Association of Nutrition with ovarian reserve and timing of menopause

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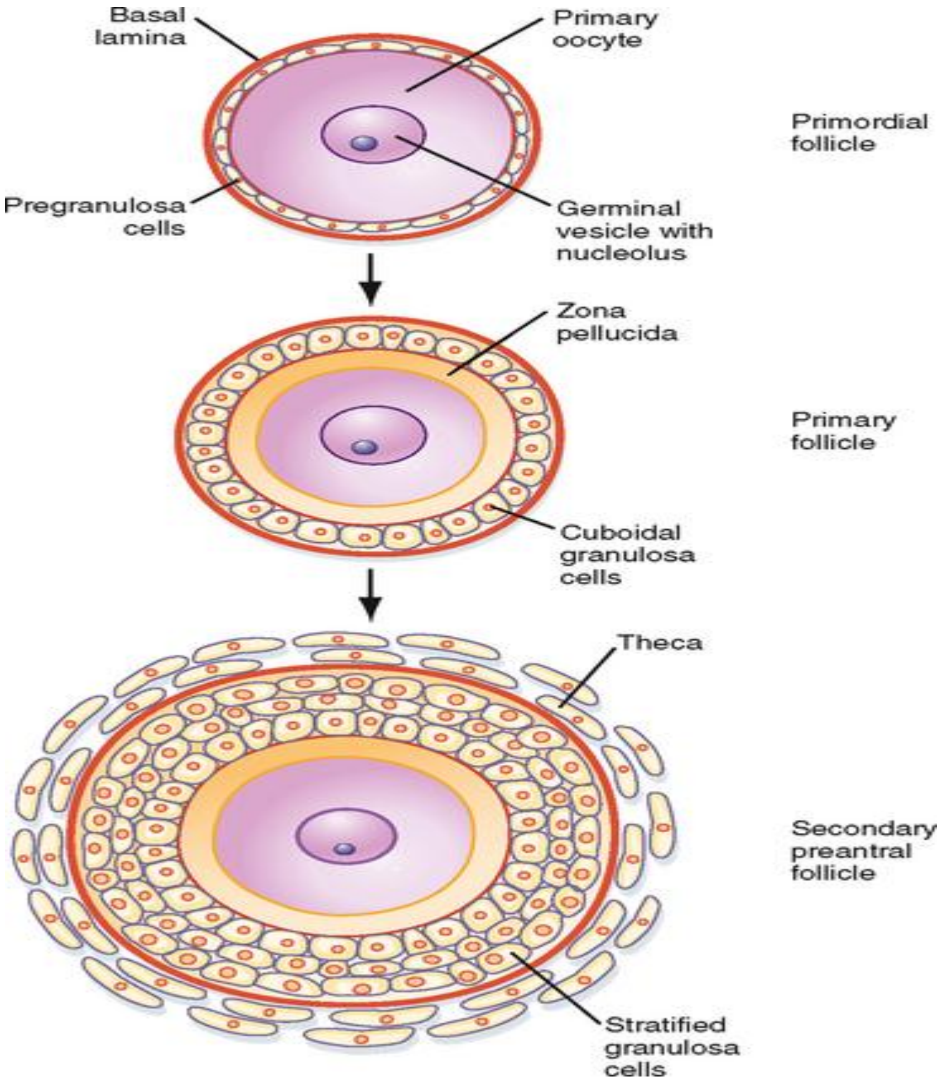
Content

