

Nutrition and Supplements - Helpful or Harmful

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- Co-Author- Getting to Baby A Food First Fertility Plan to Improve Your Odds and Shorten Your Time to Pregnancy (2024)

Disclosures

Nothing to Disclose

Objectives

1. Discuss potential benefits of commonly used dietary supplements for fertility patients.
2. Review research describing food sources of nutrients vs supplements.
3. Offer strategies to guide patients in selecting high-quality, evidence-based supplements that complement their nutritional needs and fertility goals.



Nutrition: Food First

Is there a best eating plan for fertility?

- Low carbohydrate? High protein?
- Ketogenic diet?
- Whole 30? Ideal protein?
- Avoid gluten, soy, dairy?

Food delivers most of our micro and macronutrients.

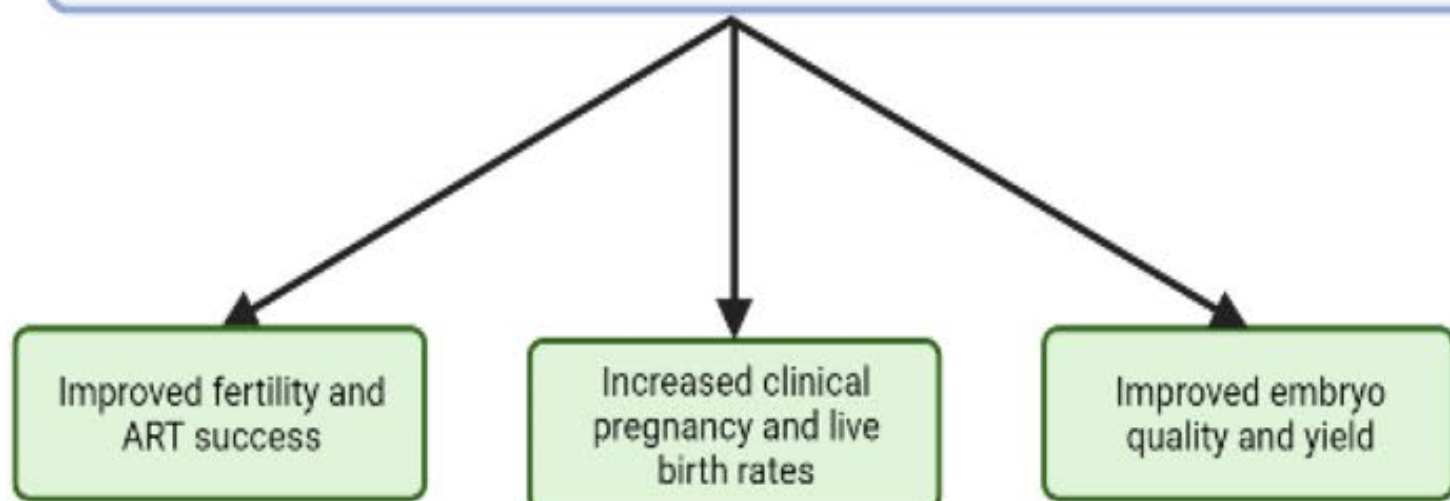
Anti-inflammatory diet

Flavonoids and biologically active polyphenolic compounds

Carotenoids

Biologically active n-3 PUFAs, EPA, and DHA

Reduced inflammation



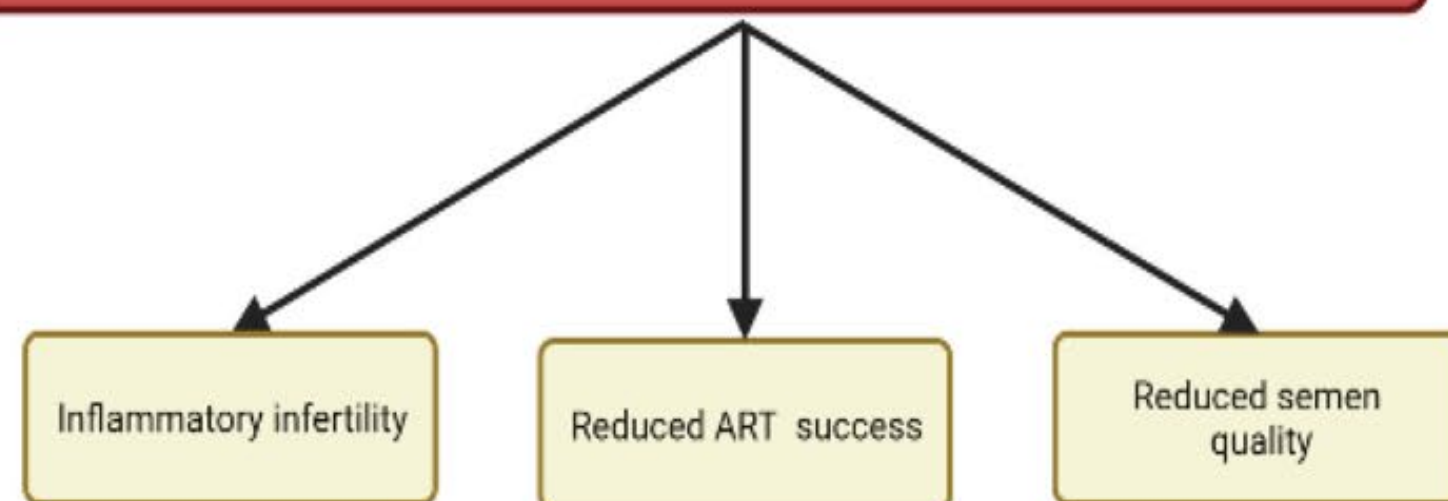
Western diet

Saturated fat

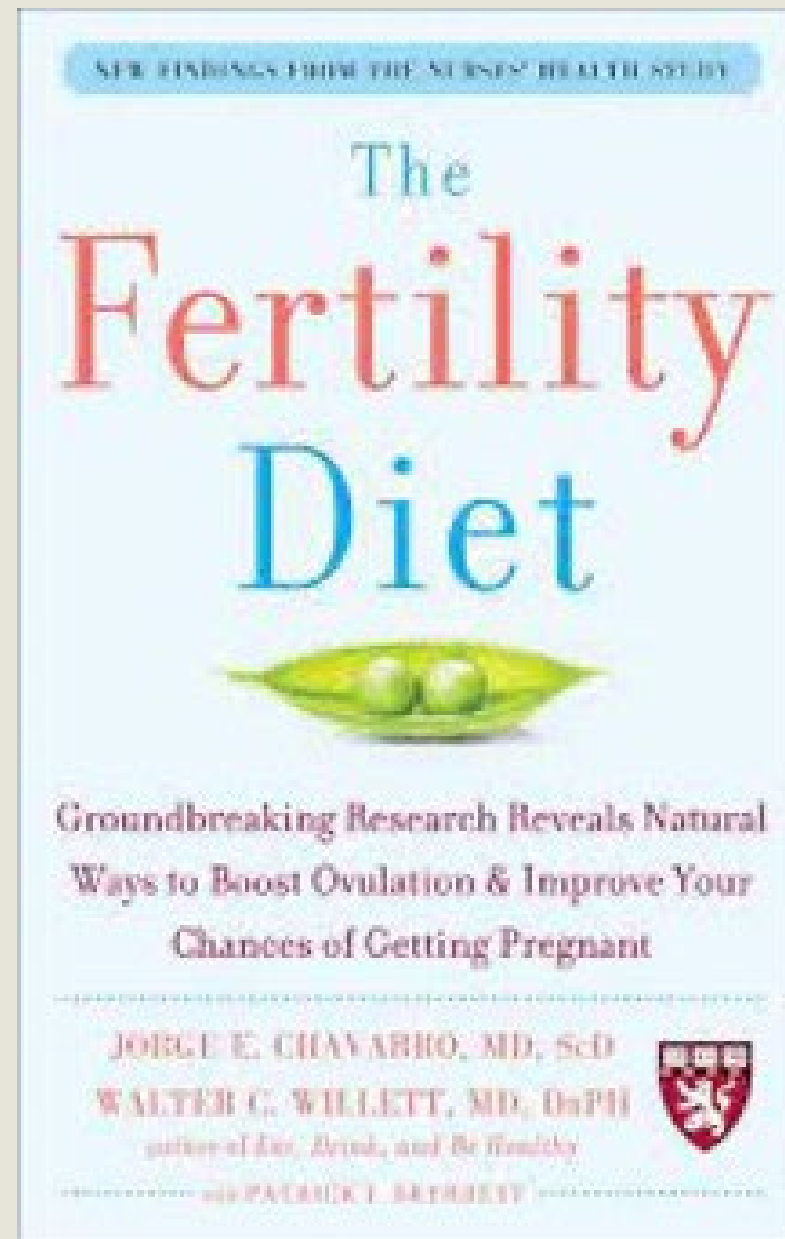
Refined carbohydrates

Processed meat

Increased inflammation



Fertility nutrition research



- The Nurses' Health Study, Part II (1989)
- 17,500 women were trying to conceive completed health surveys about lifestyle and pregnancy.
- “Fertility Diet” may improve fertility success in otherwise healthy women.

Can diet improve IVF outcomes?

Am J Obstet Gynecol. 2019 Jun;220(6):567.e1-567.e18. doi: 10.1016/j.ajog.2019.02.004.
Epub 2019 Feb 8.

Dietary patterns and outcomes of assisted reproduction

