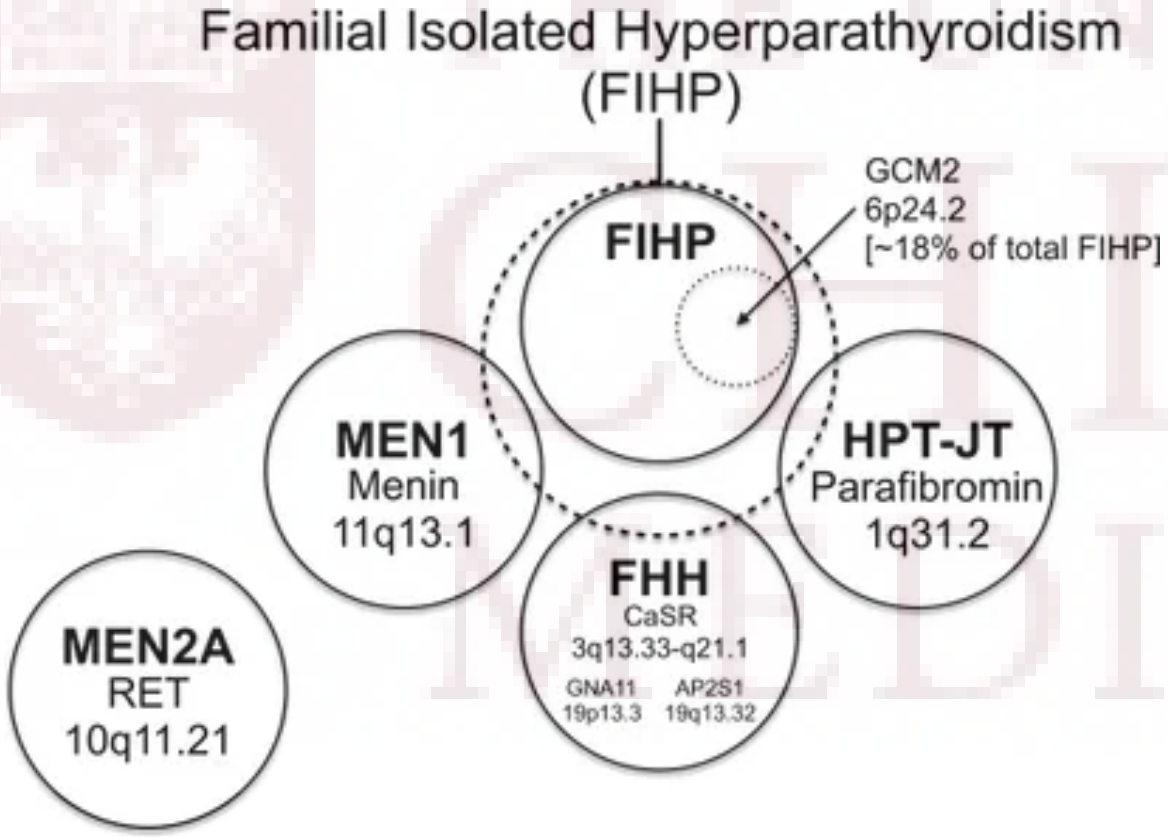
- She delivered a few weeks later at 37 weeks gestation by c-section which was uncomplicated
- After delivery, her baby had hyperPTH and saw Dr. Maria Salguero but these normalized after a few months
- The patient returned after delivery to get the following labs:
  - Ca 10.7, phos 2.1, albumin 4.5, PTH 152
  - PTHrp 0.5 (normal)
  - 25-OH vitamin D 8, 1,25-OH vitamin D 71 (normal)
  - Vitamin A 37.9 (normal)
  - TSH 1.26
  - 24-hour urine Ca 118.1, Cr 169 (625 cc collection)
  - Urine Ca/Cr clearance ratio 0.0443 (expected >0.01)



PARATHYROID GLANDS: Inferior to the left thyroid gland, an oval hypoechoic nodule without definite fatty hilum measures 0.7 x 0.4 x 0.4 cm. A second more inferior hypoechoic nodule appears to have a fatty hilum and measures 0.6 x 0.4 x 0.5 cm.

