Leah Hechtman
PhD(Candidate),M.Sci Med(RHHG),BHSc(Nat),ND
FERTILITY AND REPRODUCTIVE HEALTH
Clinician, Researcher, Author and Educator

FOUNDATIONAL FERTILITY

Male fertility

(This is NOT an exhaustive list)

DISCLAIMER

Subjective	Possessive Adjective	Objective	Possessive Pronoun	Reflexive
he	him	his	his	himself
she	her	her	hers	herself
they	them	their	theirs	themself
xie	hir ("here")	hir	hirs	hirself
yo	yo	yos	yos	yoself
ze	zir	zir	zirs	zirself
ve	vis	ver	ver	verself
co	co	cos	cos	coself
en	en	ens	ens	enself
ey	em	eir	eirs	emself

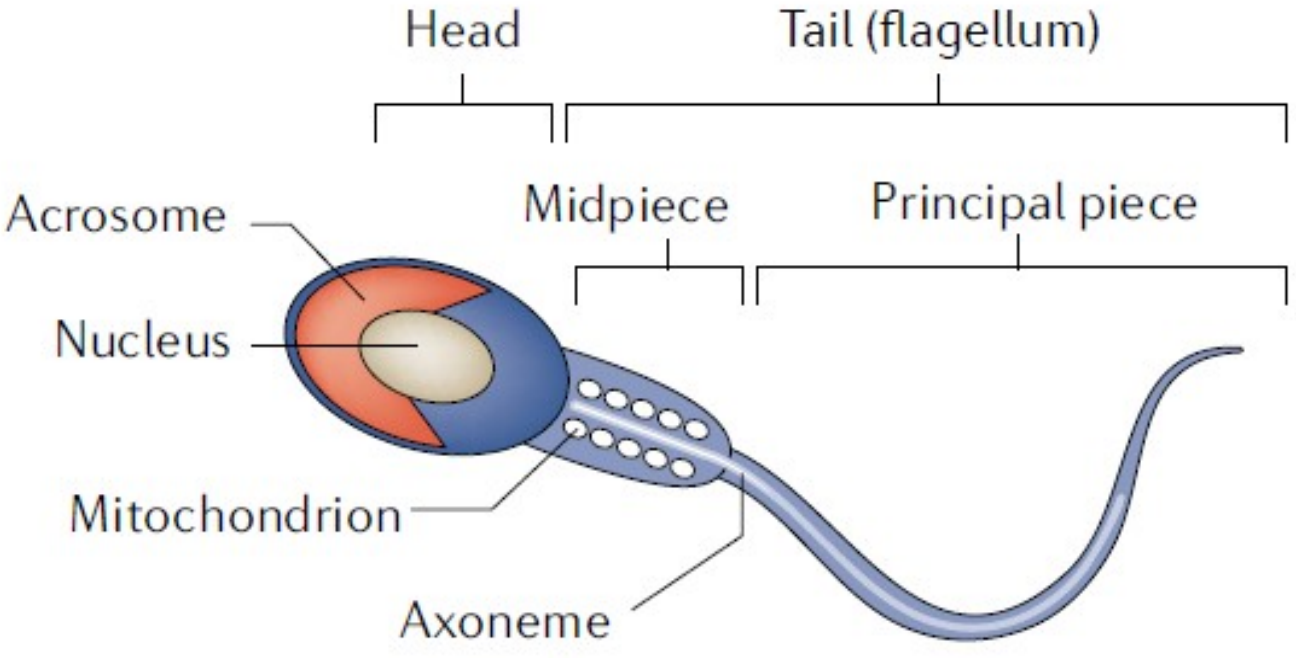
DISCLOSURES

- Director, The Natural Health and Fertility Centre
- PhD Candidate – UNSW, Women's and Children's Health, Faculty of Medicine
- Clinical Advisory Board – Invivo Healthcare
- Scientific Advisory Board – MINDD Foundation
- Scientific Advisory Board – MothersBabies
- KOL – Kaneka (Fertility and Ubiquinol)
- Panel and Board member – Association of Naturopathic Practitioners (UK)
- Patron - College of Naturopathic Medicine (CNM)
- Lecturer - Various
- Product advisor - Various

OUTLINE

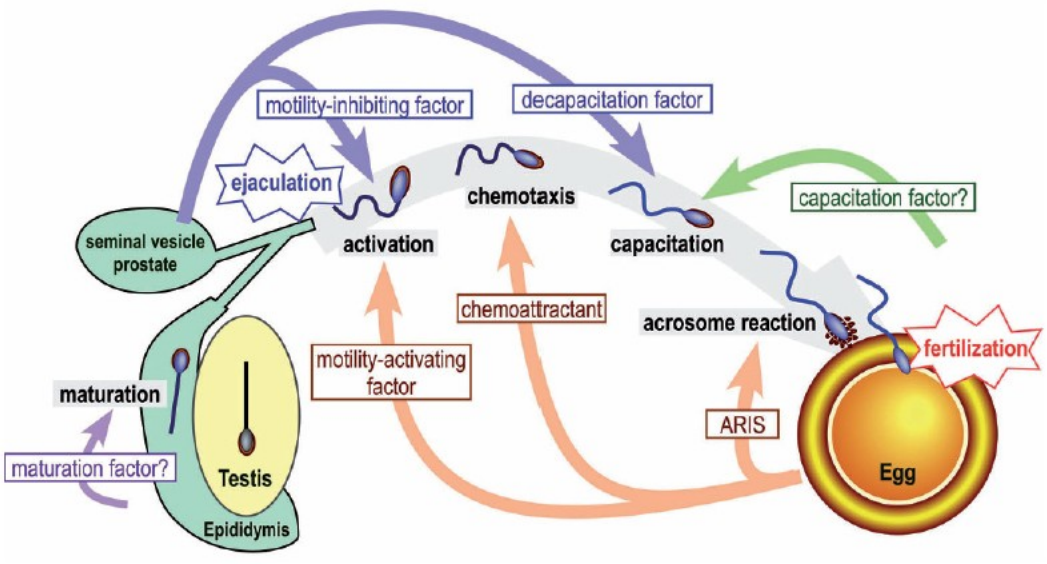
- The components of healthy male fertility
- Appropriate assessments and interpretation
- Influencing male fertility – treatment strategies, prescriptions, recommendations

THE HUMBLE SPERMATOZOA



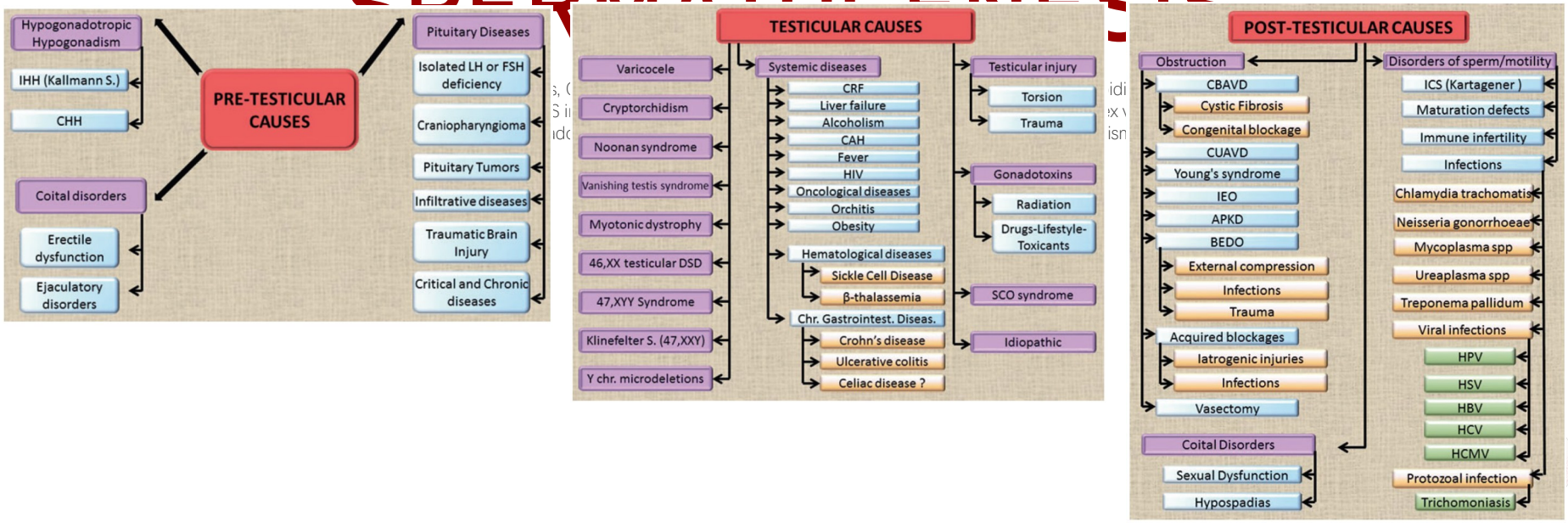
Dai et al., 2021

THE JOURNEY OF A SPERMATOZOA



Yoshida et al., 2008

DISRUPTION OF SPERMATOGENESIS

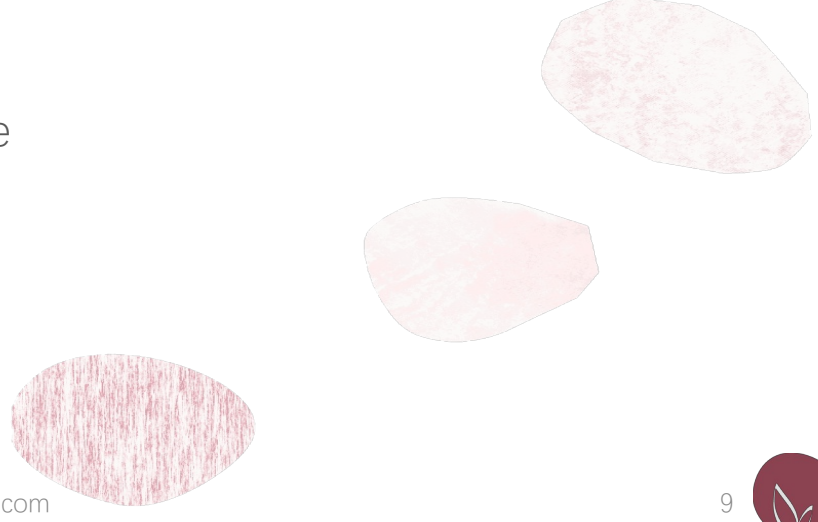


Dimitriadis et al., 2017

ASSESSMENTS

ASSESSING THE MALE PATIENT

- Semen analysis
  - Time of collection
  - Volume
  - pH
  - Agglutination
  - Viscosity
  - Count
  - Morphology
  - Motility – progressive %, motile vs immotile
  - DNA fragmentation
  - Sperm antibodies
  - Semen culture



TYPES OF ANALYSES

SEMEN ANALYSIS REPORT **Sample: Seminal fluid @ room temperature** **Reason for Test: Outside patient**

Gross examination				Days of Abstinence: 3		Vitality :	(RR >58%)
Volume:	2.7 ml	(RR ≥1.5 ml)	Viscosity:	Severely elevated		Leukocytes:	< 1M/ml (RR:<1M/ml)
pH:	8.5	(RR ≥7.2)	Liquefaction:	Complete		Sample complete	Yes

Microscopic Examination Collected by: Masturbation — Accredited for compliance with NPAAC standards and ISO 15189. NATA/RCPA Accredited Laboratory Number 19491

Concentration:	1.4 mill/ml	(RR:15 mill/ml)	Total Count:	3.8 million	(>39)
Motile/ml:	0.36 mill/ml	(26% motile)	Total Motile:	0.988 million	

Motility Grading (RR: A+B+C ≥40% and A+B ≥32%)

Grade A+B:	24% Progressive
Grade C:	2% Non progressive
Grade D:	74% Non motile

Morphology*

Normal forms: (RR ≥4%)

< 4% - associated with poor IVF outcome
>12% - associated with good IVF outcome

Date of test	Conc.	Motile	Norms
18 Aug 22	0.3	<0.01	-
16 Jun 22	4	0.64	-
21 Jul 21	2.2	0.11	-

Scientist

Reference ranges as per WHO laboratory manual, Fifth Edition,2010. *From 1/9/2010

Direct ASAB Result

Result	Binding*	Region

ASAB Comments * Biological Reference Range <10%

Previous IgA		Other IgG	
Date	Direct IgA	Date	Indirect IgG
25 Jan 17			
17 Mar 17			
27 Jun 17		12 Jun 19	
28 Aug 17		31 May 18	
1 Sep 17		5 Apr 17	
12 Jun 19		16 Dec 16	Negative
21 Nov 19			

Direct MAR test is performed when sperm motility is normal. Reference ranges as per manufacturers guidelines.

Comments

- An oligoasthenozoospermic sample.
- Severely viscous specimen. Specimen required resuspension by using a 1ml syringe and 18 inch gauge needle.
- Accurate sperm morphology count NOT performed due to insufficient sperm concentration cutoff. Semen samples should have a total concentration of >5 million/ml before sperm morphology can be performed.
- Accurate sperm vitality count NOT performed due to insufficient sperm concentration cutoff. Semen samples should have a total concentration of >10 million/ml before sperm vitality can be performed.
- Halosperm test result to follow.
- Further investigations or clinical referral may be indicated.

