Leah Hechtman
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FERTILITY AND REPRODUCTIVE HEALTH
Clinician, Researcher, Author and Educator

FOUNDATIONAL FERTILITY

Female fertility

DISCLAIMER

(This is NOT an exhaustive list)

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

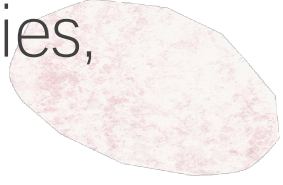
OUTLINE

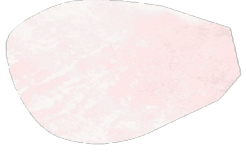
The dance

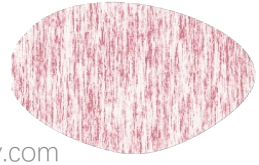
The components of healthy female fertility

Appropriate assessments and interpretation

Influencing female fertility – treatment strategies, prescriptions, recommendations







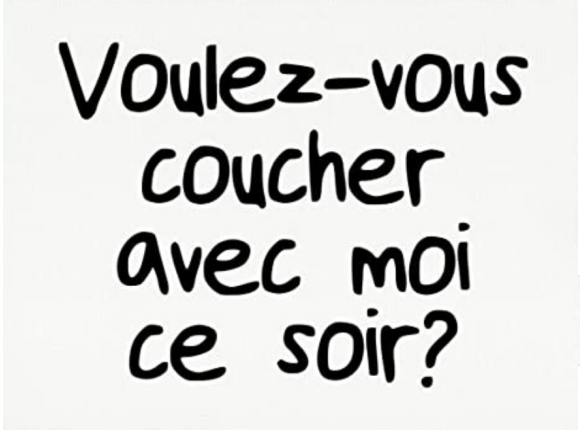
THE DANCE

BASIC STEPS

Female needs to be ovulating

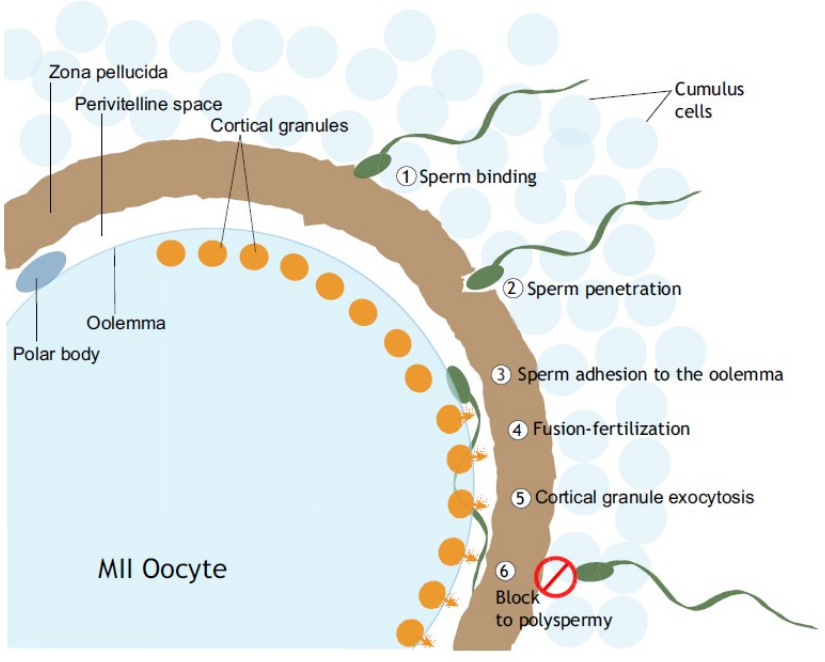
Male needs viable healthy sperm

Need to have sex (or be creative)



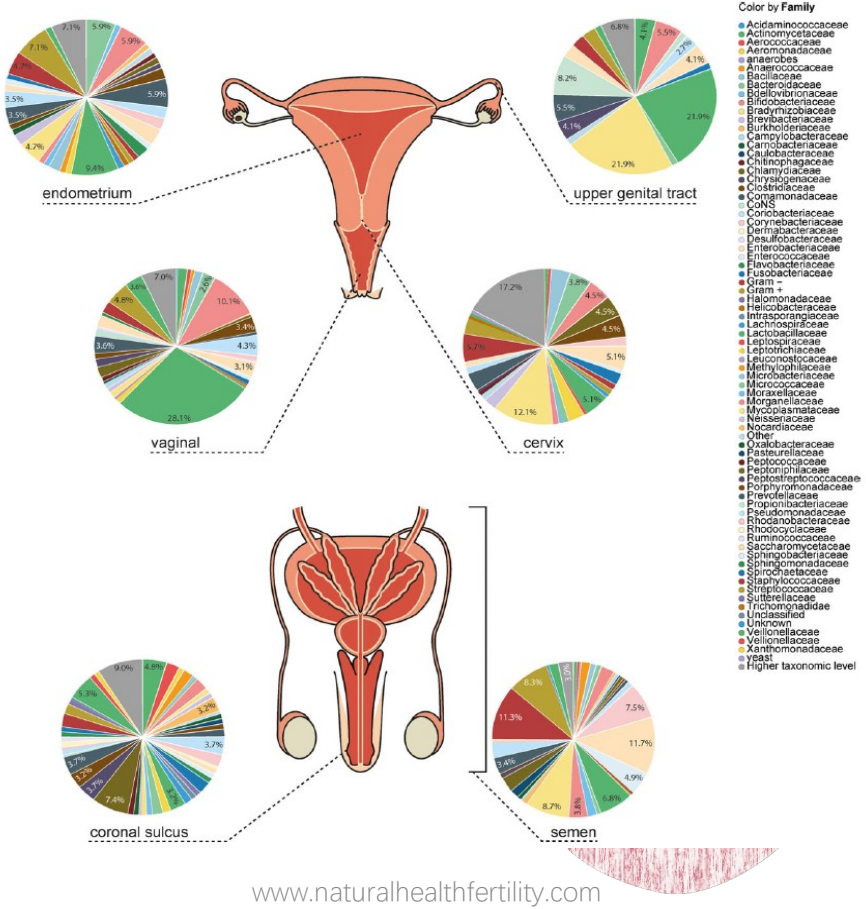
COMPLICATED STEPS

1. ‘You smell good’
2. Sperm Binding
3. Zona pellucida penetration: Sperm penetration
4. Acrosome reaction: Sperm adhesion to oolemma
5. Fusion-fertilisation
6. Cortical granule exocytosis
7. Block to polyspermy
8. Oocyte (and embryo) does her thing…



Steps required	Treatment objectives
'You smell good'	Microbiome
Sperm Binding	Microbiome
Zona pellucida penetration: Sperm penetration	Structural aspects – nutrients especially Zinc, Ubiquinol, E, C, B vitamins
Acrosome reaction: Sperm adhesion to oolemma	Progesterone secreted by cumulus cells
Fusion-fertilisation	Release of intracellular Calcium - Calcium oscillations
Cortical granule exocytosis	Continuation of #5
Block to polyspermy	Zinc
Oocyte (and embryo) does her thing…	Mitochondrial health (ubiquinol) and young gametes (antioxidants and NAD_8

REPRESENTATION OF ALL THE DETECTED AND REPORTED MICROBIOTA (REVIEW OF 51 STUDIES)



Koedooder, R., et al 2019

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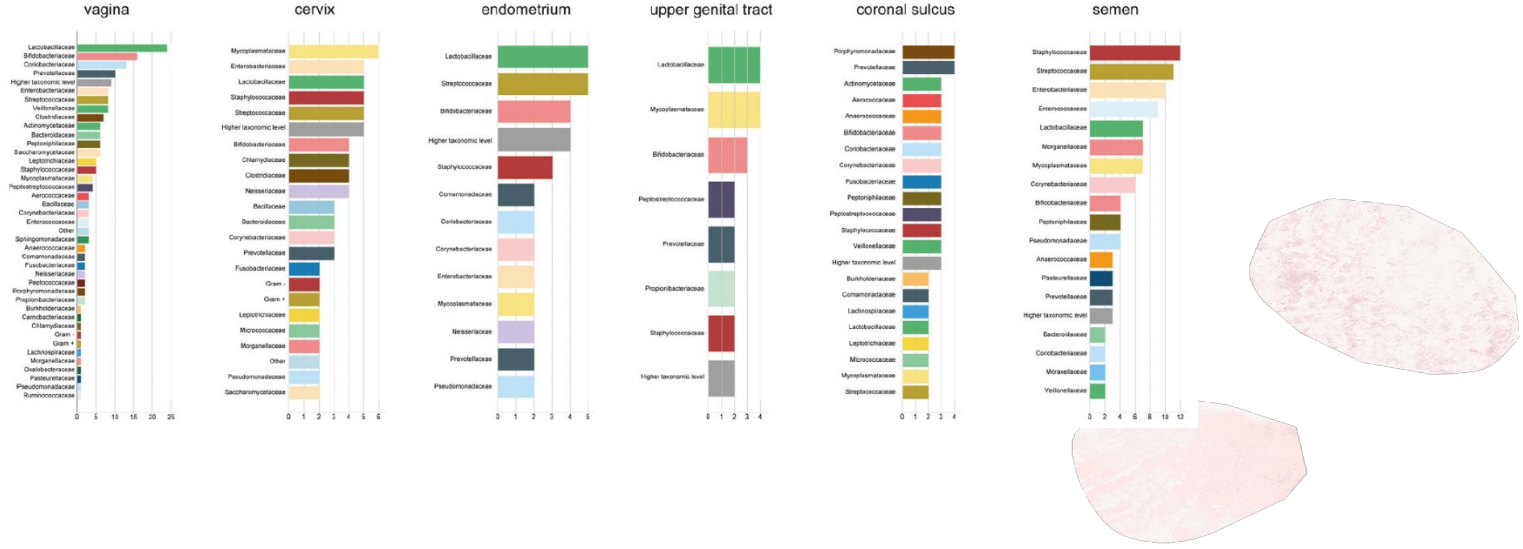
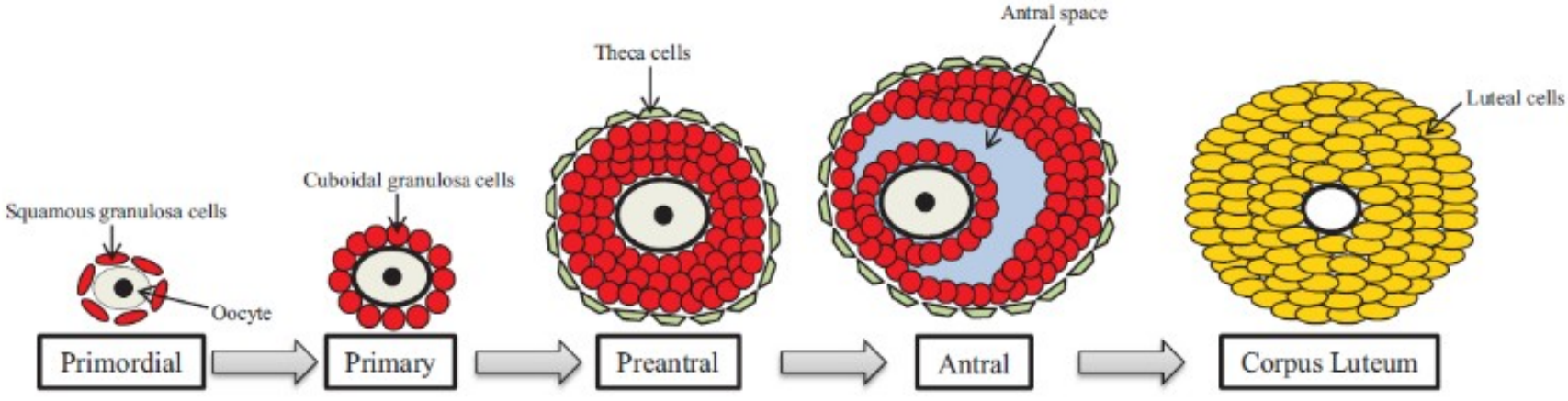


Koedooder, R., et al 2019

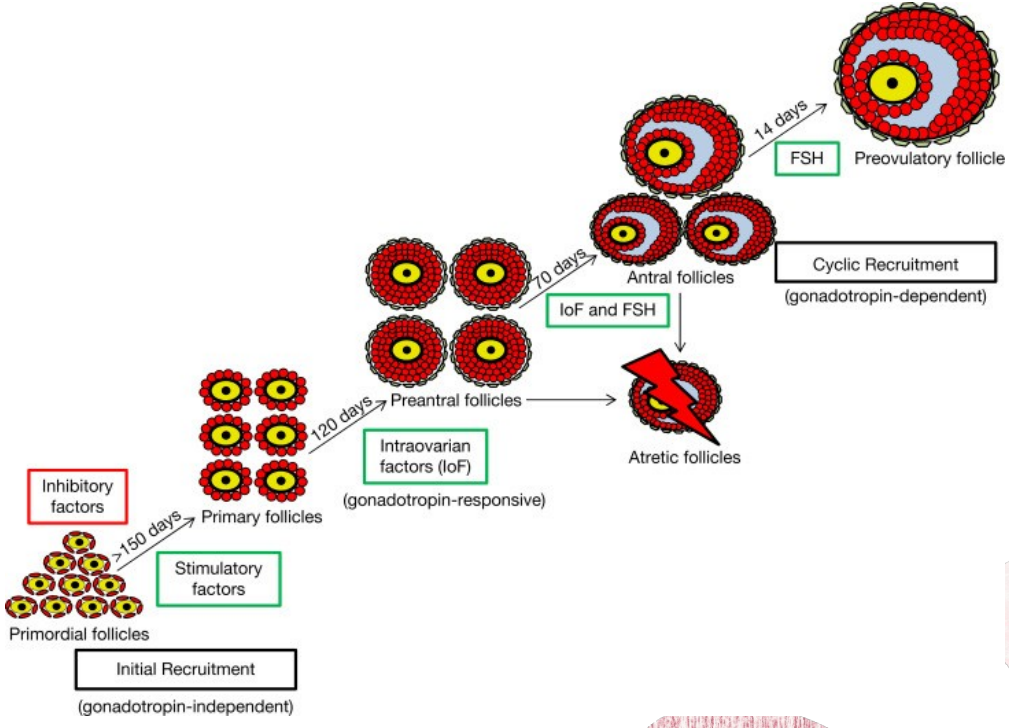
IT ALL STARTS WITH THE EGG

OVARIAN FOLLICULOGENESIS



Hannon & Flaws 2015

PROGRESSION AND REGULATION OF OVARIAN FOLLICULOGENESIS



Patrick R. Hannon, Thomas E. Curry, in Encyclopedia of Reproduction (Second Edition), 2018

