

Thirsty and pregnant

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History of Presenting Complaint

- 36 yr old - first pregnancy
- Has lost some weight unintentionally over past 6/12
- Feels washed out and is very thirsty (fluid intake 3-4/L day)
- Passing a lot of urine → wakes 5 times/night
- Presented with painful fibroid (12 x 12 x 9 cm) and hypertension 168/83 at 12 wks gestation

Past Medical History

- None

Social History

- Project manager for an international development firm and has spent a lot of time in India

Examination

- Normal cardiorespiratory exam

Question 1 What would you use to treat the hypertension?

- a) Labetolol 400 mg QDS
- b) Amlodipine 10 mg OD
- c) Ramipril 10 OD
- d) Methyldopa 500 mg TDS

Answer

a) Yes

b) Yes

c) No

d) Yes

Question 2 What would you do next?

- a) Stop the anti-hypertensives and measure urine/plasma metadrenalines
- b) Urine protein:creatinine ratio and paired osmolalities and electrolytes
- c) U+Es, LFTs, bone profile, uric acid, FBC
- d) CXR, ECG, U/S Kidneys

Answer

a) No

b) Yes

c) Yes

d) Yes

Urine/Plasma Mets

Test	Result	Units	Range	Help	Cum
URINE CREAT.	2.0	mmol/L			<input type="checkbox"/>
NORMETADRENALIN	1.74	umol/24Hr	0.00-3.00		<input type="checkbox"/>
METADRENALINE	1.31	umol/24Hr	0.00-1.40		<input type="checkbox"/>
3METHOXYTYRAMIN	1.19	umol/24Hr	0.00-2.75		<input type="checkbox"/>
U. CREATININE	2.0	mmol/L			<input type="checkbox"/>
URINE VOLUME	5.30	L			<input type="checkbox"/>
URINE PERIOD	24	Hours			<input type="checkbox"/>
CREAT/COLLECT	10.6	mmol/24Hr	7.9-15.4		<input type="checkbox"/>

Test	Result	Units	Range	Help	Cum
NORMETANEPHRINE	<50	pmol/L	* 120-1180		<input type="checkbox"/>
METANEPHRINE	287	pmol/L	80-510		<input type="checkbox"/>
3-METHOXYTY	<180	pmol/L	0-180		<input type="checkbox"/>
COMMENTS					
Specimen sent to the referral laboratory on the 03/02/16					
Results do not suggest presence of pheochromocytoma.					
Assay performed by Freeman Hospital, Newcastle.					

Biochemistry

Test	Result	Units	Range	Help	Cum
SODIUM	135	mmol/L	135-145		<input type="checkbox"/>
POTASSIUM	3.6	mmol/L	3.5-5.0		<input type="checkbox"/>
UREA	3.2	mmol/L	2.5-6.7		<input type="checkbox"/>
CREATININE	62	umol/L	49-90		<input type="checkbox"/>
eGFR	>90	ml/min/1.73m ²			<input type="checkbox"/>
BILIRUBIN	9	umol/L	0-21		<input type="checkbox"/>
ALT	15	IU/L	10-45		<input type="checkbox"/>
ALK.PHOSPHATASE	58	IU/L	30-130		<input type="checkbox"/>
ALBUMIN	33	g/L	32-50		<input type="checkbox"/>
CALCIUM	2.83	mmol/L			<input type="checkbox"/>
ADJUSTED CALC.	2.91	mmol/L	* 2.20-2.60		<input type="checkbox"/>
URIC ACID	271	umol/L	150-350		<input type="checkbox"/>
COMMENTS					
For patients of African-American origin the best estimate of eGFR is 1.21 x the value given above					