ANDROLOGY REPORT

Sample Provided:	07-Aug-2020
Abstinence Period (2-7 days):	3 day(s) abstinence
Sample Produced by:	Masturbation at lab
Specimen:	Incomplete semen sample
Testing Performed at:	Genea Andrology at 37 degrees
Sample Analysed:	39 mins post ejaculation

	Patient Result:		Reference Range: WHO (2010) 5th Edition
Ejaculate Volume:	3.7 ml		>= 1.5
Sample Viscosity:	Normal		
Liquefaction:	Complete		
Sperm Clumping:	5% aggregate only		
Debris:	Normal		
Round Cells:	Few		
pH:	Not required		> 7.2
Sperm Concentration:	150 million/ml		>= 15
Total Sperm Count:	555.00 million/ejaculate		>= 39
Progressive Motility:	65% progressive		>= 32
Total Motility:	72% motile		>= 40
Progression Rating:	3/4		>= 3
Sperm Vitality:	Not required		>= 58
Normal Forms:	18% normal forms		>= 4
Antisperm Antibodies Isotypes:	0% IgG		< 50
	0% IgA		< 50
DNA Fragmentation:	12%	Excellent DNA Integrity	< 29
High Green Stain:	4%	Normal	< 15

Comments : **SCITs2 + culture. 10% of sample not collection from the end of ejaculate. Semen analysis performed by SQA-Vision. Culture results to follow from DHM. CC: Dr Leah Hechtman (1/300 Pacific Highway, Crows Nest NSW 2065).**

Other Significant Findings:

COPY

	Semen composition
Seminal plasma	• Lipids • Sugars • >2500 proteins (enzymes, cytokines, chemokines, cell-cell signaling factors)
Seminal cells	• Spermatozoa (>85% of seminal cells, with normally > 39 million per ejaculation) • Exfoliated immature germ cells • Exfoliated epithelial cells • Seminal leukocytes (normally < 1 million/ml, in a part coming from epididymis): 50-60% granulocytes 20-30% macrophages 5% T lymphocytes Rare dendritic cells in individuals with chronic inflammation of the MGT

Le Tortorec et al., 2020

OTHER ASSESSMENTS

GENERAL

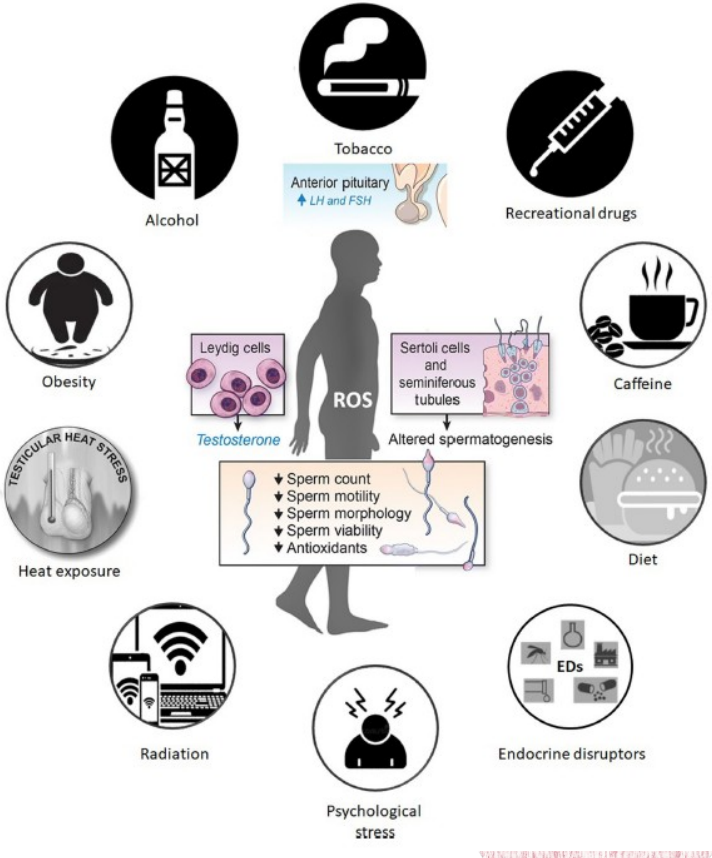
- FBC
- UEC/LFT
- Fasting lipids
- Full iron studies +/- HFE
- Vitamin D3
- T (free and bound), P4, FSH, LH, PRL, E2, DHEA-S
- TSH + as needed
- Fasting glucose, insulin, HbA1c, HOMA
- Full STI panel
- Infective screen – EBV, CMV, HSV1/2, HHV6, Mycoplasma, Ureaplasma
- MSU

FUNCTIONAL

- Methylation profile
  - Fasting homocysteine
  - Active B12, red cell folate
  - SAM, SAH, SAM:SAH
  - THF, Folinic acid, L-5MTHF
- Red cell selenium
- Plasma zinc
- Serum copper
- Caeruloplasmin
- Seminal microbiome
- Others as indicated

AETIOLOGY

MULTIFACTORIAL AETIOLOGY



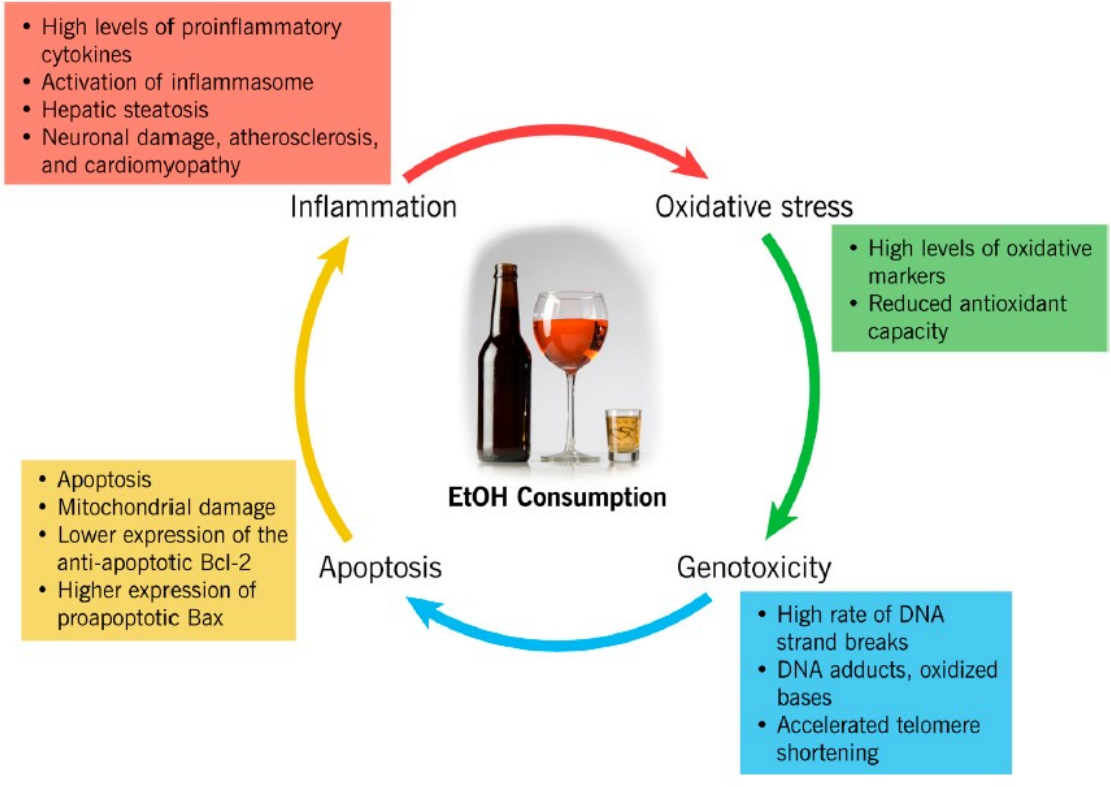
Leisegang & Dutta, 2021

ALCOHOL AND FERTILITY

Impact of Alcohol	Animal Studies	Human Studies
Effects on Reproductive Hormonal Regulation	Reduced levels of LH, FSH [67–72]. Reduced levels of testosterone [73–77]. Altered Leydig cell number and morphology [78].	Contradictory evidence in literature on levels of FSH, LH, and testosterone [79–83].
Effects on Semen Quality	Reduced sperm concentration and motility [84–87]. Increased abnormal sperm morphology [84–87]. Defects in chromatin condensation [86,87].	Reduced sperm concentration [88–90]. Altered semen volume and increased abnormal sperm morphology [91–93]. Increased sperm DNA fragmentation and defects in chromatin condensation [89,90,94,95]. Moderate consumption associated with better semen volume and concentration [96].
Effects on Gene Transcription, Genetic, and Epigenetic Regulation	Altered expression of RNA involved in sperm function [97,98]. Altered expression of proteins involved in apoptosis [99]. Aberrant gene acetylation of sperm DNA [100].	Altered expression of RNA involved in sperm function [101]. Aberrant gene methylation in sperm DNA [102,103].
Transgenerational Effects	Low fetal and birth weight, and limited growth in offspring [101,104]. Nervous system anomalies in offspring [105,106]. Altered reproductive development of offspring [107].	Higher incidence of psychopathological disorders [108–110], congenital heart defects [111], cancer [112], and altered reproductive development [113] in the offspring.

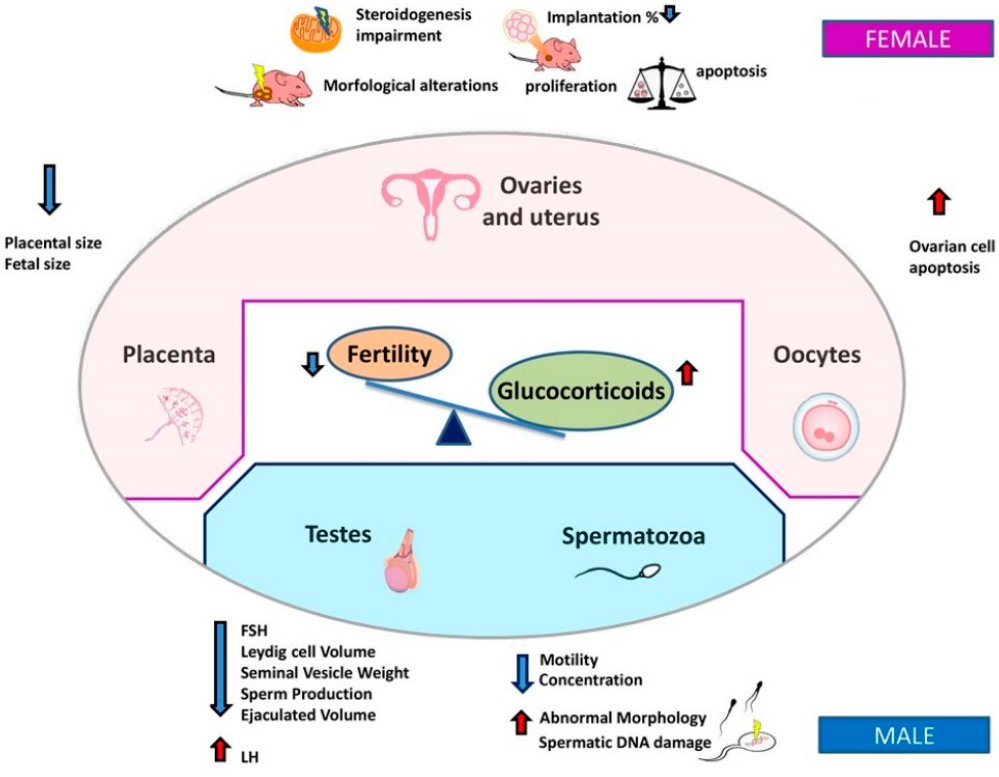
Finelli et al., 2021

ALCOHOL AND FERTILITY



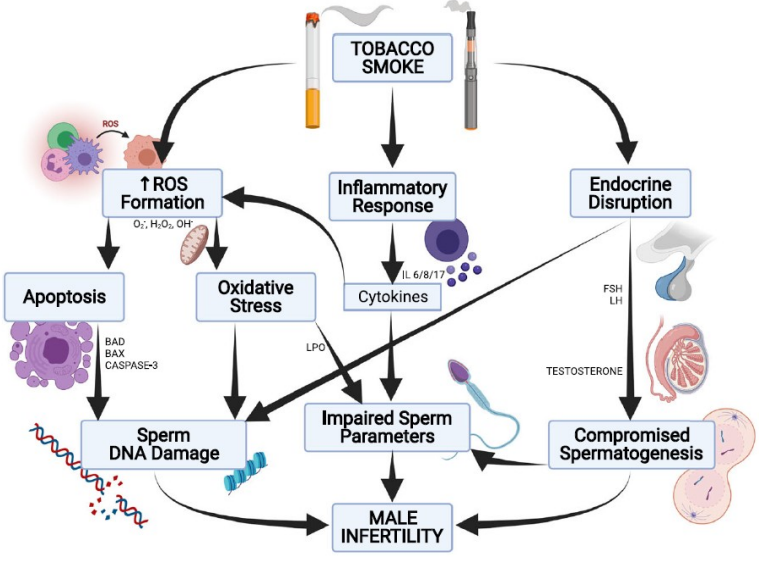
Finelli et al., 2021

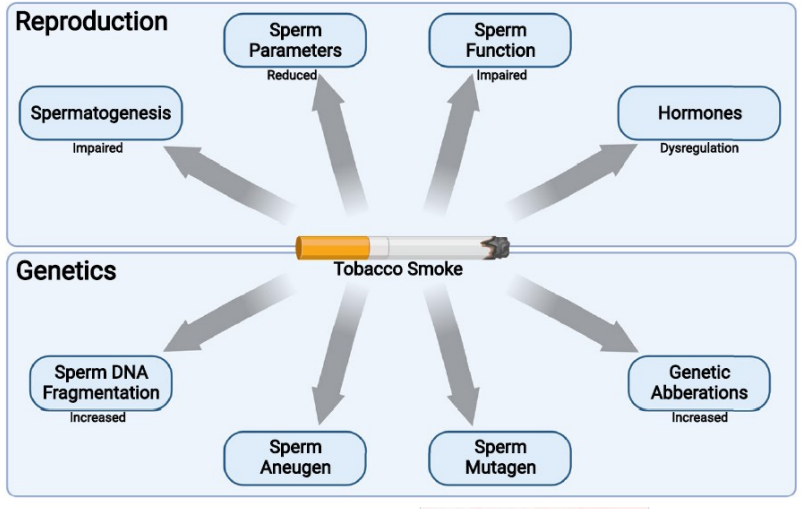
SLEEP AND FERTILITY



Sciarra et al., 2020

TOBACCO AND FERTILITY





Omolaoye et al., 2022

Lifestyle Factor	Semen Parameters	Endocrine Parameters	Proposed Mechanisms
Alcohol Consumption	↑ Seminal leukocytes SDF ↓ Concentration Motility Viability Morphology	↑ LH FSH Prolactin Estrogen ↓ Testosterone Progesterone	• Impaired spermatogenesis and steroidogenesis • Spermatogenic arrest • Impaired Leydig cell • Apoptosis • Testicular atrophy and OS
Tobacco Consumption	↑ Seminal leukocytes SDF ↓ Concentration Motility Viability Morphology	↓ Testosterone	• Impaired spermatogenesis and steroidogenesis • Testicular OS • Hypoxia
Cannabis, Opioids and Anabolic Steroids	↓ Concentration Motility Sperm functions	↓ LH Testosterone	• Impaired HPT axis and spermatogenesis
Caffeine	• No significant impact confirmed • May increase sperm motility • May increase SDF	• May increase testosterone • May decrease LH and FSH	Not determined

