31 year old female with Hypercalcemia

Milad Abusag, M.D.

Fellow section of Endocrinology Diabetes and Metabolism

09/04/2014

HPI

- 31 year old Mexican female, G4P3, 8 weeks pregnant with PMH of type 2 DM, HTN and NASH
- In her usual state of health until 4 months ago (c/o generalized weakness and found to have Ca level of 11)
- Found to be pregnant 3 weeks ago
- Went to an Endocrinologist in Urbana, IL and was told that there is no current treatment for hyperparathyroidism in pregnancy
- No h/o kidney stone to her knowledge, no h/o fractures

PMH:

✓HTN
✓DM type II (Dx 5 months ago)
✓Anxiety
✓Depression
✓NASH

Family History:

✓Type 2 DM (mother/sister/MGM)
✓ Maternal aunt with hyperparathyroidism S/p Surgery

Social history

✓Married, 3 children, no smoking no illicit drugs use. Drink alcohol socially

Home medications

- Metformin (switched to Levemir/Novolog)
- Procardia XL 30 mg daily
- Zoloft 50 mg daily
- Folic acid

ROS

Constitutional: Negative for fevers, chills, night sweats, or heat/cold intolerance. **generalized weakness**

HEENT: Negative for headaches, blurry vision, double vision, tinnitus, rhinorrhea, sore throat

Respiratory: Negative for cough, wheezing

Cardiovascular: Negative for nausea, vomiting, chest pain, shortness of breath, lightheadedness, palpitations

Gastrointestinal: nausea and vomiting present Negative for abdominal pain,, diarrhea, constipation

Genitourinary: **polyuria** no hematuria

Skin: Negative for diaphoresis, new rash

Musculoskeletal: Negative for myalgia

Neurological: Negative for weakness, numbness, tingling

All other systems reviewed and are unremarkable

On examination

Vitals: BP 117/78, Pulse 88, no fever, RR 14, **BMI 39**

General: awake alert, comfortable

HEENT: normocephalic non traumatic, no pallor, no jaundice. Mild hirsutism

Neck: supple, no thyromegaly, no lymphadenopathy

CVS/Pulm: good air entry bilateral, no added sounds

Abd: soft, non tender, no organomegaly, audible bowel sounds.

Skin: no ulcers, not diaphoretic, **mild acanthosis**

Neuro: alert, no tremor, CN intact, DTR normal, sensation intact

Psych: normal mood, and affect

General labs on admission

Test/date	8/15/2014
Na/K	136/3.4
Glucose	85
HbA1c	5.4%
Cr/GFR	0.6/117
Albumin	4.3
ALP	99
ALT/AST	50/47
Hb	10.5
WBC	8
Plt	228
Phos (2.5 – 4.5)	2.3
Ca	13.7

Differential diagnosis ?

Causes of hypercalcemia

PTH-mediated
Primary hyperparathyroidism (sporadic)
Familial
MEN-I and -IIa
FHH
Familial isolated hyperparathyroidism
Tertiary hyperparathyroidism (renal failure)
PTH-independent
Hypercalcemia of malignancy
PTHrp
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Medications
Thiazide diuretics
Lithium
Teriparatide
Excessive Vitamin A
Theophylline toxicity
Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk alkali syndrome

MEN: multiple endocrine neoplasia; FHH: familial hypocalciuric hypercalcemia; PTHrp: parathyroid hormone-related peptide.

Adapted from: Khairallah W, Fawaz A, Brown EM, and El-Hajj Fuleihan G. Hypercalcemia and diabetes insipidus in a patient previously treated with lithium. Nat Clin Pract Nephrol 2007; 3:397.

UpToDate

UpToDate®

What should we do next?

More labs

Test/date	8/15/2014 (11am)
PTH	284
25 OH vit D	11
TSH	0.3
FT4	0.94

Patient started on

- IV NS 250 cc/hr
- Lasix 40 mg po Q12hrs
- Fetal monitoring
- Surgical and OB consultation

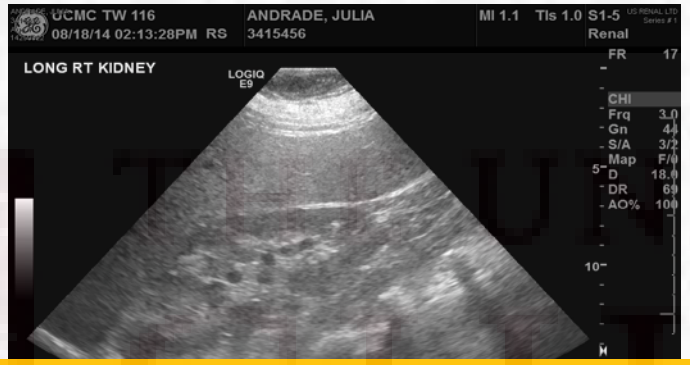
Test/date	8/15	8/16
Ca	13.7	12.6

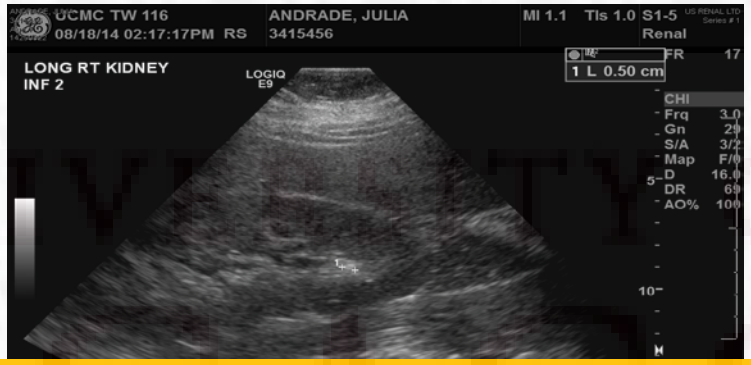
Next morning:

- Patient became confused → facial asymmetry → Head CT& MRI were normal
- BP 120/78
- Medical management continued

