Infertility in women aged over 40 years

Viveca Söderström-Anttila, dos

Väestöliitto Clinics Ltd

Helsinki

Viveca Söderström-Anttila
Engagements 2007-09

- MD, PhD, specialist in gynecology, obstetrics and reproductive endocrinology

- **Main occupation**
  - Väestöliitti Clinics Ltd, Helsinki

- **Other engagements**
  - Member of working group in Nordic Fertility Society (unconditional support from Schering-Plough Oy)

Infertility in women aged 40 years and older

- Reproductive biological facts
- Testing of ovarian reserve
- The effect of biological ovarian aging on ART
- Potential treatment strategies
- Oocyte donation
- Preservation of female fertility
- Not including: obstetric and perinatal outcome in women with advanced age

Percentage of recently married couples who delivered a living child by age of marriage - 1600-1930
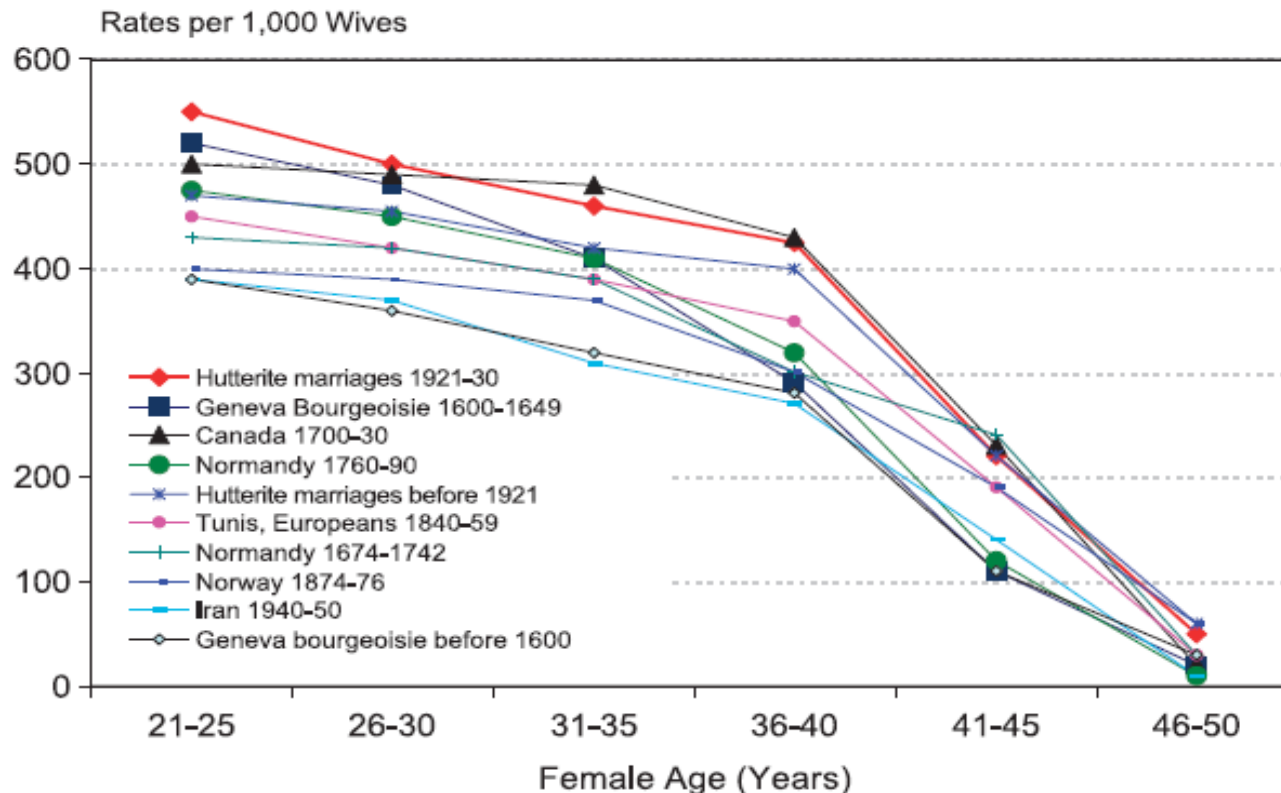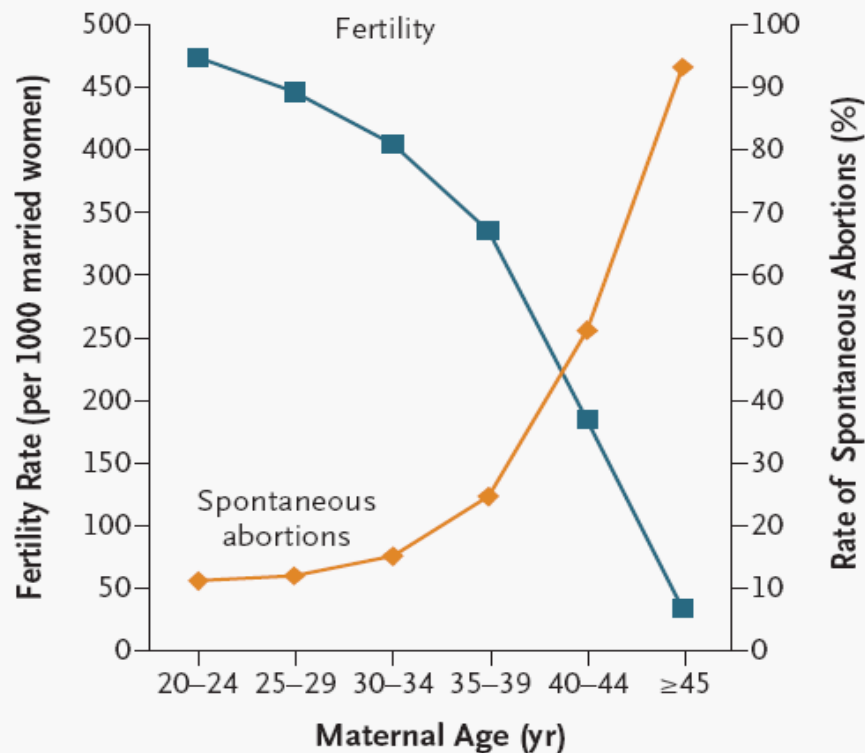
Rates per 1,000 Wives

Legend:
- Hutterite marriages 1921–30
- Geneva Bourgeoisie 1600–1649
- Canada 1700–30
- Normandy 1760–90
- Hutterite marriages before 1921
- Tunis, Europeans 1840–59
- Normandy 1674–1742
- Norway 1874–76
- Iran 1940–50
- Geneva bourgeoisie before 1600

Female Age (Years)

Table III. Age of marriage and risk of childlessness

Age (years)	Risk of childlessness (%)
20–24	5.7
25–29	9.3
30–34	15.5
35–39	29.6
40–44	63.5

Menken et al, Science 1986;233:1389-94

The age-related decline in female fecundity and increased risk of spontaneous abortion

Fertility

Spontaneous abortions

Maternal Age (yr)

Crosignani

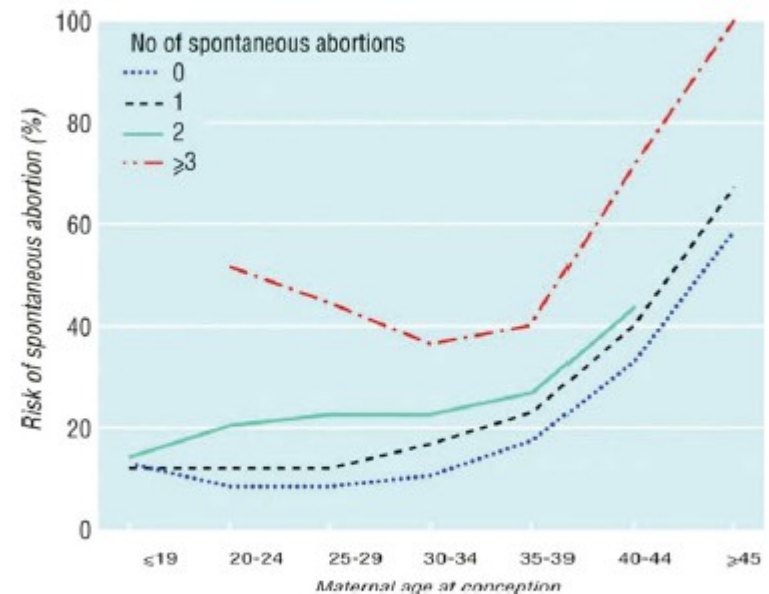No of spontaneous abortions
- 0
- 1
- 2
- ≥3

Figure 4: Spontaneous miscarriage rates in nulliparous women by maternal age at conception and number of previous spontaneous miscarriages (Nybo Andersen *et al.*, 2000).

