A 26 year old pregnant woman with hypercalcemia

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Endorama

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AT THE FOREFRONT
UChicago Medicine

*I have no relevant financial relationships with any commercial interests or other conflicts of interest.

Learning Objectives

- Evaluate and treat hypercalcemia in the setting of pregnancy
- Review pregnancy complications related to hypercalcemia
- Review safety of diagnostic and treatment modalities for hypercalcemia in the setting of pregnancy
- Acknowledge the barriers to care caused by COVID-19

A 26 year old woman with a past medical history of asthma presented to the UC emergency department following a motor vehicle accident in which she was an unrestrained passenger in the backseat. The force of the impact caused her to be propelled into the front area of the car. She was hemodynamically stable on arrival. Her initial exam was notable for head and extremity abrasions and right ankle tenderness.

To assess for head and neck injury, she underwent a CT head, CTA of the neck, and CT of the thoracic and lumbar spine:

- CT head: hemorrhagic left front scalp contusion, without underlying fracture; subtle foci of bifrontal and biparietal subarachnoid hemorrhage

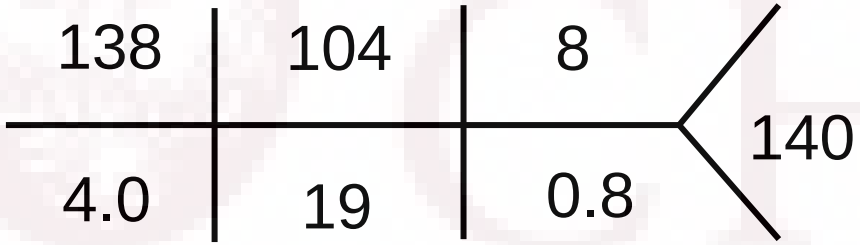
- CTA neck and cervical spine: unremarkable vasculature, c-spine vertebrae without fracture of malalignment

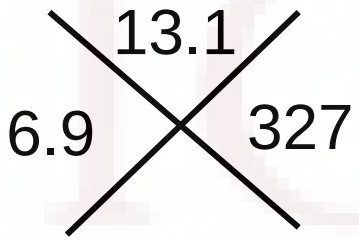
- **T spine: mild anterior height loss of T11 and T12 of uncertain acuity**

- L spine: no evidence of fracture

The patient was evaluated by the neurosurgical service, which recommended dedicated T spine XR, TLSO brace, and repeat head imaging after 1 month. The XR did not redemonstrate any fractures. The patient was discharged in stable condition.

Labs from ED evaluation:





Total protein: 8.0
Albumin: 4.5
T bil: 0.4
AST: 22
ALT: 19
Alk phos: 80

Calcium: **11.3**

She followed up in the neurosurgery clinic 1 month later with additional imaging. Head CT showed resolved SAH. Repeat L (not T) spine XR showed possible minimal wedging of T12.

August, 2020

How frequently are wedge fractures detected by CT chest imaging?

Study population:
- 200 consecutive patients undergoing CT chest imaging
- No exclusions were made based on clinical reason for imaging

Methods:
- Images were reformatted to bone windows in sagittal view
- Fractures were determined by consensus of 3 radiologists using a semi-quantitative method

Results: (see tables)

Table 1 Severity of fracture versus type of fracture found using the semiquantitative technique

	Wedge	Biconcave	Crush	Total
Grade 1 (mild)	43	8	0	51
Grade 2 (moderate)	8	5	0	13
Grade 3 (severe)	4	2	0	6
Total	55	15	0	70

Table 2 Age demographics of patients with vertebral fractures

Age (years)	Total number of patients	Number of patients with vertebral fractures
<50	61	4 (7%)
51–60	24	12 (50%)
61–70	36	12 (33%)
71–80	52	26 (50%)
81–90	26	15 (58%)
>90	1	1 (100%)
Total	200	70 (35%)

Clin Radiol. 2008 Feb ;63(2):160-4.

The patient presented again to the UC emergency department, this time with nausea and vomiting of 6 days duration. She had a positive at-home pregnancy test about 1 month prior. She also endorsed headache, palpitations, lightheadedness, and blurry vision. Also with urinary frequency and some occasional right-sided abdominal/flank pain. No uterine bleeding, diarrhea, or fever/respiratory symptoms.

