Dr Kate Van Harselaar

Obstetrician and Gynaecologist

Fertility Associates

Dunedin

Saturday, August 10, 2019

(Room 7)

15:05 - 16:00 WS #123: Aging Sperm and Eggs - What Can Be Done? (Not Repeated)

Aging Sperm and Eggs - What Can Be Done?

Winding back the clock…

Kate van Harselaar,

FRANZCOG, MBChB, MSc (Distinction)

Fertility Specialist

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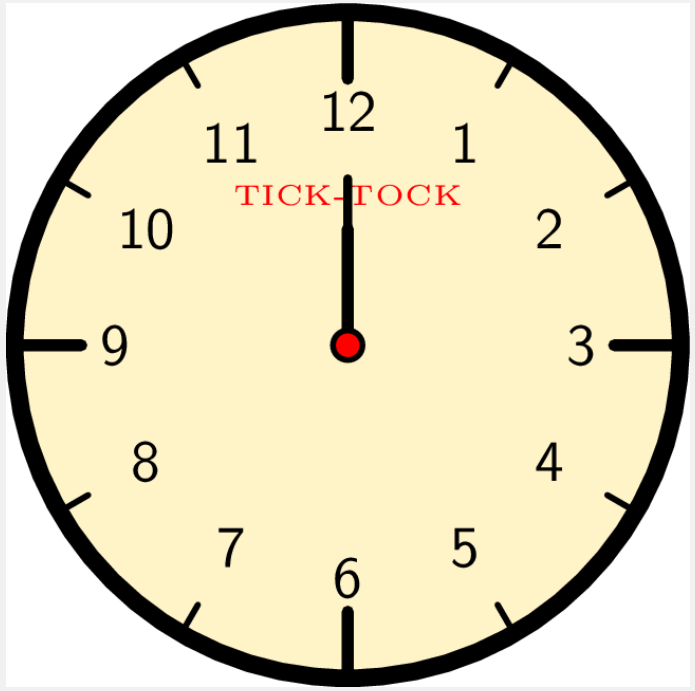
TE RAUHANGA O TE WHARETANGATA



- **Why is the biological clock so important in the 21st century?**
- Quantifying the biological clock
- AMH – reading the clock
- Donor eggs – substituting the clock
- Freezing eggs – stopping the clock
- What makes the clock tick?
- Mitochondria – adding extra cog wheels to the clock
- Pharmacological agents – oiling the cogs
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- Out of options? What's a person to do in 2019?

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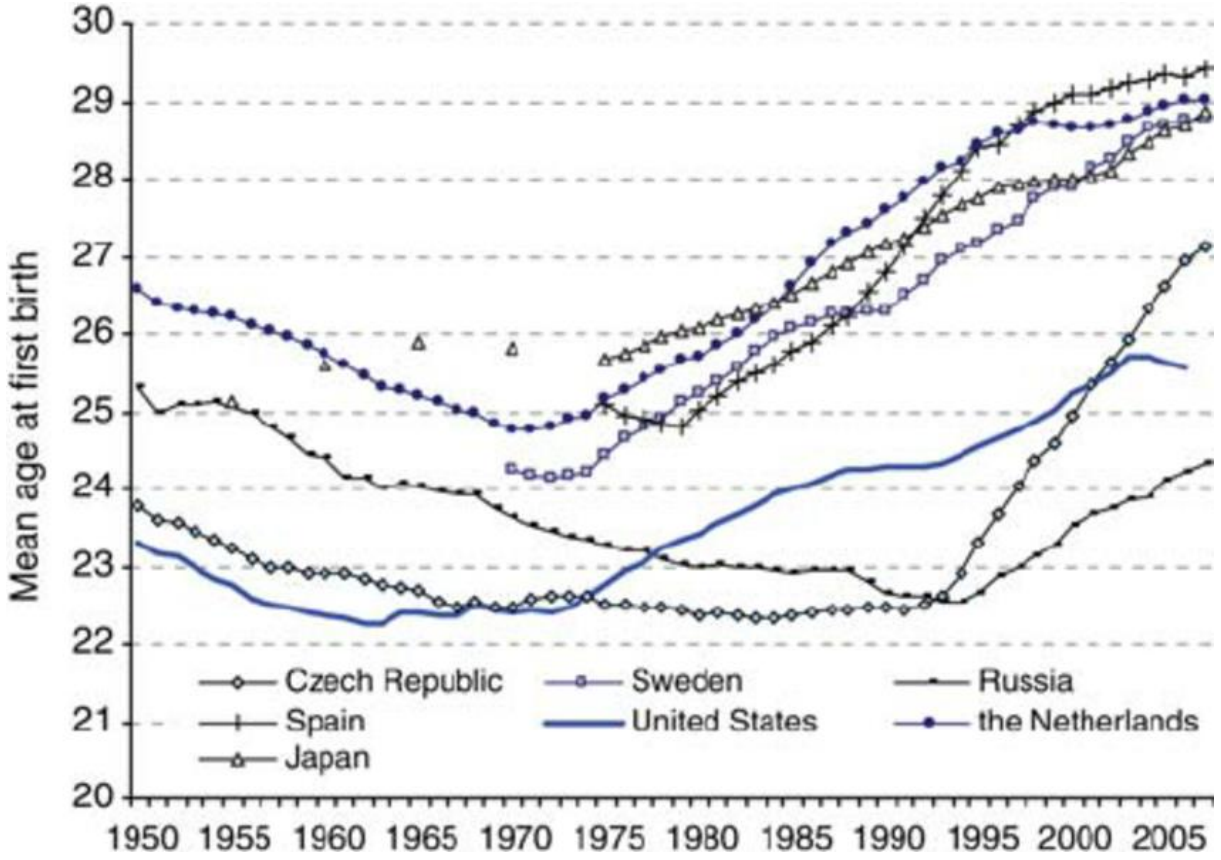
Age at first child



2019?

Why is it so important?
When do women have the greatest number of eggs?
Ovarian reserve – egg quality and quantity

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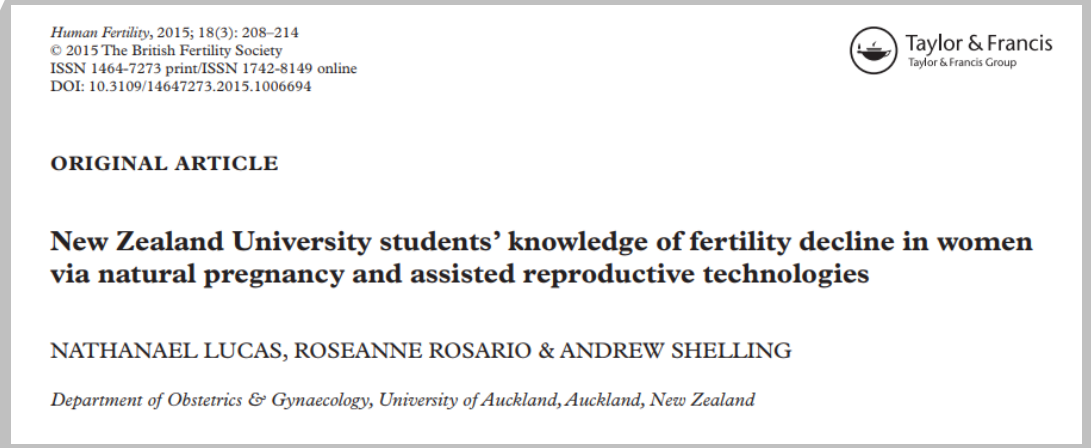
Survey - What people 'know' about fertility and women's age

- Overestimated natural pregnancy rate by age
- Overestimated effectiveness of IVF
- Students studying medicine, nursing, biomed no better than those studying law, education
- Nurses most over-optimistic
- Medical students most convinced technology would help
- 85% wanted children
- 29 considered the best age to become a parent (but how many take note?)



Human Fertility, 2015; 18(3): 208–214

ISSN 1464-7273 print/ISSN 1742-8149 online
DOI: 10.3109/14647273.2015.1006694

Taylor & Francis
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ORIGINAL ARTICLE

New Zealand University students' knowledge of fertility decline in women via natural pregnancy and assisted reproductive technologies

NATHANAEL LUCAS, ROSEANNE ROSARIO & ANDREW SHELLING

Department of Obstetrics & Gynaecology, University of Auckland, Auckland, New Zealand