Test/date	8/15	8/16	8/17	8/18	8/19	8/20
Ca	13.7	12.6	12.1	11.5	11.4	11.2

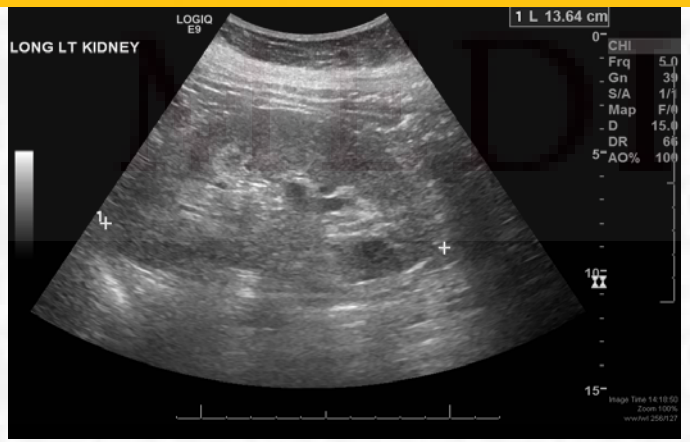
Kidney U/S

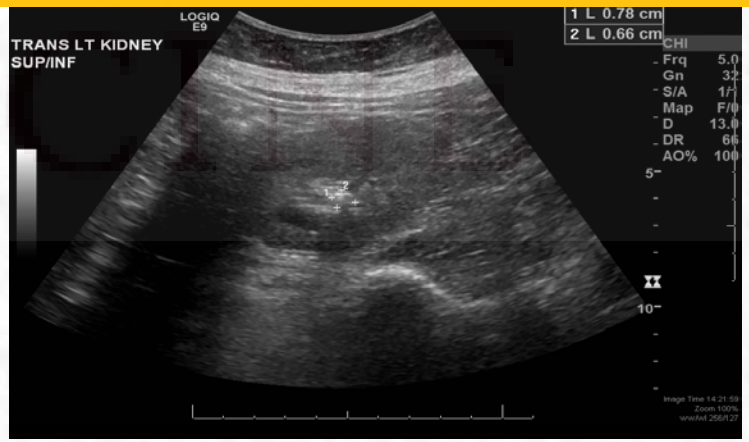




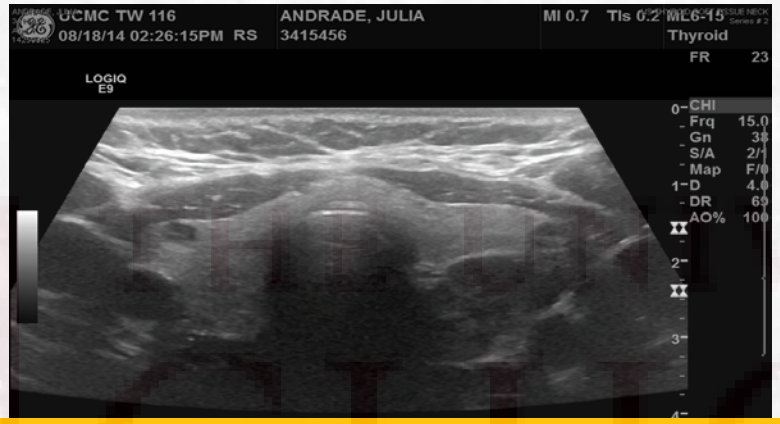
Report:

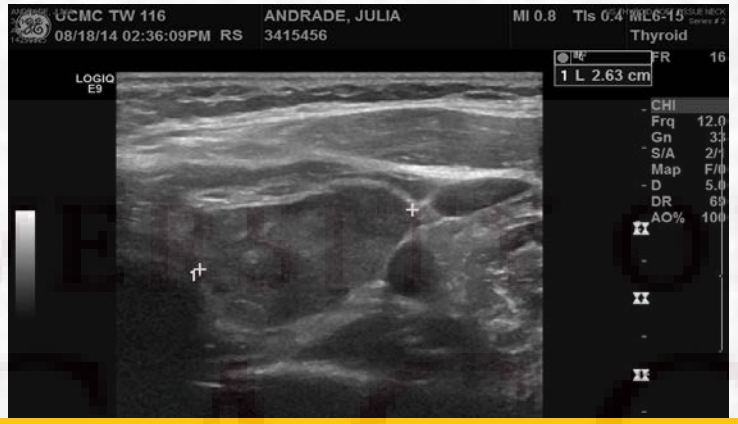
Rt & Lt kidneys → There are multiple subcentimeter hyperechoic foci within the inferior pole with twinkle artifact consistent with renal stones.



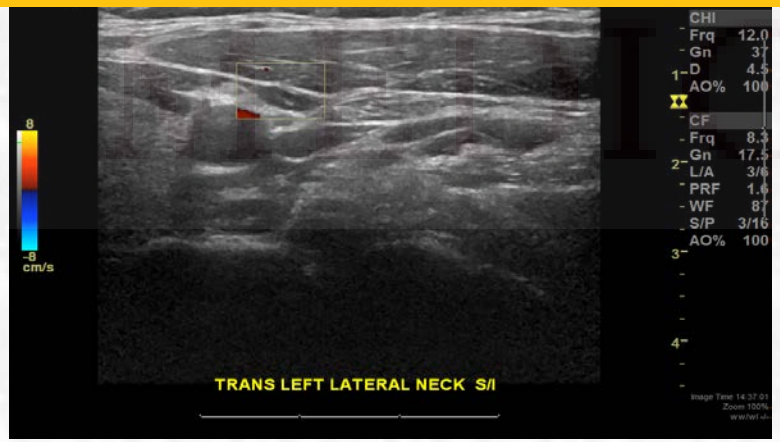


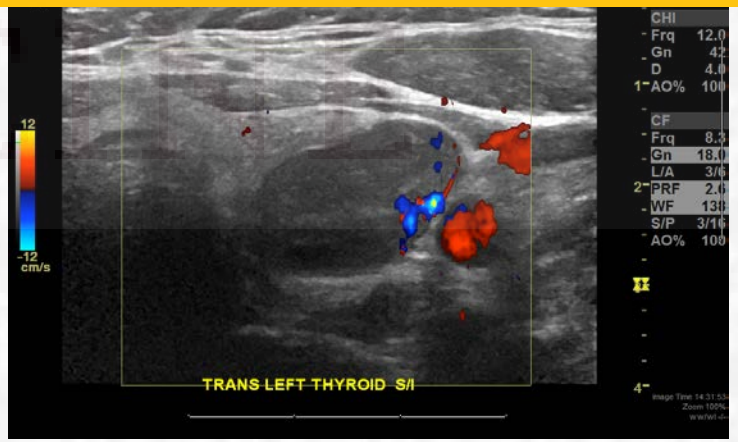
Thyroid Ultrasound





Report: There is a large heterogeneous extrathyroidal nodule which is inferior/posterior to the left thyroid lobe. The nodule measures **2.8 x 1.7 x 2.6 cm** in the largest dimension.





Clinical Qs

i. What is maternal calcium Homeostasis in Pregnancy?

ii. In patient with PHP during pregnancy is parathyroidectomy better than medical management?