Audrey J Gaskins¹, Feiby L Nassan², Yu-Han Chiu³, Mariel Arvizu³, Paige L Williams⁴, Myra G Keller⁵, Irene Souter⁶, Russ Hauser⁷, Jorge E Chavarro⁸, EARTH Study Team

Affiliations + expand

PMID: 30742825 PMCID: PMC6545142 DOI: 10.1016/j.ajog.2019.02.004

- 357 women in the EARTH Study and evaluated their diet
- Pro-fertility diet
- Mediterranean diet pattern
- Original fertility diet
- Alternate Healthy Eating Index 2010

Earth Study Findings: Pro fertility diet

- Supplement Vitamin D*
- Supplement Vitamin B12*
- Folic acid 800-1000 mcg daily
- Consume fish rather than other sources of animal protein.
- Diets rich in whole grains, seafood, dairy and soy.

*if deficiency exists



Dietary Patterns and Fertility

- Mediterranean
- Dutch
- Profertility
- Dietary Guidelines for Americans



Nutrition Foundation:

- minimally processed fruits and vegetables, whole grains, legumes, nuts, fish
- Monounsaturated fats
- rich in B-vitamins, antioxidants, omega-3 PUFAs, and dietary fiber and low in saturated fat and sugar

Plant Based Diet Patterns Associated with Positive Pregnancy Outcomes

The Effect of Dietary Patterns on Clinical Pregnancy and Live Birth Outcomes in Men and Women Receiving Assisted Reproductive Technologies: A Systematic Review and Meta-Analysis

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Plant Forward Diet Patterns



Reduce inflammation

Promote uterine environment and
implantation

Low glycemic to reduce inflammation and
insulin resistance

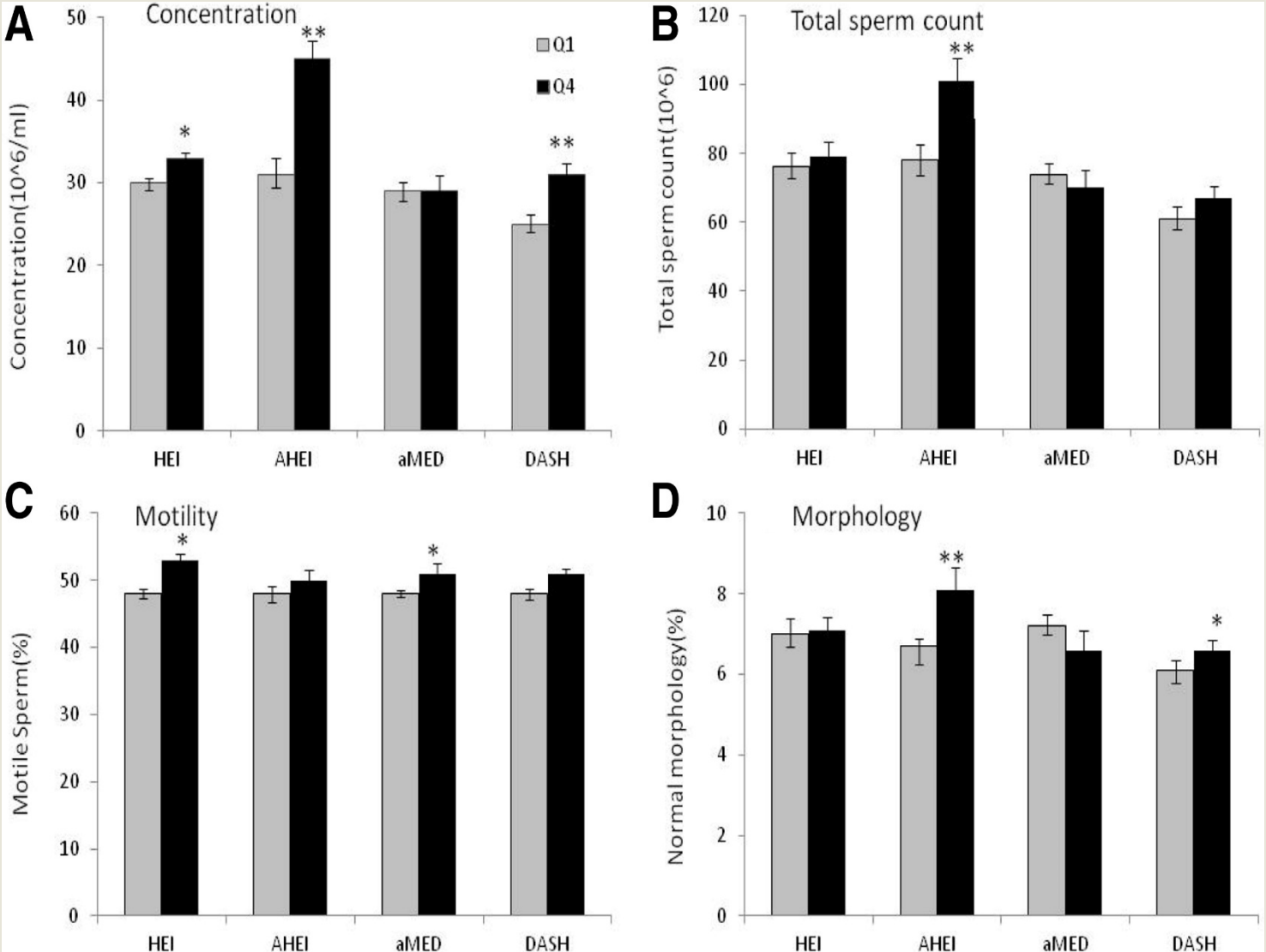
Rich in antioxidants to strengthen sperm and
egg function.

