

# **Association of Nutrition with ovarian reserve and timing of menopause**

---

Nazanin Moslehi

Assistant Professor

Nutrition and Endocrine Research Center

Research Institute for Endocrine Sciences

Shahid Beheshti University of Medical Sciences

*moslehinazanin@yahoo.com*

*August 29, 2024*

# Content

## 1. Introduction

- ✓ Follicles
- ✓ Ovarian aging
- ✓ Ovarian reserve
- ✓ Markers of ovarian reserve

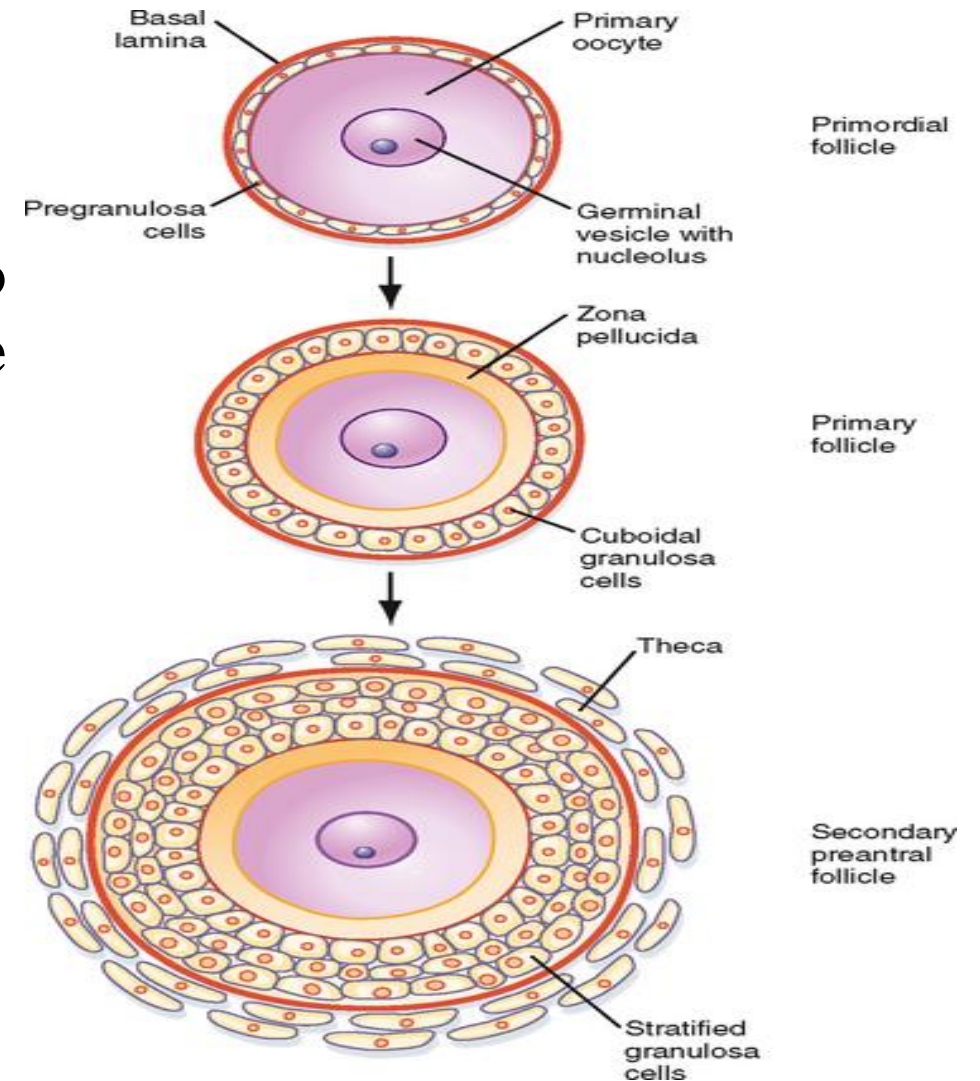
## 2. Nutrition, ovarian reserve, and menopause

- ✓ Developmental and environmental influences on ovarian reserve
- ✓ Body mass index and reproductive aging
- ✓ Antioxidants and reproductive aging
- ✓ Vitamin D and reproductive aging
- ✓ Other dietary factors and reproductive aging