- ✓ **PHP is the most common cause of hypercalcemia seen in the outpatient setting with a prevalence of 0.15% in the general population**

- ✓ **The occurrence of PHP during pregnancy is a rare event, with less than 200 cases reported in the English literature**
- ✓ **The incidence of PHP in pregnant is reported to be 8/100,000 population/year**
- ✓ **PHP has been reported to lead to maternal complications in 2/3 of cases. The presentation is variable and ranges from asymptomatic in 23% to symptoms such as nausea, vomiting, and anorexia in 36%, weakness and fatigue in 34%, and neurological/psychiatric manifestations in 26%.**
- ✓ **PHP has been also reported to cause complications in about 45% of both neonatal and perinatal, with tetany being the primary cause of morbidity.**
- ✓ **Other fetal complications include premature birth, intrauterine growth retardation, low birth weight, transient hypoparathyroidism, or even fetal demise**
- ✓ ***Perinatal death occurred in nearly 25% of cases.***

Calcium Homeostasis during pregnancy

- **Maternal *calcium homeostasis* has an important role *during pregnancy* because of the calcium requirements of the growing fetus**
- **Many of the physiological changes associated with pregnancy present a challenge to the diagnosis of hypercalcemia, namely, hemodilution related to intravascular fluid expansion, an increase in glomerular filtration rate resulting in maternal hypercalciuria.**
- **physiologic fall in serum albumin leads to a fall in total calcium levels; however, ionized calcium levels are similar to the non-pregnant state.**
- **The lower levels of total serum calcium seen in pregnancy may mask mild hypercalcemia.**

Pregnancy as State of Physiologic Absorptive Hypercalciuria

Gertner JM, Coustan DR, Kliger AS, Mallette LE, Ravin N, Broadus AE.

September 1986 The American Journal of Medicine Volume 61

16 pregnant women volunteered to participate in the study.

Their ages ranged from 27 to 43 years

The mean times of study were 12.0, 20.8, 34.6, and 67.4 weeks

One had a spontaneous abortion at 12 weeks, and another had termination of the pregnancy at 20 weeks because of hydrocephaly

(TSH, serum Ca, 1-25 OH VitD, serum phosphorous, 24 hrs urine Ca and urine phosphate) were carried out in each trimester and postpartum

September 1986 The American Journal of Medicine Volume 61

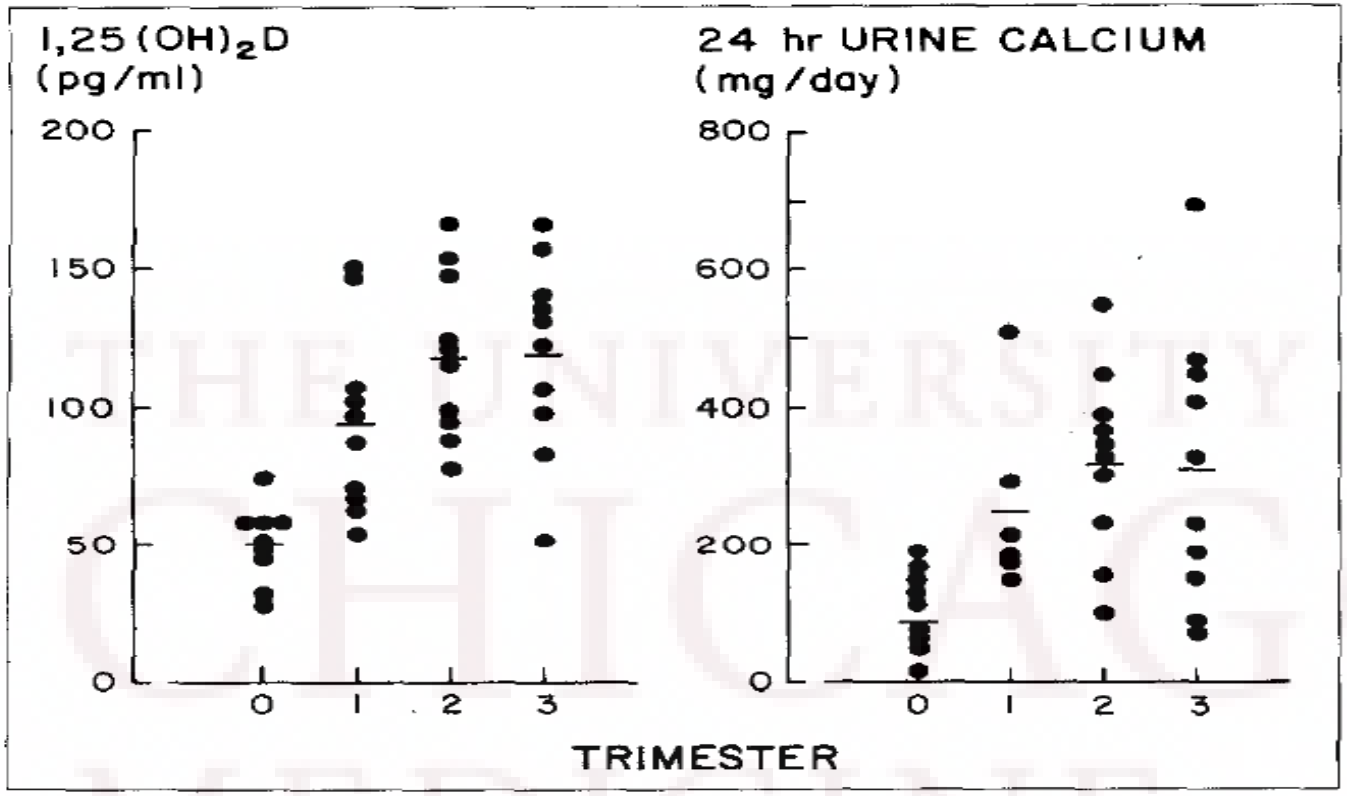
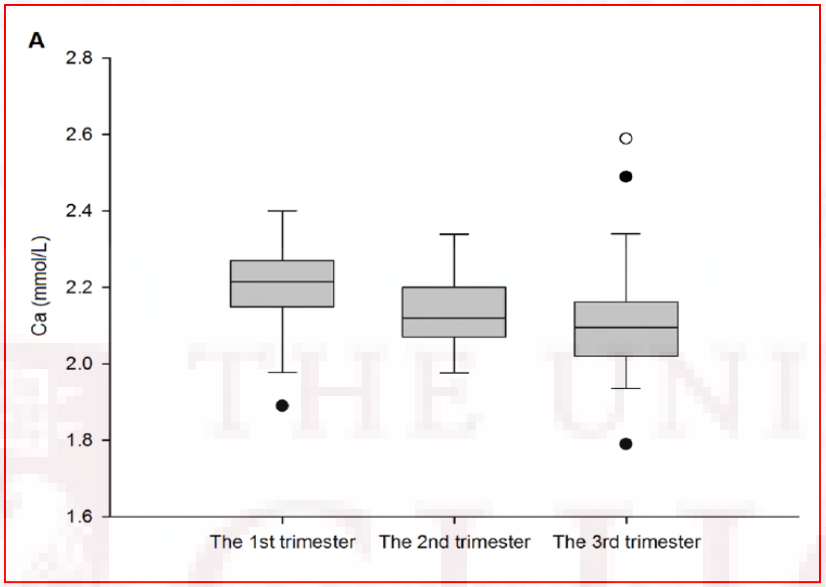
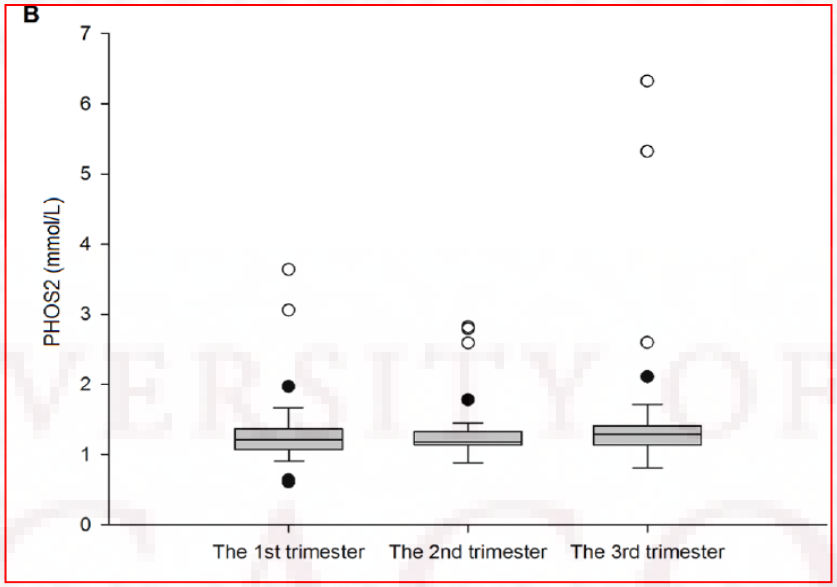
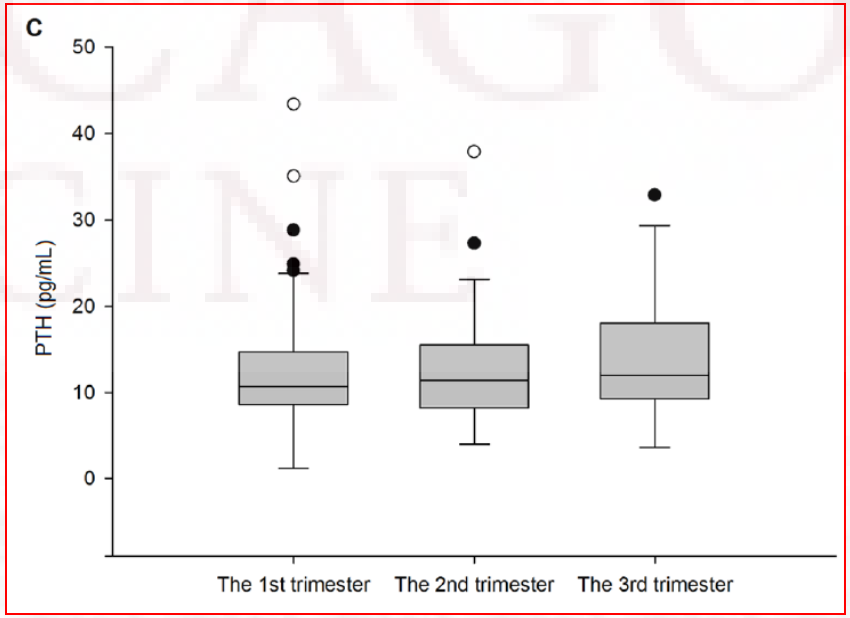