Male Diet Patterns

Component	HEI†	Alternate HEI‡	Mediterranean§
Dairy products	↑	–	↓
Vegetables	↑	↑ (no potatoes)	↑
Fruit	↑	↑	↑
Nuts, seeds	↑ (w/ meat)	↑	↑ (w/ fruit)
Bread/grains	↑	↑ cereal fibre	↑
Meat, poultry & fish	↑	↑ fish/poultry to red meat ratio	↓ meat & poultry; ↑ fish
Cholesterol	↓	–	–
Fat	↓ tot & SF	↑ P:S ratio ↓ trans fat	↑ M:S ratio
Sodium	↓	–	–
Alcohol	–	↑ moderate	↑
Multivitamins	–	↑	–

- Cross-sectional single-center study of 280 men attending fertility center
- To study the association between 4 dietary indexes (as indicators of real-world food consumption) and semen parameters:
 - Healthy Eating Index (HEI)
 - Global approach to assess diet quality
 - Includes most foods in total score calculation
 - Alternative Healthy Eating Index (AHE) and alternate Mediterranean Diet score (aMED)
 - Assess foods and chronic disease
 - DASH Index – adherence to DASH diet

Male Diet Patterns



	HEI	AHEI	aMED	DASH
Sperm Concentration	X (10%)	X (45%)		X (24%)
Total Sperm count		X (29%)		
Motility	X (11%)		X (6%)	
Morphology		X (21%)		X (8%)

Adherence to any of 4 diet indexes is associated with better overall sperm quality, with AHEI best associated

Efrat M et al., 2018

Diet Pattern: Western + Nuts

FERTINUTS study:

14 week randomized, controlled, parallel trial (n=116)

- Intervention group: 'Western-style' diet enriched with 60 g of nut mixture (n=56)
- Control group: 'Western-style' diet avoiding nuts (n=50)
- Western-style diet (based on answers to questionnaire):
 - Saturated fats; red and processed meat; butter; high-fat dairy products; refined grains; white potatoes; refried beans; sugar drinks; fried foods
- Nuts:
 - 30 g walnuts; 15 g almonds; 15 g hazelnuts



Diet Pattern: Western + Nuts

	Intervention (Nuts) [n=56]		Control [n=50]		P-value
Age (y)	24 ± 4.6		25 ± 4.7		
BMI (kg/m ²)	23.55 ± 2.84		24.09 ± 3.43		
	Baseline	Change	Baseline	Change	
Volume (mL)	3.00 (1.98, 4.15)	0.00 (-0.83, 0.50)	3.15 (2.05, 4.99)	-0.65 (-1.38, 0.15)	0.112
Concentration (M/mL)	26.20 (14.85, 44.30)	0.10 (-2.11, 10.35)	21.20 (9.80, 37.60)	0.00 (-4.05, 4.14)	0.086
Total Count (M)	75.55 (29.95, 111.25)	4.45 (-15.60, 34.95)	69.75 (29.25, 123.25)	-15.15 (-42.05, 7.15)	0.002
Motility (%)	64.23 (44.44, 70.45)	3.41 (-0.87, 13.14)	67.96 (60.42, 77.93)	0.00 (-4.93, 6.30)	0.006
Strict Morphology (%)	6.55 (5.00, 8.08)	0.82 (-0.17, 2.12)	6.32 (5.47, 7.74)	-0.04 (-1.06, 0.65)	0.008

Age; BMI: Mean ± SD
 Semen Parameters: Median (IQR)

Fertility Supplements



- Prenatal
- Antioxidants
- Vitamins & minerals
- Safety
- Efficacy
- Costs

What is a dietary supplement?

Dietary supplements defined:

- Vitamin, mineral, herb, botanical, or amino acid intended to supplement the diet
- Cannot make 'drug claims' or already be marketed as a drug



Supplement Certification Programs

- Independent, third-party lab-analysis
- Only two non-profit programs currently exist (NSF, USP)
- Voluntary
- Results of analytical testing available to consumers



How are Supplements Regulated?

Dietary Supplement Health and Education Act of (DSHEA) 1994

Manufacturers are responsible for ensuring that their products are safe.

Product claims must be substantiated, not false or misleading

FDA does not have authority to approve supplements for safety or efficacy or labeling before they are sold

Food Drug Administration(FDA) Responsibilities

- Remove unsafe, adulterated products from market
- Develop regulatory guidance for labeling and claims (2000)
- Develop adverse event reporting standards (2006)
- Establish Dietary Supplement GMPs (2007)



What Claims are permitted?

Federal law permits dietary supplement manufacturers and marketers to make certain claims that **describe how the product affects either:**

- 1. Structure/function**
- 2. Health claim**
- 3. Nutrient content claims**

“Qualified health claims (QHCs) are supported by scientific evidence, but do not meet the more rigorous “significant scientific agreement” standard required for an authorized health claim. ”

MUST be accompanied by a disclaimer.

Supports the development of baby’s brain, eyes, & nervous system*

*These statements have not been evaluated by the Food and Drug Administration

Supplement Label

Supplement Facts

Serving Size: 2 capsules
Servings Per Container: 30

Amount Per Serving	% Daily Value
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Vitamin B6 (50% P5P, 50% Pyridoxine HCL) 25mg	1250%
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Vitamin B12 (as Methylcobalamin) 500 mcg	8333%
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Proprietary Blend containing: N-Acetyl Cysteine, Arginine, Quercetin, L-Carnitine (as L-carnitine L-tartrate), Macuna Pruriens (seed) Extract (standardized to 40% L-Dopa), CoQ10 (Ubiquinone) 1455 mg**	
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** Daily Value not established

Other ingredients: Cellulose, rice flour, magnesium stearate, silicon dioxide.