OVARIAN FOLLICLE CLASSIFICATION

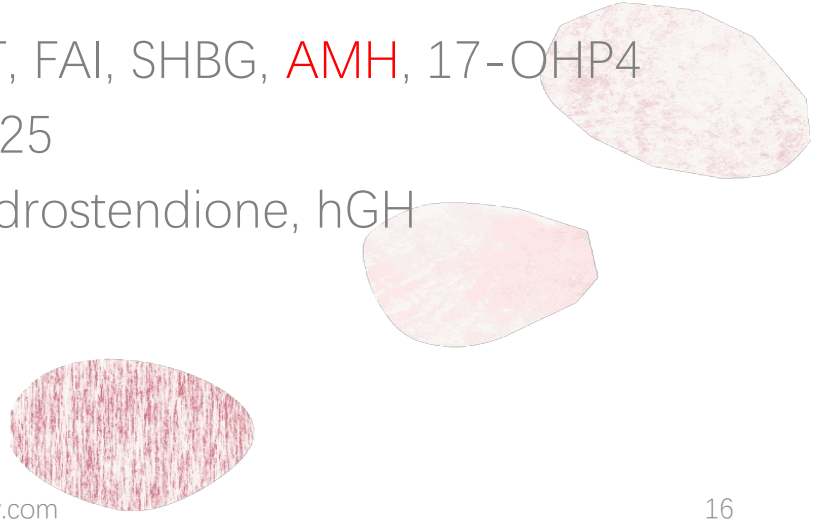
Class	Alternate nomenclature	Type	No. of cells	Size (diameter)	Size ultrasound
Primordial follicle	Small	1, 2, 3	25	<50µm	
Primary follicle	Preantral	4 5	26 – 100 101 - 300	Up to 200µm	
Secondary follicle	Antral Small antral Large antral	6 7	300 – 500 501 - 1000	500µm 1000-6000µm	< 18mm
Preovulatory follicle	Graafian	8	> 1000	> 6000µm	18 – 28mm

ASSESSMENTS

ASSESSING THE FEMALE PATIENT

Fertility testing

- TV US with AFC
  - +/- hycosy, sonohysterogram
- Hormone panel
  - D2: FSH, LH, E2, PRL, DHEA-S, T, FAI, SHBG, AMH, 17-OHP4
  - D21 (or equivalent): P4, +/-CA125
  - Possible additions: Inhibin B, Androstendione, hGH



OTHER ASSESSMENTS

GENERAL

FBC
UEC/LFT
Fasting lipids
Full iron studies
Vitamin D3
TSH, fT4, fT3, +/- rT3
Thyroid Abs
Fasting glucose, insulin, HbA1c, HOMA
Infective screen – EBV, CMV, HSV1/2, HHV6, Mycoplasma, Ureaplasma
Pre pregnancy screen
- Rubella, Blood group and antigens, Full STI panel

Pap smear
Breast examination
As needed – autoimmune, immune, coagulation,

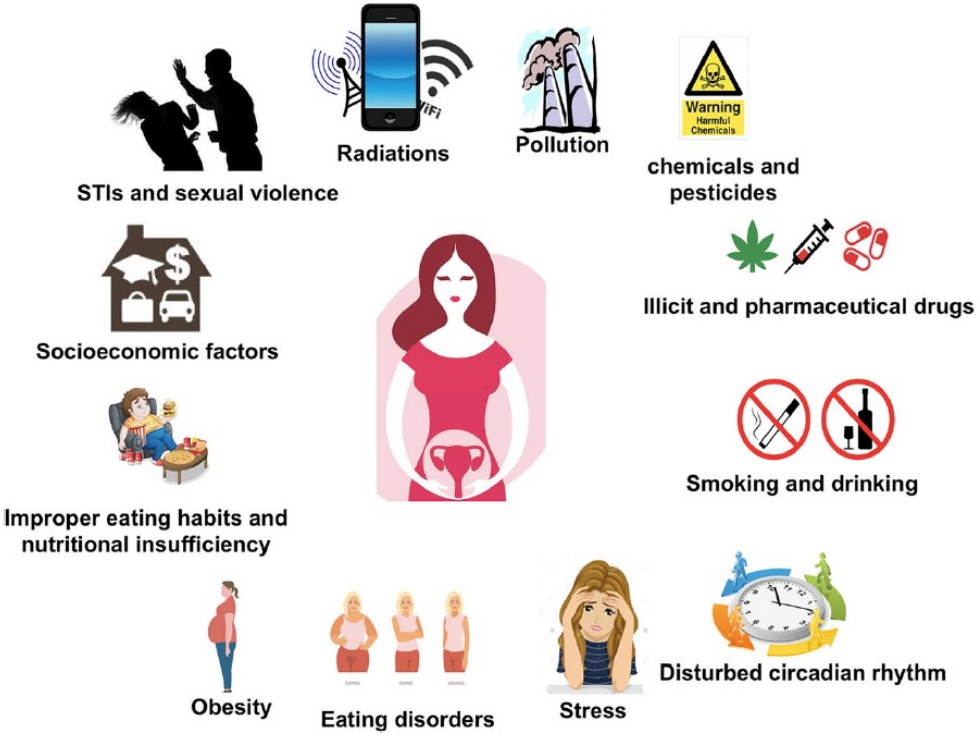
FUNCTIONAL

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
Urinary iodine
Vaginal microbiome
Deeper hormone analysis – dried urine, saliva, cortisol mapping/CAR, melatonin
Others as indicated

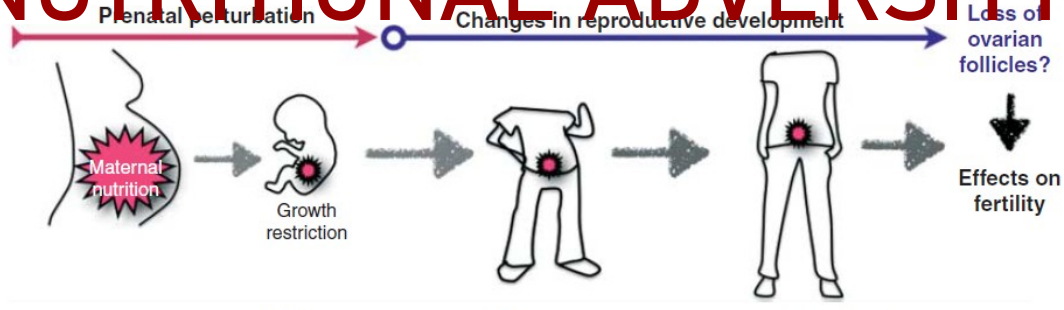
AETIOLOGY

MULTIFACTORIAL AETIOLOGY



Bala et al., 2021

SUMMARY OF REPRODUCTIVE OUTCOMES AFTER EARLY-LIFE NUTRITIONAL ADVERSITY



	Birth	Puberty	Adulthood
Nutrient restriction	• Reduced ovarian size[1] • Increased circulating FSH[2] • Decrease in primordial follicles[3]	• Advanced[4,5]/delayed menarche[6] • Advanced[7]/delayed vaginal opening[8] • Increaased adrenal androgen secretion[9] • Hyperinsulinemia[9,10]	• Decrease in follicle number[5,11] • Early onset menopause[12] • Decrease in follicle growth factor (GDF9)[5] • Low ovulation rates[4,13]
Excess nutrients	• Decrease in primordial follicles[14]	• Early menarche in humans[15,16,17] and rodents[18,19] • Hyperleptinemia and increased adiposity[18]	• Decrease fecundity in sheep[20] • Decrease in fertility index in mice[7] • Increase in atretic follicles[20] • Disruption of estrous cyclicity in young adult rats[21,22]

Chan et al., 2015

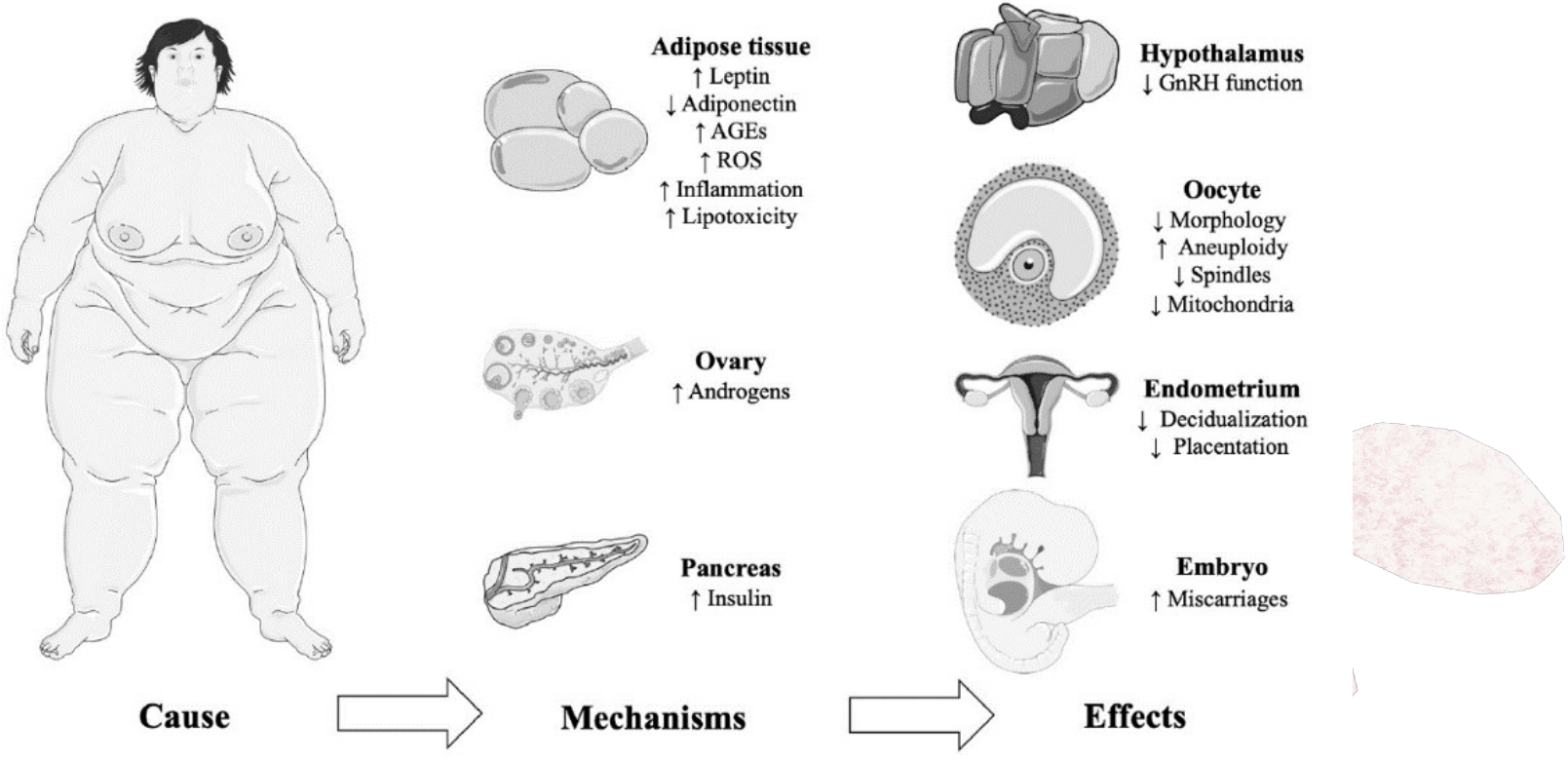
ALCOHOL

Level of alcohol consumption	Effects on female reproduction	Reference
> 1 drink per day vs. abstaining	No increased risk of ovulatory infertility (after controlling for confounders)	Chavarro, et al. 2009
1-3 drinks per week vs. abstaining	No difference in adjusted fecundability	Mikkelsen, et al. 2016
4-7 drinks per week vs. abstaining		
8-13 drinks per week vs. abstaining		
≥ 14 drinks per week vs. abstaining		
1-5 drinks per week vs. abstaining	Decreased chance of clinical pregnancy (OR 0.61, 95% CI 0.4 - 0.93)	Jensen, et al. 1998
> 10 drinks per week vs. abstaining	Decreased chance of clinical pregnancy (OR 0.34, 95% CI 0.22 - 0.52)	
Low consumers (< 50 g per week) vs. Moderate consumers (50 - 140 g per week) vs. High consumers (> 140 g per week)[a]	Increased risk of seeking fertility treatment with increasing alcohol intake: High vs. moderate RR 1.58 (95% CI 1.07 - 2.34) Low vs. high RR 0.64 (95% CI 0.46 - 0.90)	Eggert, et al. 2004
1-6 drinks per week vs. < 1 drink per week (in women over age 30)	Increased incidence of infertility (Adjusted HR 1.95, 95% CI 1.04 - 3.66)	Tolstrup, et al. 2003
Binge drinking ≥2 times per week vs. drinkers who do not binge	26% lower AMH level ($p < 0.04$)	Hawkins, et al. 2016

[a]One standard drink in the U.S. has roughly 14 g of alcohol [65]

