European Society of Endocrinology

ECE 2024 Pre Congress Course

PARAT 2024 Workshop on Parathyroid Disorders: What Has Happened Since the Pandemic and Further Perspectives

Summary Report & Abstract Booklet

Editors: Luís Miguel Cardoso, Elena Tsourdi, Peter Kamenický, and Jens Bollerslev

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PARAT 2024

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Contents

Overview

Within the field of endocrinology, the emphasis on parathyroid disorders has been limited in comparison to other areas, but new developments in molecular and pathophysiological mechanisms, as well as in the treatment options for patients with parathyroid disorders, has renewed and increased the interest in this field. This generates educational needs for medical doctors looking after patients with parathyroid disorders to further develop and update their knowledge on such complex conditions.

Between 2018 and 2022, ESE developed an educational programme **"PARAT: An ESE Educational Programme on Parathyroid Disorders"** (see here). The **ESE PARAT Programme** has had tremendous success, resulting in the production of a wide number of educational events and medical education materials, including the **"European Expert Consensus on Practical Management of Specific Aspects of Parathyroid disorders in Adults and in Pregnancy"** published in the European Journal of Endocrinology (i.e., an invited article consisting of 33 recommendations of more than 100 parathyroid experts from 20 countries who contributed to the PARAT programme; see here), **on demand webinars**, plus an online **"Learning Zone"** with 25 faculty focused videos, 18 clinical case e-Multiple Choice Questions, patient education leaflets, and emergency cards for patients with hypoparathyroidism translated into several languages (see here).

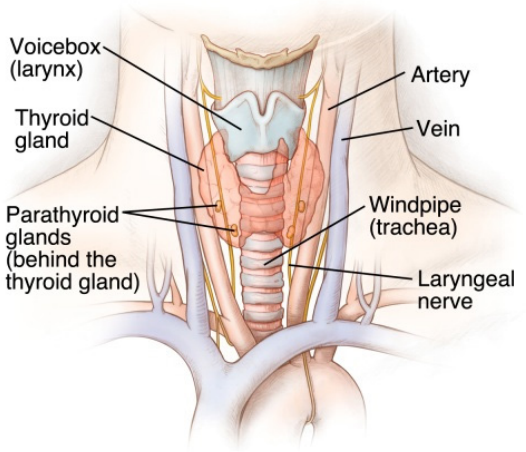
Following the successful completion of the **ESE PARAT Programme**, and the publication of the consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy, there was a proposal to hold a **satellite workshop** focused on parathyroid disorders at the ECE in May 2024, in Stockholm, Sweden.

The workshop was an opportunity to consolidate and refresh the knowledge generated by the **ESE PARAT Programme**, while providing updates on the latest novelties and developments in the field. It was focused on 3 main areas: primary hyperparathyroidism, hypoparathyroidism, and parathyroid disorders in pregnancy; however, other controversial aspects related to the management of parathyroid conditions were also discussed. Moreover, this initiative was important to further enhance the awareness of parathyroid disorders, as well as to educate medical doctors, including junior doctors and doctors training in Endocrinology. This initiative will ultimately improve the medical care and outcomes of patients with parathyroid disorders across Europe.

Parathyroid Disorders

Parathyroid conditions are disorders that affect the four small glands in or around the thyroid gland. They release parathyroid hormone (PTH) – the hormone that controls your body's ability to regulate calcium and phosphorus.

When this hormone is too low or too high, it can lead to other health problems such as muscle cramps and nerve or bone disorders.



Treatment for parathyroid conditions focuses on restoring the balance of calcium and phosphorous in the blood. If a tumour is detected, it may be necessary to carry out minimally invasive procedures or other surgical options.

Welcome to the PARAT Workshop 2024

On behalf of the ESE and our fellow Workshop Steering Committee colleagues, we are delighted to publish this **Summary Report and Abstracts Booklet of the ECE 2024 Pre Congress Course – "PARAT 2024 Workshop on Parathyroid Disorders: What Has Happened Since the Pandemic and Further Perspectives"**.

Earlier this year, we welcomed **121 delegates, from 40 different countries,** to our PARAT Workshop held on Saturday, 11 May 2024 in Stockholm, Sweden. Through expert presentations by prominent speakers in the field, and through lively discussions at end of each presentation prompted by the high-quality and very relevant questions by the delegates, the PARAT Workshop was a great learning opportunity and a forum for sharing opinions, research ideas and management experiences, as well as to identify the unmet needs of patients with parathyroid diseases and ways to overcome these.

This **Summary Report and Abstracts Booklet** provides the readers with an overview of the **PARAT Workshop** held during ECE 2024, together with the abstracts of the Workshop, as well as with key references per lecture.

We sincerely acknowledge the hard work of the editors of this booklet, particularly Luís Miguel Cardoso and Elena Tsourdi, as well as the contributions of all abstract authors.

We would like to thank all Steering Committee colleagues, faculty, speakers and delegates for contributing to a high quality and educative event. Lastly, we acknowledge and thank Amolyt and Ascendis Pharma for their sponsorship, which has enabled ESE to deliver the **PARAT Workshop**.