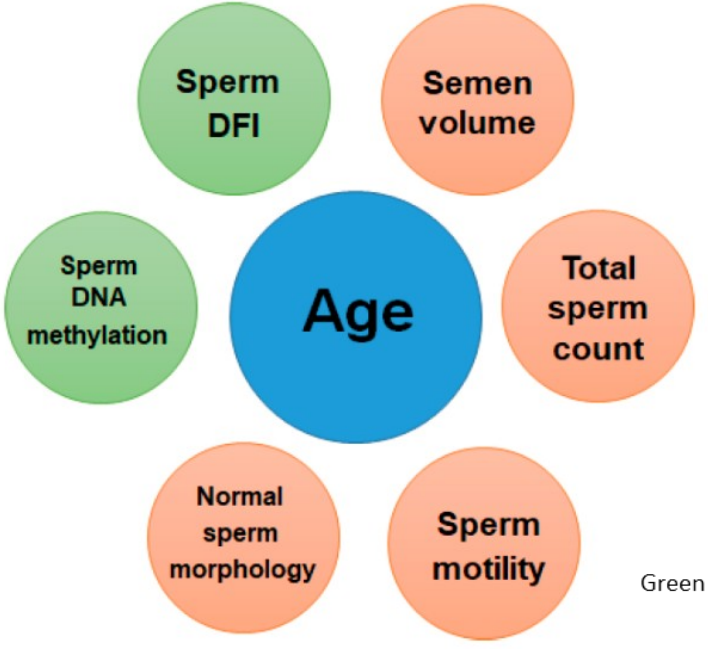
Leisegang & Dutta, 2021

PHARMACEUTICALS AND FERTILITY

Drugs	Effect on reproductive function
Antibiotics	
Penicillin G, ampicillin, cephalotin, spiramycin, gentamycin, neomycin, nitrofurantoin, cotrimoxazole	Reversible impairment of spermatogenesis
Dicloxacillin, tylosin, lincomycin, tetracycline, erythromycin, quinolones, neomycin, nitrofurantoin, cotrimoxazole	Reversible impairment of sperm motility
Antimalarials: quinine and its derivatives	Reversible impairment of sperm motility
Antischistozomal: niridazole	Reversible impairment of spermatogenesis and sperm motility
Antimetabolites/Antimitotics: colchicines, cyclophosphamide	Irreversible arrest of spermatogenesis and azoospermia
Non-steroidal anti-inflammatory drugs, Cox-2 inhibitors	Reversible impairment of follicle rupture and ovulation, impairment of tubal function
Anti-inflammatory 5-ASA and derivatives: mesalazine, sulfasalazine	Reversible impairment of spermatogenesis and sperm motility
Corticosteroids	Reversible impairment of sperm concentration and motility
Antiandrogens: cyproterone acetate, danazol, finasteride, ketoconazole, spironolactone	Reversible impairment of spermatogenesis and erectile dysfunction
Exogenous testosterone, GnRH analogues	Reversible impairment of spermatogenesis
Anabolic steroids	Reversible impairment of spermatogenesis (up to one year recovery), may induce hypogonadism by affecting pituitary–gonadal axis
Anti-oestrogens, eg clomiphene citrate	Reversible impairment of endometrial development
Anti-progestins, emergency contraceptive pills, progesterone-only pills	Impairment of implantation and tubal function
Local anaesthetics, halothane	Impair sperm motility
Antiepileptics: phenytoin	Reversible impairment of sperm motility
Antipsychotics	
Phenothiazine, antidepressants (particularly SSRIs), a blockers	Raise prolactin concentrations and lead to sexual dysfunction
Butyrophenones	Reversible impairment of spermatogenesis and sperm motility
Antihypertensives	
Calcium channel blockers (nifedipine)	Fertilisation failure
Beta blockers, a blockers (prazocin), a agonists (clonidine),thiazide diuretics, hydralazine, methyldopa	Erectile dysfunction
H2 blockers: cimetidine, ranitidine	Raise prolactin concentrations and lead to impairment of luteal function, loss of libido and erectile dysfunction
Metoclopramide	Erectile dysfunction
Methadone	Depress spermatogenesis and sperm motility

K. Anderson et al., 2010

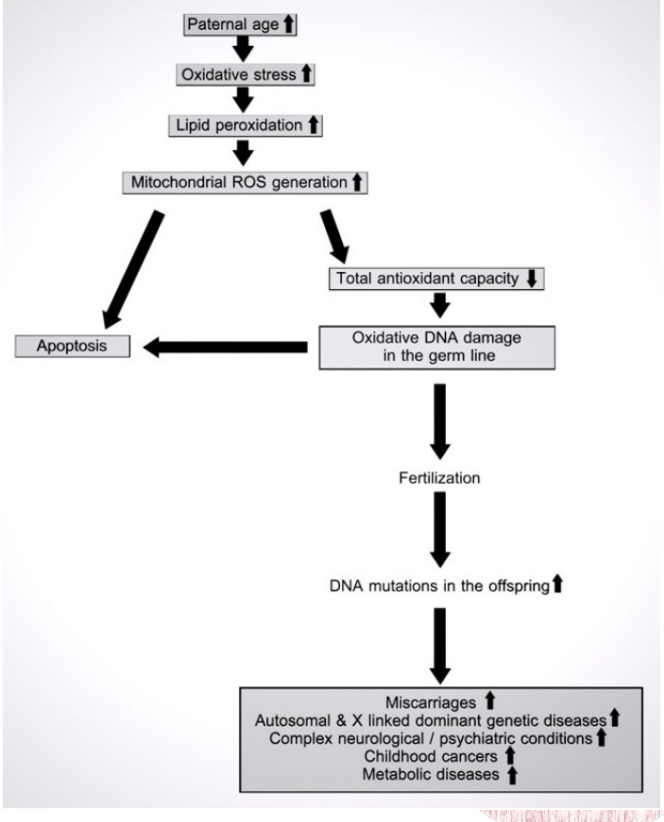
AGE AND SPERM HEALTH



Green = positive association; orange = negative association

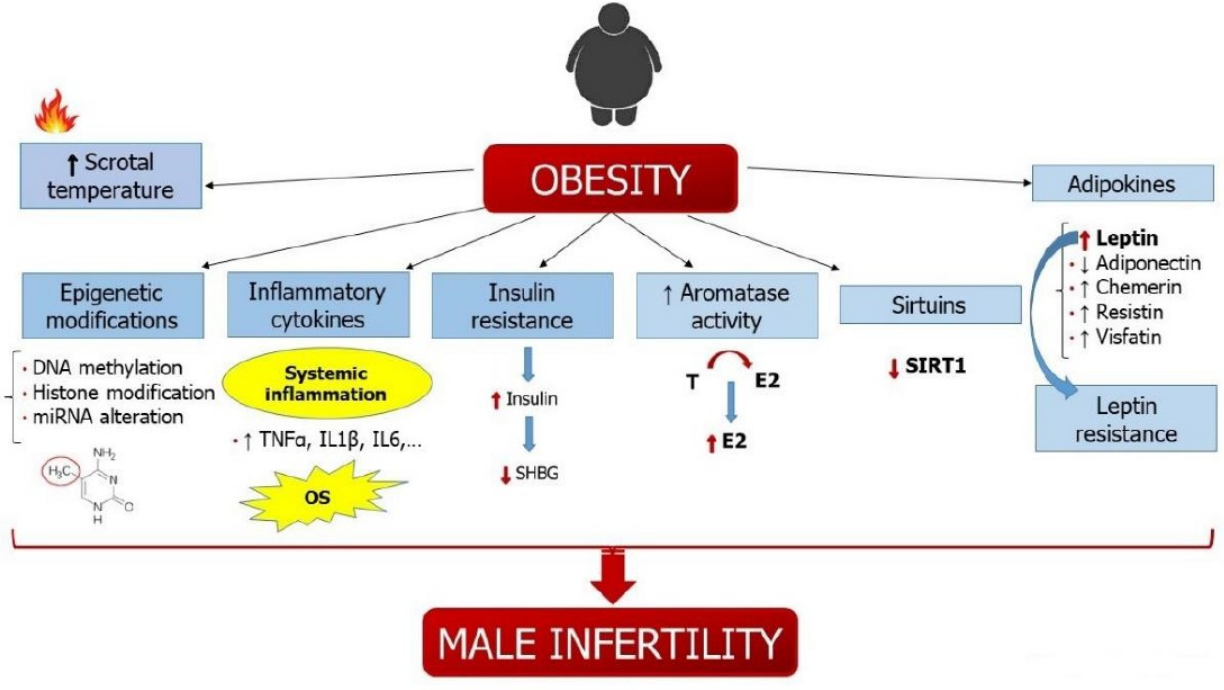
J.-J. Wang et al., 2022

ACCUMULATION OF OXIDATIVE DAMAGE AND AGEING



Gunes et al., 2016

OBESITY AND SPERM HEALTH



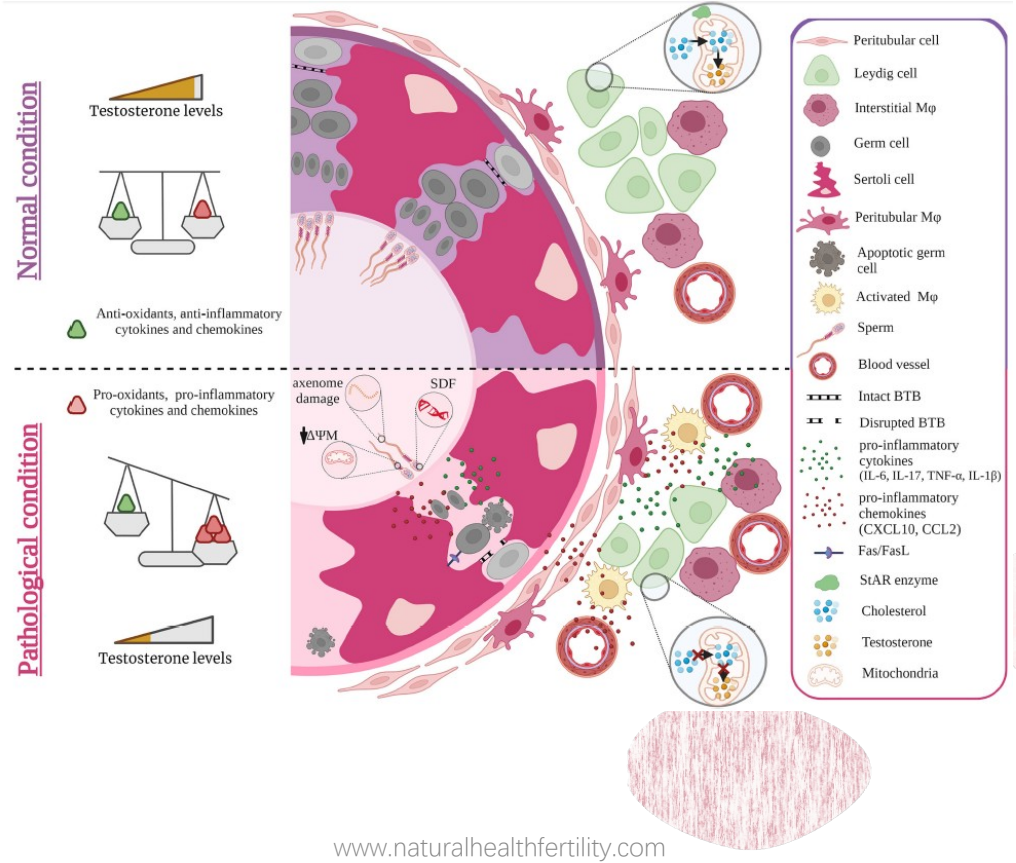
Barbagallo et al., 2021

ENVIRONMENTAL

- Levine et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update 2017; 23: 646-659.
  - between 1973 and 2011, found an average decline in mean sperm concentration of 1.6% per year, and an overall decline of 59.3%
- Levine et al. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. Hum Reprod Update 2022
  - A follow-up to the 2017 meta-analysis - sperm count is declining at an accelerated pace - 2.64% post-2000 and an overall fall of 62.3%, decline of ~4.70 million/year

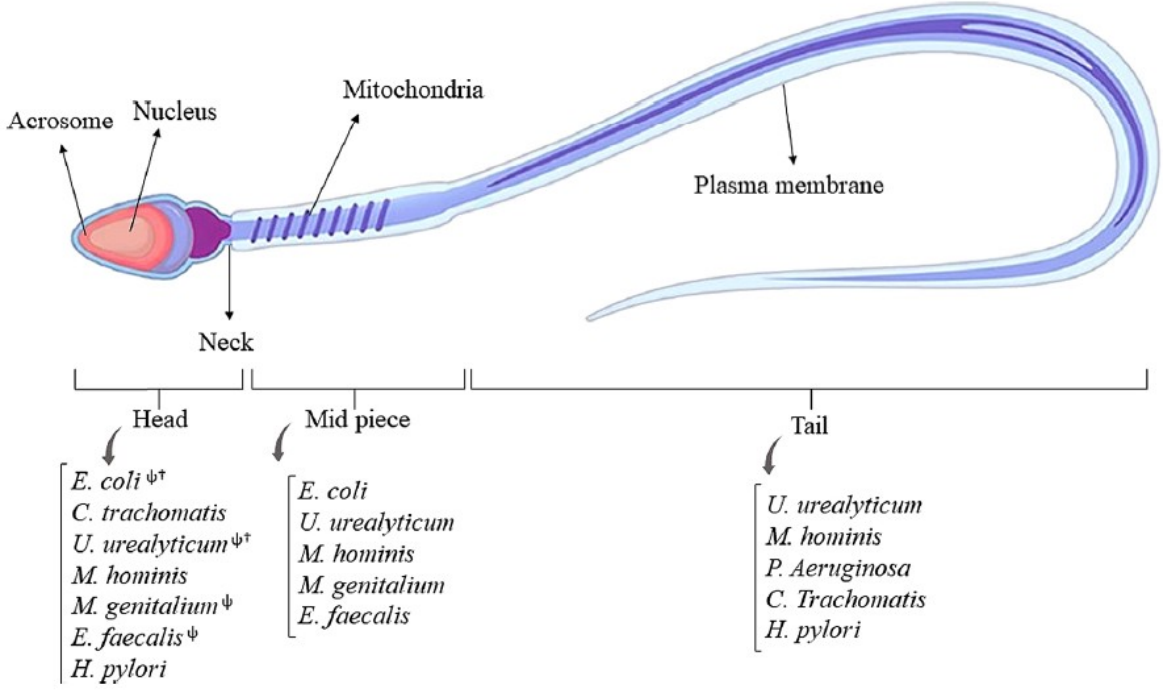
IMMUNOLOGY AND MICROBIOME

INFECTION AND SPERM HEALTH



Hasan et al., 2022

DIFFERENT PARTS OF SPERM STRUCTURE AND THE IMPACT OF DIFFERENT BACTERIA



ψ indicates the impact of mentioned bacteria on the neck region and † shows the impact of pathogen on the acrosomal regions

Farsimadan & Motamedifar, 2020

PATHOGENS AND SPERM HEALTH

Bacteria	Effects on male infertility	Locus of infection
Escherichia coli	Breakdown of mitochondrial membrane, impairment of acrosome reaction, sperm motility and morphology, decrease in sperm concentration, DNA damage	Prostate Epididymis Testis Seminal vesicles Urethra
Chlamydia trachomatis	Impairment of acrosome reaction, decrease in sperm concentration, sperm motility, viability and morphology, DNA damage	Prostate Epididymis Testis Seminal vesicles Urethra
Ureaplasma urealyticum	Impairment of acrosome reaction, sperm motility and morphology, decrease in sperm concentration, vitality, DNA damage	Prostate Epididymis Urethra
Mycoplasma hominis	Impairment of sperm, motility morphology, decreased sperm concentration and viability, DNA damage	Urethra Prostate
Mycoplasma genitalium	Impairment of sperm motility, decreased sperm concentration and vitality, DNA damage	Urethra Prostate
Neissseria gonorrhoeae	Impairment of Sperm integrity and DNA damage	Prostate Epididymis Testis Seminal vesicles Urethra