Her initial laboratory and imaging work up is notable for:

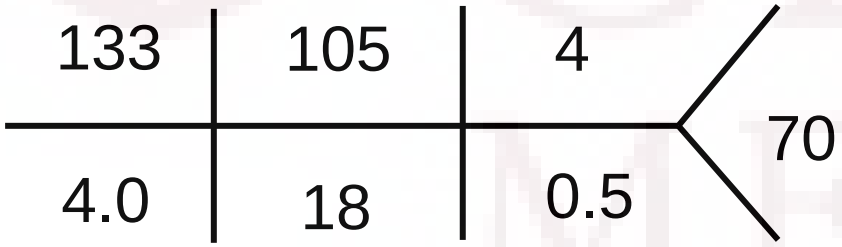
- A serum β-HCG level of 144106 mIU/mL
- Urinalysis suggestive of infection. Urine culture had no growth but GC PCR urine probe was positive
- **Calcium is again elevated, to 13.9.** Albumin is 4.4.
- No hemorrhage or edema on head CT

Physical exam, laboratory, and ultrasound results:

Obese habitus. Arousable but fatigued.
BP 98/52. HR 84. Temp 36.4. BMI 41.
Neck: supple, no obvious thyromegaly
CV: regular rate and rhythm
Chest: clear to auscultation bilaterally
Abdomen: mild tenderness in lower quadrants
GU: tenderness over R inguinal chain
Neuro: grossly intact
Skin: warm, dry
Extremities: trace edema bilaterally

Renal ultrasound:
Unremarkable. No suggestion of hydronephrosis or renal stone.

Thyroid ultrasound:
1.3 x 1.3 1.6 cm isoechoic ovoid mass with hypoechoic rim adjacent to the posterior lower pole of the R thyroid lobe



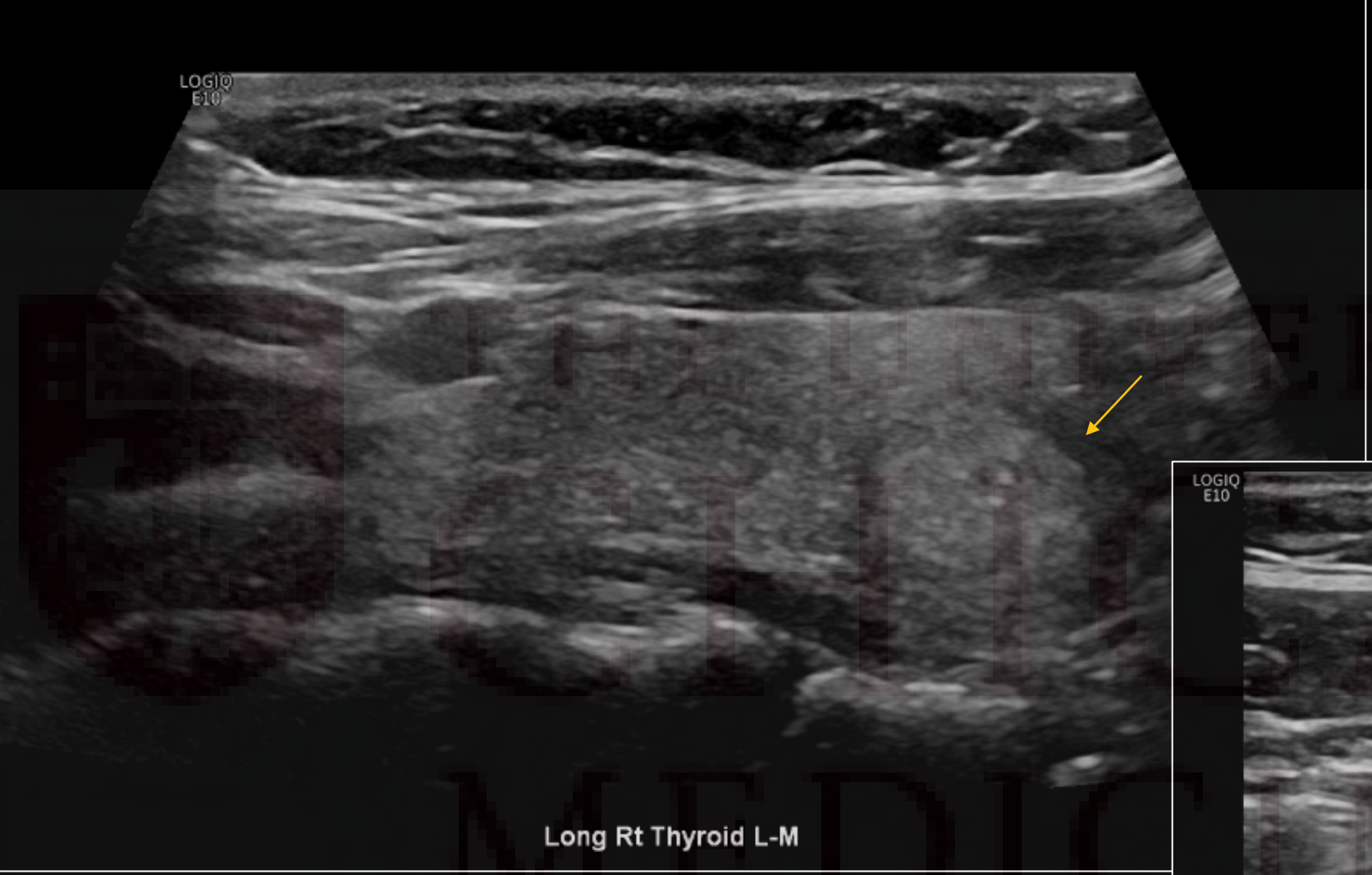
Calcium: **12.9**
Phosphate: 2.4
Magnesium: 1.8

