
بسم الله الرحمن الرحيم

Management of parathyroid disorders

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Advances in the clinical management of parathyroid disorders: report from the 2024 workshop by the ESE educational program on parathyroid disorders

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Invited Review

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Abstract

The present report from the ESE Educational Program on Parathyroid Disorders (PARAT Program) presents recent developments and novelties in the clinical care of parathyroid disorders in a question-and-answer format, based on a satellite workshop held in relation to the European Congress of Endocrinology in Stockholm, May 2024.

The workshop focused on clinical aspects of 3 main themes: primary hyperparathyroidism (PHPT), chronic hypoparathyroidism (HypoPT) in adults, and parathyroid disorders in pregnancy, with an emphasis on advances since the 2022 PARAT consensus report.

- The first section focuses on the long-term complications—including fractures, renal impairment, mental health, and quality of life—in patients with asymptomatic or mild forms of PHPT and on treatment strategies for syndromic PHPT (multiple endocrine neoplasia 1-4).
- In the latter, we explore appropriate surgical and non-surgical approaches, imaging techniques for gland localization, and preservation strategies in cases of multiglandular involvement

The second section addresses transient and partial forms of HypoPT in comparison to chronic and complete parathyroid hormone deficiency. It highlights the potential skeletal consequences of chronic HypoPT, the underlying etiologies, and discusses treatment modifications in light of the evolving therapeutic landscape.

- The final section, dedicated to the specific considerations of parathyroid disorders during pregnancy and lactation, focuses on pregnancy planning in patients with hereditary syndromic forms of PHPT, the differentiation between parathyroid-related and unrelated causes of hypercalcemia, and the associated risks for both mother and fetus. Additionally, it addresses the practical aspects of managing pregnant women with HypoPT, aiming to provide practical guidance for clinicians. Clinical vignettes featuring cases illustrate common clinical situations.

Introduction

the parathyroid glands were first described approximately 150 years ago by Sandström in Uppsala, with a connection to calcium metabolism being established a decade later. The first parathyroidectomy (PTX) for primary hyperparathyroidism (PHPT) was performed in 1925. Parathyroid diseases span a broad spectrum of classical endocrine disorders related to the secretion of parathyroid hormone (PTH), like PHPT (with a high prevalence) and hypoparathyroidism (HypoPT) (a rare disease), or the inter- play between the calcium-sensing receptor and PTH secretion, as in familial hypocalciuric hypercalcemia (FHH), an autosomal dominant inherited condition.

- However, during the last decade following the 2015 approval by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) of the first PTH replacement therapy, major advances in the understanding of morbidity and patient burden of chronic HypoPT in adults have emerged.

Primary hyperparathyroidism Primary hyperparathyroidism is one of the most common endocrine disorders, especially in the elderly and with a clear (3:1) female preponderance. As the clinical presentation has changed dramatically after the common access to biochemical screening programs, most patients are identified by chance without disease-specific symptoms; however, potentially with related complications. In current terminology, this is designated asymptomatic PHPT with or without target organ involvement.

Why are patients with asymptomatic PHPT prone to fractures?

In some parts of the world, symptomatic PHPT with multiple organ involvement and severe hypercalcemia remains the predominant form. However, in most developed countries, PHPT is now mainly asymptomatic and characterized by mild hypercalcemia.

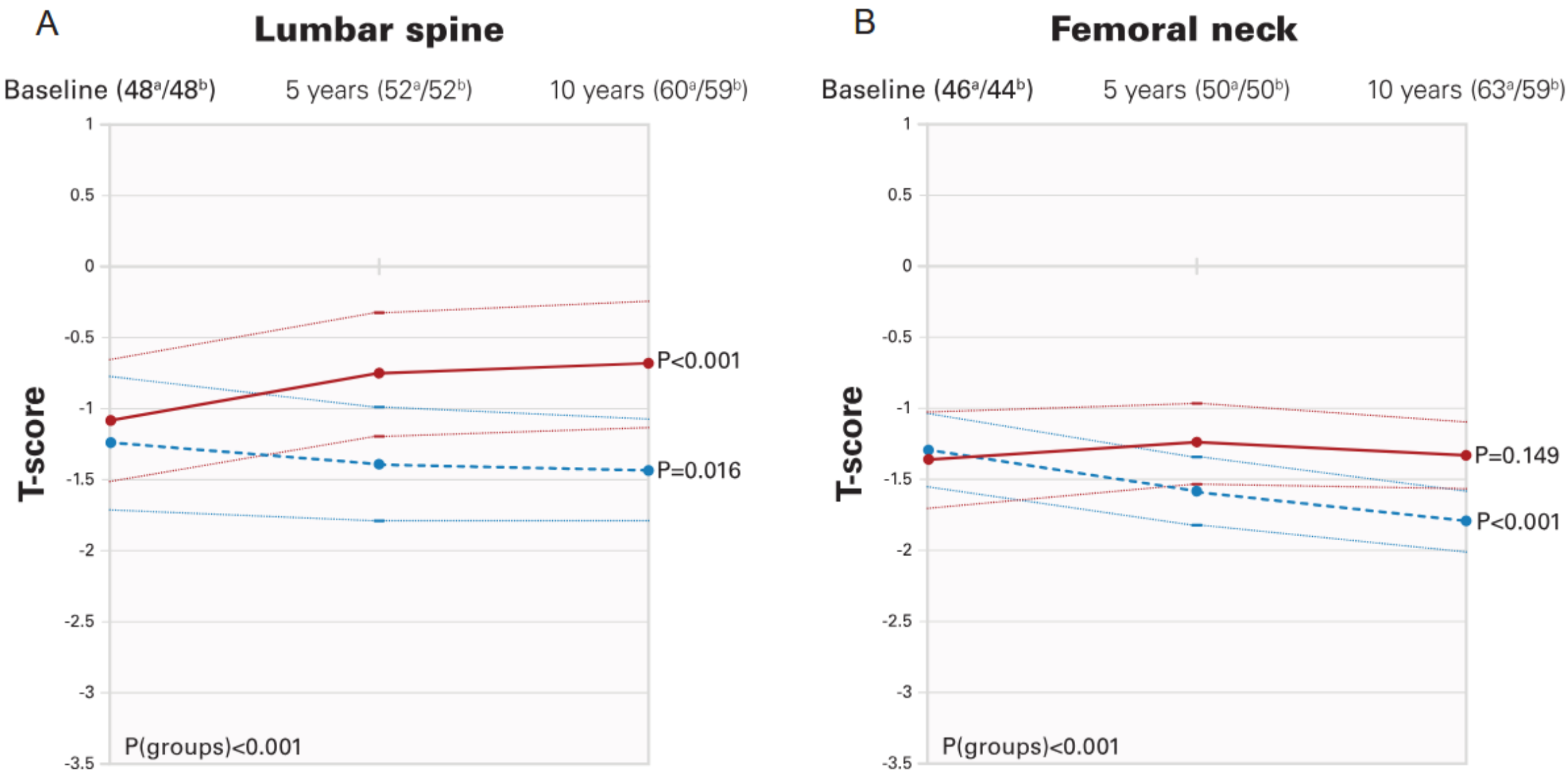
Still, observational data suggest that fracture risk is increased even in mild disease.

- Mechanistically, increased bone resorption and enhanced urinary calcium filtration would presumably lead to a reduced bone mineral quantity or quality over time. Additionally, phosphate loss due to chronically elevated PTH may further compromise bone health.

In accordance, a recent meta-analysis on published studies reporting the risk of fractures in PHPT compared with a control group demonstrated an increased odds ratio (OR) of 2.01 (95% CI, 1.61-2.50) for any fractures and an OR of 3.00 (95% CI, 1.41-6.37) for vertebral fractures (vFX) in patients with PHPT compared with controls. Interestingly, when considering only patients with mild disease, the OR for vFX was even higher at 4.22 (95% CI, 2.20-8.12).

Does PTX normalize fracture risk (or markers of) in asymptomatic PHPT?

Five randomized controlled trials (RCTs) have been conducted to evaluate bone health following PTX. Two of these had observation periods of 12 and 24 months, respectively, and demonstrated an increase in BMD in the spine and hip after PTX, with significant improvements in all compartments compared with the observation group. However, in the distal third of the radius, both groups experienced a decline in BMD, despite a treatment effect in the operated group as compared with observation without intervention, see Figure 1.