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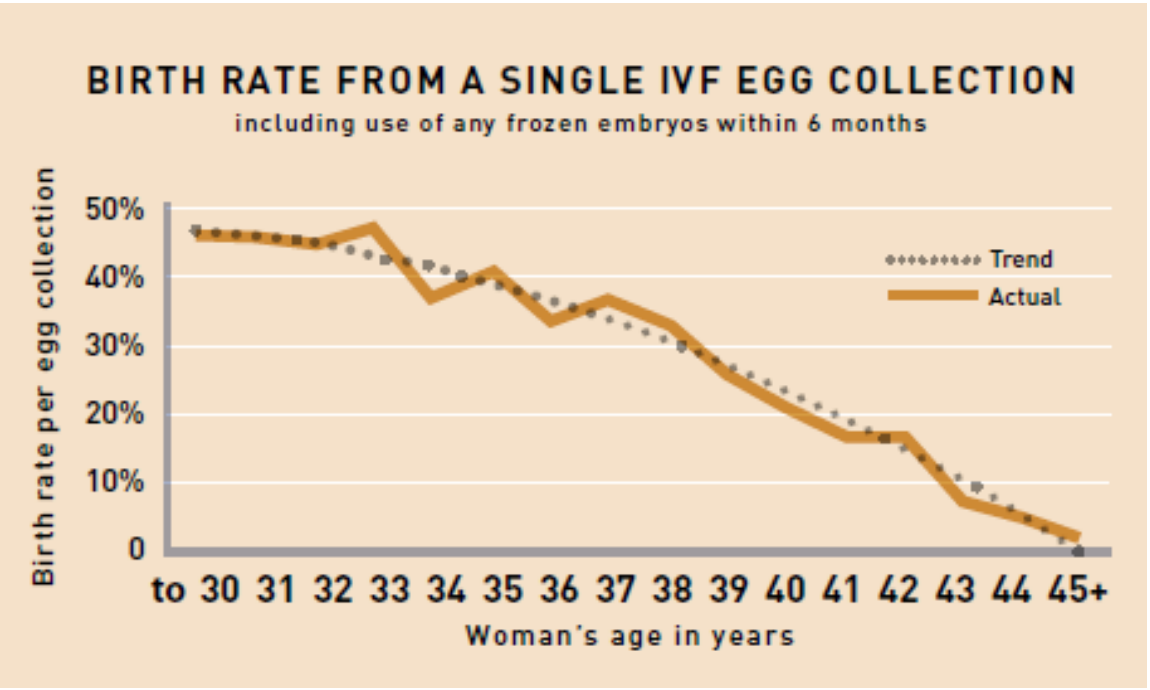
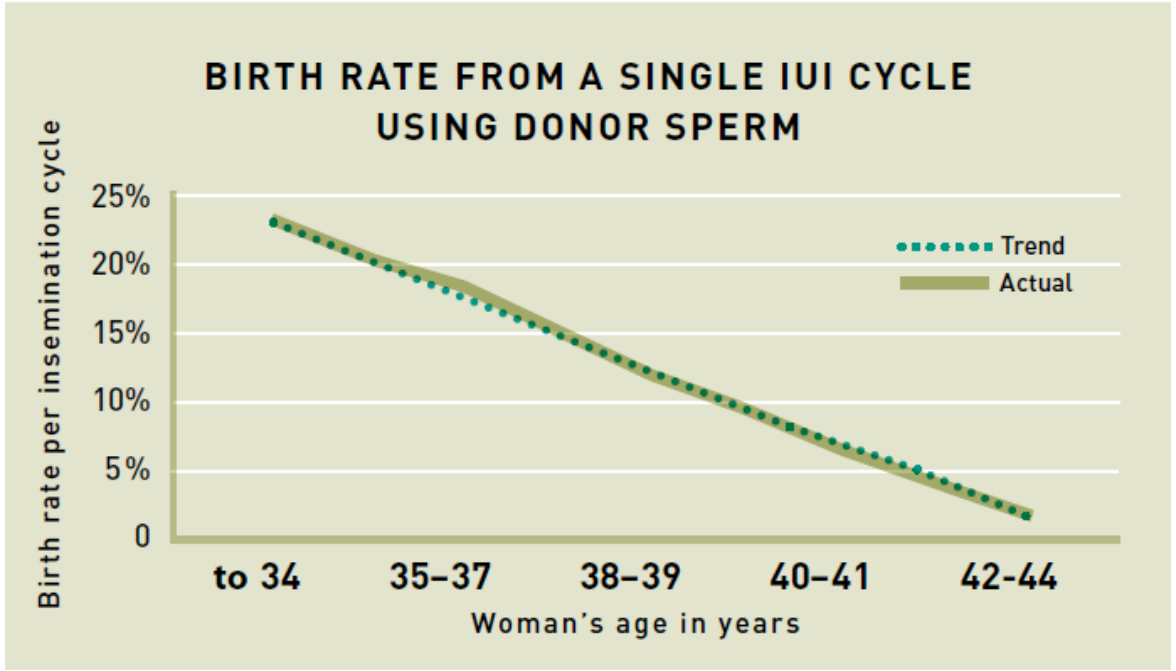
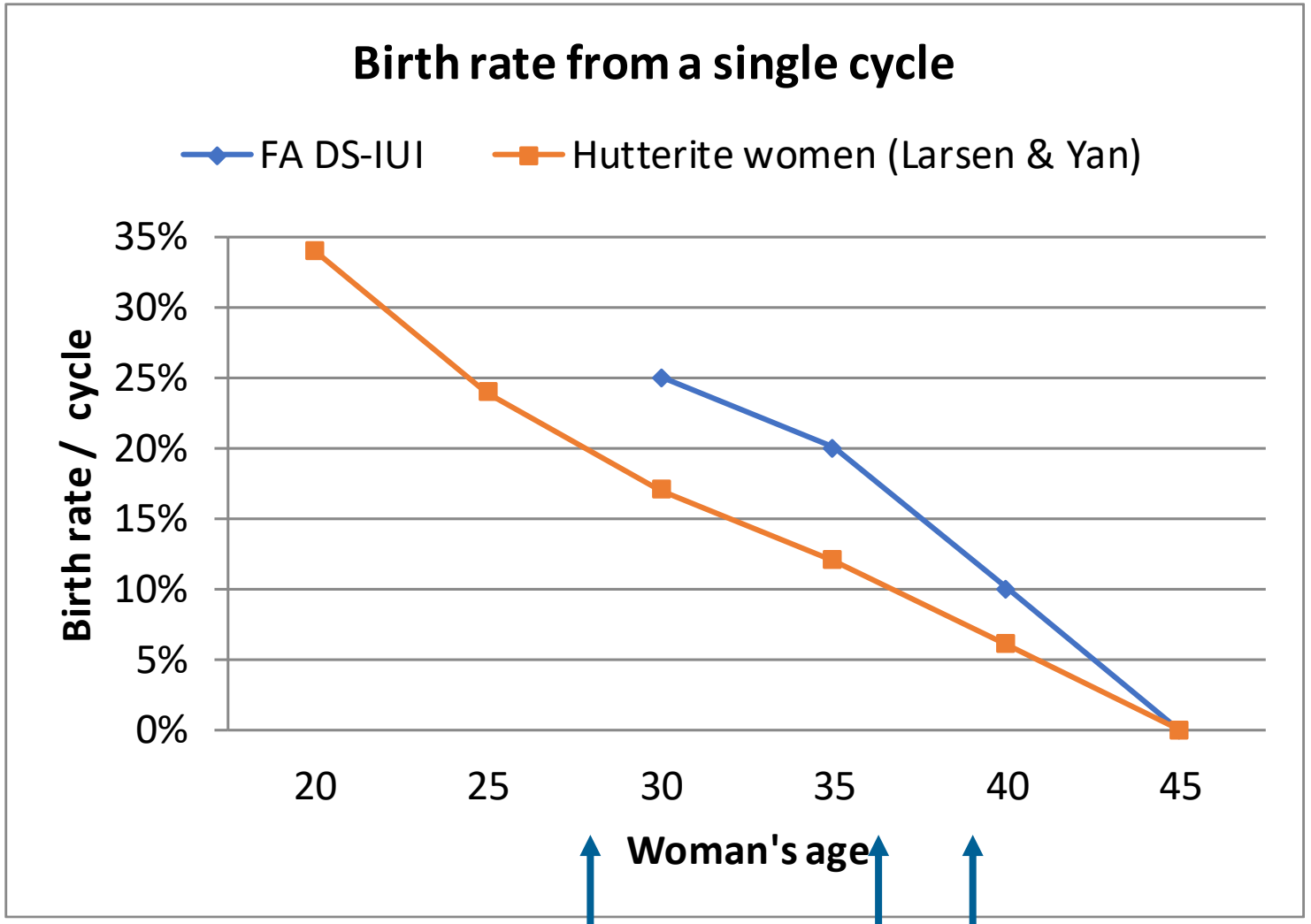
ART Fecundability and women's age





Age and trying to become pregnant



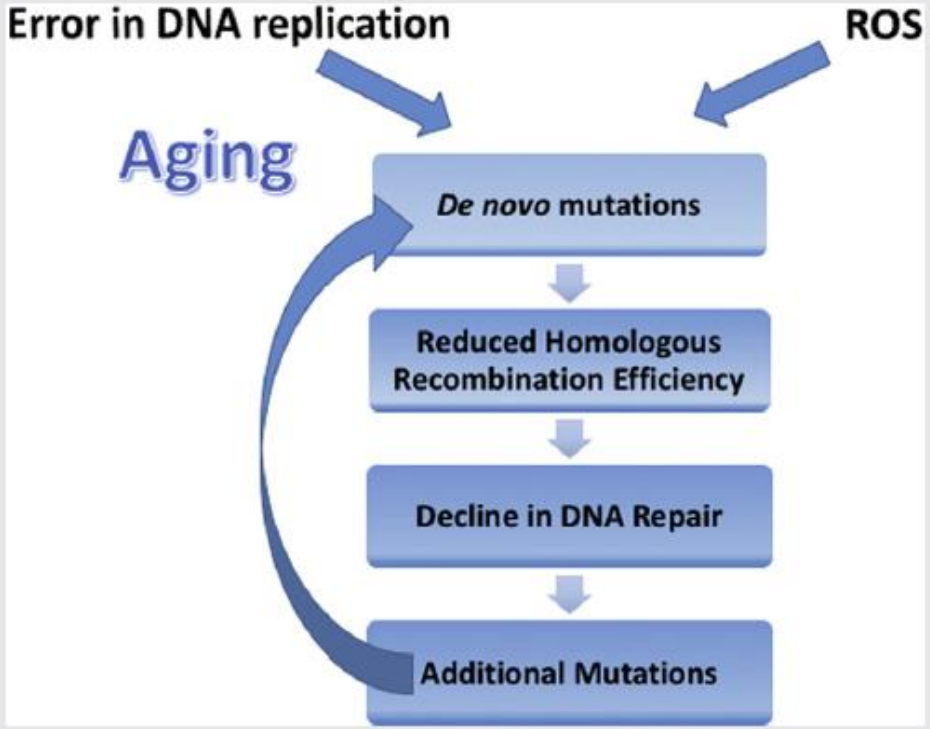
Average age at first birth in NZ now

Average age at presenting to a fertility clinic - elig MOH IVF Rx?

Average age at presenting, single women - waitlist donor sperm?

Advanced Paternal Age

FIGURE 2



Development of genomic instability with aging.

Herati. Paternal aging and the male germ line. Fertil Steril 2017.

TABLE 1

Offspring genetic conditions associated with advanced paternal age.

Condition	Paternal age (y)	Relative risk
Achondroplasia	>50	7.8
Apert syndrome	>50	9.5
Pfeiffer syndrome	>50	6
Crouzon syndrome	>50	8
Neurofibromatosis I	>50	3.7
Retinoblastoma	>45	3
Down syndrome	40–44	1.37
Klinefelter syndrome	>50	1.6
Epilepsy	40–45	1.3
Breast cancer	>40	1.6
Childhood leukemia	>40	1.14
Childhood central nervous system tumor	>40	1.69

Note: Adapted with permission from Ramasamy et al. (10).
[a] Maternal age 20–29 years.

Herati. Paternal aging and the male germ line. Fertil Steril 2017.

Men 40-50 yo RR 1.1-3
Men >50 yo RR up to 9.5

Age of presentation and resolution of infertility

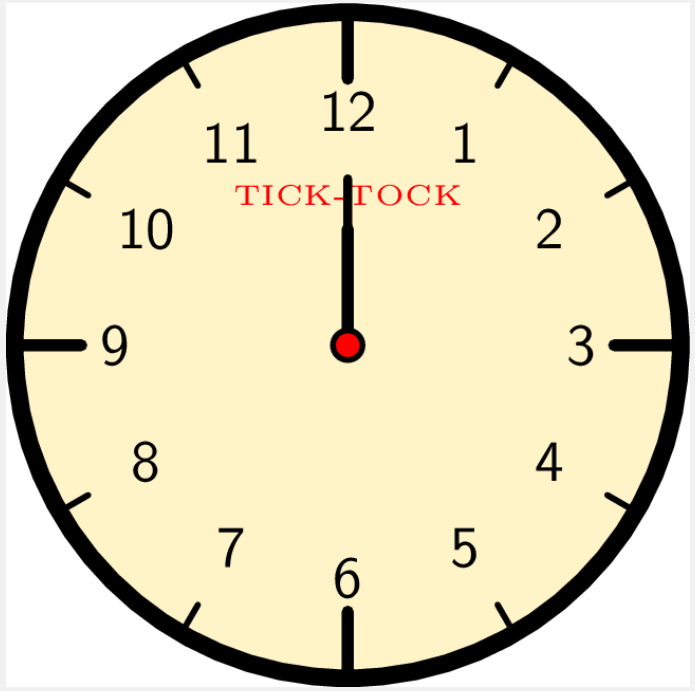
Human Reproduction, Vol.32, No.10 pp. 2042–2048, 2017
Advanced Access publication on August 29, 2017 doi:10.1093/humrep/dex271

human reproduction ORIGINAL ARTICLE *Infertility*

Resolution of infertility and number of children: 1386 couples followed for a median of 13 years

A.A. Righarts[1,2,*], A. Gray[2], N.P. Dickson[2], L. Parkin[2], and W.R. Gillett[1]