Jens Bollerslev and **Peter Kamenický**,

Chairs of the PARAT Workshop

PARAT Workshop Objectives

With a programme focused on parathyroid disorders, specifically on **primary hyperparathyroidism**, **hypoparathyroidism**, and **parathyroid disorders in pregnancy**, the key objectives of this course are:

- To identify the challenges faced during the diagnosis, management, and long-term follow-up of patients with these conditions.
- To update physicians regarding the new advances in the field, particularly concerning the pathophysiology and treatment of these conditions.
- To continue raising awareness and educate physicians in treating patients with these conditions, focusing also on critical stages of the lifespan, particularly in pregnancy.
- To bring together leaders and experts in the field, including endocrinologists, endocrine surgeons, pathologists, radiologists, and researchers, as well as junior doctors in training and residents in Endocrinology, enhancing the multidisciplinary cooperation and collaboration of these healthcare professionals.

Steering Committee & Expert Faculty

PARAT Workshop Steering Committee

Jens Bollerslev (*Norway*)
Peter Kamenický (*France*)
Elena Tsourdi (*Germany*)
Karin Amrein (*Austria*)
Lars Rolighed (*Denmark*)
Luís Miguel Cardoso (*Portugal*)

PARAT Workshop Expert Faculty

Mikkel Pretorius (*Norway*)
Lars Rolighed (*Denmark*)
Heide Siggelkow (*Germany*)
Elena Tsourdi (*Germany*)
Line Underbjerg (*Denmark*)
Luís Miguel Cardoso (*Portugal*)
Stefan Pilz (*Austria*)
Karin Amrein (*Austria*)

PARAT Workshop Team

Pedro Marques (*European Society of Endocrinology*)
Vicki Di Guisto (*European Society of Endocrinology*)

Meet the PARAT Workshop Steering Committee & Expert Faculty

Jens Bollerslev
Oslo University Hospital and Faculty of Medicine
University of Oslo, Norway

Steering Committee & Expert Faculty

Jens Bollerslev is Professor of Endocrinology at the University of Oslo, Norway. He was a recent member of the Executive Board, the European Society of Endocrinology (ESE), chair of the ESE Education Committee, and chair of the ESE Committee for Post Graduate Courses. Presently he chairs the ESE PARAT project.

His special interest is within clinical and translational endocrinology, and in particular in classical endocrine diseases, such as Acromegaly and Cushing's, often studying bone as target tissues for clinical activity. A major interest has been devoted to metabolic bone disorders, other than post-menopausal osteoporosis, as illustrated by his work for The Scandinavian Investigation of Primary Hyperparathyroidism. He has a deep interest in the control of bone remodelling as seen in classical endocrine and inherited metabolic diseases, and in relation to solid organ transplantation.

Elena Tsourdi
University of Dresden, Germany

Steering Committee & Expert Faculty

Elena Tsourdi studied medicine at the University of Athens Medical School and completed her first doctoral thesis on the interactions of the pituitary gland and the male reproductive system at the University of Thessaloniki, Greece.

As of 2008 she became particularly interested in the bone field and completed her second doctoral thesis on zoledronic acid for the therapy of osteoporosis at the University of Dresden, Germany.

Since December 2012, she has been working as a Senior Consultant at the Department for Metabolic Bone Diseases, University Dresden Medical Centre, gaining significant expertise in the field of osteoporosis and rare bone diseases. She is an investigator in several clinical phase 2/3 studies in the field of osteoporosis/rare bone disease, a Supervisor of Ph.D. students at University Clinic Dresden, and a Tutor in Endocrinology, Diabetes, and Bone Diseases at University Clinic Dresden.

Peter Kamenický
Bicêtre Hospital and Paris-Saclay University, France

Steering Committee & Expert Faculty

Prof Peter Kamenický is a professor of endocrinology at the French reference centre for rare pituitary diseases, and for rare diseases of calcium and phosphate metabolism, at the Bicêtre Hospital and Paris-Saclay University, France.

His clinical expertise is mainly in the field of pituitary and adrenal diseases including acromegaly and Cushing's syndrome, and around disorders of calcium and phosphate metabolism, such as hypoparathyroidism and X-linked hypophosphataemia.

Karin Amrein
Medical University of Graz, Austria

Steering Committee & Expert Faculty

Karin Amrein trained in Switzerland and Austria and obtained her MD at the Medical University of Graz, in 2001. She has a degree in Internal Medicine/ Endocrinology and a sub-speciality degree in intensive care medicine.

Karin currently works mostly in private practice in Graz and continues to be an active researcher (e.g., parathyroid disorders, vitamin D deficiency in the ICU). She has two children and likes stand-up paddling, swimming, climbing and traveling.

Karin is also PI of the VITDALIZE trial, that started in 2017, and aims to include 2400 severely vitamin D deficient ICU patients in several European countries (UK, Germany, Belgium, Austria, current recruitment > 1600 patients). She was PI of the VITdAL-ICU study that started in 2010 and was published in JAMA in September 2014. This was the first large randomized controlled trial on vitamin D in critical care. Although the primary endpoint length of hospital stay was similar between placebo and vitamin D group, there was a significant benefit for hospital survival (relative risk reduction 44%) in the severely vitamin D deficient subgroup. Her major research interests are vitamin D in critical illness, bone health and blood donation induced iron depletion (and its therapy) and women in science.

Lars Rolighed

Aarhus University Hospital, Denmark

Steering Committee & Expert Faculty

Endocrine Surgeon with special interest in parathyroid diseases. I performed a clinical Ph.D. regarding Vitamin D treatment in primary hyperparathyroidism.

After some years of specialization, I now only perform surgery on the adrenal, parathyroid, and thyroid glands.