A
Lumbar spine
Baseline (48[a]/48[b])
5 years (52[a]/52[b])
10 years (60[a]/59[b])
T-score
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
P<0.001
P=0.016
P(groups)<0.001
B
Femoral neck
Baseline (46[a]/44[b])
5 years (50[a]/50[b])
10 years (63[a]/59[b])
T-score
P=0.149
P<0.001
P(groups)<0.001

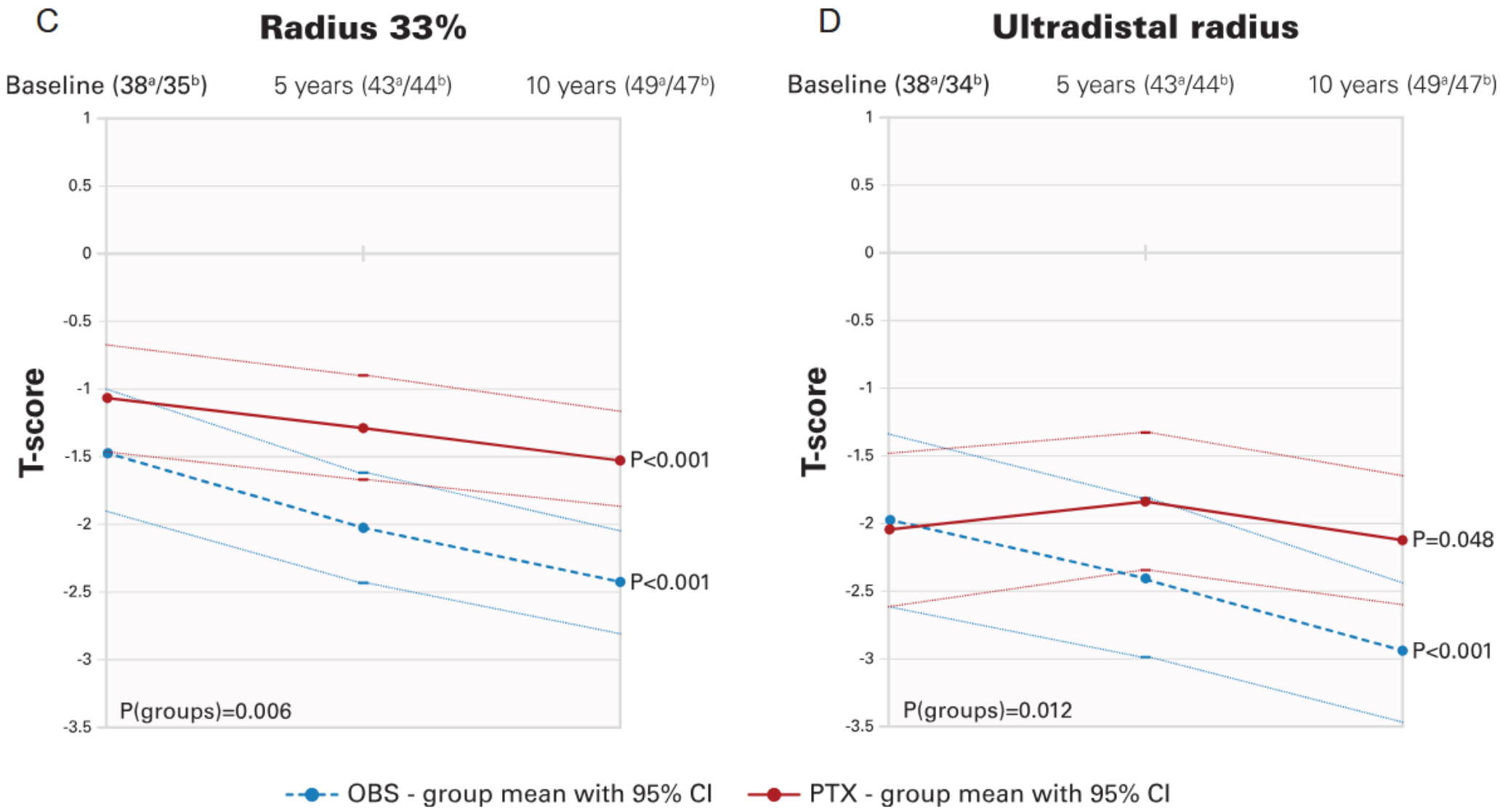


Figure 1. T-score differences in the classical 4 compartments in patients with asymptomatic primary hyperparathyroidism (mild PHPT) randomized to parathyroidectomy versus observation without intervention. End of study data from the Scandinavian Study of Primary Hyperparathyroidism giving baseline, 5 years, and 10 years data for (A) lumbar spine, (B) femoral neck, (C) radius 33%, and (D) ultra-distal radius. P denotes *P* value for longitudinal changes from baseline to 10 years within each group. P (groups) denotes *P* value for longitudinal changes between groups from baseline to 10 years. [a]Number of validated scans for each compartment in the OBS group. [b]Number of validated scans for each compartment in the PTX group. Figure reprinted with permission from Lundstam *et al.*[17] OBS, observation; PTX, parathyroidectomy.

Clinical case presentation

A 63-year-old woman was evaluated after sustaining a distal radius fracture. Her calcium level was 2.63 mmol/L (2.15-2.55), and her PTH level was elevated. A 3-site dual-energy X-ray absorptiometry (DXA) scan was performed, revealing a T-score for bone mineral density (BMD) of −2.7 at the lumbar spine, −1.8 at the total hip, and −2.9 at the distal third of the radius. She had no symptomatic kidney stones and normal renal function. She did not receive any medication. The diagnosis of PHPT was established, and due to skeletal involvement, a selective PTX was performed, resulting in normalization of both calcium and PTH levels.

Clinical case discussion

The optimal monitoring and treatment strategy following successful PTX is not well defined in current international guidelines. In this case, an improvement in BMD would be expected after PTX, particularly in the lumbar spine. However, the low T-score in the distal third of the radius is unlikely to be resolved.

- Performing a follow-up DXA scan 1 or 2 years after PTX to assess the treatment effect seems to be a reasonable approach. A recent RCT investigating intravenous bisphosphonate administration 3 months after PTX showed improved BMD outcomes, but this strategy is not yet routinely implemented post-surgery.
- This approach could be considered in patients with prior fragility fractures or at high risk of fractures. Bisphosphonates, denosumab, and anabolic therapies have all been shown to be effective in PHPT patients after successful PTX and remain viable treatment options if osteoporosis persists or new fractures occur.

During observation before potential surgical intervention, antiresorptive treatment, being bisphosphonates, denosumab, or estrogen treatment are effective in controlling calcium levels, reducing bone turnover thereby increasing BMD and potentially decreasing fracture risk.

For denosumab, a caution should be made, as severe rebound hypercalcemia following discontinuation has been observed. This severe complication can be treated by re-institution of the drug or treatment with bisphosphonates.

- Given the successful resolution of PHPT, it is unlikely that this type of patient will develop renal complications.
- Therefore, routine monitoring with imaging, urinary analysis, or biochemical testing is not warranted. Non-specific physical and mental symptoms are unlikely to resolve with PTX in mild PHPT. If present, patients should be informed that surgery may not necessarily alleviate them.

Bone turnover markers are often used to evaluate osteoporosis. The elevated bone turnover associated with PHPT normalizes rapidly following PTX. This normalization appears to be sustained for at least a decade, which may be beneficial for bone health. Only one of these RCTs was specifically designed to assess fracture risk in a long-term setting. In 191 patients with PHPT, 48 fractures (32 peripheral fractures and 16 vFX) occurred during 10 years of follow-up.

Case presentation

A 22-year-old female patient was referred to the out-patient clinic with hypercalcemia. Her mother and older sister had established MEN1 syndrome. She had no symptoms or other diseases and only mildly elevated levels of calcium and PTH. Several family members were previously operated on the parathyroid glands.

Case discussion

In a 22-year-old patient with hypercalcemia and a family history of MEN1, the risk of MEN1 is almost 100%. It is recommended to perform genetic testing in such patients, since the test result is of importance for life-long follow-up, including monitoring for other organ lesions, and for cascade testing of potentially affected family members. If genetic testing shows a pathogenic or likely pathogenic variant in the MEN1 gene, the clinical management should be adjusted according to the patient's preferences and surgical experience.

- With only mildly elevated calcium levels, no end-organ affection, and no subjective symptoms, this young patient with MEN1 has a low chance of gaining any short-term benefits of PTX at this stage. However, there is a very high risk of a need for later reoperation on the neck, with an increasing risk of RLN palsy and other adverse outcomes. If PTX is not immediately planned, a schedule for follow-up and calcium monitoring is made. This includes considerations regarding increasing calcium levels, pregnancy plans, PTH target-organ evaluation (kidneys and bones), etc.

Follow-up is performed by a tertiary referral center with high experience in MEN1. If PTX is planned, preoperative imaging is important before any surgery. Planning the surgical procedure is challenging. Excision of a single gland will lead to potential reoperations and only lead to a transient reduction in calcium and PTH.

- Unilateral clearance reduces the need for later surgery along the ipsilateral RLN and has a low risk of HypoPT, but a high risk of relapse, thereby requiring later PTX on the contralateral side. With different bilateral procedures (subtotal or total PTX), there is an increased risk of HypoPT but also a reduced risk of the need for any later reoperations. All these considerations must be discussed between the patient, surgeon, and endocrinologist before any PTX is performed.

Is long-term kidney function preserved in PHPT independent of calcium levels?

