Managing Parathyroid Disorders: **Preconception, pregnancy and lactation**

European Society of Endocrinology

This guide summarizes the 10 consensus recommendations on the management of parathyroid disorders during preconception, pregnancy and lactation published within "European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy". *European Journal of Endocrinology* 186 (2) February 2022' Please access the article for recommendations in full.

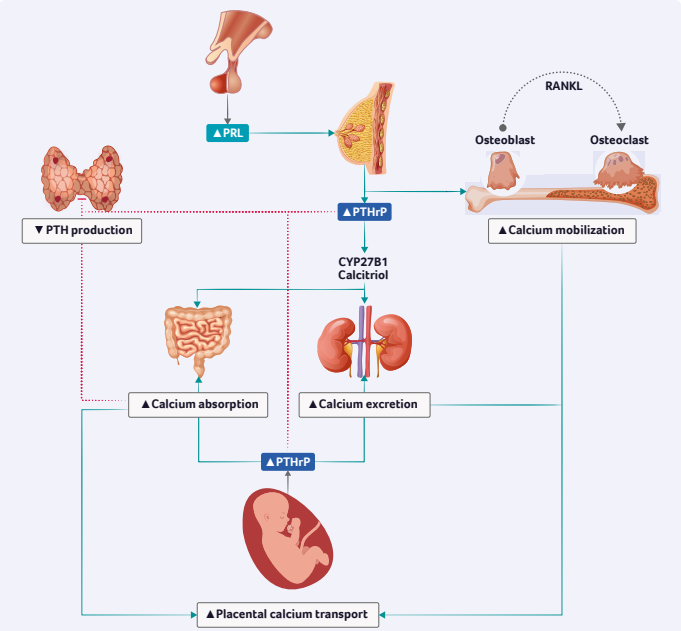

Figure 1. Overview of calcium homeostasis and calciotropic hormones in pregnancy. Parathyroid hormone-related protein (PTHrP) production in the placenta will gradually decrease endogenous parathyroid hormone (PTH) secretion. PRL, prolactin; RANKL, receptor activator of nuclear factor kappa-B ligand.

As many patients with parathyroid disorders are diagnosed before or during fertile age, special attention should be paid to the course of pregnancy, from the planning period to the end of lactation.

Major physiological changes to calcium metabolism develop in pregnancy and during lactation ensuring mineralization of the skeleton in the fetus and newborns. These are mainly driven by the PTH-related peptide (PTHrP).

PTHrP is largely produced by the placenta and mammary tissue, contributing to calcium transport over the placenta in pregnancy and into breast milk during lactation. (Figure 1 & 2)

Q1 What preconception advice should be given to women with primary hyperparathyroidism (PHPT)?

If possible, pregnancy should be deferred until curative surgery for PHPT has been performed.

Q2 How to treat PHPT during pregnancy?

Parathyroidectomy is preferred, especially if total albumin-adjusted calcium levels are >2.85 mmol/L (>11.42 mg/dL) and/or >0.25 mmol/L (>1 mg/dL) above upper limit of normal and/or an ionized calcium >1.45 mmol/L (>5.81 mg/dL). **Surgery should be planned in the second trimester.**

Conservative treatment options primarily include:
- Oral and i.v. rehydration, and
- Cinacalcet for severe hypercalcemia. Cinacalcet has been used in several pregnant women without significant safety concerns, although it crosses the placenta, and safety evidences are still considered insufficient for official approval.

Bisphosphonates also cross the placenta and should not be used during pregnancy. **Calcitonin** does not cross the placenta, but its efficacy to control hypercalcemia declines after a few days due to tachyphylaxis.

For surveillance, in medically treated pregnant women with PHPT:
- We consider it as a reasonable approach to monitor **calcium levels** and estimated glomerular filtration rate **(eGFR)** approximately **every 4 weeks** in pregnant women with PHPT, and
- Even more frequently (e.g., **all 1-2 weeks**) **after changes in medical therapy.**

In case of parathyroidectomy, perioperative evaluation and calcium plus vitamin D supplementation are recommended, as in non-pregnant women (Table 1).

Q3 What is the preferred surgical approach for parathyroidectomy during pregnancy?

In **sporadic PHPT, minimally invasive parathyroidectomy** in combination with intraoperative PTH monitoring is recommended.

In **hereditary PHPT** (i.e., multiple endocrine neoplasia type 1, 2A and 4, hyperparathyroidism-jaw tumor syndrome, and familial isolated hyperparathyroidism) and **other causes of parathyroid hyperplasia** (e.g., lithium intake), **bilateral neck exploration** may be needed.

Q4 Which parathyroid imaging modalities should be used in pregnant women with PHPT and indication for surgery?

Preoperative localization of abnormal parathyroid glands is crucial for the success of minimally invasive parathyroidectomy, and concordance of two different imaging methods should be aimed for.
- Preferably, ultrasonography in combination with
- 99mTc-MIBI scan or 4D-dynamic contrast-enhanced MRI.