Supplements and Male Infertility

- Despite low-quality evidence, supplements have always been part of the management of male infertility
- Antioxidants are seen a way of counteracting the detrimental effect of oxidative stress on sperm quality
- Methyl donors
- Energy production /motility



Physiology



Environmental Factors

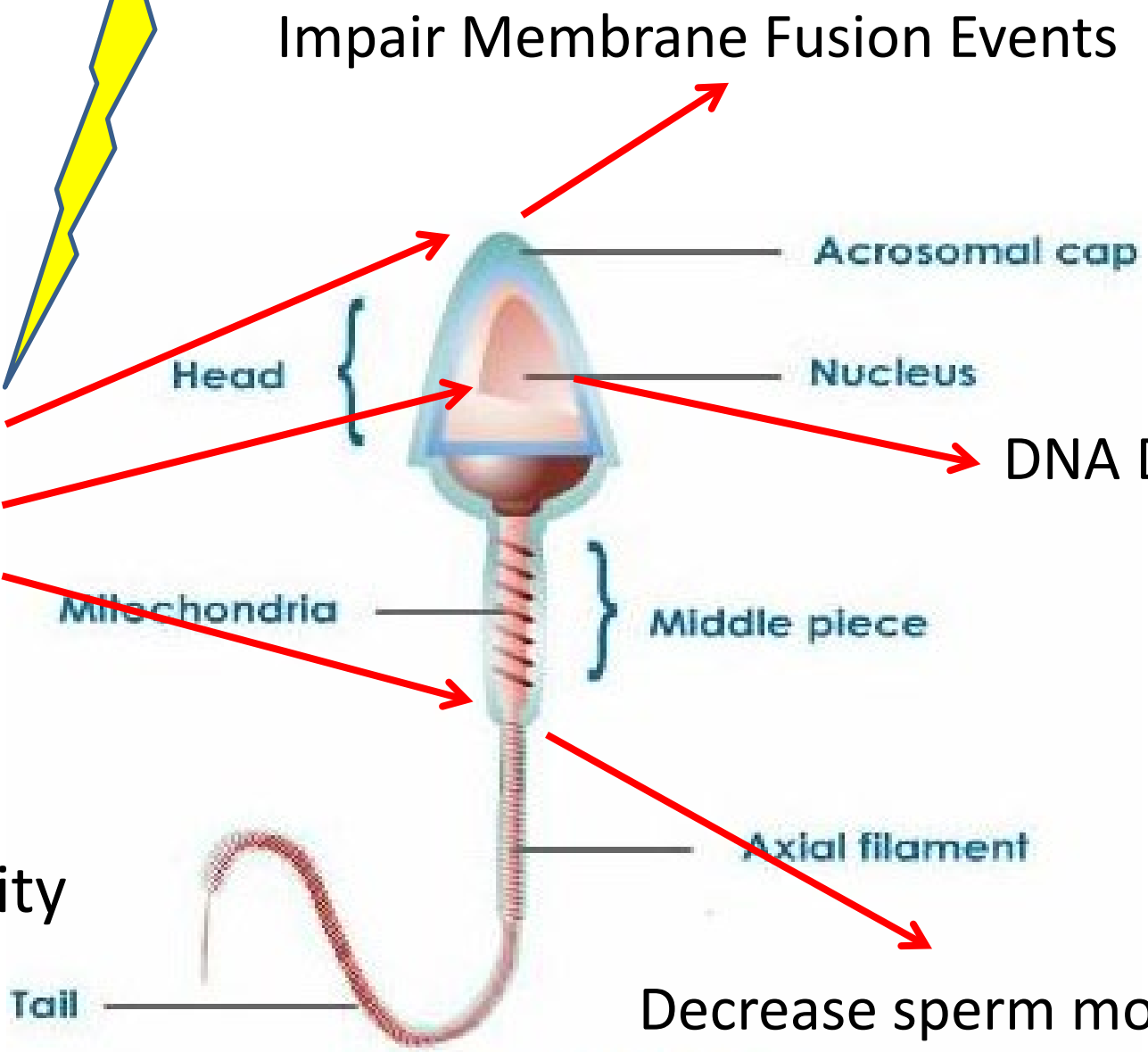
Lifestyle Factors

Reactive Oxygen Species (ROS) in Semen

Infections

Autoimmunity

Chronic Disease



Impair Membrane Fusion Events

DNA Damage

Decrease sperm motility

Decrease fertilization and pregnancy rates

Impaired embryonic development

Pregnancy loss

Offspring birth defects

Decrease in vivo fertilization and pregnancy rates

Supplements Enhancing Seminal TAC

- Vitamin E – stabilizes sperm cell membranes
- Vitamin C – primary antioxidant in the epididymis
- Lycopene – quenches singlet oxygen, highly concentrated in testicular tissue
- NAC – precursor of glutathione peroxidase
- Selenium – cofactor for glutathione peroxidase
- Zinc – cofactor for superoxide dismutase
- CoQ10 – protects cell membranes
- Carnitine – weak antioxidant

Nutrients for Male Fertility

Folic acid - DNA synthesis, deficiency increases DNA frag

Vitamin D - improves motility and acrosome reaction

CoQ₁₀ - key role in sperm energy production, supplementation improves motility

L-carnitine - transports LCFA , improves motility

Antioxidant Supplements






Human Reproduction Open, 2023, 2023(3), hoad020

<https://doi.org/10.1093/hropen/hoad020>

Advance Access Publication Date: May 17, 2023

Review

The lack of evidence behind over-the-counter antioxidant supplements for male fertility patients: a scoping review

Wiep R. de Ligny ^{1,*}, Kathrin Fleischer², Hilde Grens ³, Didi D.M. Braat¹, and Jan Peter de Bruin ³

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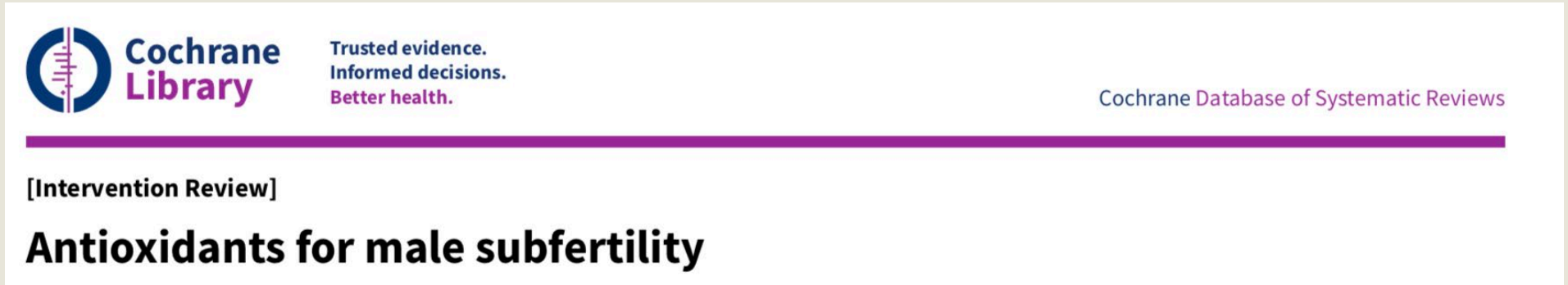
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- June 2022 internet search (89)
- 34 eligible antioxidant supplements
- 79 % exceeded RDA or UL
- Price \$53 / 30 days
- Only 2 supplements tested in a good clinical trial
- Use not supported by research