A recent observational study compared more than 6000 patients with PHPT to 16 000 matched controls. In patients with mild hypercalcemia, the decline in kidney function was comparable to the control group. Conversely, in a subset of patients with serum calcium levels above 2.87 mmol/L, an accelerated decline in estimated glomerular filtration rate (eGFR) was observed compared with matched controls. The preservation of kidney function in mild PHPT has been demonstrated in a randomized controlled setting with the 10-year data from the Scandinavian Investigation of Primary Hyperparathyroidism. Over the course of a decade, there was no difference in kidney function between the PTX and observation groups, as measured by either creatinine-based eGFR or the more modern cystatin C-based eGFR.

Does PTX improve mental health and physical morbidity in asymptomatic PHPT?

The classical symptoms of severe hypercalcemia and multiorgan involvement in PHPT are now rarely seen in most developed countries. However, subtle symptoms have been described in observational studies, and several specific quality of life (QoL) measurement tools have been developed, some of which have been validated for PHPT.

Three RCTs have evaluated the effect of PTX on QoL in these patients. While the 2 previously mentioned studies, with follow-up periods of 12 and 24 months, showed minor changes, the results remained inconclusive. The final RCT, with a 10-year follow-up, assessed QoL using the SF-36 (ie, a generic measure of physical and mental health) and CPRS (ie, a disease-specific psychosocial questionnaire for PHPT). Only subtle improvements were observed in some mental health domains after PTX, with the greatest differences occurring in the early phase of the study; however, over time, QoL levels converged .Since all studies on this topic have been conducted as open-label trials, a placebo effect related to surgery cannot be ruled out.

How to diagnose MEN1 in patients with PHPT?

For young patients diagnosed with PHPT, there is an important risk that PHPT is due to an underlying genetic disorder. It could be MEN1 or another hereditary syndrome. The following questions and answers concern patients with genetically verified MEN1. We recommend these patients to be referred to expert centers. Genetic verification is important to plan a potential PTX and to diagnose any other MEN1-associated endocrinopathy (neuroendocrine tumors of the pituitary gland, lungs, or pancreas, etc.). Family history is important, but not always sufficient for clinical decision making.

In PHPT patients in whom genetic testing does not identify pathogenic or likely pathogenic variants in the MEN1 gene, MEN1 is unlikely. The original data from the Dutch MEN1-database, based on 323 MEN1 patients, of whom 30 (9.3%) were mutation negative, indicated that ‘clinical MEN1 patients’ (based on two out of three MEN1-related tumors with negative MEN1 genetic test) do not have true MEN1.Genetic negative patients developed manifestations at a higher age than genetic positive patients, did not develop new manifestations during follow-up, and had a presumably normal life expectancy. Conversely, almost half of the genetic positive patients developed new manifestations during follow-up (48%) and had reduced life expectancy, as compared with the background population and the genetic negative patients.

- Patients without MEN1 variants should be treated according to standard clinical recommendations and may, in most cases, be operated on with a minimally invasive procedure, if PTX is indicated. However, currently unknown mutations affecting parathyroid pathogenesis may be identified in the future. This should indeed be explored in case of multiglandular disease or persistence of PHPT following otherwise successful PTX.

How can we manage patients with MEN1 without PTX?

There is currently no evidence of a specific medical treatment or supplementation with a beneficial effect on postponing PHPT or hypercalcemia in MEN1 patients. Common health recommendations should be followed, including the recommended intake of calcium and vitamin D to avoid vitamin D deficiency and increase diagnostic accuracy for PHPT. In patients with symptomatic hypercalcemia, medical treatment with calcimimetics (eg, cinacalcet) may be used as symptomatic treatment and to postpone any surgical procedure.

This treatment does reduce calcium and PTH concentrations significantly, but does not reduce the negative impact on BMD. With increasing calcium levels, the patient is recommended to undergo evaluation of end-organ affections, including kidneys and bones. Further, when pregnancy is considered, PTX may be relevant, as discussed later in this paper. Finally, multidisciplinary team counseling should be pursued in these patients.

When is there an indication for PTX in patients with MEN1?

PHPT is, in general, a benign condition with equilibrium hypercalcemia and can often be stable for many years without a need for active medical or surgical treatments . In MEN1 patients there is a very high risk of developing PHPT at a young age (ie, penetrance >90% at the age of 40 years).When PHPT is diagnosed in MEN1 patients, the level of calcium is commonly mildly elevated, and the patients are without subjective symptoms or complications.

PTX in MEN1 patients has a high risk of either persistent PHPT, recurrent PHPT, or chronic HypoPT. Accordingly, with a low chance of long-term normocalcemia following surgery, PTX should not be offered for young MEN1 patients with asymptomatic PHPT. There is little data to inform when to perform PTX in MEN1. Since surgical outcomes in MEN1 patients carry a high risk of hypo- or hyperparathyroidism, the operation should only be performed in patients with a clinical need for PHPT and calcium reduction (expert opinion). Further, PTX is also recommended before biochemistry becomes severely increased and before end-organ damage (kidney, bones, and cardiovascular system), as organ complications may be more prevalent at an earlier stage in MEN1, as compared with sporadic PHPT.

Are any surgical adjuncts needed when performing PTX in patients with MEN1?

In general, PTX procedures in patients with multiglandular disease should always be performed with intraoperative PTH measurements. The values of PTH decrease after resection of pathologic glands, and the levels may guide the surgeon throughout the operation. Both the percentage decrease and the final levels of PTH are indicative of postoperative remission. Further, many surgeons prefer to use intraoperative neuromonitoring to avoid damage to the recurrent laryngeal nerve (RLN).

Some surgeons advocate total PTX with autotransplantation and cryopreservation in MEN1 patients. The aim is to reduce the risk of repeated operative procedures due to recurrent/ persistent PHPT, when less than total PTX is performed. With a reduced number of procedures, the number of other surgical complications, such as palsy of the RLN, is reduced. Accordingly, cryopreservation and “aggressive” PTX are not widely recommended.

since the discovery of parathyroid autofluorescence (PAF), many studies have explored the use of PAF in thyroid and parathyroid procedures (Figure 2). They all utilize the fact that parathyroid glands have a fluorescent ability when excited by a laser at 785 nm. The primary gain from the use of PAF is to increase the identification rate of parathyroid glands during thyroid and parathyroid operations. However, despite identification and preservation of parathyroid glands in the neck during thyroidectomy, the patient may still suffer from Hypo PT.

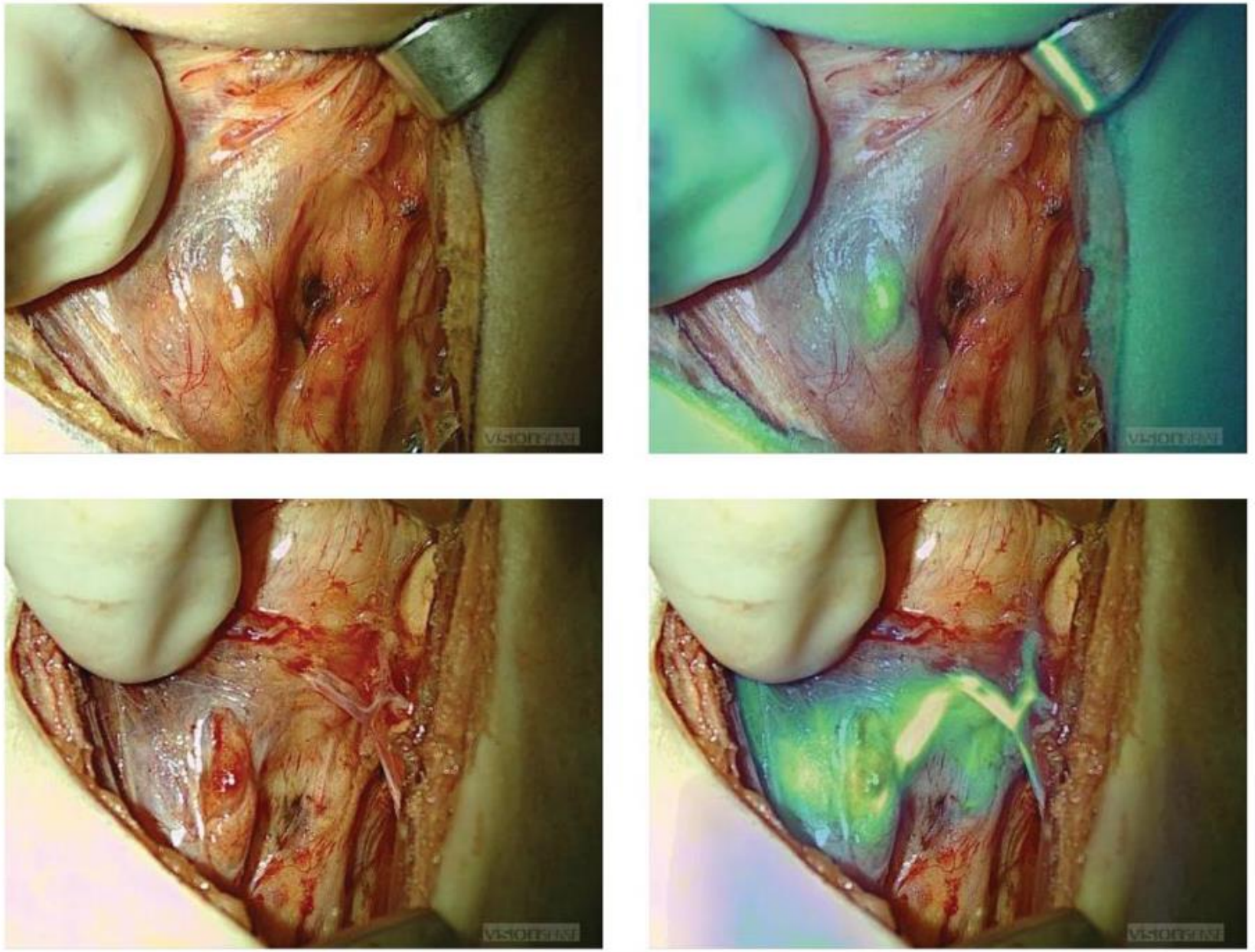


Figure 2. (A) Upper left, identification of a normal parathyroid gland with the "naked eye." (B) Upper right, the same parathyroid gland is more easily seen with the use of parathyroid autofluorescence (PAF). (C) Lower left, dissecting the vascular supply to the parathyroid gland is difficult with the "naked eye." (D) Lower right, dissecting the vascular supply to the parathyroid gland is easier when indocyanine green dye is used to illustrate the essential vessels to the parathyroid gland.