Introduction

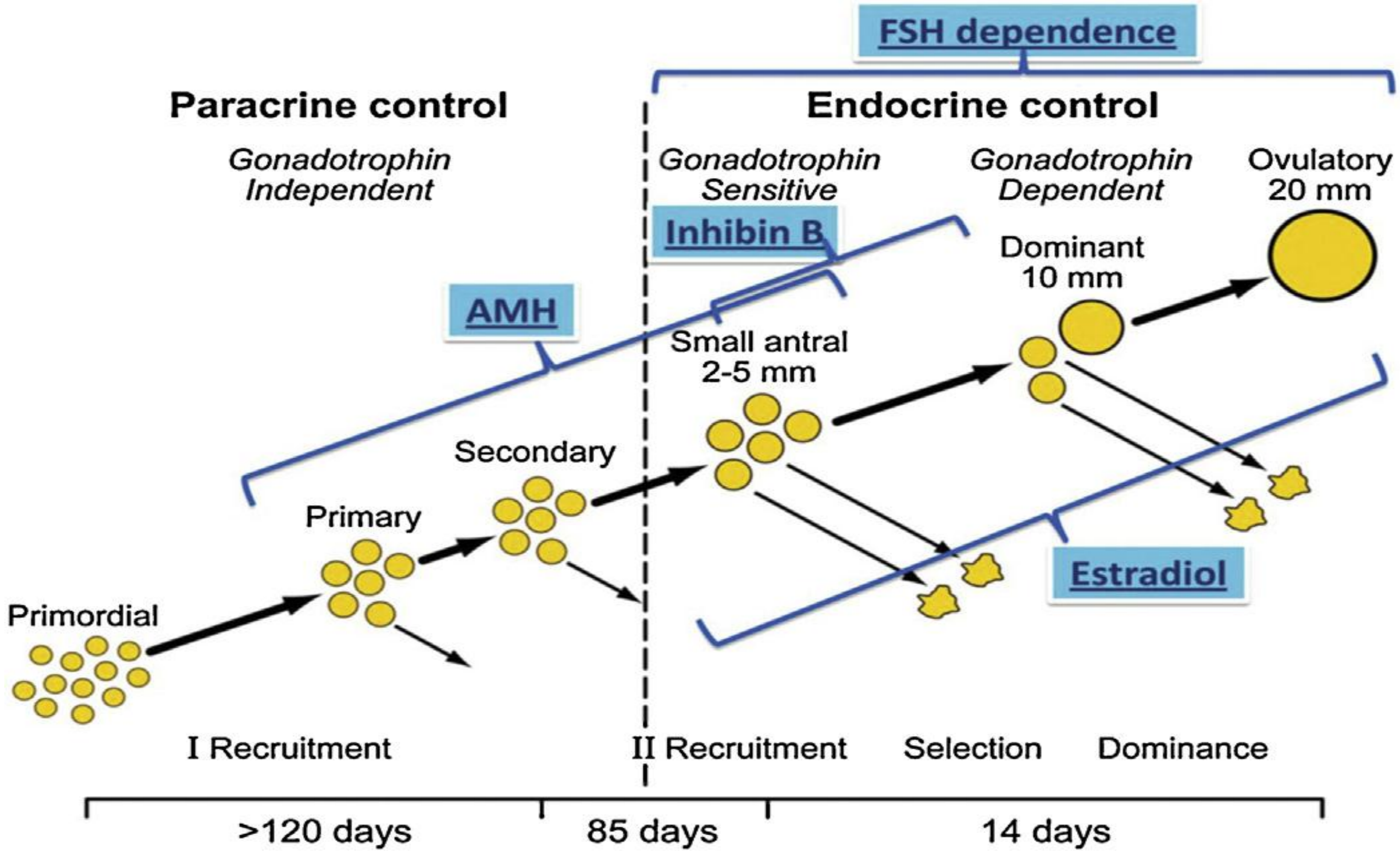
Follicle

- 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

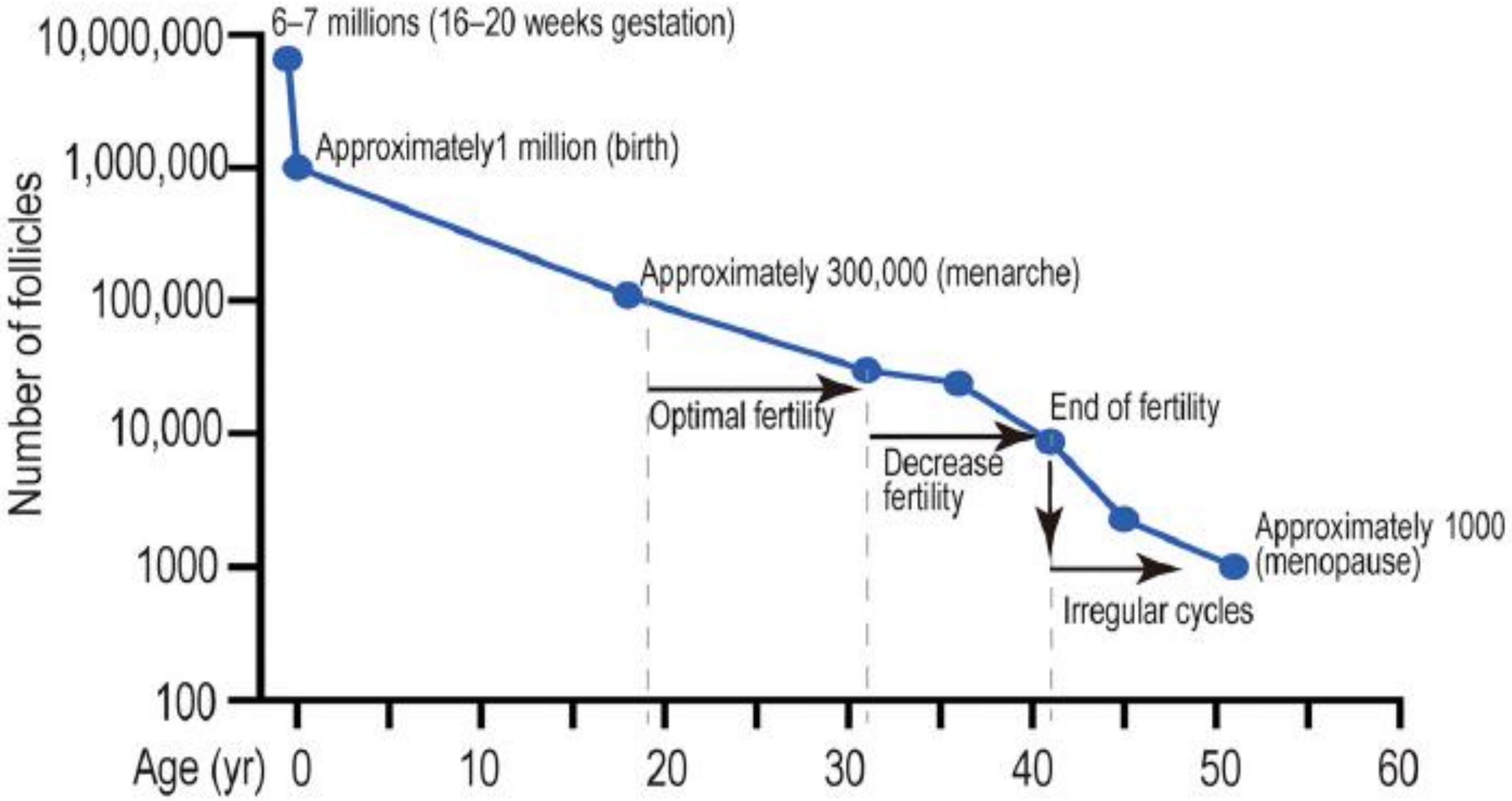


Folliculogenesis