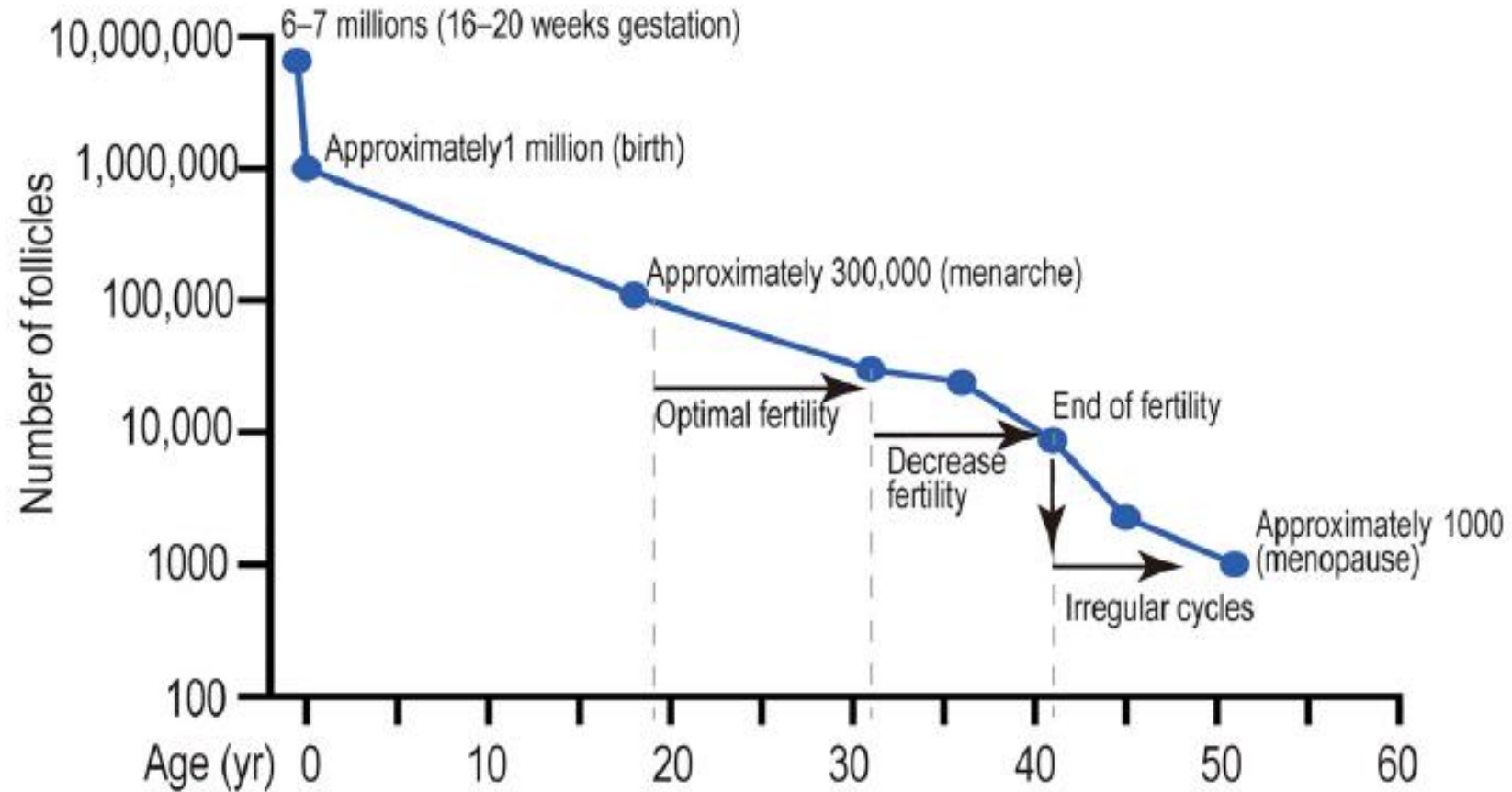
## 3. Conclusions

# Follicle

- The functional unit of the ovary is the follicle
- The ovarian follicle can be classified into different types according to the degree of **oocyte maturity** and its **histological structure**:
  - ✓ Primordial
  - ✓ Primary
  - ✓ Secondary
  - ✓ Antral
  - ✓ Pre-ovulatory