Since PAF is helpful in identifying normal parathyroid glands, the use of PAF has also been evaluated in PHPT. It has been hypothesized that the fluorescence intensity could help to distinguish between normal and pathologic glands. In a large cohort study, PAF was very helpful in mild multiglandular disease, such as MEN1. Although the fluorescence intensity differs markedly between normal and an adenoma, PAF may not be useful in hyperplasia.

Case presentation

A 52-year-old woman developed chronic HypoPT following total thyroidectomy for multinodular goiter. Despite high-dose treatment with alfacalcidol and oral calcium carbonate, she experienced frequent episodes of hypocalcemia, paresthesia, and muscle cramps, significantly affecting her quality of life. Biochemical monitoring revealed persistent low calcium levels and high phosphate concentrations. Due to poor symptom control and fluctuating calcium levels, she was transitioned to PTH(1-84) replacement therapy (subcutaneous injections). Over the following months, her calcium levels stabilized, symptoms improved, and calcium/vitamin D supplementation were first reduced and finally discontinued. PTH therapy led to improved biochemical control and a marked improvement in daily functioning.

Clinical case discussion

This case illustrates a common scenario in which patients with chronic HypoPT remain symptomatic despite treatment with high doses of activated vitamin analogues and calcium supplements. Persistent hypocalcemia, neuromuscular irritability, and reduced quality of life often occur even with normalized laboratory values, suggesting that spot biochemical analyses may not reflect variations of calcium homeostasis over the course of a day.

Hypoparathyroidism

HypoPT is a rare disease due to deficient release of PTH leading to hypocalcemia and hyperphosphatemia, resulting in variable symptomatology and target organ damage. First-line treatment usually includes activated vitamin D analogues and oral calcium supplements. However, this therapy does not replace the normal physiologic actions of PTH, is associated with increased risk of hypercalciuria and hyperphosphatemia, and may lead to additional complications. Hormone replacement therapy with subcutaneously administered PTH molecules is therefore being considered as a second-line treatment in an increasing number of patients inadequately controlled by activated vitamin D analogues and oral calcium supplements.

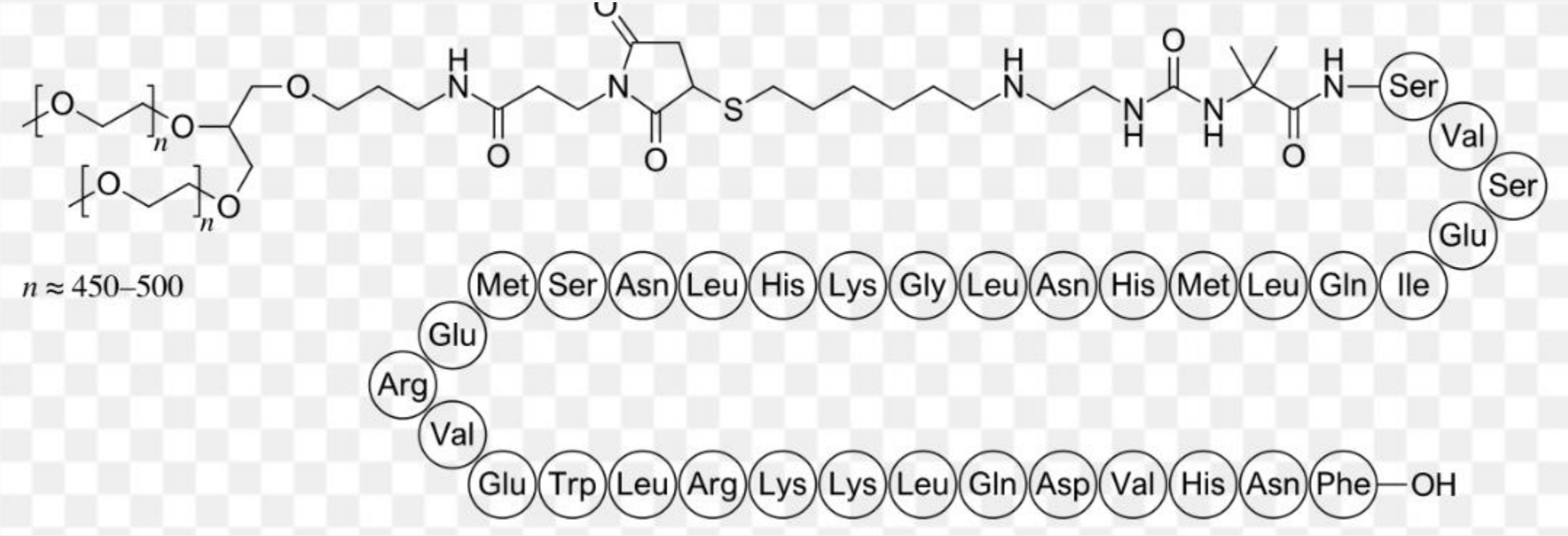
Are there any differences in the treatment with alfacalcidol versus calcitriol?

Pharmacologic differences exist between calcitriol and alfacalcidol regarding intestinal calcium absorption and urinary calcium excretion. In 1 cohort study, the onset of maximal action, ascertained by an increase in urinary calcium excretion, was more gradual with alfa calcidol (5 to 10 days) compared with calcitriol (2 to 5 days). Moreover, the duration of effect varied; the half-life for disappearance of the effect on urinary calcium was longer for alfa calcidol (1.5-2.7 days) versus calcitriol (1.1-2.0 days). These data support the recommendation that calcitriol should preferentially be used for a fast increase in calcium absorption, and should be taken once or twice a day (common practice is once daily for lower doses and twice daily for higher doses), whereas alfa calcidol may be given only once daily due to the longer half-life.

How to switch from alfacalcidol to calcitriol and vice versa?

Only a single study has compared both compounds in non-surgical HypoPT patients in an open-label RCT for 6 months. Based on these data, the authors concluded that alfacalcidol has approximately 45% of the potency of an equivalent dose of calcitriol. The results translate to a comparative dose of 1 µg calcitriol to 2.2 µg alfacalcidol or 1 µg alfacalcidol to 0.45 µg calcitriol. The official recommendation, therefore, is to use a weight-by-weight 1.5-2.0 times higher dose of alfacalcidol compared with calcitriol.

Practical aspects of the change from therapy with activated vitamin D analogues and calcium supplements to parathyroid hormone substitution



Therapy with activated vitamin D analogues and calcium supplements does not substitute for the missing hormone. There is growing evidence that either the disease itself or the treatment are associated with both reduced QoL and a significant number of complications. Currently available formulations of PTH substitution include the PTH(1-34) fragment teriparatide, used off-label for more than 2 decades, and the recently approved pegylated PTH(1-34) form, palopegteriparatide, developed as a pro-drug with sustained release, ensuring stable PTH levels for about 24 h. Teriparatide is still the only available formulation in many middle and low income countries and is usually administered twice or 3 times daily, or by a continuous infusion (insulin pump), due to its short half-life of only about 1 h. Palopegteriparatide was approved by the EMA in 2023 and by the FDA in 2024 for the treatment of adults with chronic HypoPT.

It is recommended to start with 18 µg palopeg teriparatide once daily and simultaneously reduce activated vitamin D dosages and/or calcium supplementation. Due to the long half-life of 60 h and the sustained release, the first control of albumin adjusted calcium or ionized calcium levels should occur after 7 days and can be performed weekly thereafter for dose adjustment. It is advisable to monitor for clinical symptoms of hypocalcemia and hypercalcemia. Finally, the PTH receptor 1 agonist eneboparatide is in clinical testing and could expand the current treatment .

What are the practical aspects of changing from other PTH formulations to palopegteriparatide?