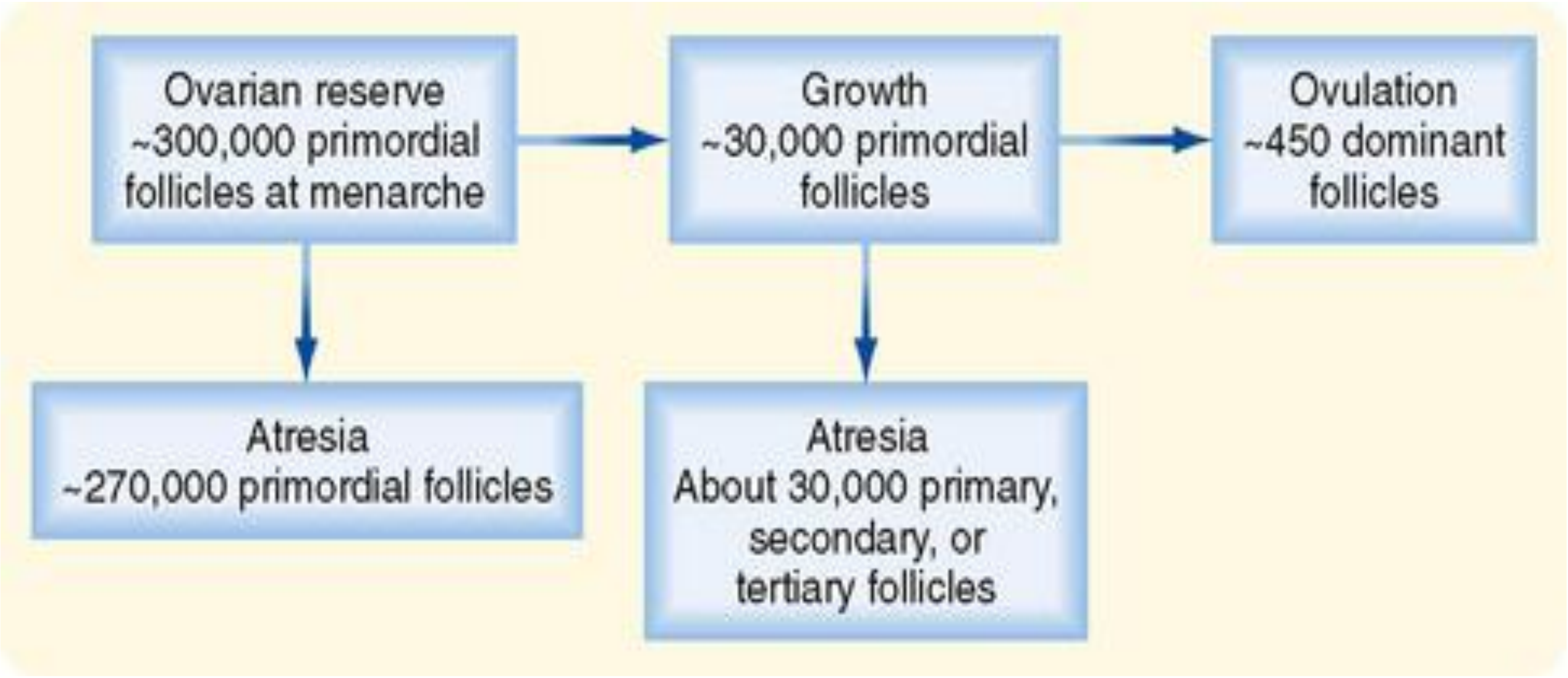
Maturitas.2015;82(3):257-65.

The dynamics of human follicular development



Med Rev. 2022; 2(6): 590–610.

The dynamics of human follicular development (cont.)