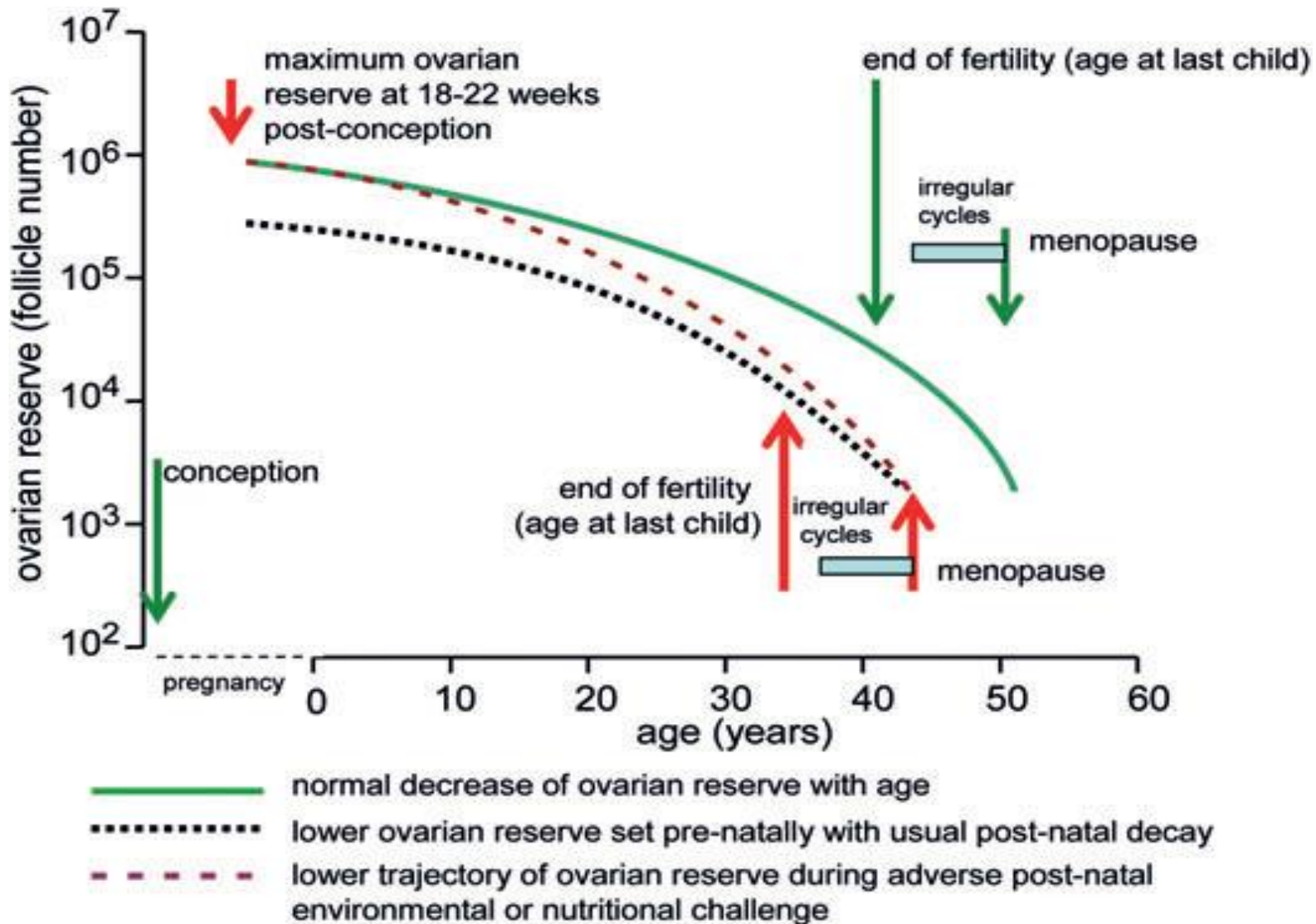
# Ovarian aging



# Ovarian reserve

- Ovarian reserve is a term used to estimate the total number of immature follicles present in the ovaries.
- Ovarian reserve can predict:
  - ✓ Risk of infertility
  - ✓ Success of assisted reproductive treatments (ARTs)
  - ✓ Age at which menopause occurs
- The ovarian follicular reserve represents a fixed, finite number
- The rate at which resting primordial follicles die or begin to develop (or both) will determine the reproductive life span of a woman.

# Variations in decline of ovarian reserve



# Oocyte quality

- ❖ In addition to the diminishing follicle reserve, oocyte quality also is declined with increasing age.
- ❖ The gradual deterioration in oocyte quality begins at least after the age of 31 years.

# Markers of ovarian reserve

Characteristics of a good marker	Age	AMH	FSH	AFC
Low intercycle variability	+++	+++	-	++
Low intracycle variability	+++	++	-	++
Applicable to all patients	+++	+++	+	+
Operator independency	+++	+++	+++	-
Prediction of poor response	+	+++	++	+++
Prediction of hyper response	+	+++	+	+++
Prediction of oocyte retrieval	++	+++	+	+++
Individualization of treatment	+	+++	-	+++
Economics	+++	-	-	-