Since the commercial production of PTH(1-84) was terminated by the end of 2024, patients have been switched to alternative hormone substitution regimens or treatment with activated vitamin D analogues and calcium supplements. In a recent study of 40 patients with HypoPT, treatment with PTH(1-84) was stopped the day before the first dose of palopegteriparatide, while the concurrent treatment with activated vitamin D and calcium supplements was continued unchanged. Palopeg teriparatide was started with 18 µg daily, as indicated above. During the first 4 weeks, hypocalcemic values were detected in 25% of the patients, while 35% were hypercalcemic, 38% were normocalcemic, and a single patient was both.

However, the palopegteriparatide dose correlated significantly with the prior PTH(1-84) dose. The authors propose a dosage adjustment for patients who have previously received doses below 50 µg of rhPTH1-84, recommending an initial dose of 15 µg of palopegteriparatide. For patients who have received 50 or 75 µg of rhPTH1-84, the recommendation is to maintain the initial dosage of 18 µg of palopegteriparatide. Finally, for patients with prior doses above 75 µg of rhPTH, the recommendation is to transition to an initial dosage of 21 µg of palopegteriparatide. Calcium control remains essential for 7 days after a dose change for all patients. Thus, minor dose adjustments may be justified when switching from PTH(1-84) to palopegteriparatide. There is currently no published data on the switch from PTH1-34 to palopegteriparatide.

How to change from hormone substitution therapy back to activated vitamin D analogues and calcium supplements?

Data on change from hormone substitution therapy back to activated vitamin D analogues and calcium supplements are scarce. Due to phases of severe hypocalcemia after discontinuation of PTH(1-84) or teriparatide, down-titrating hormone treatment in small steps seems advisable. The use of the same dose of activated vitamin D and calcium given before teriparatide treatment is advised .Frequent controls of calcium levels are important (eg, daily to twice a week). To date, there is no experience with palopegteriparatide, but the change to activated vitamin D analogues might be easier due to the much longer half-life of this formulation, inducing different changes in bone dynamics.

How are chronic versus transient HypoPT and complete versus partial HypoPT defined?

Postoperative HypoPT is characterized by low levels of PTH, leading to hypocalcemia. This condition is categorized into chronic and transient forms based on the duration and persistence of hypocalcemia. Transient HypoPT occurs when hypocalcemia is temporary, typically resolving within a few weeks to months after anterior neck surgery, as the parathyroid glands recover their function. Resolution of HypoPT occurs in the majority (70% to 80%) of patients within 1 month following surgery. Patients who still require supplement therapy due to persistently low or absent PTH after 1 month are considered to have protracted postsurgical HypoPT. The prevalence of protracted postsurgical HypoPT varies from 13% to 44%.

The definition of chronic HypoPT after surgery is debated, with international guidelines regarding the condition as chronic if the HypoPT persists for more than 6 month or 12 after surgery. A recent systematic review identified 89 articles that employed 20 different definition of HypoPT; thus, the incidence of HypoPT varied from 0% to 20%.

Are there any differences in symptoms and overall well-being, and in treatment in patients with complete versus partial HypoPT and chronic versus transient HypoPT?

Patients with complete HypoPT had lower PTH concentrations than patients with partial HypoPT, while both groups were characterized by similar calcium and phosphate values. The mean dose of calcium supplements did not differ; however, the dosages of calcitriol required to achieve calcium values in the targeted range were higher in patients with com-plete HypoPT. There was a trend of more severe renal function impairments in patients with complete than in those with partial HypoPT, with 5% of patients with partial HypoPT depicting eGFR < 60 mL/min versus 23.1% of patients with complete HypoPT ($P = .08$).

Is recovery from postoperative HypoPT possible? Could preoperative vitamin D deficiency influence parathyroid gland function postoperatively?

A recent meta-analysis of 39 observational studies reporting on 61 915 cases with transient- and 5712 with chronic HypoPT investigated the association between vitamin D deficiency and the risk postoperative HypoPT. Patients with vitamin D deficiency demonstrated a higher risk for transient HypoPT compared with those with preoperative vitamin D sufficiency (RR 1.92, 95% CI, 1.50-2.45).83 However, the risk for permanent HypoPT was only demonstrated for patients with severe Vitamin D deficiency (25(OH)D ≤10 ng/mL (<25 nmol/L), The risk of permanent HypoPT was increased only in cases with severe vitamin D deficiency (RR 2.45, 95% CI, 1.30-4.63).

Conversely, a retrospective study was conducted in 397 patients undergoing total thyroidectomy. Preoperative deficiency, defined by vitamin D concentration <20 ng/mL (<50 nmol/L) deficiency, was associated with faster parathyroid function recovery and behaved as a protective factor for protracted HypoPT in the multivariable analysis. Similar findings were reported in another retrospective study, including 139 patients, where no postoperative hypocalcemia occurred in vitamin D deficiency patients, but was reported in 10% of patients with adequate vitamin D levels.

Thus, at present, uncertainty remains regarding the role of preoperative vitamin D in the development of postoperative HypoPT, but severe vitamin D deficiency should be corrected before surgery.

Bone consequences of chronic HypoPT

What changes are seen in bone microarchitecture in patients with HypoPT receiving treatment with activated vitamin D analogues or PTH replacement therapy?

PTH has a direct and indirect effect on bones and acts both in an anabolic and catabolic manner, depending on the length of exposure. Short exposure results in an anabolic effect, while long exposure is catabolic. The anabolic effect is mainly due to an increased number of osteoblasts and stimulation of bone lining cells .

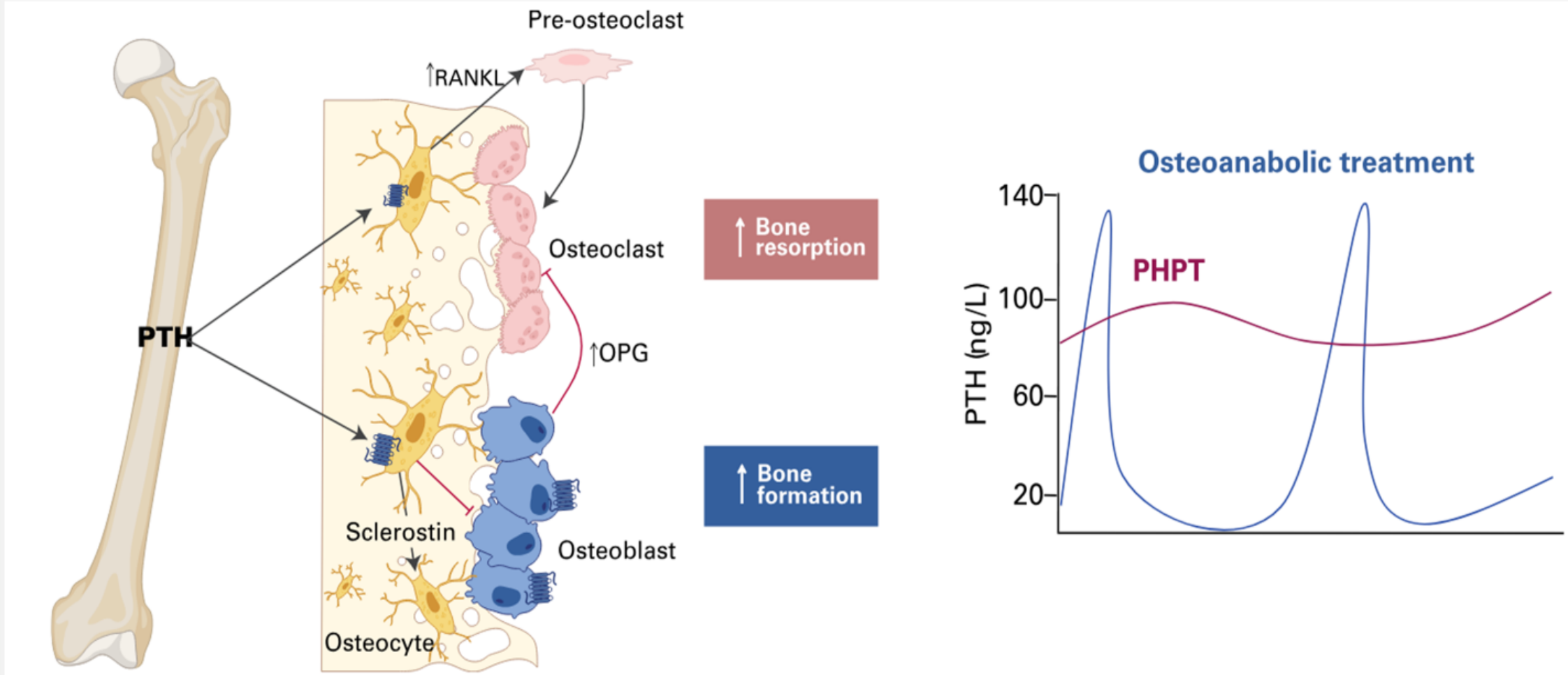


Figure 3. Parathyroid hormone (PTH) actions on bone cells and mass. OPG, osteoprotegerin; PTHT, parathyroid hormone treatment.