18F-Fluorcholine PET/CT or methionine PET/CT may be considered in selected cases, after careful consideration of potential risks and benefits. **Avoiding radiation exposure in pregnancy** is critical for guiding decisions on the choice of imaging methods and any imaging method with radiation exposure should only be performed if considered to have a favorable benefit/risk ratio. Ultrasound and 4D-dynamic contrast-enhanced MRI lack ionizing radiation, and fetal exposure by a 99mTc-MIBI scan is lower than the exposure associated with fetal harm.

Q5 What are important considerations for the postpartum and lactation period for mothers with PHPT and their newborns?

Fetal PTH is likely suppressed due to elevated maternal calcium levels, but immediately after birth, the calcium transfer via the placenta is abruptly stopped. This increases the risk of fetal hypocalcemia (particularly during the first 2-3 weeks of life) and hypocalcemic seizures, and maternal hypercalcemic crisis.

Newborn considerations:
- **Ionized calcium** should be measured in the newborns **at least every 2 days starting on day 2 until 1 to 2 weeks of life;**
- Consider active vitamin D treatment in case of hypocalcemia in the newborns.

Maternal considerations:
- **During lactation,** maternal **calcium levels** and **eGFR** should be measured **every 4 to 8 weeks;**
- **Parathyroidectomy** should be performed **a few weeks after delivery.**
- **Cinacalcet** is excreted in the milk of lactating rats, and a careful benefit/risk assessment decision should be made to discontinue either breastfeeding or treatment.

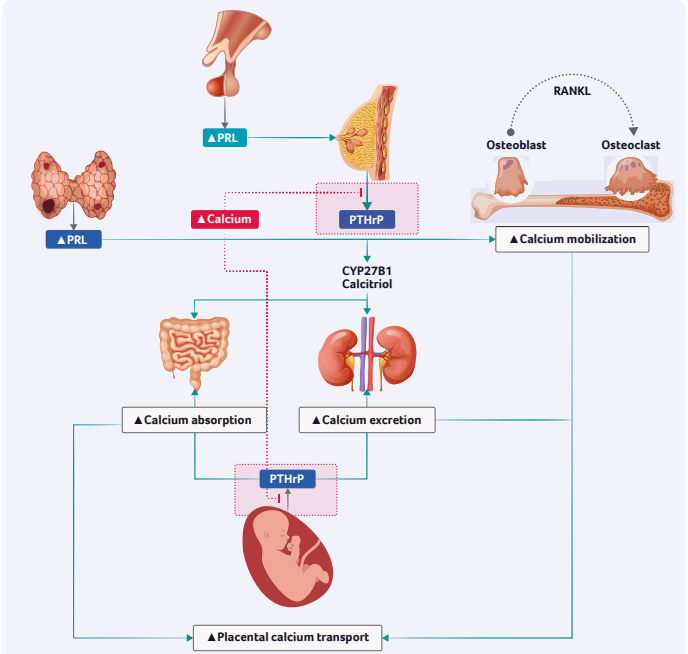

Figure 2. Overview of calcium homeostasis in primary hyperparathyroidism during pregnancy. Parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) will counterbalance the equilibrium hypercalcemia. PRL, prolactin; RANKL, receptor activator of nuclear factor kappa-B ligand.

Q6 What are the treatment targets and surveillance recommendations during pregnancy in women with chronic hypoparathyroidism (HypoPT)?

Aim to keep calcium levels (ionized or albumin-adjusted) in the lower end **of the reference range with patients being free of symptoms**.

It is difficult to predict precise doses of calcium and active vitamin D needed.

Monitoring patients on stable treatment:

• Monitor **calcium, phosphate, eGFR,** and **magnesium every 3 to 4 weeks** and **weekly** within **one month before giving birth.**

Monitoring patients after treatment adjustments:

• Measurement of **calcium** should be **repeated in 1–2 weeks** if the doses of calcium and/or active vitamin D are changed.

Maintain 25(OH)D levels in the reference range.

Q7 What are the required doses of calcium and active vitamin D during pregnancy in women with chronic HypoPT?

There is a wide variation in the required doses of calcium and active vitamin D (alfacalcidiol or calcitriol) during pregnancy.

Furthermore, dose requirements may change during the course of pregnancy, an this may reflect variations in dietary intakes, and variations in PTHrP production, and in calcitriol production from the maternal kidneys (Figure 3).

Inadequate calcium intake in the first trimester may contribute to inadequate mineral accrual of the developing fetus.

Q8 Is treatment with PTH analogues and hydrochlorothiazide safe during pregnancy?

No.

Adjunctive therapy with **PTH analogs** has not been evaluated during pregnancy.

Hydrochlorothiazide should be **stopped** during pregnancy **in the first trimester** and should only be used after careful risk evaluation in the second and third trimester.

Q9 How to manage chronic HypoPT during lactation?

During lactation, calcitriol levels normalize, PTHrP levels, bone resorption, and renal calcium reabsorption increase, which may lead to lower the dose requirements for active vitamin D and calcium supplementation.