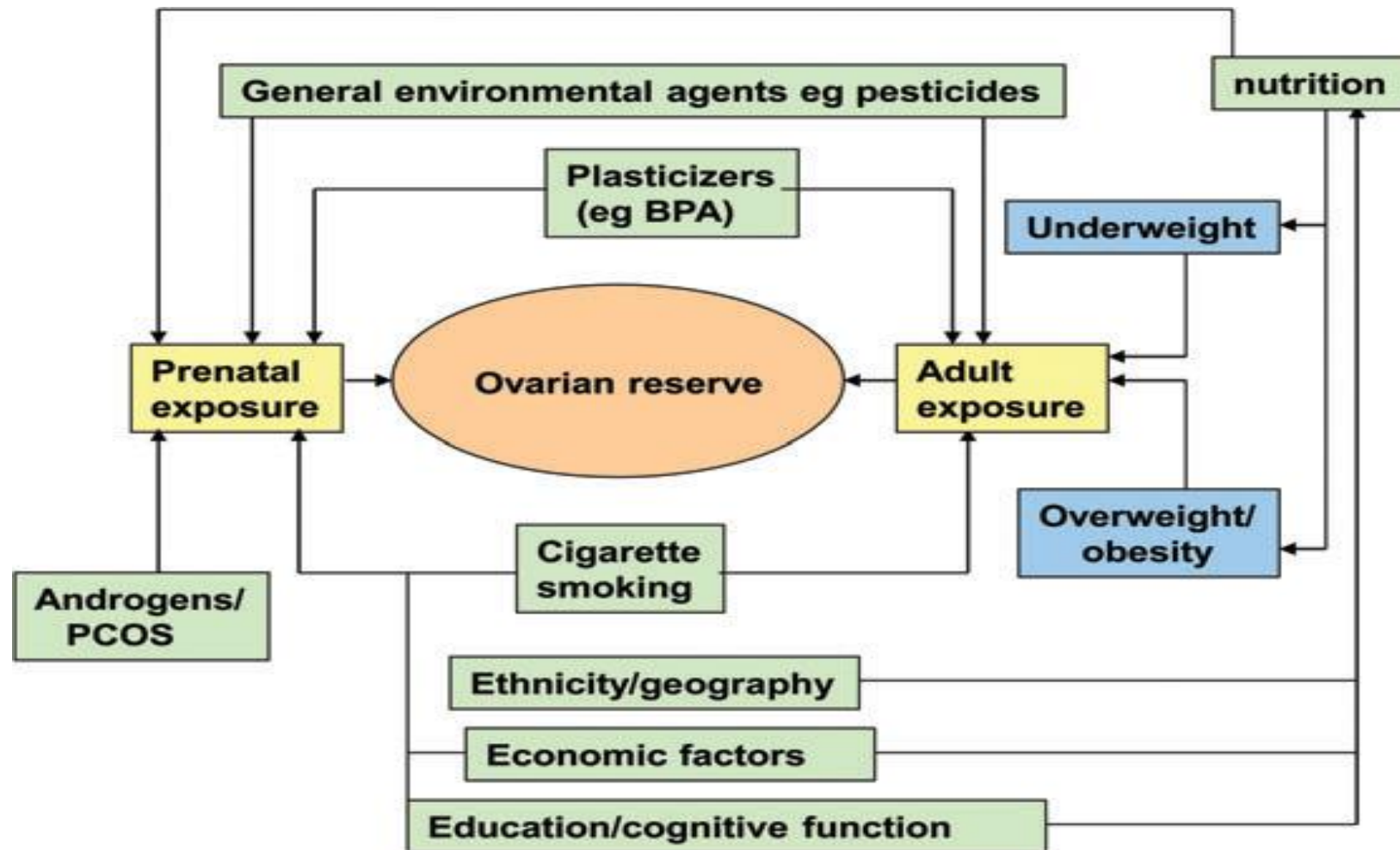
-: not appropriate, +: not very appropriate, ++: appropriate, and +++: very appropriate.



# Anti-Mullerian hormone (AMH)

- AMH is produced by the granulosa cells of growing follicles, from primary follicle to small antral follicles.
- The production of AMH commences around 36 weeks of gestation.
- Detectable serum AMH levels rise during early puberty up until they reach a plateau around the age of 20–25 years. Thereafter serum AMH levels gradually decline with advancing age, resulting in undetectable concentrations around 5 years prior to menopause.
- AMH is currently the most promising marker for predicting age at natural menopause

# Developmental and environmental influences on ovarian reserve



# Body mass index and ovarian reserve

- Obesity is known to affect human reproduction in both males and females.
- Adiposity can influence the metabolism of sex steroid hormones:
  - Androgenicity ↑ (higher expression of enzymes involving metabolism of androgens in adipose tissue)
  - Peripheral conversion of androgens to estrogens ↑ (aromatase activity of adipose tissue)
  - Availability sex steroid hormones ↑ (reducing hepatic sex hormone binding globulin synthesis in obese women)



Negative feedback effect on the hypothalamic-pituitary-gonadal axis



Arresting ovarian folliculogenesis

# Body mass index and ovarian reserve (cont.)

- Chronic inflammation caused by obesity induces ovarian oxidative stress, which affects the different stages of folliculogenesis (development, maturation, and ovulation).
- Overweight/obesity have a negative impact on ovarian function: women with a high BMI had significantly lower AMH levels and AFC than those with a normal BMI.

# Body mass index and menopause

Mata-analysis on association between BMI and early menopause (< 45 years)

Group	No. studies	Hazard ratio (95% CI)	I <sup>2</sup> (%)
<b>Compared to normal weight women</b>			
Underweight	9	1.08 (1.03, 1.14)	71
Overweight	4	0.93 (0.91, 0.96)	0
Obese	4	0.95 (0.79, 1.15)	79
<b>Compared to underweight women</b>			
Overweight	3	0.92 (0.90, 0.94)	43
Obese	3	0.88 (0.82, 0.95)	60

# Body mass index and menopause (cont.)

## Mata-analysis on association between BMI and late menopause ( $\geq 56$ years)

Group	No. studies	Hazard ratio (95% CI)	I <sup>2</sup> (%)
<b>Compared to normal weight women</b>			
Overweight	8	1.52 (1.29, 1.79)	26.8
Obese	8	1.35 (1.14, 1.60)	0