Based on these findings, what would you do next?

Genetic testing for hyperparathyroidism



- FHH: ***AP2S1***, ***GNA11***, ***CASR***
- HPT-JT: ***CDC73***
- MEN types 1 and 2: ***MEN1***, ***RET***
- MEN type 4: ***CDKN1B***
- Familial isolated hyperPTH: ***GCM2***
- Jansen's metaphyseal chondrodysplasia, Blomstrand's lethal chondrodysplasia, Eiken familial skeletal dysplasia: ***PTH1R***
- Transient neonatal hyperparathyroidism: ***TRPV6***

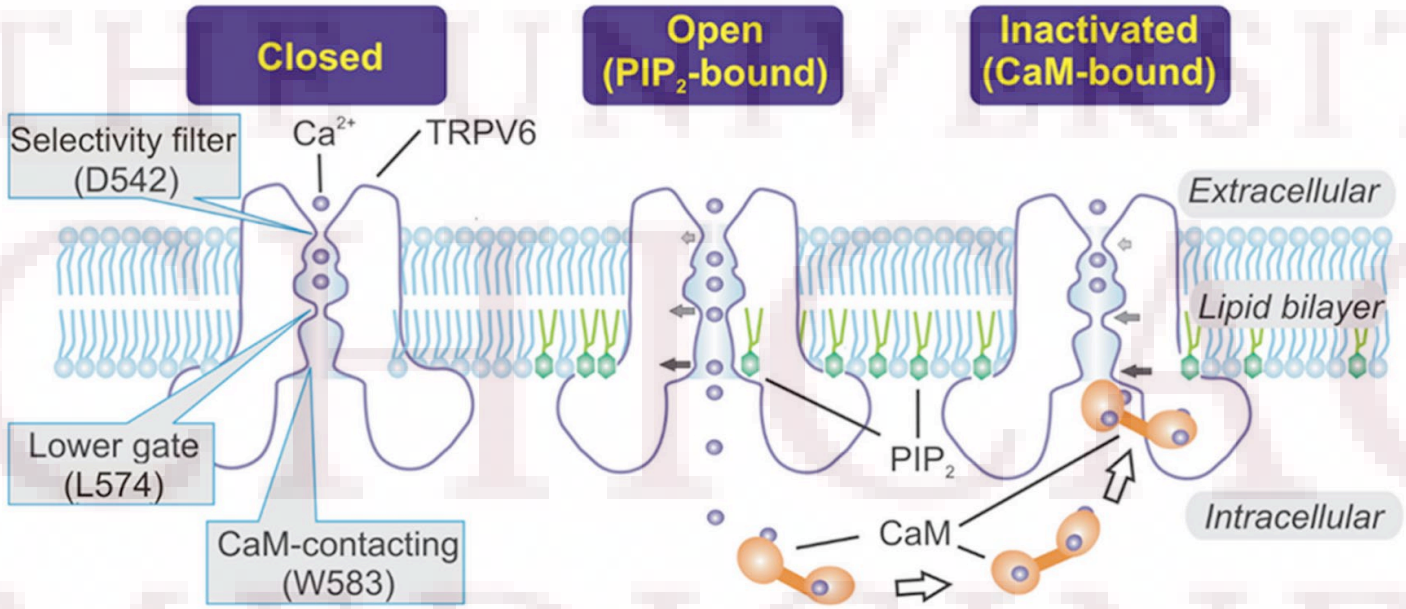
Blau et al. Familial Hyperparathyroidism. Front Endocrinol 2021 Feb 25;12.