Figure 1. *Circulating 1,25-dihydroxyvitamin D concentration and 24-hour calcium excretion during pregnancy, by trimester. The values for both determinations were significantly increased ($p < 0.05$) during pregnancy (trimesters 1 to 3) as compared with postpartum values (trimester 0). The* ***horizontal bars*** *represent mean values. The upper-normal limit for plasma 1,25-dihydroxyvitamin D is 66 pg/ml [10].*

September 1986 The American Journal of Medicine Volume 61







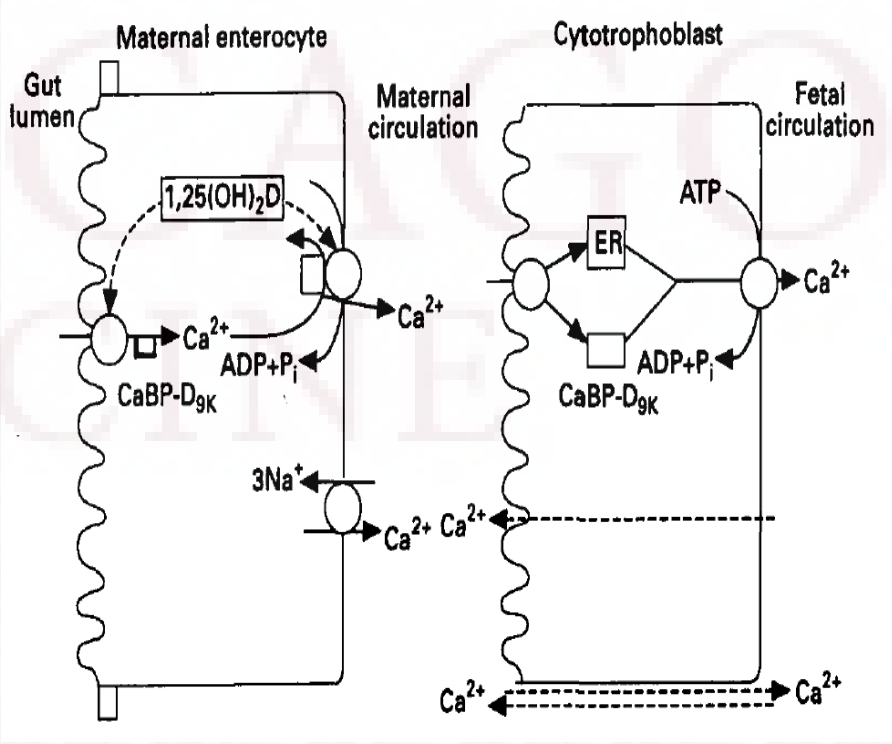
Serum Ca levels of the 2nd and the 3rd trimester were significantly lower than the 1st trimester (p = 0.000), and with no changes during the latter two trimesters (p = 0.334) (A). No significant changes were observed in levels of PHOS2 (p = 0.288) (B) and PTH (p.0.279) (C) during pregnancy.

September 1986 The American Journal of Medicine Volume 61

Result

- 1,25-dihydroxycholecalciferol is **elevated 2-fold** as a result of the **increased activity of maternal 1 α hydroxylase activity under the regulation of** PTHrp, prolactin, estradiol, and human placental lactogen rather than direct stimulatory effects of intact PTH

- **PTH, PTHrP, 1-25 VitD and calcitonin don't cross the placenta, whereas 25 OH VitD does freely cross it.**
- **The most important effect of placenta is the active transport of maternal Ca to the fetus. (placental-fetal calcium gradient of 1.0 : 1.4 throughout pregnancy.**
- **The fetal blood has a higher concentration of calcium compared to maternal blood resulting in suppression of fetal parathyroid development.**
- **At birth, the neonate has relative hypercalcemia and suppressed PTH levels.**