Heffmer, L. NEJM 2004; 351: 1927

The ESHRE Capri Workshop Group; Hum Reprod Update 2008

Increased maternal age and rates of chromosomal abnormalitites (live births) and fetal death

Age	Risk
20	1/526
25	1/476
30	1/384
35	1/204
40	1/65
45	1/20

Table adapted from Obstetrics: normal and problem pregnancies, third edition. Edited by Gabbe, Niebyl, Simpson. 1996
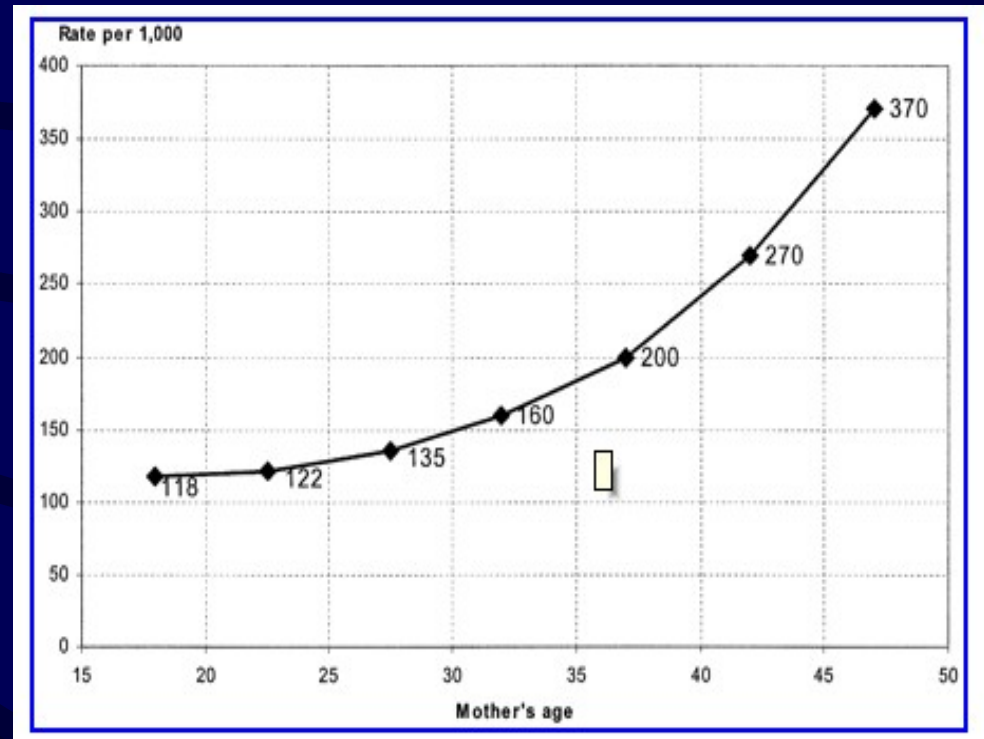
Mean rates of fetal death according to the age of the mother

Leridon; Hum Reprod 2004

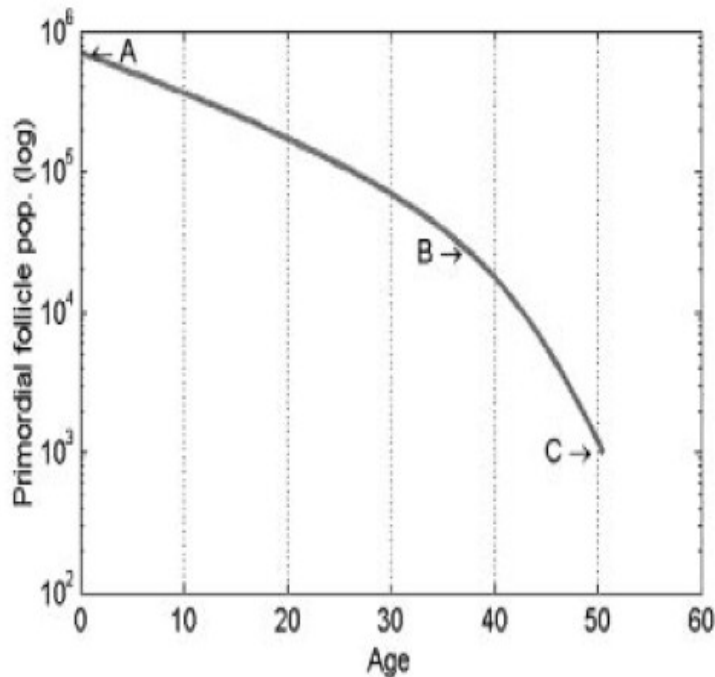# Subfertility or infertility because of reproductive aging = ovarian aging

Figure 1. The solution of the Faddy–Gosden differential equation for the primordial follicle population from birth to menopause. The primordial follicle population at birth is ~701 000 (**A**), and at menopause is ~1000 at 50.4 years (**C**), with an accelerated decline occurring at ~25 000 remaining primordial follicles (**B**).

- Decline of both the quantity and quality of the oocyte/follicle pool

Wallace & Hamish, Hum Reprod 2004

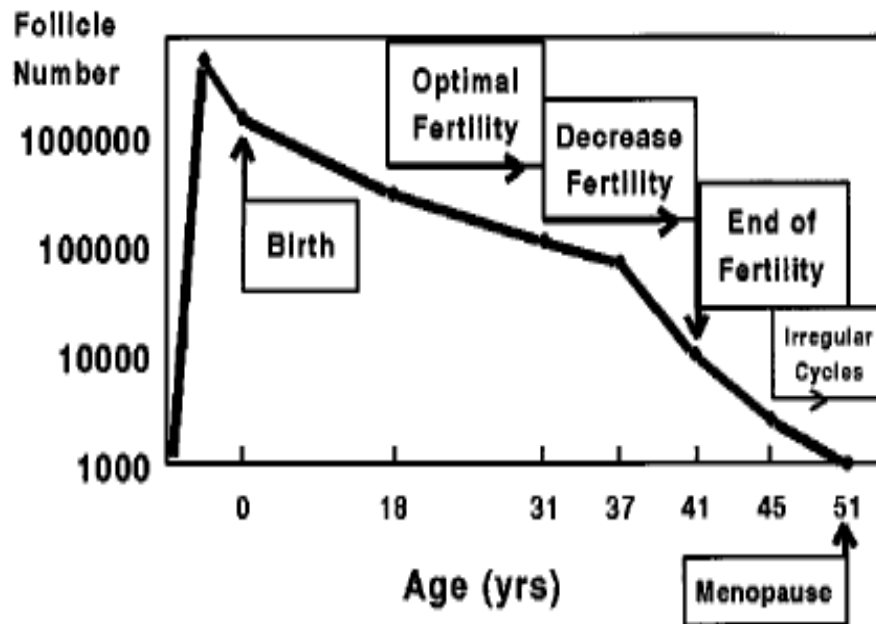# The progressive loss of follicles related to reproductive events in women´s life
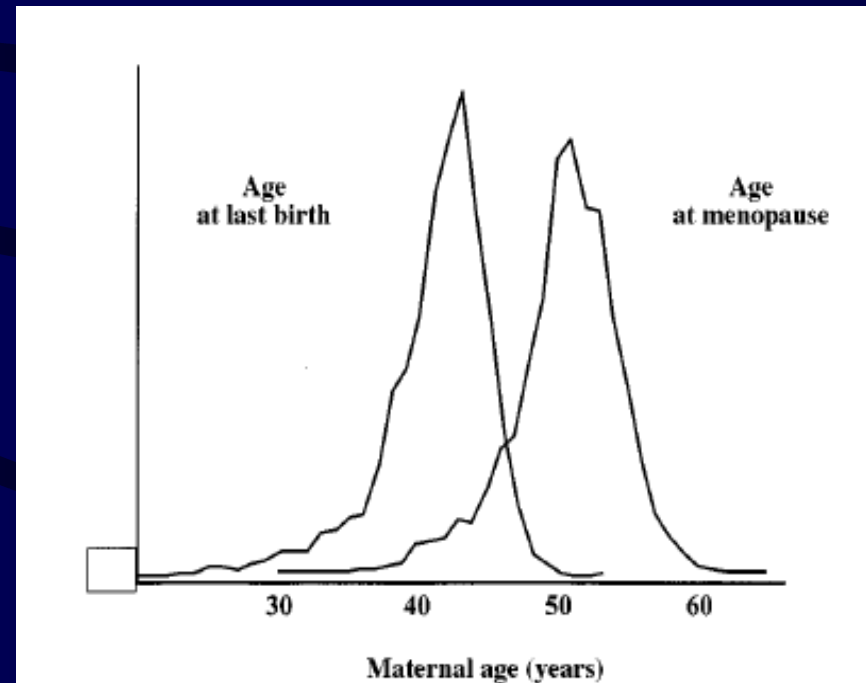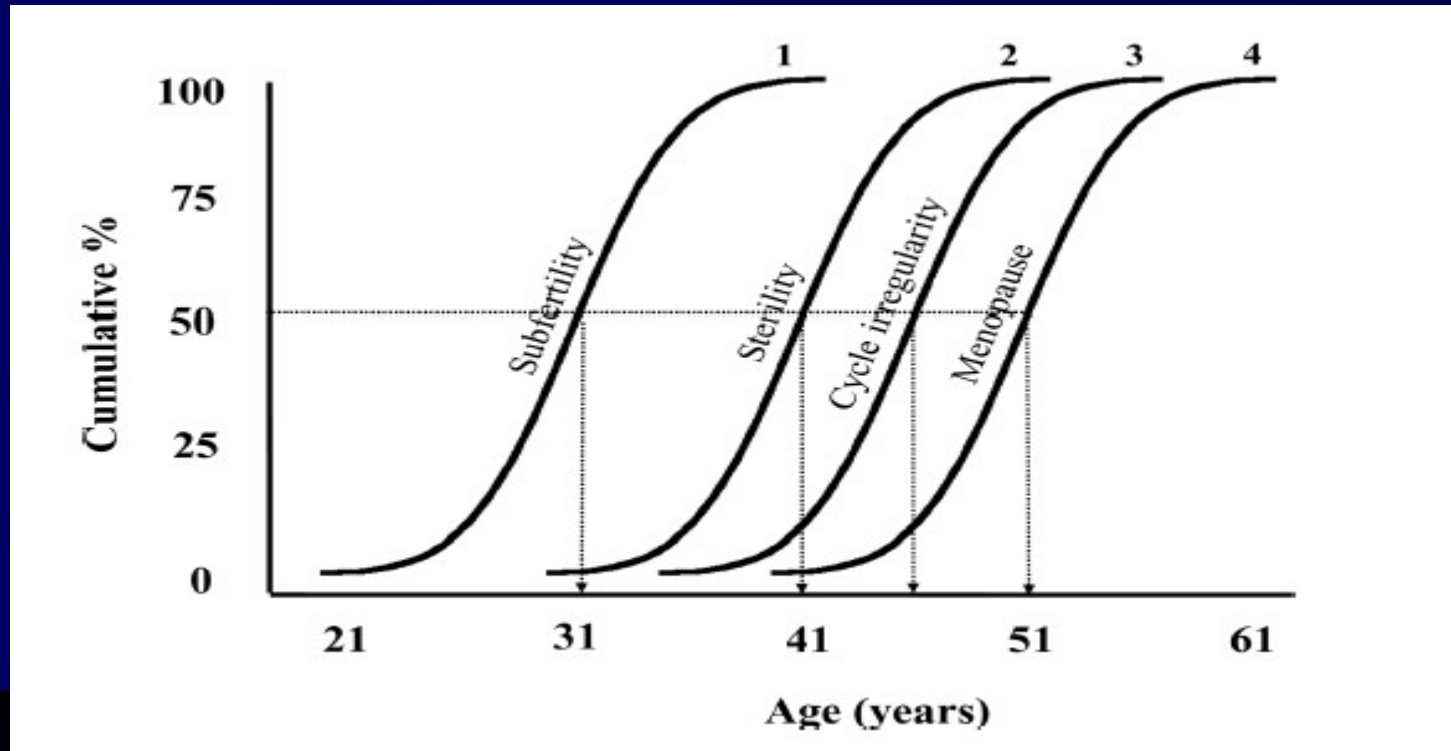