Chronic low levels of PTH, as seen in HypoPT, reduce bone remodeling, increase bone density at both cortical and trabecular sites, and change the bone micro-architecture. Bone histomorphometry in patients with HypoPT has shown a prolonged resorption period with a reduced mean total resorption rate and resorption depth, as well as an altered trabecular microarchitecture with increased trabecular bone volume and thickness.

- In patients receiving activated vitamin D analogues and calcium supplements as treatment, data from high-resolution peripheral quantitative computed tomography (HR-pQCT) showed an increased trabecular number and decreased trabecular spacing.

Treatment with PTH(1-34) affects the endocortical surface, stimulates bone formation, and increases bone remodeling. Data on HypoPT patients treated with PTH(1-84) showed that hormonal replacement was associated with a reduced trabecular width and an increase in trabecular number, primarily due to trabecular tunnelling. Trabecular tunneling is a formation of tunnels within the trabeculae, indicating a more dynamic bone remodeling state; whether this phenomenon translates into biomechanical properties of the bone is, however, unknown.

Vertebral fractures

Several, but not all studies, have pointed towards an increased risk of vFX, especially in patients with nonsurgical HypoPT. Three clinical studies, as well as large public-based epidemiological studies, have investigated the risk of morphometric vFX. In the population-based studies, as stated above, overall, no differences were seen among patients with postsurgical HypoPT compared with the general population with regard to the risk of vFX.

Trabecular bone score

To explain the potentially increased risk of vFx in patients with HypoPT despite a high BMD seen in patients with HypoPT, different measurements of bone quality have been used. In a study of 62 patients with postsurgical HypoPT, a normal average TBS score was found; however, with lower values in patients with diabetes mellitus, obesity, and advanced age. This suggests that bone microarchitecture in HypoPT may be affected by the same risk factors known to be of importance for the general population.

What other factors are involved in fractures and falls in patients with HypoPT?

Patients with HypoPT may have impaired muscle strength and function. Undertreated patients have an increased risk of neuromuscular irritability, followed by cramps and seizures. On the other hand, a prior study on treatment with PTH(1-84) did not show an improved muscle function in response to therapy. Rather, maximal force production decreased by 30% at elbow flexion in the PTH group compared with the placebo group.

Parathyroid disorders during pregnancy and lactation

Changes in the endocrine regulation of bone and mineral metabolism during pregnancy and lactation have to be considered when taking care of women with parathyroid disorders, who wish to conceive, are pregnant, or are nursing.

Evidence and guidance on these issues is scarce, in particular for syndromic forms of PHPT and nonsurgical forms of HypoPT (Figure 3). During pregnancy, the calcium demands of the fetus are mainly met by increased gastrointestinal absorption, but a significant demineralization of the maternal skeleton occurs during lactation to ensure a sufficient calcium supply for the newborn via breast milk.

- These changes in calcium metabolism during pregnancy are induced by hormonal changes such as an increased synthesis of active vitamin D, ie, calcitriol, and PTH-related peptide (PTHrP).
- During lactation, an even further increase of PTHrP may occur, accompanied by a decrease in estradiol levels and normalization of calcitriol levels. PTH, which does not cross the placenta, is typically at the lower end of the normal range or slightly below during pregnancy and lactation.

How prevalent is maternal hypercalcemia in pregnancy?

Data are limited, but a large retrospective cohort study reported a hypercalcemia prevalence of 0.8% among 5197 pregnant women tested for serum calcium levels. While maternal hypercalcemia is rare, it may be occasionally overlooked if only total calcium is measured. In pregnancy, albumin-adjusted and/or ionized calcium concentrations should be measured, as total serum calcium concentrations may underestimate true calcium levels due to the low albumin levels and hemodilution.

What is the risk associated with maternal hypercalcemia in pregnancy?

Retrospective cohort data indicate that slightly elevated albumin-adjusted calcium concentrations (eg, 2.7 or 2.8 mmol/L) are not associated with adverse pregnancy outcomes.

Marked hypercalcemia is, however, associated with an increased risk of maternal and fetal complications such as preterm delivery, nephrolithiasis, or pregnancy losses.

According to limited evidence, there seems to be an increase in risk at albumin-adjusted serum calcium levels above 2.85 mmol/L.

What are the causes of maternal hypercalcemia in pregnancy?

The major specific cause is PHPT, but in most cohort studies on hypercalcemic women, no specific cause of hypercalcemia could be identified.

These women may often have transient gestational hypercalcemia that resolves after delivery, and that may be due to gestational adaptations in the regulation of calcium homeostasis. Some of these women may suffer from so-called pseudohyperparathyroidism, an excessive PTHrP production during pregnancy, that might be treated by dopamine agonists (eg, bromocriptine), if required.

Other rare causes of hypercalcemia are inherited disorders of vitamin D metabolism (eg, 24-hydroxylase deficiency), granulomatous diseases (sarcoidosis or tuberculosis), malignancies, FHH, milk-alkali syndrome (due to excess intake of calcium and antacid drugs), certain drugs (eg,lithium, etc.), or vitamin D intoxication.

Which are the main diagnostic tests to evaluate the cause of maternal hypercalcemia in pregnancy?

PTH should be measured to differentiate PTH-dependent (PHPT and FHH) and PTH-independent causes of maternal hypercalcemia. Differentiation of PHPT and FHH can be challenging due to absorptive hypercalciuria in pregnancy that increases 24-hour urine CCCR. Clinicians should consider pre-pregnancy calcium levels, family history, and genetic testing to differentiate FHH and PHPT in pregnancy. Diagnostic procedures for PTH-independent causes are dependent on the individual case and its clinical symptoms and severity.

How should maternal hypercalcemia in pregnancy be treated?

Adequate hydration and avoidance of too much calcium intake can be recommended for all causes of hypercalcemia. In addition, treatment of the specific cause of hypercalcemia is indicated. Treatment of hypercalcemic crisis during pregnancy should be based on individual risk benefit considerations due to safety concerns of drug treatment.

Of note, calcitonin does not cross the placenta and is only effective for a few days due to tachyphylaxis. Bisphosphonates cross the placenta, but the evidence of their effect on fetal outcomes is still inconclusive, with no observed increase in adverse neonatal outcomes.

They might be considered for the treatment of hypercalcemic crisis (eg, albumin adjusted serum calcium >3.5 mmol/L) in pregnancy. Denosumab, on the other hand, should be avoided as data are very limited. For PHPT, surgery, preferably in the second trimester, should be pursued, in particular for cases with albumin-adjusted serum calcium levels above 2.85 mmol/L. There are safety concerns regarding the use of calcimimetics (cinacalcet) in pregnancy, but it has been used in a few pregnant women with PHPT, though with frequent occurrence of nausea and neonatal hypocalcemia in some cases.

The planning of pregnancy for women with syndromic PHPT

What are the syndromic forms of PHPT?

The earliest cases of PHPT reported during pregnancy were more than 90 years ago . PHPT is rare during childbearing years, with cases occurring during pregnancy accounting for <1% of PHPT, but since ~45% remain undiagnosed, the true prevalence, particularly of syndromic forms, remains uncertain. PHPT can occur as part of several genetic syndromes—MEN type 1, 2, 4, and 5, caused by germline mutations in the genes MEN1, RET, CDKN1B, and MAX, respectively, and hyperparathyroidism-jaw tumor syndrome (HPT-JT) caused by CDC73 Mutations.

Knowledge of these syndromic forms is crucial for proper diagnosis, management, and genetic counseling of patients with PHPT in relation to pregnancy. Undiagnosed maternal PHPT can result in adverse maternal and fetal outcomes during pregnancy, including increased rates of pregnancy loss, preterm birth, intrauterine growth restriction, neonatal hypocalcemia, and maternal complications such as pre-eclampsia or maternal nephrolithiasis. In addition, the syndrome-specific complications may require individualized interventions before pregnancy.

Why is pre-pregnancy planning important in patients with syndromic forms of PHPT?

Pre-pregnancy planning is essential for patients with syndromic forms of PHPT due to several critical factors:

1) genetic counseling is crucial and can assist patients in under-standing the risk of transmitting the condition to their off-spring and making informed decisions regarding family planning;

2) PTX may be recommended before pregnancy to mitigate potential complications during gestation;

3) vitamin D deficiency may warrant supplementation before pregnancy is achieved;

4) syndromic forms of PHPT necessitate careful monitoring of the other features of syndromes that may impact maternal and fetal outcomes..

Is it important to identify FHH in pregnancy?

FHH should be considered as a differential diagnosis of hypercalcemia during pregnancy, as there is no specific treatment, and PTX will not normalize calcium levels.

Although typically asymptomatic, FHH can present with mild hypercalcemia-related symptoms (eg, muscle weakness, fatigue, arthralgias, and increased thirst), as well as chondrocalcinosis and nephrolithiasis. A ´CCCR < 0.01 is used as a screening tool indicative of FHH, but its interpretation during pregnancy is challenging due to absorptive hypercalciuria, increasing the risk of false negative results.

Are there differences in fertility outcomes between women with syndromic and sporadic PHPT?