	Resolved infertility	Number of children for those resolving
<30	79%	2.0
30-34	69%	1.7
35-37	51%	1.4
38-39	39%	1.2
40-41	33%	1.2
≥42	8%	1.0



- **AMH – reading the clock**
- Donor eggs – substituting the clock
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- What makes the clock tick?
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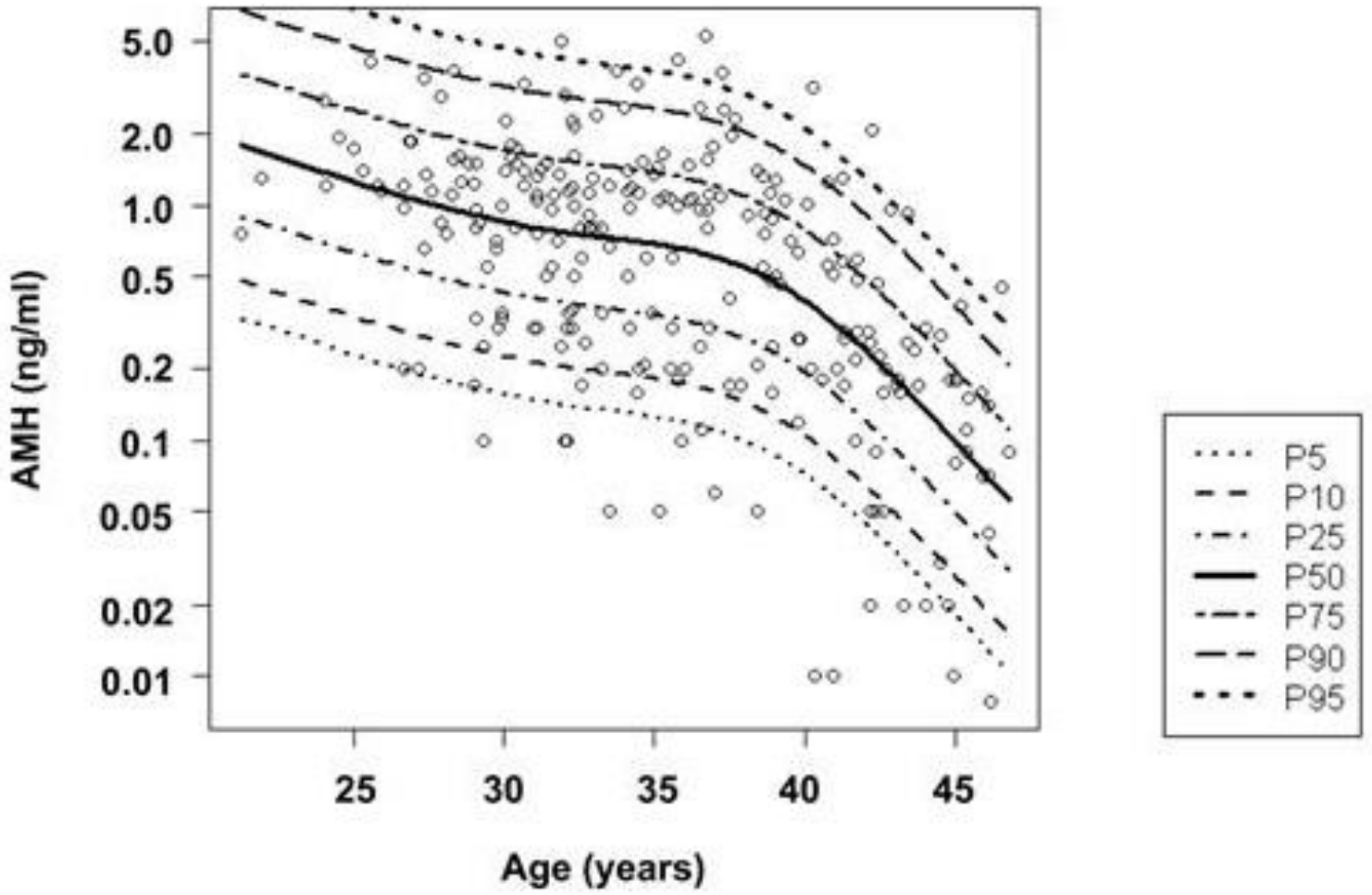
Distribution of AMH levels



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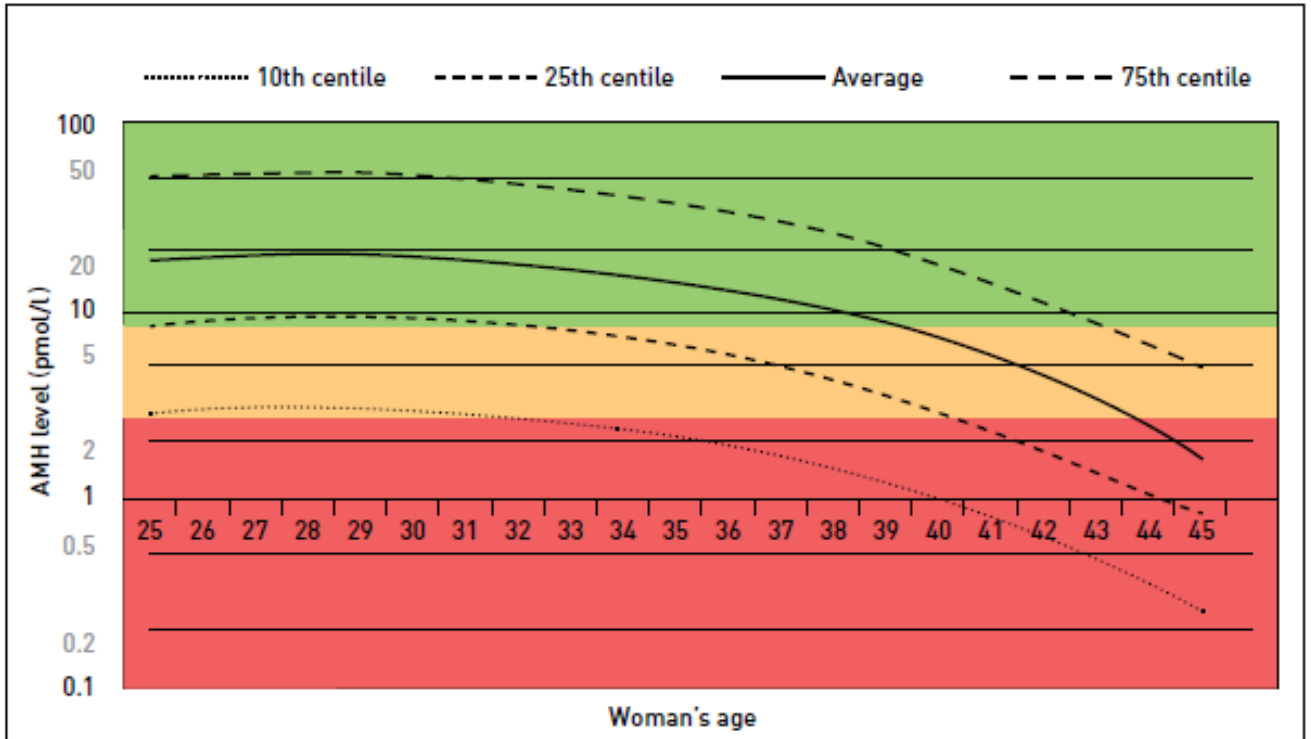
AMH and fecundability

- Steiner et al (2017) JAMA 318(14):1367
- N = 750 women aged 30-44, trying to conceive =< 3 months, NO history of infertility
- **Conclusion** - Age rather than AMH key factor

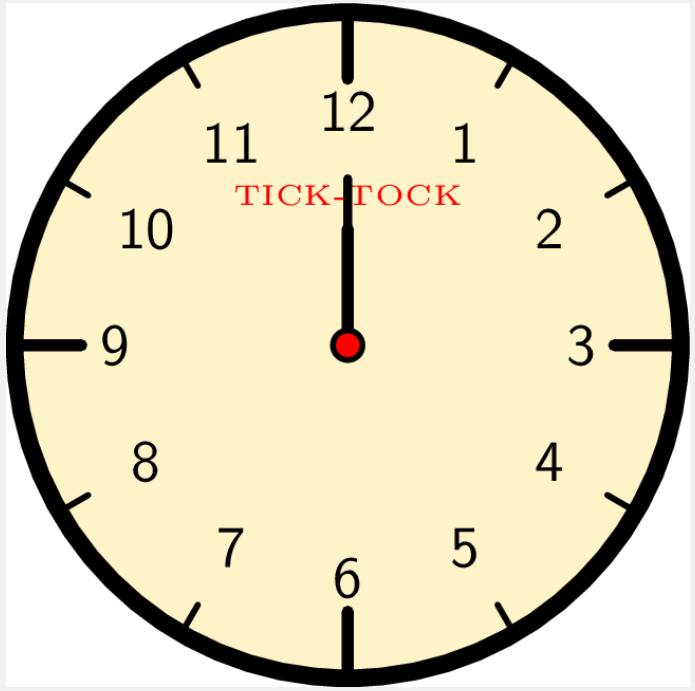
	Pregnant after 6 months	Pregnant after 12 months
AMH < 5 pmol/l	65% (50-75)	82% (70-91)
AMH > 5 pmol/l	62% 57-66)	75% (70-78)

AMH and the number of eggs in IVF

But if need IVF and low AMH - need more eggs



Green zone	Above the 25th centile for younger, fertile women	Very likely normal ovarian reserve – age is the best predictor of your future fertility	80% chance of 6 or more eggs in IVF
Orange zone	Between the 25th and 10th centiles for younger, fertile women	Some women in this range will have reduced ovarian reserve	50% chance of 6 or more eggs in IVF
Red zone	Below the 10th centile for younger, fertile women	Very likely reduced ovarian reserve	20% chance of 6 or more eggs in IVF