Genetic panel shows c.428C>T *TRPV6* allele

GENE	NUCLEOTIDE CHANGE	AMINO ACID CHANGE	ZYGOSITY	INHERITANCE	INTERPRETATION
TRPV6	c.428C>T	p.Pro143Leu	Heterozygous	Recessive	Variant of unknown significance

DNA sequence analysis of the *TRPV6* gene demonstrated a sequence change, c.428C>T, in exon 3 that results in an amino acid change, p.Pro143Leu. This sequence change does not appear to have been previously described in individuals with *TRPV6*-related disorders and has been described in the gnomAD database with a frequency of 0.03007% in the European subpopulation (dbSNP rs754442854). The p.Pro143Leu change affects a highly conserved amino acid residue located in a domain of the TRPV6 protein that is known to be functional. *In-silico* pathogenicity prediction tools (SIFT, PolyPhen2, Align GVGD, REVEL) provide contradictory results for the p.Pro143Leu substitution. Due to insufficient evidences and the lack of functional studies, the clinical significance of the p.Pro143Leu change remains unknown at this time. Bi-allelic pathogenic variants in *TRPV6* are associated with transient neonatal hyperparathyroidism which is characterized by interference with placental maternal-fetal calcium transport, causing fetal calcium deficiency resulting in hyperparathyroidism and metabolic bone disease.

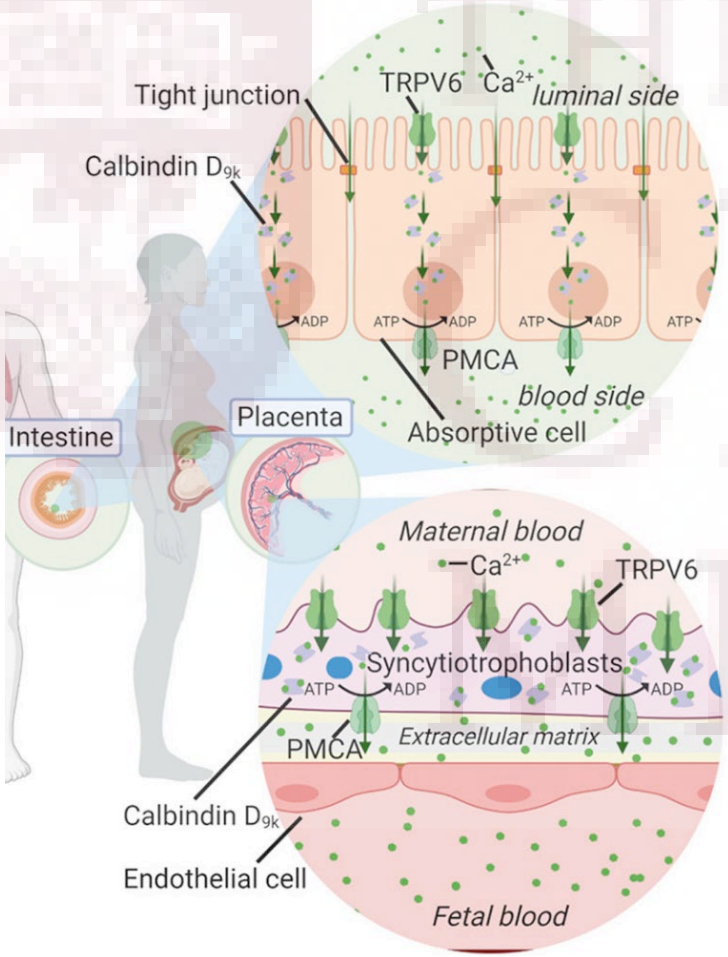
TRPV6 and calcium homeostasis



- TRPV channels function in ionic homeostasis and sensation
- TRPV6 plays a role in intestinal and renal absorption of calcium
- In the absence of Ca^{2+}, PIP2 binds TRPV6 and keeps the channel open
- Ca^{2+} influx activates CaM which inactivates TRPV6

Khattar et al. Gene. 2022 Apr 5;817:146192.