Ovarian reserve

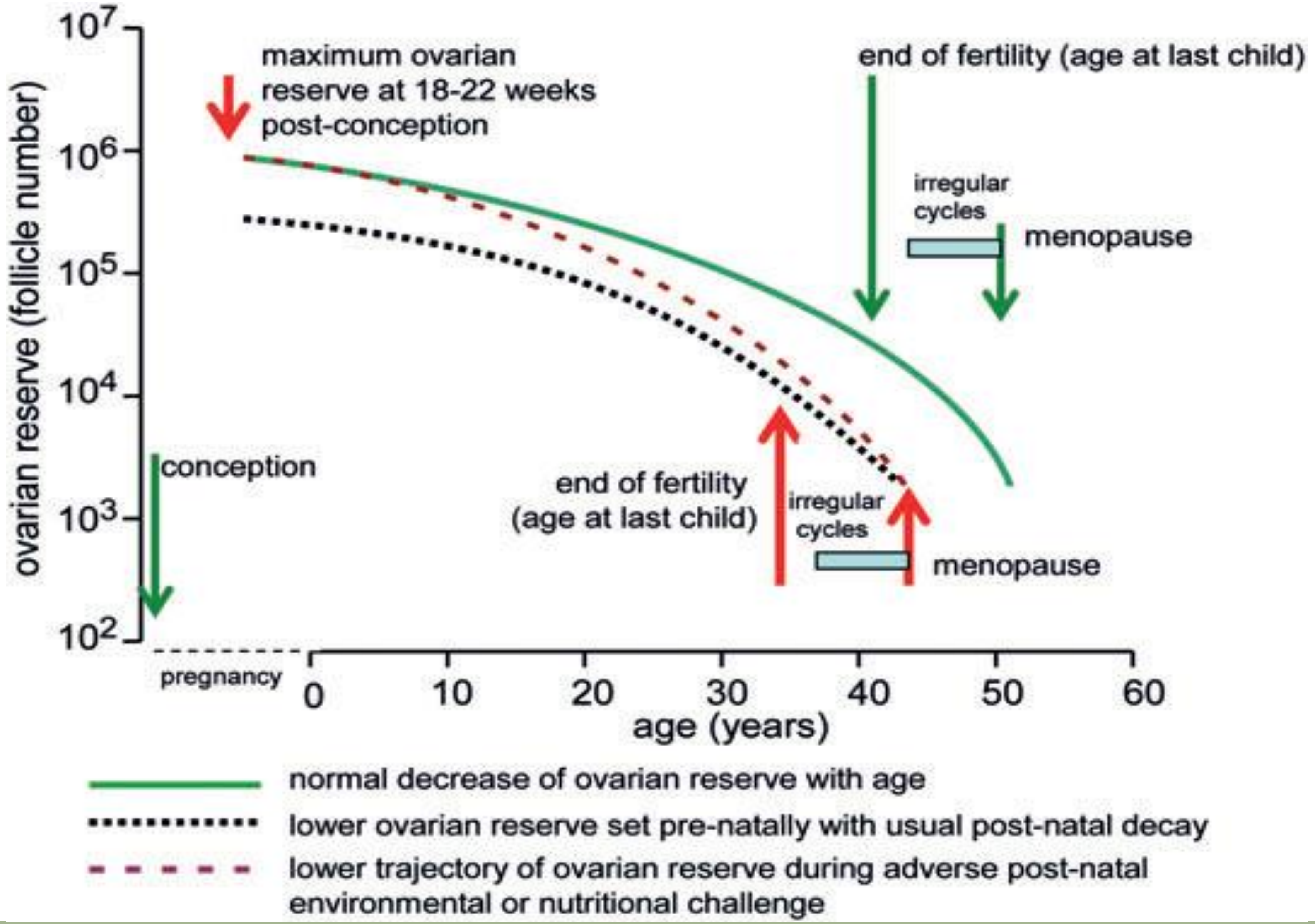
- Ovarian reserve is a term used to estimate the total number of immature follicles present in the ovaries.

- 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, <u>the rate at which resting primordial follicles die or begin to develop</u> (or both) will determine the reproductive life span of a woman.

Geroscience. 2023;45(4):2121-2133.

Variations in decline of ovarian reserve



Oocyte quality

- In addition to the diminishing follicle reserve, oocyte quality also is declined with increasing maternal age.

- The gradual deterioration in oocyte quality begins at least after the age of 31 years.

Med Rev. 2022; 2(6): 590–610.

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.

Dis Markers 2016; 2016:5246217.

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.