14 weeks pregnant

Haematology

Test	Result	Units	Range	Help	Cum
HAEMOGLOBIN	115	g/L	* 120-150		<input type="checkbox"/>
WHITE CELLS	8.83	x10 ⁹ /L	4.0-11.0		<input type="checkbox"/>
PLATELETS	166	x10 ⁹ /L	150-400		<input type="checkbox"/>
HAEMATOCRIT	0.340	L/L	0.30-0.46		<input type="checkbox"/>
RED CELL COUNT	3.96	x10 ¹² /L	3.8-4.8		<input type="checkbox"/>
MEAN CELL VOL.	85.9	fl	83-105		<input type="checkbox"/>
MEAN CELL HGB	29.0	pg	27.0-32.0		<input type="checkbox"/>
MEAN CELL HGB CONC	338	g/L	315-345		<input type="checkbox"/>
NEUTROPHILS	7.09	x10 ⁹ /L	* 2.0-7.0		<input type="checkbox"/>
LYMPHOCYTES	1.06	x10 ⁹ /L	1.0-4.0		<input type="checkbox"/>
MONOCYTES	0.62	x10 ⁹ /L	0.2-1.0		<input type="checkbox"/>
EOSINOPHILS	0.04	x10 ⁹ /L	0.0-0.5		<input type="checkbox"/>
BASOPHILS	0.02	x10 ⁹ /L	0.0-0.1		<input type="checkbox"/>
NRBC A	0.01	x10 ⁹ /L			<input type="checkbox"/>
IG	0.03	x10 ⁹ /L			<input type="checkbox"/>
NRBC %	0.1	/100WBC			<input type="checkbox"/>
MPV	10.9	fl			<input type="checkbox"/>

14 weeks pregnant

Biochemistry – Urine PCR

Test	Result	Units	Range	Help	Cum
URINE CREAT.	5.3	mmol/L			<input type="checkbox"/>
URINE PROTEIN	425	mg/L			<input type="checkbox"/>
PROT:CREAT	81.0	MG/MMOL			<input type="checkbox"/>
COMMENTS					
Normal protein-to-creatinine ratio in pregnancy is <30 mg/mmol creatinine.					
URINARY PROTEIN / CREATININE EXCRETION RATIO = 80 MG/MMOL					

Investigations

- ECG – borderline left ventricular hypertrophy
- CXR: normal
- U/S Kidneys: Normal kidneys and bladder. No hydronephrosis.

Biochemistry – Urine

Test	Result	Units	Range	Help	Cum
URINE SODIUM	<20	mmol/L			<input type="checkbox"/>
URINE POTASSIUM	27	mmol/L			<input type="checkbox"/>
URINE CALCIUM	3.5	mmol/L			<input type="checkbox"/>
URINE OSMOL.	186	MOSMOL/KG	* 350-1000		<input type="checkbox"/>

Plasma

Sodium 137

Potassium 3.6

Calcium 2.75

Osm 281

Question 3 What would you do next?

- a) TFTs
- b) Water deprivation test
- c) TB Elispot test
- d) PTH

Answer

a) Yes

b) No

c) Yes

d) Yes

Additional tests

- PTH <0.4 pmo/L
- TSH 2.48 mU/L (0.3-4.20), FT4 16.6 pmol/L (9.0-19.0)
- TB Elispot Negative

Question 4 What would you do next?

- a) Sestamibi parathyroid scan
- b) Vitamin D, ACE, 1,25 OH vitamin D
- c) Urine/serum protein electrophoresis
- d) PTH-rP

Answer

a) No

b) Yes

c) Yes

d) Yes

Additional Biochemistry

- PTH-rP 1.0 (ref <1.8) at 17 wks
 - Comment: PTHrP 1.0-1.7 pmol/L Eminently detectable PTHrP. Tumour likeliest source. Please repeat to confirm.
 - PTH-rP 1.5 pmol/L (<1.8) at 22 weeks gestation
- Vit D 83 nmol/L (>50 nmol/L is sufficient)
- 1,25 Vit D 324 pmol/L (43-144)
- ACE 45 U/L (18-55)
- Urine/serum protein electrophoresis - normal

Question 5 What are the non-malignant causes of hypercalcaemia in pregnancy?