Figure 3. The declining oocyte/follicle pool according to Faddy et al. (1992) and the corresponding reproductive events.

High variability in female reproductive aging

Curve 1: variation in age at the beginning of subfertility (mean age 31 years)

Curve 2: variation in age at the beginning of sterility (mean age 41 years)

Curve 3: variation in age at the transition from cycle regularity to irregularity (mean age 46 years)

Curve 4: variation in age of menopuse (mean age 51 years)

How to test for ovarian reserve?

- Biochemical
  - FSH
  - AMH
  - Inhibin A
  - Inhibin B
  - E2
- Imaging
  - Antral follicular count (AFC)
  - Ovarian volume
  - Uterine dynamic flow
- Dynamic testing
  - Clomphene challenge test

Basal FSH in regularly cycling women

- Screening test for counselling purposes
- Not sufficient predictor of IVF success
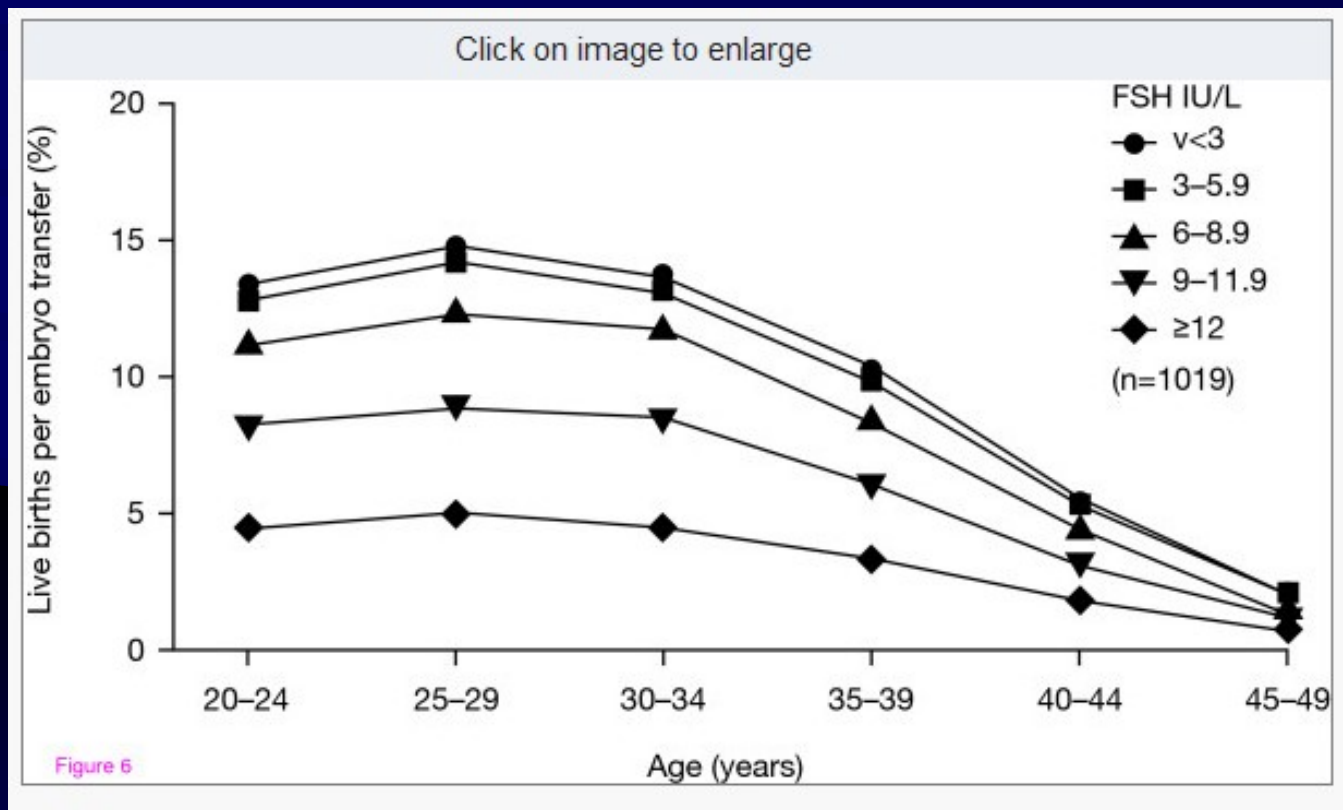
Reduction in the rate of live births per ET against both increasing chronological age and increasing basal FSH   Alviggi et al., 2009

Anti-Műllerian hormone (AMH)

- Produced by granulosa cells of early developing follicles and inhibits the transition from the primordial to the primary follicular stage

- Shows a progressive decline throughout reproductive life as the follicular reserve becomes depleted

- Low inter- and intra-cycle variability in serum levels

- Correlate with AFC, poor response and hyperresponse, IVF cancellation, the number of oocytes retrieved, oocyte and embryo quality

The number of antral follicles (AFC) as predictor of outcome

-AMH and AFC similar in the prediction of poor response
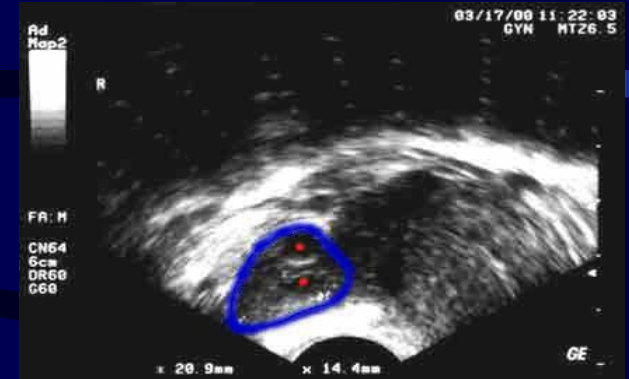
- AFC less than 4: no pregnancy (Chang *et al.*, 1998)

Table I. Median values and ranges of endocrine and sonographic characteristics in the three age categories

Characteristics	Young 25–34 years (n = 49)	Middle 35–40 years (n = 53)	Old 41–46 years (n = 60)
FSH (IU/l)	6.7 (2.0–21.2)	6.8 (2.7–21.4)	8.1 (3.2–35.9)[a]
Estradiol (pmol/l)	193 (51–290)	206 (77–528)	278 (51–816)[a]
Inhibin B (pg/ml)	101 (18–180)	104 (0–177)	97 (0–210)
No. of follicles (2–10 mm)	15 (3–30)	9 (1–25)[b]	4 (1–17)[ac]
Total ovarian volume (ml)	11.8 (4.7–40.3)	11.4 (4.9–32.2)	8.3 (4.5–19.7)[ac]

Ovarian volume and reproductive age

- Adult ovaries measure ~3-5 cm (DI) x 1.5-3 cm x 0.6-1.5 cm and weigh 5-8 g (Clement, 1991)
- Volume is calculated from the ellopsoid formula $V = D1 \times D2 \times D3 \times 0.523$
- Mean ovarian volume for post-menopausal women 2.2 ml (Pavlik et al., 2000)
- Low volume predicts poor ovarian response and remaining years before menopause
- Normal volume does not predict likelihood of pregnancy