Further, my research activities have been concerning hyperparathyroidism, hypoparathyroidism, vitamin D, bone metabolism, quality of life, and use of intra-operative fluorescent techniques in close collaboration with colleagues from Department of Endocrinology.

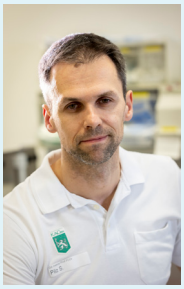
Luís Miguel Cardoso

Coimbra University Hospital, i3S - Institute for Research and Innovation in Health, Portugal

Steering Committee & Expert Faculty

Consultant endocrinologist and European Board Exam in Endocrinology, Diabetes & Metabolism certified. My main areas of research interest are parathyroid tumours and pituitary tumours, with particular focus on functioning pituitary tumours. Currently based at Coimbra University Hospital and i3S - Institute for Research and Innovation in Health of the University of Porto, I dedicate myself to translational and clinical research.

Over the years, I have been actively involved in several activities of the European Society of Endocrinology (e.g., ESE Young Endocrinologists & Scientists [EYES] Committee, Education Committee, ESE News, ESE Summer School) and the Portuguese Society of Endocrinology, Diabetes and Metabolism (served on the executive board and treasurer from 2021-2023). I have recently been appointed Editor-in-chief of the journal Endocrinology Insights and coordinator of the Portuguese Registry of Endocrine Diseases.



Stefan Pilz

Medical University of Graz, Austria

Expert Faculty

Stefan Pilz (MD, Ph.D.) is an associated professor at the Department of Endocrinology and Diabetology, Medical University of Graz, Austria. Stefan Pilz received his MD from the Karl-Franzens University of Graz, Austria in 2003 and his Ph.D. from the Department of Epidemiology and Biostatistics, VU University of Amsterdam, The Netherlands in 2012.

He is a consultant for endocrinology and for internal medicine and a general practitioner. He is currently the president of the Austrian Society of Endocrinology and Metabolism and works as the head of the outpatient clinic at the Department of Endocrinology and Diabetology at the Medical University of Graz, Austria.

His main research interests are vitamin D, and related mineral disorders, and steroid hormones with a focus on endocrine hypertension. He published over 300 Medline papers and has an H-index of 71.

Mikkel Pretorius

Oslo University Hospital, Norway

Expert Faculty

Mikkel Pretorius is a senior consultant at Oslo University Hospital (OUHwith a speciality in endocrinology and internal medicine. He is head of the osteoporosis and calcium section at OUH and works clinically with patients suffering from primary and secondary osteoporosis, as well as patients with rare bone diseases.

He holds a Ph.D. in calcium and bone disease and is connected to a broad Scandinavian research environment related to these diseases.

He is the author of several chapters on this topic in the National Guidelines in Endocrinology and has a special interest in primary hyperparathyroidism, osteogenesis imperfecta, clinical densitometry, osteoporosis in young individuals, and phosphate disorders. He is a member of the ESE Special Interest Group for Calcium and Bone Disorders.

Heide Siggelkow

University Medical Center, Germany

Expert Faculty

Heide Siggelkow works in an outpatient clinic for endocrine or metabolic bone diseases, including osteoporosis, hypoparathyroidism, hyperparathyroidism, and rare bone diseases.

Between 2011 and 2015, she was head of the Association of German Language Societies in the special Field of Osteology (DVO). In this position, she initiated and supported the development of the Osteologic Research Centres DVO. She was president of the German Society of Osteology (DGO) from 2017–2019.

In 2017, the Intensive Course for Clinical Endocrinology of the German Society of Endocrinology (DGE) took place in Göttingen under her leadership, and in 2019 she hosted the yearly congress of the society DGE in Göttingen.

From 2018-2022 she has been spokesperson of the German network of rare bone diseases, "Netzwerk für seltene Osteopathien NetsOs".

2017-2020 she was member of the European Calcified Tissue Society (ECTS) Website and Social Media Action Group, and since 2021 she joined the ECTS Action group of Rare Bone Diseases and is member of the ECTS Board since 2022.

2020-2024 she was member of the ESE Education Committee and representative in the PARAT programme of the European Society of Endocrinology (ESE). She is now Expert Panel member of the ESE Educational Programme on Rare Calcium, Phosphate and Bone Disorders (RCPBD). Her basic scientific work at the University of Göttingen Medical Centre focuses on molecular and metabolic mechanisms important for the interplay between fat and bone in primary and secondary forms of osteoporosis, with a special focus on cortisol and bone. Another main topic is the investigation of mechanisms of osteoporosis in mastocytosis. Her clinical research is now concentrated on secondary forms of osteoporosis and on hypoparathyroidism with a special focus on quality of life.

Line Underbjerg

Aarhus University Hospital, Denmark

Expert Faculty

Line Underbjerg, MD, Ph.D., is a resident at Department of Endocrinology and Internal Medicine, Aarhus University Hospital.

She has published 20 papers in peer-reviewed journals focusing on primarily on chronic hypoparathyroidism (both post-surgical and non-surgical), pseudohypoparathyroidism and bone metabolism.

Underbjerg has participated in drafting the clinical guidelines regarding the epidemiology of chronic hypoparathyroidism.