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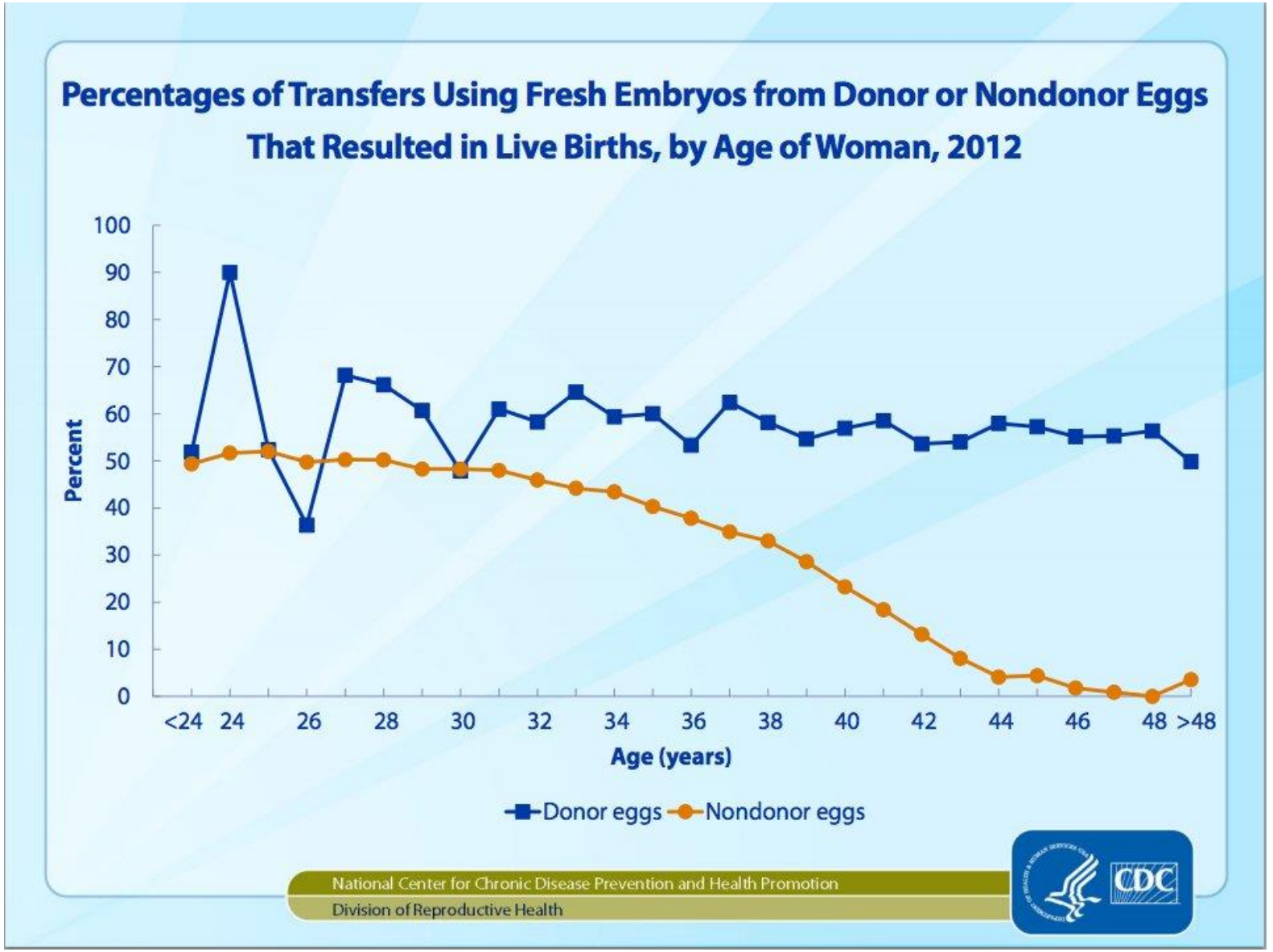
Impact of Donor Eggs on IVF Outcomes



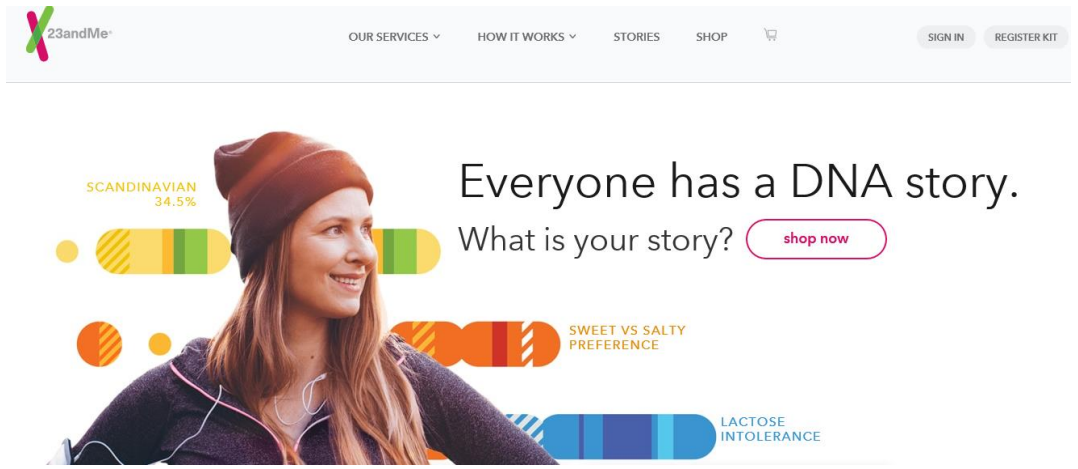
Egg quality not endometrial receptivity

Donor egg – ‘demand and supply’

Proportion of IVF cycles using donor eggs

- **~ 5% Australia and NZ**
  - unknown vs unknown
  - clinic vs social media
- **~ 10% USA**
- **~ 25% Spain**
  - Spain does 50% of all donor egg treatment in Europe
- **~ 0% in Japan**
  - 2017 – 1st anonymous egg donor
  - 50,000 Japanese women go to Korea and SE Asia for donor eggs each year

The ‘BUT’ with donor egg



Discover DNA relatives from around the world

- There will be no donor anonymity in the 21st century, despite
  - The laws of the country
  - The wishes of the patients and donor
  - 23andMe

- Sperm donation teaches us that
  - Offspring want to know their origins
  - Some offspring will want contact with their donor or half siblings
  - Reason reduction sperm donors?

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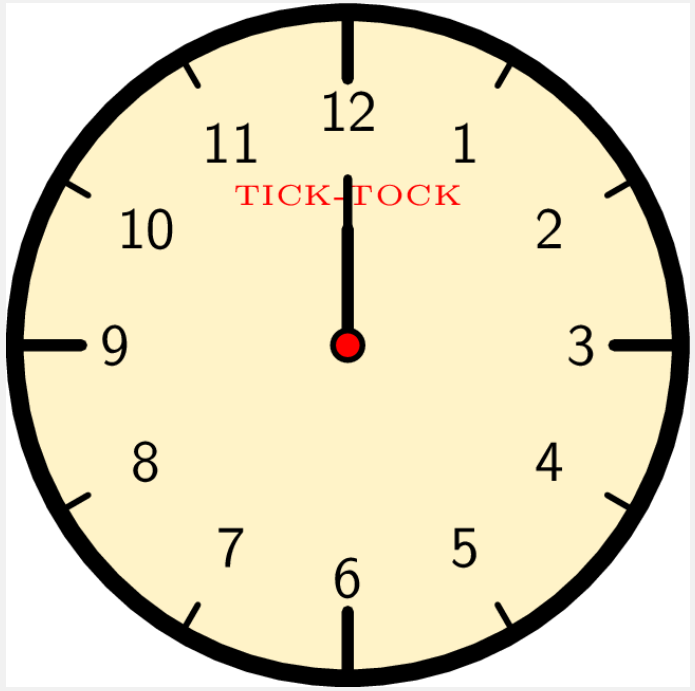

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Egg freezing makes egg banks practical for donor eggs

In favour of egg banks

- Specialisation → well documented processes
- Choice of donors for patients
- Patient information – disclosure of medical history

THE WORLD EGG BANK®

GLOBAL DONOR EGG BANK

Donor Egg Bank USA™
fulfilling dreams, delivering joy

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Egg freezing - a market with players

EggBanxx
SMART WOMEN FREEZE

Attitudes to egg freezing

O'Brien et al (2017) Eur J Gynecol Reprod Biol 217:71

- N=663 women 18-44, Dublin
- 90% knew about egg freezing
- 62% considered it acceptable for social reasons
- 59% women > 30 interested

Laillemant et al (2016) Acta Obstet Gynecol Scand 95(12):1402

- N=973 women, Denmark UK
- 83% knew about egg freezing
- 89% considered it acceptable for social reasons
- 46% active or possible interest

NZ - FA experience?

Social egg freezing – is there a 'sweet spot'?

Age at banking	Age at using	Chance of a baby naturally before 'infertility'	Average pay off in IVF birth rate
30	35	85%	40% → 47%
30	40	60%	23% → 47%
35	40	60%	23% → 40%
35	43	40%	8% → 40%
37	43	40%	8% → 35%

➔Don't bank too early

➔Don't bank too late

EXAMPLES OF OUTCOMES

25-37 YEARS OF AGE

Average Outcomes by Age and AMH

AMH RANGE	AVERAGE NUMBER OF EGGS	ESTIMATED NUMBER OF CYCLES
<5 pM	5 EGGS	2-3 CYCLES
5-15 pM	9 EGGS	1-2 CYCLES
>15 pM	15 EGGS	1 CYCLES

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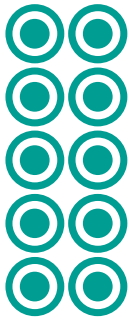
HOW MANY EGGS DO I NEED?

Studies demonstrate how many eggs are required per baby
(50% chance)

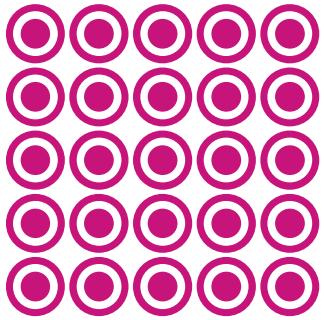


25-37 YEARS

10 eggs

38-40 YEARS

15 eggs



41-42 YEARS

25 eggs

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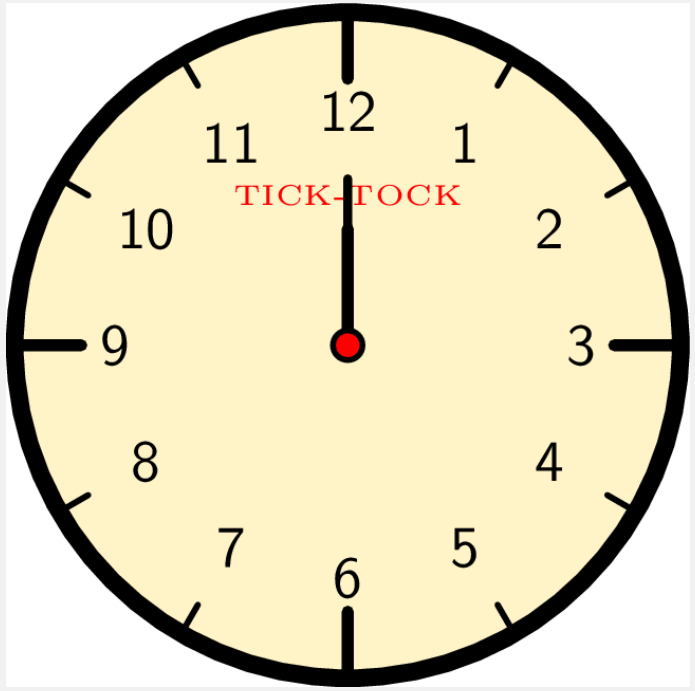