Van Heertum & Rossi, 2017

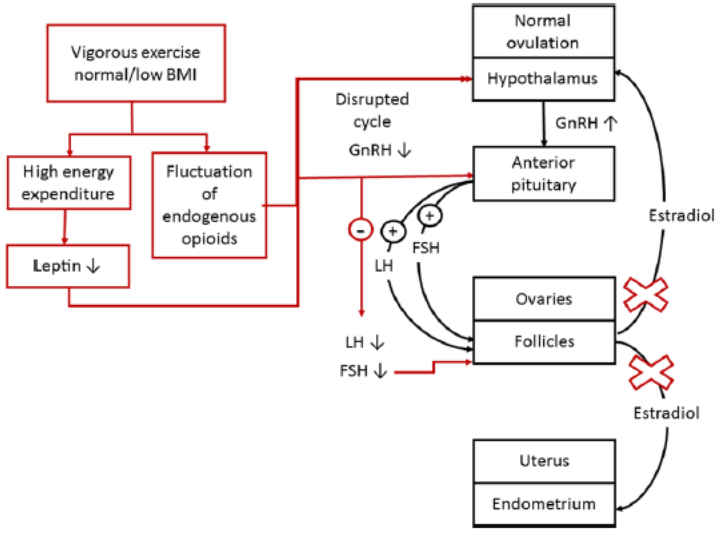
OBESITY



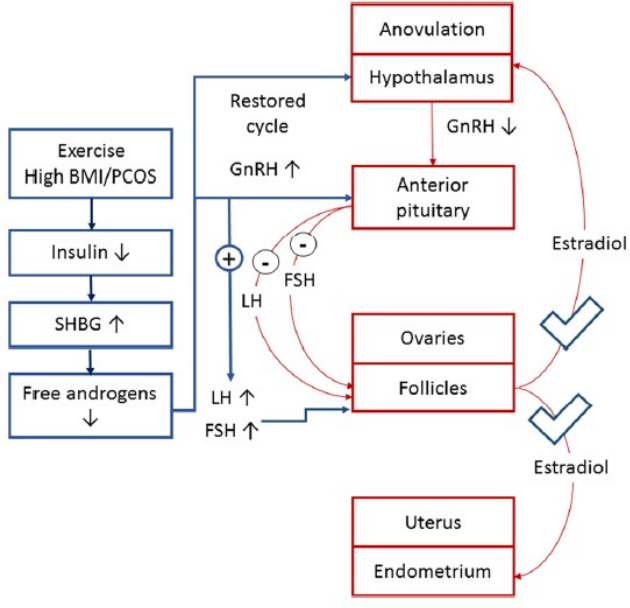
Mintziori et al., 2020

EXERCISE BALANCE

MECHANISM BY WHICH VIGOROUS EXERCISE DISRUPTS OVULATION (RED) IN WOMEN WITH NORMAL AND LOW BMI VIA ENERGY DEFICIENCY

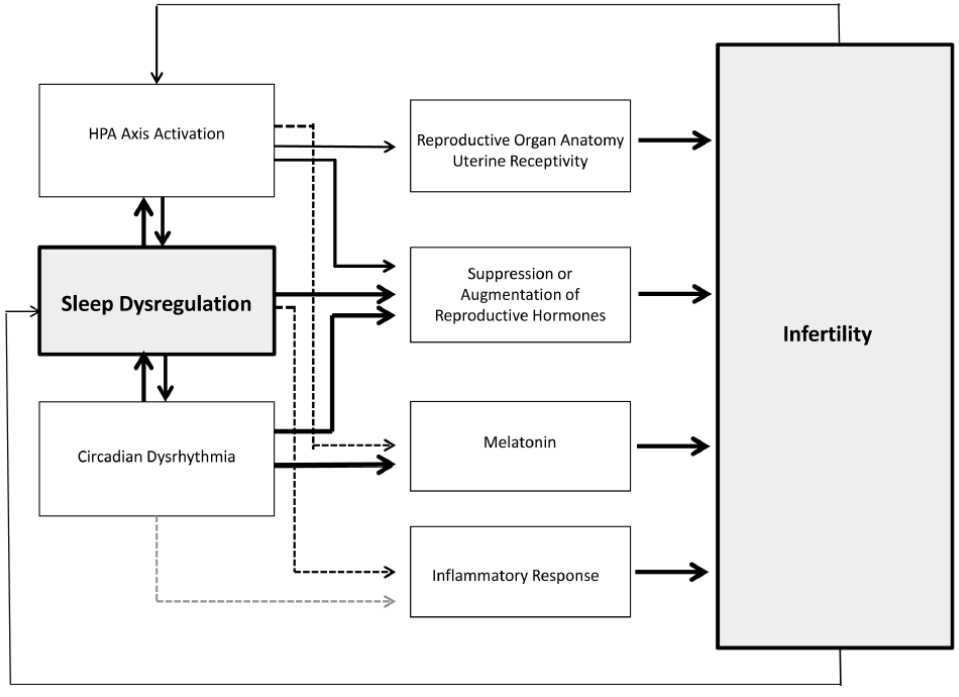


MECHANISM BY WHICH EXERCISE RESTORES OVULATION (BLUE) IN OVERWEIGHT AND OBESE WOMEN WITH OVULATORY DISORDERS SUCH AS PCOS (ANOVULATION IS IN RED)



Hakimi & Cameron, 2017

SLEEP



Kloss et al., 2015

SLEEP

HORMONES								
	TSH	**LH**	**FSH**	**PRL**	**Androgens**	**Estradiol**	**AMH**	**Progesterone**
Role in Fertility	↑levels:: anovulation, miscarriages	↑LH:: Infertility	↑FSH:: poor ovarian reserve; reproductive aging; ↓luteal phase dysfunction	↑ PRL indicates anovulation, PCOS, endometriosis	↑androgens: PCOS	Irregular estradiol secretion::anovulation	AMH::DOR	Progesterone:: Implantation; ↓levels linked to infertility
Sleep/Wake Changes	TSH ↑ around sleep onset; ↑ throughout night; ↓during daytime	Sleep:: ↓ LH pulses; Awakenings:: ↑ LH pulses in early follicular phase	Short sleep:: ↓ FSH	Sleep onset:: PRL ↑ Awakenings:: PRL ↓	Sleep onset:: ↑testosterone following sleep onset; Sleep duration in men:: ↑testosterone	?	?	Second half of night: ↑ progesterone
PATHWAYS								
1. Stress	?	Stress:: ↓ LH	Stress:: ↓FSH	?	?	?	?	Stress:: ↓ progesterone
2. Sleep Dysregulation	Acute SD:: ↑ TSH; Chronic SD: ↓ TSH Insomnia::↓ TSH	PSD and TSD:: ↑ LH amplitude	PSD :: no change in FSH	Narcolepsy:: ↓PRL; Night eating syndrome:: ↑ PRL	PCOS:: testosterone ; ↑ OSA risk; TSD in men and women with depression:: ↓ testosterone	PSD:: ↑ estradiol Variable sleep schedules:: ↓ estradiol	↑ sleep disturbance :: DOR	SDB, PCOS :: ↓ Progesterone
3. Circadian Rhythmicity	+	−/+ ultradian pulsatility	−	+	+ in men	−	+ subtle	?
Dysrhythmia	− ?	Shift work:: ↑ LH during daytime and nighttime sleep	Shift workers:: ↑ FSH during daytime sleep and nighttime sleep	Shift work::↑ PRL in shift workers	?	Shift workers: ↑ estradiol in those who did not nap; E1C unchanged	?	?

+ There is evidence to support that this hormone has a circadian rhythm

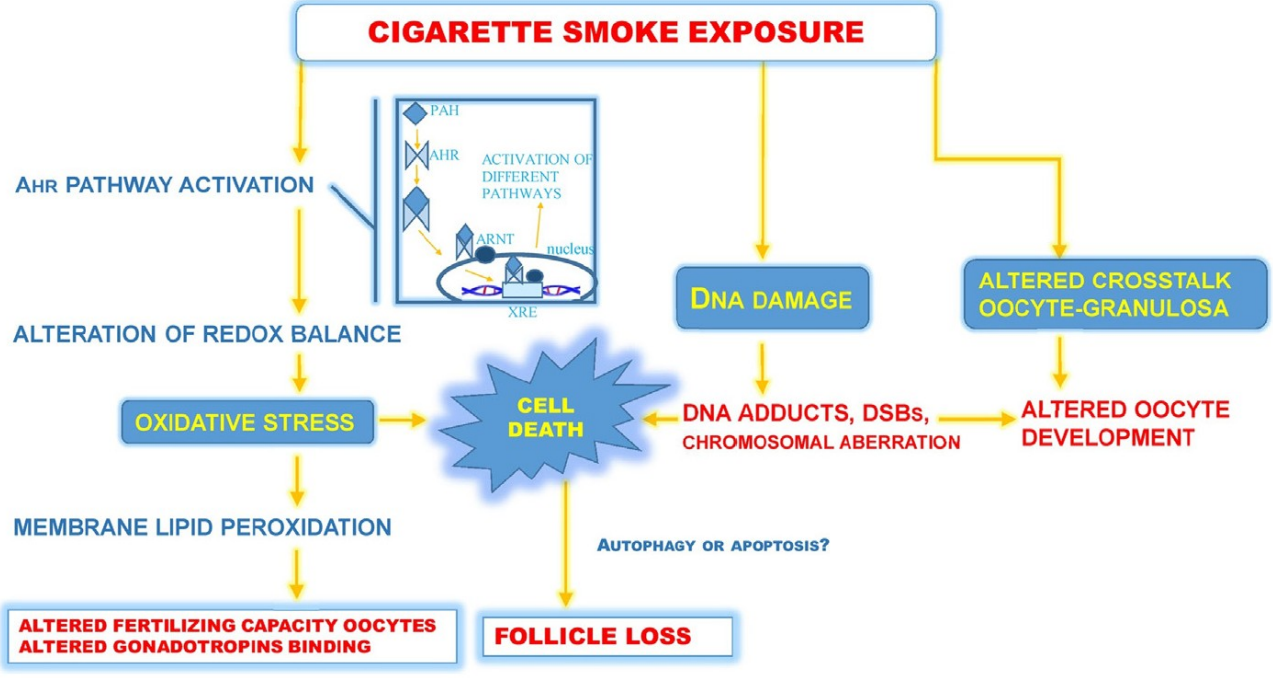
− There is evidence to support that this hormone does *not* have a circadian rhythm

:: associated with/is related to

SD Sleep Deprivation PSD Partial Sleep Deprivation TSD Total Sleep Deprivation SDB Sleep Disordered Breathing
OSA Obstructive Sleep Apnea DOR Diminished Ovarian Reserve

Kloss 2015

SMOKING



Budani & Tiboni, 2017

HEAVY METALS

Exposure	Effects
	Mercury (Hg)
Dental personnel exposed to Hg	Limited evidence of SAb, reduced fertility, congenital abnormalities[4]
Maternal exposure to Hg in pregnancy	Offspring with 34 g LBW and increased risk of SGA[6]
Dental staff exposed to Hg	SAb, preeclampsia and SGA babies, and this might be due to Hg-induced oxidative stress[5]
Elemental Hg exposure	Higher prevalence of irregular menstrual cycles[7]
Hg exposure	Abdominal pain, dysmenorrhoea and abnormal menstruation[8]
	Lead (Pb)
Men occupationally exposed to Pb	Increased risk of infertility and pregnancy delay in wives of men occupationally exposed to Pb[9]
Girls exposed to environmental Pb	Delay in pubertal development and growth of girls[10]
Prenatal higher blood Pb level	Preterm delivery, lower head circumference and crown-heel length[11]
Higher blood and cord Pb level	LBW offsprings of mothers with higher blood Pb and a negative association between cord Pb levels and birth length[12]
Pregnant women with blood Pb level ≥10 µg/dl	Three-fold higher risk PTB and four-fold of SGA birth[13]
Pb exposure to women	Risk of SAb but blood Pb (<5 µg/dl) not a risk factor for SAb[14]
Low to moderate Pb exposure	Risk of SAb[15]
	Cadmium (Cd)
Women living in Cd polluted area	Abnormal menstrual cycle, dysmenorrhoea in unmarried women and sterility in married women[16]
Cd exposure	Associated with preeclampsia[17]
Maternal Cd exposure	High-risk of early delivery and LBW[18]
Low level Cd exposure	Interferes steroid hormones and disrupts steroidogenesis leading to alter sex differentiation and gametogenesis[19]
	Arsenic (As)
As-contaminated drinking water	Negative effect on menarcheal age[20] SAb, stillbirth and PTB[21] Non-significant risk of PTB and LBW[22]
As exposure during pregnancy	Decreasing gestational age and lower maternal weight gain[23] Six-fold risk of stillbirth, no relation with infant mortality or SAb[24] Increases oxidative stress and inflammation in the placenta[25]
	Zinc (Zn)
Role of Zn	Normal growth, development, cellular integrity, protein synthesis, nucleic acid metabolism. Beneficial to infant's neurobehavioural development[26]
Maternal Zn deficiency	Infertility and embryo/foetal death, intrauterine growth retardation and teratogenesis[27]
	Mangnese (Mn)
Maternal Mn level	High concentration related with LBW[28]
Maternal and cord blood Mn	Birth weight elevated with Mn upto 4.18 µg/dl and reducted at higher levels[29]
Mn exposure	Birth weight increased with Mn upto 3.1 µg/l and reducted at higher levels[30]
	Chromium (Cr)
Female workers exposed to occupational Cr	Increased risk of SAb and threatened abortion[31]
Female exposed to Cr during pregnancy	Higher risk of PTB (particularly male offsprings)[33] and LBW (mainly female offsprings)[32]
	Vanadium (V)
Vanadium exposure through food, water and polluted air	Positive relationship between LBW and maternal urinary V[34]

SAb, spontaneous abortion; LBW, lower birth weight; SGA, small gestational age; PTB, preterm birth