Farsimadan & Motamedifar, 2020

VIRUSES AND MALE GUT

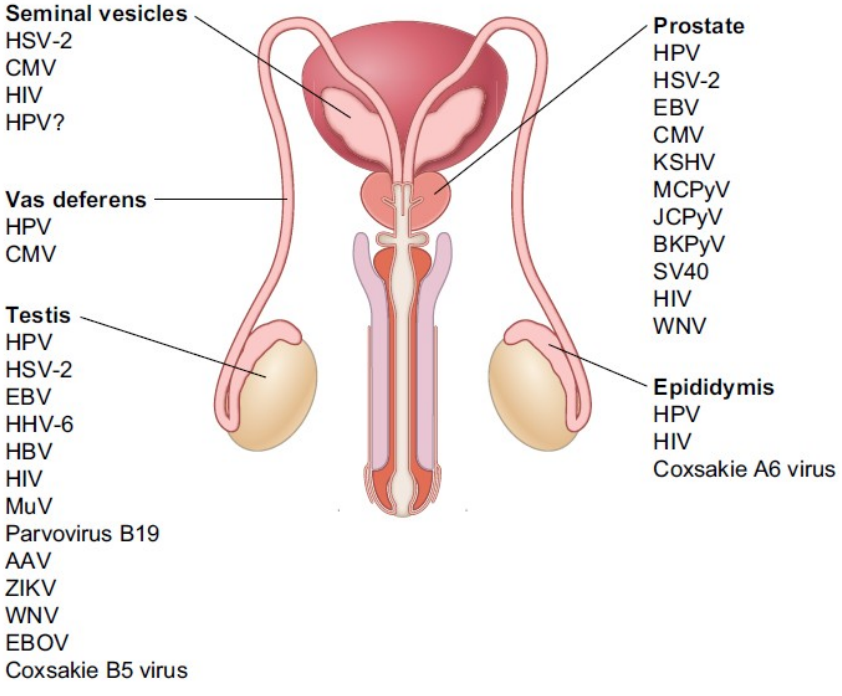
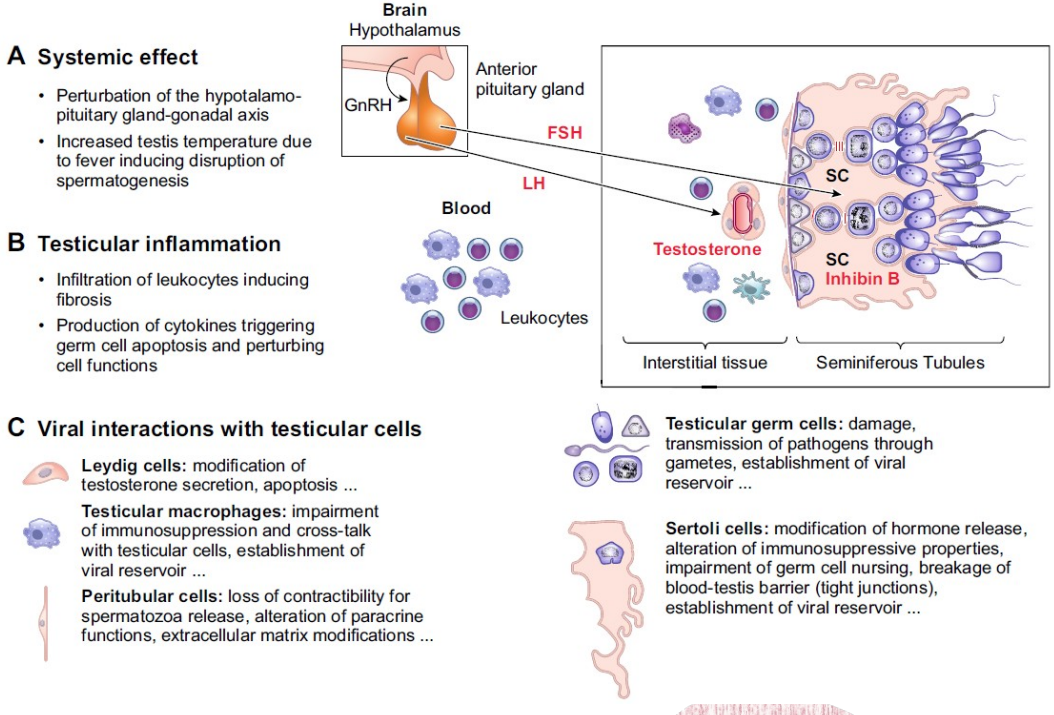


FIGURE 6. Viruses detected in human male genital tract in vivo. The figure recapitulates the viruses detected in human biopsies or secretions of the internal genitalia. HPV, human papillomavirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HHV, human herpesvirus; KSHV, Kaposi sarcoma-associated herpesvirus; HIV, human immunodeficiency virus; HBV, hepatitis B virus; MuV, mumps virus; AAV, adeno-associated virus; ZIKV, Zika virus; WNV, West-Nile virus; EBOV, Ebola virus; MCPyV, Merkel cell polyomavirus; JCPyV, JC polyomavirus; BKPyV, BK polyomavirus; SV40, simian virus 40.

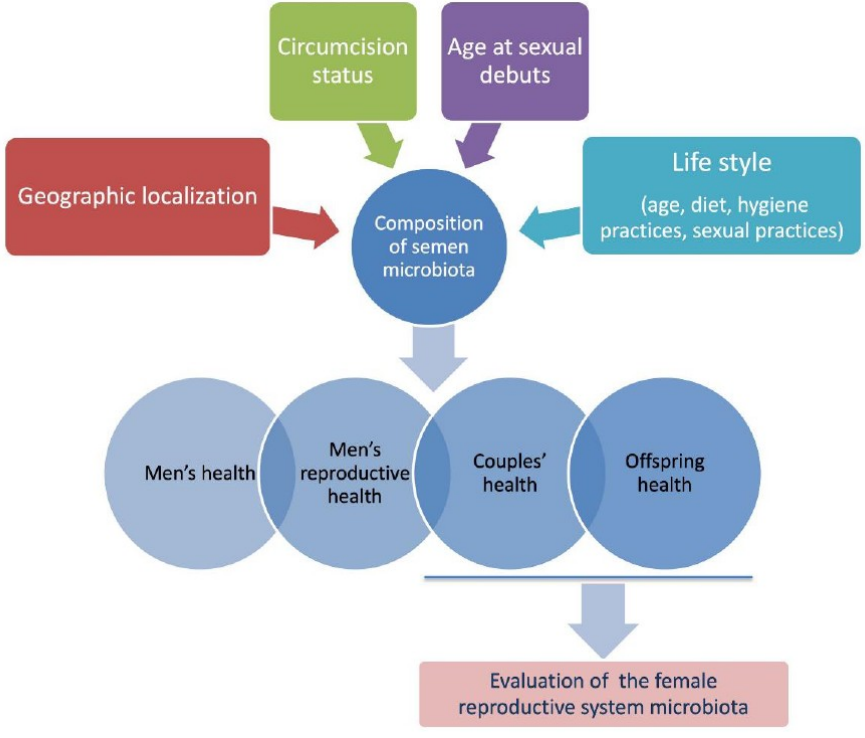
Le Tortorec et al., 2020

VIRAL INFECTIONS AND TESTICULAR PRETURBATION



Le Tortorec et al., 2020

INDIVIDUAL VARIABILITY FACTORS



Tomaiuolo et al., 2020

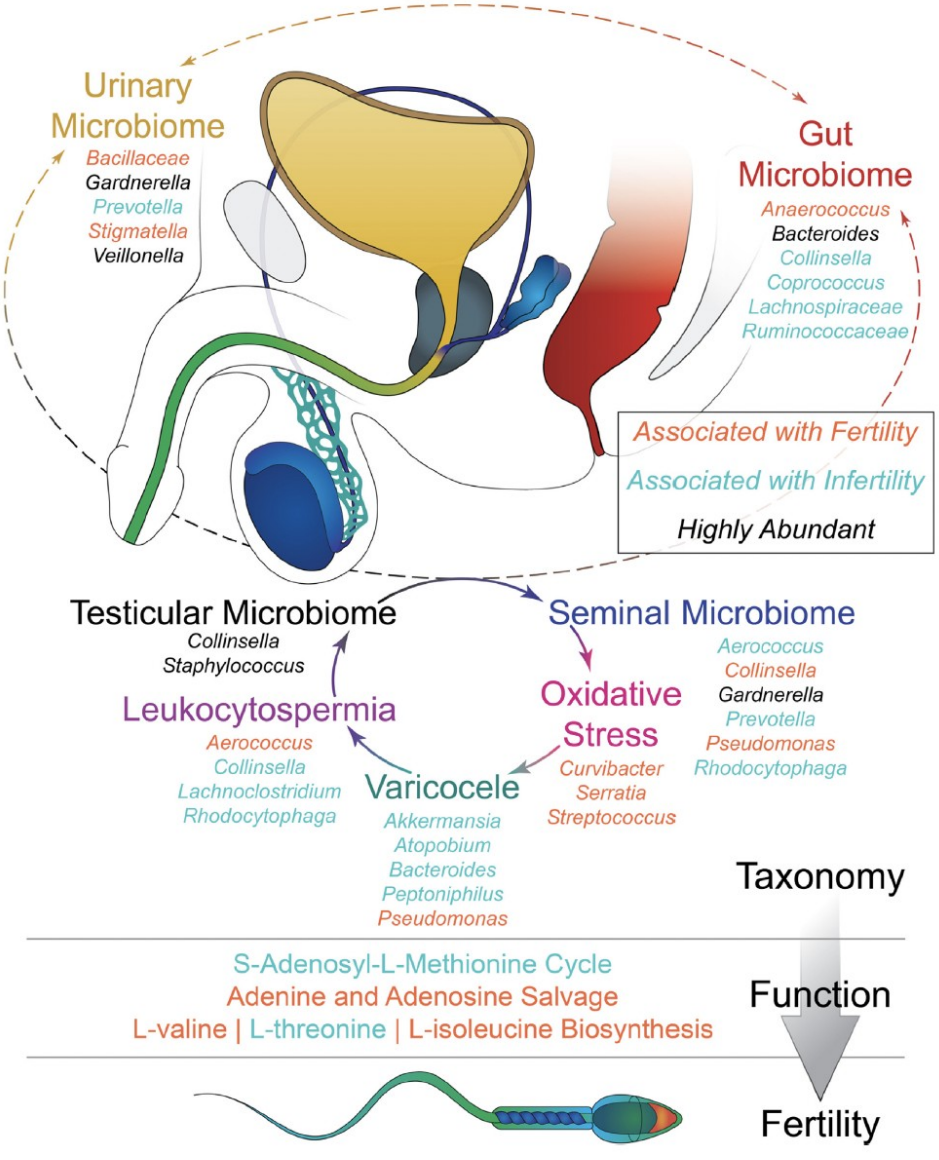
European Association of Urology

Platinum Priority – Sexual Medicine – Editor's Choice
Editorial by Petar Bajic and Alan J. Wolfe on pp. 837–838 of this issue

Functional and Taxonomic Dysbiosis of the Gut, Urine, and Semen Microbiomes in Male Infertility

Scott D. Lundy[a,b,], Naseer Sangwan[c], Neel V. Parekh[a], Manesh Kumar Panner Selvam[a], Sajal Gupta[a], Peter McCaffrey[d], Kovi Bessoff[d], Ayin Vala[d], Ashok Agarwal[a], Edmund S. Sabanegh[a], Sarah C. Vij[a], Charis Eng[b,e]*

[a] *Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA;* [b] *Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA;* [c] *Center for Microbiome and Human Health, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA;* [d] *Vastbiome, Millbrae, CA, USA;* [e] *Department of Genetics and Genome Sciences and Germline High Risk Cancer Focus Group, Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA*



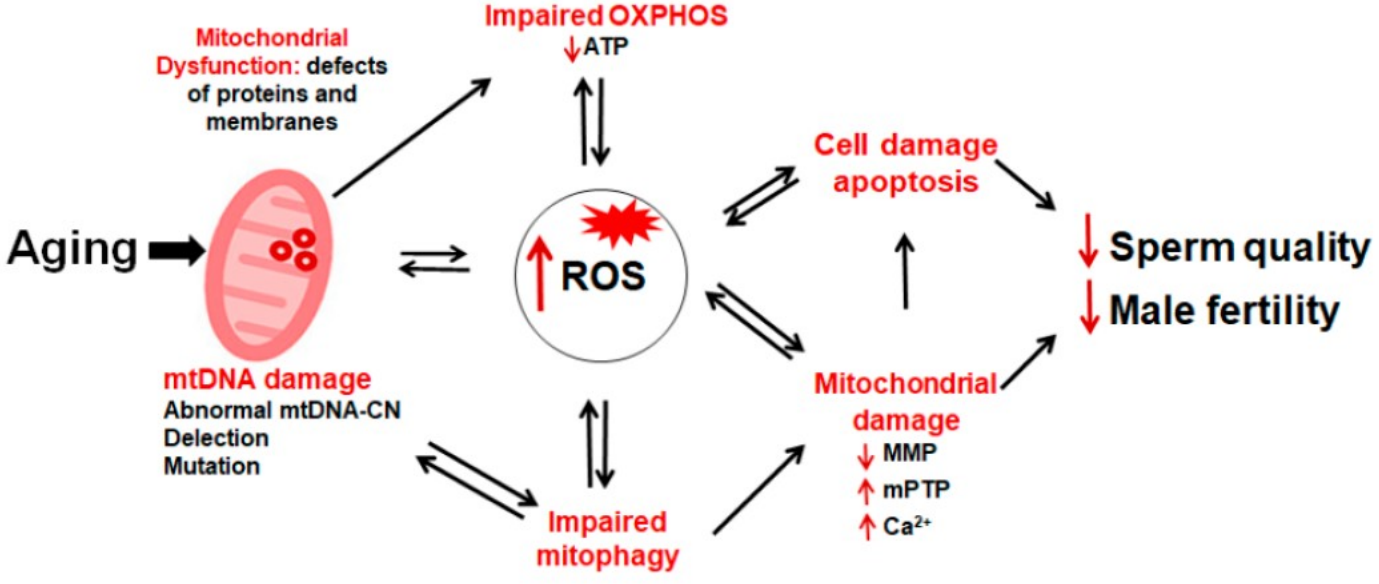
Lundy et al 2021

STRATEGIES TO ADDRESS SEMINAL MICROBIOME

- Investigate comprehensively – semen, urine, GIT
- Investigate both partners
- Sexual debut influence
- pH variables
- Address infection thoroughly
- Microbiome restoration