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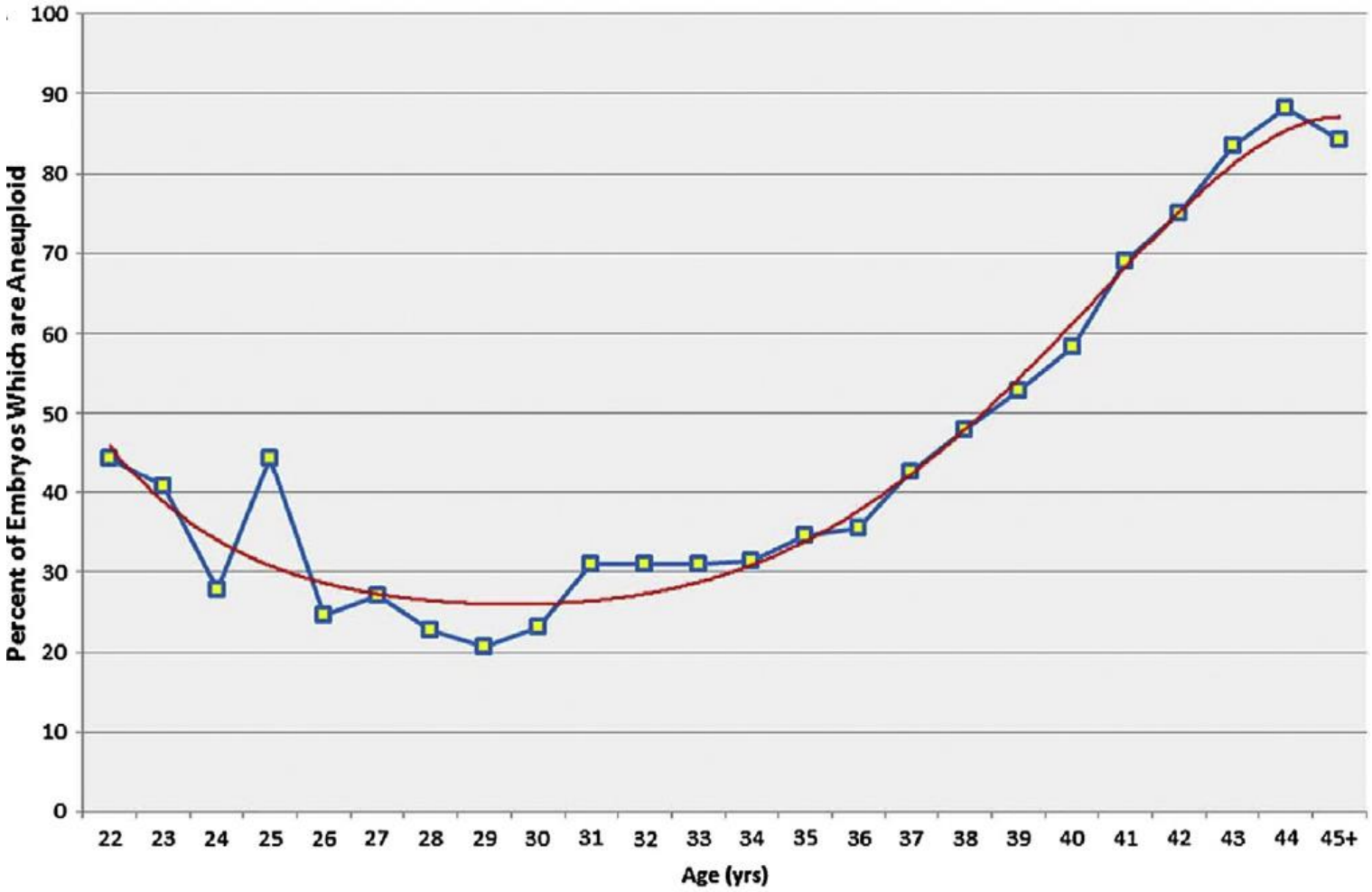
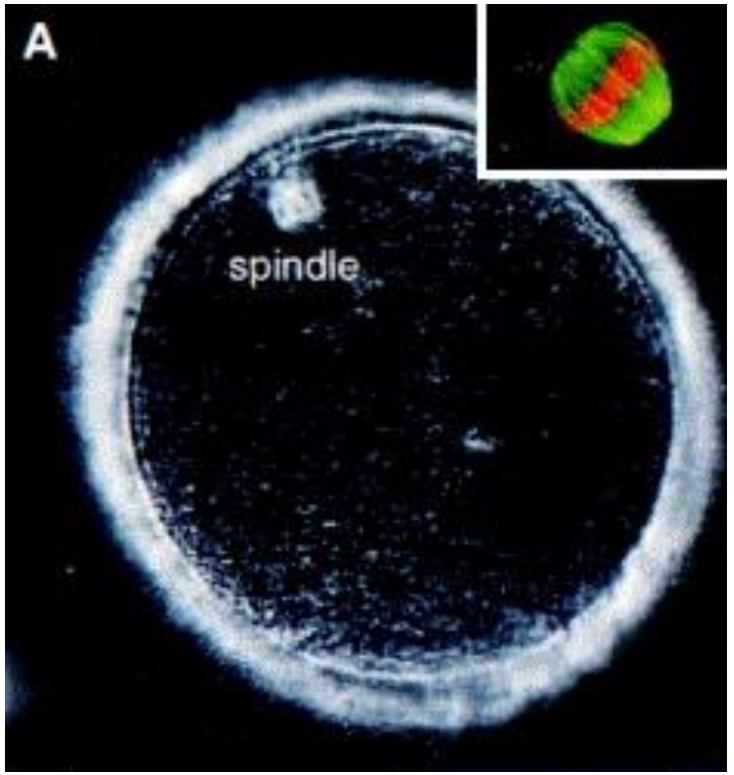
Aneuploidy vs Age

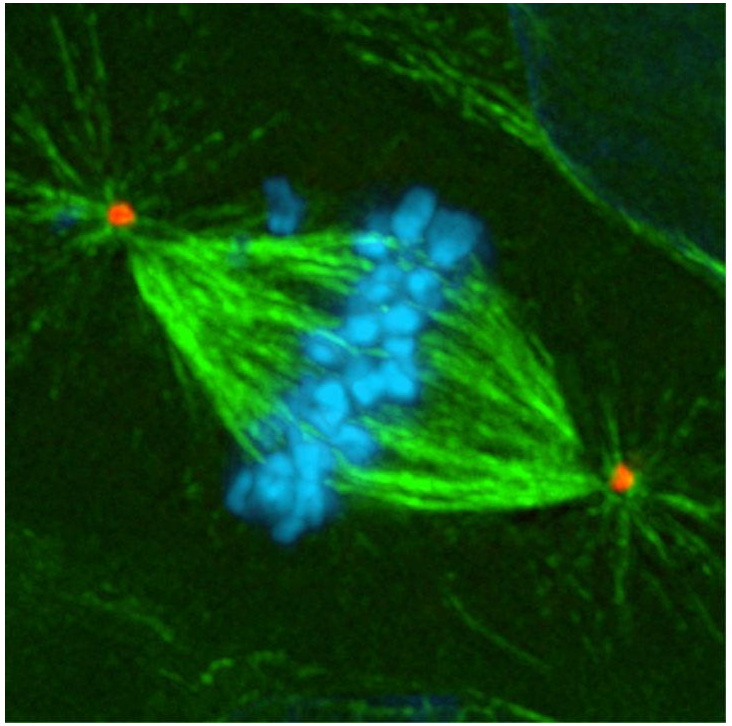


Forman et al Fertil Steril 103(5):1136

Age-related poor reproductive performance

- reduced ovarian reserve AND increase aneuploidy





Where does aneuploidy come from?

80% of embryo aneuploidy arises during meiosis

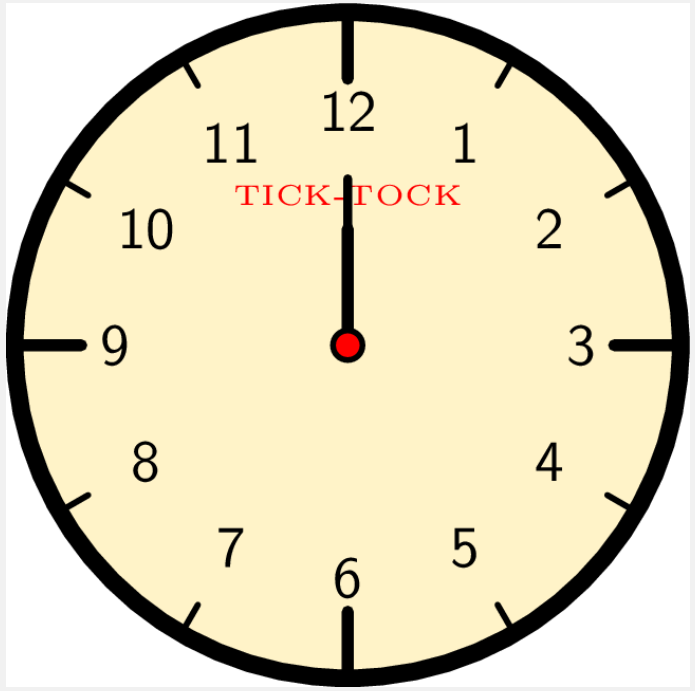
Mitochondria are Important

Table I mtDNA and oocyte quality.

	Species	Relationship	Oocyte mtDNA integrity	Oocyte mtDNA content	Granulosa cells mtDNA integrity	Granulosa cells mtDNA content	Granulosa cells mitochondrial genes expression or oxidative function	mtDNA haplogroups
Oocyte quality and embryonic development	Human	No			(Au *et al.*, 2005; Chan *et al.*, 2006)			
		Yes	(Brenner *et al.*, 1998; Barritt *et al.*, 1999; Hsieh *et al.*, 2002)	(Reynier *et al.*, 2001; Santos *et al.*, 2006; Wang *et al.*, 2010; Mao *et al.*, 2012; Murakoshi *et al.*, 2013; Xu *et al.*, 2015; Zhao *et al.*, 2016)	(Tsai *et al.*, 2010)	(Pawlak *et al.*, 2015; Ogino *et al.*, 2016)	(Hammond *et al.*, 2015)	
Oocyte quality and ageing	Human	No	(Chen *et al.*, 1995; Barritt *et al.*, 1999; Brenner *et al.*, 1998)				(Shufaro *et al.*, 2012)	
		Yes	(Keefe *et al.*, 1995; Barritt *et al.*, 2000; Chan *et al.*, 2005)	(Chan *et al.*, 2005; May-Panloup *et al.*, 2005a,b; Duran *et al.*, 2011; Bonomi *et al.*, 2012; Murakoshi *et al.*, 2013; Boucret *et al.*, 2015)	(Tsai *et al.*, 2010)	(Seifer *et al.*, 2002; Boucret *et al.*, 2015)	(Tatone *et al.*, 2006; Pacella-Ince *et al.*, 2014; Boucret *et al.*, 2015)	(May-Panloup *et al.*, 2014)

May-Panloup et al (2016) Hum Reprod Update 22(6):725

Age – decreases mtDNA integrity and oocyte quality



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Oocyte – largest number mitochondria and mtDNA of ANY cell

Empirical grounds for mitochondrial transfer

Mitochondria Studies	No. of Cycles	Pregnancies	Success Rate
Huang(1)	9	4	44%
Cohen(2)*	30	13	43%
Tzeng(3)	71	25	35%
Levron(4)	15	5	33%
Lanzendorf(5)*	4	1	25%

(1) Huang et al., 1999.
(2) Cohen et al., 1997, 1998; Brenner et al., 2000; Barritt et al., 2000, 2001.
(3) Tzeng et al., 2004.
(4) Levron et al.
(5) Lanzendorf et al., 1999.
* Studies conducted in the U.S.