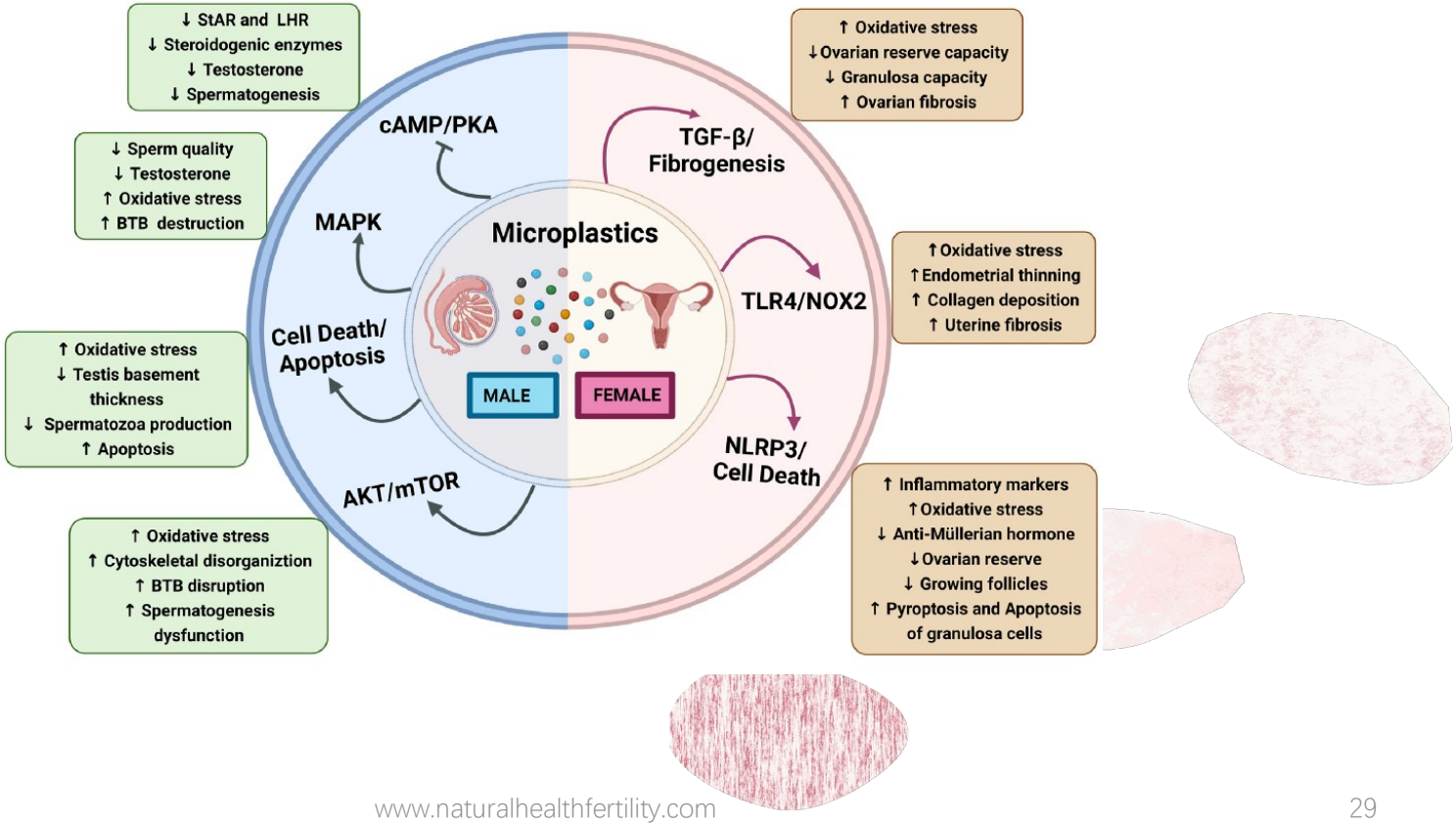
Kumar et al., 2019

RADIATION

Exposure	Effects
Ionizing radiation	An ovarian exposure to 4 Gy may cause a 30% sterility in young women, 100% sterility in over 40 yr women[93]
Ionizing radiation	Induce DNA damage in germ cells, harmful effects in progeny, miscarriage, lower birth weight (LBW) and congenital abnormalities based on experimental data. No proofs of such effects in epidemiological studies[94]
High frequency electromagnetic radiation	Associated with LBW, but only for male newborns, other outcomes were statistically nonsignificant[95]
Women using visual display terminals in Ist trimester	No significant elevated risk for birth defects and positive findings might be due to unmeasured factors *i.e.*, poor ergonomic conditions, job stress[96]
Exposure to shortwaves in women	Increased congenital malformations and LBW[97]

Kumar et al., 2019

MICROPLASTICS



Dubey et al., 2022

ENDOCRINE DISRUPTING CHEMICALS (EDCS)

Kowalczyk 2022

BPA

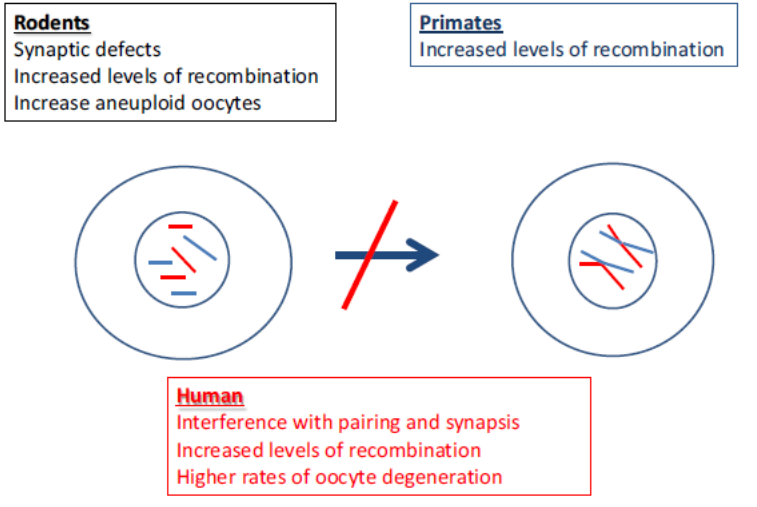


Figure 1 The effects of bisphenol A during the early stages of oogenesis.

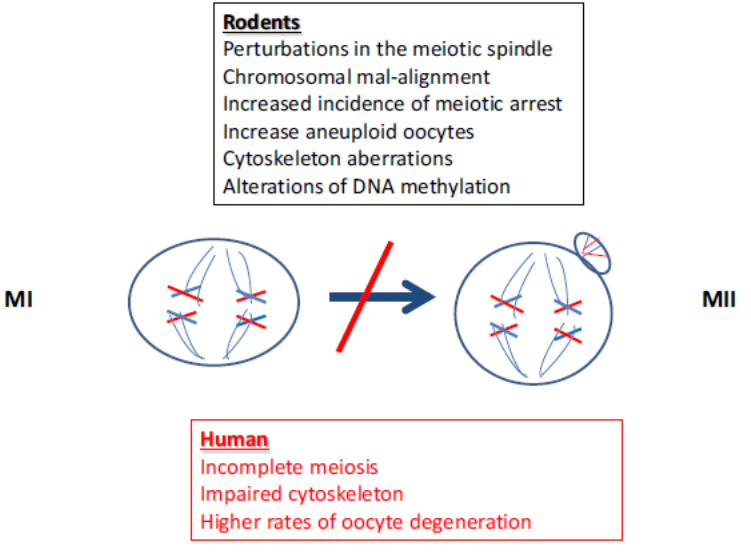


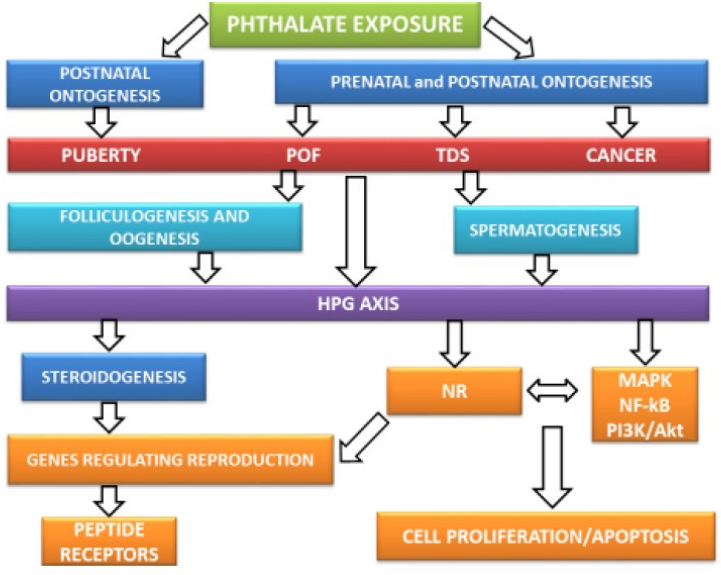
Figure 2 The effects of bisphenol A during the final stages of oocyte maturation. MI, metaphase I; MII, metaphase II.

Machtinger & Orvieto, 2014

PTHALATES

Exposure	Effects
Phthalates exposure on reproductive outcomes and children health	(*i*) Affect LH, free testosterone, sex hormone-binding globulin and anogenital distance and thyroid function. (*ii*) Urinery phthalates higher in pubertal gynecomastia individuals, girls with thelarche and precocious puberty[51]
Level of phthalates in thelarche and control individuals	High levels of phthalates (dimethyl, diethyl, dibutyl and DEH) and its metabolite mono-(2-ethylhexyl) phthalate in thelarche patients[52]
DEHP metabolite, MBP and MEP exposures during pregnancy	Linked with prenatal sex steroid hormone concentrations but sex steroid hormone levels not associated with infant reproductive outcome[53]
DEH and its metabolite, MEHP in endometriosis	Women with endometriosis had higher plasma level of DEHP, and 92.6% had detectable level of DEHP and MEHP in the peritoneal fluid[54]
Phthalate metabolites MBP, MBzP, mono (3-carboxylpropyl) phthalate and four metabolites of DEH phthalate urinary levels	Higher phthalates urinary concentrations of women who delivered PTB[55]

MEHP, monoethyl hexyl phthalate; DEHP, di-2-ethylhexyl phthalate; MBP, monobutyl phthalate; DEH, di-2-ethylhexyl; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; LH, luteinizing hormone

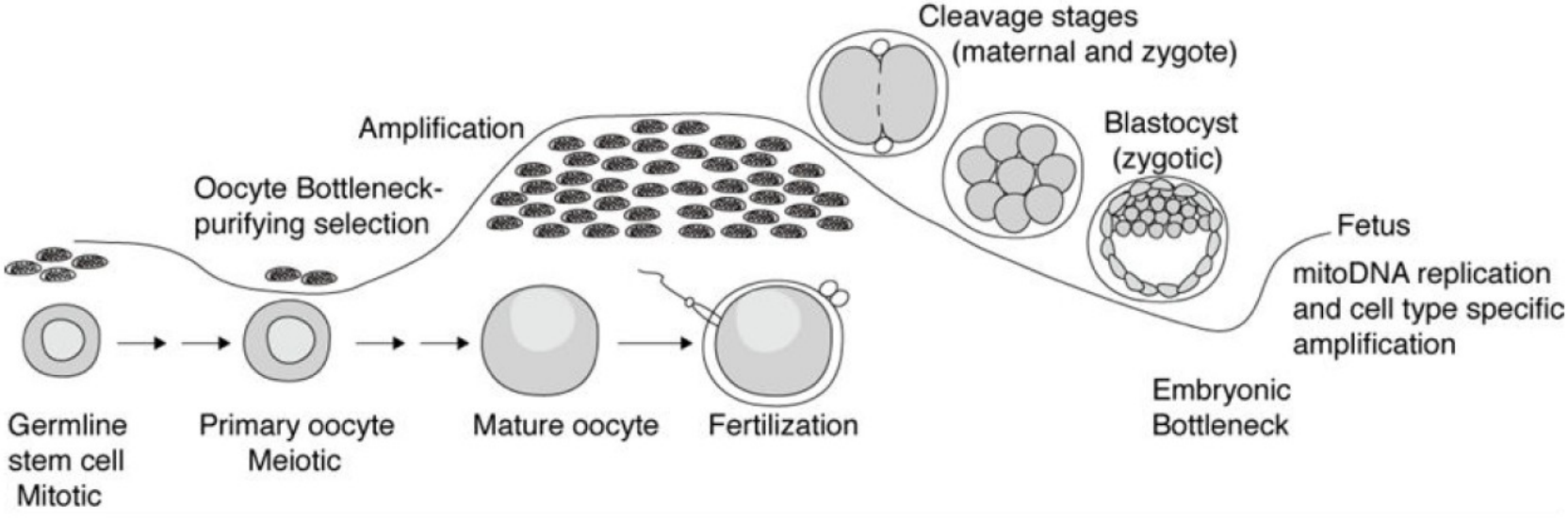


Kumar et al., 2019 , Hlisníková et al., 2020

MITOCHONDRIAL HEALTH

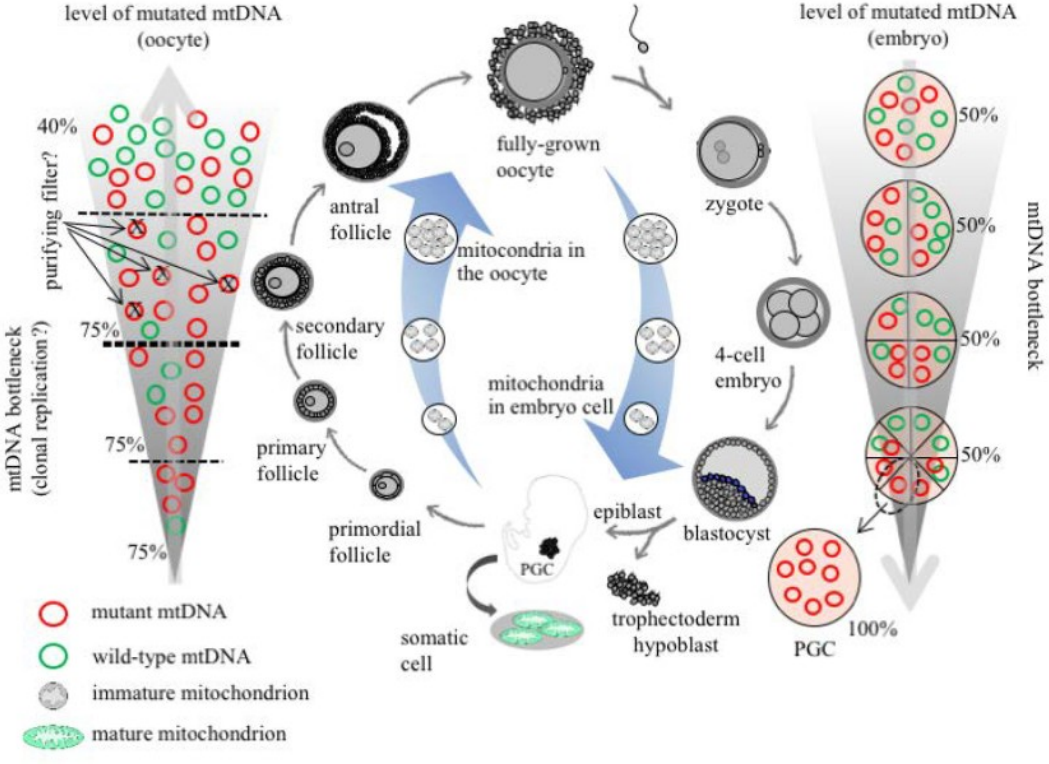
MITOCHONDRIAL TRANSFERENCE

STAGES OF OOGENESIS AND THE TIMING OF MITOCHONDRIAL BOTTLENECKS AND AMPLIFICATION IN OOCYTES AND EARLY EMBRYOS



Marlow, 2017

MITOCHONDRIAL CYCLE IN THE FEMALE GERMLINE



Chiaratti et al., 2018

MITOCHONDRIAL TRANSFERENCE

"The existence of a purifying filter against deleterious mtDNA in oocytes and early embryos, coincident with a more pronounced dependence on mitochondria as energy supplier, restricts accumulation of deleterious mtDNAs in the germline"

Healthy mitochondria protect against mtDNA mutations preferentially being selected and passed on to subsequent generations

