

Primary hyperparathyroidism in pregnancy: a retrospective review of management and maternofetal outcomes at the Royal Brisbane and Women's Hospital 2000 to 2015.



JANE RIGG^{1,2}, ELISE GILBERTSON^{3,4}, HELEN BARRETT^{1,2,5}, FIONA BRITTEN^{1,2}, KARIN LUST^{1,2}

¹ ROYAL BRISBANE AND WOMEN'S HOSPITAL, BUTTERFIELD ST, HERSTON, QLD 4006, AUSTRALIA.

² THE UNIVERSITY OF QUEENSLAND, ROYAL BRISBANE CLINICAL UNIT, HERSTON, QLD 4029, AUSTRALIA.

³ SUNSHINE COAST UNIVERSITY HOSPITAL, 3 DOHERTY ST, BIRTINYA QLD 4575, AUSTRALIA.

⁴ THE UNIVERSITY OF QUEENSLAND, SUNSHINE COAST CLINICAL UNIT, SUNSHINE COAST HEALTH INSTITUTE, BIRTINYA QLD 4575, AUSTRALIA.

⁵ UQ CENTRE FOR CLINICAL RESEARCH, RBWH CAMPUS, HERSTON, QLD 4029, AUSTRALIA.

Primary hyperparathyroidism in pregnancy

- ▶ Estimated prevalence in pregnancy: 0.15 to 1.4% (1)
- ▶ Biochemistry is not part of routine antenatal testing

Maternal Complications	Neonatal Complications
Nephrolithiasis, urinary tract infections	Neonatal hypocalcaemia ± tetany/seizures
Radiographic bone disease	Stillbirth
Pancreatitis	Miscarriage
Hyperemesis gravidarum	Premature birth
Pre-eclampsia	Intrauterine growth restriction
Hypercalcaemic crisis	

Rationale and Aims

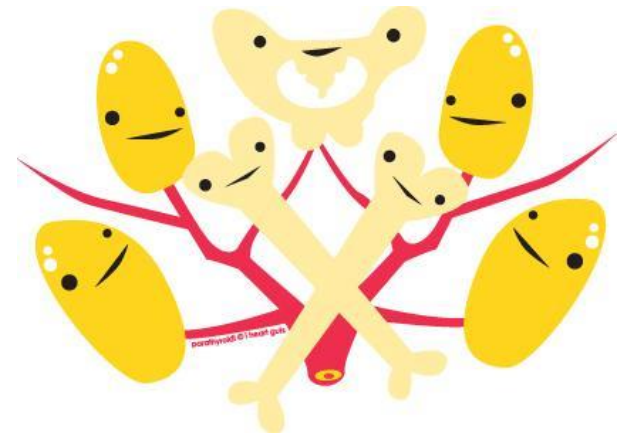
- ▶ Increased detection and management of Primary Hyperparathyroidism (PHPT) in pregnancy during the 1970s led to a decline in perinatal morbidity and mortality (2)
but
- ▶ No clear consensus about the role of medical therapy versus parathyroidectomy in pregnancy
- ▶ Aim: review maternal and fetal outcomes of PHPT in pregnancy amongst medically and surgically managed patients 1/1/00 to 31/12/15

Methods

- ▶ Queensland Health Pathology Services data and Health Information Services data interrogated to identify patients with PHPT in pregnancy
- ▶ Exclusions: secondary or tertiary hyperparathyroidism
- ▶ Chart review
 - ▶ Demographic information, gravidity, parity, miscarriages, body mass index, smoking status, comorbidities, date of diagnosis
 - ▶ Biochemical information
 - ▶ Imaging
 - ▶ Treatment
 - ▶ Conservative: intravenous fluid, frusemide, cinacalcet, phosphate, antihypertensive medications, pamidronate
 - ▶ Surgery: type & date, complications, histology results