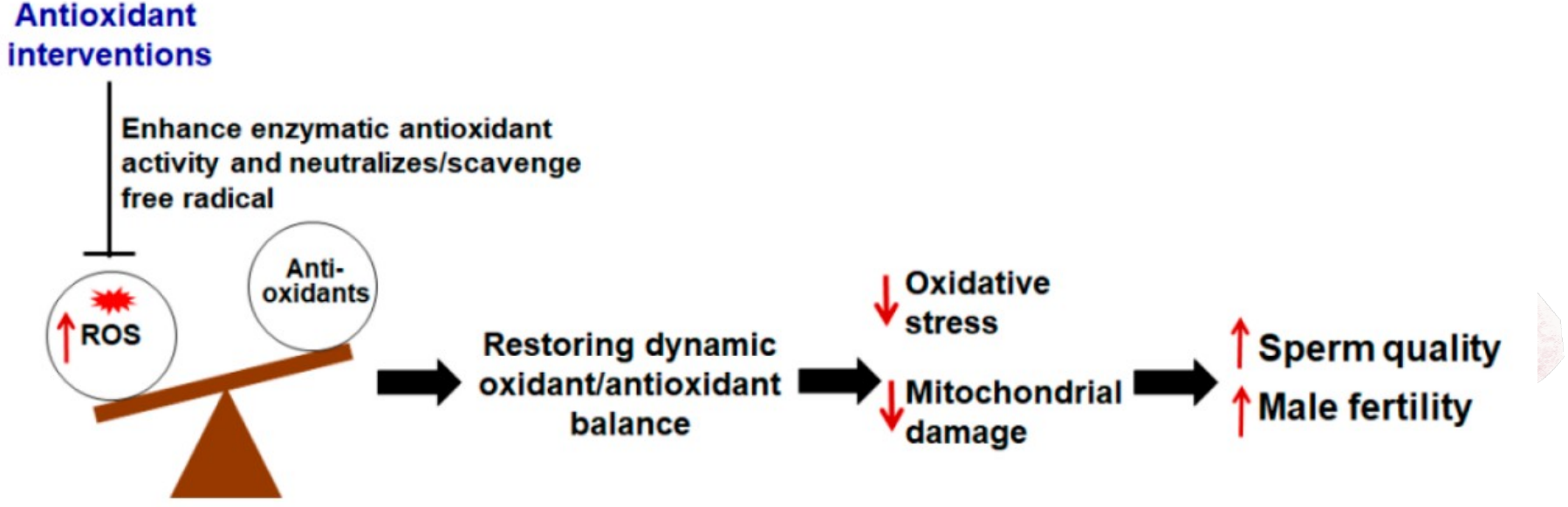
MITOCHONDRIAL HEALTH

MITOCHONDRIAL DYSFUNCTION



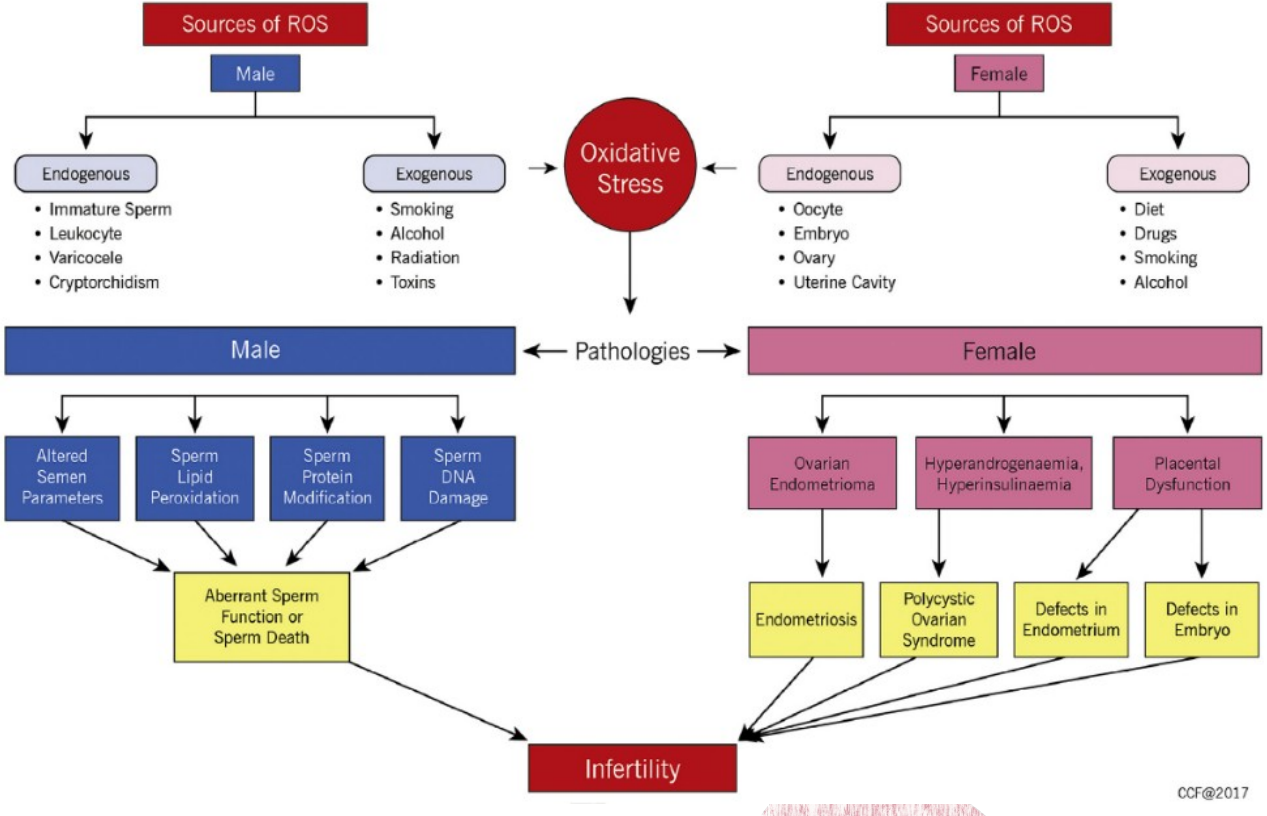
J.-J. Wang et al., 2022

ANTIOXIDANTS

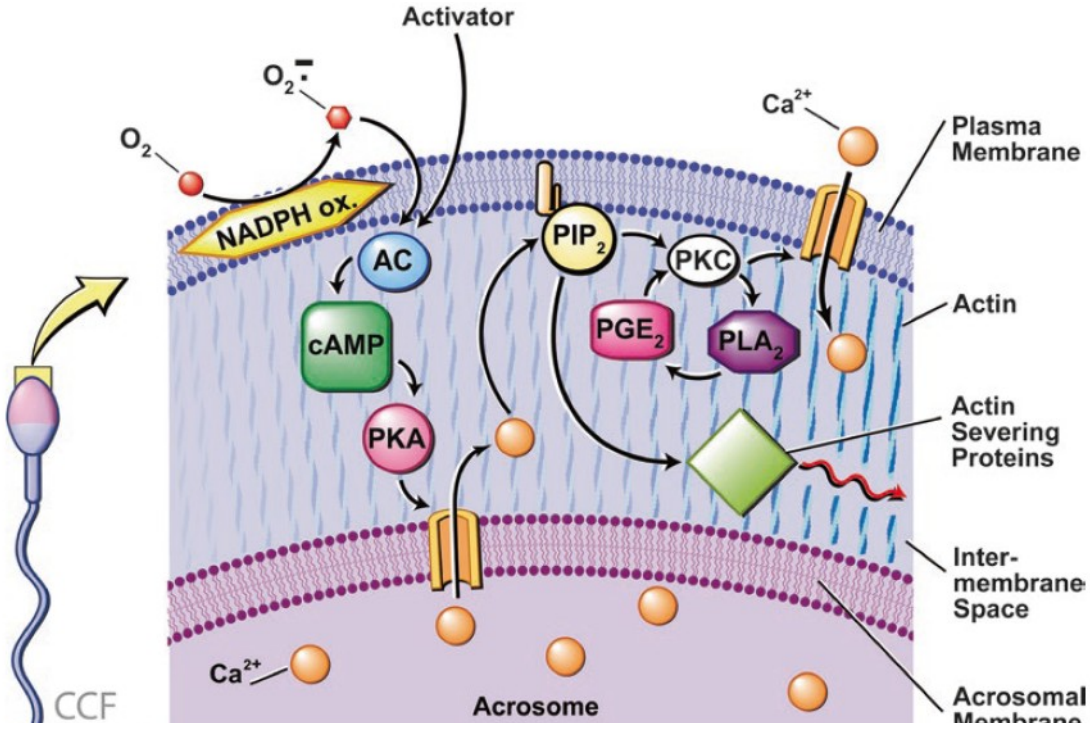


J.-J. Wang et al., 2022

SOURCES OF OXIDATIVE STRESS



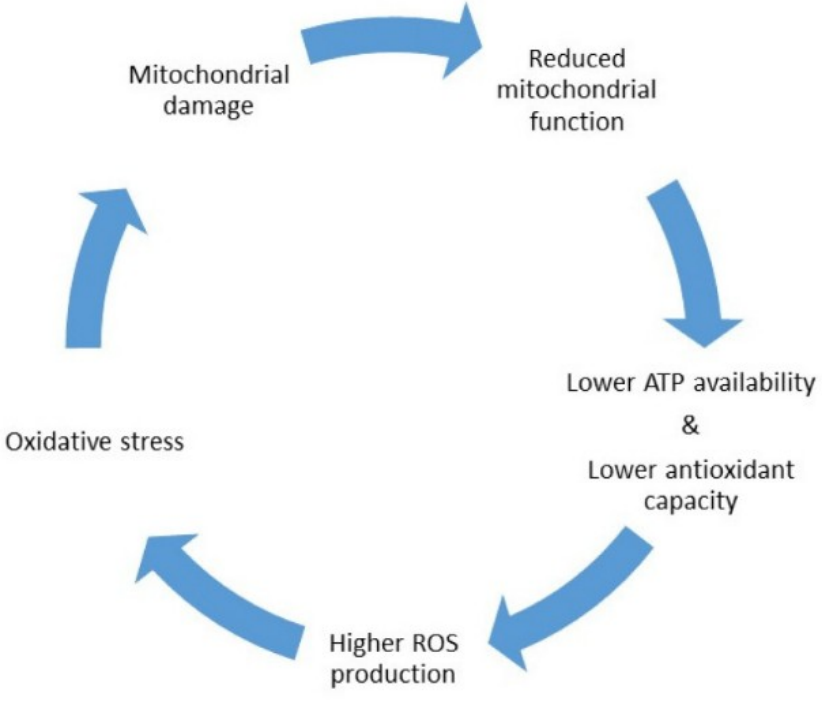
Roychoudhury, S., 2017



SPERM-OOCYTE INTERACTION IS SENSITIVE TO THE REDOX BALANCE

Dutta et al., 2019; Kothari et al., 2010, Henkel & Agarwal, 2020, Dutta et al., 2020; Khosrowbeygi & Zarghami, 2007; Otasevic et al., 2020, Agarwal et al., 2021, Otasevic et al., 2020

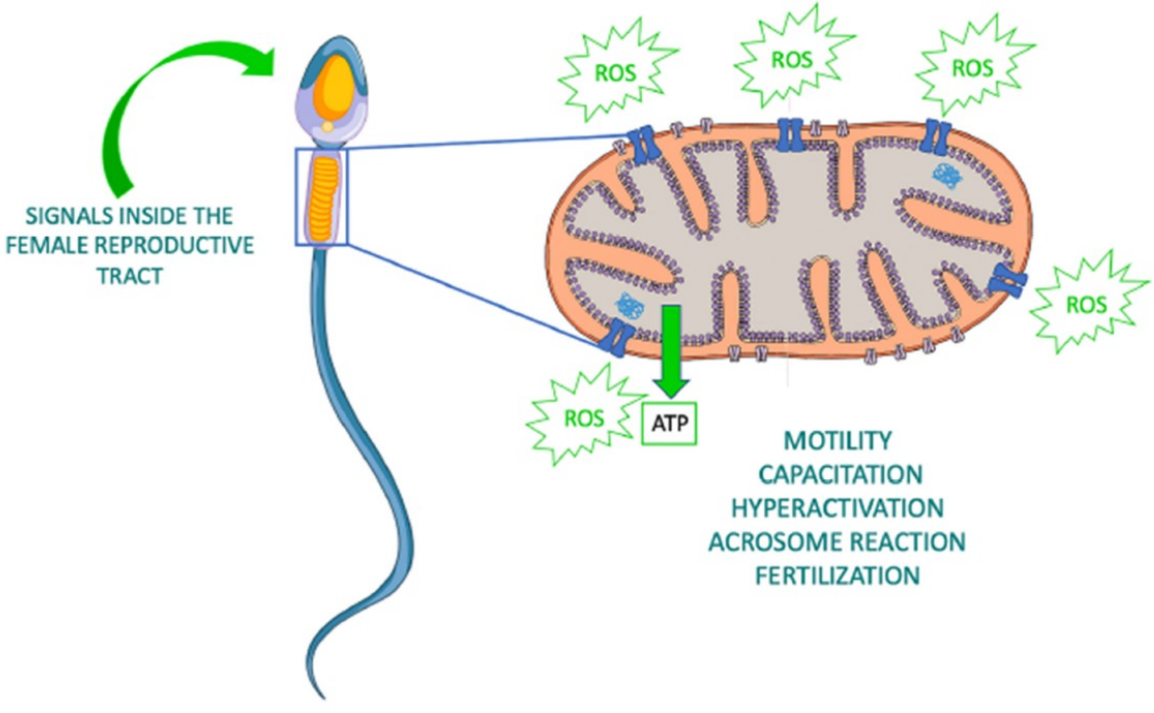
AGEING AND THE MITOCHONDRIA



Rodríguez-Varela & Labarta, 2021

- Vicious cycle between mitochondrial dysfunction and oxidative stress damage

ROLE OF SPERM MITOCHONDRIA IN HEALTH



Gualtieri, Kalthur, Barbato, Di Nardo, et al., 2021

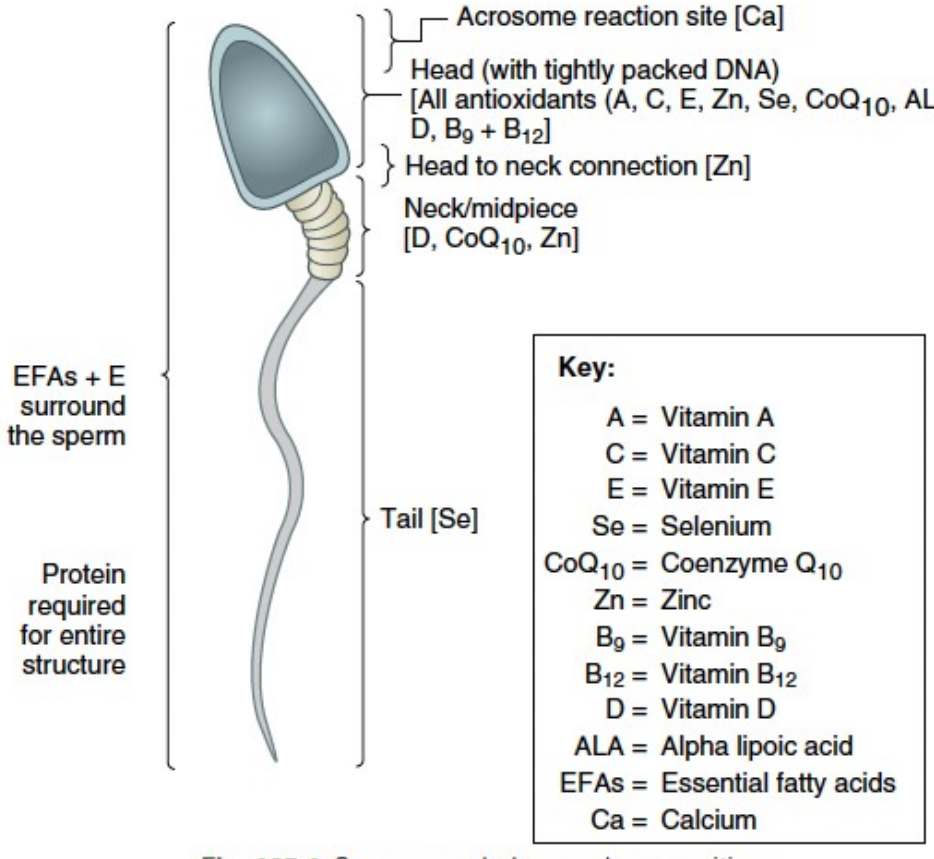


Fig. 185.1 Sperm morphology and composition.