iCal: **6.63** (4.6 – 5.4 mg/dL)
PTH: **189** (15 -75 pg/mL)
25-OH vit D: 10

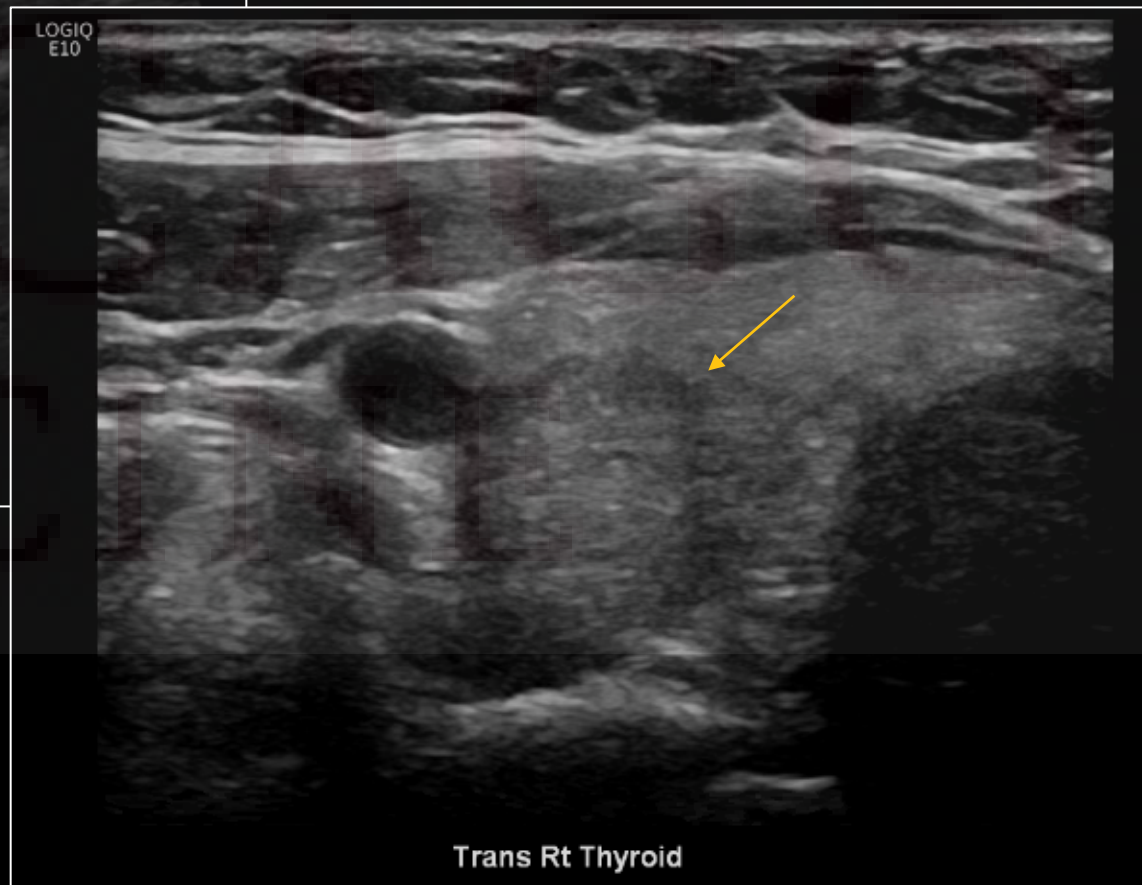
TSH: 1.41

Total protein: 6.9
Albumin: 3.7
T bil: 0.5
AST: 14
ALT: 14
Alk phos: 60

24 hour urine collection:
Volume: 2.3 L
Calcium: **1110 mg**



Long Rt Thyroid L-M



Trans Rt Thyroid

Overview of hospital course:

- Nausea and vomiting improve with fluids and symptomatic treatment
- The patient received a single course of IV antibiotic therapy for cervical infection (GC)
- The patient endorsed to multiple providers that she wished to terminate the pregnancy
- Family Planning was consulted to assist with arranging pregnancy termination
- Endocrine surgery was consulted and arranges for follow up in clinic (*no show*), with a tentative plan for surgery either following termination or during the second trimester. Sestamibi scan on hold given concern for safety during pregnancy.
- Patient is discharged in stable condition although remains hypercalcemic.
- (No endocrinology consult at this point.)

Guidelines for surgery in asymptomatic PHPT: A comparison of current guidelines with the previous one*

Measurement ¶	2008	2014
Serum calcium (>upper limit of normal)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	1. BMD by DXA: T-score <–2.5 at any site ¶ 2. Previous fragility fracture Δ	1. BMD by DXA: T-score <–2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius ¶ 2. Vertebral fracture by radiograph, CT, MRI, or VFA
Renal	1. eGFR <60 mL/min 2. 24-hour urine for calcium not recommended	1. Creatinine clearance <60 mL/min 2. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis ◇ 3. Presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT
Age (years)	<50	<50

Patients need to meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

What additional concerns does primary hyperparathyroidism pose in the setting of pregnancy?

Although quite uncommon, it is possible that gestational primary hyperparathyroidism is underdiagnosed in general due to relatively mild disease, changes in calcium metabolism during pregnancy (e.g. hypoalbuminemia, etc.) that may mask subtle disease, and non-specific symptoms that are attributed to pregnancy itself.

Maternal hypercalcemia has been associated with hyperemesis, nephrolithiasis, muscular weakness, cognitive abnormalities, increased risk of pre-eclampsia, and, rarely, pancreatitis.

Neonatal complications include neonatal hypoparathyroidism, hypocalcemic tetany, intellectual disability, and low birth weight.

Retrospective studies have found an association between primary hyperparathyroidism and pregnancy loss, although it appears to be a function of average serum calcium level. One 2015 study (referenced) found no difference in pregnancy loss between the study cohort and the control group, but few women had average serum calcium levels >12 mg/dL.

J Clin Endocrinol Metab. 2015 May;100(5):2115-22.

What data are available on safety of ^{99m}Tc-sestamibi scan in the setting of pregnancy?

It is well-established generally that fetal irradiation should be avoided whenever possible.

A prospective study of 122 women exposed to ^{99m}Tc scintigraphy in the first trimester showed no association with adverse pregnancy outcomes when doses were limited to <5 mGy.

There are case reports of pregnant women receiving ^{99m}Tc-MIBI parathyroid localization studies (along with CT scan of the neck and chest) in which the standard 20-mCi dose was reduced by 50%, leading to fetal radiation exposure of <5 mGy, with acceptable imaging results.

Due to potential exposure from radioactive material accumulating in the bladder, maternal hydration and frequent voiding are recommended.

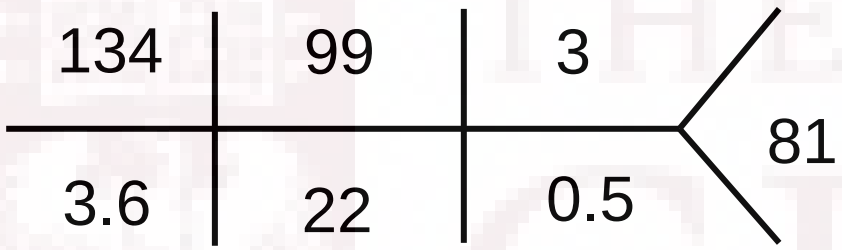
Radionuclide compounds are excreted in breast milk. This should be considered when recommending a scan for women who are breast-feeding.

n.b. ^{99m}Tc and radioactive iodine have different properties (I-131 readily crosses the placenta and has a half-life of ~8 days). Radioactive iodine is not used in women who are pregnant or breast-feeding.

J Endocr Soc. 2017 Sep 1; 1(9):1156-59.

ACOG Committee Opinion. Number 723. Oct 2017. Guidelines for Diagnostic Imaging During Pregnancy and Lactation.