# Antioxidants and reproductive aging

- Aging is accompanied by a decline in mitochondrial mass and function in different tissues.
- Mitochondrial alterations during aging trigger increased ROS production, which, in turn, boosts mitochondrial dysfunctions.
- Antioxidants, such as resveratrol, N-acetyl-L-cysteine (NAC), melatonin and CoQ10, and vitamin E and C may prevent oxidative damage and delay ovarian aging.
- Some natural antioxidants such as quercetin and curcumin can also protect the ovaries.
- Dietary sources of quercetin: Fruits and vegetables, particularly citrus fruits, apples, onions, parsley, tea, olive oil, grapes, dark cherries, and dark berries such as blueberries, blackberries, and bilberries

# Resveratrol

- Resveratrol is a polyphenolic compound with antioxidant, anti-inflammatory, cardioprotective and anti-neoplastic properties.
- Dietary sources : grapes, peanuts, cocoa, and some berries such as strawberries and cranberries
- Resveratrol could improve fertility and quantity and quality of oocyte in experimental studies
- There is a recommendation not to use doses  $\geq 1.0$  g/day due to possible side effects: headache, dizziness, nausea, diarrhea, and liver dysfunction





# CoQ10

- CoQ10 is a natural substance present in all human cells :
  - Acting as an electron shuttle in the mitochondrial respiratory chain
  - Lipid-soluble antioxidant in cellular metabolism
- CoQ is mainly produced inside the mitochondria and then distributed to cell membranes.
- A reduction in CoQ10 biosynthesis has been linked to aging and aging-related diseases
- CoQ10 synthesis decreases in the oocyte with age, coinciding with the decline in oocyte quality and general fertility.

# CoQ10 (cont.)

- The use of CoQ10 has been described as an effective and safe strategy to postpone oocyte aging.
- Dietary sources: oily fish, organ meats, meats, nuts, dairy, whole grains, fruits
- Physical activity increases the CoQ10 levels during aging.
- Further work is needed to determine the optimal timing and dosage of CoQ10 supplementation.

# Vitamin D and reproductive aging

- Vitamin D receptor is found in reproductive organs
- The existence of vitamin D-responsive elements on the AMH gene promoter
- A meta-analysis on 20 studies: no significant correlation between serum vitamin D and AMH
- Meta-analysis on 5 interventional studies: showed no significant effect of vitamin D supplementation and AMH
- It is possible that 25(OH)D may only be associated with changes in AMH concentrations among vitamin D-deficient women.
- In one nested case-control study, total 25(OH)D and free 25(OH)D unrelated to early menopause

# Other dietary factors and reproductive aging

- Limited studies investigated the associations of soy products, different food groups, macronutrients, and micronutrients with ovarian reserve and time of menopause.
- Results of the studies provided a promising evidence on the influential role of nutrition in ovarian aging and menopause
- A limited number of studies, heterogeneous in their design and study of nutritional factors, makes it difficult to draw definite conclusions.

# Conclusion

- ✓ The progressive decline in the ovarian reserve with age is natural; however, it can be accelerated by several factors, like diet and lifestyle.
- ✓ The findings of some studies suggest modest associations of some single nutrients or food items with ovarian reserve and age at menopause.
- ✓ To better understand this issue, more studies examining the associations of dietary intakes and dietary patterns with concentrations of AMH and age at menopause are needed.

# **Nutrition and health in postmenopausal women**

---

Nazanin Moslehi

Assistant Professor

Nutrition and Endocrine Research Center

Research Institute for Endocrine Sciences

Shahid Beheshti University of Medical Sciences

*moslehinazanin@yahoo.com*

*August 29, 2024*

# Content

- ✓ Introduction
- ✓ Symptoms of menopause
- ✓ Metabolic changes of menopause
- ✓ Dietary intake and menopausal symptoms
- ✓ Benefits of Mediterranean Diet
- ✓ Isoflavones
- ✓ Nutritional interventions and menopause-related sleep disturbances
- ✓ Bone health
- ✓ Conclusions

# Introduction

- ❖ Menopause can be a challenging time for many women due to physical and psychological symptoms that may impact daily activities and quality of life.
- ❖ Menopausal symptoms can impact economic participation due to lower productivity, reduced job satisfaction and problems with time management.
- ❖ 75-80% suffer from the menopausal symptoms.
- ❖ Symptoms are more severe in 20–30% of women.



# Introduction

- ❖ Supporting women to manage their symptoms is important from a public health and economic perspective.
- ❖ Every woman's experience of the menopausal transition is unique, and management strategies should be individualized.

