Hellenic Endocrine Society position statement:
Clinical management of Vitamin D Deficiency

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Pregnancy

- We recommend a minimum intake of 600 international units of vitamin D per day in pregnant women, either through diet and sun exposure or supplementation.

- We recommend evaluation of 25-hydroxyvitamin D concentration [25 (OH) D] during the 1\textsuperscript{st} and 2\textsuperscript{nd} trimester during pregnancy.

- 25-hydroxyvitamin D [25 (OH) D] and its interpretation should be individualized according to body weight and sun exposure.
Pregnancy

• We recommend a minimum concentration of 25 (OH) D at 20 ng/ml during pregnancy with a daily or weekly administration of 1,000-4,000 vitamin D per day.

• Supplementation targeting at >30 ng/ml reduces the risk of premature births, small for gestational age births (SGA), and wheeze in offspring (moderate quality).

• Routine supplementation during pregnancy without prior 25 (OH) D evaluation is not recommended.
Pregnancy

- The incidence of vitamin D deficiency during pregnancy varies from 20 - 84%, worldwide, according to geographical and ethnic parameters.

- The main reasons for this phenomenon are the increased needs for vitamin D during pregnancy, avoidance of sun exposure, use of sunscreen dark skin type and sartorial habits.

- Limited data from Greece indicate that vitamin D deficiency during pregnancy has a high prevalence.
Pregnancy

• In a recent Cochrane analysis, results from 477 pregnant women from 3 RCTs reported a decreased rate of premature births compared to the control group (3.3% vs. 9.9% relative risk 0.36; 95 CI 0.14 -0.93 )

• In addition, results from 493 pregnant women from 3 RCTs reported a decreased rate of SGA (<2500 g) compared to the control group (9.2% vs. 19.6% relative hazard 0.40; 95 CI 0.24 -0.67)

• Mean concentrations of 25 (OH) D achieved in the vitamin D-supplementation groups were on average >30 ng / ml
Pregnancy

• Results from 493 pregnant women from 3 RCTs reported a tendency to reduce the risk of *preeclampsia*, compared to the control group, but no statistical significance was evident (8.9% vs. 15.5.9% relative risk 0.52; 95 CI 0.25 -1.05)

• The wide heterogeneity between international and Mediterranean studies (with generally high and similar degrees of sun exposure) significantly limits the interpretation of results for other outcomes

• More studies are necessary with optimal homogenization, stratification and adjustment for confounders
**Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials**

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**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Numerous randomised trials and systematic reviews of vitamin D supplementation during pregnancy have been published, with conflicting results and conclusions. Recommendations regarding vitamin D supplementation vary widely among medical and professional organisations, and WHO currently recommends against routine prenatal vitamin D supplementation.

**WHAT THIS STUDY ADDS**

Systematic review and meta-analyses of 43 trials including 8406 participants showed that prenatal vitamin D supplementation was associated with increased maternal and cord serum 25-hydroxyvitamin D concentrations, increased mean birth weight, reduced the risk of small for gestational age, reduced the risk of wheeze in offspring, and increased infant length at one year of age. There was a lack of evidence of benefits of prenatal vitamin D supplementation for maternal health conditions related to pregnancy, no effect on other birth outcomes of public health importance such as preterm birth, and scant evidence on safety outcomes. Few of the trials were designed to test the effect of vitamin D on clinical or functional outcomes, and most trials were small and at overall high or uncertain risk of bias. Thirty-five planned or ongoing prenatal vitamin D trials could contribute an additional 12530 participants to future systematic reviews.

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**RESULTS**

43 trials (8406 participants) were eligible for meta-analyses. Median sample size was 133 participants. Vitamin D increased maternal/cord serum concentration of 25-hydroxyvitamin D, but the dose-response effect was weak. Maternal clinical outcomes were rarely ascertained or reported, but available data did not provide evidence of benefits. Overall, vitamin D increased mean birth weight of 58.33 g (95% confidence interval 18.88 g to 97.78 g; 37 comparisons) and reduced the risk of small for gestational age births (risk ratio 0.60, 95% confidence interval 0.40 to 0.90; seven comparisons), but findings were not robust in sensitivity and subgroup analyses. There was no effect on preterm birth (1.0, 0.77 to 1.30; 15 comparisons). There was strong evidence that prenatal vitamin D reduced the risk of offspring wheeze by age 3 years (0.81, 0.67 to 0.98; two comparisons). For most outcomes, meta-analyses included data from a minority of trials. Only eight of 43 trials (19%) had an overall low risk of bias. Thirty-five planned/ongoing randomised controlled trials could contribute 12530 additional participants to future reviews.
Lactation

- We recommend nursing mothers to maintain 25 (OH) D concentrations above 30 ng / ml, during lactation

- To maintain adequate concentrations of 25 (OH) D > 30 ng / ml, nursing mothers should receive at least 600 international units of vitamin D per day though regular diet, sun exposure or supplements

- These needs are likely to be higher in exclusively breastfed neonates and infants (1500-2000 international units)
Chronic kidney disease (CKD)

- We do not recommend routine vitamin D supplementation in patients with CKD (stages 3 and 4) to reduce parathyroid hormone (PTH) concentrations and cardiovascular complications.

- We recommend the measurement of 25 (OH) D in patients with CKD (stage 3 and 4) with established bone disease (osteoporosis, osteomalacia).