The patient presented to ob/gyn clinic in December for pre-operative planning prior to planned pregnancy termination. By ultrasound, her pregnancy was dated at 13 weeks at this time. At the visit, she had complaints of nausea, dizziness and fatigue. She had a BMP drawn due to these symptoms:



Calcium: **15.4**

Albumin: 4.4

The patient was transported to the ED and then admitted to medicine for treatment of hypercalcemia and nausea/vomiting. IV fluids are continued. The gynecological procedure is scheduled 48 hours following admission.

COVID-19 testing returned **positive.** Procedure is delayed at least 10 days following positive test per policy.

The endocrine consult service is called to assist with management of hypercalcemia.

December, 2020

Management of hypercalcemia and primary hyperparathyroidism in pregnancy

What initial recommendations would you make to the medicine team regarding the management of this patient?

Calcium: 15.4

Albumin: 4.4

PTH: 189

25-OH Vit D: 10

Initial “rapid” recommendations:

- continue fluids at 250 cc/hr
- start Lasix 20 mg IV BID
- start cinacalcet at 30 mg daily
- start calcitonin 4U/kg sc BID for 48 hours
- monitor calcium, albumin, phos BID
- consider vitamin D replacement once calcium improves

Historical lab values:

	30 9/23/2013 0450	29 11/27/2016 1422	28 5/29/2017 1143	27 5/30/2017 1058	26 5/31/2017 0842	25 6/28/2018 1058	24 8/18/2020 1325	23 10/17/2020 0206	22 11/15/2020 1313
Calcium	10.9	10.2	11.9	11.8	10.8	11.0	11.3	11.3	13.9 *
Albumin		4.2	4.4	4.6			4.5	4.2	4.4
Inorganic Phosphate					1.6				
Magnesium					1.8				

calcitonin

Admission days 1 – 6:

	12/7/2020 1406	12/8/2020 0243	12/8/2020 1741	12/9/2020 1033	12/10/2020 0450	12/10/2020 1653	12/11/2020 0615	12/11/2020 1819	12/12/2020 0501	12/12/2020 1725
Calcium	15.4 *	15.6 *	12.7	10.8	12.0	12.1	12.5	13.4 *	13.0 *	14.1 *
Albumin	4.4	4.4		3.2						
Inorganic Phosphate		2.7	1.0	<1.0 *	1.9	2.9	2.0	2.7	2.4	2.2
Magnesium		1.7	1.2	1.2	1.4	1.4	2.0	1.5	2.1	1.7

Management of hypercalcemia and primary hyperparathyroidism in pregnancy

What data are available on the safety of cinacalcet in the setting of pregnancy?

The calcium-sensing receptor (CaSR) is expressed not only on the chief cells of the parathyroid but also kidney, bone, breast, brain, thyroid tissue and placenta.

Thus, calcium metabolism in the placenta and fetus could be disrupted via maternal cinacalcet administration.

Animal studies have not clearly shown harm and doses equivalent to 180 mg/day. It is currently a category C medication (potential benefits may outweigh risks).

The patient's tolerance of oral medications, including cinacalcet, at this point of the admission is only fair.

Do you consider additional therapies at this time?

J Endocr Soc. 2017 Sep 1; 1(9):1156-59.

	12/12/2020 0501	12/12/2020 1725	12/13/2020 0714	12/13/2020 1836	12/14/2020 0427	12/14/2020 1724	12/15/2020 0641	12/15/2020 1756
BASIC & COMPREHENSIVE								
Calcium	13.0 *	14.1 *	13.2 *	12.6	12.2	11.5	10.7	10.1