Antioxidant Supplements



- Conclusions:

- For **semen parameters**, findings were unreliable as heterogeneity was extremely high in each analysis
- The use of antioxidants **may** improve a couple's chances of live birth

“Overall, the quality of evidence was low to very low”

and

“Subfertile couples should be advised that overall, the current evidence is inconclusive based on serious risk of bias”

Antioxidants and Male Infertility

Since the publication of the Cochrane Review, there have been two high-quality studies looking at the antioxidant use in subfertile men:

The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial

Anne Z. Steiner, M.D., M.P.H.,^a Karl R. Hansen, M.D., Ph.D.,^b Kurt T. Barnhart, M.D.,^c Marcelle I. Cedars, M.D.,^d Richard S. Legro, M.D.,^e Michael P. Diamond, M.D.,^f Stephen A. Krawetz, Ph.D.,^g Rebecca Usadi, M.D.,^h Valerie L. Baker, M.D.,ⁱ R. Matthew Coward, M.D.,^j Hao Huang, M.D., M.P.H.,^k Robert Wild, M.D., M.P.H., Ph.D.,^b Puneet Masson, M.D.,^l James F. Smith, M.D., M.S.,^m Nanette Santoro, M.D.,ⁿ Esther Eisenberg, M.D., M.P.H.,^o and Heping Zhang, Ph.D.,^k for the Reproductive Medicine Network

JAMA | **Original Investigation**

Effect of Folic Acid and Zinc Supplementation in Men on Semen Quality and Live Birth Among Couples Undergoing Infertility Treatment A Randomized Clinical Trial

Enrique F. Schisterman, PhD; Lindsey A. Sjaarda, PhD; Traci Clemons, PhD; Douglas T. Carrell, PhD; Neil J. Perkins, PhD; Erica Johnstone, MD; Denise Lamb, BSN; Kayla Chaney, BA; Bradley J. Van Voorhis, MD; Ginny Ryan, MD; Karen Summers, MPH; Jim Hotaling, MD; Jared Robins, MD; James L. Mills, MD; Pauline Mendola, PhD; Zhen Chen, PhD; Elizabeth A. DeVilbiss, PhD; C. Matthew Peterson, MD; Sunni L. Mumford, PhD

CONCLUSIONS

- Oxidative stress has a well documented deleterious effect on semen parameters and male infertility
 - May play a role in a large proportion of sub fertile men (30-80%)
- While the oxidative stress data presents a clear rationale for antioxidant therapy, studies do not support their use
- Newer diagnostic tools including total antioxidant capacity (TAC) may allow for men with high levels of oxidative stress to be identified
 - These patients may represent a subgroup for further investigation

Micronutrients and Female Fertility

Prenatal
Vitamins

Antioxidants

Vitamin D

DHEA

Myo-
inositol

Coenzyme
Q10

Preconception and Pregnancy Micronutrients

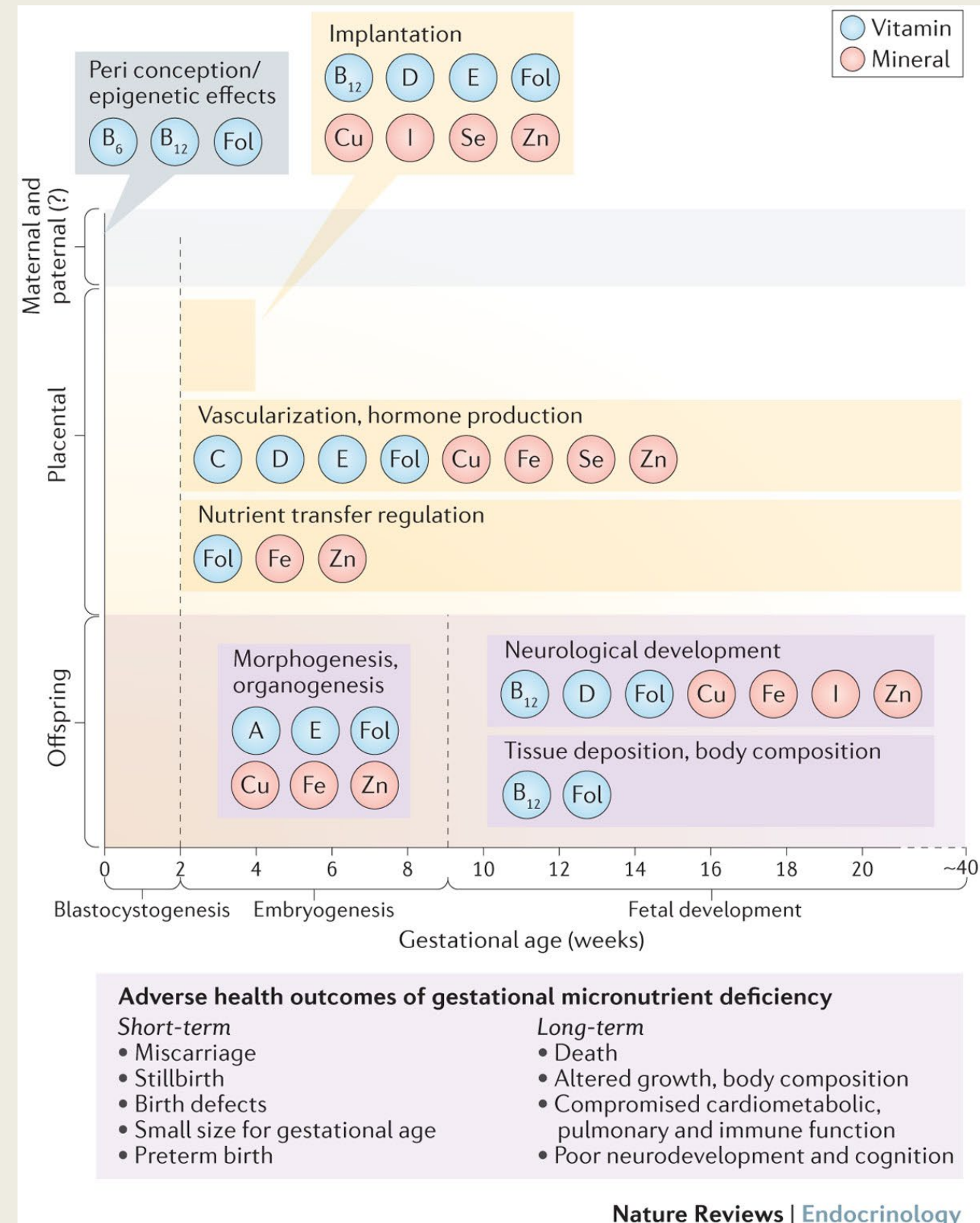


Figure 1 The function and timing of micronutrients that affect outcomes in offspring

Christian, P. *et al.* (2016) Micronutrient deficiencies in pregnancy worldwide: health effects and prevention
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2016.37

Original Investigation | Obstetrics and Gynecology

Estimation of Total Usual Dietary Intakes of Pregnant Women in the United States

Regan L. Bailey, PhD, MPH, RD; Susan G. Pac, MS, RD; Victor L. Fulgoni III, PhD; Kathleen C. Reidy, DrPH, RD; Patrick M. Catalano, MD

How do the usual dietary intake of pregnant women compare with the National Academies of Science, Engineering and Medicine Dietary Reference Intakes for nutritional adequacy and excess?