Chiaratti et al., 2018

MITOCHONDRIAL HEALTH IN FEMALES

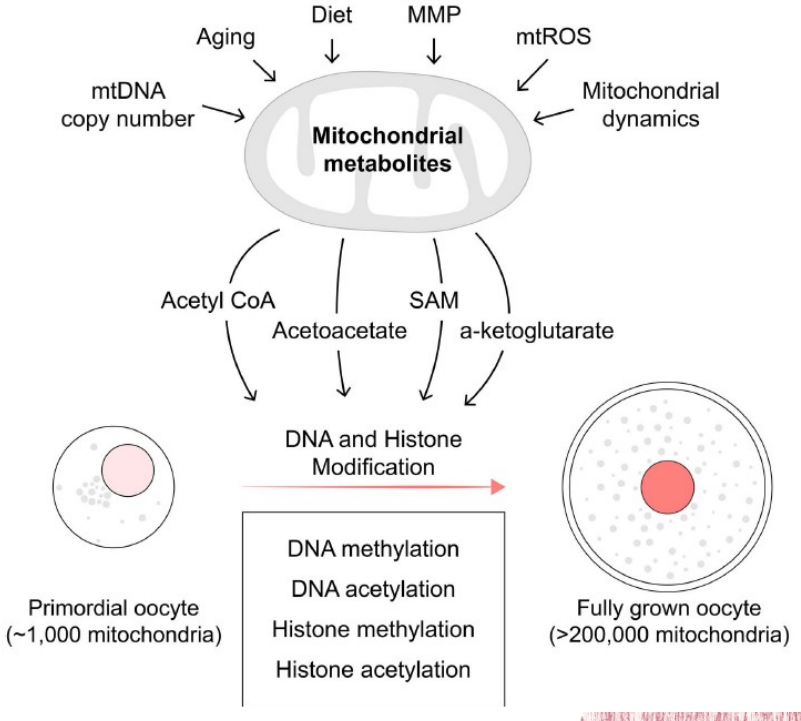
The role for high-potential mitochondria in the fertilization process is well documented

Viable embryos require a critical number of mitochondria

Inverse correlation between maternal age and mitochondrial DNA copy/mitochondrial number

Wai et al., 2010, May-Panloup et al., 2005; T. A. Santos et al., 2006, Dumollard et al., 2004; Eichenlaub-Ritter et al., 2011; Van Blerkom, 2011

OOCYTE NUCLEAR EPIGENETIC MODIFICATION BY MITOCHONDRIAL METABOLITES



Adhikari et al., 2022

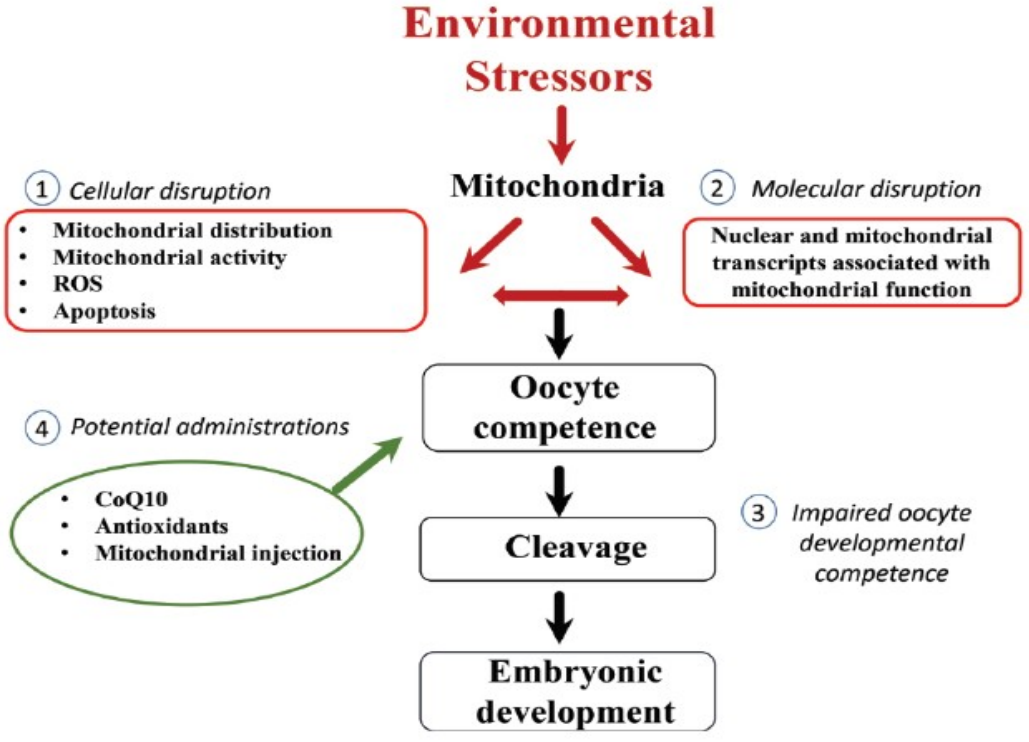
THE MIRACULOUS OOCYTE

Mature human oocyte contains more mitochondria and mtDNA than other cell types

Mitochondria - key factors mediating reproductive competence

Cecchino, G., et al, 2018

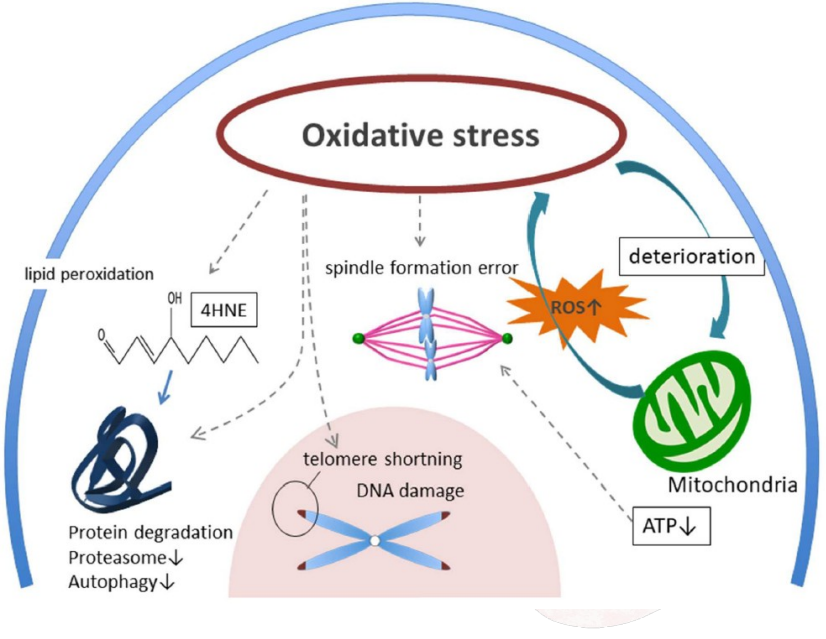
EFFECTS OF ENVIRONMENTAL STRESSORS ON THE OOCYTE MITOCHONDRIA



Roth, Z. 2018

OOCYTE DETERIORATION & MITOCHONDRIAL HEALTH

Possible mechanism of aged oocyte deterioration with accumulating oxidative stress



Sasaki et al., 2019

COENZYME Q10 (COQ10) AND FEMALE FERTILITY

- Highest concentration in the mitochondria of the oocyte
- Decrease in mitochondrial activity associated with CoQ10 deficiency affects the granulosa cells' capacity to generate ATP
- Supplementation delays age-mediated oocyte loss
- CoQ10 production slows with ageing, making the body less effective at protecting the eggs from oxidative damage

Hernández-Camacho, Bernier, López-Lluch, & Navas, 2018; Xu et al., 2018; Ben Meir et al, 2015; Ben-Meir A et al 2015b; Özcan, P., et al, 2016

COENZYME Q10 (COQ10) AND FEMALE FERTILITY

- Lowered aneuploidy rate
- Delayed ovarian reserve depletion
- Restored oocyte mitochondrial gene expression
- Improved mitochondrial activity and distribution
- Lowered ROS levels in oocytes
- Increased mitochondrial mass and polarization
- Increased ATP levels in oocytes

Cecchino, G., et al 2018

MITOCHONDRIAL HEALTH, OOCYTES AND UBIQUINOL

Improvement in oocyte quality by improving mitochondrial health

Improve ovarian reserve, poor response to ovarian stimulation, advanced age, PCOS – anything that presents with fewer, less competent or mature oocytes

Protects female gametes from OS – declining concentration
in follicular fluid

Rodríguez-Varela & Labarta, 2021; Xu et al., 2018 ; Turi et al., 2012

MITOCHONDRIAL HEALTH, OOCYTES AND UBIQUINOL

Dose is proven to be the most important variable in outcome….

- Enhancement in oocyte quality seen in poor responders with minimally effective dose at 600mg/day

The acceptable daily intake (ADI) of CoQ10 has been set at 12 mg/kg/day. This is calculated from the no-observed-adverse-effect level (NOAEL) by applying a safety factor of 100 (i.e ≥600 mg/day for adults weighing 50 kg)

Rodríguez-Varela & Labarta, 2021; Xu et al., 2018 ; Turi et al., 2012; Hidaka et al., 2008

METHYLATION

METHYLATION DYNAMICS IN HUMAN CELLS

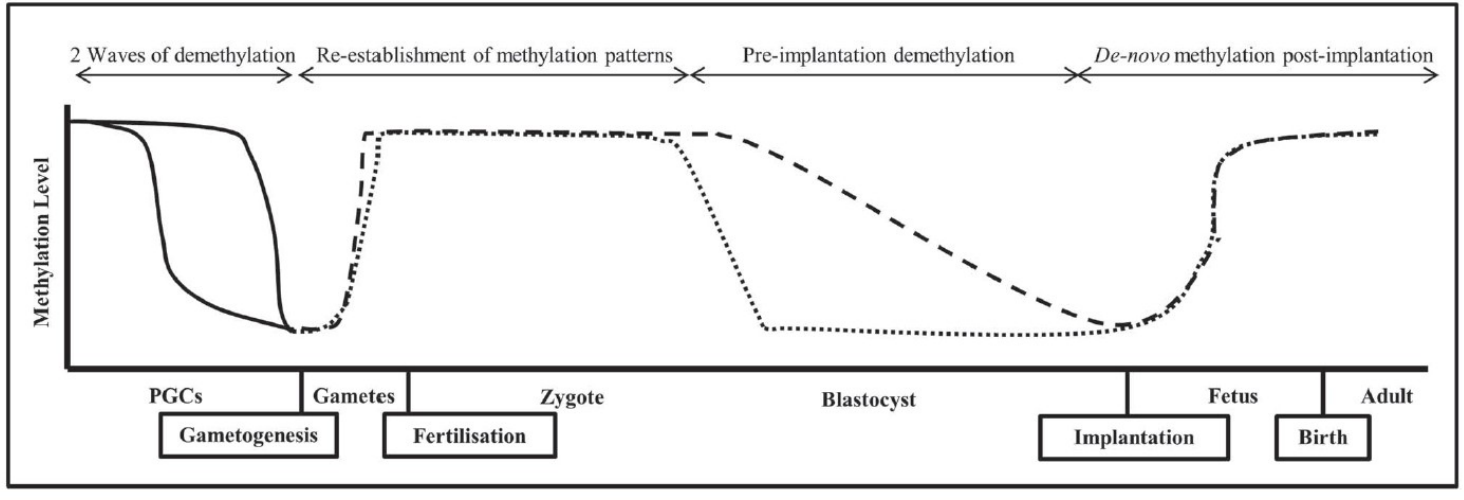
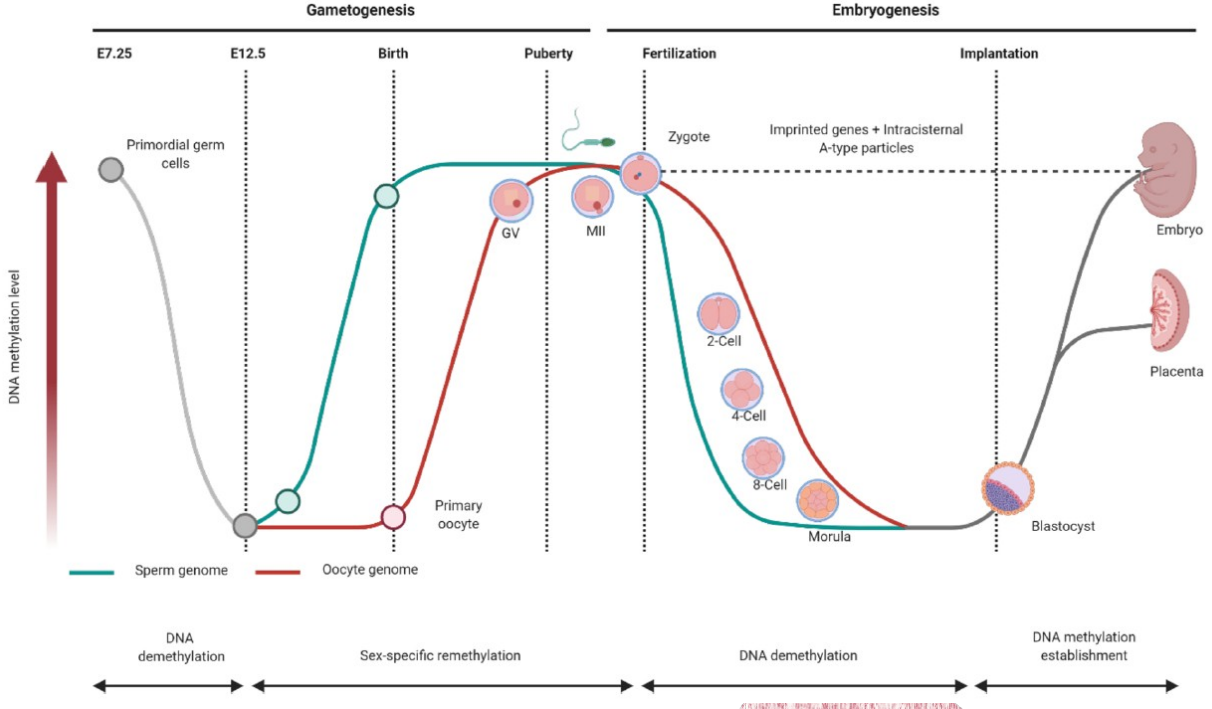


Figure 2 DNA methylation dynamics in human cells. Epigenetic reprogramming erases pre-existing DNA methylation patterns in PGCs in two consecutive waves of demethylation (black lines). During the final stages of gametogenesis, sex imprinting re-establishes sex-specific methylation patterns in spermatozoa (dotted line) and in oocytes (dashed line). After fertilization, paternal- and maternal-derived genomes undergo passive and active DNA methylation erasure, followed by formation of a highly demethylated blastocyst. *De-novo* DNA methylation patterns are established post-implantation and are unique to the resulting offspring.

