Ovarian reserve: quantity or quality

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Objectives

- Oocyte demise – follicular atresia - apoptosis
- Aging – fertility – oocyte quality
- Chromosomal abnormalities
- Quantity and quality of follicular endocrine function
- Outcome of IVF/ICSI – oocyte number and quality

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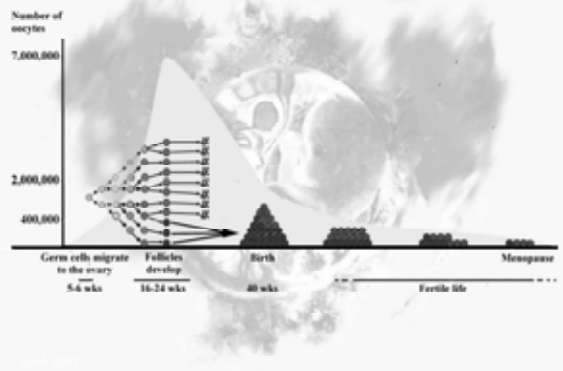
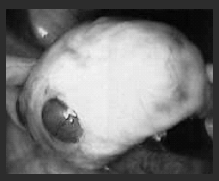


Oocytes

- Fetus 7×10^6
- Newborn 1×10^6
- Puberty 4×10^5
  - Ovulation 300-400
- Menopause 100-1000

= 99.9% of oocytes die



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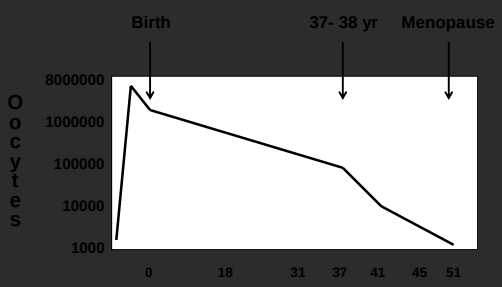
Oocyte number



Modified from te Velde and Pearson 2002

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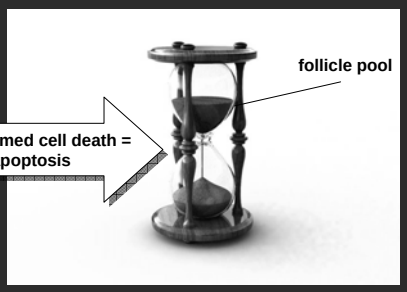
Decreasing follicle pool



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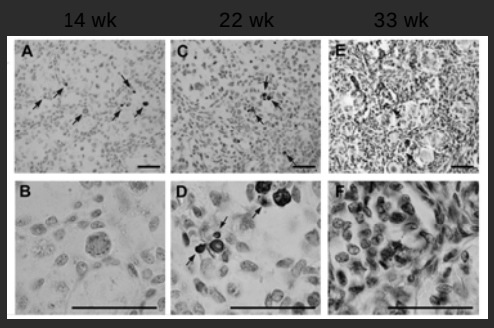
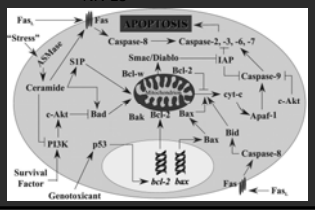
Apoptosis in fetal ovary