Methods

- ▶ Pregnancy outcomes
 - ▶ Complications attributable to PHPT (miscarriage, pregnancy-induced hypertension or pre-eclampsia, urinary tract infections, nephrolithiasis, pancreatitis and hypercalcaemic crisis)
 - ▶ Gestation at delivery
 - ▶ Indication for and mode of delivery
- ▶ Neonatal outcomes
 - ▶ Birth weight
 - ▶ Apgar scores at 5 minutes
 - ▶ Admission to neonatal intensive care unit (NICU)
 - ▶ Neonatal hypocalcaemia (with or without tetany or seizures)
- ▶ Number and duration of admissions



Results – study population

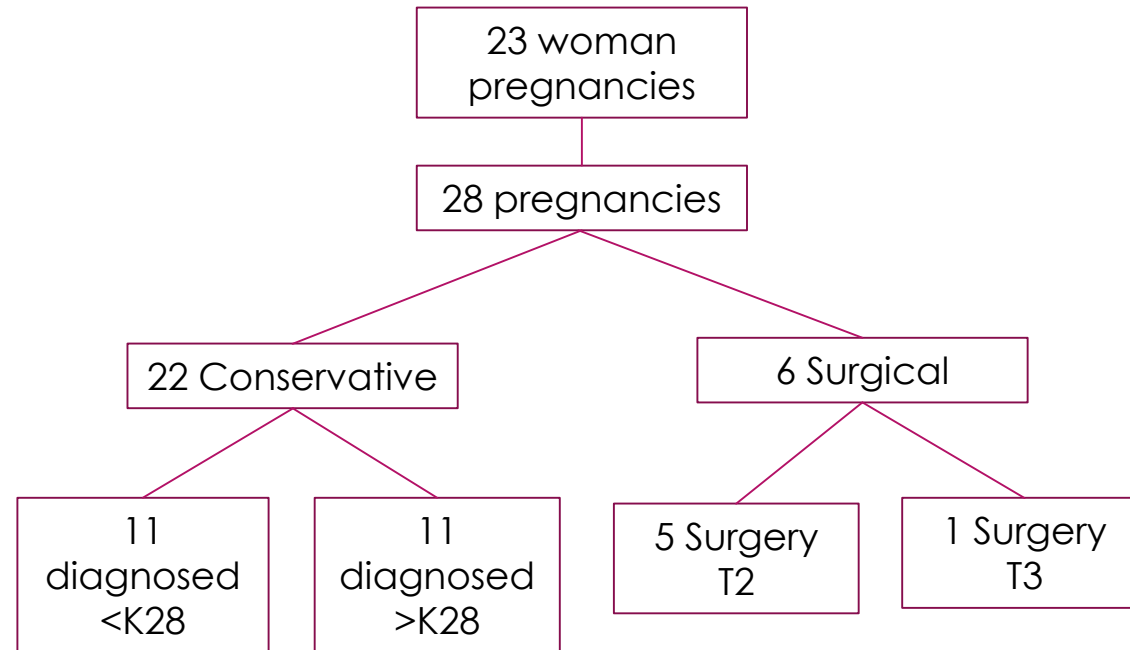


Table 1. Patient baseline characteristics.

	Conservative, diagnosed <K28 (N = 11)	Conservative, diagnosed >K28 (N = 11)	Surgical (N= 6)
Average age, years	35	32	31
Average body mass index	31	30	30
Gravida, N			
1	1	1	3
2 – 5	9	8	3
≥6	1	2	0
Parity, N			
0	3	3	4
1 – 5	8	8	2
Ethnicity, N			
Indian	1	1	1
Caucasian	8	9	5
Caucasian/African	1	0	0
Aboriginal	1	1	0
Smoking, N			
Yes	0	2	0
No	11	8	6
Unknown	0	1	0
Chronic hypertension, N			
Yes	2	4	0
No	9	7	6
Gestational Diabetes, N			
Yes	1	1	2
No	10	10	4
T1DM/T2DM*, N			
Yes	1	1	1
No	10	10	5

Results – maternal biochemistry

Table 2. Maternal corrected serum calcium concentrations.

	Conservative, diagnosed <K28 (N = 11)	Conservative, diagnosed >K28 (N = 11)	Surgical (N= 6)
Mean gestation at diagnosis, K	7 ²	33 ¹	13 ¹
Mean corrected serum calcium at diagnosis (mmol/L)	2.7	2.9	2.9
Mean peak corrected serum calcium (mmol/L)	2.8	3	3

Conservatively managed diagnosed <K28: 9/11 patients had corrected serum Ca < 2.85 mmol/L

Results – maternal treatment

Table 3. Pharmacological treatment.