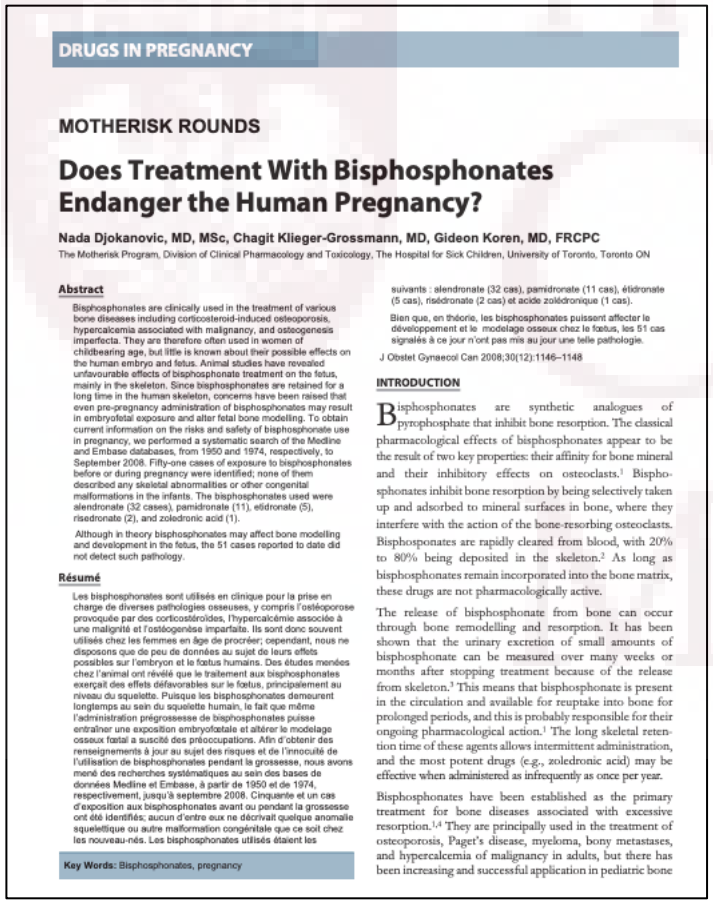
4 mg zoledronic acid IV given

Increased cinacalcet to 30 mg BID
Started vitamin D 5000 IU daily

	12/11/2020 1819	12/12/2020 0501	12/12/2020 1725	12/13/2020 0714	12/13/2020 1836	12/14/2020 0427	12/14/2020 1724	12/15/2020 0641	12/15/2020 1756
Inorganic Phosphate	2.7	2.4	2.2	2.0	2.3	1.5	1.0	1.3	1.4
Magnesium	1.5	2.1	1.7	1.4	1.4	1.8	1.5	1.4	2.0

Management of hypercalcemia and primary hyperparathyroidism in pregnancy

What data are available on the safety of bisphosphonate therapy in the setting of pregnancy?



DRUGS IN PREGNANCY

MOTHERISK ROUNDS

Does Treatment With Bisphosphonates Endanger the Human Pregnancy?

Nada Djokanovic, MD, MSc, Chagit Klieger-Grossmann, MD, Gideon Koren, MD, FRCPC

The Motherisk Program, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, University of Toronto, Toronto ON

Abstract

Bisphosphonates are clinically used in the treatment of various bone diseases including corticosteroid-induced osteoporosis, hypercalcemia associated with malignancy, and osteogenesis imperfecta. They are therefore often used in women of childbearing age, but little is known about their possible effects on the human embryo and fetus. Animal studies have revealed unfavourable effects of bisphosphonate treatment on the fetus, mainly in the skeleton. Since bisphosphonates are retained for a long time in the human skeleton, concerns have been raised that even pre-pregnancy administration of bisphosphonates may result in embryofetal exposure and alter fetal bone modelling. To obtain current information on the risks and safety of bisphosphonate use in pregnancy, we performed a systematic search of the Medline and Embase databases, from 1950 and 1974, respectively, to September 2008. Fifty-one cases of exposure to bisphosphonates before or during pregnancy were identified; none of them described any skeletal abnormalities or other congenital malformations in the infants. The bisphosphonates used were alendronate (32 cases), pamidronate (11), etidronate (5), risedronate (2), and zoledronic acid (1).

Although in theory bisphosphonates may affect bone modelling and development in the fetus, the 51 cases reported to date did not detect such pathology.

Résumé

Les bisphosphonates sont utilisés en clinique pour la prise en charge de diverses pathologies osseuses, y compris l'ostéoporose provoquée par des corticostéroïdes, l'hypercalcémie associée à une malignité et l'ostéogenèse imparfaite. Ils sont donc souvent utilisés chez les femmes en âge de procréer; cependant, nous ne disposons que de peu de données au sujet de leurs effets possibles sur l'embryon et le fœtus humains. Des études menées chez l'animal ont révélé que le traitement aux bisphosphonates exerçait des effets défavorables sur le fœtus, principalement au niveau du squelette. Puisque les bisphosphonates demeurent longtemps au sein du squelette humain, le fait que même l'administration prégrossesse de bisphosphonates puisse entraîner une exposition embryofœtale et altérer le modelage osseux fœtal a suscité des préoccupations. Afin d'obtenir des renseignements à jour au sujet des risques et de l'innocuité de l'utilisation de bisphosphonates pendant la grossesse, nous avons mené des recherches systématiques au sein des bases de données Medline et Embase, à partir de 1950 et de 1974, respectivement, jusqu'à septembre 2008. Cinquante et un cas d'exposition aux bisphosphonates avant ou pendant la grossesse ont été identifiés; aucun d'entre eux ne décrivait quelque anomalie squelettique ou autre malformation congénitale que ce soit chez les nouveau-nés. Les bisphosphonates utilisés étaient les suivants : alendronate (32 cas), pamidronate (11 cas), étidronate (5 cas), risédronate (2 cas) et acide zolédronique (1 cas).