- **Dietary supplements do help women increase intake of key nutrients.**
- **Significant number of women are not meeting recommendations for key nutrients: vitamins D, C, A, K and E as well as iron and folic acid, calcium, magnesium and choline even with supplements.**
- **Some women are exceeding the UL for some nutrients because of supplements.**
- **Responsible formulations (standards) would benefit pregnant women.**

Supplements to Avoid In Pregnancy

- Saw Palmetto
- Goldenseal
- Dong Quai
- Ephedra
- Yohimbe
- Pay D'Arco
- Passion flower
- Black Cohosh
- Blue Cohosh
- Roman Cahomie
- Pennyroyal



**Prenatal
Vitamin
Supplement
(minimum)**

Folic acid
800 mcg

Vitamin B12
2.6 mcg

Vitamin D
400 IU

Iodine 150
mg

Iron 18 mcg

DHA 300
mg



Prenatal Supplements

- OTC or prescription
- No standards for PNV
- ACOG recommends multivitamin with at least 400 mcg folic acid
- Wide variation in cost, formulation and content

Commercially Available Prenatal Vitamins Do Not Meet American College of Obstetricians and Gynecologists Nutritional Guidelines

Fei Cai, MD¹, Benjamin K. Young, MD, MS², Jennifer A. McCoy, MD, MSCE¹

¹Division of Maternal Fetal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

²Department of Ophthalmology, Casey Eye Institute, Oregon Health and Sciences University, Philadelphia, Pennsylvania

Prenatal Supplement Label

Supplement Facts

Serving Size 1 Gelcap
Servings Per Container 100

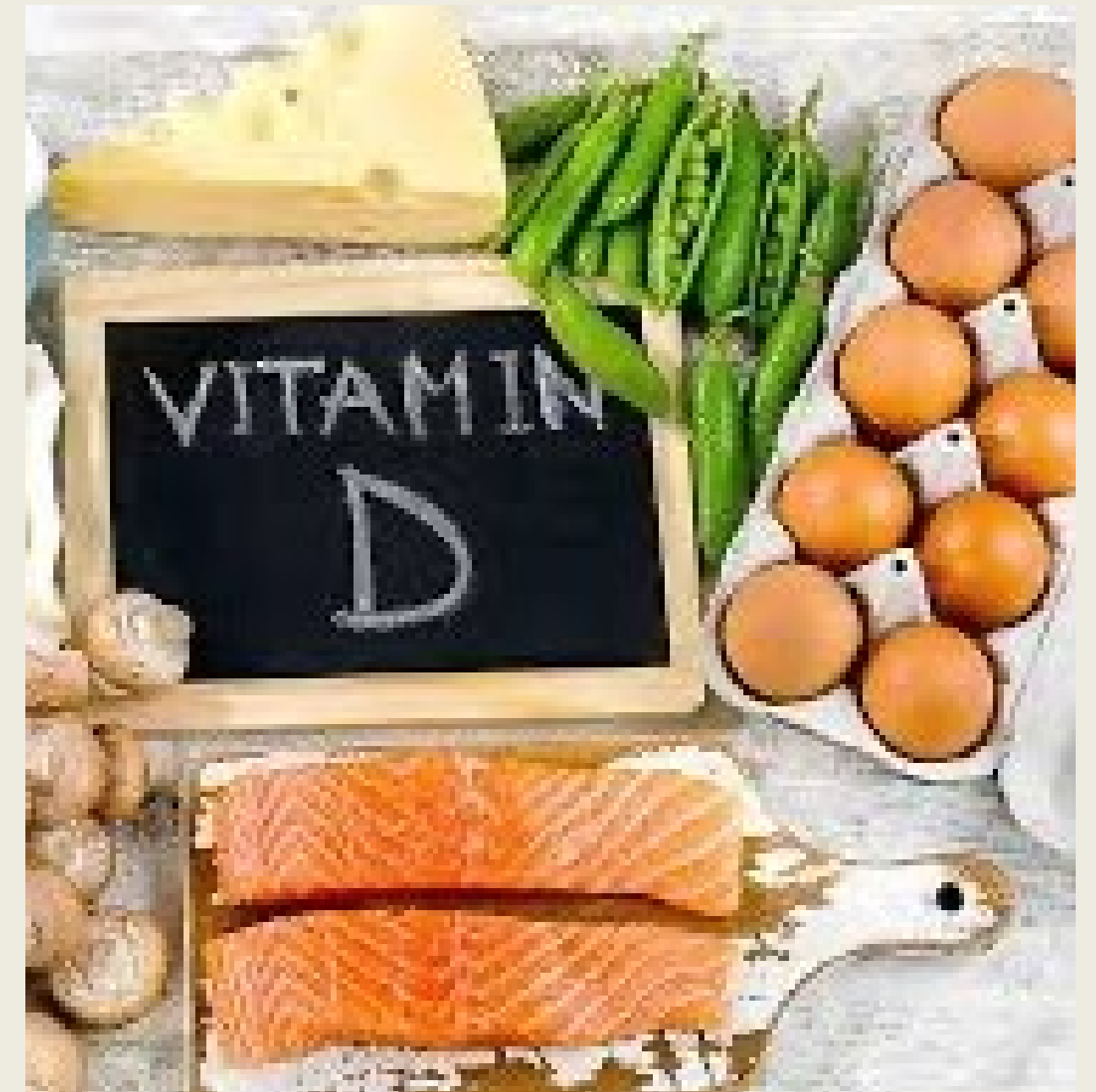
	Amount Per Serving	% Daily Value
Vitamin A (as retinyl acetate and 50% as beta-carotene)	900 mcg	100%
Vitamin C (as ascorbic acid)	90 mg	100%
Vitamin D (as cholecalciferol)	20 mcg (800 IU)	100%
Vitamin E (as dl-alpha tocopheryl acetate)	15 mg	100%
Thiamin (as thiamin mononitrate)	1.2 mg	100%
Riboflavin	1.3 mg	100%
Niacin (as niacinamide)	16 mg	100%
Vitamin B ₆ (as pyridoxine hydrochloride)	1.7 mg	100%
Folate	400 mcg DFE (240 mcg folic acid)	100%
Vitamin B ₁₂ (as cyanocobalamin)	2.4 mcg	100%
Biotin	3 mcg	10%
Pantothenic Acid (as calcium pantothenate)	5 mg	100%

Other ingredients: Gelatin, lactose, magnesium stearate, microcrystalline cellulose, FD&C Yellow No. 6, propylene glycol, preservatives (propylparaben and sodium benzoate).