Ooplasmic transfer (non patient matched)

- aim boost female germline mitochondria for developmentally compromised eggs

FDA Moratorium – gene transfer for human reproduction

Poor *in vitro* fertilization (IVF) success rates in women of advanced maternal age reflect unmet energy needs in the egg

= mitochondrion

Egg to be fertilized

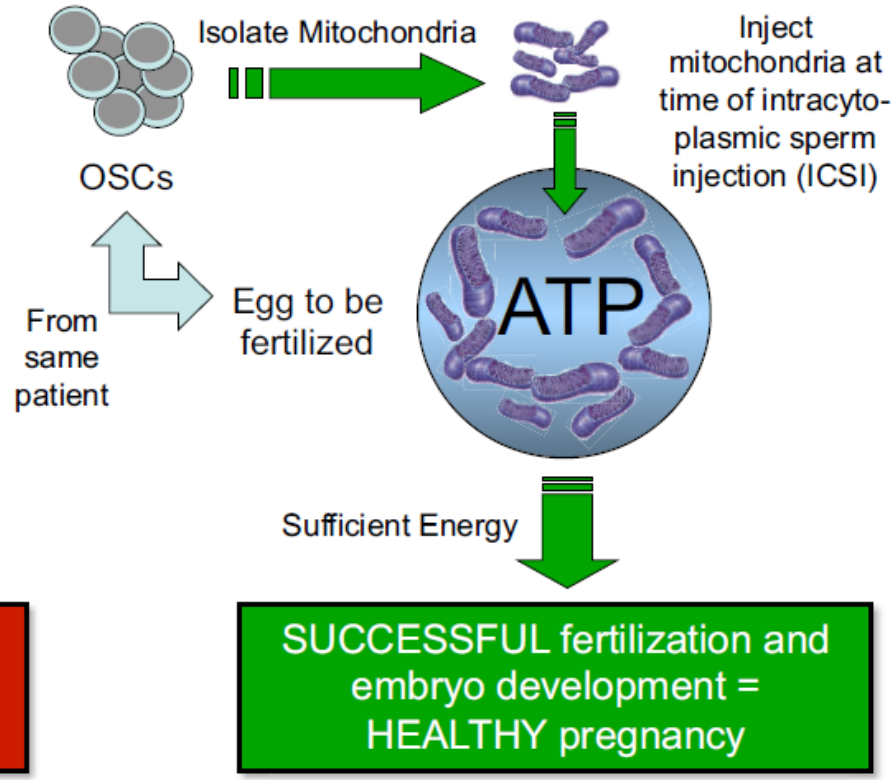
ATP

Insufficient Energy

NO fertilization or POOR embryo development = FAILED pregnancy

AUGMENT-IVF

(Autologous Germline Mitochondrial Energy Transfer-IVF)



Success? Small studies, low level trials

Tilly & Sinclair (2013) Cell Metab Perspective 17(6):838

OSC – egg precursor cells (ovaries)

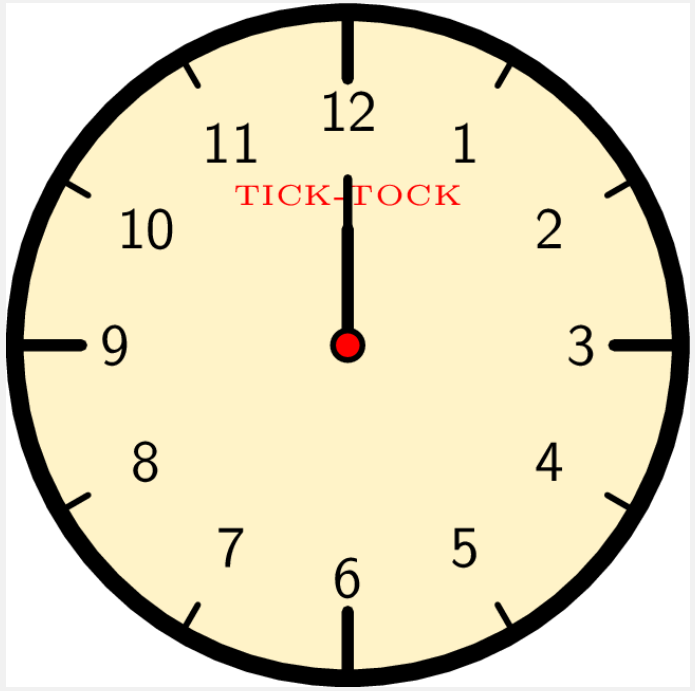
Clinical Success?

Autologous mitochondrial transfer as a complementary technique to intracytoplasmic sperm injection to improve embryo quality in patients undergoing in vitro fertilization—a randomized pilot study

Elena Labarta, M.D., Ph.D.,[a,b] Maria José de los Santos, Ph.D.,[a,b] Sonia Herraiz, Ph.D.,[a,b] Maria José Escribá, Ph.D.,[a,b] Alicia Marzal, M.D.,[a] Anna Buigues, B.Sc.,[b] and Antonio Pellicer, M.D.[a,c]

[a]IVI-RMA Valencia and [b]IVI Foundation, Valencia, Spain; and [c]IVI Rome, Rome, Italy

Objective: To study if autologous mitochondrial transfer (AUGMENT) improves outcome in patients with previously failed in vitro fertilization (IVF).



- **Pharmacological agents – oiling the cogs**
- Residual primordial follicles - shaking the clock
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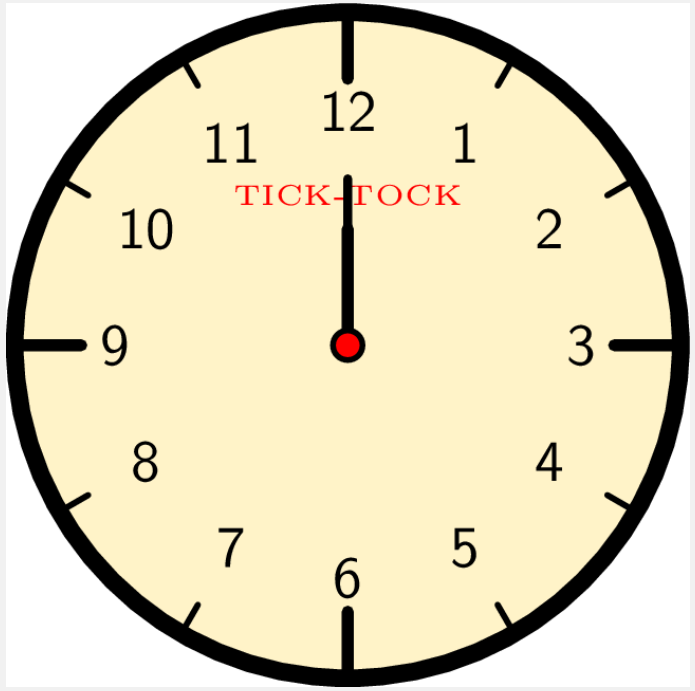
- When and how long?
- Does it delay, reverse oocyte aging?

Supplements to Improve Oocyte Quality?

Table III Pharmacological improvement of oocyte competence.

Drug or nutrient	Potential mechanism	Model	Consequence via mitochondrial effect
Rapamycin	Increase the mitochondrial autophagy and renewal	Rat (intraperitoneal injection)	Oocyte pool preservation Increased genital life length
		Pig (*in vitro*)	Oocyte developmental capacity
Resveratrol	Inductor of mitochondrial biogenesis and activity via sirtuin pathway	Mouse (oral administration/gastric canula)	Oocyte pool preservation Increased oocyte quantity and quality Improved embryonic development
		Cattle (*in vitro*)	Improved embryonic development
		Pig (*in vitro*)	Improved embryonic development
CoEnz Q10	Alternative component of mitochondrial respiratory chain with anti-oxidant	Mouse (subcutaneous injection)	Improved response to stimulation with increasing number of scalable embryos and births
		Cattle (*in vitro*)	Improved fecundation, embryonic cleavage, blastocyst formation and implantation

MitoQ - promoted better absorbed, better bioavailability
- delivers CoQ10 directly to mitochondria



- **Residual primordial follicles - shaking the clock**
- Artificial gametes – bypassing the clock
- Out of options? What's a person to do in 2019?

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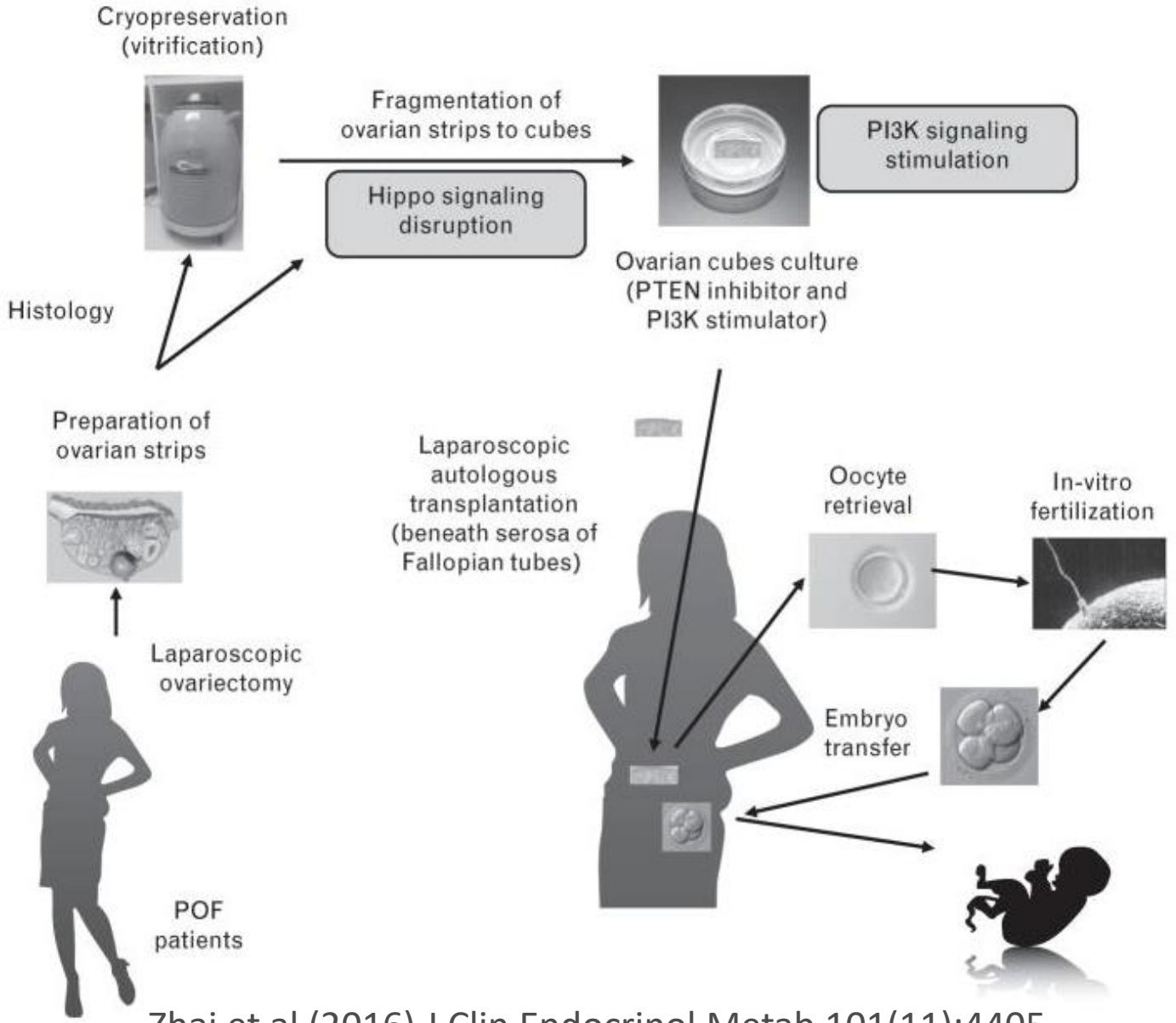
- N=14 patients with POI, no stim IVF, mean age 29
- 1000's primordial follicles
- One ovary removed, treated with AKT stimulators (promotes growth)
- Tissue auto-transplanted