Bien que, en théorie, les bisphosphonates puissent affecter le développement et le modelage osseux chez le fœtus, les 51 cas signalés à ce jour n'ont pas mis au jour une telle pathologie.

J Obstet Gynaecol Can 2008;30(12):1146–1148

Key Words: Bisphosphonates, pregnancy

INTRODUCTION

Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption. The classical pharmacological effects of bisphosphonates appear to be the result of two key properties: their affinity for bone mineral and their inhibitory effects on osteoclasts.[1] Bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorbing osteoclasts. Bisphosponates are rapidly cleared from blood, with 20% to 80% being deposited in the skeleton.[2] As long as bisphosphonates remain incorporated into the bone matrix, these drugs are not pharmacologically active.

The release of bisphosphonate from bone can occur through bone remodelling and resorption. It has been shown that the urinary excretion of small amounts of bisphosphonate can be measured over many weeks or months after stopping treatment because of the release from skeleton.[3] This means that bisphosphonate is present in the circulation and available for reuptake into bone for prolonged periods, and this is probably responsible for their ongoing pharmacological action.[1] The long skeletal retention time of these agents allows intermittent administration, and the most potent drugs (e.g., zoledronic acid) may be effective when administered as infrequently as once per year.

Bisphosphonates have been established as the primary treatment for bone diseases associated with excessive resorption.[1,4] They are principally used in the treatment of osteoporosis, Paget's disease, myeloma, bony metastases, and hypercalcemia of malignancy in adults, but there has been increasing and successful application in pediatric bone

Because of the long persistence and slow release from bone over time, it is hypothesized that even pre-pregnancy administration of bisphosphonates may alter fetal bone modelling and reduce the amount of calcium available to the fetus.

<u>Animal studies</u>:

Alendronate given to rats was shown to cross the placenta, accumulate in fetal bone, and decrease fetal bone growth.

Very high doses of pamidronate in rats and rabbits led to fetal demise and severe skeletal retardation.

Symptomatic hypocalcemia was seen in rats in the later stages of pregnancy.

J Obstet Gynaecol Can. 2008 Dec; 30(12):1146-1148.

Management of hypercalcemia and primary hyperparathyroidism in pregnancy

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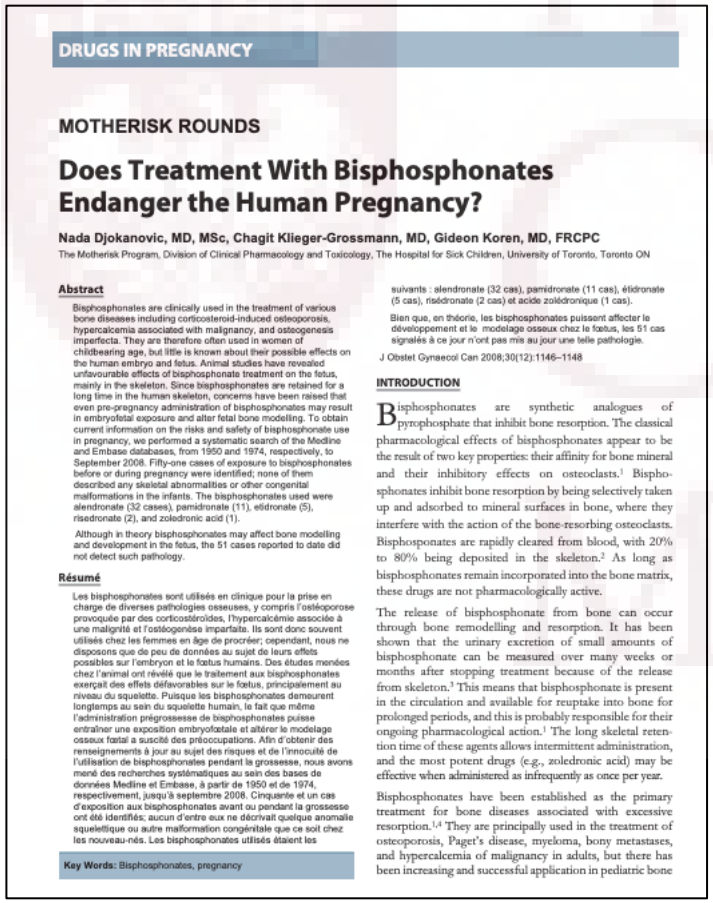

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<u>Human case studies</u>:
The authors found 51 pregnancies total in the literature with bisphosphonate exposures.