In a recent retrospective matched-cohort study, comparing 386 women with PHPT and 1158 age-matched controls, the pregnancy rate was similar (10.6% vs. 12.8%, and the adjusted rate ratio of pregnancy was 0.89, 95% CI, 0.64-1.24).

However, the rate of live births was significantly lower in patients with co-existing PHPT (79% and 88.0%, respectively, P = .023). Further studies are required to clarify the relationship between PHPT and fertility. Research on fertility differences between syndromic and sporadic PHPT is even more limited, and the presence of other syndrome-associated conditions further complicates the study of PHPT's impact on fertility.

How to treat HypoPT in pregnancy?

It requires meticulous management to ensure the health of both mother and fetus. During pregnancy, physiological changes increase intestinal calcium absorption, which may reduce the need for supplemental calcium and activated vitamin D, but some women may even require higher doses. Therefore, frequent monitoring of serum calcium, phosphate, and magnesium, and dose adjustments are paramount .

As outside of pregnancy, the primary goal is to maintain maternal serum calcium within the low-normal to mid-normal range to prevent complications, especially during the first few months, when the skeleton of the fetus is formed. Taking care of pregnant women with HypoPT is challenging and warrants a multidisciplinary approach in a tertiary care center with specialized endocrinologists, obstetricians, and pediatricians familiar with the condition before and after birth, facilitating optimal maternal and fetal outcomes.

Table 1. Recommendations for surveillance of hypoparathyroidism during pregnancy.

Evaluation	Recommendation
Calcium levels	Check every 3-4 weeks, aiming for low-normal to mid-normal levels
25-Hydroxy vitamin D levels	Assure a sufficient status throughout pregnancy (30-60 ng or 75-150 nmol/L)
Phosphate and magnesium levels	Regular assessments to detect and correct abnormalities
Renal function tests	Monitor for impaired kidney function
Fetal monitoring	Ultrasound evaluations to assess growth and development

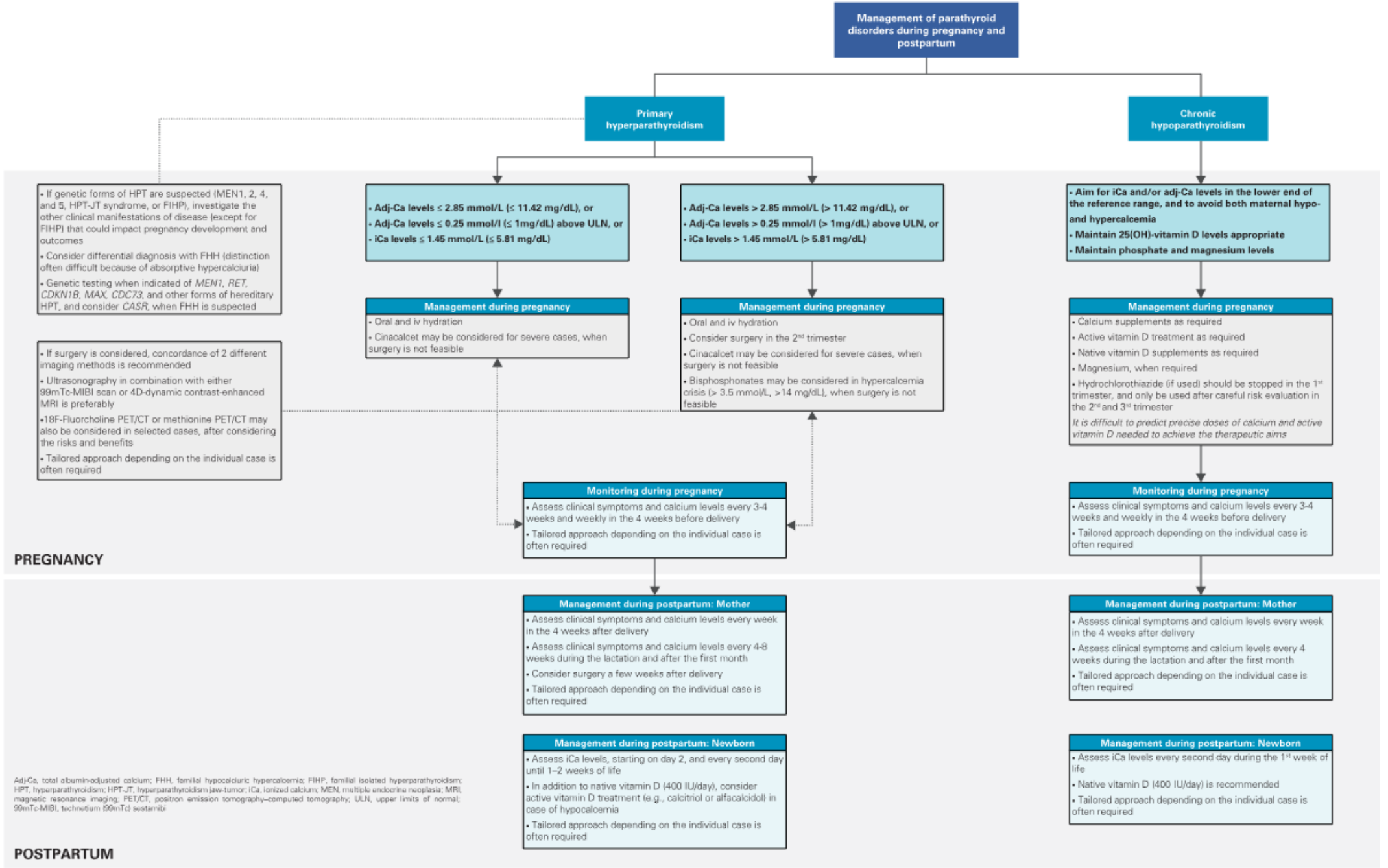
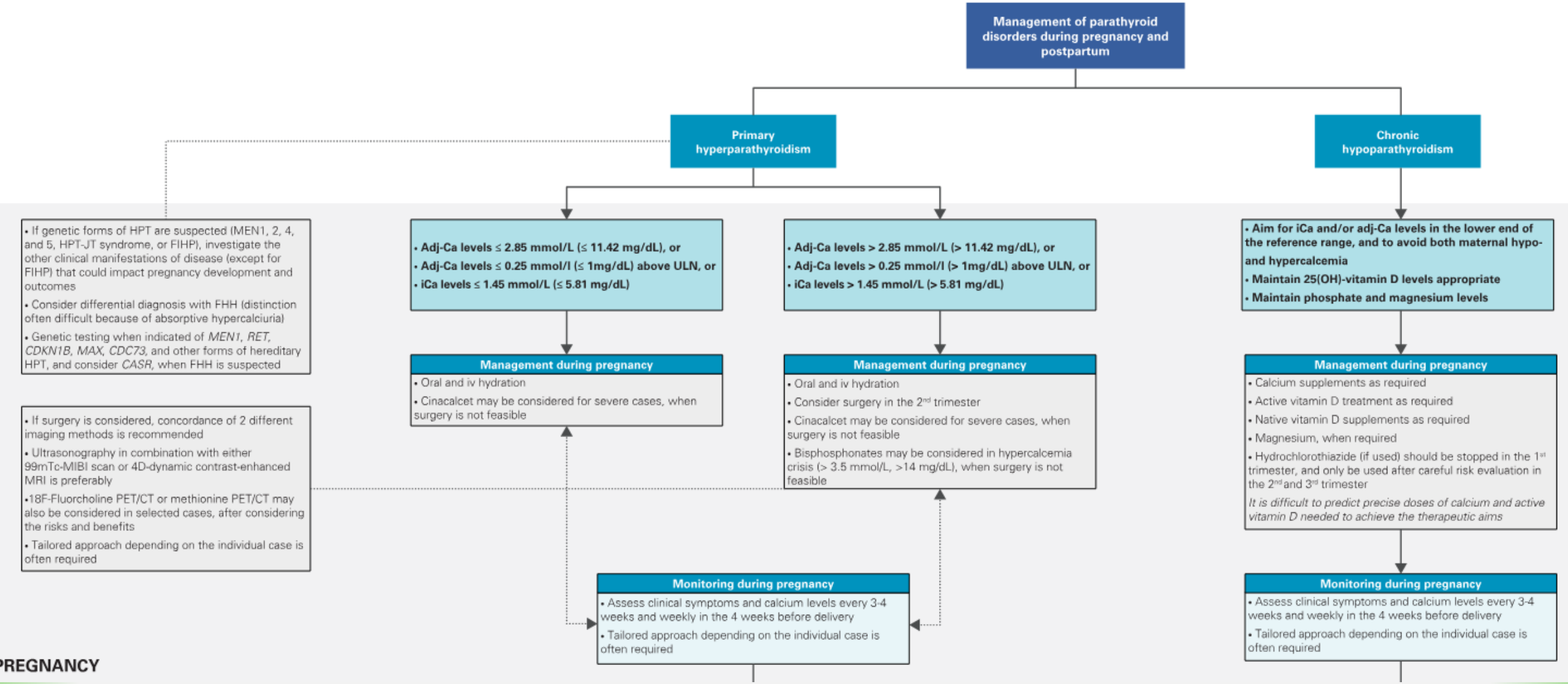


Figure 4. Management of parathyroid disorders during pregnancy and postpartum.