ECE 2024

26th European Congress of Endocrinology

11-14 May 2024, Stockholm, Sweden

PARAT Workshop Programme

11:00 – 11:10 Welcome and introduction (Jens Bollerslev, Peter Kamenický)

11:10 – 12:00 Primary hyperparathyroidism (Chairs: Jens Bollerslev, Peter Kamenický)

- Evidence for long term complications of mild primary hyperparathyroidism (Mikkel Pretorius)
- Treatment of syndromic primary hyperparathyroidism (MEN 1-4) (Lars Rolighed)
- Discussion

12:00 – 13:05 Hypoparathyroidism (Chairs: Elena Tsourdi, Peter Kamenický)

- How to manage a change of treatment, including guidance for patients (Heide Siggelkow)
- Importance of residual PTH function for management (Elena Tsourdi)
- Bone in patients with hypoparathyroidism conventionally treated and receiving rhPTH or PTH analogues (Line Underbjerg)
- Discussion

13:05 – 14:00 Networking Lunch

- **14:00 – 15:15 Parathyroid disorders in pregnancy** (Chairs: Karin Amrein, Jens Bollerslev)
- The planning of pregnancy for women with syndromic primary hyperparathyroidism (Luís Miguel Cardoso)
- Hypercalcemia in pregnancy - parathyroid disorders and PTH independent causes (Stefan Pilz)
- How to tailor treatment of hypoparathyroidism in the weeks before and after delivery (Karin Amrein)
- Discussion

15:15 – 15:30 Conclusions (Jens Bollerslev, Peter Kamenický)

Speaker: **Mikkel Pretorius**
Norway

KEY MESSAGES

- **Mild primary hyperparathyroidism without organ manifestations is now the predominant form in the developed world.**
- **In mild disease, parathyroidectomy does not seem to affect cardiovascular disease, kidney function, or mortality.**
- **Parathyroidectomy increases bone mineral density compared with observation; however, fracture risk seems unchanged.**

Evidence for long term complications of mild primary hyperparathyroidism

Today, primary hyperparathyroidism (PHPT) is a common endocrine disorder, especially among peri- and post-menopausal women (1). PHPT is characterised by elevated calcium levels and inappropriately high levels of PTH. In countries with highly developed healthcare systems, the mild form (previously termed asymptomatic) is now predominant. There is an ongoing debate on how to manage these patients without symptoms or signs of end-organ disease. International consensus guidelines on the management of asymptomatic PHPT have been issued five times between 1991 and 2022 in an attempt to address this still challenging question. European consensus statements have also evolved, mainly through the PARAT Programme initiated by the European Society of Endocrinology (2).

The net effect of continuous PTH stimulus on bone is to release more calcium into the circulation, thereby increasing bone resorption more than formation. A recent systematic review and meta-analysis on fractures included 12 studies on the topic (3). An increased risk of fracture was found in PHPT patients (risk of any fractures (OR: 2.01), forearm (OR: 2.36), and spine (OR: 3.00)). There was high heterogeneity in the studies, and the methods of diagnosing, for example, vertebral fractures, were not uniform. A recently published randomised controlled trial with a 10-year follow-up did not find evidence for a treatment effect of parathyroidectomy on fracture incidence (4). PTH increases bone turnover, and several observational studies have demonstrated decreased bone mineral density in patients with the diagnosis. A significant treatment effect of parathyroidectomy (PTX) compared to observation has been confirmed in all measured dual-energy X-ray absorptiometry (DXA) compartments within a randomised controlled setting (5).

Concerns have been raised about whether renal impairment could exacerbate mild PHPT, or if PHPT could directly promote deteriorating kidney function through nephrocalcinosis, urolithiasis, or through a direct effect of PTH or calcium (6). Recently, several cohort studies have independently shown a deterioration of kidney function following PTX, even when compared to observation (7, 8). In contrast, a recent population-based retrospective study observed a decline in estimated glomerular filtration rate (eGFR), but only in patients with severe hypercalcaemia (9).

Several epidemiological and observational studies have demonstrated an increased risk of mortality and cardiovascular disease in PHPT . Notably, in contrast to these data, the largest randomised controlled trial designed to evaluate mortality, with up to 20 years of follow-up, did not show any treatment effect of PTX on these important clinical endpoints (4).

Speaker: **Lars Rolighed**
Denmark

KEY MESSAGES

- **In young patients with primary hyperparathyroidism (PHPT), evaluation of familial forms of hyperparathyroidism should be considered.**
- **Patients with PHPT and multiple endocrine neoplasia type 1 (MEN1) often present with mild hypercalcaemia and multi-gland disease.**
- **Parathyroidectomy in MEN1 patients has a high risk of hypoparathyroidism or persistent hyperparathyroidism.**
- **Intra-operative fluorescent techniques may improve the *in vivo* evaluation of parathyroid glands and help to improve long-term outcomes.**

Treatment of syndromic primary hyperparathyroidism (MEN 1-4)

Development of primary hyperparathyroidism (PHPT) is very common in patients with multiple endocrine neoplasia type 1 (MEN1) and also seen in other hereditary conditions (1). These young patients have increased risk of multi-gland disease and higher risk of either persistent PHPT, recurrent PHPT, or hypoparathyroidism (hypoPT) after parathyroidectomy (PTX) (2-5). Accordingly, aims and potential benefits from surgical treatment must be evaluated carefully together with long-term risks of adverse outcome.

The literature and clinical guidelines on the evaluation of medical and surgical treatment options in patients with PHPT in MEN1-4, as well as the possible benefits of new intra-operative fluorescent imaging is evaluated are reviewed herein.