Vitamin D and Reproductive Health

Maternal Vitamin D deficiency :

- Increases the risk of gestational diabetes
- Increases the risk of pre-eclampsia
- May improve IVF outcomes
- Associated with risk for miscarriage



Folic Acid vs. Methylfolate (5-MTHF) Supplements

- Emerging evidence suggests 5-MTHF may help reduce symptoms for some health outcomes
 - Extremely limited number of RCTs comparing 5-MTHF vs. folic acid for some health outcomes
- No RCTs have assessed 5-MTHF for NTD prevention
- **Folic acid is the only folate form recommended for NTD prevention by USPSTF, IOM, USPHS**
 - No clinical justification to substitute 5-MTHF for a proven, safe, effective dosage of folic acid for NTD prevention



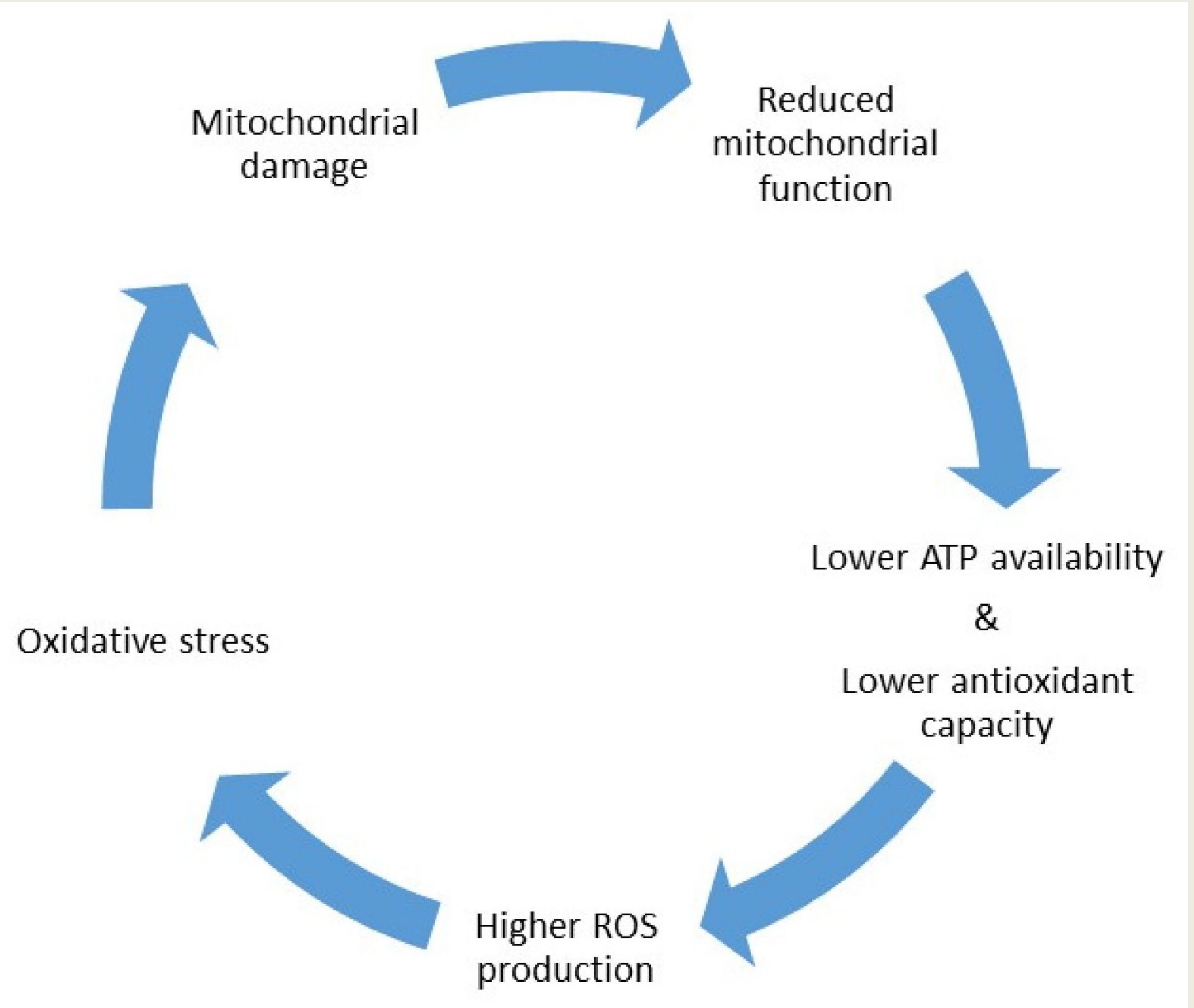
Vitamins and Supplements

	Recommended or optional	
Folic acid	Recommended	Reduces risk of NTD, essential DNA formation and cell division
Vitamin D	Recommended	Steroid hormone supports Ovulation, bone remodeling, reduces adverse outcomes pregnancy
Antioxidants	Optional	May improve pregnancy rates.
CoQ10	Optional	Supports mitochondrial energy production
Vitamin B12	Recommended	Supports DNA production, cell metabolism, nerve function, red blood cell formation.

Vitamins and Supplements

	Recommended or optional	
Iron	Recommended	Supports red blood cell production.
Zinc	Recommended	Support cell division, cell growth, immune system.
Choline	Recommended for women who don't consume eggs or animal products.	Reduce risk of NTD and aids in brain development.
DHA	Recommended for those who don't eat fish.	Supports brain and neurological health.
Inositol	Optional for those with PCOS	Improves insulin sensitivity, may help ovulation.