The relationship between ovarian volume and reproductive age for women of chronological ages 25-45 years at 5 years interval

Wallace&Kelsey, Hum Reprod 2004
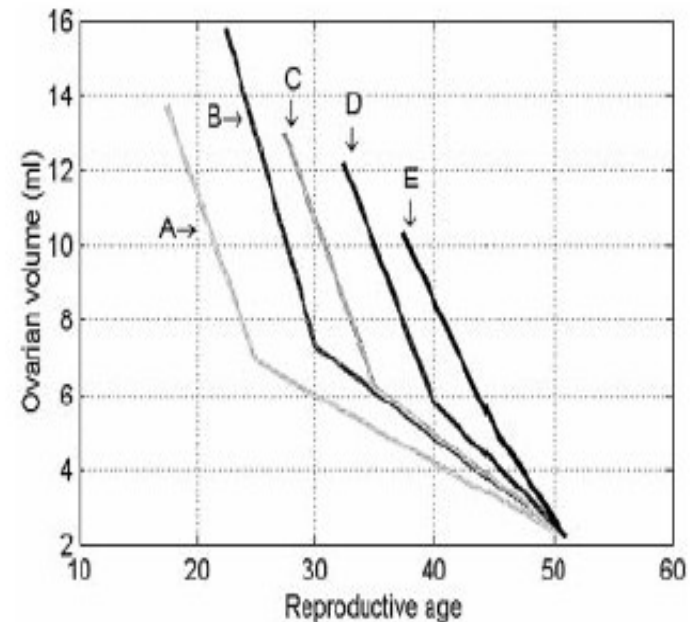
Ovarian reserve testing (ORT)

- AMH and AFC are the best ORT available to predict poor response
- Poor predictor of ongoing pregnancy
- Prediction of non-pregnancy only 2-3 %

Councel of the basis of female age

Just do fertility treatment if appropriate

In case of poor response: ORT testing

Broekmans et al., Hum Reprod Update 2006

Henriks et al., RBMOnline 2008

Medical reasons for fertility problems in women at 40+ years

- Subfertility or infertility because of decline in the number of follicles and impaired quality of the oocytes (higher rate of aneuploidy in the oocytes)
- Advanced age increases the risk of various gynecological diseases that may affect the fertility
  - Increased risks of uterine pathology, such as fibroids and endometrial polyps
  - Uterine factors have not a significant impact on age-related infertility
- Decreased sexual activity
- Male factor reasons
  - Male factor infertility
  - Age-related decline in male fertility?

Most studies suggest that the semen volume, the percentage of motile sperm and the percentage of the sperm cells with normal morphology decline with age

Sperm Parameters Related to Age
"Normal Count"

Age Group, y	n	Volume (ml)	Concentration (10^6ml)	Motility	Total Count	Sexual Abstinence (days)
0 (<25)	838	3.21	62.32	44.39	194.41	4.73
25-29	1751	3.38	64.28	42.34	208.27	4.50
30-34	1528	3.51	68.86	41.91	228.59	4.79
35-39	1025	3.44	67.51	39.29	224.74	5.08
40-44	557	3.25	73.69	39.05	225.38	5.34
45-55	280	2.81	77.26	37.38	204.24	6.57
>55	43	2.21	95.58	24.76	173.13	5.30
		⬇	⬆	⬇		⬇

# Oocyte donation outcome according to male age groups

- Increased age of the man
  - has no effect on outcome (Gallardo, 1996, Paulson, 2001)
  - has a negative effect on outcome (Campos, 2008; Girsh, 2008)
  - increases the risk of spontaneous abortions (Gallardo et al., Fertil Steril 1996)

When and how to treat?

- Refer to examinations after 6 months
- Counselling
- Treatment options
  - AIH
  - IVF/ICSI
  - Oocyte donation

# Poor success achieved with AIH in women aged 40 years and older

Sperm Injected into Uterus
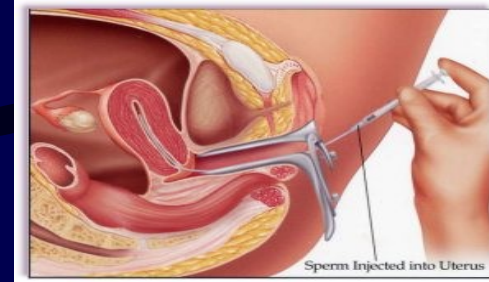
Age	No of patients	No of CC-OI cycles	PR/IUI	Cumulative PR
<35	983	2351	11.5	24.2
35-37	422	947	9.2	18.5
38-40	265	614	7.3	15.1
41-42	81	166	4.3	7.4
>42	55	120	1.0	1.8

Dovey S *et al* Fertil Steril 2008; 90:2281-6

Poor success achieved with AIH in women aged 40 years and older

Age	No of patients	LBR/FSH-OI/ cycle	Comments
38-39	57	6.1 %	No births occurring after the second cycle
≥40	73	2.0 %	All births in the first cycle