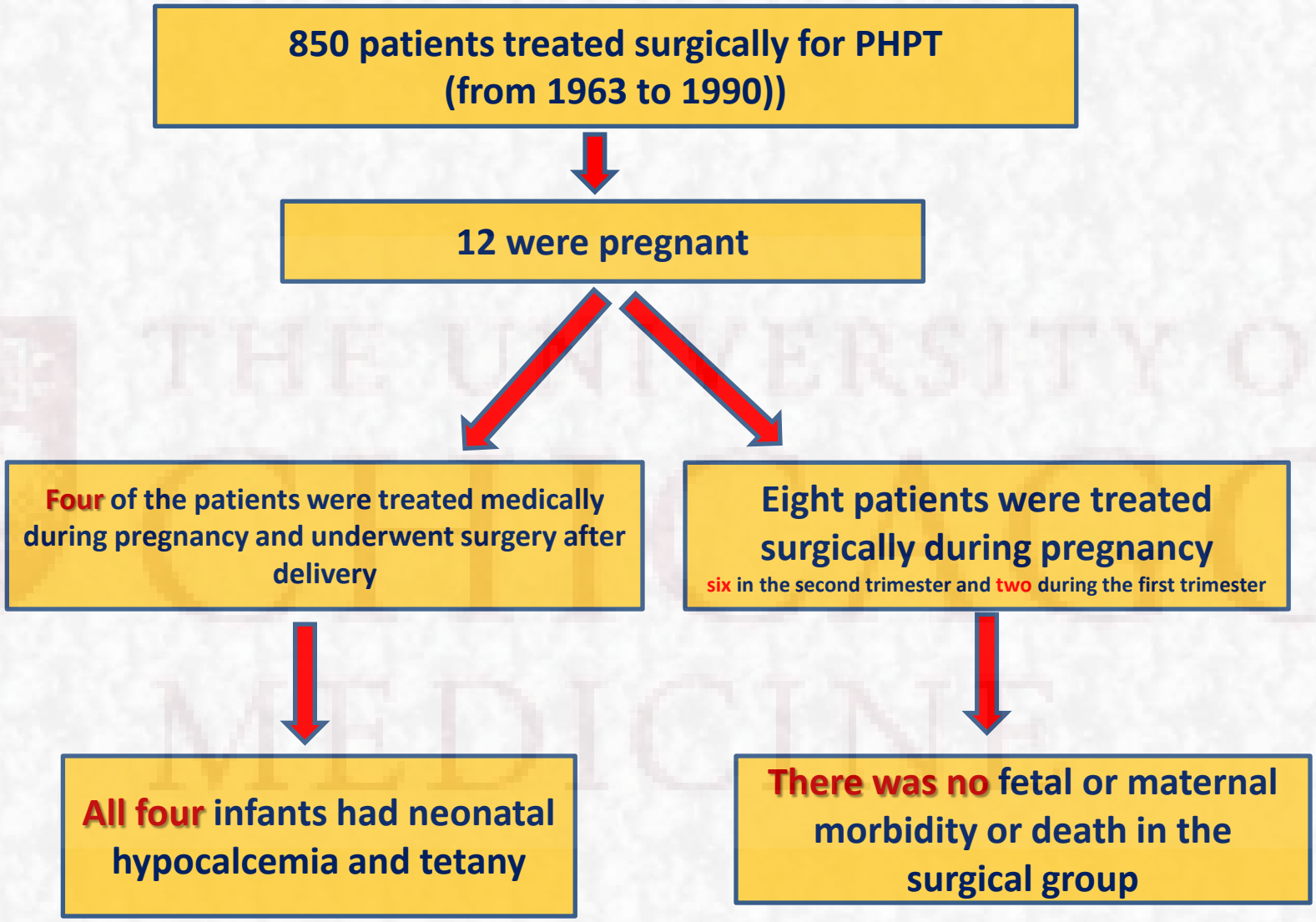


Surgery vs medical management

Primary hyperparathyroidism during pregnancy

Kelly TR
Department of Surgery, Northeastern Ohio Universities College of Medicine, Akron City Hospital

Surgery 1991 Dec;110(6):1028-33; discussion 1033-4



Surgery 1991 Dec;110(6):1028-33; discussion 1033-4

Bendinelli *et al. BMC Pregnancy and Childbirth* 2013, **13**:130
http://www.biomedcentral.com/1471-2393/13/130

BMC Pregnancy & Childbirth

CASE REPORT **Open Access**

Is minimally invasive parathyroid surgery an option for patients with gestational primary hyperparathyroidism?

Cino Bendinelli[1,2*], Shane Nebauer[2], Tuan Quach[3], Shaun Mcgrath[3] and Shamasunder Acharya[3]

Abstract

Background: Gestational primary hyperparathyroidism is associated with serious maternal and neonatal complications, which require prompt surgical treatment. Minimally invasive parathyroidectomy reduces pain, improves cosmesis and may achieve cure rates comparable to traditional open bilateral neck exploration. We report the clinical course of a woman with newly diagnosed gestational primary hyperparathyroidism and discuss the decision making behind the choice of video-assisted minimally invasive parathyroidectomy, amongst the other minimally invasive parathyroidectomy techniques available.

Case presentation: A 38-years-old pregnant woman at 9 weeks of gestation, with severe hyperemesis and hypercalcaemia secondary to gestational primary hyperparathyroidism (ionised calcium 1.28 mmol/l) was referred for surgery. Ultrasound examination of her neck identified 2 suspicious parathyroid enlargements. In view of pregnancy, a radioisotope Sestamibi parathyroid scan was not performed. Bilateral four-gland exploration was therefore deemed necessary to guarantee cure. This was performed with video-assisted minimally invasive parathyroidectomy, which relies on a single 15 mm central incision with external retraction and endoscopic magnification, allowing bilateral neck exploration.
Surgery was performed at 23 weeks of gestation. Four glands were identified in orthotopic positions of which three had normal appearance. The fourth was a right superior parathyroid adenoma of 756 mg. Ionized calcium (1.12 mmol/l) and PTH (0.9 pmol/l) normalised postoperatively. Patient was discharged on the second postoperative day, needing no pain relief. Cosmetic result was excellent. Her pregnancy progressed normally and she delivered a healthy baby.

Conclusion: Video-assisted minimally invasive parathyroidectomy allows bilateral four-gland exploration, and is an optimal technique to treat gestational primary hyperparathyroidism. This procedure removes the need for radiation exposure, reduces pain, improves cosmesis and may achieve cure rates comparable to traditional open bilateral neck exploration.

Keywords: Minimally invasive, Parathyroidectomy, Gestational primary hyperparathyroidism, Video assisted, Hypercalcemia without Sestamibi

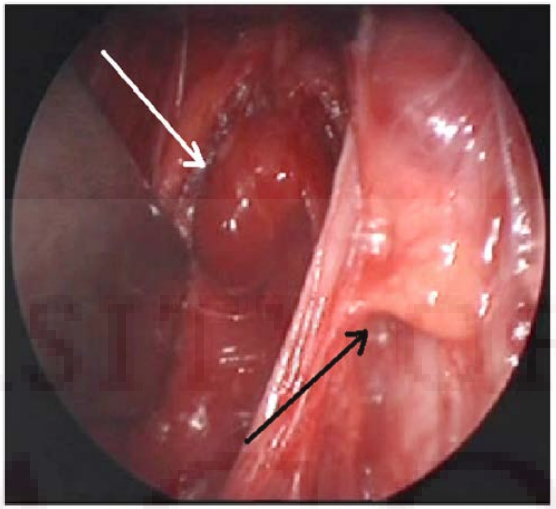


Figure 1 Right superior parathyroid adenoma (white arrow) and left inferior normal parathyroid gland (black arrow).