Xavier et al., 2019

OVERVIEW OF DNA METHYLATION DYNAMICS DURING MAMMALIAN DEVELOPMENT



van der Reest et al., 2021

EPIGENETIC REPROGRAMMING CYCLES

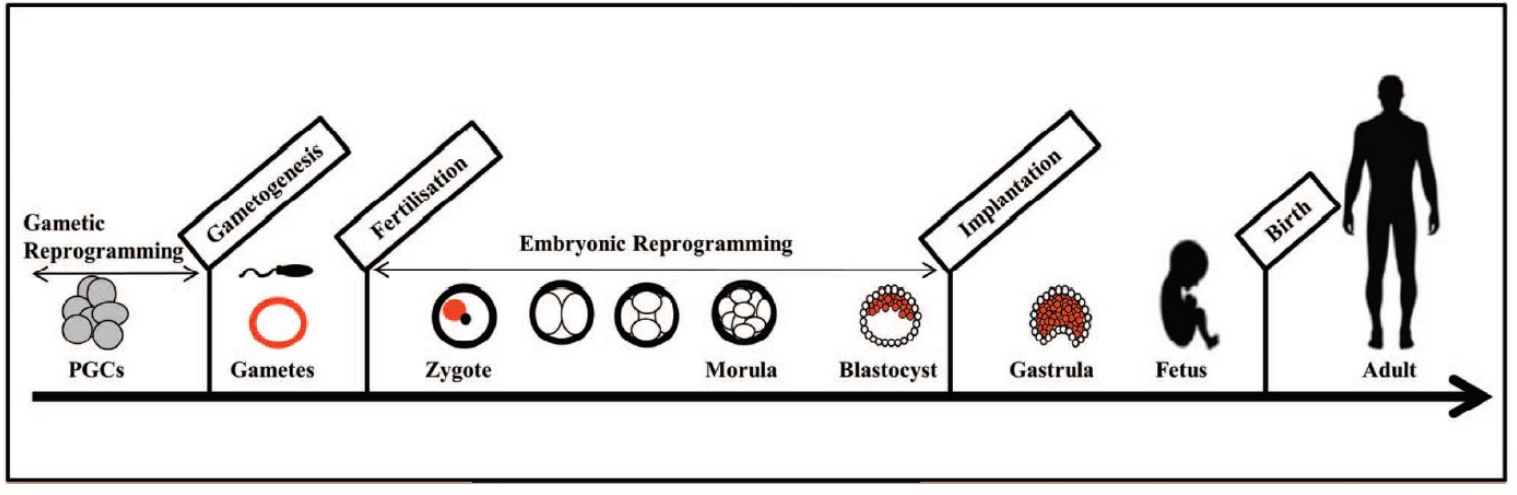


Figure 1 Epigenetic reprogramming cycles. During mammalian life, cells are submitted to two major genome-wide epigenetic reprogramming events. The Gametic Reprograming event takes place in PGCs of embryos during germline cell development, as PGCs migrate to the genital ridge. PGCs experience genome-wide DNA demethylation, removal and resetting of parental imprints, histone modifications and inactive-X-chromosome reactivation. The Embryonic Reprogramming event starts immediately after fertilization and lasts until the blastocyst stage of embryo development, when cells experience DNA demethylation, the removal and resetting of parental imprints and histone modifications.

Xavier et al., 2019

METHYLATION AND OVARIAN FUNCTION

Differences in methylation of genes correlate with ovarian dysfunction

Hormone activity (such as AMH)