Harris et al., Fertil Steril 2009

Cumulative live birth delivery rates after donor insemination in five pre-specified age groups, i.e. 20-29, 30-34, 35-37, 38-39, 40-45 years and in all age groups (20-45 years)
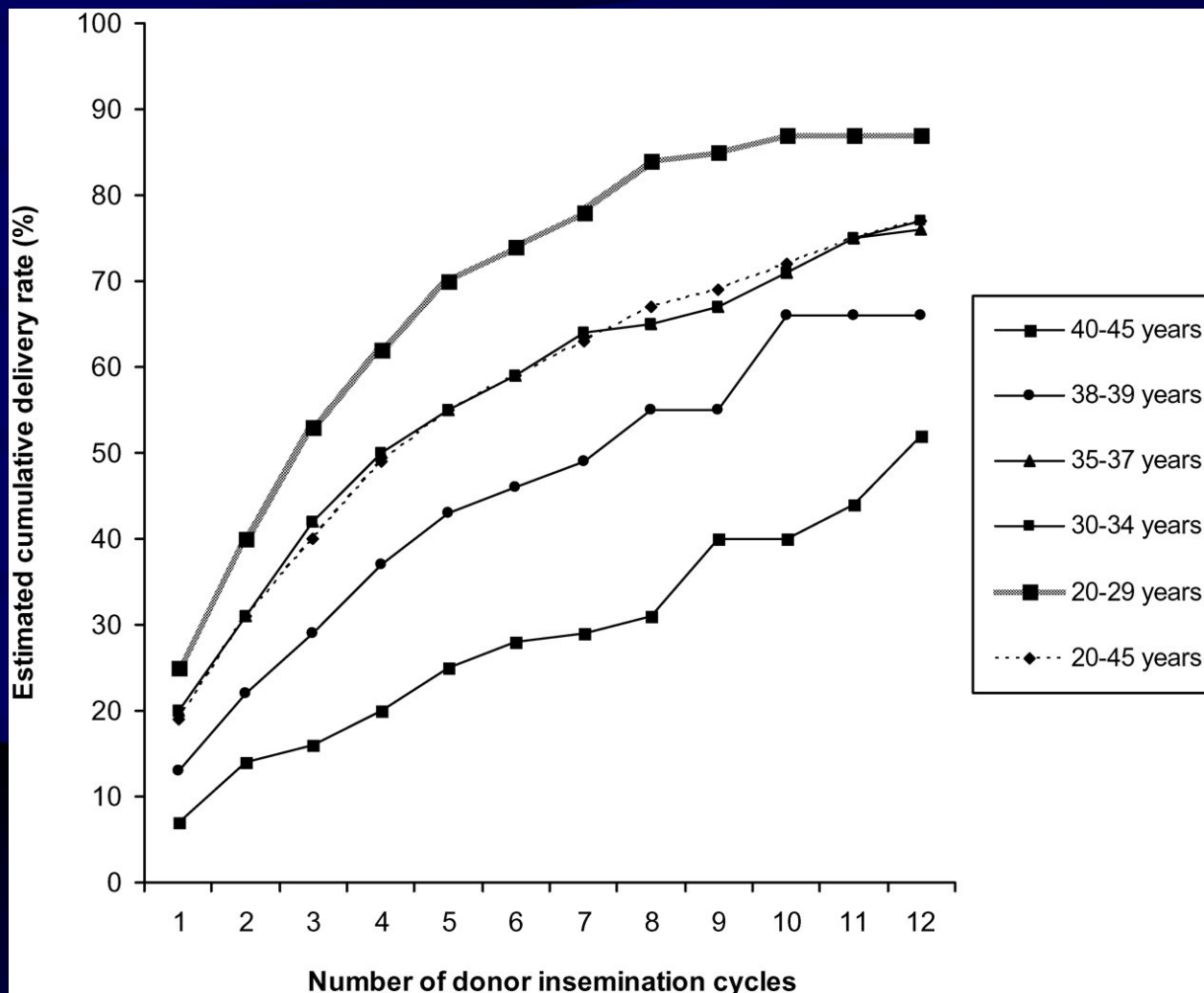
Cumulative live birth delivery rates after donor insemination in four pre-specified age subgroups of the oldest patients, i.e. 40, 41, 42 and the >43 years age groups
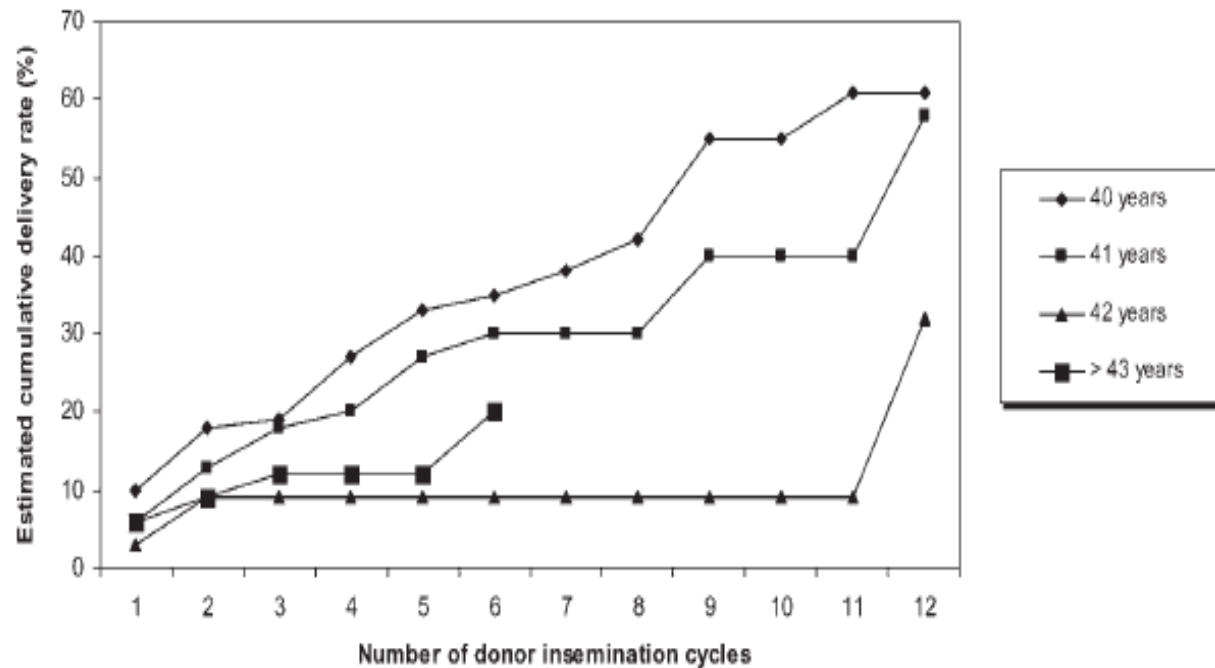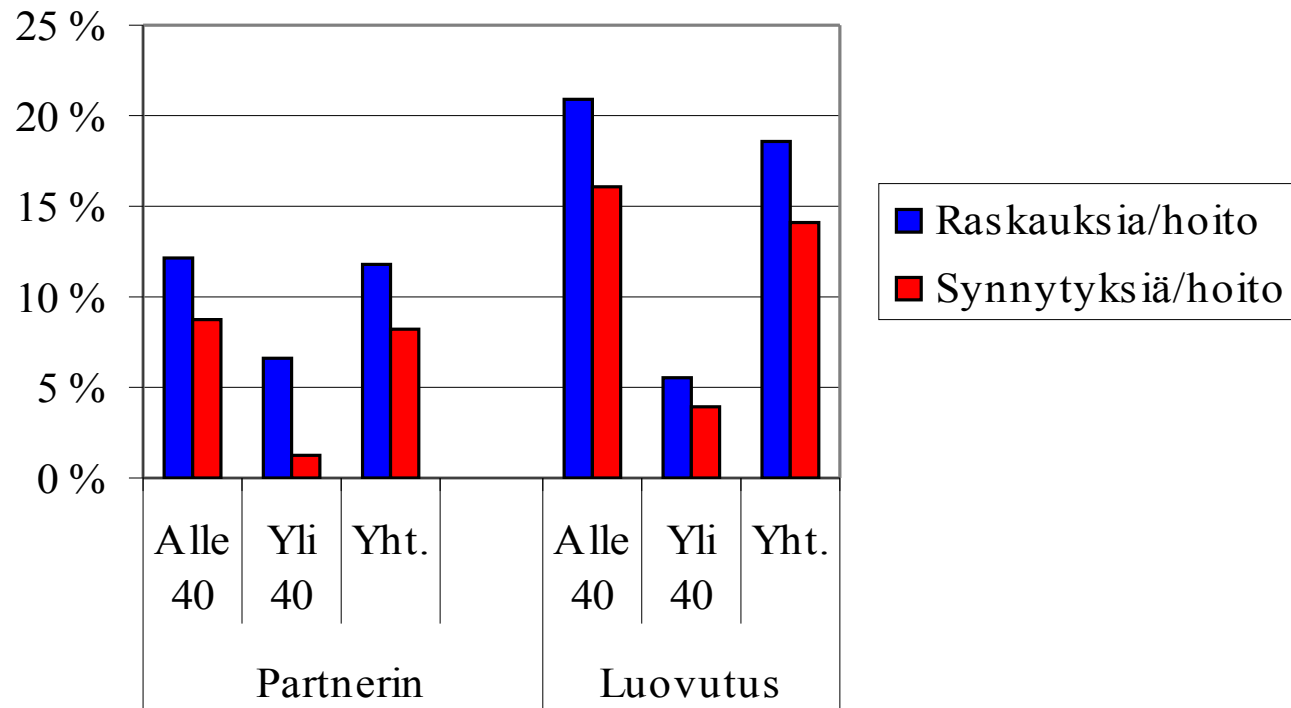

Figure 2 Cumulative live birth delivery rates after donor insemination in four pre-specified age subgroups of the oldest patients, i.e. 40, 41, 42 and the >43 years age groups.

Clinical pregnancies and deliveries after IUI according to the age of the mother and sperm origin 2007
National Institute for Health and Welfare (M. Gissler, 2009)

What about IVF?

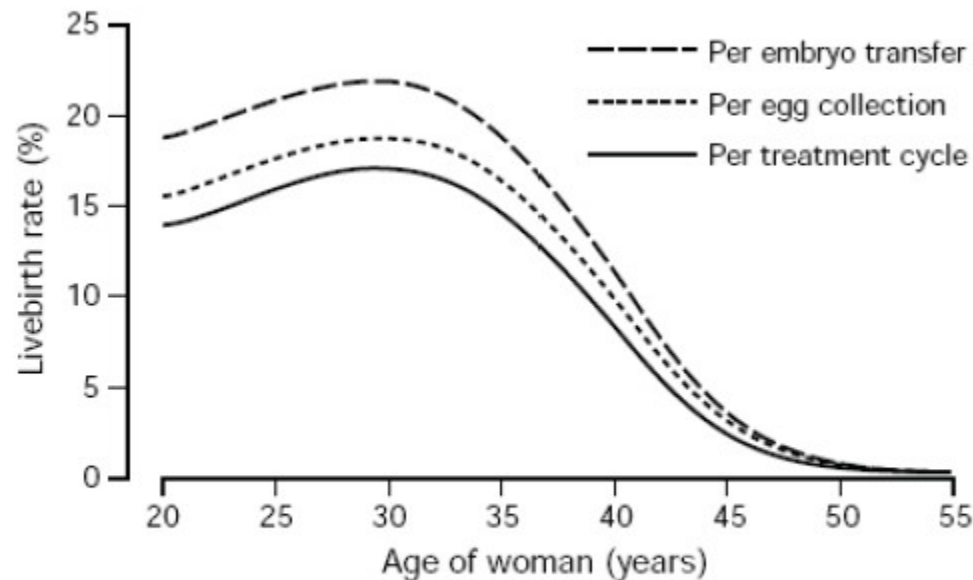# Outcome of standard IVF according to age

Fig. 6. Effect of age of women on LBR per cycle started, per egg collection and per ET. Reproduced, with permission, from Templeton *et al.* [161].

161. Templeton A, Morris JK & Parslow W (1996) Factors that affect outcome of in-vitro fertilisation treatment. Lancet 348(9039): 1402–1406.