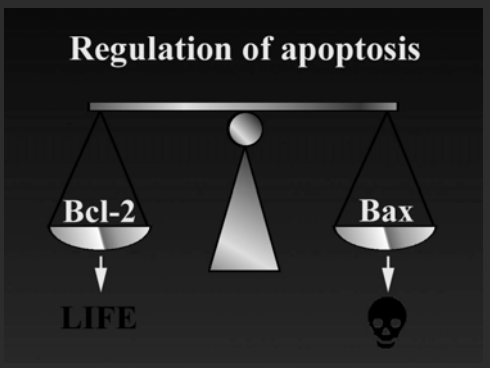
Vaskivuo et al. JCEM 2001

Apoptosis regulating genes

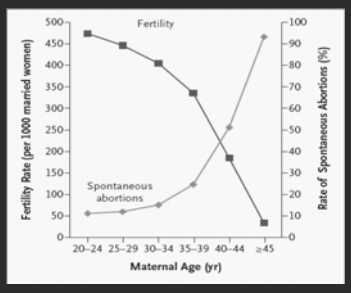
- Antiapoptotic
  - Bcl-2
  - Bcl-x_L
  - Mcl-1
  - A1/Bfl-1
  - Bcl-w
  - Bcl-B
  - NR-13
- Proapoptotic
  - Bax
  - Bcl-x_S
  - Bak
  - Bad
  - Hrk/DP5
  - Bid
  - Bik/Blk
  - Bim
  - Bok/Mtd
  - Noxa
  - Bcl-rambo
  - Bcl-G_L
  - Bcl-G_S



Regulation of apoptosis

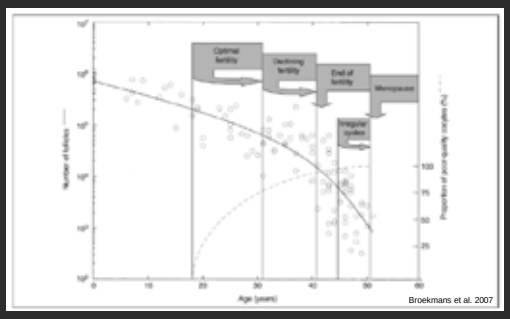


Fertility and age



Heffner, L. NEJM 2004; 351: 1927-1929

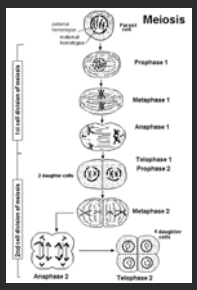
Poor-quality oocytes



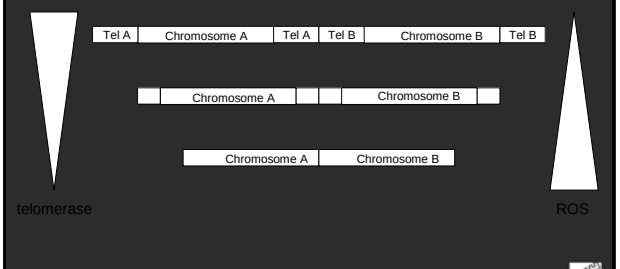
Broekmans et al. 2007

Chromosomal abnormalities

- Non-disjunction during meiosis I or II
- Premature separation of chromatids during meiosis
  - degradation of cohesins etc.
- Mitochondrial dysfunction
  - damage of mitochondrial DNA by reactive oxygen species (ROS) -> abnormalities in the meiotic spindle
- Telomere shortening
  - prolonged exposure to ROS
  - telomerase deficiency



Telomere shortening



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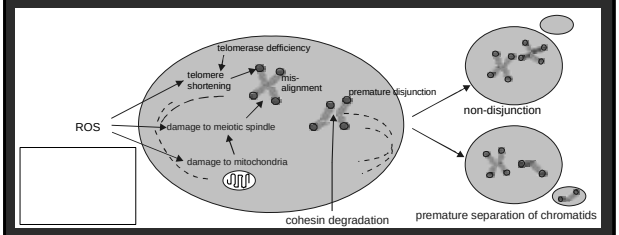
Chromosomal abnormalities - aging



Modified from Djahanbakhch et al. 2007

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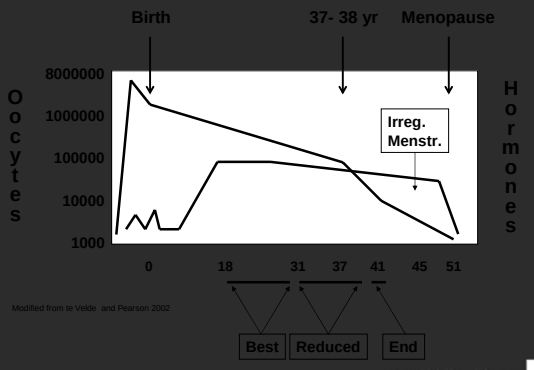
Ovarian life cycle and Fertility