Hechtman in Murray & Pizzorno 2020

MITOCHONDRIAL DYSREGULATION AND ROS LEAKAGE – EFFECT ON SPERM FUNCTION

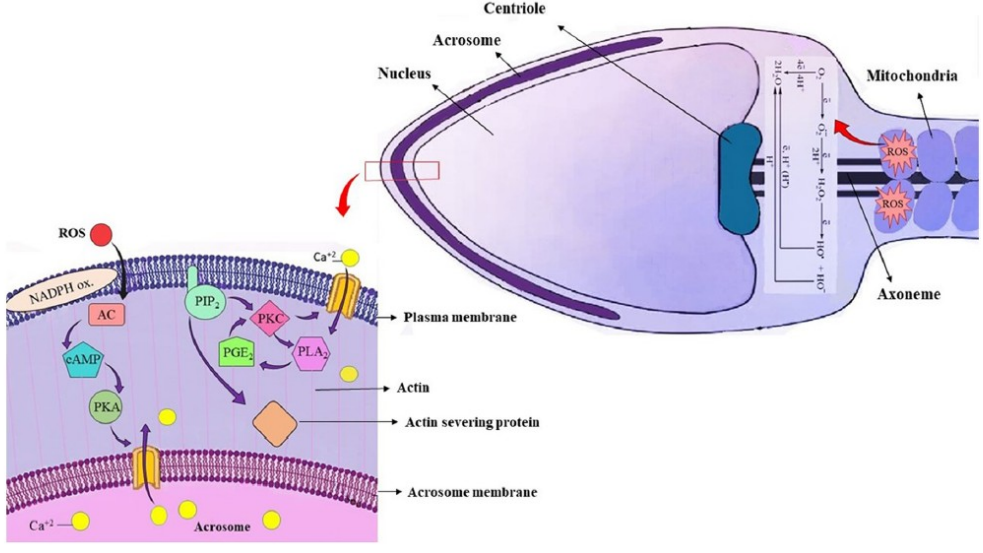


Fig. 2. Mitochondrial dysregulation and ROS leakage from the inner mitochondrial membrane that would affect acrosomal reaction and sperm function negatively. If the ROS production exceeds concentrations of antioxidants in the spermatozoa, oxidative stress occurs. Increases levels of ROS damage the inner and outer mitochondrial membranes and induce premature capacitation that would affect acrosomal morphology and function; hence, impact fertilizing capacity of human spermatozoa significantly. ROS in pathogenic bacteria such as *E. coli, Mycoplasma, Chlamydia, streptococci, staphylococci,* and *Ureaplasma* leads to apoptosis and breakdown of mitochondrial membrane. Both superoxide (O_2^{-}) and the hydroxyl radical (OH^{-}) are toxic to cells and cause chromosome deletions, dicentrics and sister chromatid exchanges.

Farsimadan & Motamedifar, 2020

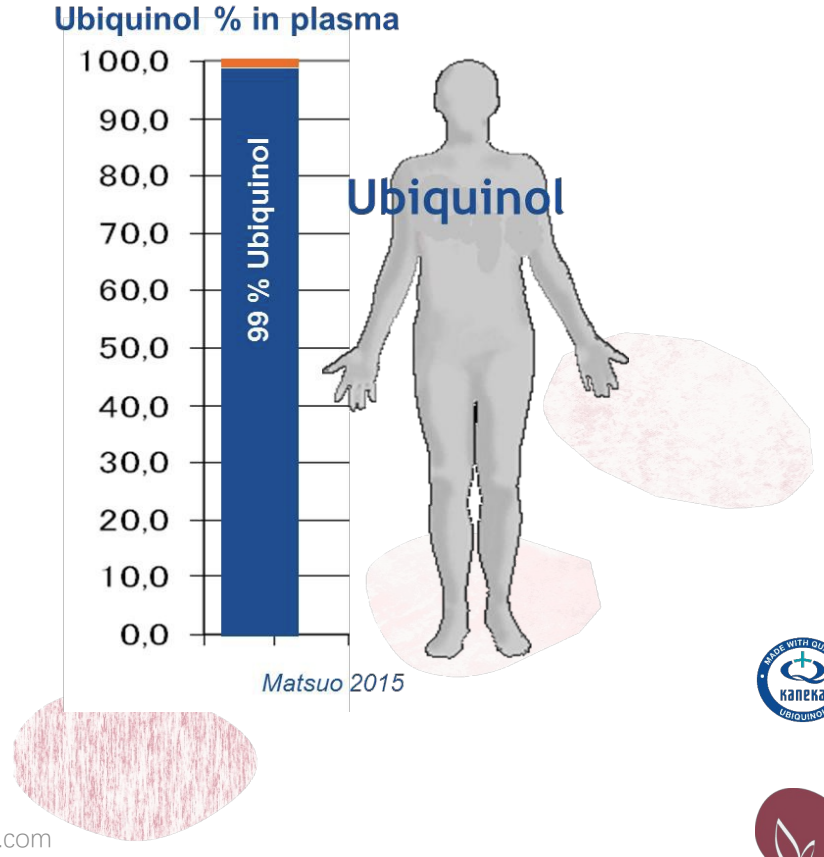
MITOCHONDRIAL HEALTH IN MALES

- Mitochondria are essential in several sperm functions and through ATP production, they regulate spermatogenesis, capacitation, induction of acrosome reaction, oocyte fusion, and fertilization
- Several sperm mitochondrial proteins were found to undergo capacitation-dependent tyrosine phosphorylation, indicating that mitochondrial functionality is required for sperm capacitation.
- High mitochondrial membrane potential (MMP) has been suggested to be necessary for acrosin activity, induction of AR and maintenance of chromatin integrity of human sperm
- Several studies proposed that assessment of MMP predicts the sperm fertilization competence both in natural conception and IVF
- Mitochondria represent the major source of ROS and reactive nitrogen species (RNS) in sperm and have a central role in redox signalling that drives fundamental events in the sperm life such as the activation of motility, hyperactivation, capacitation, AR, and fertilization

Ankel-Simons & Cummins, 1996; Rajender et al., 2010; Vertika et al., 2020; Durairajanayagam et al., 2021; Y.-J. Park & Pang, 2021; Shivaji et al., 2009; Gallon et al., 2006; G. Zhang et al., 2019; Marchetti et al., 2012; Sousa et al., 2011; Vončina et al., 2016; Moraes & Meyers, 2018

UBIQUINOL VS UBIQUINONE

- Over 99% of CoQ10 in circulation exists in the UBIQUINOL form in human subjects



UBIQUINOL

The dual nature of CoQ10 as a pro-oxidant and antioxidant makes it a key regulatory element of the oxidative state balance in the cell

Insufficient CoQ10 levels could lead to

- diminished mitochondrial respiration activity
- which may result in lower ATP production, less ROS counteraction, increased OS, mitochondrial damage, and subsequent mitochondrial dysfunction

Rodríguez-Varela & Labarta, 2020; Rodríguez-Varela & Labarta, 2021

UBIQUINOL

- This shapes a positive feedback system, in which lower mitochondrial activity may lead to increased OS damage, which subsequently induces mitochondrial impairment and, thus, affects the activity of these organelles.

- Therefore, OS can be caused by, or be the cause of, mitochondrial dysfunction, and insufficient CoQ10 levels may contribute to generate them both.

Rodríguez-Varela & Labarta, 2020; Rodríguez-Varela & Labarta, 2021

UBIQUINOL AND MALE FERTILITY VIA MITOCHONDRIA/OS ACTIVITY

- CoQ_{10} supplementation in males has been investigated and is associated with improved sperm count, motility, density and morphology
- One meta analysis found significant improvement in sperm motility and forward motility, without a significant impact on sperm count, sperm morphology, ejaculate volume or seminal plasma level of CoQ_{10}
    - 3 RCTs, unknown preparations included

Cirilli et al., 2021; Vishvkarma et al., 2020

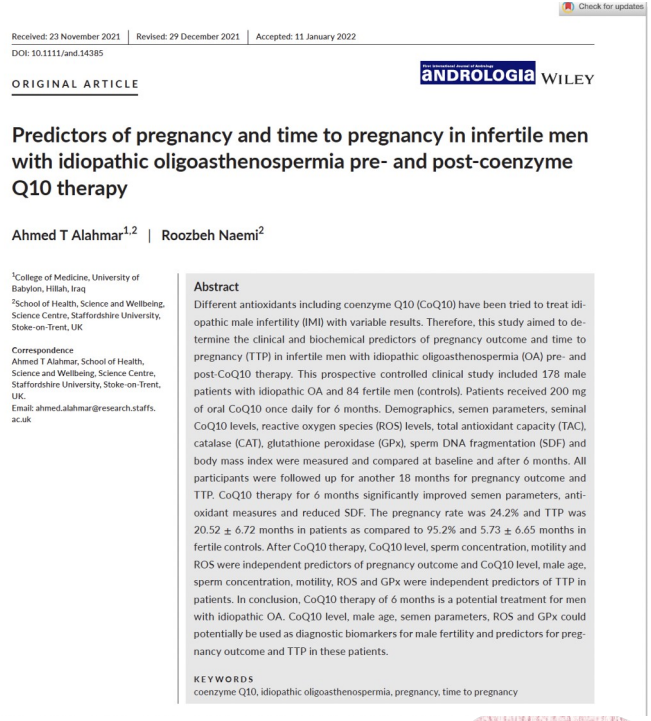
UBIQUINOL AND MALE FERTILITY

Study	Participan	RCT	Intervention	Intervention period	Outcome
Alahmar et al. (2021) [37]	Infertile patients with idiopathic oligoasthenozoospermia; 65 patients	Yes	CoQ10 200 mg/day orally	3 mo	Improved sperm concentration, progressive motility, total motility, seminal fluid CoQ10 concentration, TAC, ROS levels and SDF percentage, and glutathione peroxidase levels.
Alahmar and Sengupta (2021) [38]	Men with OAT; 70 patients	Yes	CoQ10 200 mg/day	3 mo	Improved sperm concentration, motility, and antioxidant status.
Alahmar (2019) [21]	Men with idiopathic OAT 35 subjects treated with CoQ10 at the dose of 200 mg/day and 30 patients with 400 mg/day	Yes	CoQ10 200 mg/day, 400 mg/day	3 mo	Idiopathic OAT with a greater improvement shown in men who took 400 mg/day than in those who took 200 mg/day
Cheng et al. (2018) [55]	Idiopathic oligoasthenozoospermia; 262 patients	Yes	L-carnitine 10 mg twice daily and CoQ10 20 mg thrice daily	3 mo	Combination of L-carnitine and CoQ10 can improve the sperm motility and outcome of clinical pregnancy in idiopathic OAT patients. Pretreatment with CoQ10 improves ovarian response to stimulation and embryological parameters in young women with poor ovarian reserve in IVF-ICSI cycles.
Tiseo et al. (2017) [35]	Subfertile couples; 211 subjects	No	CoQ10 19.2 mg/day (2.4–247.2 mg/day)	Not specified	Mean dietary intake of CoQ10 in this study was 10-fold lower than the supplemental dose used in clinical trials, showing improved sperm motility.
Giacone et al. (2017) [56]	12 Normozoospermic men and 12 asthenozoospermic patients	No	Zinc, D-aspartic acid, CoQ10 12 mg	Not specified	Improved sperm motility and increased fertilization rate in IVF/ICSI.
Nadjarzadeh et al. (2014) [51]	Idiopathic OAT; 60 patients	Yes	CoQ10 200 mg/day or placebo	3 mo	Enhanced semen quality and motility.
Gaby et al. (2013) [57]	Idiopathic OAT; 228 patients	Yes	CoQ10/200 mg/day	26 wk	Increased sperm concentration and morphology. Decreased motility and follicle stimulating hormone activity.
Abad et al. (2013) [58]	Asthenteratozoospermic patients; 20 subjects	No	L-carnitine 1,500 mg, CoQ10 20 mg, vitamin C 60 mg, vitamin E 10 mg, vitamin B 9200 µg, vitamin B12 1 µg, zinc 10 mg, selenium 50 µg	3 mo	DNA damage reduced from 28.5% to 20.12%.
Safarinejad (2012) [39]	Idiopathic OAT; 287 patients	No	CoQ10 300 mg twice daily	12 mo	Increased sperm concentration, progressive motility, and normal morphology.
Nadjarzadeh et al. (2011) [49]	Infertile men with idiopathic OAT; 60 patients	Yes	CoQ10 200 mg once daily	19 mo	Improved seminal parameters, lipid peroxidation.
Safarinejad et al. (2009) [59,60]	Infertile men with idiopathic OAT; 212 patients	Yes	CoQ10 300 mg once daily	26 wk	Improved seminal parameters and testicular volume.
Balercia et al. (2009) [61]	Idiopathic asthenozoospermia; 60 patients	No	CoQ10 200 mg/day	3 mo	Administration of CoQ10 increased CoQ10 levels in semen. It could be effective in enhancing sperm kinetic features in idiopathic asthenozoospermic patients.

CoQ10, coenzyme Q10; RCT, randomized clinical trial; TAC, total antioxidant capacity; ROS, reactive oxygen species; SDF, sperm DNA fragmentation; OAT, oligoasthenoteratozoospermia; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection.