# Symptoms of menopause

- Hot flashes
- Night sweats
- Poor sleep
- Genitourinary symptoms/sexual dysfunction
- Psychological symptoms: Mood changes, depression, anxiety

# Metabolic changes of menopause

- Weight gain and increased risk of obesity (60-70%)
- Changes in body composition and increased risk of sarcopenia
- Reduced bone mineral density and increased risk of osteoporosis
- Impairment of insulin secretion and insulin sensitivity
- Dysregulation of lipid metabolism
- Increased release of pro-inflammatory cytokines
- Increased risk of cardiovascular diseases, type 2 diabetes, metabolic syndrome, and hormone-sensitive breast cancer

# Dietary intake and menopausal symptoms

- Dietary intake was associated with intensity of menopausal symptoms.
- Obesity and a high proportion of body fat have been associated with the symptoms.
- Obese women have exacerbated menopausal symptoms.
- High intake of processed foods, saturated fat, refined grains, fried foods, fatty meats, sweets, and sugar-sweetened have been associated with more severe **psychological symptoms, sleep disorders, vasomotor symptoms.**
- Higher consumption of vegetables, fruits, and whole grains have been associated with a lower intensity of **psychological, vasomotor, urogenital symptoms, and sleep disorders.**

# Achieving/maintaining a healthy weight

- ✓ Managing bodyweight and composition before, during and after the menopausal transition is important.
- ✓ Losing just 5 kg of weight improves the tolerability of hot flashes by 30%.
- ✓ Ideal rate of weight loss is 0.5–1 kg of body weight loss per week.
- ✓ This means 500–1000 kcal lower energy intake than requirement.
- ✓ Diets with an energy content of less than 1200 kcal/day are associated with a higher risk of micronutrient deficiency.
- ✓ Regular physical activity is essential

# Macronutrient composition

- ✓ A Balanced Nutrition should be Recommended.
- ✓ The best diet for weight loss is still debatable.
- ✓ Protein intake should be 1–1.2 g/kg body weight (20% of energy).
- ✓ Low-fat diets ( $\leq 30\%$  of energy) tend to reduce low-density lipoprotein (LDL) cholesterol levels.
- ✓ Low-carbohydrate diets ( $< 45\%$  of energy) may be more effective to low triglycerides and increase high-density lipoprotein cholesterol.
- ✓ Low-carbohydrate-high-fat diet should not be recommended in order to reduce fat mass.

# Carbohydrate quality

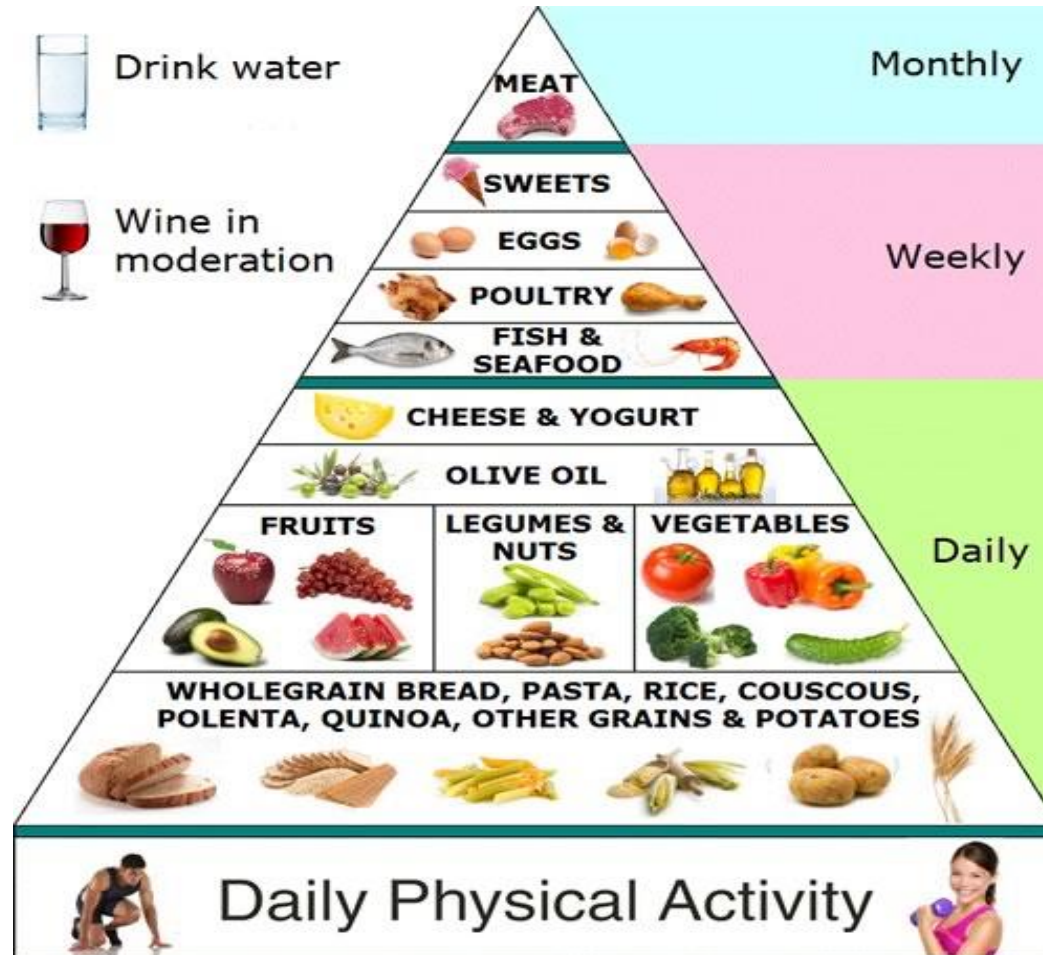
- ✓ Eating carbohydrate with low glycemic index and high fiber
- ✓ Regarding carbohydrate sources, preference should be given to vegetables, whole-grain foods, fruits, and dairy products without added sugar.
- ✓ Dietary fiber: 30–45 g/day ( whole grain, fiber-rich cereals)
- ✓ Vegetables: 300–400 g/day, 3–4 portions/day
- ✓ Fruits: 100–200 g, 1–2 portions/day
- ✓ Added sugar no more than 10% of energy (less than 5% of energy has additional benefit)