Management of parathyroid disorders during pregnancy and postpartum
Primary hyperparathyroidism
Chronic hypoparathyroidism
• If genetic forms of HPT are suspected (MEN1, 2, 4, and 5, HPT-JT syndrome, or FIHP), investigate the other clinical manifestations of disease (except for FIHP) that could impact pregnancy development and outcomes
• Consider differential diagnosis with FHH (distinction often difficult because of absorptive hypercalciuria)
• Genetic testing when indicated of MEN1, RET, CDKN1B, MAX, CDC73, and other forms of hereditary HPT, and consider CASR, when FHH is suspected
• If surgery is considered, concordance of 2 different imaging methods is recommended
• Ultrasonography in combination with either 99mTc-MIBI scan or 4D-dynamic contrast-enhanced MRI is preferably
•18F-Fluorcholine PET/CT or methionine PET/CT may also be considered in selected cases, after considering the risks and benefits
• Tailored approach depending on the individual case is often required
• Adj-Ca levels ≤ 2.85 mmol/L (≤ 11.42 mg/dL), or
• Adj-Ca levels ≤ 0.25 mmol/l (≤ 1mg/dL) above ULN, or
• iCa levels ≤ 1.45 mmol/L (≤ 5.81 mg/dL)
Management during pregnancy
• Oral and iv hydration
• Cinacalcet may be considered for severe cases, when surgery is not feasible
• Adj-Ca levels > 2.85 mmol/L (> 11.42 mg/dL), or
• Adj-Ca levels > 0.25 mmol/l (> 1mg/dL) above ULN, or
• iCa levels > 1.45 mmol/L (> 5.81 mg/dL)
Management during pregnancy
• Oral and iv hydration
• Consider surgery in the 2nd trimester
• Cinacalcet may be considered for severe cases, when surgery is not feasible
• Bisphosphonates may be considered in hypercalcemia crisis (> 3.5 mmol/L, >14 mg/dL), when surgery is not feasible
Monitoring during pregnancy
• Assess clinical symptoms and calcium levels every 3-4 weeks and weekly in the 4 weeks before delivery
• Tailored approach depending on the individual case is often required
• Aim for iCa and/or adj-Ca levels in the lower end of the reference range, and to avoid both maternal hypo- and hypercalcemia
• Maintain 25(OH)-vitamin D levels appropriate
• Maintain phosphate and magnesium levels
Management during pregnancy
• Calcium supplements as required
• Active vitamin D treatment as required
• Native vitamin D supplements as required
• Magnesium, when required
• Hydrochlorothiazide (if used) should be stopped in the 1st trimester, and only be used after careful risk evaluation in the 2nd and 3rd trimester
It is difficult to predict precise doses of calcium and active vitamin D needed to achieve the therapeutic aims
Monitoring during pregnancy
• Assess clinical symptoms and calcium levels every 3-4 weeks and weekly in the 4 weeks before delivery
• Tailored approach depending on the individual case is often required

PREGNANCY

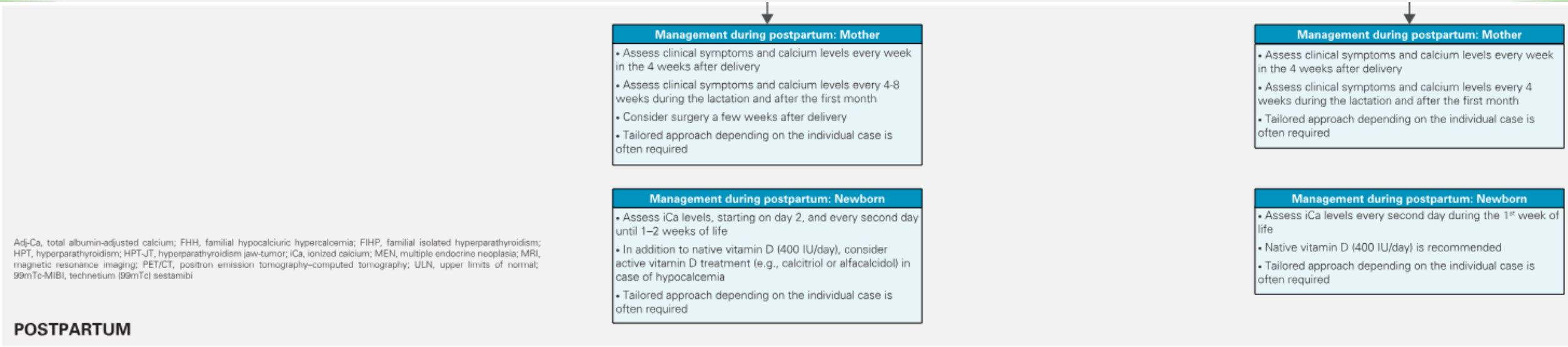


Figure 4. Management of parathyroid disorders during pregnancy and postpartum.

Are PTH formulations/analogues possible in pregnancy?

The use of PTH or its analogues during pregnancy is not recommended due to limited safety data and needs to be carefully weighed against routine care.

Table 2. Case reports on the use of parathyroid hormone therapy in pregnant patients with hypoparathyroidism.

Study	Patients	Type of PTH treatment	Comments
Ilany et al. (2013)[154]	36 years old woman, postoperative HypoPT	s.c. rh PTH (1-34) infusion (Medtronic Minimed 508® pump)	Patient initially treated with 2 mcg of alfacalcidol/day and 10 g elemental calcium/day (compliance uncertain). Due to high serum phosphorus level and recurrent convulsions, patient was converted to teriparatide twice daily 20 mg s.c. injections, but without success in controlling thesymptoms. Therefore, patient was changed to a teriparatide infusion regime using an insulin pump Patient gave birth a healthy 2700 g baby at 37 weeks' gestation with normal calcium levels with no need for intravenous calcium infusion during birth. The patient did not breastfeed.
Shulman et al. (2022)[155]	26 years old woman, ADH1	s.c. rh PTH (1-34) infusion (OmniPod® pump)	No tetany or hospitalizations during pregnancy, serum calcium levels 7.2-9.8 mg/dL. Due to mild preeclampsia, her infant was delivered at 37 weeks. There were no physical anomalies. The patient continued pump therapy while nursing her daughter, who was ultimately confirmed to have the same *CASR* mutation. Breastfeeding appeared to protect the infant from significant hypocalcemia without the need for calcium or calcitriol supplementation until weaning at a year of age.
Appelman-Dijkstra et al. (2023)[10]	28 years old woman, idiopathic HypoPT	sc. PTH (1-84)—25 µg once daily throughout pregnancy and nursing period	Additional calcium supplement with 500 mg once daily to ensure an adequate oral calcium intake and regular vitamin D3 intake of about 1000 IU daily. Healthy male baby delivered at gestational week 38 + 4 (Apgar 9/10/10; weight: 3365 g, length: 49 cm), breastfeeding was uncomplicated.
Liao et al. (2023)[156]	40 years old woman, postoperative HypoPT	Intermittent sc. PTH (1-84) during 2 pregnancies Patient 1: stopped at 5 weeks gestation, resumed while breastfeeding Patient 2: informed decision to continue PTH (1-84), recalled in the USA at 15 weeks of gestation	The daughter's serum calcium was borderline elevated at 8 days postpartum but within the normal range at 8 weeks postpartum. The patient stopped nursing at around 6 months postpartum. Her daughter is now at 4 years and 5 months of age and is healthy and meeting developmental milestones. She was again pregnant at 8 months postpartum from her first pregnancy, at 15 weeks of gestation, resumed calcium and calcitriol supplements. She gave birth to a baby boy at 39 weeks in January 2020. At 3 years and 2 months of age, he is overall healthy.

ADH1, autosomal dominant hypocalcemia type 1; *CASR*, calcium-sensing receptor; HypoPT, hypoparathyroidism; PTH, parathyroid hormone; rh, recombinant human; s.c., subcutaneous.

What are the risks associated with HypoPT in pregnancy? Does it differ according to the etiology of the disease?

Some observational studies from Italy, Sweden, Denmark, Canada, Turkey, and Australia have been published to date Several case reports have been reported on the use of PTH analogues in pregnancy.

Possible risks include:

- Maternal risks: Hypocalcemia can lead to neuromuscular irritability or seizures, while hypercalcemia poses risks such as nephrolithiasis and acute problems during birth, and abortions.
- Fetal risks: Intrauterine growth restriction, skeletal deformities, preterm birth, or neonatal hyper- or hypocalcemia.

Which precautions should be taken for birth regarding the mother and newborn?

Maternal management: Ensure regular testing so that calcium levels are stable to prevent peripartum complications.

Neonatal care: Be aware of possible neonatal calcium disturbances and monitor calcium levels promptly as needed, as infants may experience transient hyper- or hypocalcemia. Early detection and treatment are crucial to prevent neonatal complications.