Patients with PHPT and MEN1 are younger than other PHPT patients and often present with mild asymptomatic PHPT and multi-gland disease. Medical treatment with the calcimimetic cinacalcet is an option to reduce hypercalcaemia at several stages: 1) before any operative procedures; 2) after insufficient PTX; 3) in case of recurrent PHPT (6,7). Despite a reduction in PTH and calcium, cinacalcet does not improve bone mineral density in PHPT (8). Medical treatment for osteoporosis should be started when indicated.

Retrospective evaluation of PTX in MEN1 patients reveal a very high risk of adverse outcomes (2-5). Subtotal PTX is considered the optimal surgical treatment (9). Recently, single gland excision (SGE) and less than subtotal PTX have been proposed to avoid a high risk of chronic hypoparathyroidism (2,10). Further, use of new intra-operative fluorescent techniques may improve *in vivo* evaluation of parathyroid glands and potentially also long-term outcomes.

With a common presentation of mild, asymptomatic and multi-gland PHPT in MEN1 patients, the threshold for surgery may need to be higher than in other PHPT patients due to higher risks of complications. Long-term adverse outcomes are common after PTX in MEN1 patients and must be addressed before initial surgery.

Speaker: **Heide Siggelkow**
Germany

KEY MESSAGES

- **Stable conventional medication is only reached after 3 months.**
- **Calcitriol and alfacalcidol lead to comparable hyperphosphataemia and hypercalciuria; possible differences on hypercalciuria.**
- **To change from calcitriol to alfacalcidol use 1.5 fold dose.**
- **Calcium citrate, if available and tolerated, may be advantageous.**
- **Start treatment with TransCon (palopegteriparatide) with 18µg and check calcium after 7 days.**
- **Change from hormone treatment back to conventional treatment is complicated – take your time and use higher doses of active vitamin D than before.**

How to manage a change of treatment, including guidance for patients

At the beginning of the treatment of post-surgical hypoparathyroidism, check-ups and changes in medication are common. In most cases, a stable phase is only reached after 3 months, but even then, fluctuations in calcium levels can still occur (1).

Both active vitamin D compounds, alfacalcidol and calcitriol, are common in the management of patients with hypoparathyroidism. At optimal calcium control, both alfacalcidol and calcitriol lead to comparable but high serum phosphate levels, hypercalciuria, physiological circulating 1,25(OH)2D3 (2). Other studies propose that higher doses of alfacalcidol may accumulate, and a higher risk of hypercalciuria has been demonstrated with higher doses (3).

If a change from alfacalcidol to calcitriol or vice versa is planned the half-life and differences in dosing have to be taken into account. The actual guidance suggests to use 1.5 fold doses for alfacalcidol compared to calcitriol. Alfacalcidol may be given once daily (4).

Different calcium preparations were tested and demonstrated a higher and faster resorption for calcium citrate and calcium gluconate (5).

Calcium citrate compared with calcium carbonate in a double blind, one month, crossover study in 24 adults with post-surgical chronic hypoparathyroidism, was associated with a reduction in urinary oxalate excretion that could have a potential beneficial effect on nephrolithiasis risk (6).

Hormone treatment with palopegteriparatide starts with 18 µg daily by reducing active vitamin D or calcium supplementation according to the protocol provided. Due to the long half-life of 60 hours, the first control should be after 7 days and weekly thereafter for dose adjusting. The dosage should not be reduced more than 3 µg every 3 days in response to hypercalcaemia. For the change from rhPTH1-84 to Palpegteriparatide use the starting dose of 18 µg, there seems to be no clear correlation to prior rhPTH1-84 dose yet (Siggelkow, personal communication).

Data on change from hormone treatment to active vitamin d are scarce. During follow-up, after rhPTH(1–84) treatment ended and patients returned to baseline oral calcium and active vitamin D doses, hypocalcaemia was reported as an adverse event in a higher proportion of patients in the rhPTH(1–84) group than in the placebo group (28 [31%] patients vs four [9%] patients) (7). Finishing teriparatide was partly followed by severe hypocalcaemia, and the authors concluded that bone formation exceeds bone resorption for weeks to months after hPTH 1-34 discontinuation, as the skeleton reverts from a high-turnover to a low-turnover state (8). Down-titrating of hormone treatment seems therefore advisable. The use of 2-3 times the dose of active vitamin D and calcium given before hormone treatment over weeks or possibly months is recommended (Gafni, personal communication). Frequent controls of calcium levels are important (e.g., twice the week). To date there is no experience with palopegteriparatide yet, possibly the change to conventional treatment might be easier due to the longer half-life (Gafni, personal communication)

There are some remaining questions. There will be a huge number of patients on conventional therapy. Hence, it would be of value to know if higher doses of alfacalcidol increase hypercalciuria more than equivalent doses of calcitriol. Due to the end of rhPTH1-84 production, the change to conventional therapy, teriparatide, or palopegteriparatide is of concern. First data on the change to palopegteriparatide are promising. Systematic data on change to teriparatide are missing. Another important question is the decrease of hormone treatment before or during pregnancy. Especially during pregnancy, the possible complication of sudden hypocalcaemia versus the risk of continuous treatment for the child have to be balanced.