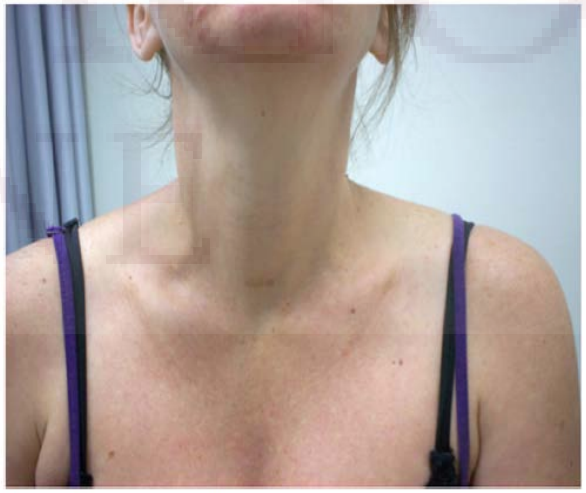


Figure 2 Cosmetic result at 6 weeks post surgery.

Bendinelli et al. BMC Pregnancy and Childbirth 2013, 13:130

Hyperparathyroidism presenting in pregnancy can present with sever N/V (mimicking hyperemesis gravidarum)

Primary Hyperparathyroidism Mimicking Hyperemesis Gravidarum

Brian C. Benson MD; Roy E. Guinto DO; and Jonathan R. Parks MD

Abstract

Nausea and vomiting are common complaints during pregnancy. Their severity and persistence can lead to the diagnosis of hyperemesis gravidarum, which is associated with weight loss, ketonuria, and decreased fetal birth weight. Hypercalcemia in pregnancy can confound these common gastrointestinal symptoms as well as have its own intrinsic maternal-fetal risks. A 23-year-old woman was diagnosed with primary hyperparathyroidism after multiple visits to the emergency department and the obstetrical clinic with symptoms of nausea and vomiting. Her symptoms were initially attributed to hyperemesis gravidarum and only after multiple hospital visits was her hypercalcemia discovered. Her workup led to the diagnosis of primary hyperparathyroidism caused by a solitary parathyroid adenoma. The patient was treated conservatively with intravenous fluids and eventually surgical resection of the parathyroid adenoma which led to complete resolution of her symptoms. This case demonstrates the diagnostic and therapeutic challenges associated with hyperparathyroidism in pregnancy.

Case Report

A 23-year-old Caucasian woman at 15 weeks gestation presented to the emergency department with nausea, vomiting, and 15 pounds weight loss. She had been treated for similar symptoms for the previous six weeks with a trial of antiemetics and intravenous fluids with minimal relief of her symptoms. On presentation, she also noted worsening lightheadedness, diffuse abdominal pain, and was admitted to the hospital due to her inability to tolerate oral fluids. Admission lab tests were significant only for an elevated calcium level of 12.8mg/dL (reference range 8.8-10.2mg/dL). Her past medical history included nephrolithiasis as a teenager. She had no family history of hypercalcemia. She was not taking any medications except antiemetics and prenatal vitamins. Her vital signs were unremarkable and her abdominal exam showed a gravid uterus

HAWAI'I JOURNAL OF MEDICINE & PUBLIC HEALTH, JANUARY 2013, VOL 72, NO 1

Summary

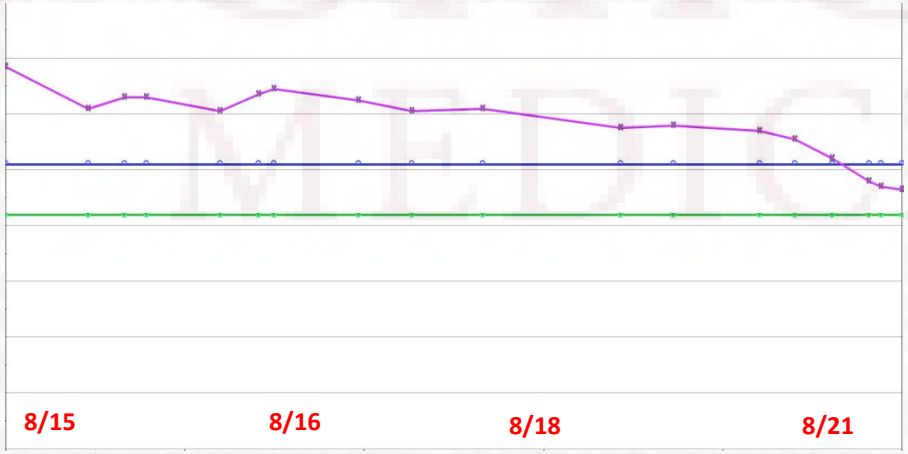
- During pregnancy, PHP can manifest with life-threatening hypercalcemia. It is associated with a high risk of fetal and neonatal complications, including death.
- Management of lifethreatening hypercalcemia during pregnancy requires a team effort by obstetricians, neonatologists, surgeons, and endocrinologists.
- Definitive treatment is surgical, which is ideally performed during the second trimester.
- Hydration and calciuretic drugs are the cornerstone of medical therapy.
- The neonates of mothers with hypercalcemia should be carefully observed and assessed for hypocalcemia and parathyroid suppression.
- All pregnancies in patients with hypercalcemia should be considered high risk.

Back to my patient

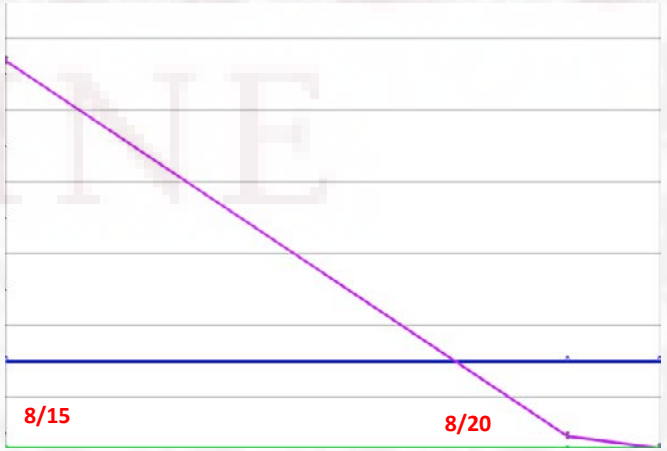
- Underwent surgical parathyroidectomy on 8/20 by Dr Angelos
- During surgery PTH dropped to 15 (284 on admission)