Alahmar et al., 2021

PREGNANCY PREDICTION AND COQ10



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ORIGINAL ARTICLE

ANDROLOGIA WILEY

Predictors of pregnancy and time to pregnancy in infertile men with idiopathic oligoasthenospermia pre- and post-coenzyme Q10 therapy

Ahmed T Alahmar[1,2] | Roozbeh Naemi[2]

[1]College of Medicine, University of Babylon, Hillah, Iraq
[2]School of Health, Science and Wellbeing, Science Centre, Staffordshire University, Stoke-on-Trent, UK

Correspondence
Ahmed T Alahmar, School of Health, Science and Wellbeing, Science Centre, Staffordshire University, Stoke-on-Trent, UK.
Email: ahmed.alahmar@research.staffs.ac.uk

Abstract

Different antioxidants including coenzyme Q10 (CoQ10) have been tried to treat idiopathic male infertility (IMI) with variable results. Therefore, this study aimed to determine the clinical and biochemical predictors of pregnancy outcome and time to pregnancy (TTP) in infertile men with idiopathic oligoasthenospermia (OA) pre- and post-CoQ10 therapy. This prospective controlled clinical study included 178 male patients with idiopathic OA and 84 fertile men (controls). Patients received 200 mg of oral CoQ10 once daily for 6 months. Demographics, semen parameters, seminal CoQ10 levels, reactive oxygen species (ROS) levels, total antioxidant capacity (TAC), catalase (CAT), glutathione peroxidase (GPx), sperm DNA fragmentation (SDF) and body mass index were measured and compared at baseline and after 6 months. All participants were followed up for another 18 months for pregnancy outcome and TTP. CoQ10 therapy for 6 months significantly improved semen parameters, antioxidant measures and reduced SDF. The pregnancy rate was 24.2% and TTP was 20.52 ± 6.72 months in patients as compared to 95.2% and 5.73 ± 6.65 months in fertile controls. After CoQ10 therapy, CoQ10 level, sperm concentration, motility and ROS were independent predictors of pregnancy outcome and CoQ10 level, male age, sperm concentration, motility, ROS and GPx were independent predictors of TTP in patients. In conclusion, CoQ10 therapy of 6 months is a potential treatment for men with idiopathic OA. CoQ10 level, male age, semen parameters, ROS and GPx could potentially be used as diagnostic biomarkers for male fertility and predictors for pregnancy outcome and TTP in these patients.

KEYWORDS
coenzyme Q10, idiopathic oligoasthenospermia, pregnancy, time to pregnancy

Alkmar, AT; Naemi, R., 2022

Ubiquinol used
200mg/day
Best results >6/12

ANTIOXIDANTS

Ubiquinol	Improves count, motility, morphology, vitality, mitochondrial health, DNA, reduces ROS	600mg+/d
Carnitine	Improves count, motility and morphology	25mg+/d
Lycopene	Improves count, motility, reduces ROS	20-25mg+/d
NAC/GSH	Morphology, volume, DNA fragmentation, protamine deficiency, reduces ROS	600-1000mg
Melatonin	Reduced DNA damage, higher viability, motility	2-10mg/d
R-ALA	Viability, motility, count, reduced DNA damage	600mg/d
Vitamin C	Reduces ROS	1-2g/d divided doses
Vitamin E	Reduces ROS	1000-1200mg/d
Zinc	Inhibition of NADPH oxidase	50-150mg/d
Selenium	Count, morphology, motility, vitality, DNA fragmentation	300mcg/d

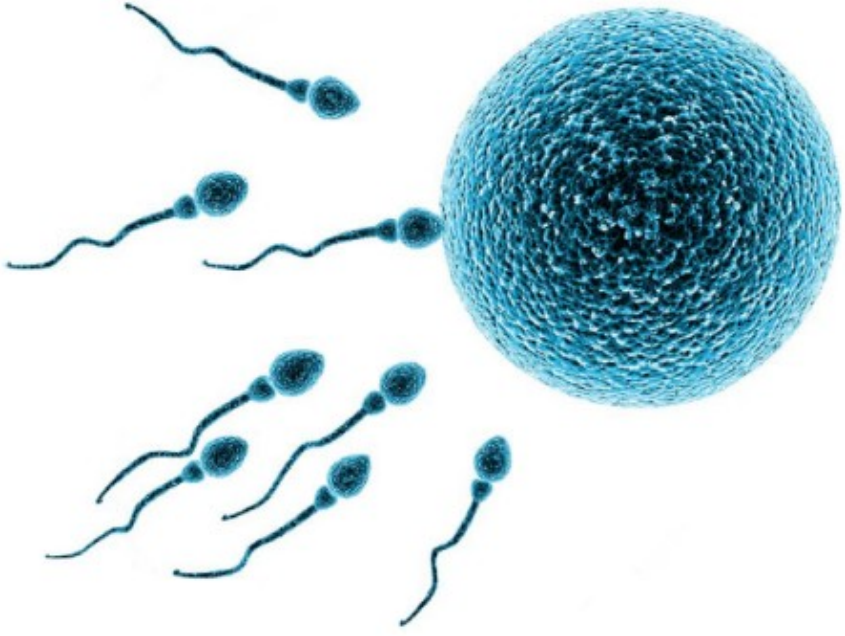
ZINC

Organ or System/Role	Action	Zn Deficiency
HPG axis/ hormone production	Inhibition of 5α reductase and affinity to LH receptor	Low serum T, testicular failure, changed sex steroid hormone receptor levels, damaged LH receptors, increase in circulating LH, decrease in T synthesis in Leydig cells
Antioxidant defense system/ free-radical scavenging	Inhibition of DNases and activity of Cu/Zn SOD	Oxidative damages (lipids, proteins, DNA), increase in LPO, increased MDA in the serum and seminal plasma and reduced levels of SOD, damage to the Leydig cells, apoptosis
cell physiology/ anti-apoptotic agent	Inhibition of caspases, Bcl-2/Bax ratio increase	DNA fragmentation, apoptosis, decreased population of the Leydig cells, germ cells, cell and tissue death
Epigenetics/ gene regulation, DNA methylation	Zn expression Zn transport binding proteins, testis-GC specific genes	Reduced reproductive potential, delayed sperm maturation
Testes/ testes development	participation in spermatogenesis (mitosis of spermatogonia and spermatocyte meiosis)	Retarded genital development, reduced testes weight, changes in the structure of Leydig cells, lower sperm concentration of the ejaculate, hyperviscosity of semen
Spermatozoa physiology/ cell metabolism	lipid and protein metabolism, oxygen consumption, nucleic acid synthesis, epithelial membrane integrity, chromatin condensation	Abnormal morphology, count, viability, motility of sperm, head–tail attachment problem, inhibition of spermatid differentiation, dysfunction of the zinc finger motif Cys2/His2 of P2 protamines
Fertilization/ embryonic formation	capacitation, the acrosome reaction	Change in pH, proteasomal activities, transfer of the amino peptidase from prostasomes, lower sperm membrane fluidity, improper fertilization

Abbreviations: deoxyribonucleases (DNases).

Maciejewski et al., 2022

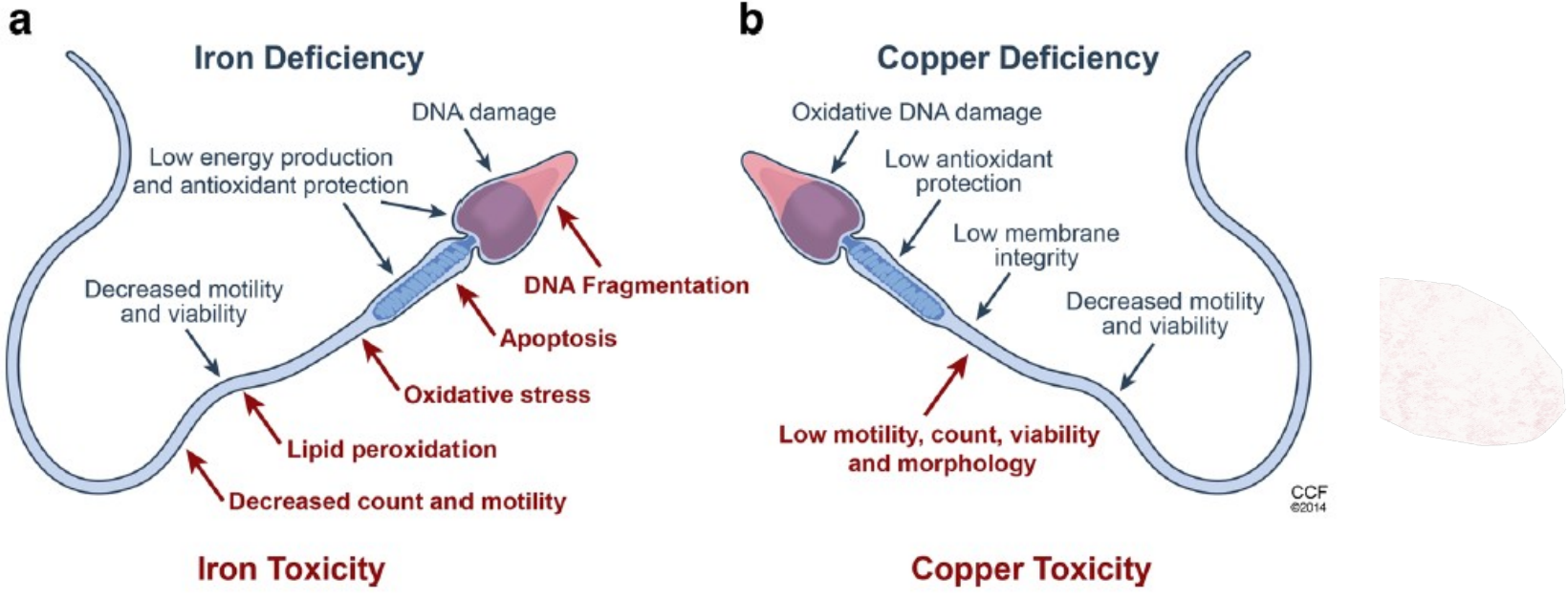
VITAMIN D



- Reduced sperm counts
- Altered sperm morphology
- Altered sperm motility
- Impaired egg binding and acrosome activation

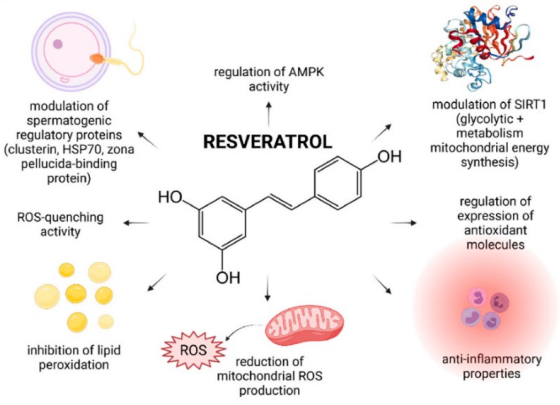
Heyden & Wimalawansa, 2018

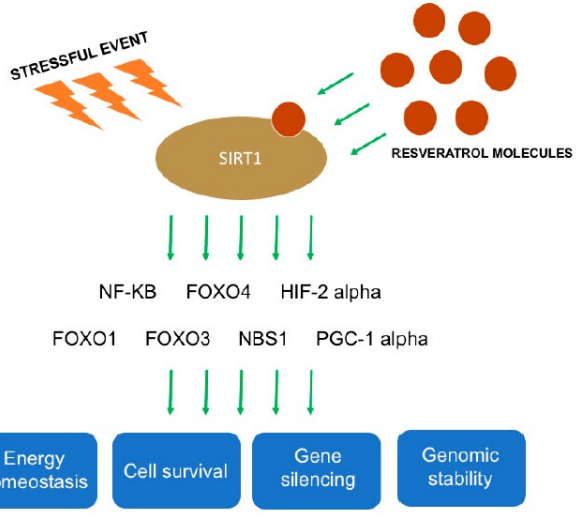
IRON, COPPER AND SPERM HEALTH

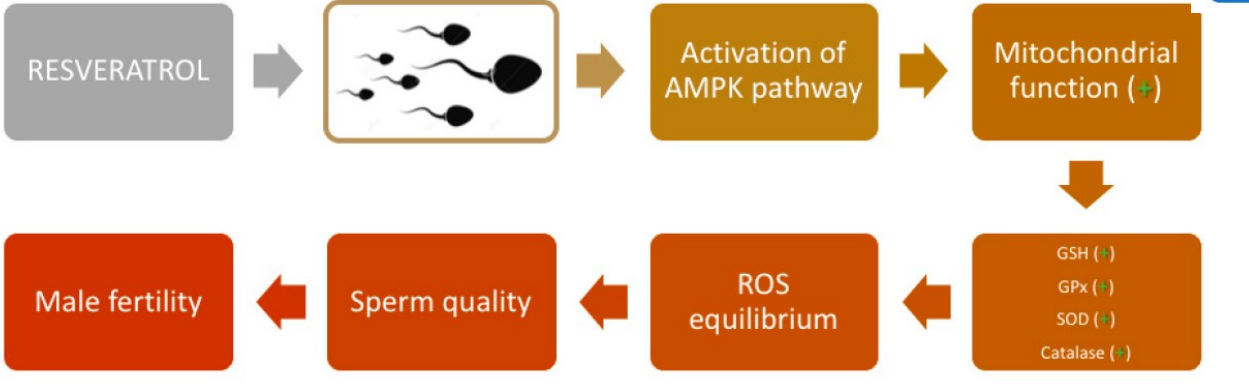


Tvrda et al., 2015

RESVERATROL







Pasquariello et al., 2020; Tvrdá et al., 2021

METHYLATION

frontiers in Cell and Developmental Biology

REVIEW
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Check for updates

Epigenetics of Male Infertility: The Role of DNA Methylation

John Charles Rotondo†, Carmen Lanzillotti†, Chiara Mazziotta†, Mauro Tognon*† and Fernanda Martini*†*

Laboratories of Cell Biology and Molecular Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

OPEN ACCESS

Edited by:

DNA METHYLATION AND SPERMATOGENESIS

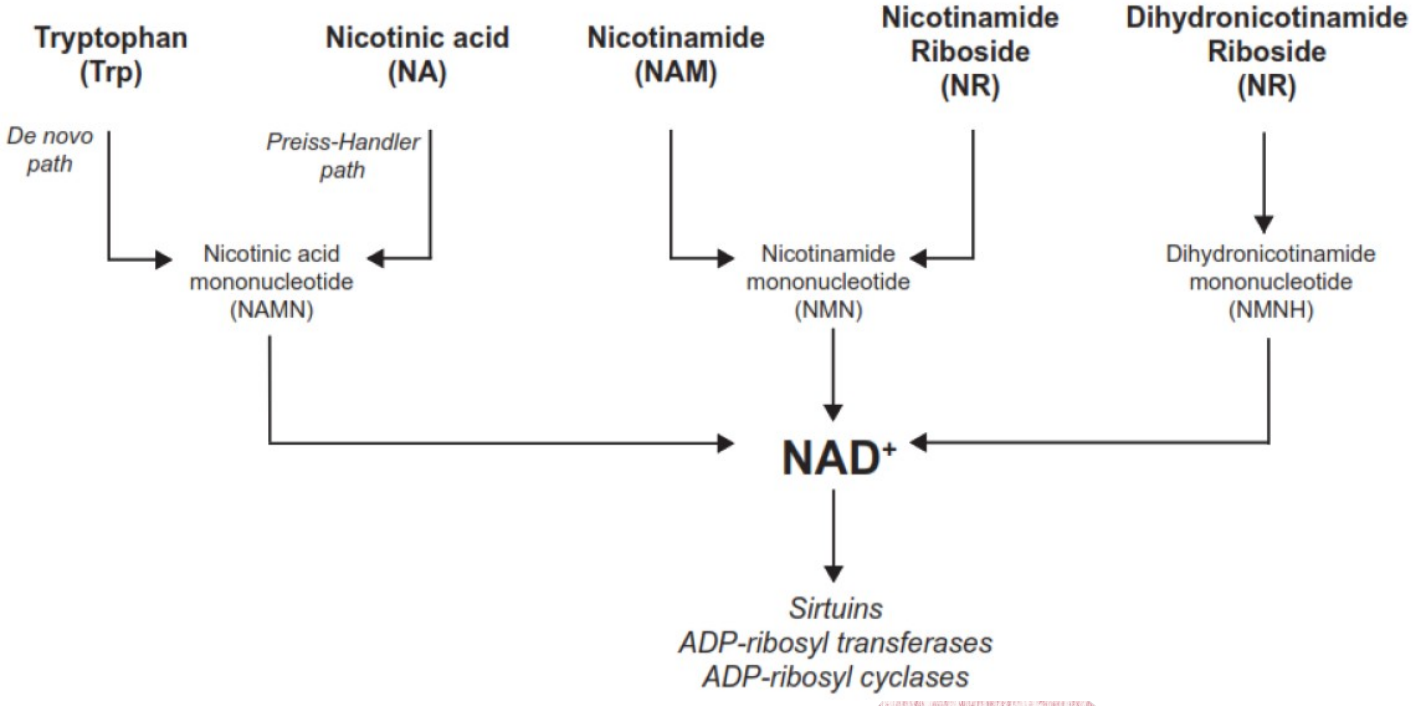
- Correct methylation of DNA ensures proper chromatin condensation in the sperm head, enabling sperm maturation and its ability in fertilization and post-fertilization events
- Incomplete or abnormal condensation of the sperm chromatin results in damaged DNA, leading to the impairment of egg cell fertilization and/or reduction in pregnancy rates
- Everything he does changes DNA methylation

METHYLATION CO FACTORS

- Folate and its derivatives
- Vitamin B12 and products
- Vitamin B3 and NAD precursors (Tryptophan included)
- Methionine
- SAMe
- TMG
- Magnesium
- Zinc
- Vitamin B6
- GSH
- Others

AUTOPHAGY AND REPAIR

NAD+ PRECURSORS AND CONVERSIONS



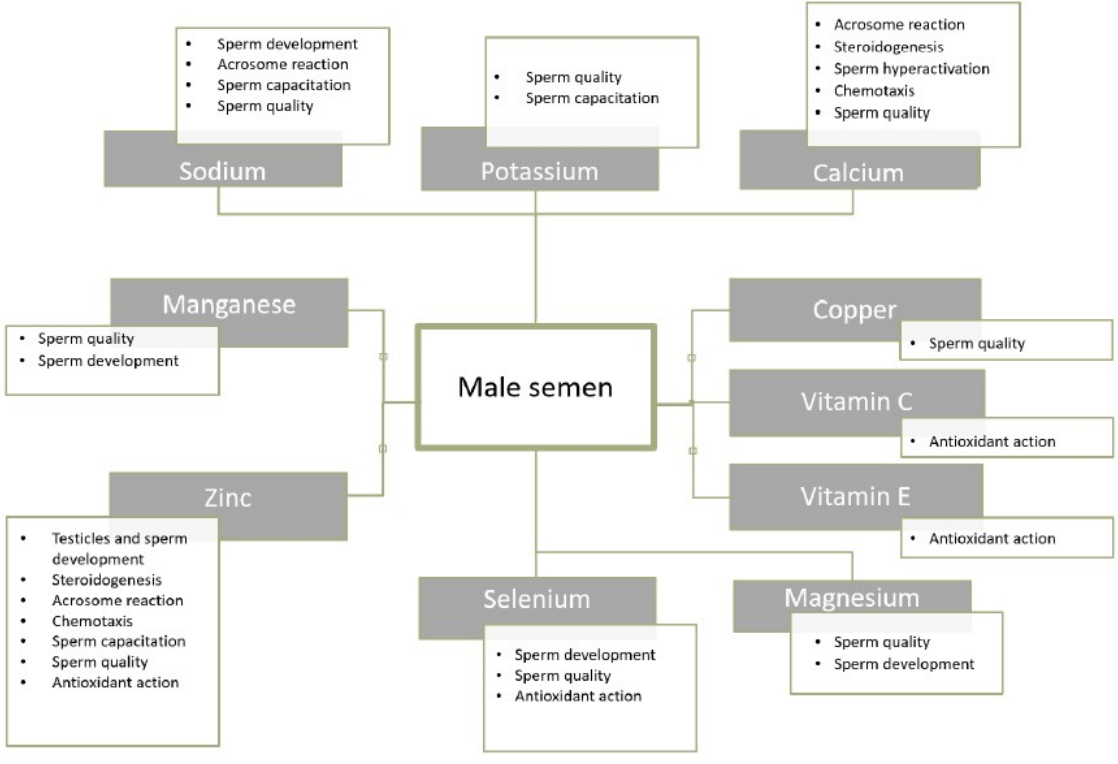
Canto, 2022

THERAPEUTIC OPTIONS

- IV NAD+ – Only recognized effective means of clinically increasing systemic NAD^+ levels
- NAD^+ precursors – NA, NAM, NMN, NR, and nicotinic acid riboside (NAR), are likely to provide some benefits
- Contrasting evidence indicates that NAD^+ precursors are not equal in their beneficial pathways and the effects on their hosts
- The liver makes NAD^+ from tryptophan and from orally delivered NR

Braidy et al., 2019; L. Liu et al., 2018; Palmer et al., 2021

MICRONUTRIENTS



Skoracka et al., 2020

MICRONUTRIENTS

Elements	Study models	Findings
Ca deficiency	Human seminal	↓Steroidogenesis; ↓testosterone
Ca deficiency	Human seminal	↓Sperm acrosome reaction
Ca deficiency	Human seminal	↓Fertilization process
Ca deficiency	Human seminal	↓Semen volume, ↓sperm counts; ↓sperm motility
Na & K deficiency	Human seminal	↓Fertilization rate
Na & K deficiency	Human seminal	↓Sperm quality
Na & K deficiency	Human seminal	↓Semen volume
Na deficiency	Intracellular	↓Sperm capacitation
K deficiency	Human seminal	↓Testosterone
Na deficiency	Human seminal	↓Progesterone; ↓sperm acrosome reaction
Mg deficiency	Human seminal	↓Premature ejaculation
Mg deficiency	Human seminal	↓Sperm motility
Zn deficiency	Human seminal	↓Sperm quality
Zn deficiency	Body	↓Testicular development & function
Zn deficiency	Human seminal	↓Sexual maturation; ↑hypogonadism; ↑gonad dysfunction; ↓testicular weight; ↑Leydig cells damage; ↑testicular atrophy; ↑seminiferous tubules damage
Zn deficiency	Human seminal	↓Steroidogenesis; ↓testosterone; ↓spermatogenesis
Zn deficiency	Human seminal	↓Sperm capacitation; ↓acrosome reaction
Zn deficiency	Human seminal	↓Sperm quality; ↑ROS; ↑oxidative stress; ↑lipid peroxidation; ↓sperm membrane fluidity; ↓sperm–egg interaction; ↓fertilization; ↓antioxidant capacity
Se deficiency	Dietary intake	↑Oxidative stress; ↓spermatogenesis; ↓sperm quality
Se deficiency	Human seminal	↓Secretion of testosterone; ↓spermatogenesis
Se deficiency	Human seminal	↓Sperm count; ↓motility; ↓normal morphology; ↓vitality
Mn deficiency	Human seminal	↓Sperm quality
Mn deficiency	Human seminal	↓Seminal fluid volume; ↓sperm normal morphology
Increased Mn level	Human seminal	↓Sperm motility; ↓sperm count
Cu deficiency	Human seminal	↓Sperm quality
Cu deficiency	Human seminal	↑Oxidative stress; ↓SOD activity
Increased Cu level	Human seminal	↓Sperm motility

Mirnamniha et al., 2019

MICRONUTRIENTS

Micronutrient	Description	Effect on male	Recommended dose	Sources
Folic acid	• Known as vitamin B9 • Essential compound involved in key biochemical processes	• Provides carbon for DNA synthesis and methylation • Critical to spermatogenesis	400 µg/day	Vegetables, fruits, nuts, seafood, eggs, dairy, meat
Calcium	• Plays a role in reproductive health • Facilitates fertilization	Regulates sperm motility	1 g/day	Dairy products, cabbage, kale, broccoli, almonds, tofu, sardines with bones
Iron	• Maintenance of healthy red blood cells • Oxygen transport in the blood • Immune function • Free radical homeostasis	• Essential to ejaculate fluidity • Maintains sperm pH • Sources of ferritin, which protects testicular tissue • Developing sperm	30–60 mg/day	Beans, vegetables, cereals, breads
Vitamin B12	• Known as cobalamin • Cofactor in DNA and fatty acid synthesis • Amino acid metabolism	• Improves the sperm quality	50 µg/day	Fish, meat, poultry, eggs, milk
Selenium	• Selenoprotein • Plays a potential role in both female and male fertility	• Maintains the spermatozoa integrity and viability • Protects them from oxidative damage	60 µg/day	Nuts, seafood, fish, shrimp, muscle meats, cereals, dairy products
Zinc	• Plays a key role in fertility for both female and male • Has a greater importance for men	• Testosterone synthesis • Sperm viability • Testicle development	20 mg/day	Oysters, eggs, red meat, poultry, seafood, beans, nuts, grains, dairy
Vitamin E	• A vital antioxidant in the cell membrane • Supports reproductive functions	• Supports reproductive function in men • Increases sperm quality and quantity	22–30 mg/day	Nuts, seeds, vegetable oils, green leafy vegetables, fortified cereals
Vitamin A	• Supports the immune system • Protects the gonads, reproductive tissues from oxidative stress	• Has influence on sperm morphology and concentration	370 µg/day	Liver, fish oil, eggs, milk, leafy greens, vegetables, tomatoes, fruits
Vitamin C	• Aiding in tissue, hormone development • Cofactor for enzymes, reducing oxidative damage	• Affects the integrity and structure of sperm • Promotes an environment for sperm to thrive	85 mg/day	Citrus, berries, pepper, kiwis, broccoli, brussels sprouts, tomatoes, potatoes

Ma et al., 2022

NUTRIENT AND SPERM IMPACT

	Effect on Sperm Parameters			
	Count	**Total Motility**	**Morphology**	**DNA Damage**
Active ingredients	Zinc Selenium Folic acid Vitamin B_{12} Folic acid L-citrulline L-arginine α-Lipoic acid L-carnitine C-Q10 DAA TT Inositol Vitamin C DHA Lycopene	Zinc Selenium Folic acid L-arginine L-citrulline α-Lipoic acid L-carnitine NAC C-Q10 Astaxanthin DAA TT Inositol α-Tocopherol Vitamin C Lycopene DHA	Zinc NAC Coenzyme Q10 TT α-Tocopherol	Zinc NAC α-Tocopherol Vitamin C DHA

Key:
DAA: D-aspartic acid
TT: Tribulus terrestris

Garolla et al., 2021

NUTRIGENOMICS

NUTRIGENOMICS

Dietary component	Gene and SNP	Impact
Ratio of unsaturated to saturated fat	*TCFL2*: *rs7903146* (45,46)	Improper ratio can lead to obesity, insulin resistance, negatively impacting semen quality (47,48)
Omega-3	*NOS3*: *rs1799983* (49); *FADS1*: *rs174547* (50); *FADS2*: *rs2727270*, *rs498793* (51,52)	Sperm motility; membrane fluidity; sperm concentration (53,54)
Saturated fat	*APOA2*: *rs5082* (55)	Elevated BMI; sperm count, concentration, motility, morphology (56,57)
Sugar	*GLUT2*: *rs5400* (58)	Sperm motility and count (59)
Fiber	*TCF7L2*: *rs12255372* (60)	Low fiber diet can lead to insulin resistance and type 2 diabetes, negatively impacting spermatogenesis, sperm maturation (61)
Gluten	*HLA*: *rs2395182*, *rs7775228*, *rs2187668*, *rs4639334*, *rs7454108*, *rs4713586* (62)	Androgen resistance (63); sperm morphology and motility (64)
Caffeine	*CYP1A2*: *rs7662551* (65)	Sperm motility, count and morphology improved at low amounts (66); testosterone levels and sperm volume impaired on high amounts (67)

Vanderhout et al., 2021

NUTRIGENOMICS

Micronutrient	Gene and SNP	Impact
Retinoic Acid	*BCMO1*: rs11645428 (11)	Meiosis I/II and post meiotic spermatid development (12,13)
Vitamin B_{12}	*FUT2*: rs602662 (14)	Sperm count, quality and motility (15)
Vitamin C	*GSTT1*: *insertion or deletion* (16)	Semen volume, concentration, sperm count, morphology and motility (17)
Vitamin D	*CYP2R1*: *rs10741657* (18); *GC*: *rs2282679* (18,19)	Sperm motility and morphology (20); sex hormone binding globulin (SHBG) (21)
Vitamin E	*CYP4F2*: *rs2108622* (22); *SCARB1*: *rs11057830* (22); *APOA5*: *rs12272004* (22)	Acrosome reaction (23); sperm morphology (24)
Folate	*MTHFR*: rs1801133 (25)	Sperm density and morphology (26)
Choline	*CHDH*: *rs12676* (27,28); *PEMT*: *rs4646343* (29); *PEMT*: *rs7946* (29)	Sperm motility (27,28)
Betaine	*CHDH +432*: *rs12676* (30); *PEMT -744*: *rs12325817* (30)	Spermatogenesis (31)
Iron	*TMPRSS6*: *rs4820268* (32); *TFR2*: *rs7385804* (33); *HFE*: *rs1800562* (34); *SLC17A1*: *rs17342717* (35); *HFE*: *rs1799945* (34); *TF*: *rs3811647* (34)	Spermatogenesis (36); sperm volume, density, motility and morphology (37); excess leads to oxidative DNA damage (38)
Calcium	*GC*: *rs7041* (39); *GC*: *rs4588* (39)	Sperm maturation (40), motility (41), morphology (42), and overall function (43,44)

Vanderhout et al., 2021