Managing Parathyroid Disorders: Preconception, pregnancy and lactation

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.

**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. Calcitriol 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-fluorocholine 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.

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 during 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)

**Figure 1** Overview of calcium homeostasis and calcitropic 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.

**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 (alfalcacodil or calcitriol) during pregnancy. Furthermore, dose requirements may change during the course of pregnancy, as 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.

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 Tsouri, (Germany), Luis Cardosa, (Portugal), Claudio Marconi, (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/parat

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

<table>
<thead>
<tr>
<th>PHPT</th>
<th>HypoPT</th>
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</thead>
<tbody>
<tr>
<td><strong>Mother (preconception)</strong></td>
<td>Pregnancy should be avoided until curative surgery has been performed and calcium concentrations are normalized.</td>
</tr>
<tr>
<td><strong>Mother (pregnancy)</strong></td>
<td>Surgery is advised, preferably in the second trimester, and especially if albumin-adjusted calcium is &gt;2.85 mmol/L (&gt;11.42 mg/dL) and/or &gt;0.25 mmol/L (&gt;1 mg/dL) and/or ionized calcium is &gt;1.45 mmol/L (&gt;5.81 mg/dL).</td>
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<tr>
<td><strong>Mother (lactation)</strong></td>
<td>Surveillance every 4-8 weeks.</td>
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<tr>
<td><strong>Newborns</strong></td>
<td>Measure ionized calcium every second day until about 1-2 weeks of life.</td>
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PHPT, chronic hyperparathyroidism; HypoPT, primary hypoparathyroidism; ULN, upper limit of normal.