	Conservative, diagnosed <K28 (N = 11)	Conservative, diagnosed >K28 (N = 11)	Surgical (N= 6)
Intravenous fluid, N	3	3	3
Frusemide, N	0	1	0
Antihypertensive medications, N	2	4	1
Pamidronate, N	0	2	0
Phosphate, N	0	0	1
Cinacalcet, N	0	0	1

Results – maternal treatment

▶ Surgery

- ▶ All surgeries conducted 2011 to 2014
- ▶ 4 patients minimally invasive surgery, 2 patients bilateral neck exploration
- ▶ Indications for surgery
 - ▶ Two patients referred directly to endocrine surgeons by GP
 - ▶ Three patients had serum calcium concentrations greater than 3 mmol/L despite intravenous fluids
 - ▶ One patient had serum calcium concentrations between 2.82 and 2.92 mmol/L. The reason for surgery was not documented

Results – maternal and fetal outcomes

Table 4. Materno-fetal outcomes.

	Conservative, diagnosed <K28 (N = 11)	Conservative, diagnosed >K28 (N = 11)	Surgical (N= 6)
Gestation at Delivery			
<K37	1	3	0
>K37	9	7	6
Miscarriage	1	1	0
Pre-eclampsia, N	2	4	0
Birthweight (g)			
<K37	2180	1633	N/A
>K37	3405	3725	3368
NICU >1day*, N			
<K37	1	3	0
>K37	0	0	1 ← PPHN

* Admission to neonatal intensive care for >1 day.

Results – length of stay

Table 5. Total length of stay.

	Conservative	Surgery (including admission for surgery)	Surgery (excluding admission for surgery)
Mean total length of stay (days)	4.3 (range 1-16)	6.3 (range 2-10)	3.3 (range 1-5)

Mean total length of stay women with pre-eclampsia: 8.8 days (range 4-16)

Results – additional outcomes

▶ Maternal

▶ Recurrent UTI

- ▶ 1 conservatively managed patient, 2 surgically managed patients.
- ▶ Rate of nephrolithiasis unknown

▶ No cases of maternal pancreatitis or hypercalcaemic crisis

▶ Neonatal

▶ Neonatal hypocalcaemia: 1 asymptomatic case born to a conservatively managed mother at K32⁴. Maternal serum calcium >3 mmol/L

▶ Apgar scores <7 at 5 mins: Two babies born to conservatively managed women

- ▶ One admitted to NICU in the setting of prematurity, the other did not require any medical intervention

Discussion

- ▶ Most women with PHPT in study population managed conservatively
 - ▶ Gestation at diagnosis
 - ▶ Degree of elevation of serum calcium concentrations
- ▶ 30% of viable conservatively managed pregnancies developed pre-eclampsia, pre-term delivery in 66% of this group
 - ▶ Rate of pre-eclampsia general population: 3 to 7% (3, 4)
- ▶ 100% pre-term neonates required admission to NICU for prematurity complications
- ▶ Total length of stay greater for women with pre-eclampsia
- ▶ There were no cases of pre-eclampsia amongst surgically managed patients

Question

- ▶ Should we be offering surgery to women, even if their serum calcium concentration is <2.85 mmol/L at diagnosis?