A case series of 24 pregnancies with exposure to alendronate found reduce birth weight and increased rate of miscarriage than in controls, however the rate of use of glucocorticoids and other therapies for maternal disease was much higher as well.

Several case reports were identified of pregnant women receiving pamidronate or zoledronic acid for hypercalcemia related to metastatic breast cancer without any significant pregnancy complications or birth defects.

J Obstet Gynaecol Can. 2008 Dec; 30(12):1146-1148.

Multi-center, prospective cohort study of 21 women exposed to bisphosphonates during or just before pregnancy. A control group was selected based on maternal age, gravidity, previous miscarriages, smoking, alcohol, and gestational age to minimize bias.

Table 1
Maternal baseline characteristics

Characteristic	Bisphosphonate exposed group (n=21)	Comparison group (n=21)	P value
Maternal age (years: mean±SD)	32.4±3.9	32.6±4.1	0.46
Gravidity (mean±SD)	2.0±1.1	2.0±1.5	1.00
Parity (mean±SD)	0.7±0.8	0.6±0.7	0.41
Previous spontaneous abortion (no: mean±SD)	0.3±0.6	0.3±1.2	0.96
Previous therapeutic abortion (no: mean±SD)	0	0.1±0.3	0.18
Alcohol consumption in pregnancy (number of women [percentage])	None: 21 [100%] light: 0 [0%]	None: 21 [100%] light: 0 [0%]	1.00
Smoking habits in pregnancy (number of women [percentage])	None: 20 [95%] light: 1 [5%]	None: 20 [95%] light: 1 [5%]	1.00

Table 2
Pregnancy and neonatal outcome

Outcome	Bisphosphonate group	Comparison group	P value
Maternal outcome	(n=21)	(n=21)	
Pregnancy outcome (%)			
Live birth	18 (85.7%)	19 (90.5%)	P=0.63[a]
Spontaneous abortion	2 (9.5%)	2 (9.5%)	
Therapeutic abortion	1 (4.8%)	0 (0%)	
Neonatal outcome	(n=18)	(n=19)	
Birth defects (%)	1[b](5.6%)	0 (0%)	P=0.30
Gestational age (weeks, mean±SD)	38.7±1.9	39.3±1.9	P=0.42
Birth weight (kg, mean±SD)	3.1±0.3	3.3±0.5	P=0.11
Neonatal health problems (%)	2 (11.2%)[c]	1 (5.3%)[d]	P=0.50

[a] Live birth vs spontaneous abortions.
[b] Apert syndrome.
[c] Premature birth, and jaundice.
[d] Jaundice.

No significant adverse effect on maternal or neonatal outcomes were seen with bisphosphonate exposure.

Bone. 2009 Mar;44(3):428-30.

Single center, retrospective cohort study of 36 women (23 with systemic diseases, 13 with bone diseases) with exposure to bisphosphonates and 92 controls with systemic diseases but without bisphosphonate exposure and 52 “healthy” controls.

Systemic disease w/ and wo BP exposure:
BP exposure was not associated with increased rate of miscarriage, decreased birth weight, or increased rate of congenital malformations.

The rate of neonatal complications was higher in the bisphosphonate group (25% vs 6%) (ex. polycythemia, arrhythmia, acute fetal distress, maternal-fetal infection).

Bone disease with BP exposure vs “healthy” controls:
Of those women with bone disease exposed to bisphosphonates, a higher rate of miscarriage was seen (20% vs 0%).

No increase in congenital malformation or neonatal complication rate was seen in the bisphosphonate group.

Authors speculate that the underlying disease process, more than exposure to bisphosphonates, led to the findings above.

These studies highlight the challenges inherent to studying the effects of medical therapy during pregnancy.

Osteoporos Int. 2019 Jan;30(1):221-29.

COVID-19: Barriers to care on the consult service and beyond

- Procedural delays (delayed care, loss to follow up)

- Balance between minimizing exposure and delivery of timely, necessary care (frequency of blood draws, timing of medications)

- Challenge of having nuanced conversations over the phone in the setting of trying minimize face-to-face interactions (discussing the risks and benefits of a medical therapy)

- Limitations of telephone/video follow up, especially for those with limited access or skill with a computer or smart phone (increased delay in outpatient labs)

- What changes should we anticipate given increased vaccination of healthcare providers? What risk do we still pose to spread the disease?