Speaker: **Elena Tsourdi**
Germany

KEY MESSAGES

- **The development of permanent post-surgical hypoparathyroidism (HypoPT) can be assessed through measurement of parathyroid hormone (PTH) levels on day 1 postoperatively.**
- **Postoperative PTH levels do not have a substantially negative impact on quality of life, if the symptoms are managed appropriately.**
- **More prospective studies are needed investigating the clinical manifestations and management of patients with complete vs. partial post-surgical HypoPT.**

Importance of residual PTH function for management

The reported frequency of post-surgical hypoparathyroidism (HypoPT) and hypocalcaemia varies greatly. A Danish systematic review identified 89 articles that employed 20 different definitions of HypoPT, accordingly the incidence of HypoPT varied from 0.0% to 20.2% (1). Post-surgical measurement of parathyroid hormone (PTH) is necessary to assess the development of permanent HypoPT. If PTH values are >10 pg/mL (1.05 pmol/L) 12–24 hours post-surgery, the development of permanent HypoPT is unlikely (2,3).

A very recent study compared the drop in perioperative PTH to postoperative day 1 PTH in predicting hypocalcaemia and HypoPT (4). The study included 295 patients who had either total or completion thyroidectomy, with or without central neck dissection. Sixty-four (21.7%) had hypocalcaemia on the day after surgery, while HypoPT persisted in 10.5% of patients at 6 months. Both day 1 PTH and a drop in PTH predicted day 1 hypocalcaemia ($p < 0.001$) and 6-month HypoPT ($p < 0.001$) (4).

Data on clinical manifestations and management of patients with complete vs. partial post-surgical HypoPT are scarce. A retrospective, longitudinal cohort study included 33 patients with medullary thyroid cancer (5). Patients with complete HypoPT had significantly lower PTH values than patients with partial HypoPT, while both groups were characterised by similar values for serum calcium, serum phosphate, and calcium phosphate product. The mean dosage of calcium supplements was not significantly different between patients of the two groups, however, the dosages of calcitriol required to achieve serum calcium values in the targeted range were significantly higher in patients with complete HypoPT. The frequencies of tetanic symptoms and impaired well-being were similar between patients with complete and partial hypoPT (5).

Postoperative PTH levels do not have a substantially negative impact on quality of life, if the symptoms are managed appropriately, as shown in a prospective analysis of 62 patients after total thyroidectomy (6). Preoperative levels of 25(OH) vitamin D could influence parathyroid function recovery. A retrospective observational study including 397 patients reported that rates of vitamin D deficiency were higher in the early-recovery HypoPT group and behaved as a protective factor for protracted hypoPT in the multi-variable analysis (7). This finding needs to be validated in further prospective trials.

Speaker: **Line Underbjerg**
Denmark

Bone in patients with hypoparathyroidism conventionally treated and receiving rhPTH or PTH analogues

KEY MESSAGES

- **Parathyroid hormone (PTH) deficiency is associated with a profound reduction in bone remodelling (both cortical and trabecular), with increase in bone density and changes in bone microarchitecture.**
- **Treatment with PTH1-84 results in an initial increase in bone mineral density (BMD) and bone turnover markers.**
- **Fracture studies are limited. Epidemiological studies have found compatible fracture risk between patients and matched controls from the background population.**
- **BMD is not a reliable predictor of vertebral fractures.**

Parathyroid hormone (PTH) is one of the key regulators in bone remodelling. Chronic deficiency of PTH is associated with a profound reduction in bone remodelling, with increase in bone density and changes in bone microarchitecture. This effect is manifested in both trabecular and cortical bone (1).

Conventional treatment of hypoparathyroidism (HypoPT) includes active vitamin D and calcium supplements, however over the recent years new treatments have emerged, i.e., PTH1-84, palopegteriparatide, eneboparatide, and encaleret. Treatment with PTH1-84 results in an initial increase in bone mineral density (BMD) and bone turnover markers, leading to a decrease in BMD at the hip, spine and whole body (2). Phase 2 trials from palopegteriparatide, a new investigational drug, shows that changes in bone turnover markers reflect the physiological bone remodelling effects of PTH (3).

Despite a significant impact on bone remodelling, fracture studies on HypoPT are limited. Studies on bone density, architecture, and remodelling state could indicate that patients with HypoPT have very dense but old bones, with very little remodelling or the capacity to repair for instance micro cracks (4,5). Epidemiological studies on patients with either post-surgical or non-surgical HypoPT have shown identically fracture risk between patients and matched controls from the background population (6-9). Various results have been reported investigating the risk of vertebral fractures, both among post-surgical as well as non-surgical HypoPT, and studies indicate that BMD is not a reliable predictor of vertebral fractures in HypoPT (10-12).

In conclusion, PTH replacement therapy has, so far, only been sparsely used. All available studies on the risk of fracture in HypoPT are based on findings in patients on treatment with conventional therapy. Despite having a high BMD, patients with HypoPT generally do not appear to be protected from fractures and may be at increased risk of vertebral fractures.

Treating HypoPT patients with PTH has been shown to affect bone structure and strength, making it likely that the risk of fracture may also be affected. As most fractures are caused by falls, further studies should focus on whether an impaired muscle function affects risk of fractures, and how to improve muscle function in HypoPT. Moreover, skeletal parameters other than BMD need to be further investigated to define mechanisms that may protect against or predispose to fracture.