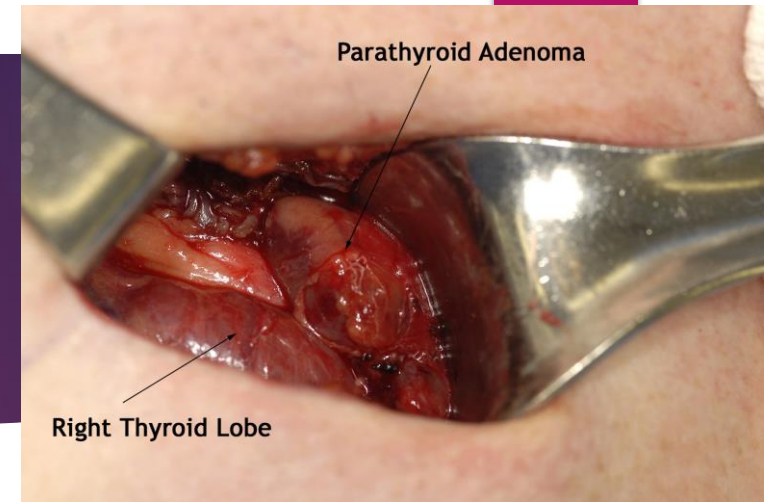
Discussion – serum calcium threshold

- ▶ Some authors have proposed surgery for all patients in trimester 2 regardless of serum calcium (5-7)
- ▶ Others: surgery if serum calcium > 2.75 mmol/L due to miscarriage risk (8)
 - ▶ Retrospective cohort studies reassuring that no increased risk of miscarriage at low maternal serum calcium concentrations (9, 10)
- ▶ Other thresholds: 2.87 mmol/L, 3 mmol/L (2, 11)
- ▶ Risks proportional to maternal serum calcium concentration elevation
 - ▶ Stillbirth
 - ▶ Neonatal tetany
 - ▶ Maternal pancreatitis
 - ▶ Maternal hypercalcaemic crisis

Discussion – serum calcium threshold

- ▶ It is unclear whether the degree of hypercalcaemia is predictive of pre-eclampsia
- ▶ The risk of pre-eclampsia remains elevated 2 to 5 years post-parathyroidectomy (12)
- ▶ It is unclear whether the risk post-surgery is lower than it otherwise would have been
 - ▶ If it is then a lower threshold may need to be considered
- ▶ Should we perform surgery during pregnancy to prevent patients being lost to follow up?

Discussion – risks of surgery



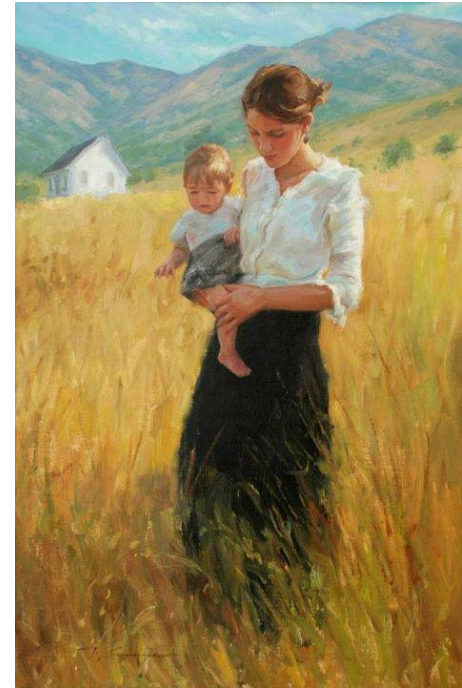
- ▶ Surgical techniques and anaesthesia have improved over time.
- ▶ There were no complications of parathyroid surgery in our study or amongst 5 patients treated between 2009 and 2013 described by Walker *et al.* (13)
- ▶ Risk of laryngeal nerve palsy and post-operative hypocalcaemia, is low at 1 to 3% (14)
- ▶ Most surgical complications have occurred in symptomatic patients with maternal serum calcium concentrations >3 mmol/L (15, 16)
- ▶ Stillbirth, neonatal tetany, maternal pancreatitis and hypercalcaemic crisis are rare if serum calcium is <3 mmol/L (5, 7, 17-19)

Limitations

- ▶ Retrospective
- ▶ May not have identified all patients with PHPT
 - ▶ PTH not measured
 - ▶ Biochemistry not routine
- ▶ Small sample size, esp surgical group, limits firm conclusion precluded extensive examination of risk factors contributing to adverse outcomes
- ▶ Not all potential complications of PHPT assessed
- ▶ Surgically managed cases were relatively recent