Livebirth rates per ET in women who used their own eggs and women who received donated eggs

Templeton *et al.*, Lancet 1996

Age	No of ETs Own eggs	No of ETs Donated eggs	Livebirth rate/ET Own eggs	Livebirth rate/ET Donated eggs	p
<29	1740	111	23.7	21.6	0.6
30-34	3907	174	21.9	28.2	0.05
35-39	3352	185	17.6	26.0	0.004
40-44	1104	229	8.1	18.8	<0.001
≥ 45	85	132	3.5	22.0	<0.001

Factors that affect outcome in IVF treatment

- Age
- Significant decrease in live birth rate with increasing duration of infertility from 1 to 12 years (p <0.001)
- Previous pregnancy and livebirth significantly increased the treatment success
- The possibility of success decreased with each IVF treatment cycle
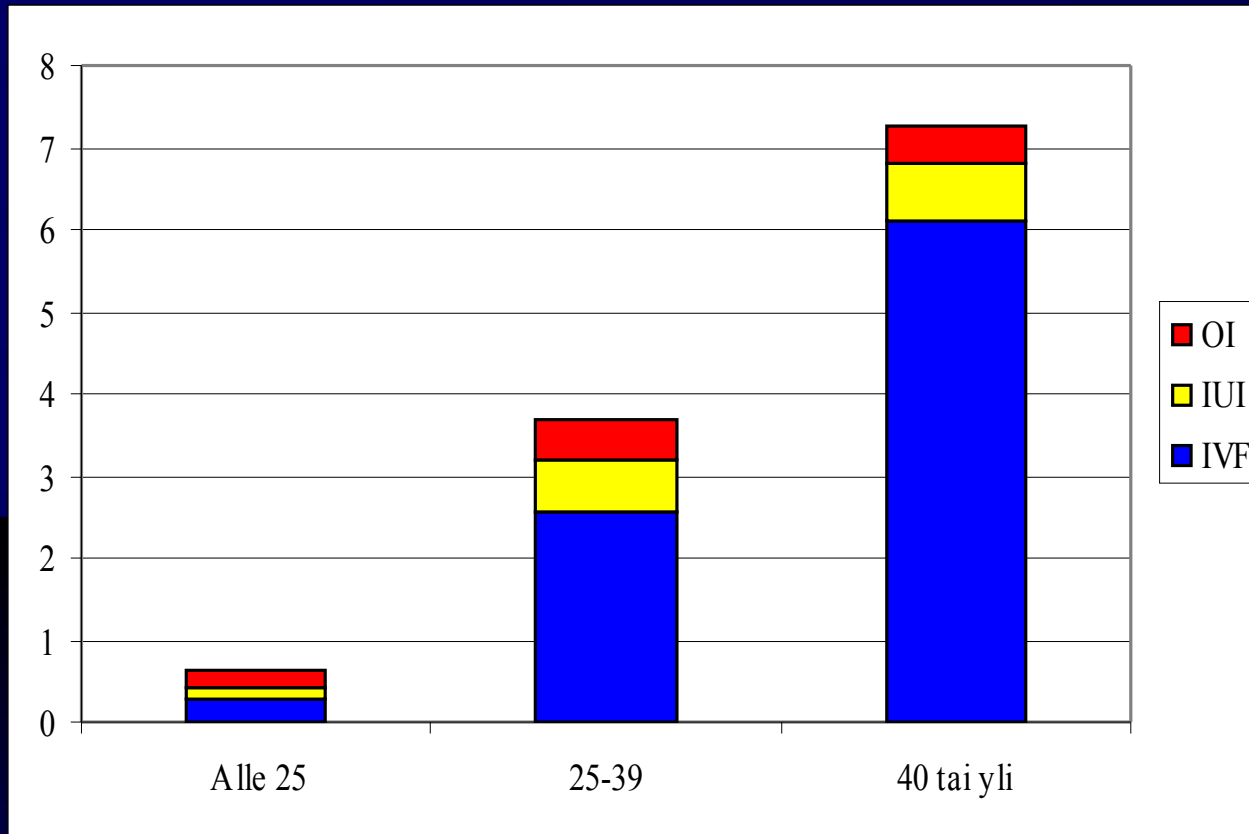
Templeton *et al*., Lancet 1996

Age of women when starting IVF/ICSI; 1992-2007, %
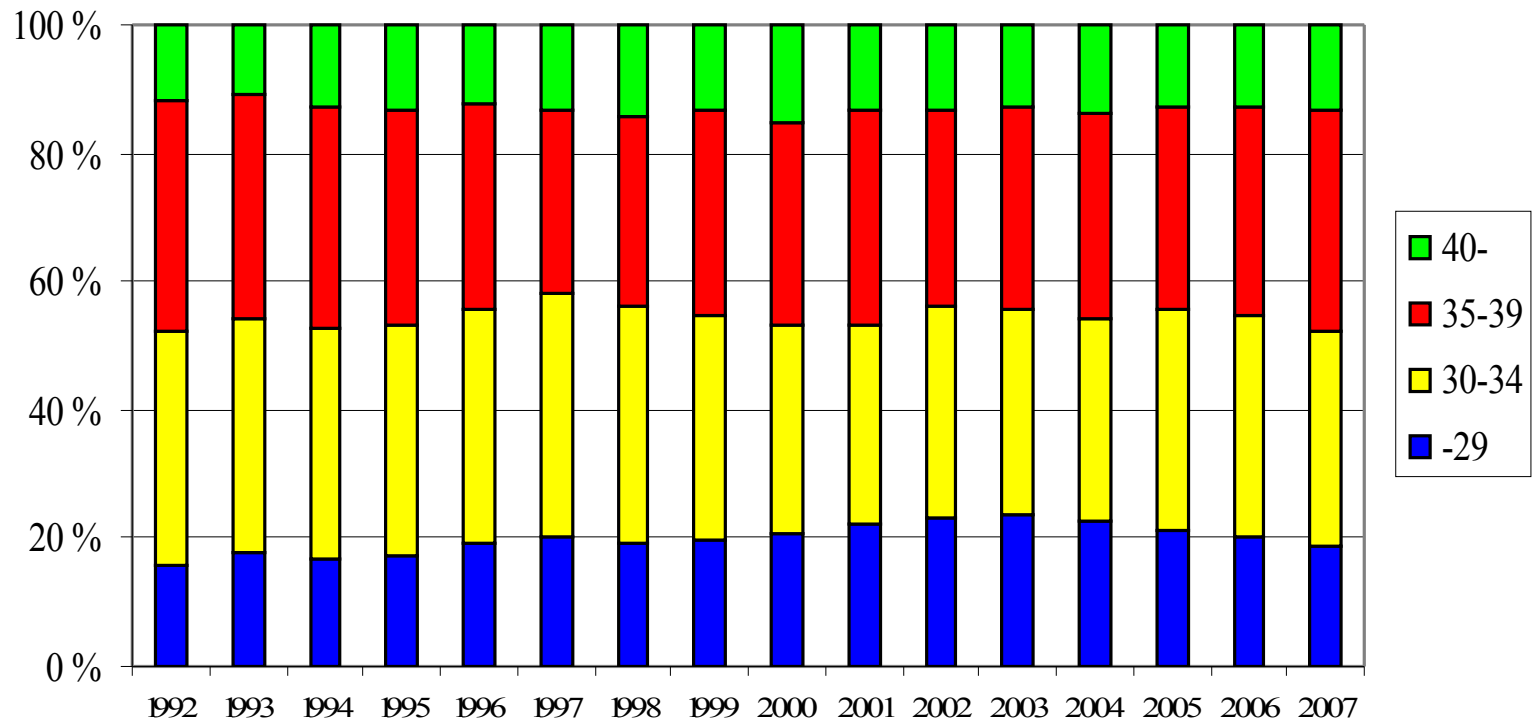
# Clinical pregnancies/OPU; IVF/ICSI according to age of the women 1992-2007, %
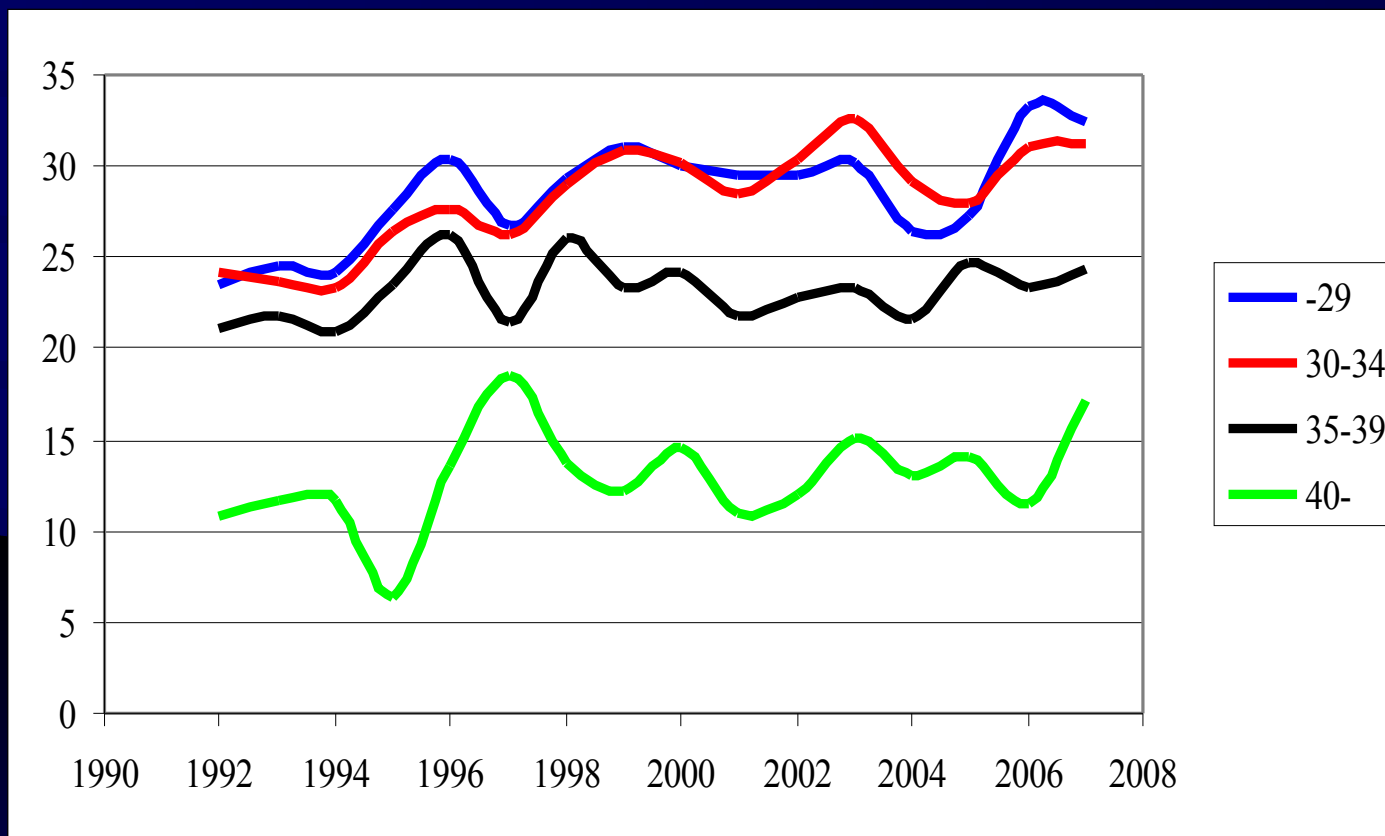
Percentage of children born after ART in according to age of the mother 2004-2007 (data from Finnish Birth Register)