The planning of pregnancy for women with syndromic primary hyperparathyroidism

Speaker: **Luís Miguel Cardoso**
Portugal

KEY MESSAGES

- **Primary hyperparathyroidism (PHPT) is rare during pregnancy, and diagnosis is frequently missed.**
- **Multiple endocrine neoplasia types 1, 2, 4, and 5, as well as hyperparathyroidism-jaw tumour syndrome, may present or co-occur as syndromic PHPT during pregnancy.**
- **Familial hypocalciuric hypercalcaemia should be considered in the differential diagnosis, but interpreting the calcium-to-creatinine clearance ratio during pregnancy can be challenging due to absorptive hypercalciuria.**
- **Planning a pregnancy for women with syndromic PHPT requires a comprehensive and multidisciplinary approach.**

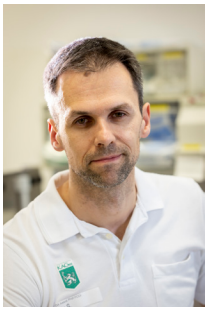
Primary hyperparathyroidism (PHPT) rarely occurs during childbearing age and the documented cases during pregnancy represent <1% of PHPT (1). A significant proportion of the cases (i.e., ~45%) remain undiagnosed during pregnancy, therefore the real prevalence of PHPT, particularly the syndromic forms in pregnancy is unknown. Approximately ~10-15% of PHPT cases have a genetic aetiology, which may present isolated or in syndromic form, e.g., multiple endocrine neoplasia (MEN) type 1, 2, 4, and 5 and hyperparathyroidism-jaw tumour syndrome (HPT-JT), caused by mutations in the genes *MEN1*, *RET*, *CDKN1B*, *MAX*, and *CCD73*, respectively (2,3). One of the primary concerns in women with syndromic PHPT who are planning pregnancy is the impact of the condition on maternal and foetal health. Uncontrolled hypercalcaemia can pose risks to both the mother (e.g., pre-eclampsia or maternal nephrolithiasis) and the developing foetus (e.g., increased rates of pregnancy loss, pre-term birth, intrauterine growth restriction, and neonatal hypocalcaemia). In addition, the syndrome-specific features may require individualised interventions before pregnancy is achieved.

In a series of eight pregnant patients with PHPT, five underwent MEN1 gene testing, and mutations were identified in two (4). Other study reported one MEN1 case out of three pregnant patients with PHPT (5). The calcium levels appear to be slightly lower than in the non-genetic counterparts, but any definite conclusion is hindered by the very low number of cases reported. However, additional features of MEN1 can pose additional challenges if they occur during pregnancy, as was the case of a patient with PHPT and Zollinger-Ellison Syndrome not treated before pregnancy (6).

HPT-JT, another form of syndromic PHPT, is rarely diagnosed during pregnancy (7,8). Patients with *CDC73* germline mutations are at increased risk for parathyroid carcinoma (9). From the two cases reported, one was treated conservatively, while the other a relapse of parathyroid carcinoma requiring surgery during pregnancy. No maternal or foetal complications were reported. However, both in MEN1 and HPT-JT patients with PHPT the definite risk of maternal and foetal complications is yet to be determined due to the very low number of cases reported (4-8).

Familial hypocalciuric hypercalcaemia (FHH) should be considered in the differential diagnosis of pregnant women with hypercalcaemia because there is no specific treatment, and parathyroidectomy will not restore calcium levels to normal. Calcium-to-creatinine clearance ratio <0.01 is suggestive of FHH, but in pregnancy, the absorptive hypercalciuria limits its interpretation (i.e., risk of false negative results). Four cases of FHH in pregnancy have been reported (10-14). No adverse maternal outcomes were reported, but one pregnant patient underwent unnecessary bilateral neck exploration and excision of three parathyroid glands (13,14). No adverse foetal outcomes were reported, but the offspring in these limited cases were genetically concordant with the mothers. In fact, neonatal outcomes will depend on the genotype: 1) unaffected neonates born to an affected mother are at risk of hypocalcaemia initially after birth because of parathyroid gland suppression in utero; 2) heterozygous neonates born to an affected mother will have mild hypercalcaemia, but no adverse outcomes; 3) heterozygous neonates born to an unaffected mother may have severe hypercalcaemia caused by secondary hyperparathyroidism in utero; 4) homozygous or compound heterozygous neonates are at risk of neonatal severe hyperparathyroidism, requiring urgent parathyroidectomy (12).

Taken all together, women with syndromic PHPT should preferentially have a pre-pregnancy appointment at a reference centre to assess the severity of PHPT and the associated syndromic features, discuss treatment options to ensure optimal calcium and vitamin D levels, and to address any other health concerns related to the specific syndrome. Genetic counselling is an essential component of the planning process, and understanding the underlying genetic cause of the condition can help women make informed decisions about potential pregnancy complications and the risk of passing the condition on to their children. Once the PHPT is under control, regular monitoring of calcium levels and individualised monitoring of syndromic features throughout pregnancy is advised. Overall, the planning of pregnancy for women with syndromic PHPT requires a comprehensive and multidisciplinary approach focused on individualised treatment and monitoring plans to improve outcomes for both themselves, and their babies.



Speaker: **Stefan Pilz**
Austria

KEY MESSAGES

- **Marked hypercalcaemia in pregnancy is rare but may cause various pregnancy complications.**
- **Adequate hydration is generally recommended for hypercalcaemia in pregnancy.**
- **Primary hyperparathyroidism in pregnancy with significant hypercalcaemia should be treated by parathyroid surgery in the second trimester.**
- **Interdisciplinary care and regular active surveillance is required for pregnant women with hypercalcaemia.**

Hypercalcaemia in pregnancy - parathyroid disorders and PTH independent causes

Hypercalcaemia in pregnancy is a rare condition but is associated with an increased risk of adverse pregnancy outcomes for the mother, foetus, and newborn, with some studies suggesting a particular risk increase at albumin-adjusted calcium concentrations above 2.85 mmol/L (11.42 mg/dL) (1-4).