Modified from te Velde and Pearson 2002

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Slide 13

JT1 Juha Tapanainen; 13/04/2008

Ovarian endocrine function – quantity or quality

- Aging of granulosa/theca cells
  - decrease of circulating basal hormone levels
  - decreased ovarian response to gonadotropic stimulation
- Impaired microcirculation

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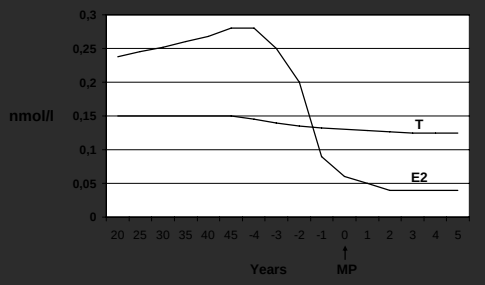
Estradiol and Testosterone



Adopted from:
Reame et al. 1998
Burger et al. 1999
Welt et al. 1999
Burger etal. 2000
Piltonen et al. 2003
Randolf et al. 2004
Overlie et al. 2005

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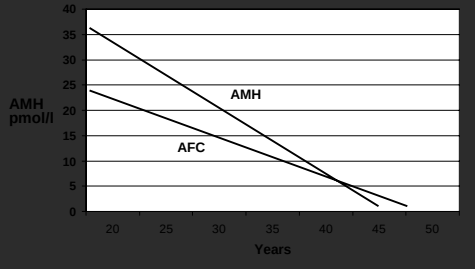
Anti-Mullerian hormone (AMH) Antral follicle count (AFC)



Adopted from:
Scheffer et al. 1999
van Rooij et al. 2002
de Vet et al. 2002
Laven et al. 2004
Broekmans et al. 2004
Piltonen et al. 2005

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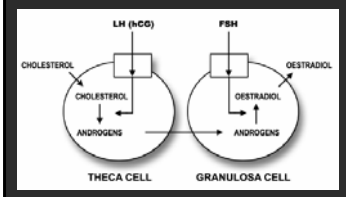
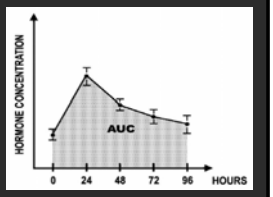
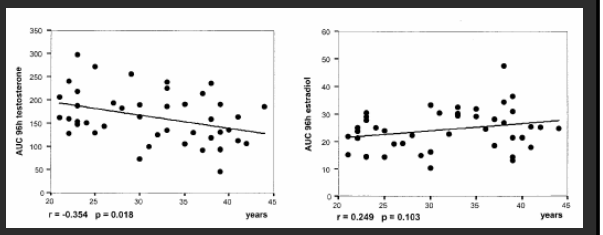
Ovarian steroid secretion capasity
HCG stimulation 5000 test





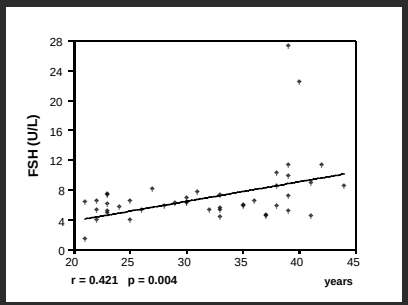
AUC 96h

Testosterone Estradiol



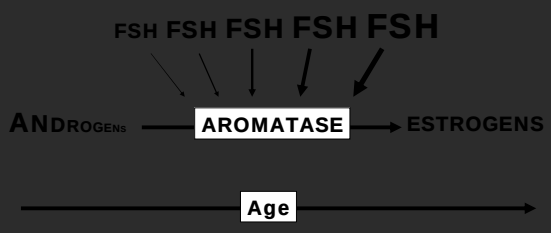
Piltonen et al. JCEM 2003

FSH



Piltonen et al. JCEM 2003

Why estrogen production maintains until premenopause ?