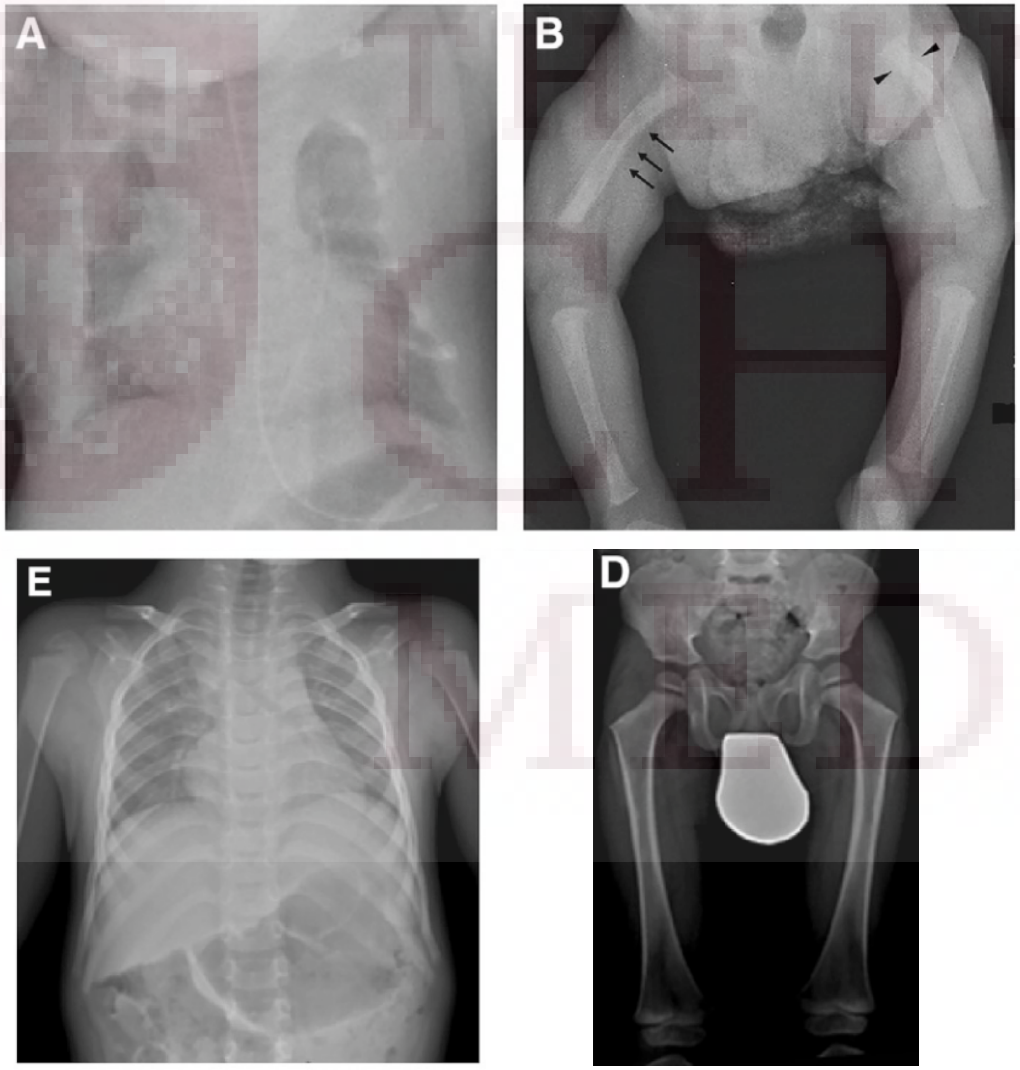
TRPV6 in fetal–maternal calcium homeostasis



- Ca^{2+} in the fetus is highest in the 3rd trimester when fetal bone mineralization peaks
- TRPV5 and TRPV6 are expressed in placenta on the apical and basolateral cell surface trophoblasts and syncytiotrophoblasts
- *Trpv6*$^{-/-}$ mouse fetuses are hypocalcemic due to disrupted calcium transport

Khattar et al. Gene. 2022 Apr 5;817:146192.
Suzuki et al. J Bone Miner Res. 2008 Aug;23(8):1249–56.