# Fat quality

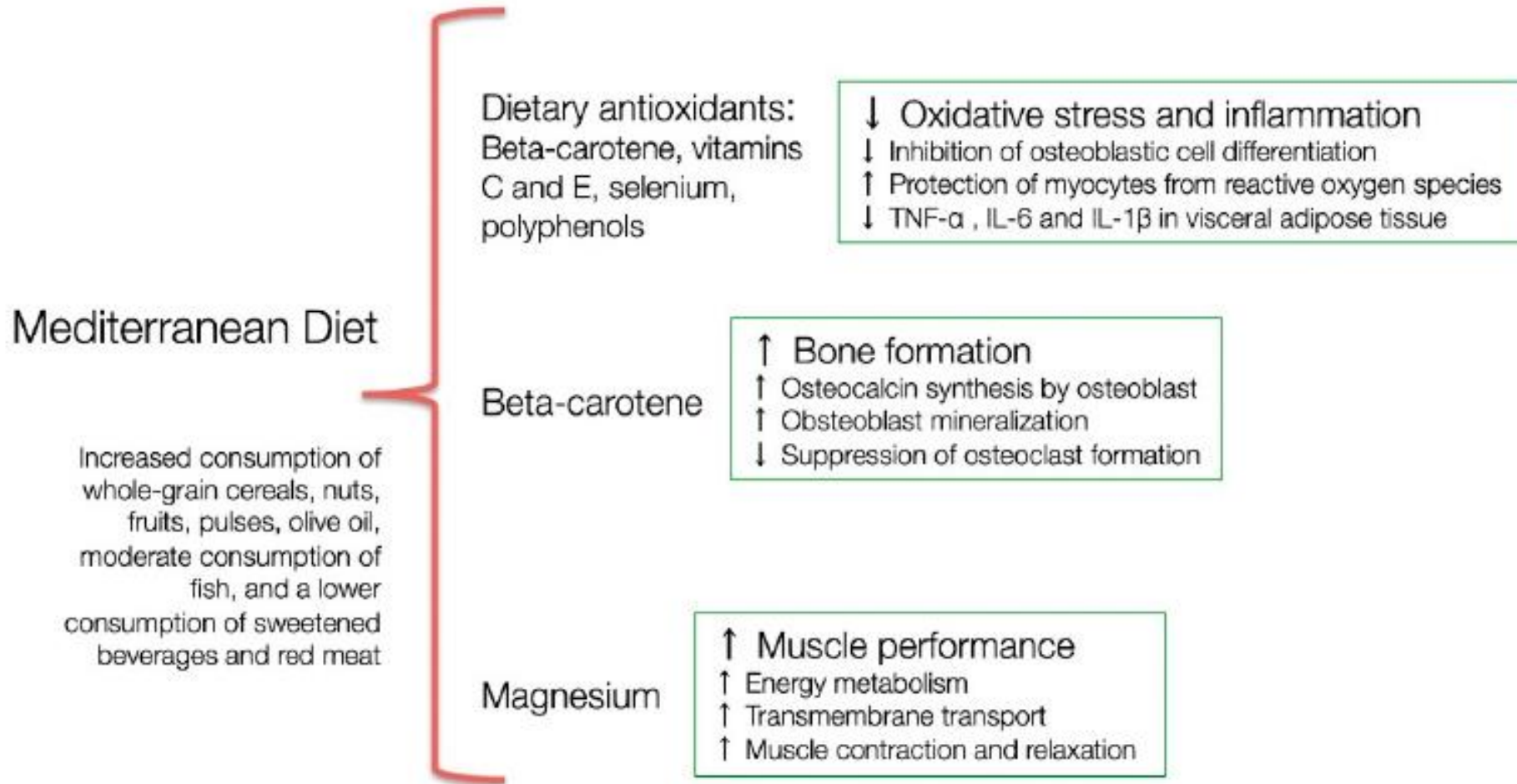
- ✓ The fatty acid composition (quality) of the diet is more important than its total amount
- ✓ SFA intake <10%
- ✓ Increased dietary intakes of omega-3 fatty acids
- ✓ Liquid vegetable oils are recommended instead of tropical oils (coconut, palm, and palm kernel), animal fats (butter and lard), and partially hydrogenated fats
- ✓ Increased intake of MUFA from olive and olive oil