Test/date	8/20 11pm	8/21 10am	8/21 3pm
Ca	9.6	9.3	9.5

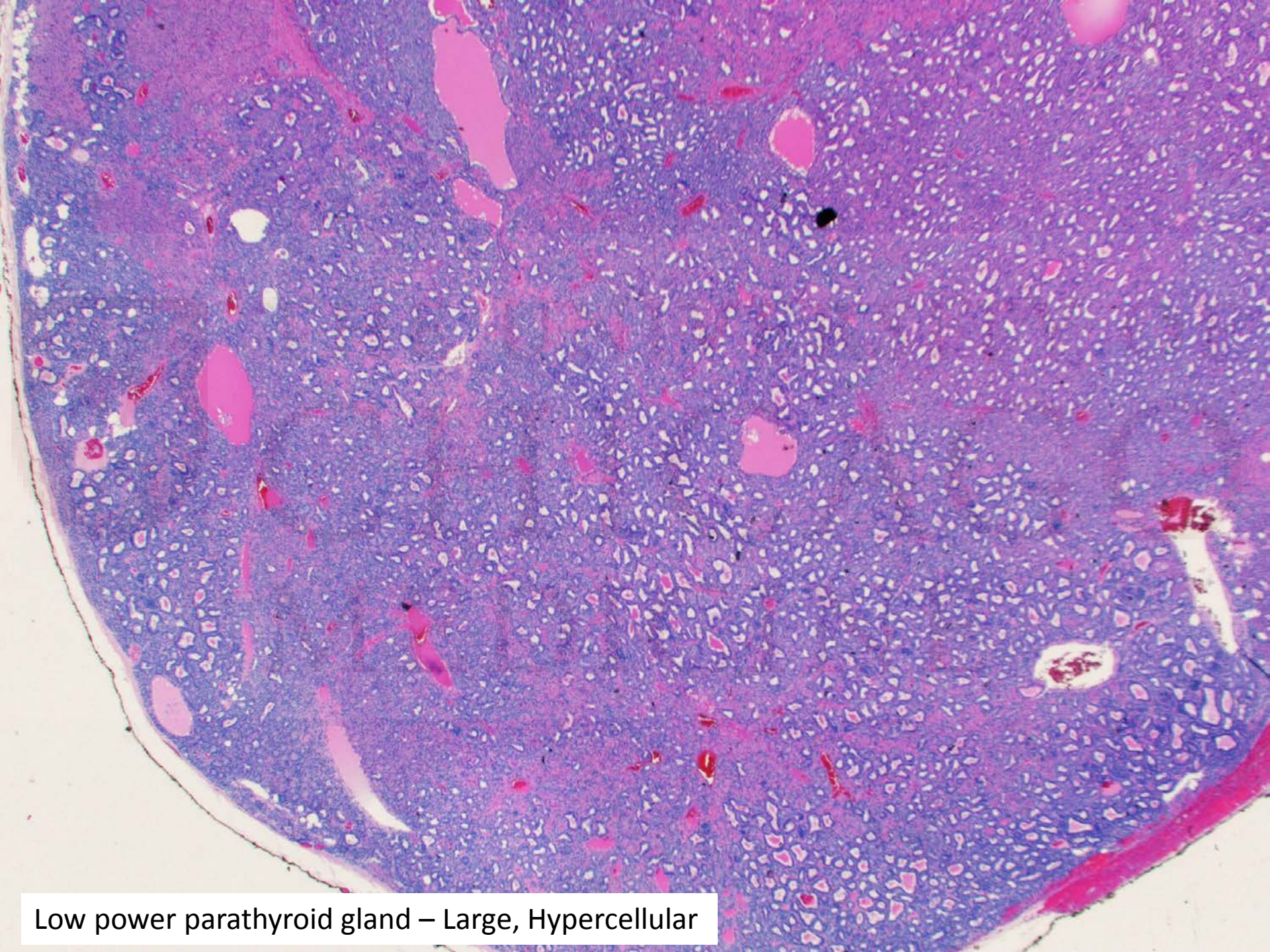
Test/date	8/15	8/20	8/21
PTH	284	23	15



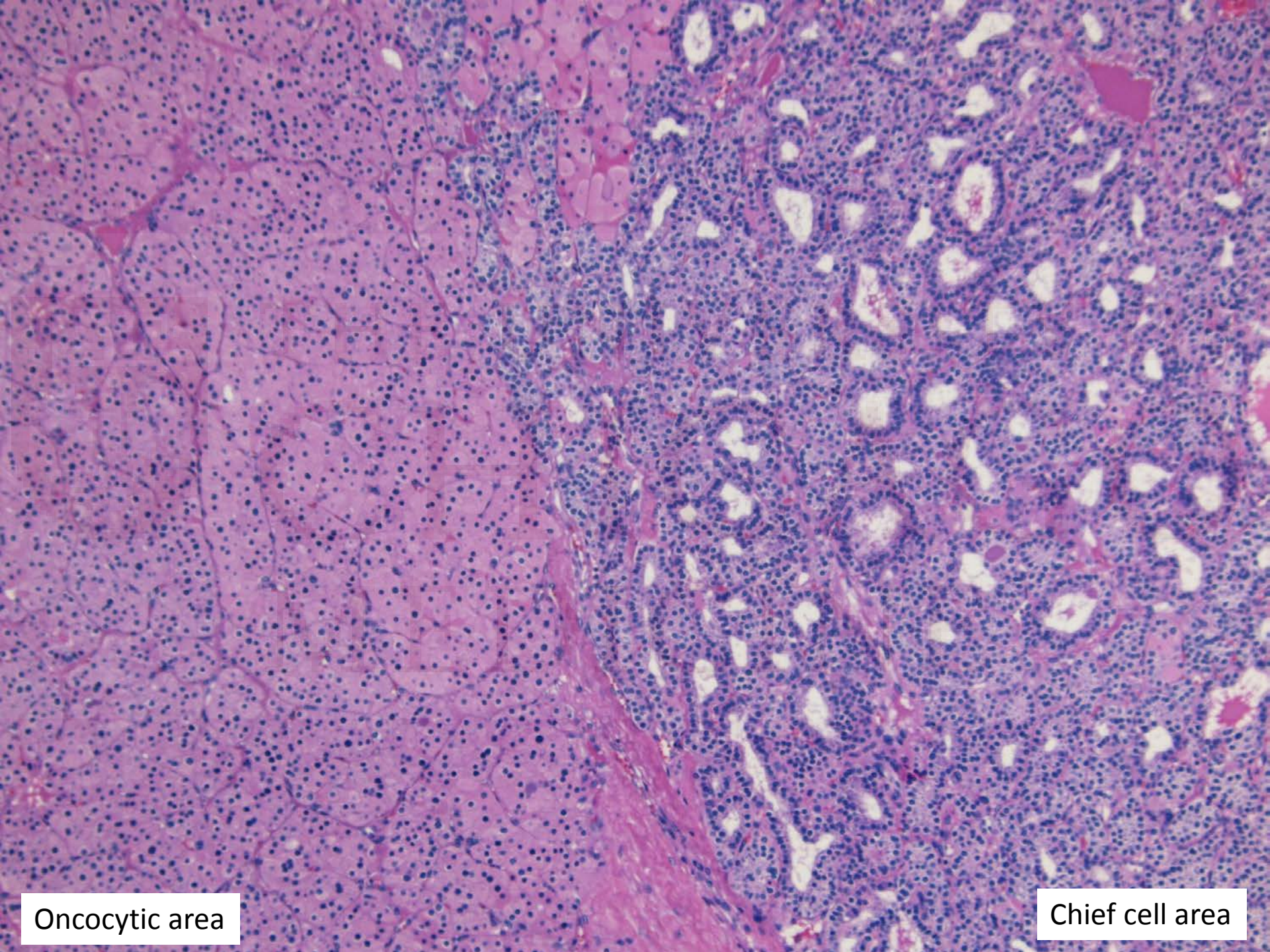
Ca

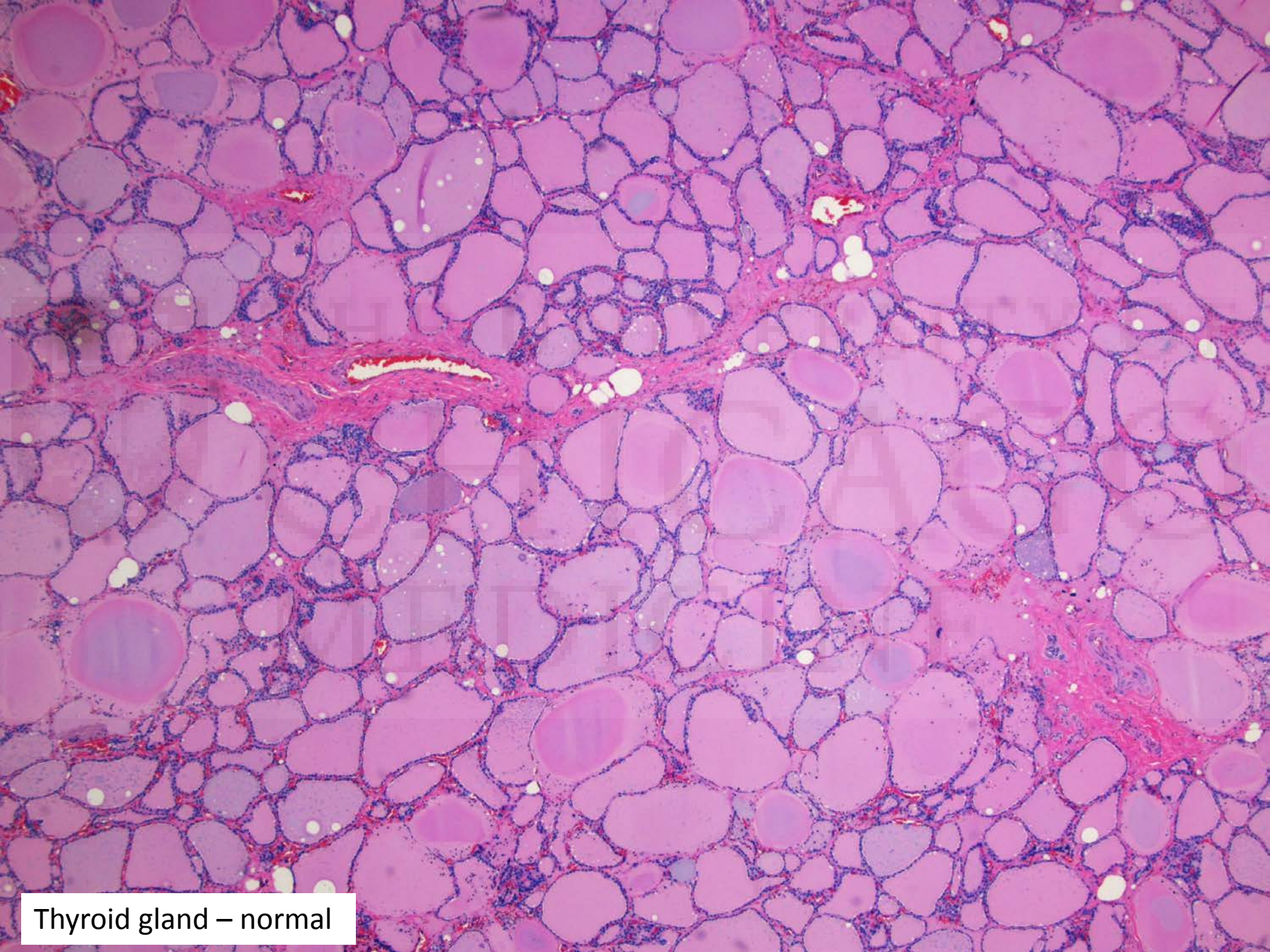


PTH



Low power parathyroid gland – Large, Hypercellular


Oncocytic area
Chief cell area



Thyroid gland – normal

References

- **Heath H III, Hodgson SF, Kennedy MA.** Primary hyperparathyroidism: incidence, morbidity and potential economic impact in a community. *N Engl J Med.* 1980; 302:189-193.
- **Ludwig GD.** Hyperparathyroidism in relation to pregnancy. *N Engl J Med.* 1962;267:637-643.
- **Delmonico FL, Neer RM, Cosimi AB, Barnes AB, Russell PS.** Hyperparathyroidism during pregnancy. *Am J Surg*. 1976;131:328-337.
- **Stander HJ, Ahearn RE.** The parathyroids in pregnancy. *J Mount Sinai Hosp.* 1947;14:629-644.
- **Matthias GS, Helliwell TR, Williams A.** Postpartum hyperparathyroid crisis: case report. *Br J Obstet Gynaecol.* 1987;94:807-810.
- **Pitkin RM.** Neonatal tetany in 2 siblings: effects of maternal hyperparathyroidism. *Pediatrics.* 1954;13:227.
- **Carella MJ, Gossain VV.** Hyperparathyroidism and pregnancy: case report and review. *J Gen Intern Med.* 1992;7:448-453.
- **Ammann P, Irion O, Gast J, Bonjour JP, Beguin F, Rizzoli R.** Alterations of calcium and phosphate metabolism in primary hyperparathyroidism during pregnancy. *Acta Obstet Gynecol Scand.* 1993;72:488-492.
- **Kelly TR.** Primary hyperparathyroidism during pregnancy [with discussion]. *Surgery.* 1991;110:1028-1034.
- **Bendinelli C, Nebauer S, Quach T, Mcgrath S, Acharya S**. Is minimally invasive parathyroid surgery an option for patients with gestational primary hyperparathyroidism? BMC Pregnancy Childbirth. 2013 Jun 11;13:130. doi: 10.1186/1471-2393-13-130. PubMed PMID: 23758620; PubMed Central PMCID: PMC3691590.

Thank you

Milad Abusag MD

09/04/2014