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Aging - Outcome of IVF/ICSI – oocyte number and quality

- Lower number of oocytes
- Fewer embryos created
- Lower PRs
- Lower LBRs
- Increased miscarriage rate

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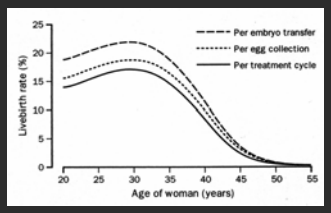
IVF



Templeton et al. 1996

U.K.	Life birth/embryo transfer
<30 yrs	24%
40-44 yrs	8%
≥45 yrs	3.5%

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IVF/ICSI in Oulu Fertility Center 2000-2006

Age	< 30	30 - 34	35 - 39	p
n	1000	1191	965	
BMI	23.2 ± 4.2	23.6 ± 3.9	24.0 ± 4.6	<0.0001
Oocytes	**13.5 ± 7.4**	**12.4 ± 6.8**	**10.2 ± 6.9**	**< 0.0001**
Tops	**1.4 ± 2.0**	**1.3 ± 1.8**	**1.2 ± 1.9**	**0.03**

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Cumulative PR, age and embryo quality
1999-2004

Top embryos	*< 30*	*30 - 34*	*35 - 39*
None	21.7 %	22.5 %	14.9 %
One	44.1 %	48.1 %	36.7 %
Two	50.0 %	46.2 %	48.2 %
Three +	72.0 %	67.5 %	50.0 %

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from Hannu Martikainen

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Cumulative LBR, age and embryo quality

Top embryos	*< 30*	*30 - 34*	*35 - 39*
None	17.4 %	18.5 %	10.7 %
One	35.5 %	43.5 %	28.3 %
Two	43.8 %	37.6 %	41.1 %
Three +	62.4 %	57.8 %	42.9 %

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Conclusions

- Decrease of oocyte/follicle number is associated with a decline in oocyte quality reflected with increasing rate of chromosomal abnormalities, spontaneous abortions and decreased fertility
- Damage of resting oocytes may accumulate with age as the oocytes "rest" in the ovaries for decades.
- Perhaps the best oocytes are selected first for further development
- The number of top quality embryos (oocytes) decreases moderately by age
- c-PR and c-LBR in IVF/ICSI are highly dependent on the total number of top quality embryos in all age groups
- this information is valuable in selecting patients for SET both in fresh and frozen cycles and in counselling the couple of the benefits of e-SET

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- increased incidence of chromosomal abnormalities, especially aneuploidies

Hassold & Jacobs 1984
Sherman et al. 2005138.
Lim & Tsakok 1997
Pellestor et al. 2003
Munne et al. 1995
Benadiva et al. 1996

- hormonal disturbances, abnormal follicular development due to aging of granulose/theca cells and impaired follicular microcirculation
- Environmentally induced mutations and genetic
- Damage may accumulate with age and possibly the best oocytes are recruited first

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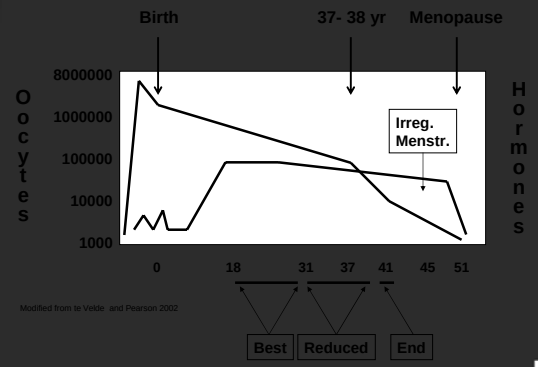
Ovarian life cycle and Fertility



Modified from te Velde and Pearson 2002

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Fertility rates

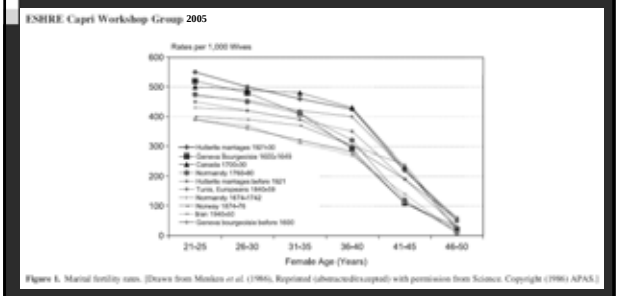

Figure 1. Marital fertility rates. [Drawn from Menken *et al.* (1986), Reprinted (abstracted/excerpted) with permission from Science. Copyright (1986) APAS.]

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