Antioxidants

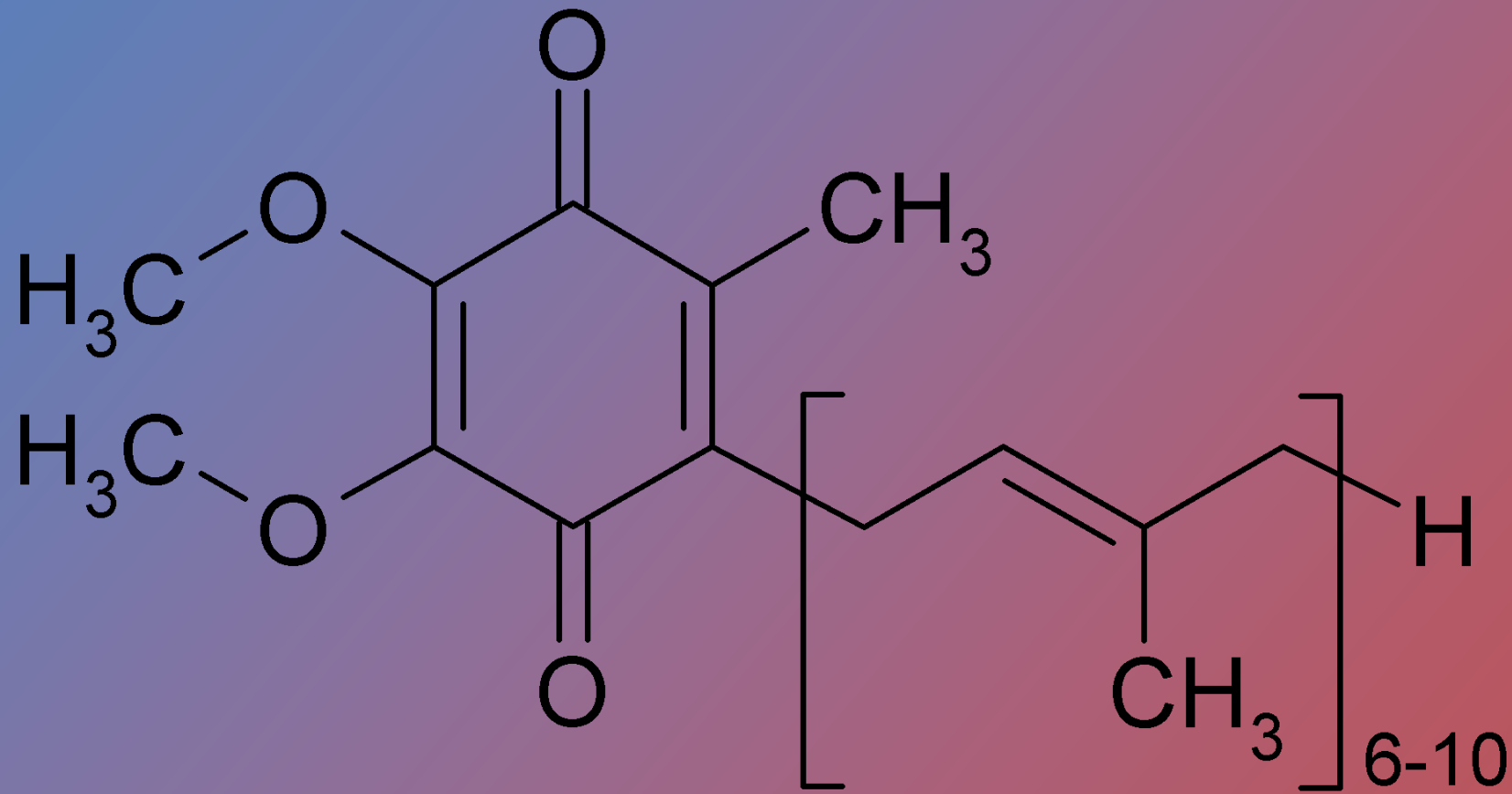


Antioxidants

- Antioxidants from food sources have been shown to be beneficial for fertility.
- Antioxidants from supplements are of limited value. Cochrane review 2020
- N-acetylcysteine, melatonin, L-arginine, myo-inositol, carnitine, selenium, vitamin C, E, and omega-3



Coenzyme Q10



- A fat-soluble compound, aka “ubiquinone,” present in virtually every cell, primarily in the mitochondria
- Ubiquinone /Ubiquinol
- Critical intermediary in electron transport and ATP phosphorylation during mitochondrial energy production

Coenzyme Q10: Treatment considerations

- Ubiquinone vs. Ubiquinol?
- What daily dose and what duration of treatment?
- Bioavailability issues
 - Large, fat-soluble molecule – absorption generally poor
 - Significant variation in dissolution and absorption among different supplement

CoQ10 may help reduce oxidative stress and mitochondrial dysfunction, so far it hasn't shown increase in birth outcomes.

Coenzyme Q10 Supplementation Meta-analysis

REVIEW

Does coenzyme Q₁₀ supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials

Panagiota Florou¹  · Panagiotis Anagnostis^{1,2}  · Patroklos Theocharis¹ · Michail Chourdakis³  · Dimitrios G. Goulis² 

Received: 4 April 2020 / Accepted: 28 July 2020 / Published online: 7 August 2020
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- 5 randomized control trials
- Oral supplementation ↑ CR
- No impact on LBR or MR
- Limitation small number of studies

Does Iron Intake Impact Fertility?

- Most PNVs are formulated with 27 mg per day or more
- But the pre-conception RDA is only 18 mg per day
- Excess iron intake during fertility treatment can create two problems:
 - Constipation and other GI side effects
 - Ferroptosis may*** compromise oocyte quality and early embryo development



Emerging Melatonin Research

- 161 women 38-43 years old randomized to 2 mg melatonin vs. placebo for 60 days prior to IVF
- Cumulus/granulosa cells analyzed for markers of ferroptosis and mitochondrial function
- Melatonin supplementation significantly reduced ferroptosis and improved mitochondrial function
- *“Melatonin enhances cellular resilience against oxidative stress and metal-induced toxicity in the ovarian microenvironment”*

	Melatonin	Placebo	
Clinical Pregnancy rate	46%	20.3%	P = .01
Live birth rate	33.3%	15.3%	P = .05

Case Study

36 yo female

DX: RPL and possible endometriosis

List your prescribed drugs, prescribed and non-prescribed supplements and herbs

Name the Drug, Supplement or Herb	Strength	Frequency Taken
Levothyroxine 25 mcg 1x/day	Vitamin E 400 IU 1x/day	Omeprazole 20mg 1x/day
B12 1000 mcg 1x/day	Vitamin C 500mg 1x/day	Inositol-D Chiro inositol 2000-50mg 1x/day
Prenatal vitamin	Probiotic	Rizatriptan/Metoclopramide as needed for migraine
L-arginine 1000mg 2x/day	Pycnogenol 100mg 1x/day	█
Fish oil 1250mg 1x/day	Acai 500mg 2x/day	█
CoQ10 400mg 2x/day	Aspirin 81mg 1x/day	█

Magnesium Citrate 360 mg and Riboflavin 400 mg for migraines

Best Practices

- Include supplements and diet in your intake assessment
- Check with patients that they have stopped any supplement that may not be safe in pregnancy.
- Consider guidelines for your practice to provide guidance for your patients.
- Remind patients food first, supplements supplement.
- Encourage patients to purchase supplements that are independently certified.
- Partner with registered dietitians to assure your patients are optimizing their diets and supplementation as needed.
- Screen patients for dietary restrictions such as vegan, vegetarian, Kosher, Halal to guide them to appropriate supplements.
- Be aware of supplement interactions with medications.

Resources

- Consumer Lab www.consumerlab.com
(subscription) independent testing
- NATMEDPRO
www.naturalmedicines.therapeuticresearch.com
- NIH Office of Dietary Supplements
www.ods.od.nih.gov Supplement Fact Sheets

Conclusions

1. Hundreds of nutritional supplements are being marketed for both male and female fertility
2. Many of the nutrients contained in those products have little or no evidence of benefit
3. For certain clinical conditions, there are nutrients which appear to enhance fertility in both natural conception and ART settings. We need more research.
4. FDA/FTC regulatory oversight of the supplement industry remains inadequate, requiring clinicians to make their own judgment about the formulation and quality of any particular product

Questions?

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