Noin 2000 naista ≥40 v (3.6-3.7 % kaikista) synnyttää vuosittain Suomessa

≥40 naisten lapsista 7.2 % on saanut alkunsa lapsettomuushoidoista

IVF/ICSI ≥ 40 years 2000-2007; Väestöliitto; H:ki
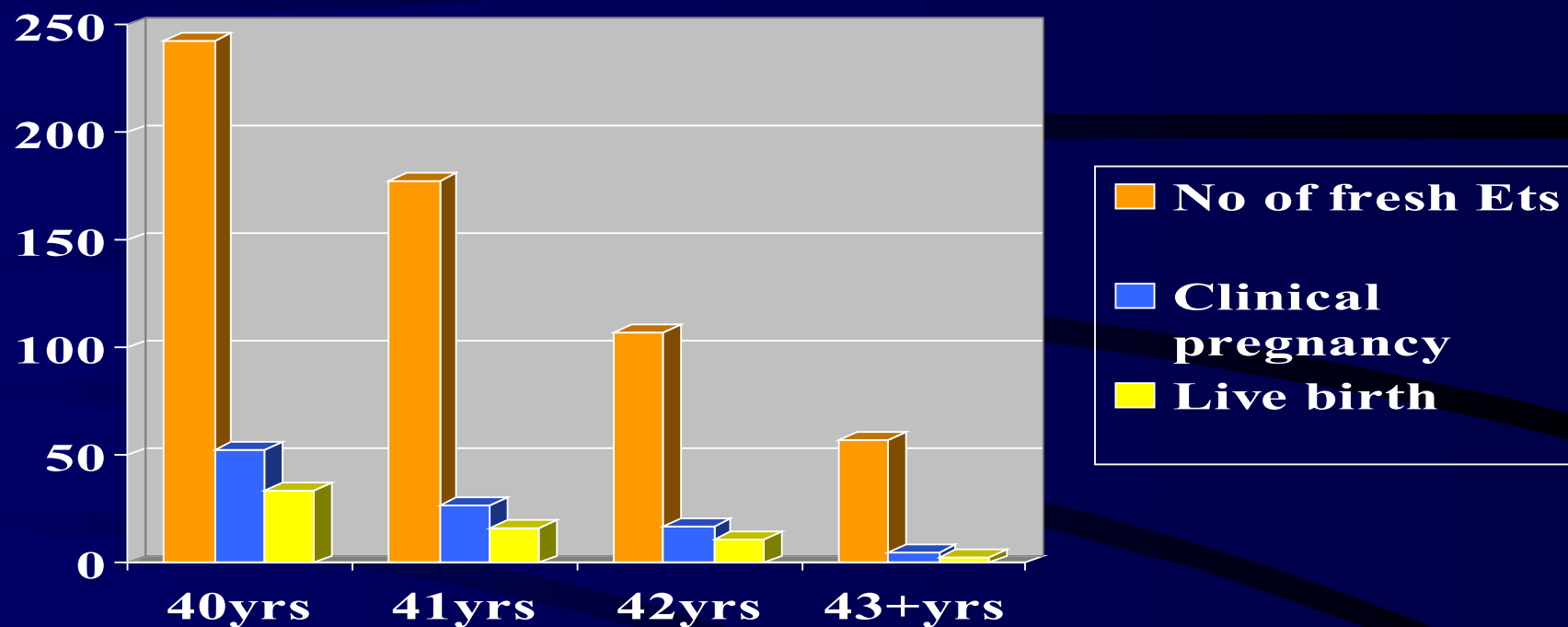
Age	40 years	41 years	42 years	43+ years	All
No of ETs	243	178	107	57	585
Clinical preg	53 (21.8%)	27 (16.4%)	17 (15.9%)	5 (8.8 %)	102 (17.4%)
Live birth	34 (14 %)	16 (9 %)	11 (10.3%)	3 (5.3%)	64 (10.9%)

Possibilities to improve the outcome in older women ?

- **Improvement of poor response/poor oocyte quality**
  - Various attempts with different protocols
    - Luteal E2 patch/antagonist protocol
    - Androgen supplementation
    - LH supplementation
    - GH supplementation
  - Kyrou *et al*, meta-analysis Fertil Steril 2009 "Insufficient evidence exist to recommend most of the treatments proposed to improve pregnancy rates in poor responders." Exception: GH?
- **Management of abnormal embryos**
  - PGS?
  - Blastocyst culture?
  - Metabolomics in the future?

Preimplantation genetic screening of aneuploidy (PGS)

- available evidence does not support the use of PGS currently to improve LBR in patients with advanced maternal age

RCT reference	N	Age	Conclusion
Staessen 2004	81 P vs 121C	>37	NS
Mastenbroek 2007 Re-analysis by Twisk 2008	206P vs 202C	35-42	PGS lower PR NS
Hardarson 2008	56P vs 53C	>37	PGS lower CPR

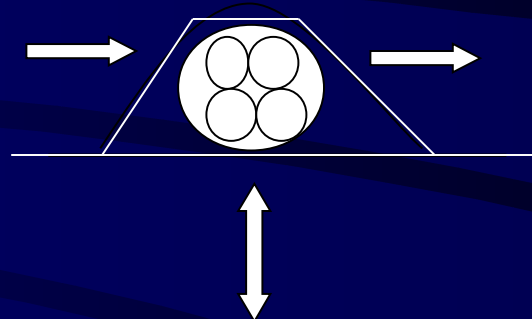# Metabolomics
Non-invasive examination of embryo viability

UPTAKE

- Oxygen
- Puruvate
- Lactate
- Glucose
- Lipid
- Amino Acids

PRODUCTION

H_2O

CO_2

Lactate

NH_4^+

Enzymes

Hormones

Amino Acids

Other factors

HLA-G, HoxA10, Ubiquitin

Gardner D and Leese H 1999

Oocyte donation (OD)

- the most effective treatment for women over 40 years and for those with compromised ovarian reserve

Oocyte donation outcome

- Clinical pregnancy rate/ET 30-60%

- Cumulative live birth rate after 4 treatments 88-94%

- OD outcome is highly dependent on the age of the donor (Cohen *et al.*, 1999)

- Similar success rate regardless of recipient age

Toner et al, 2002
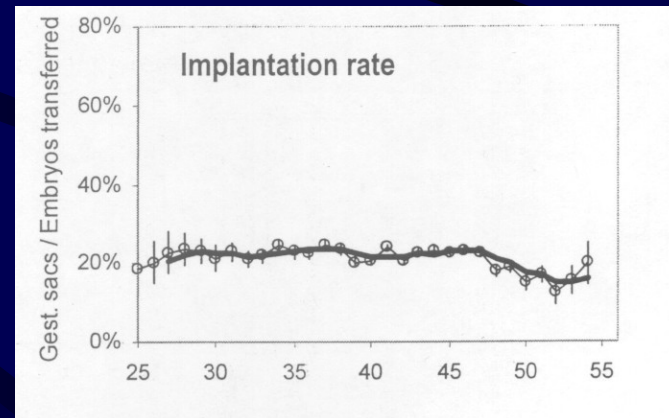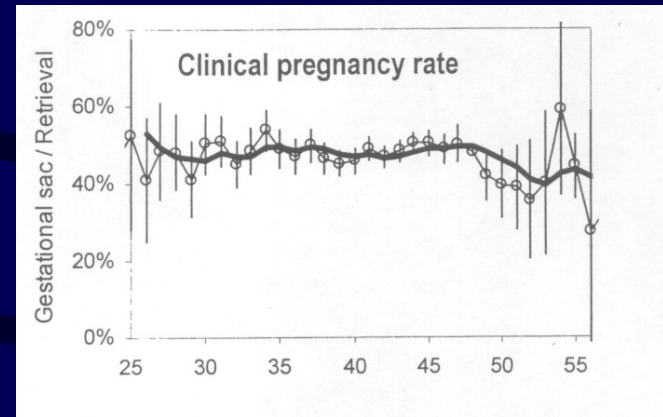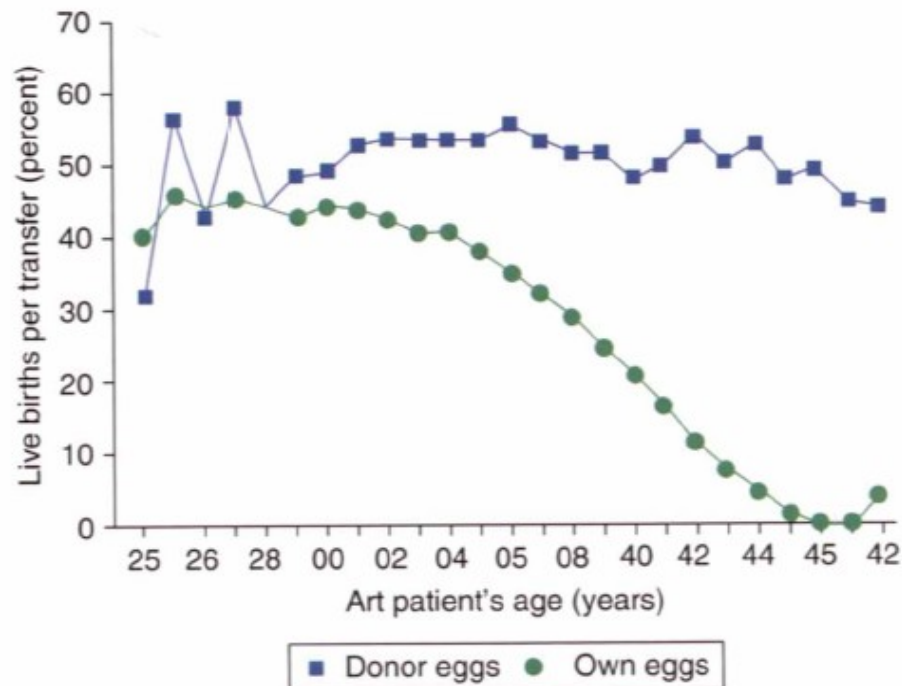
OD outcome and recipient age