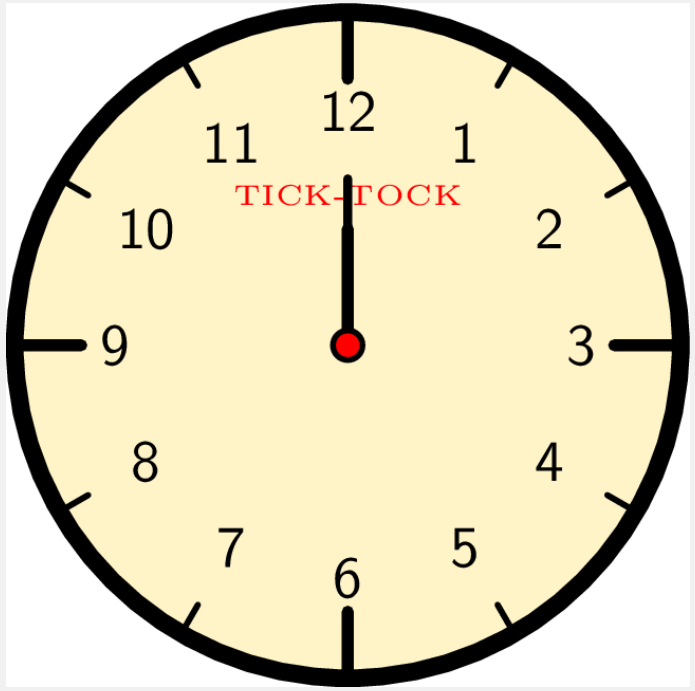
Ex Vivo Primoridal Follicle Activation



- Follicular growth waves detected 6 : 14
- 4 OPU - 1-2 eggs
- 2 deliveries, 2 pregnancies ongoing

Zhai et al (2016) J Clin Endocrinol Metab 101(11):4405

Based on mouse study that phosphatidylinositol-3-kinase-AKT forkhead box O3 (Foxo3) pathway activated dormant primordial follicles



- **Artificial gametes – bypassing the clock**
- Out of options? What's a person to do in 2019?

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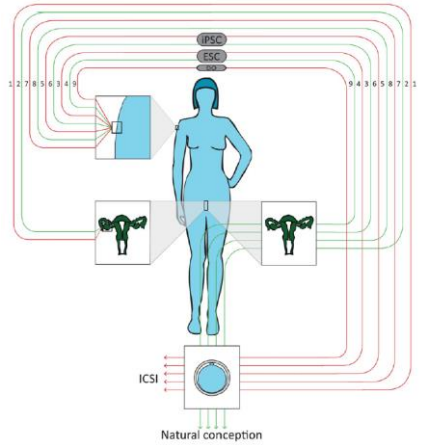
Ways of making artificial gametes?

Is it ethical?

Hendriks et al (2015) Hum Reprod Update 21(3):285



21st Century – In Vitro Gametogenesis (IVG)

- Converting somatic cells into artificial gametes (giving biological parent)
- Options
  - Heterosexual couple, Same sex couple
  - Single parent
  - Grieving widow

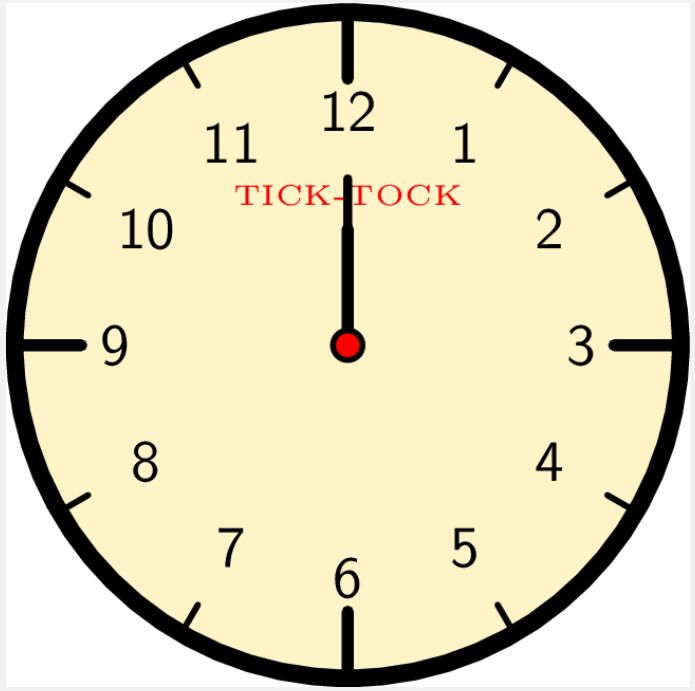
Crispr-Cas9 (gene editing)

- Repair, add, remove genes during IVG process

1978 – Louise Brown

- *Nova* magazine : ”IVF biggest threat since atomic bomb”
- American Medical Association – halt research
- Time and evidence – where we are today

NB Mice - $500,000 create sperm for one mouse



- **Out of options? What's a person to do in 2019?**

Healthy Lifestyle for Optimal Reproductive Outcomes

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Cigarette Smoking and IVF Outcomes

Prevalence of smoking in reproductive age women

- Europe 33% (2005)
- USA 28% (2008)
- IVF/ICSI Patients, NZ 2% (2015)

Gormack et al., Hum Rep 2015; 30:1617-1624

	Studies (N)	Cycles (N)	OR	CI
Clinical Pregnancies	24	6014	0.59	(0.51-0.68)
Live Births	7	8851	0.52	(0.37-0.74)
Miscarriage	8	1756	2.48	(1.79-3.43)

Meta-analysis of Effects of Cigarette Smoking and IVF Outcomes

Zhang et al., J Gyn Ob Hum Rep 2018; 47:461-468

	Smokers	Second-Hand Smoke	Non-Smokers	
Fertilization Rate	57%	58%	63%	NS
Pregnancy Rate	19.4%	20.0%	48.3%	P<0.001
Implantation Rate	12.0%	12.6%	25.0%	P<0.01

Second-Hand Smoke

Neal et al.,Hum Rep 2005; 20:2531-35

	Adjusted OR	95% CI	P
Implantation Failure	1.52	1.20-1.92	0.0005
Live Births	0.76	0.58-0.99	0.045

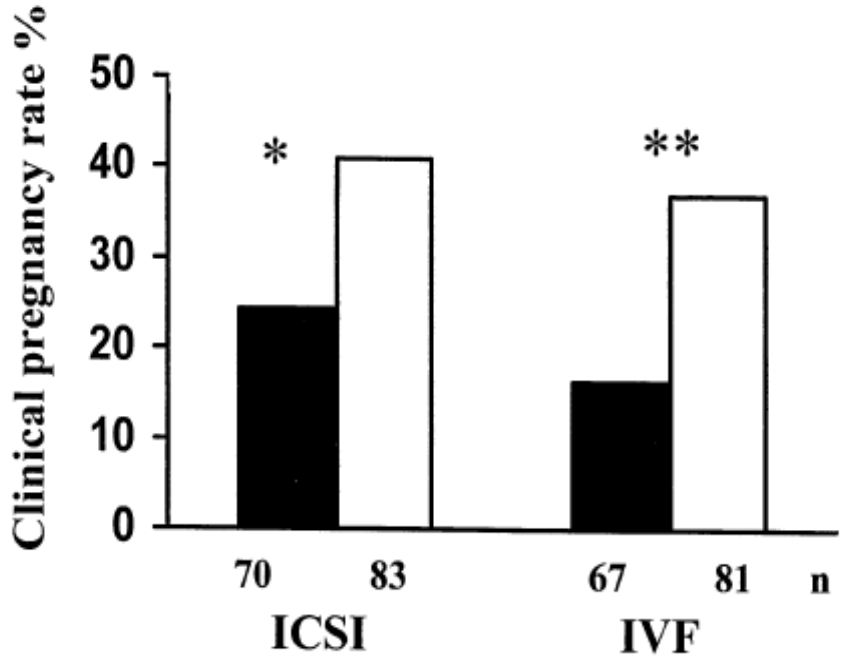
Second-Hand Smoke – Quantified by Cotinine in Follicular Fluid (measurement tobacco smoke exposure)

Second-hand smoke defined as cotinine >1.12 ng/ml

Benedict et al.,Hum Reprod 2011; 26:2525-31

Male Cigarette Smoking and IVF Outcomes

tively. Percentage of clinical pregnancies in ICSI and IVF cycles comparing smoking with nonsmoking male partners and analyzing the first treatment cycles only. *$P<.05$; **$P<.01$ (χ^2 test). *Filled bars* = male smokers; *open bars* = male nonsmokers.



Zitzmann. Male smokers and ICSI. Fertil Steril 2003.

Cigarette Smoking: Proposed Mechanisms

- Premature depletion of the oocyte pool
- Increased oxidative stress
- Impaired folliculogenesis
- Altered Steroidogenesis
- Reduced implantation

Cigarette Smoking Conclusions

- Smoking reduces IVF pregnancies ~50%
- Smoking increases IVF miscarriages ~2.6X
- Second-hand smoking decreases IVF success
- Male smoking reduces IVF success

Alcohol Consumption and IVF Outcomes

- 2545 couples, 4729 IVF cycles from 1994-2003 (Boston)
- Assessed at start of treatment

NZ
Any intake
50.8%

	Women	Men
<1 drink/week	55%	33%
1-6 Drinks/week	41%	58%
At least daily	4%	9%
Beer	25%	27%
Red wine	25%	26%
White wine	22%	22%
Spirits	23%	23%

Rossi et al.,Obstet Gyn 2011; 117:136-42

Consuming ≥ 4 drinks/week

	Women	Men	Both
Live Birth			
OR	0.84	0.90	0.79
Confidence Interval	0.71-0.99*	0.79-1.03**	0.66-0.96

*lowest = white wine
**lowest = beer

Rossi et al.,Obstet Gyn 2011; 117:136-42

Alcohol Consumption Conclusions

- Nearly half of women undergoing IVF and 2/3 of US men consume alcohol
- Live births may decrease for women and couples consuming >4 drinks/week
- Risk appears greatest if consumption is in the month prior to cycle

Caffeine Consumption and IVF Outcomes

- 2474 couples, 4716 IVF cycles from 1994-2003 (Boston)
- Assessed at start of treatment

	Low Caffeine	Moderate Caffeine	High Caffeine
	0-800 mg/wk	801-1400 mg/wk	>1400 mg/wk
Live Birth OR	1.00	0.89	1.07
Confidence Interval	(0.83-1.21)	(0.71-1.12)	(0.85-1.34)