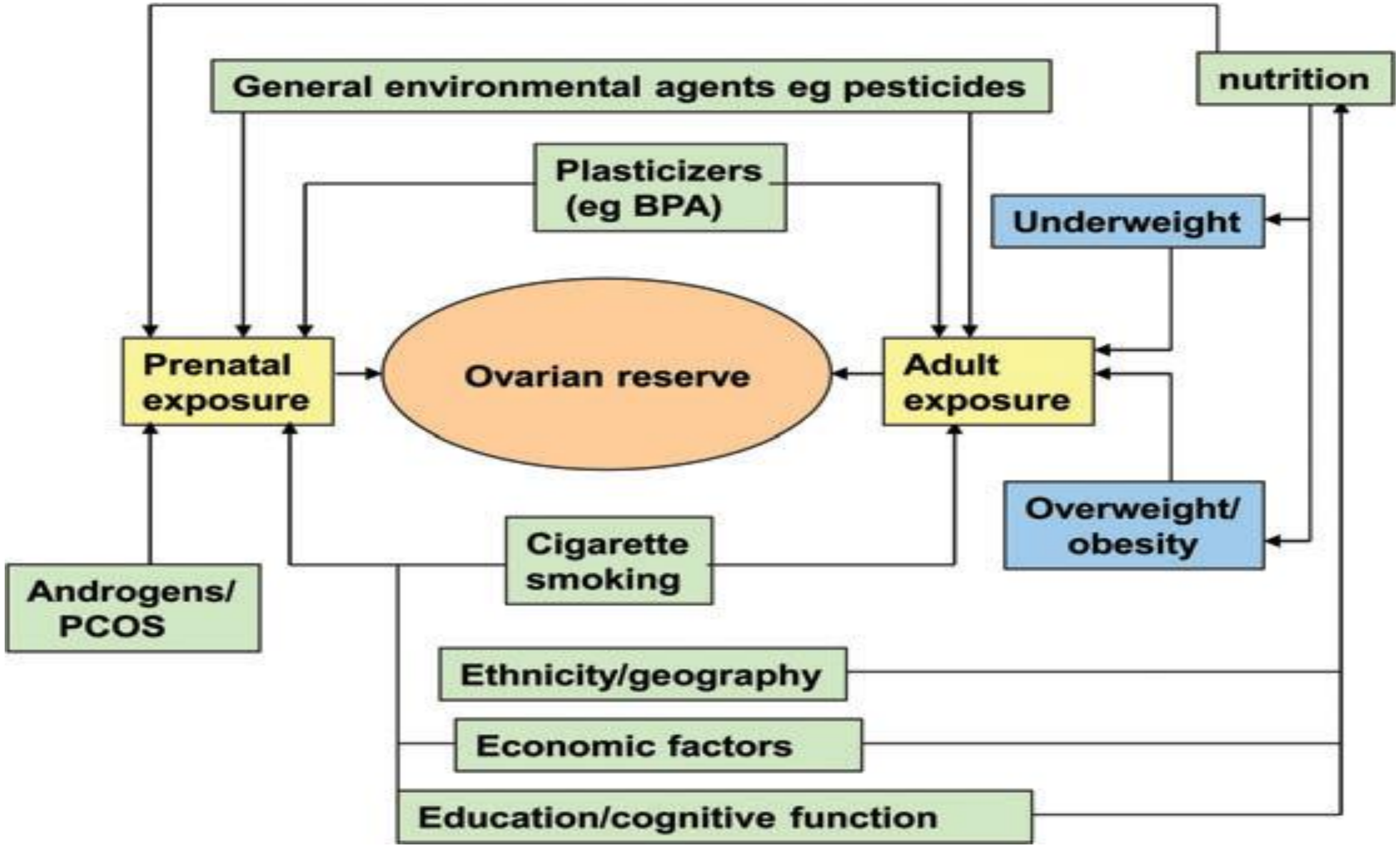
- Detectable serum AMH levels rise during early puberty up until they reach a plateau around the age of 20–25 years. Thereafter serum AMH levels gradually decline with advancing age, resulting in undetectable concentrations around 5 years prior to menopause.

- AMH is currently the most promising marker for predicting age at natural menopause

Maturitas 82 (2015) 257–265.

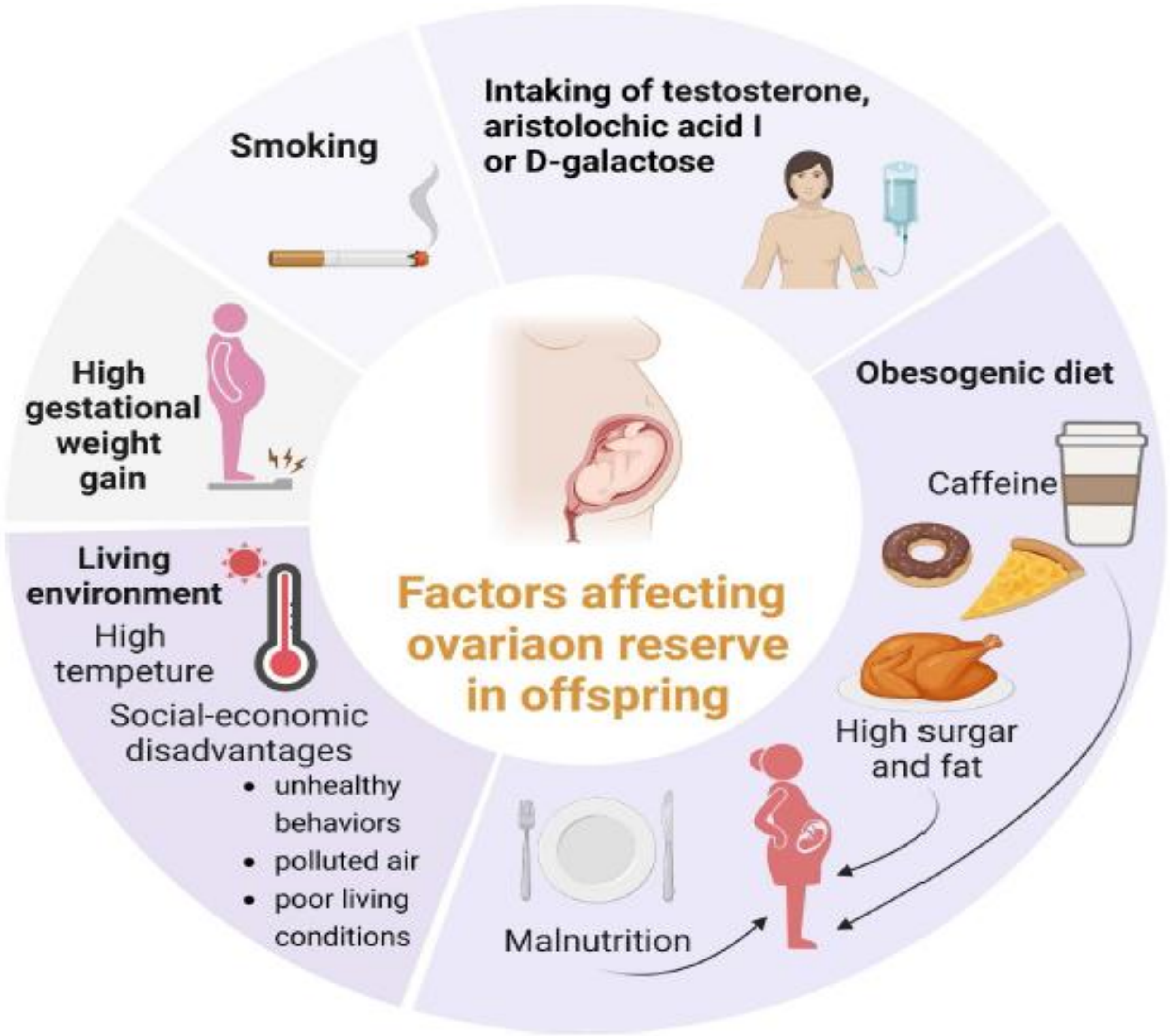
Nutrition, ovarian reserve, and menopause