Figure 60.1 Live births per transfer for ART cycles using fresh embryos from own and donor eggs, by ART patient's age, 2004.[8]
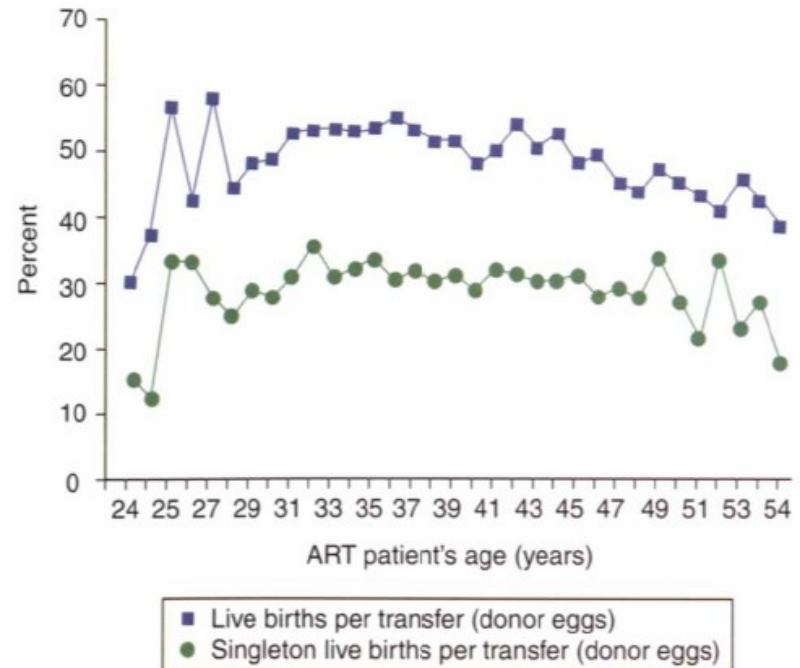
Figure 60.3 Live births per transfer and singleton live births per transfer for ART cycles using fresh embryos from donor eggs, by ART patient's age, 2004.[8]
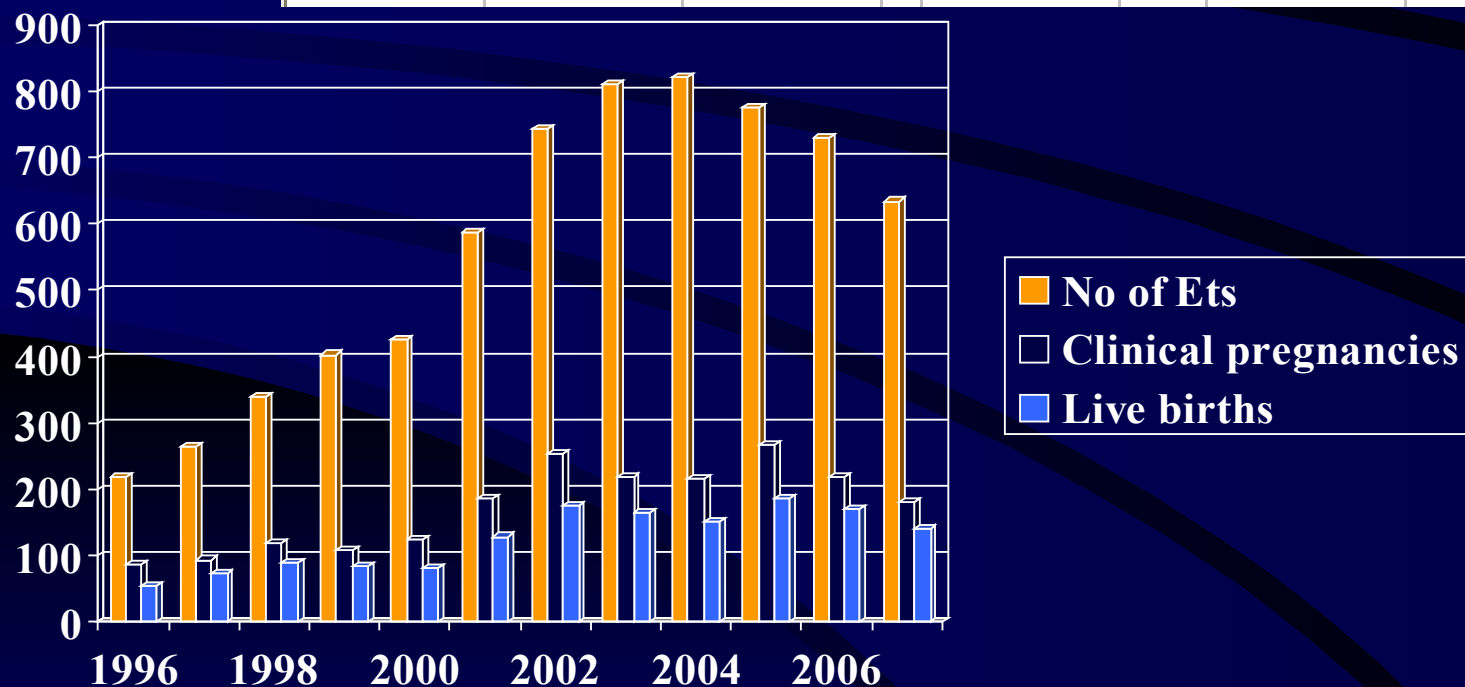
CDC/SART data 2004
from Textbook of ART

Oocyte donation in Finland

Oocyte donations 2007				
Age of treated women per transfer cycle				
	Fresh embryos		*Frozen embryos*	
	IVF or ICSI		IVF or ICSI	
- 29 years	17	5 %	21	7 %
30 - 34 years	45	14 %	44	14 %
35 - 39 years	90	29 %	93	29 %
40 - years	162	52 %	162	51 %
Missing	0	0 %	0	0 %
Total	314	100 %	320	100 %

Legend:
- No of Ets
- Clinical pregnancies
- Live births

National Institute for Health and Welfare (M. Gissler, 2009)

World's oldest mother gives birth to twins at 70

Grandmother Omkari Panwar has given birth to twins at the age of 70

907g x2

Preservation of fertility in healthy women ?
"extra time for late starters"

- Cryopreservation of ovarian tissue or oocytes
  - Experimental
  - Ethical problems
  - "There are no convincing *a priori* moral reasons why cryopreservation of ovarian tissue or oocytes should not also be available for healthy women"

    Dondorp and De Wert, Hum Reprod 2009

- 936 children born after oocyte vitrification 2009

    Noyes, RBMOnline 2009

  - Congenital malformations 1.3 %

Postponement of childbearing

- Freezing of oocytes: medical solution to what is in fact a societal problem?

- Postponement of childbearing connected to cultural development

- Couples are often unaware of the early decline of female fertility
Lampic et al., Hum Reprod 2006

- Young couples trust technology will help

Can ART make up for babies lost by delaying attempts to conceive?

Begining of attempts	Pregnant	Not pregnant	ART	Total pregnancies
30 y	91	9	-	91
35 y	82	18	4	86
40 y	57	43	7	64

Assume attempt 4 years if < 35 ; 3yr if 35-40, 2 yr if >40

2 cycles of IVF

Leridon Human Reprod 2004

In conclusion

- Female reproductive aging = ovarian aging
  - Variability between women
- ORT poor predictor of ongoing pregnancy
- Acceptable outcome after ART at least up to the female age of 42 years
- Do not postpone effective treatments
  - Avoid cosmetic medication
- Young women and men unaware of the early decline in fertility
  - Inform your patients!