- a) Milk-alkali syndrome
- b) Primary hyperparathyroidism
- c) Humoural Hypercalcaemia
- d) Acute Pancreatitis

Answer

a) Yes

b) Yes

c) Yes

d) No

Case Resolution

- She did not need any anti-hypertensives during labour
- Plasma calcium and blood pressure were normal by the end of her pregnancy and remained normal post-partum
- She did not develop pre-eclampsia
- She delivered a healthy male infant at 40 weeks gestation who weighed 3.95 kg
- The fibroid measured 12 x 12 x 9 cm in the first trimester of pregnancy
- The fibroid degenerated to 4.9 x 4.5 x 4.2 cm post-partum
- Fibroids may increase in size during early pregnancy – possibly due to HCG stimulation (*Benaglia et al. PLoS ONE, 2014, 9: e85933*)
- Hypercalcaemia probably caused the hypertension via direct vasoconstriction

Hypercalcaemia in pregnancy

- Frequency 0.03% of women of reproductive age
- Commonest non-malignant causes:
 - Primary hyperparathyroidism
 - Milk-alkali syndrome
 - Humoural hypercalcaemia
- Normal physiology during pregnancy
 - PTH may fall in third trimester
 - 1,25 OH vitamin D will progressively increase by 100% during pregnancy with increased 1 α -hydroxylase activity
 - Intestinal absorption of calcium increases 2-fold
 - PTH-rP levels increase due to secretion from the placenta and breasts

Hypercalcaemia in pregnancy

Table 1. Case reports of non-malignant hypercalcemic crisis associated with pregnancy

Diagnosis	Age	Stage	Total Ca	P	Creatinine	PTH	PTHrP	infant	Reference
1. PHPT	41	32 W*	19.4 mg/dl (8.7–10.2)	ND	2.0 mg/dl	3659 pgEq/L (150–375)	ND	stillborn	[22]
2. PHPT	26	31 W*	5 mmol/L	ND	2.5 mg/dl	1800 pmol/L (5–50)	ND	alive ^{##}	[23]
3. PHPT	28	21 W*	25.8 mg/dl (8.4–10.6)	3.8 mg/dl (2.5–4.8)	2.0 mg/dl (0.4–1.5)	790 pg/ml	ND	alive (full term)	[24]
4. PHPT	19	8 W (15 W*)	3.99 mM (2.20–2.60)	ND	141 µmol/L (<106)	11.4 pmol/L (1.1–5.4)	ND	alive (full term)	[25]
5. PHPT	41	22 W*	20.0 mg/dl (8.8–10.0)	ND	144 µmol/L (62–115)	712 pg/ml (7–53)	ND	alive (full term)	[26]
6. MAS	31	36 W	22.5 mg/dl	0.7 mg/dl	1.9 mg/dl	4 pg/ml (4–19)	ND	alive (full term)	[51]
7. MAS	35	35 W	4.0 mM [#]	0.58 mM (0.8–1.5)	0.19 mM (0.05–0.09)	0.66 pmol/L (1.3–6.8)	<1.0 pmol/L	alive ^{##}	[52]
8. MAS	38	37 W	4.0 mM	2.36 mg/dl	0.46 mM	0.8 pmol/L (1–7)	34.9 pmol/L	alive ^{##}	[53]
9. MAS	32	16 W	22 mg/dl (8.5–10.5)	0.8 mg/dl (2.5–4.5)	1.4 mg/dl (0.5–1.4)	1.0 pg/ml (10–65)	0.3 pmol/L (<0.5)	ND	[55]
10. HHP	28	33 W	19.4 mg/dl (8.5–10.5)	5.2 (2.5–4.3)	2.41 mg/dl (0.7–1.3)	<5 pg/ml (23–73)	28.4 pmol/L (<1.1)	alive (SD)	[**]

PHPT: primary hyperparathyroidism, MAS; milk alkali syndrome, HHP; humoral hypercalcemia of pregnancy [#] ionized calcium concentration; 2.64 mmol (1.12–1.3 mmol/L), ^{##} caesarian section, ND; not described, * parathyroidectomy, ** present case. SD; spontaneous delivery. Parentheses indicate reference ranges.

PTH-rP and pregnancy

- PTH-rP produced by various normal tissue and malignant cells
- Causes hypercalcaemia by stimulation of PTH-receptor
- Very few cases reported in pregnancy and tend to be in third trimester
- PTH-rP is abundantly expressed in fibroid tissue.
 - *(Rey et al. Clinical Case Reports, 2016, 4:1001–1008)*
- Treatment used:
 - IV fluid
 - Pamidronate
 - Calcitonin
 - Cinacalcet