Developmental and environmental influences on ovarian reserve



Maturitas 82 (2015) 257–265.

Maternal influences on ovarian reserve



J Ovarian Res. 2023;16(1):208.

Reactive oxygen species (ROS)

- ROS are the by-products of mitochondrial oxidative phosphorylation and include superoxide, hydroxyl, and hydrogen peroxide.
- ROS react with the surrounding DNA, proteins and lipids, leading to mutations and macromolecular damage.
- Under physiological conditions, the production and neutralization of ROS are balanced.
- Excessive ROS generation overwhelms the cellular anti-oxidant defenses, resulting in oxidative stress, mitochondrial and nuclear DNA damage, and premature aging of ovaries.

Med Rev. 2022; 2(6): 590–610.

Reactive oxygen species (cont.)

- Increasing evidences supports the notion that lifestyle modification to minimize OS preconception can improve female fertility.

- A healthy balanced diet and regular exercise can reduce excess OS and correlates positively with clinical pregnancy rate in in vitro fertilization (IVF).

Med Rev. 2022; 2(6): 590–610.

Antioxidants and reproductive aging

- Antioxidants, such as resveratrol, nicotinamide mononucleotide (NMN), N-acetyl-L-cysteine (NAC), melatonin and coenzyme Q10 (CoQ10), may prevent oxidative damage and delay ovarian aging.

- Some natural antioxidants such as quercetin and curcumin can also protect the ovaries.

- Fruits and vegetables are the primary dietary sources of quercetin, particularly citrus fruits, apples, onions, parsley, tea, and red wine. Olive oil, grapes, dark cherries, and dark berries such as blueberries, blackberries, and bilberries are also high in quercetin and other flavonoids.

Med Rev. 2022; 2(6): 590–610.

Resveratrol

- Resveratrol is a polyphenolic compound found in the skin of red grapes with antioxidant, anti-inflammatory, cardioprotective and anti-neoplastic properties.

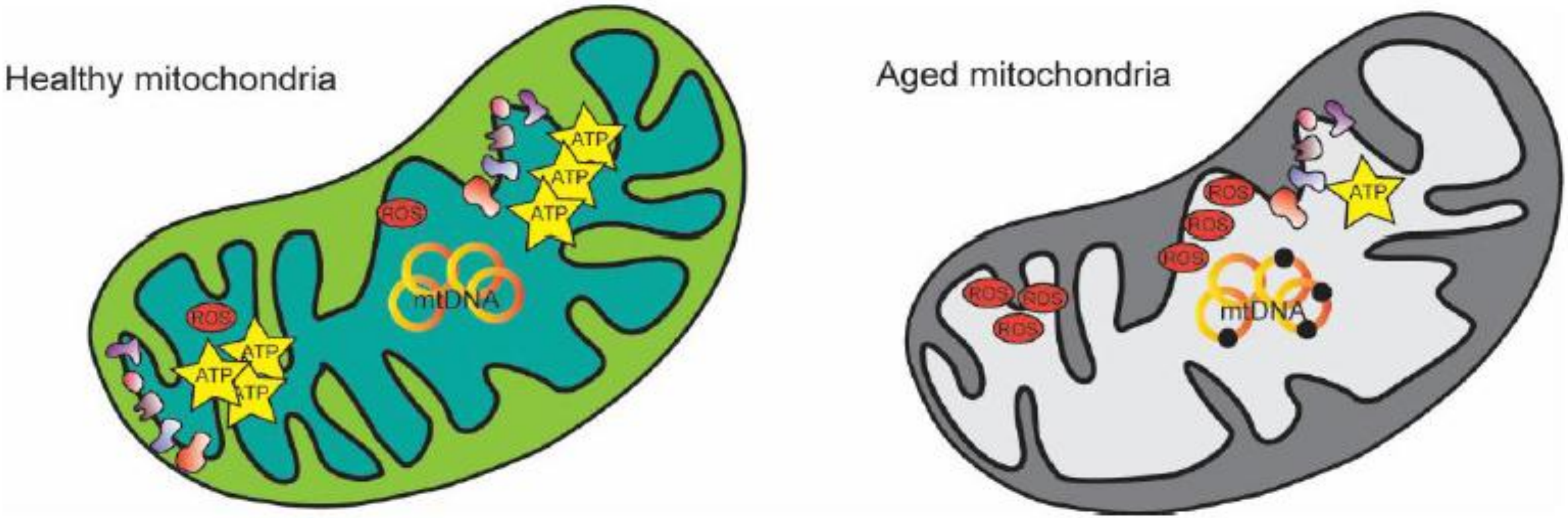
- Long-term-oral administration of resveratrol protects against the reduction of fertility with reproductive aging in mice by improving healthy follicle number, telomere length and telomerase activity, as well as oocyte quantity and quality.