Primary hyperparathyroidism (PHPT) that is characterised by increased or inappropriately high PTH concentration seems to be the main cause of hypercalcaemia in pregnancy (3-5).

Familial hypocalciuric hypercalcaemia (FHH) is caused by loss-of-function mutations of the calcium-sensing receptor (*CASR*), and it may be challenging to differentiate from PHPT due to absorptive hypercalciuria, i.e., increased postprandial and 24 hours urinary calcium excretion but normal fasting urinary calcium excretion in pregnancy (3, 6).

Hypercalcaemia in pregnancy with reduced PTH concentrations may be caused gestational hypercalcaemia (due to adaptations to pregnancy) or by various diseases and conditions, such as disorders of vitamin D metabolism (e.g. *CYP24A1* mutations causing impaired vitamin D catabolism), vitamin D intoxication, pseudohyperparathyroidism (caused by elevated PTH related peptide (PTHrP) concentrations), malignancies, granulomatous diseases (tuberculosis or sarcoidosis), milk-alkali syndrome (due to excess intake of calcium and antacid drugs), etc. that pose a diagnostic and therapeutic challenge (5-9).

Physiological changes in bone and mineral metabolism during pregnancy, such as low PTH concentrations (usually at the lower normal range or even slightly below) or two- to three-fold increased calcitriol concentrations when compared to non-pregnant women have to be considered for diagnostic investigations (3-5). Causal treatment of the underlying disease causing hypercalcaemia should, of course, be pursued, but a general recommendation for the treatment of hypercalcaemia in pregnancy is to ensure an adequate oral and/or intravenous rehydration and to avoid excessive nutritional calcium intake (2, 3).

For PHPT, observational data suggest significantly improved outcomes for women undergoing parathyroidectomy in the second trimester (2, 3, 10). Thus, several experts recommend surgery for PHPT in women with albumin adjusted calcium concentrations above 2.85 mmol/L (11.42 mg/dL) and/or ionized calcium above 1.45 mmol/L (5.81 mg/dL) (2, 3). Medical treatment of hypercalcaemia in pregnancy is limited due to insufficient safety data but may be considered for severe hypercalcaemia based on risk-benefit considerations (2, 3). Interdisciplinary care and regular active surveillance throughout pregnancy can be generally recommended for pregnant women with hypercalcaemia (2, 3).

Speaker: **Karin Amrein**
Austria

KEY MESSAGES

- **Fertility and pregnancy can be complicated by hypoparathyroidism.**
- **Calcium metabolism changes unpredictably during pregnancy and lactation.**
- **Hypo- and hypercalcaemic episodes can increase the risk of complications.**
- **Frequent monitoring is necessary.**
- **Parathyroid hormone replacement is currently off-label during pregnancy.**

How to tailor treatment of hypoparathyroidism in the weeks before and after delivery

Hypoparathyroidism (HypoPT) affects women disproportionately more (70-80%) than men (1). This is driven by postoperative HypoPT because of the underlying predominance of women with regard to thyroid disease and surgery. A substantial minority are younger women with potential topics of fertility and pregnancy. Although most pregnancies will result in a healthy child, severe hypo- or hypercalcaemia during pregnancy can lead to a phenotype similar to rickets and/or hypo-/hypercalcaemia in the newborn.

Calcium metabolism and parathyroid function are substantially altered during pregnancy and lactation (2). Case series and registry data have been published guiding treatment in these special periods (3-6). Parathyroid hormone replacement strategies are off-label but have sometimes been used during pregnancy and lactation, and the PARADIGHM registry continues to collect these data, but they have not yet been published (7,8). Therefore, primarily the use of standard therapy using calcium, active and native vitamin D, and magnesium are suggested.

A Swedish cohort study described a higher rate of pre-eclampsia, induction of labour, and a lower birth weight in 97 women and 139 pregnancies (pre-eclampsia, 5.8 vs 2.7%, $p< 0.05$; birth weight -188 g; 95% CI, -312.2 to -63.8; increased risk of labour induction; OR, 1.82; 95% CI, 1.13-2.94) compared to a control group (4).

As fluctuations in calcium levels increase the risk of foetal and maternal complications, women with HypoPT require more intensive care during this period (5, 9, 10). Patients and their gynaecologists / general practitioners should be made aware of the importance of frequent monitoring.

The following intervals for laboratory checks have been suggested:

- Calcium, magnesium and phosphate levels, and estimated glomerular filtration rate (eGFR) at least every 3-4 weeks during pregnancy (every 1-2 weeks when therapy is changed)
- Calcium levels in the baby every 2 days

In summary, the calcium dose substitution during pregnancy and lactation in women with HypoPT can vary greatly. Also, the neonate needs to be monitored closely in the first weeks of life. Every woman is different, every pregnancy is different, and the course cannot be predicted. A pregnancy with existing HypoPT can be a high-risk pregnancy for mother and child and should therefore be monitored closely and on an interdisciplinary basis to ensure the best possible outcome.

More data are needed on these topics, specifically regarding the use of parathyroid hormone replacement. Also, the fertility of HypoPT patients should be further evaluated in order to best counsel these patients on potential risks and family planning.

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