Transcriptional regulation

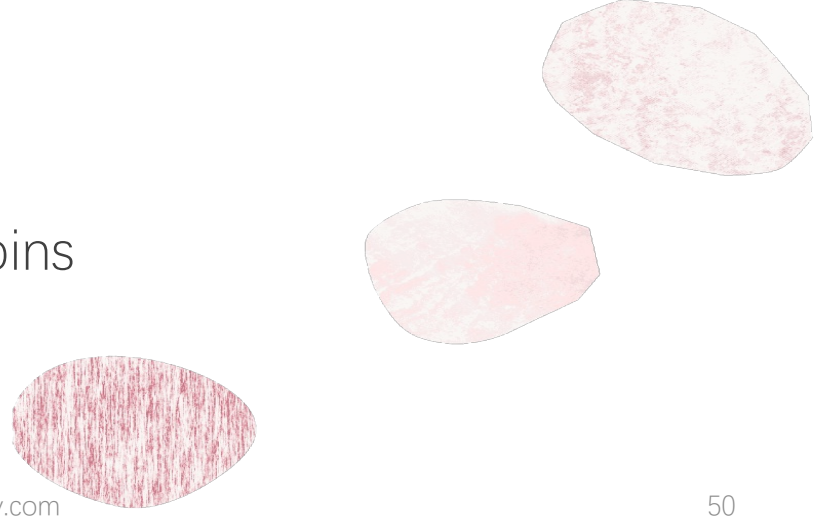
Inflammation

Glucose metabolism

Insulin signalling

Dysregulated response to gonadotropins

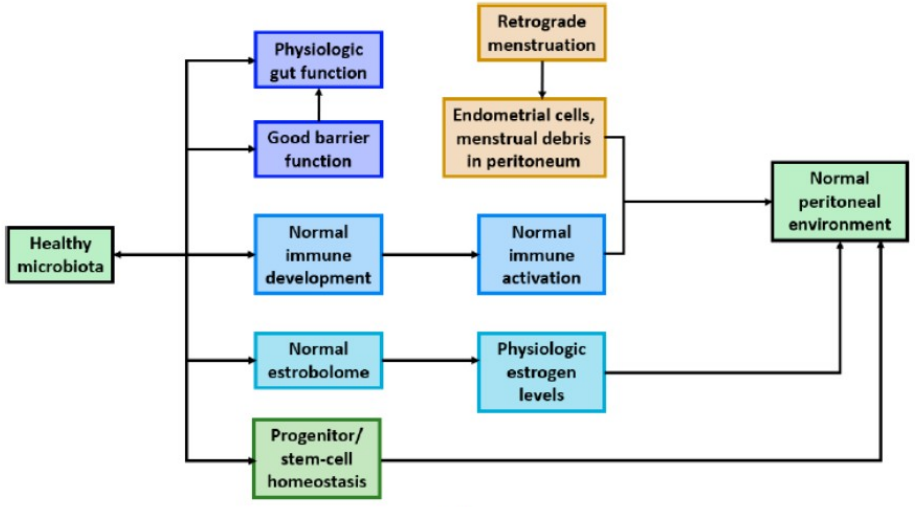
Dysregulated steroidogenesis



Scarfò et al., 2022

IMMUNOLOGY AND MICROBIOME

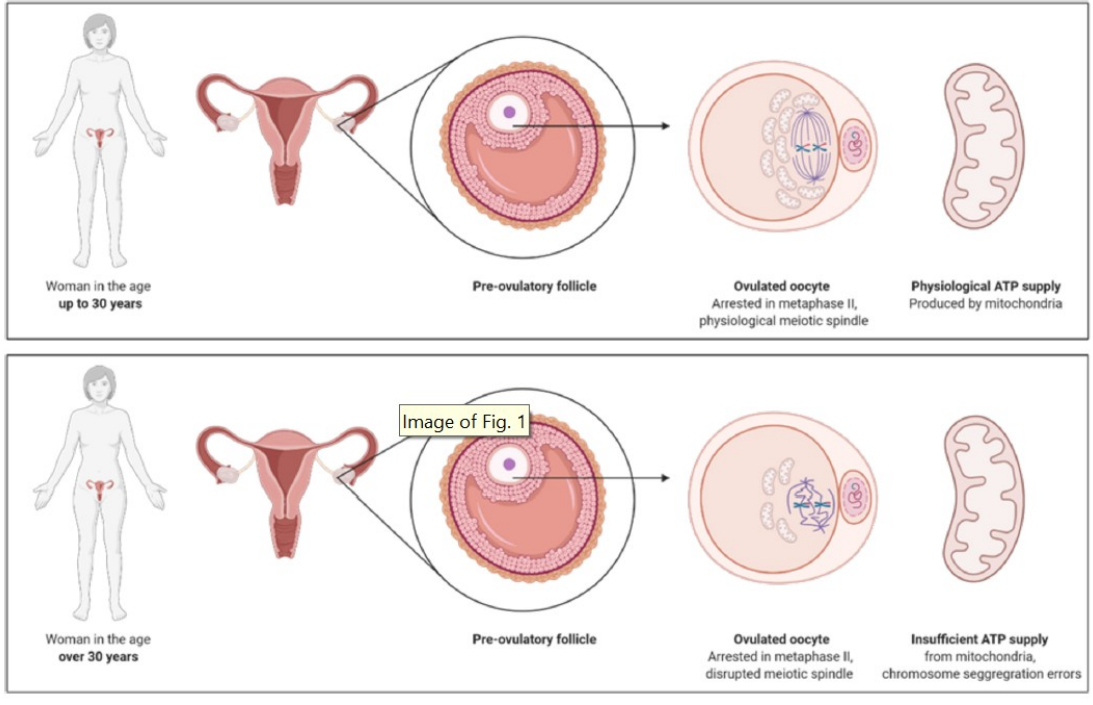
MICROBIOME



I. Jiang et al., 2021

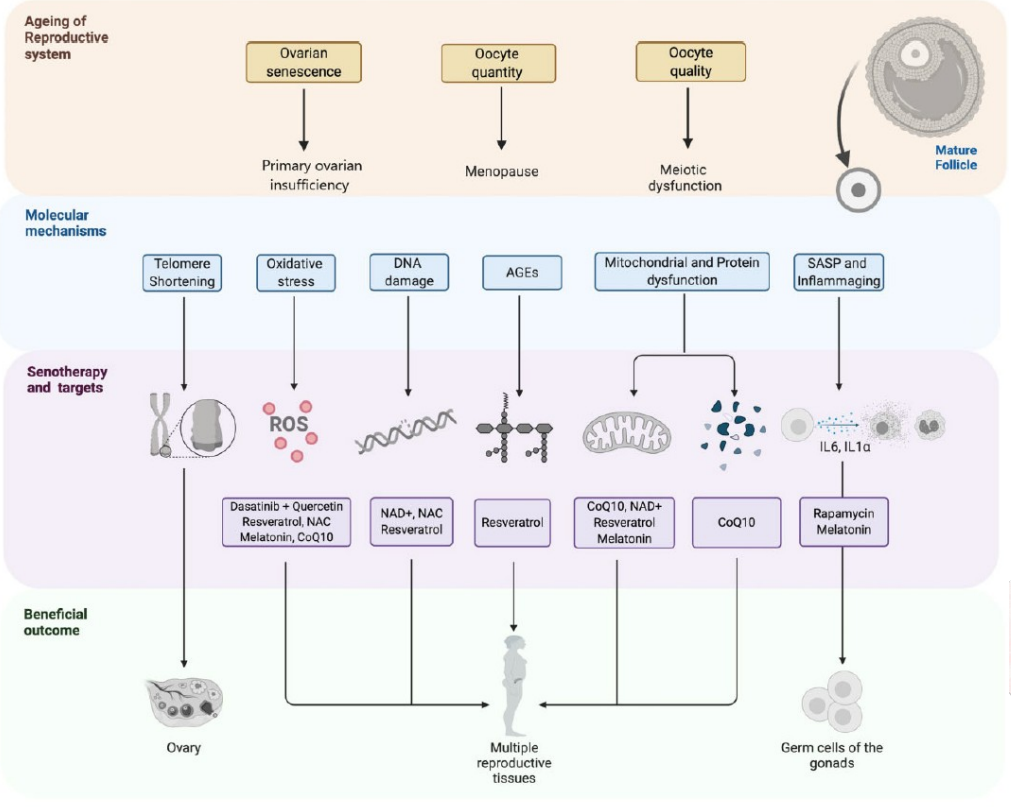
AGEING

THE AGEING OOCYTE



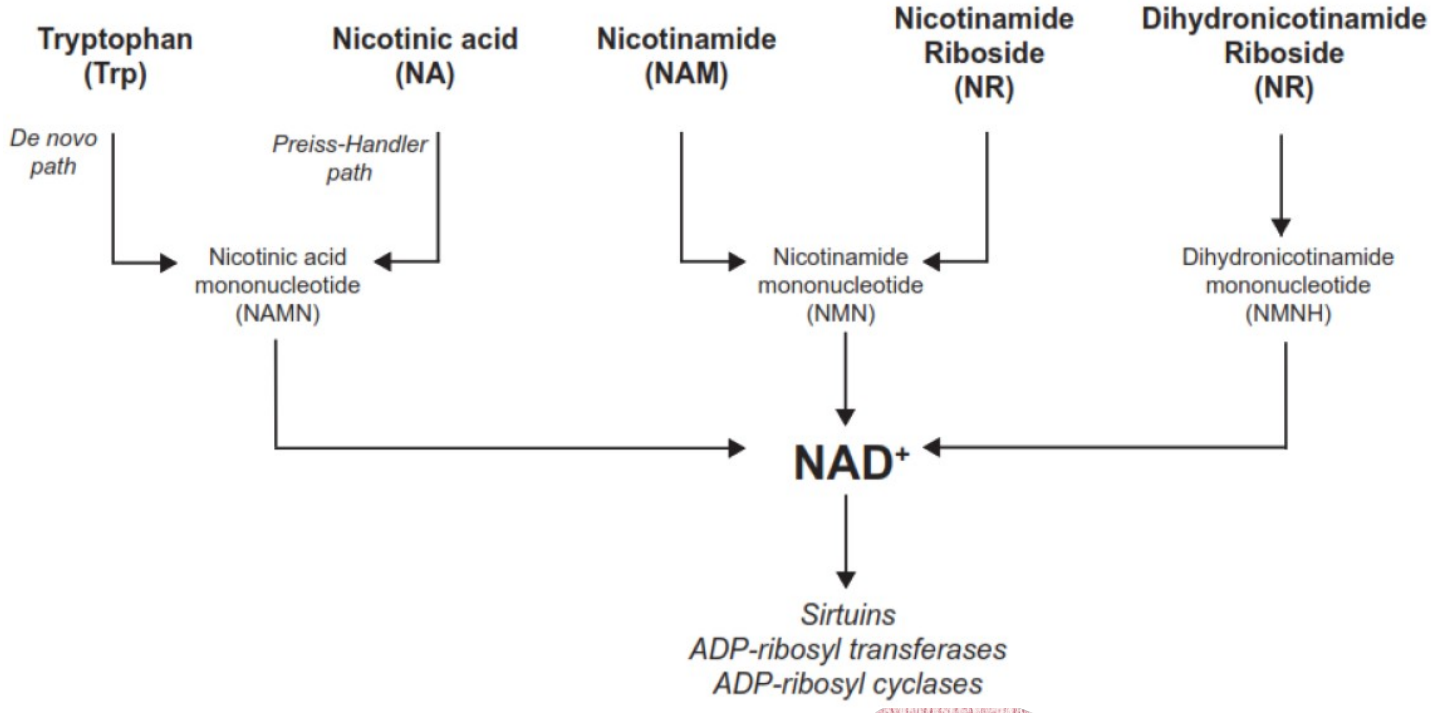
van der Reest et al., 2021

MOLECULAR PATHWAYS AND TARGETS OF REPRODUCTIVE SENESCENCE



Secomandi et al., 2022

NAD AND PRECURSORS



Canto, 2022

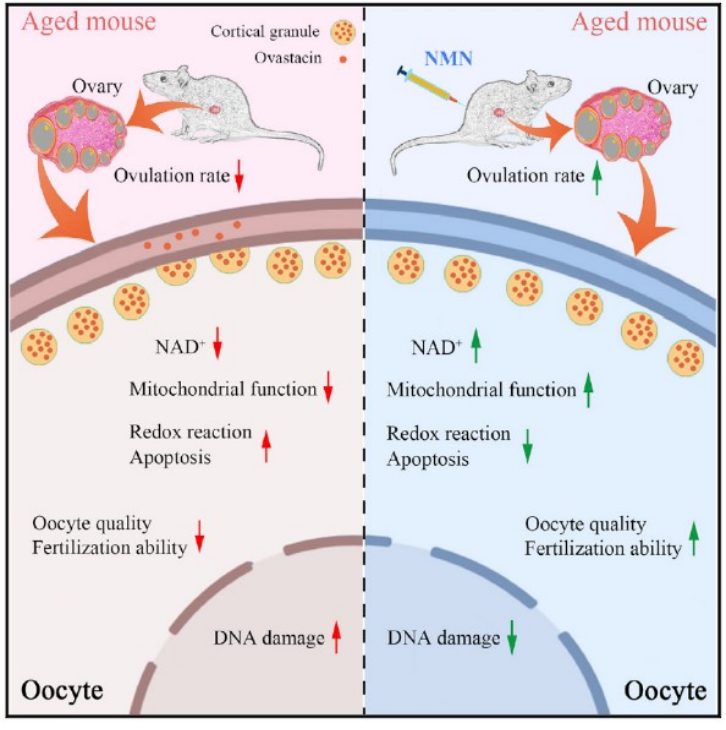
NAD PATHWAYS AND FEMALE FERTILITY

Reproductive aging in female mammals is an irreversible process that accompanies decreased levels of NAD^+

NR or NMN supplementation has helped to alleviate reproductive decline in aging female mice, in which it was found to increase NAD^+ in oocytes from mice suffering fertility decline. NMN supplementation effectively improves the quality of maternally aged oocytes by restoring their mitochondrial function and enhancing meiotic competency, fertilization ability, and subsequent embryonic development potential

Bertoldo et al., 2020; Miao et al., 2020; Q. Yang et al., 2021

FEMALE FERTILITY AND NAD+

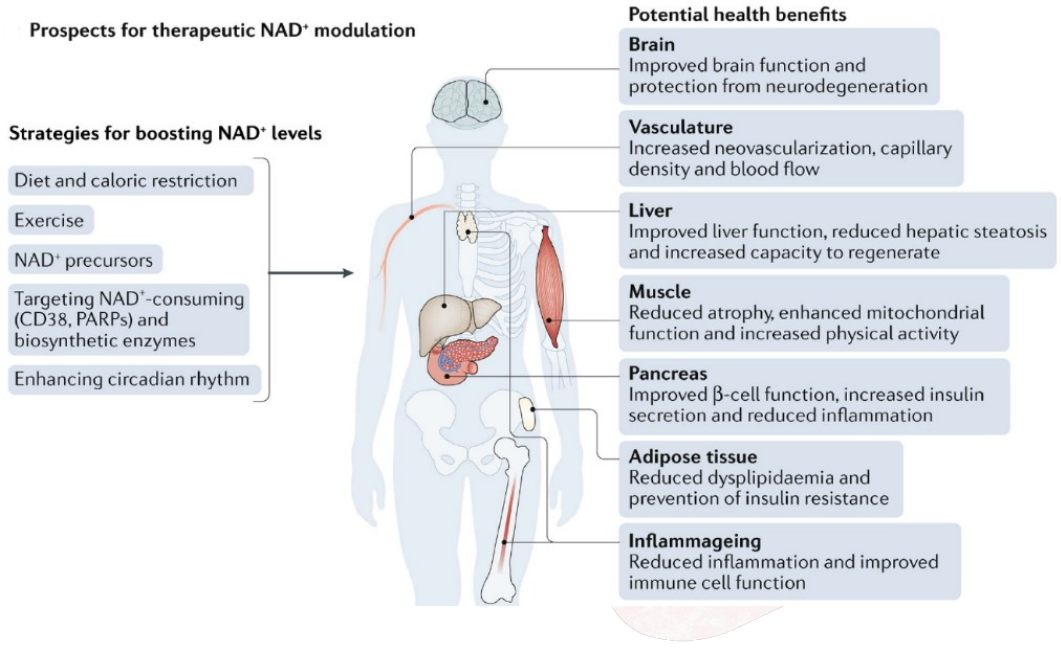


Miao et al., 2020

NMN supplementation reverses the declining quality of maternally aged oocytes

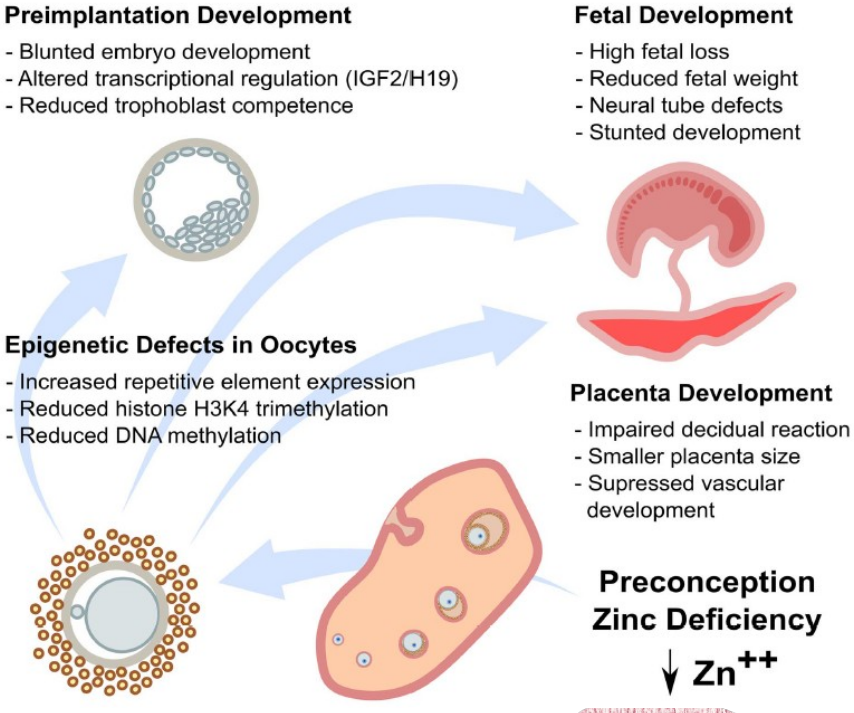
THERAPEUTIC APPROACHES TO RESTORE NAD+ LEVELS AND IMPACT ON HEALTH

- Fasting
- Caloric restriction
- Sports activity
- Sleep and circadian rhyth
- Low glucose availability
- Heat shocks
- Cold therapy



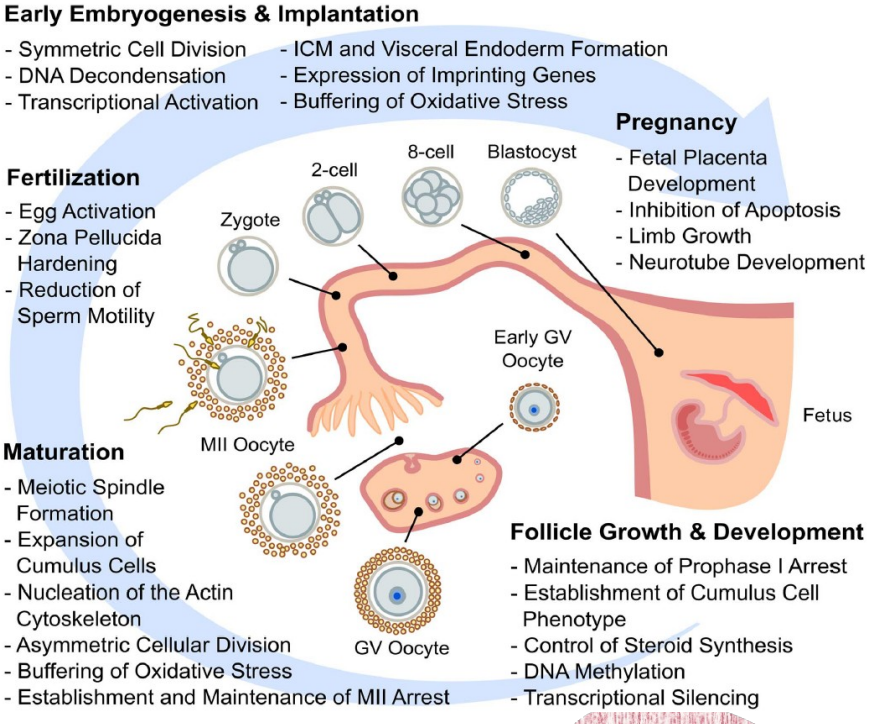
Poljsak et al., 2020; L. Liu et al., 2018; Palmer et al., 2021; Covarrubias et al., 2021

ZINC



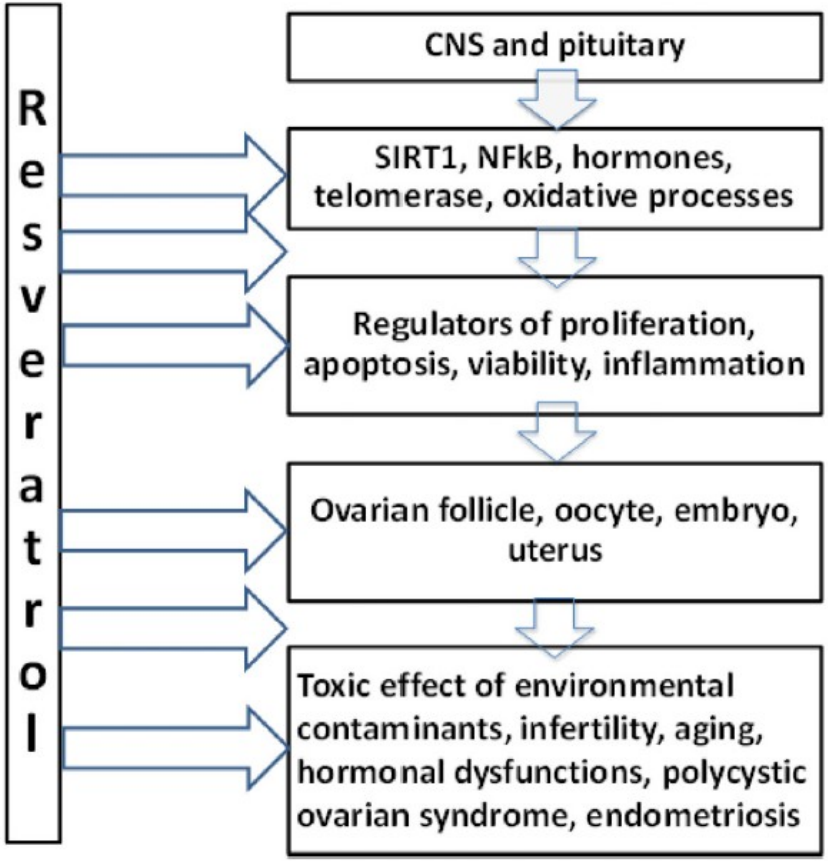
Garner et al., 2021

ZINC



Garner et al., 2021

RESVERATROL



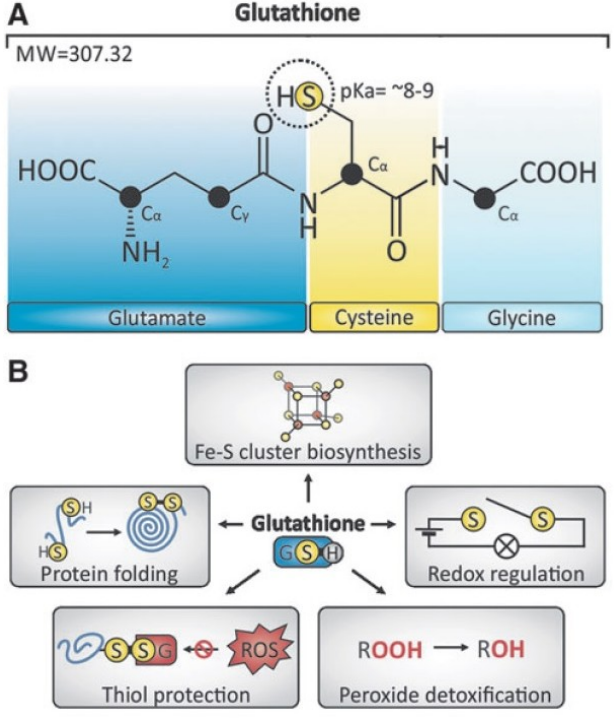
Sirotkin, 2021

SELENIUM

Lima et al., 2022

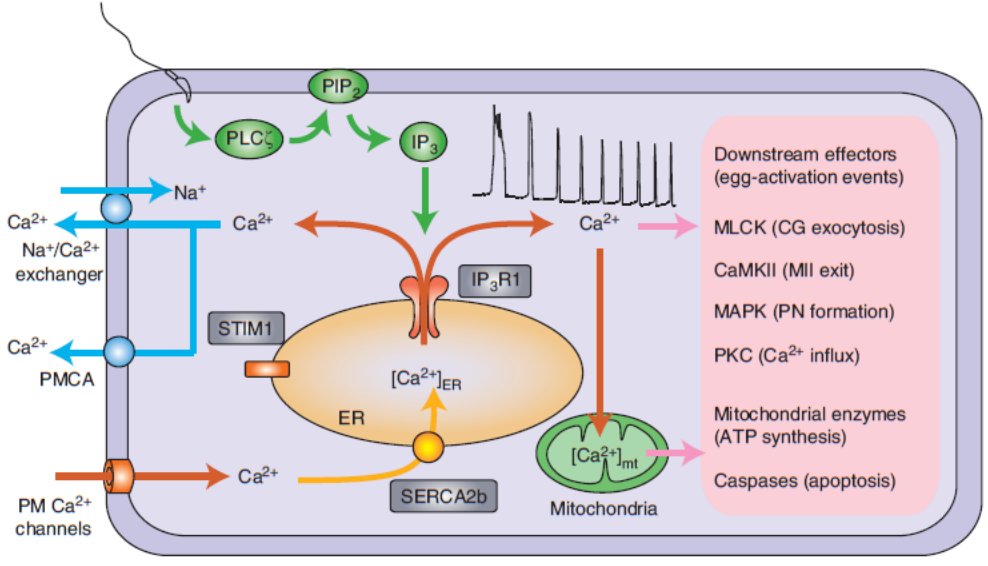
GLUTATHIONE

Mitochondria rely on a redox buffering network composed of reduced GSH and peroxiredoxins (Prx) to quench ROS generated by nutrient metabolism