Resveratrol (cont.)

- Effects of resveratrol are time and dosage dependent.
- While low dose of resveratrol promotes oocyte quality and ovarian function, the high dose leads to embryo apoptosis.
- Doses ≥ 1.0 g may produce side effects, including headache, dizziness, nausea, diarrhea, and liver dysfunction
- The optimal frequency and dosage for resveratrol treatment needs to be further explored.

Med Rev. 2022; 2(6): 590–610.

Age-related alterations in mitochondria



Nutrients 2022, 14, 4326.
Med Rev. 2022; 2(6): 590–610.

CoQ10

- Mitochondrial therapy by means of mitochondrial nutrient therapy or mitochondrial-transfer therapy to combat the stress caused by aging are among the most challenging approaches.

- CoQ10 is a natural substance present in all human cells :
    - An essential component for transporting electrons in the mitochondrial respiratory chain to produce cellular energy.
    - Lipid-soluble antioxidant in cellular metabolism via inhibition of lipid peroxidation, protein, and DNA oxidation.

- CoQ10 synthesis decreases in the oocyte with age, coinciding with the decline in oocyte quality and general fertility.

CoQ10 (cont.)

- CoQ10 supplementation in an aged animal model delayed depletion of ovarian reserve, restored oocyte mitochondrial gene expression, and improved mitochondrial activity.

- The use of CoQ10 has been described as an effective and safe strategy to postpone oocyte aging.

- Further work is needed to determine the overall effect of CoQ10 on pregnancy complications and live birth rates as well as the optimal timing and dosage of supplementation.

- Dietary sources: oily fish, organ meats, meats, nuts, dairy, whole grains, fruits

Vitam Horm. 2023;121:143-167.
Med Rev. 2022; 2(6): 590–610.

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

Menopause. 2018;25(9):1046-1055.

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).

- Obesity may also affect follicular function.

- The possible apoptotic effect of obesity on granulosa cells (the origin of AMH production) can reduce AMH production per follicle.

- In addition, this apoptotic effect may induce atresia of ovarian follicles, and therefore reduce ovarian reserve.

Menopause. 2018;25(9):1046-1055.

Mean differences in hormones concentrations of obese versus non-obese women

Groups	No. of studies	No. of obese/non-obese	Weighted mean difference (95% CI)	Heterogeneity between groups
AMH (ng/mL)				P<0.001
Fertile non-PCOS	7	211/233	**-0.94 (-1.14, -0.73)**	
Infertile	3	213/195	-0.24 (-0.71, 0.24)	
PCOS	6	346/366	**-1.95 (-3.17, -0.72)**	
Overall	16	770/794	**-1.08 (-1.52, -0.63)**	
FSH (mIU/mL)				P= 0.004
Fertile non-PCOS	9	305/484	-0.02 (-0.33, 0.29)	
Infertile	3	314/371	0.14 (-0.20, 0.48)	
PCOS	16	2071/2062	**-0.35 (-0.55, -0.16)**	
Overall	28	2690/2917	**-0.22 (-0.39, -0.06)**	
AFC				P = 0.003
Fertile non-PCOS	3	156/198	-0.14 (-1.02, 0.73)	
Infertile	1	90/93	-0.72 (-1.44, 0.00)	
PCOS	6	727/851	0.28 (-0.22, 0.87)	
Overall	10	973/1142	-0.09 (-0.60, 0.42)	

Menopause. 2018;25(9):1046-1055.

Body mass index and ovarian reserve (cont.)

- Meta-analysis of correlation coefficients showed a negative correlation between BMI and AMH in all the studies including 12,160 individuals (Fisher's Z = -0.15; 95% CI = -0.20, -0.11).

- This negative correlation was significant in all the study subgroups, with no significant heterogeneity between the groups.

- BMI and FSH correlated negatively in fertile non-PCOS women (Fisher's Z = -0.16; 95% CI = -0.28, -0.04).

- Meta-analysis of correlation coefficients (five studies involving 527 individuals) showed no significant correlation between BMI and AFC.

Menopause. 2018;25(9):1046-1055.

Body mass index and menopause

- If obesity affects ovarian reserve, it can be expected that in women with high BMI, menopause occurs earlier.
- Evidence on the relationship between BMI and age at menopause has been inconsistent.
- High BMI has been linked to both later, and earlier menopause whilst some studies have found no association.
- Low BMI has been related to early menopause, but some studies report no significant relationship.

Best Pract Res Clin Obstet Gynaecol. 2015;29:548-553.
Menopause. 2015;22(4):469-74.
European Journal of Epidemiology. 2018; 33:699–710.

Body mass index and menopause (cont.)

- A study investigated the relationship between BMI and age at menopause using data from 11 prospective studies.

- A total of 24,196 women who experienced menopause after recruitment was included.

- Compared with normal weight women, underweight women had more than twice the risk of experiencing early menopause (< 45 years).

- Overweight and obese women are 50% more likely to have late menopause (≥56 years)

European Journal of Epidemiology. 2018; 33:699–710.