Biallelic mutations in patients cause transient neonatal hyperparathyroidism, bone deformities



- X-rays of 1 of 6 patients described by Suzuki et al with homozygous or compound heterozygous mutations in *TRPV6* (left)
- Neonatally elevated alk phos, PTH and normal or low Ca
- Bone deformities included rib thinning, deformation, and fracture as well as metaphyseal constriction (arrows), diaphyseal constriction (arrowheads), femoral bowing (top 2 images)
- HyperPTH and bone deformities resolved within a few months to 1.5-2 years (bottom 2 images)

Suzuki et al. The American Journal of Human Genetics. 2018 Jun 7;102(6):1104–14.

Dizygotic twins with different genotypes

Table 1. Laboratory Findings for the Patient, Twin Sibling, and Mother

	Patient (Day 0)	Twin Sibling (Day 4)	Mother (Day 5 Postpartum)	Normal Range
Intact PTH, pg/mL	2700	176	56	14–72
Alkaline phosphatase, U/L	998	887	409	Adult: 106–322 Neonate: 530–1610
Calcium, mg/dL	7.7	8.3	8.2	Adult: 8.8–10.1 Neonate: 9.0–11.2
Phosphate, mg/dL	5.6	6.8	3.3	Adult: 2.7–4.6 Neonate: 4.6–8.0
25(OH)D, ng/mL	9	5	6	20–50
Albumin, mg/dL	3.1	3.7	3.0	Adult: 3.8–5.3 Neonate: 3.0–4.1
Creatinine, mg/dL	0.59	0.53	0.44	0.46–0.79
Urinary calcium/creatinine ratio	0.045	Undetectable	Undetectable	<0.14

Abbreviation: 25(OH)D, 25-hydroxy vitamin D.

Compound het missense alleles

No pathogenic alleles

Yamashita et al. *Journal of the Endocrine Society* 3, no. 3 (March 1, 2019): 602–6. https://doi.org/10.1210/js.2018-00374.

Next steps

- Discussed indication for parathyroidectomy, patient and her mother were hesitant but willing to proceed with referral
- Saw Dr. Angelos in Endocrine Surgery with plan for 4D CT imaging to better localize adenoma candidate

And then I saw her appear as a new consult on the inpatient service for **hyperthyroidism**…

Patient updates

- She presents with abdominal pain, hyperCa, and abnormal TFTs at 8 weeks gestation confirmed by ultrasound
- Initial calcium was 12.7 corrected 12.3 for albumin 4.5, PTH 56
- TSH 0.01 and fT4 1.84 with total T4 10.4 (normal) and negative TSI consistent with gestational transient thyrotoxicosis

Treatment of primary hyperPTH in pregnancy

- Parathyroidectomy is an option during the second trimester to minimize risk of anesthesia to the fetus
- Conservative management is possible with close surveillance if asymptomatic and only mild elevations in Ca
- Cinacalcet is class C in pregnancy—there are scattered case reports of use as a bridge to post-partum parathyroidectomy
- Calcitonin is class B2 in pregnancy and does not cross the placenta
- Zoledronic acid is class D in pregnancy and negatively impacts fetal skeletal development

Current patient status

- She follows with a certified nurse midwife here at UChicago and is doing well
- She declined establishing care with MFM for this pregnancy
- She discussed surgery with both myself and Dr. Angelos and is scheduled for surgery in a few weeks
- Most recent TSH 1.19 with fT4 0.86 and she remains asymptomatic
- Will connect her to genetics to discuss additional testing

Acknowledgements

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Questions?

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ENDORAMA

October 10, 2024

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