Calabrese 2017; Scirè 2018

CA^{2+}-SIGNALLING TOOLKIT IN OOCYTES



Wakai 2019

VITAMIN D: IMPACT TO OVARIAN TISSUE

Cholecalciferol stimulates

- Progesterone production by 13%
- Oestradiol production by 9%
- Oestrone production by 21%

Parikh 2010

VITAMIN D RECEPTOR (VDR)

Interest in the reproductive functions of vitamin D surfaced following the discovery of the vitamin D receptor (VDR) and the metabolizing enzyme 1α-hydroxylase in the decidua, placenta, ovary, endometrium and pituitary gland

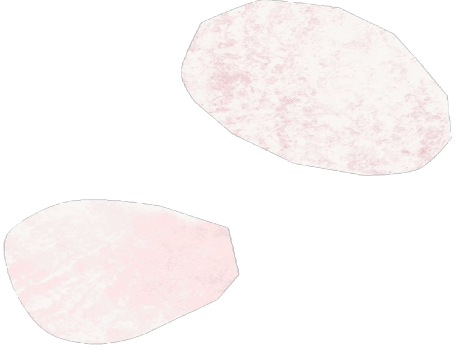
VDR is expressed in ovarian granulosa cells and fallopian epithelial cells and this expression increases during pregnancy

Dabrowski, 2015; Mousa 2016

VITAMIN D: HORMONE REGULATION

Placental steroidogenesis

Decidualization of the endometrium through different signalling pathways of the VDR



Aleyasin 2011

SENOTHERAPIES

Drug	Functional activity	Molecular target of therapy	Reference
Dasatinib and Quercetin	Antifibrotic uterine effect, reduce accumulation of ROS, reduce decline of SIRT expression	Ephrin receptors/BCL-2 family, p53/p21/serpine, PI3K/AKT	Kirkland and Tchkonia (2017), Cavalcante *et al.* (2020) and Wang *et al.* (2018)
Rapamycin	Prolong murine ovarian lifespan, improved oocyte survival, preserve fertility	mTOR, FOXO3a	Garcia *et al.* (2019) and Sun *et al.* (2018)
NAD and precursors	Improved oocyte quality and fertility, prevent meiotic spindle anomalies	SIRT pathway	Lee *et al.* (2019), Feldman *et al.* (2012), Zhang *et al.* (2014) and Bertoldo *et al.* (2020)
Resveratrol	Improves telomerase activity and telomere length, diminished ROS formation, DNA damage, and AGE product	SIRT1	Lee *et al.* (2019) and Liu *et al.* (2013b)
Melatonin	Reduce accumulation of ROS, increase telomere length, decrease inflammation	MT1/AMPK/p53-signaling pathway, Nrf2, NF-κB regulation	Zhang *et al.* (2019a,b), Reiter *et al.* (2016), Galano *et al.* (2013) and Hardeland (2019)
Coenzyme Q10	Local reduction in ROS, oocyte quantity and quality	Mitochondria	Wang and Hekimi (2016), Özcan *et al.* (2016), Bentov *et al.* (2014)
NAC	Delayed decline in fertility, ROS scavenger	Telomere	Zhang *et al.* (2019a) and Liu *et al.* (2012)

AGE, advance glycation product. AKT, protein kinase B. AMPK, AMP-activated protein kinase. BCL-2, B-cell lymphoma-2. FOXO3, forkhead box O3. MT1, metallothionein 1A. NAC, N-acetyl-L-cysteine. NAD, nicotinamide adenine dinucleotide. Nrf2, nuclear factor erythroid 2-realted factor 2. PI3K, phoshoinositide 3 -kinase. ROS, reactive oxygen species. SIRT, sirtuin. mTOR, mammalian target of rapamycin.

Secomandi et al., 2022

Micronutrient	Description	Effect on female	Recommended dose	Sources
Folic acid	• Known as vitamin B9 • Essential compound involved in key biochemical processes	• Improves chances of pregnancy • Reduces risk of ovulatory infertility	400 µg/day	Vegetables, fruits, nuts, seafood, eggs, dairy, meat
Calcium	• Plays a role in reproductive health • Facilitates fertilization	• Creates alkaline environment in vagina • Follicular production • Oocyte activation and maturation	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	Helps the fertilized ovum implantation process	30–60 mg/day	Beans, vegetables, cereals, breads
Vitamin B12	• Known as cobalamin • Cofactor in DNA and fatty acid synthesis • Amino acid metabolism	• Prevents spontaneous abortion • Necessary for the development and functionality of the placenta	50 µg/day	Fish, meat, poultry, eggs, milk
Selenium	• Selenoprotein • Plays a potential role in both female and male fertility	• Placenta development • Adequate development of the fetus' nervous system	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	• Involved in capacitation and fertilization in the female reproductive tract	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	• Participates in fertilized egg cell implantation and placenta development	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	• Affects ovarian follicular growth, uterine environments, and oocyte maturation	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	• Essential for collagen biosynthesis • Vital for adequate ovarian follicle growth and also for the ovulation and luteal phases	85 mg/day	Citrus, berries, pepper, kiwis, broccoli, brussels sprouts, tomatoes, potatoes

X. Ma et al., 2022

Nutrient	Summary	Recommended food sources
Carbohydrates	Added sugars and a high glycemic index have a negative effect on fertility.	Vegetables and fruit, whole-grain pasta, whole-grain bread, grains, rice, cereals
Fat	Intake of TFAs and excess SFAs appears to negatively affect female fertility. The direct effect of PUFAs on fertility is unclear, while MUFAs appear to have a positive effect on female fertility.	Oily fish, rapeseed oil, flaxseed oil, olive oil and other plant oil, avocado, nuts, seeds
Proteins	It is vital to include good sources of proteins in the diet. Plant proteins appear to have a positive impact on fertility, while animal protein—especially from processed meat—a negative impact.	Legumes, fish, lean meat, eggs, dairy products (particularly fermented)
Dairy	Studies regarding dairy are inconsistent—although dairy should be consumed as a part of healthy diet, it is hard to determine if it should be high-fat or low-fat in order to increase fertility. Taking current studies into the account, high-fat dairy should not be recommended in order to increase fertility, as it can have a negative impact on other risk factors for fertility.	Low-fat dairy, especially fermented dairy products
Iodine	Iodine is essential for the proper development of the fetus and proper thyroid function. While mild and moderate iodine deficiency is common among women, it is crucial to pay special attention to the supply of iodine by women planning a pregnancy.	Iodized salt, dairy, seafood
Folic acid	It appears that folic acid supplementation, particularly combined with vitamin B-12, may increase the chance of pregnancy and ART success. There is a need for the randomized trials.	Green-leafy vegetables, eggs, poultry
Vitamin D	Serum vitamin D concentrations may be associated with PCOS and endometriosis and affect ART success. In a population of healthy, fertile individuals, there is no significant association.	Fish, eggs, cheese, milk, dairy
Antioxidants	Very-low-quality evidence suggests that antioxidant supplementation may be beneficial for women suffering from infertility. More research is needed to assess the risk of the possible side effects. Inositol, L-carnitine, and NAC require particular attention due to the increasing number of studies positively assessing their impact on parameters related to female fertility.	Fresh fruits (especially berry fruits) and vegetables, vegetable oil, spices (e.g., cinnamon), tea, coffee
Phytoestrogens	The relation of phytoestrogens to female fertility remains unclear. Studies indicate that the consumption of soy isoflavones has a beneficial effect on ART success.	Pulses, flaxseed oil
Gluten	In healthy individuals, gluten does not appear to affect fertility.	Not applicable
Caffeine	High caffeine consumption may be a potential factor associated with the increased time to achieve pregnancy and an increased risk of pregnancy loss.	Coffee, cocoa—in recommended amounts
Alcohol	There is some evidence suggesting that excessive alcohol consumption correlates positively with reduced fertility and a higher risk of developing menstrual disorders.	Not applicable

[1]ART, assisted reproductive technology; NAC, N-acetylcysteine; PCOS, polycystic ovary syndrome; TFA, *trans*-fatty acid.

Skoracka et al., 2021

NUTRIGENOMICS

Genes/ Haplotypes	Nutrition and Health Pattern Involved	SNPs	Genotype Differences			Nutritional Intervention in Subjects at Risk
MTHFR	Folate metabolism	rs1801133	C/C normal enzyme activity	C/T reduced enzyme activity	T/T reduced enzyme activity	Adequate B vitamin-enriched diets (green raw vegetables, fruits, shellfish, etc.) and/or adequate supplementation (wildtype 200 µg/day; intermediate 400 µg/day; risk 800 µg/day; [101]) with adequate B6, B12 and choline intake
		rs1801131	A/A normal enzyme activity	A/C reduced enzyme activity	C/C reduced enzyme activity	
PEMT	Choline metabolism	rs7946	G/G normal enzyme activity	A/G higher choline deficiency risk	A/A higher choline deficiency risk	Increased amount of folate rich foods (raw green leafy vegetables, seeds, fruits) [103]
		rs12325817	G/G normal choline metabolism	C/G higher choline deficiency risk	G/G higher choline deficiency risk	
MTHFD1		rs2236225	G/G normal choline metabolism	A/A higher choline deficiency risk	A/G higher choline deficiency risk	
FTO	Obesity, fat mass and Met-S associated genes	rs9939609	T/T lower risk of obesity and adiposity	A/T higher risk of obesity and adiposity	A/A higher risk obesity and adiposity	Hypocaloric MedDiet in general with low saturated fats and limited carbohydrates [108–112]. Higher intake of proteins is recommended in risk allele carriers [113]
		rs1558902	T/T lower risk of obesity and adiposity	A/T intermediate risk of obesity and adiposity	A/A higher risk obesity and adiposity	
LEP		rs2167270	G/G lower risk of obesity and IR	G/A higher risk of obesity and IR	A/A higher risk of obesity and IR	Hypo/normo-caloric diet with reduced SFA and carbohydrates intakes especially from sweets and snacks [114]
		rs7799039	G/G lower risk of obesity and IR	G/A higher risk of obesity and IR	A/A higher risk of obesity and IR	
ADIPOQ		rs266729	C/C normal adiponectin levels, lower risk of Met-S	C/G diminished adiponectin levels, higher Met-S traits	G/G diminished adiponectin levels, higher Met-S traits	Reduced SFA intake [115]
LCT	Lactose metabolism	rs4988235	T/T lactase persistence	C/T intermediate phenotype	C/C lactose intolerance	Diet low in lactose (<12 g) use of fermented dairy products and/or adequate lactase [116] and probiotic supplementation [117]
FADS1	Long-fatty acids synthesis	rs174537	C/C normal biosynthesis	C/T reduced biosynthesis	T/T impaired biosynthesis	Adequate apport of foods containing omega-3 PUFAs and/or adequate omega-3 supplementation [118]
		rs174547	T/T normal D5D and D6D fatty acid desaturase enzyme activity	T/C decreased D5D and D6D fatty acid desaturase enzyme activity	C/C decreased D5D and D6D fatty acid desaturase enzyme activity	
PPAR-G	Glucose metabolism/diabetes or insulin resistance risk	rs1801282	G/G reduced risk of T2DM and IR	G/C intermediate risk of T2DM and IR	C/C Increased risk of T2DM and IR	According to the combination of genetic risk: low glycemic index diet with the characteristics of the MedDiet so adequate fiber intake (30 g/day), limitation of refined carbohydrates and replacement of animal fats with vegetable ones, especially MUFAs (extra virgin olive oil) but also PUFAs (oily fruit). Possibly support with omega3 supplementation. [119–125]
TCF7L2		rs12255372	G/G lower risk of T2DM and gestational diabetes	G/T higher risk of T2DM and gestational diabetes	T/T higher risk of T2DM and gestational diabetes	
		rs7903146	C/C normal insulin response	C/T intermediate insulin response	T/T impaired insulin response	
KCNJ11		rs5219	E/E normal glucose tolerance, lower risk of T2DM and IR	E/K intermediate risk of T2DM and IR	K/K altered glucose tolerance, higher risk of T2DM and IR	
CYP1A2	Caffeine metabolism	rs762551	A/A fast metabolizer	A/C slow metabolizer	C/C slow metabolizer	Caffeine intake <100 mg/day [126]
HLA	Celiac disease predisposition and gluten sensitivity	rs2395182 rs7775228 rs2187668 rs4639334 rs7454108 rs4713586	**DQ2/DQ8-negative**	**Half DQ2-positive** HLA-DQA1*0501 or 0505 or HLA-DQB1*0201 or 0202	**DQ2-positive** HLA-DQA1*0501 or*0505 and HLA-DQB1*0201 or *0202 **DQ8-positive** HLA-DQA1*03 and HLA-DQB1*0302	Gluten-reduced diet (from 3 g up to 13 g) [127] or gluten-free diet using naturally GF products (e.g., rice, quinoa, amaranth, buckwheat)

Fabozzi et al., 2021