Conclusion

- ▶ Most patients with PHPT in pregnancy at RBWH between 2000 and 2015 were managed conservatively
- ▶ There were no maternal or fetal deaths attributable to PHPT during this time
- ▶ The major morbidity associated with conservative management was pre-term delivery due to pre-eclampsia
- ▶ It is not known whether surgery reduces the risk of pre-eclampsia
- ▶ Surgery in trimester 2 appears safe
- ▶ There were no complications of surgery for patient who underwent surgery in trimester 3, more data is needed



Acknowledgements

- ▶ The authors would like to thank John Galligan and Kate Lunn from Queensland Health Pathology Services and Melinda Scott from Health Information Services for their assistance in conducting searches to identify patients with primary hyperparathyroidism in pregnancy

References

1. McMullen TPW, Learoyd DL, Williams DC, Sywak MS, Sidhu SB, Delbridge LW. Hyperparathyroidism in Pregnancy: Options for Localization and Surgical Therapy. *World Journal of Surgery*. 2010;34(8):1811-6.
2. Schnatz PF, Curry SL. Primary Hyperparathyroidism in Pregnancy: Evidence-Based Management. *Obstetrical & Gynecological Survey*. 2002;57(6):365-76.
3. Thornton C, Toohar J, Ogle R, von Dadelszen P, Makris A, Hennessy A. Benchmarking the Hypertensive Disorders of Pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2016;6(4):279-84.
4. Sabban H, Zakhari A, Patenaude V, Tulandi T, Abenhaim HA. Obstetrical and perinatal morbidity and mortality among in-vitro fertilization pregnancies: a population-based study. *Archives of Gynecology and Obstetrics*. 2017;296(1):107-13.
5. Carella MJ, Gossain VV. Hyperparathyroidism and pregnancy. *Journal of General Internal Medicine*. 1992;7(4):448-53.
6. Kristofferson A, Dahlgren S, Lithner F, Jarhult J. Primary Hyperparathyroidism in Pregnancy. *Surgery*. 1985;97(3):326-30.
7. Kort KC, Schiller HJ, Numann PJ. Hyperparathyroidism and pregnancy. *The American Journal of Surgery*. 1999;177(1):66-8.
8. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: a call for earlier intervention. *Clinical Endocrinology*. 2009;71(1):104-9.
9. Hirsch D, Kopel V, Nadler V, Levy S, Toledano Y, Tsvetov G. Pregnancy Outcomes in Women With Primary Hyperparathyroidism. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(5):2115-22.
10. Abood A, Vestergaard P. Pregnancy outcomes in women with primary hyperparathyroidism. *European Journal of Endocrinology*. 2014;171(1):69-76.
11. Kelly TR. Primary hyperparathyroidism during pregnancy. *Surgery*. 1991;110(6):1028-34.
12. Hultin H, Hellman P, Lundgren E, Olovsson M, Ekblom A, Rastad J, et al. Association of Parathyroid Adenoma and Pregnancy with Preeclampsia. *The Journal of Clinical Endocrinology & Metabolism*. 2009;94(9):3394-9.
13. Walker A, Fraile JJ, Hubbard JG. "Parathyroidectomy in pregnancy"—a single centre experience with review of evidence and proposal for treatment algorithm. *Gland Surgery*. 2014;3(3):158-64.
14. Dochez V, Ducarme G. Primary hyperparathyroidism during pregnancy. *Archives of Gynecology and Obstetrics*. 2015;291(2):259-63.
15. Kristofferson A, Dahlgren S, Lithner F, Jarhult J. Primary Hyperparathyroidism in Pregnancy. *Surgery*. 1985;97(3):326-30.
16. Schnatz PF, Thaxton S. Parathyroidectomy in the Third Trimester of Pregnancy. *Obstetrical & Gynecological Survey*. 2005;60(10):672-82.
17. Wagner G, Transbøl I, Melchior JC. Hyperparathyroidism and Pregnancy *Acta Endocrinologica*. 1964;47(4):549-64.
18. Hong MK, Hsieh CTC, Chen BH, Tu ST, Chou PH. Primary hyperparathyroidism and acute pancreatitis during the third trimester of pregnancy. *Journal of Maternal-Fetal Medicine*. 2001;10(3):214-8.
19. Mestman JH. Parathyroid Disorders of Pregnancy. *Seminars in Perinatology*. 1998;22(6):485-96.