- No difference in number of oocytes, fertilisation rate, or implantation rate

Choi et al.,J Caff Res 2011; 1:29-34

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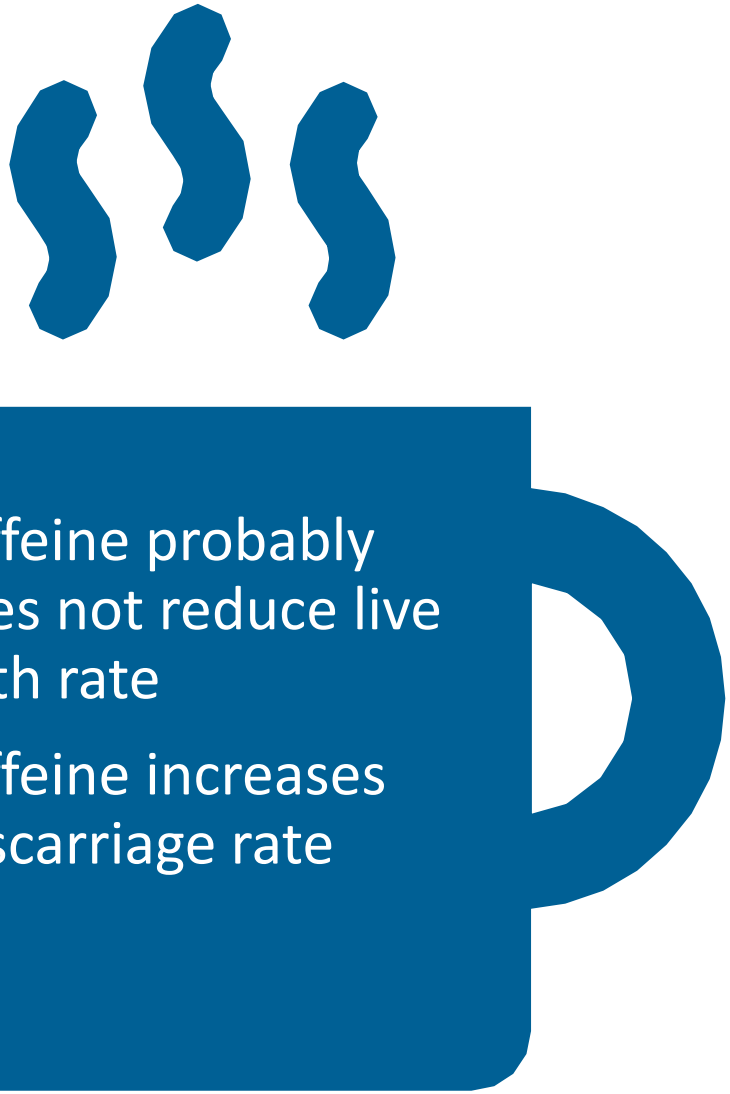
NZ
Any intake
86.8%

Caffeine Consumption and IVF Outcomes

300 women	Live birth	P
<50 mg/d	46%	0.34
50.1-100 mg/d	44%	
100.1-200 mg/d	42%	
200.1-300 mg/d	40%	
>300 mg/d	40%	

Abadia et al.,Hum Reprod 2017; 32:1846-54

Caffeine Consumption and IVF Outcomes - Conclusions



Diet and IVF Outcomes

Mediterranean Diet

- 161 couples undergoing IVF
- Completed 195 food item frequency questionnaire
- Two dietary patterns:
  - Health conscious-low processed (high intake of fruits, vegetables, fish and whole grains)
  - Mediterranean diet (high intakes of vegetable oils, vegetables, fish and legumes)

	Pregnancy OR	CI
Health conscious	0.8	0.6-1.0
Mediterranean	1.4	1.0-1.9

Vujkovic et al.,Fert Steril 2010; 94:2096-2101

Diet and IVF Conclusions

- Balanced diet may increase pregnancies
- Mediterranean diet may improve live birth rate

Exercise and Fertility

- 3628 Danish women, planning pregnancy, 2007-2009
- Vigorous = running, fast cycling, aerobics, gymnastics, swimming
- Moderate = brisk walking, leisurely cycling, golfing, gardening

	Fecundity Ratio
Vigorous Activity	
None	1.0
2 hrs/week	0.84 (0.73-0.97)
≥5 hrs/week	0.68 (0.54-0.85)
Moderate Activity	
<1 hr/week	1.0
2 hrs/week	1.15 (0.95-1.40)
≥5 hrs/week	1.18 (0.90-1.43)

Wise et al.,Fert Steril 2012; 97:1136-42

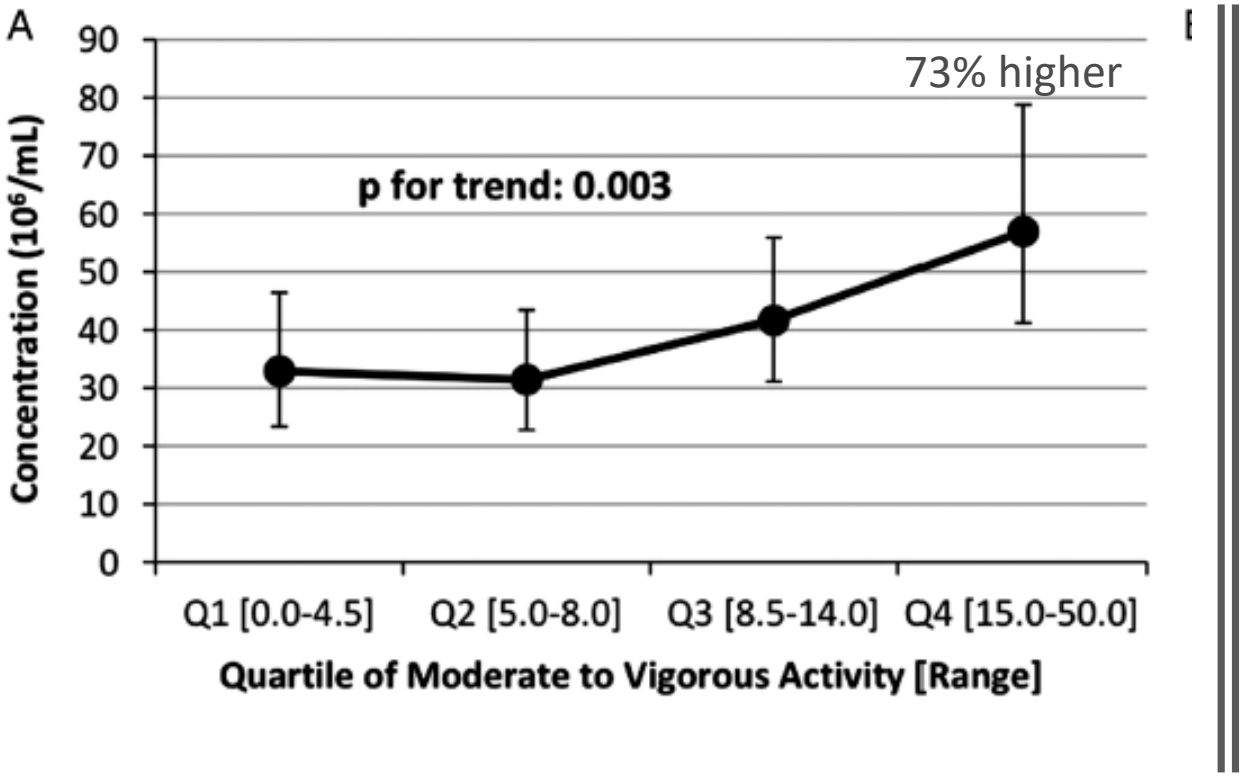
Male Exercise and Semen Parameters

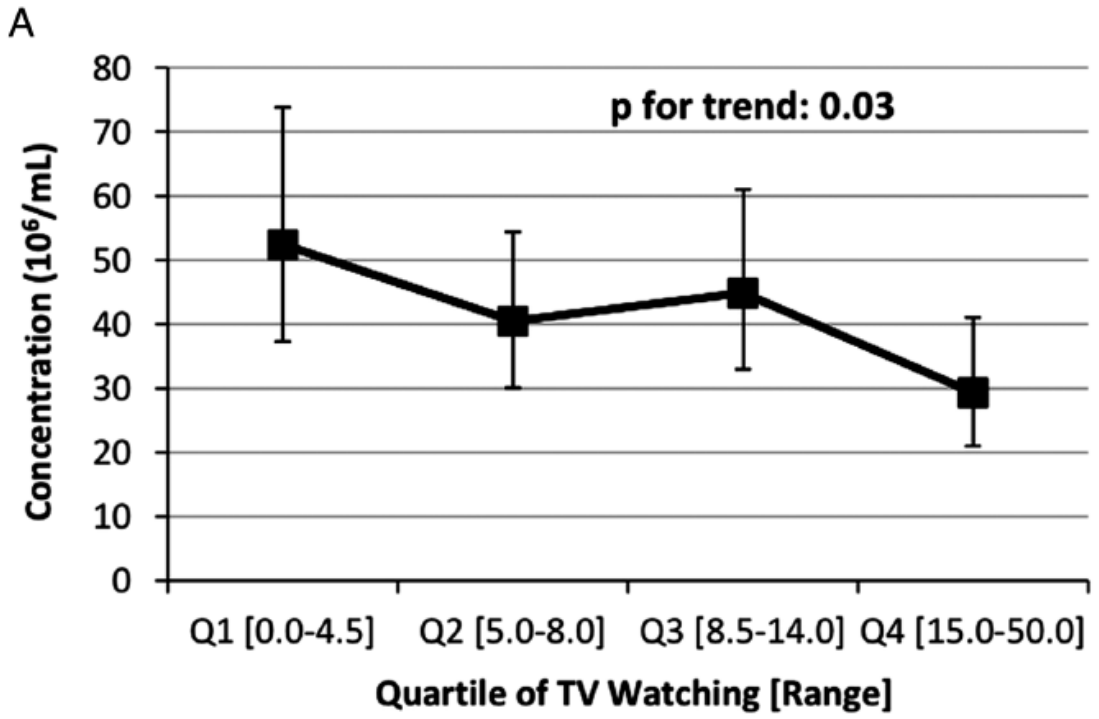
- Physical activity and semen quality
  - 2261 men, 4565 fresh semen samples (1993-2003)
  - Overall no effect of exercise on semen parameters
  - Bicycling >5hrs/week associated with low sperm concentration

Wise et al.,Fert Steril 2011; 95:1025-30

Male Exercise and Semen Parameters

Physical activity and TV watching hours per week vs semen quality





Gaskins et al.,Br J Sport Med 2015; 99:265-70

Exercise and Fertility - Conclusions

- Vigorous physical activity increases time to pregnancy
- Moderate exercise is beneficial
- Physical activity does not diminish semen parameters (other than excessive cycling)

Human Reproduction, Vol.30, No.7 pp. 1617–1624, 2015
Advanced Access publication on April 29, 2015 doi:10.1093/humrep/dev094

human reproduction ORIGINAL ARTICLE *Infertility*

Many women undergoing fertility treatment make poor lifestyle choices that may affect treatment outcome

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Table II Reported active changes in lifestyle among studied women (n = 250) about to undergo fertility treatment.

	Behaviour at the time of the interview		Behavioural change due to upcoming fertility treatment			
	Yes	No	Abstained	Reduced	Increased	No change
Smoking	2.0%	98.0%	2.8%	0.4%	0%	96.8%
Alcohol	50.8%	49.2%	24.8%	20.4%	0%	54.8%
Caffeinated beverages	86.8%	13.2%	18.0%	21.6%	0%	60.4%
BMI	–	–	–	13.2%	3.2%	83.6%
Exercise levels	–	–	0%	7.2%	28.4%	64.4%

Conclusions

- Understanding the biological clock is very important as we delay parenthood further
- Most people's knowledge is faulty
- Difficult to measure an individual's clock
- Substitution (donor egg) is the only remedy when you are too old or your own eggs don't work
- Freezing eggs when younger is a technological approach to a social problem, but its a good bet, not insurance
- Healthy lifestyles choices optimise gamete health
- There are always new promises on the horizon, but *caveat emptor* – good chance there will be a merchant before there is an RCT

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