We recommend monitoring **maternal calcium levels weekly** within **the first month after delivery** and then **every 4 weeks during lactation**.

Abrupt cessation of breastfeeding can be associated with maternal hypocalcemia.

Q10 What are the surveillance and treatment recommendations for newborns of mothers with HypoPT?

Newborns should be monitored with **ionized calcium concentrations** measured **every second day** for the **first week of life**.

Regular native vitamin D supplementation is recommended.

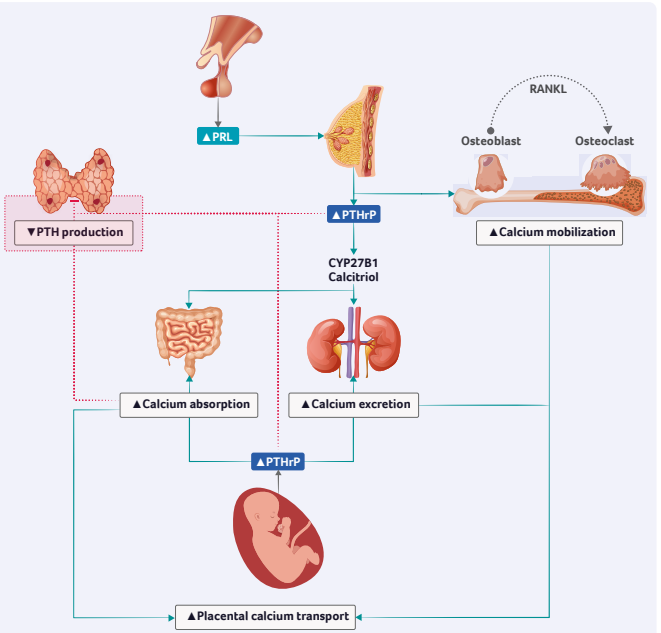

Figure 3. Overview of calcium homeostasis in chronic hypoparathyroidism during pregnancy. PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; PRL, prolactin; RANKL, receptor activator of nuclear factor kappa-B ligand.

This guide is an output of PARAT – the ESE educational programme on parathyroid disorders developed by an expert Steering committee and International community. Faculty members Elena Tsourdi, (Germany), Luis Cardosa, (Portugal), Claudio Marcocci, (Italy) and Nik Screen (ESE/Versatility.org.uk) prepared this guide.

Further summaries covering primary hyperparathyroidism (PHPT) and hypoparathyroidism (HypoPT are also available, plus other educational materials at **www.ese-hormones.org** or by searching; **bit.ly/paratlz**

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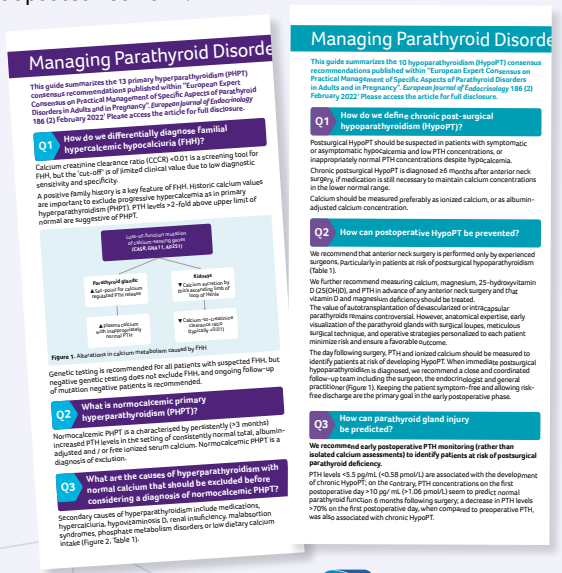

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	PHPT	HypoPT
Mother (preconception)	Pregnancy should be avoided until curative surgery has been performed and calcium concentrations are normalized	Counselling regarding frequent surveillance and potential changes in vitamin D and calcium requirements during pregnancy Most mothers will have a healthy baby
Mother (pregnancy)	Surgery is advised, preferentially in the second trimester, and especially if albumin-adjusted calcium is >2.85 mmol/L (>11.42 mg/dL) and/or >0,25 mmol/L (>1 mg/dL) ULN and/or ionized calcium is >1.45 mmol/L (>5.81 mg/dL) Surveillance every 4 weeks	Calcium and vitamin D supplements as well as active vitamin D treatment can be used. Aim for ionized and/or albumin-adjusted calcium levels in the lower end of the reference range Surveillance every 3–4 weeks Every week during the last month of pregnancy
Mother (lactation)	Surveillance every 4–8 weeks Surgery a few weeks after delivery	Surveillance weekly within the first month after birth and then every 4 weeks
Newborns	Measure ionized calcium every second day until about 1–2 weeks of life In case of hypocalcemia, consider active vitamin D treatment	Measure ionized calcium every second day during the first week of life
HypoPT, chronic hypoparathyroidism; PHPT, primary hyperparathyroidism; ULN, upper limit of normal.		

Table 1. Summary of recommendations for PHPT and HypoPT during preconception, pregnancy, and lactation