- In these patients, we recommend supplementation therapy with cholecalciferol and ergocalciferol to target 25 (OH) D > 30 ng / ml.
Chronic kidney disease (CKD)

- We recommend supplementation therapy with calcitriol, alfacalcidol or paracalcitol, in patients with CKD (stage 5), for the treatment of bone disease.
Chronic kidney disease (CKD)

- Previous results reported an increased prevalence of vitamin D deficiency in patients with CKD (GFR 20-60 ml / min / 1.73 m²) and patients with chronic dialysis.

- Main reasons for this phenomenon are reduced sunshine exposure, inadequate endogenous vitamin D3 synthesis in subcutaneous tissue, increased losses of 25 (OH) D due to reduction of vitamin D binding protein synthesis in patients with nephrotic syndrome.
Chronic kidney disease (CKD)

• In a recent review, vitamin D supplementation in patients with CKD (stages 3 and 4), resulted in a decrease mean PTH concentrations, but also contributed to an increase in phosphorus and calcium concentrations

• Available data in these patient groups are inadequate for possible positive outcomes with respect to the reduction of cardiovascular complications

• In Stage 5, meta-analyses of randomized studies revealed that the administration of paracalcitol is associated with a decrease in albuminuria
Obesity

- We do not recommend routine vitamin D supplementation in obesity.

- We recommend vitamin D supplementation in the coexistence of obesity with an additional clinical entity, where supplementation has a well documented benefit (pregnancy, osteoporosis, antiepileptics, corticosteroids, antiretroviral agents).

- We recommend 25 (OH) D target concentrations >30 ng/ml, as this may be individualized based on the co-existing entity, taking into account the seasonal variation of 25 (OH) D.
Obesity

- Obese patients (BMI > 30) may require a higher daily dose of vitamin D supplementation compared to normal weight patients.

- Although vitamin D deficiency has been documented in numerous epidemiological obesity studies, this observation may not always be a clinical problem as there is no evidence of impairment of bone mass.

- Vitamin D supplementation studies have reported no benefit in improving the metabolic complications of obesity.
Obesity

- Vitamin D is a fat soluble biometabolite that is distributed to fat

- Due to the increased redistribution resulting from increased fat mass, a volumetric decrease in vitamin D concentrations is hypothesized (*epiphenomenon*), without real evidence of systemic hypovitaminosis D

- Obese patients under chronic treatment with drugs that increase the catabolism of 25 (OH) D (antiepileptics, corticosteroids, antiretrovirals) have increased rates of vitamin D deficiency, resulting in a decrease of bone mass
Drugs

- We recommend routine evaluation of 25 (OH) D concentrations in patients under chronic treatment with antiepileptics, glucocorticoids, antiretroviral agents, antifungals (ketoconazole), cholestyramine.

- Patients undergoing chronic treatment with drugs that increase the catabolism of 25 (OH) D have an increased incidence of vitamin D deficiency, resulting in increased bone turnover and loss of impairment of bone microarchitecture.

- We recommend 25 (OH) D target concentrations >30 ng/ml in these patients, on an individualized basis and taking into account the seasonal variation of 25 (OH) D.
Malabsorption syndromes
(cystic fibrosis, inflammatory bowel diseases)

- We recommend routine evaluation of 25 (OH)D concentrations in patients (preferably at the end of the winter), in patients with malabsorption syndromes.

- We recommend 25 (OH) D target concentrations >30 ng / ml, in these patients, on an individualized basis and taking into account the seasonal variation of 25 (OH) D.

- The recommendation is based on the available evidence associating hypovitaminosis D with decreased bone mass and increased fracture risk in these populations.
Malabsorption syndromes
(cystic fibrosis, inflammatory bowel diseases)

• We recommend daily or weekly supplementation regimens that could vary from:

• 400-2000 international units daily (infants with cystic fibrosis and malabsorption syndromes)

• 800-4000 international units daily (children up to 10 years with cystic fibrosis and malabsorption syndromes)

• 800-4000 international units daily (children over 10 years of age and adults with cystic fibrosis and malabsorption syndromes)
Bariatric surgery

- We recommend routine evaluation of 25 (OH) D concentrations in patients undergoing bariatric surgery, before and after the procedure.

- We recommend 25 (OH) D target concentrations >30 ng / ml, in these patients, on an individualized basis and taking into account the seasonal variation of 25 (OH) D.

- We recommend supplementation with ergocalciferol (from 50000 international units 1-3 times weekly to 6000 international units daily in cases of severe malabsorption). The dosage is proposed to be individually tailored dosed in the range of 2000-6000 international units per day.

- We recommend parenteral administration of calcitriol at 3000 international units per day, in cases of symptomatic severe malabsorption.
Possible explanations for the Mediterranean paradox

• Skin pigmentation
• Lack of food fortification health policies
• Increased prevalence of obesity
• Type of clothing
• Limited sunshine exposure
• Use of sunscreens
• Dogma
Messages for clinical practice (pregnancy)

• Serum calcitriol rises early in the first trimester of pregnancy, doubling its concentration compared to non-gravid women by the end of the third trimester and returning to normal values after delivery.

• Measurement of 1,25(OH)2D is not recommended for the management of hypovitaminosis D during pregnancy.

• We commonly see pregnant women referred from OBs for high calcitriol concentrations attributed to vitamin D supplementation.
Messages for clinical practice (daily management)

- Measurement of 25(OH)D in specific indications – Increased economic burden as a result of unnecessary measurements

- Supplementation with alphacalcidiol is not recommended for hypovitaminosis D (except in cases of hypoparathyroidism, chronic renal failure-osteodystrophy)

- Referral to specialists and increase public awareness for unnecessary use

- Inform medical professionals about its appropriate use
Thank you for your attention!