Body mass index and ovarian reserve

According to the current evidence, the association between BMI and ovarian reserve markers seems to be through physiological processes or follicular function rather than reducing ovarian reserve.

Vitamin D and ovarian reserve

- Two studies assessed serum AMH and 25(OH)D concentrations in different seasons:
  - One reported a significant reduction in AMH concentrations during winter that could have been prevented by vitamin D3 supplementation. This study suggested the vitamin D supplementation during the seasons prevented a decline in AMH.
  - The other found no seasonal variation in AMH concentrations, despite a high decline in serum 25(OH)D during the winter.
- A small trial also suggested an increase in AMH concentrations following vitamin D supplementation in women with vitamin D deficiency.

J Clin Endocrinol Metab 2012;97:2450–5.
Hum Reprod 2015;30:2171–7.
Gynecol Endocrinol 2017;35:409–12.

Vitamin D and ovarian reserve (cont.)

- A cross-sectional study in US women reported a significant 1.1% higher log-transformed AMH for each 1-ng/mL higher 25(OH)D concentration among 388 women aged ≥40 y, but no association among younger women.
- Other observational studies could not find any significant association between 25(OH)D and AMH.
- A meta-analysis study suggested no association of 25(OH)D with any ovarian reserve markers of AFC, AMH, and FSH.
- It is possible that 25(OH)D may only be associated with changes in AMH concentrations among vitamin D–deficient women.

Fertil Steril. 2012;98:228–34.
Sci Rep. 2021;11:16005.

Soy products and ovarian reserve

- Isoflavones are non-steroid phytochemicals primarily found in soy and to a lesser extent in other legumes.

- Isoflavones share structural and functional similarities with endogenous estrogens and are therefore often referred to as phytoestrogens.

- Phytoestrogens have a weak interaction with estrogen receptors.

- A meta-analysis summarizing 7 randomized trials of soy or isoflavone supplementation revealed that short-term soy or isoflavone supplementation reduced follicle-stimulating hormone (FSH) by approximately 20% in premenopausal women.

Human Reproduction Update. 2009:15: 423–440.

Soy products and ovarian reserve (cont.)

- A cross-sectional study investigate the association of soy products and ovarian reserve (AFC, FSH, and AMH)
  - ✓ Intake of 15 soy-based foods during the previous 3 months
  - ✓ Participants were divided into 5 groups based on soy food and isoflavone intake considering those who did not consume soy as the reference group.
- No association between soy food intake with AFC or day 3 FSH level
- Participants in the highest category of soy food intake had significantly low AMH levels (-1.16 ng/ml, 95% confidence interval: -1.92, -0.41) compared to those who did not consume soy.
- The results of this study are not consistent with a strong positive or inverse association of soy or isoflavone intakes within the observed range of intake.

Fertil Steril. 2023 Jun;119(6):1017-1029.

Dietary factors and menopause

1- Early menopause

Two prospective studies using the NHS2 (1991- 2011) examined the association of dietary protein and dairy food and risk of early menopause (<45 years)

Dietary factor	Association
Vegetable protein (% of energy)	↓ (6% lower each 1% increase)
Animal protein (% of energy)	↔
Total protein (% of energy)	↔
Pasta	↓ (36 % lower each one serving/day increase)
Dark bread	↓ (7 % lower each one serving/day increase)
Cereal	↓ (18 % lower each one serving/day increase)
Red meat	↑ (12% higher each one serving/day increase)
All meat, processed meat, chicken, seafood, egg, soy, nuts, beans, eggs, and peanut butter	↔

Am J Epidemiol. 2018;187(2):270–277.
Am J Epidemiol. 2019;188(1):188–196.

Dietary factors and early menopause

Dietary factors	Association
Total dairy ≥ 4 servings/day vs. ≤ 4 servings/week	23 % ↓
Low fat dairy ≥ 2 servings/day vs. <3 servings/month Per one serving increase/day	 17% ↓ 5% ↓
High fat dairy	↔

Am J Epidemiol. 2019;188(1):188–196.

Vitamin D and early menopause

- One nested case-control in NHS2
- Cases experienced menopause between blood collection and age 45 y (*n* = 328) and were matched 1:1 by age and other factors to controls who experienced menopause after age 48 y (*n* = 328).
- Total 25(OH)D and free 25(OH)D unrelated to early menopause after adjusting for smoking and other factors

J Nutr. 2018;148:1445–1452.

Dietary factors and menopause

2- Menopause onset

Food groups	Findings (# studies)
Dairy	NS (1) Low fat dairy and skim milk associated with delay menopause in women aged <51 years (1)
Meats	NS (2) Delayed onest menopause (1)
Vegetables	NS (2) Higher vegetables related to younger age at menopause (1)
Green & yellow vegetables	Lower 6–years menopause incidence
Fruits	NS (1) Later menopause (1)
Soy products	NS (4)
Alcohol	NS (3) Later age at menopause (2)

Adv Nutr 2017;8:597–612.
Maturitas 159 (2022) 15–32.

Conclusion

Conclusion

- ✓ The progressive decline in the ovarian reserve with age is natural; however, it can be accelerated by several factors, like diet and lifestyle.
- ✓ There is an insufficient number of studies examining the associations of nutritional factors and ovarian reserve, especially measuring AMH as a marker, and timing of menopause.
- ✓ 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.