# Adherence a healthy dietary pattern



# Benefits of Mediterranean Diet



# Isoflavones

- Isoflavones (phytoestrogen) found in foods including soybeans, soy foods, beans, chickpeas and lentils.
- There is some evidence that isoflavones may relieve menopausal symptoms.
- Menopausal hot flashes are rarer in countries where regular soy consumption is a part of the diet.
- One study recommended 20 mg/day of soy isoflavones supplementation during perimenopause for symptom reduction.
- It is not clear whether the effects of dietary and supplemental soy isoflavones are comparable



# Isoflavones

- A meta-analysis showed that dietary isoflavone intake has a protective effect on breast cancer risk, with a significant dose–response correlation.
- The effectiveness of anti-estrogen therapy (e.g., Tamoxifen) can be reduced by regular soy consumption.
- However, according to an Asian population-level study, consuming 10–15 g of soy protein (equivalent to 250 mL of soy drink) with a balanced diet and a healthy lifestyle can be safe even in these cases.
- It can be said that there is no consensus among the scientific community on the effect of dietary soy on breast cancer and its treatment.
- The above safe intake applies only to soy foods included in the diet and not soy isoflavones taken as dietary supplements

# Isoflavones and lipid lowering effects

- A meta-analysis on 18 studies in postmenopausal females showed :
  - Isoflavone consumption resulted in a significant reduction in triacylglycerol concentrations ( $-12.50$  mg/dL; 95% CI:  $-23.09$ ,  $-1.91$ )
  - A modest increase in HDL cholesterol concentrations ( $1.83$  mg/dL; 95% CI:  $0.03$ ,  $3.64$ ).
- Subgroup analyses showed :
  - These effects were significant in postmenopausal females  $< 65$  y
  - Both low ( $<80$  mg/d) and high ( $>80$  mg/d) doses of isoflavones exhibited TG-lowering effects, whereas only the high dose increased HDL cholesterol.
  - Longer treatment duration ( $\geq 24$  wk) was associated with a significant reduction in TG, whereas HDL cholesterol improvement occurred during the early period ( $<24$  wk) of supplementation.

# Nutritional interventions and menopause-related sleep disturbances

Intervention	No. studies	No. studies benefiting sleep
Isoflavones	8	4
Soy	5	2
Black cohosh	3	3
Melatonin	2	1
Resveratrol/trans-resveratrol	1	0
Gincosan (Ginkgo biloba and Panax ginseng)	1	0
Omega-3	1	0
Probiotic yogurt	1	0

# Isoflavones and sleep disturbances

- The most consistent finding is that isoflavone-based interventions do appear to benefit subjective sleep despite the heterogeneity in the interventions, and the relatively low number of studies,
- One study has indicated that there might be a dose–response effect upon sleep : higher dose (25 mg daily) was more effective than a lower dose (12.5 mg)



# Black cohosh

- Black cohosh is a woodland herb native to North America.
- The root is used as medicine and *is often used for estrogen-related conditions.*
- Black cohosh also appears to improve subjective and objective sleep
- Exact mechanism of action for this intervention upon sleep is not well established.
- Black cohosh can affect the neurotransmitters that modulate sleep/wake regulation, including serotonin (5-HT) and c-aminobutyric acid (GABA).
- Cautions that interactions with medications have been reported





# Bone health

- Calcium, vitamin D, vitamin K, selenium, magnesium, and beta-carotene adequate intake could be linked with better BMD in postmenopausal women (adherence to Mediterranean diet)
- 1000-1500 mg/day of dietary calcium was recommended for postmenopausal women.
- Available evidence from completed RCTs provided no support for the use of vitamin D or calcium supplementations alone to prevent fractures.
- Daily supplementation with both vitamin D (400–800 IU/day) and calcium (1000–1200 mg/day) was a more promising strategy.
- A recently published meta-analysis showed improving BMD in postmenopausal women with isoflavone intervention when the duration was  $\geq 12$  months and when the intervention contained genistein of at least 50 mg/day.

# Conclusion

To reduce symptoms and preserve health in menopausal women:

- ✓ Maintain the healthy body weight
- ✓ Adherence to a healthy dietary pattern (e.g., Mediterranean diet)
- ✓ Adequate intake of protein from plant sources ( e.g., legumes and nuts) and low-fat protein sources (e.g., poultry, low-fat dairy products)
- ✓ Moderate consumption of red and processed meats
- ✓ Increased intake of high quality carbohydrates (fruits, vegetables, and low-GI carbohydrate sources)
- ✓ Increased intake of high quality fats ( MUFA, n-3 LCPUFA and omega-3 fatty acids)
- ✓ Using as little amount of sugar and salt as possible to flavor food and drinks
- ✓ Regular physical activity