Fertility over 40

P.G. Bianchi

World records?

- The oldest woman to deliver has been Rosanna C. who delivered at 63 years and 3 months (oocyte egg donation program).
- The oldest women to carry a spontaneous pregnancy was a Brazilian lady who delivered at 56 years of age.
- The most prolific couple seem to have lived in Siberia in the 18 century, the church register reports 67 of their children. The woman delivered her last child at 47 years and 8 months.

Decline of fertility

- Females of most mammalian species, including humans experience reproductive decline with age ending in complete loss of fertility by mid-life, even though there are still primary oocytes within the ovary.
- Demographic, anthropological, historical and clinical studies of diverse populations agree that the female fecundity declines with age.

Decline of fertility II

- Age (chronological and biological)
- Fecundability and fecundity
  - older women need a longer exposure to pregnancy but exposure can decline on behavioural grounds (i.e. duration of mariage)
    - » ***Frank O. Bianchi PG and Campana A. J Biosoc Sci 26, 349-368,1994***

USA data

- The rate of childless women at the age of 35 has nearly doubled to 25% since 1925.
- In 1994 in the United States one third of all first births were by women over the age of 35
- **Corson SL** ***Int J Fertil Womens Med 1998***

USA data

- ***Curtin SC and Martin JA***

  Natl Vital Stat Rep 2000

- ***Fertility rate (15-44 years old women) 65.8 per 1000 (slight decline)***
- ***20% decrease in birth rates among teenagers (compared to 1991)***
- ***Increase for birth rates in women in their 30 and forties***
- ***The birth rate for women aged 40 to 44 was the highest reported since 1970***

Studies on «reproductive aging» should be an urgent priority for two reasons

- 1) Senescence of the reproductive system provides a model for the study of aging itself.
- 2) Because of social changes many women delay marriage and childbearing until their late 30’, when the effect of age on fertility starts to become clinically significant.

Genetic factors ?

- In contrast to the timing of onset of the menstrual cycle for which a considerable genetic influence has been shown.
- Attempts to relate menopause with different behavioural, reproductive and anthropometric factors failed to show a consistent and replicable influence.
- Only smoking advances menopause of ~1,5-2 years

Genetic factors? II

- «Genes control the cessation of a women's reproductive life: a twin study of hysterectomy and age at menopause»
  - classical twin study
  - 628 twin pairs
  - h2 = 63%

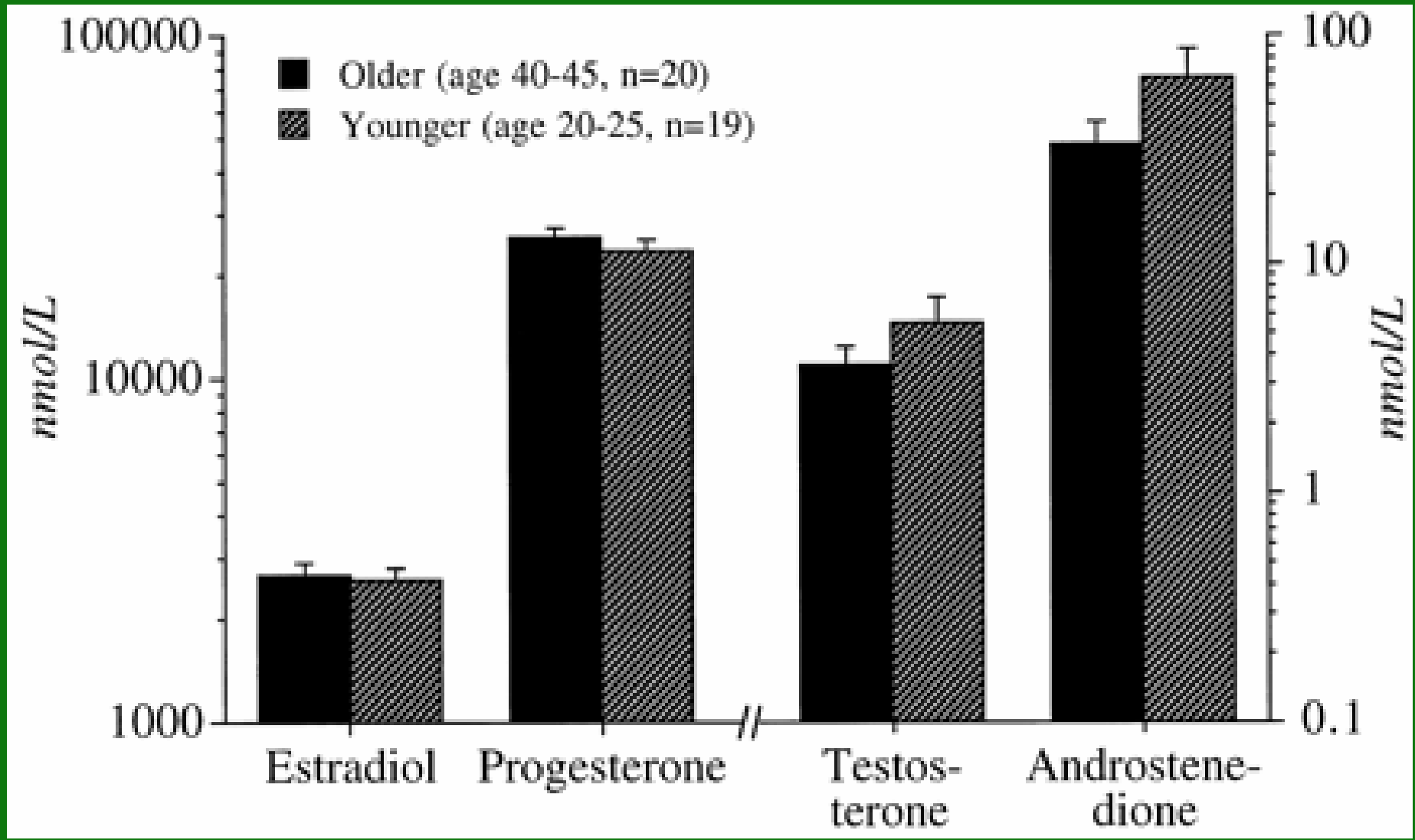
Snider H., MacGregor J., Spector T.D.
J Reprod Endocrinol Metab 1998

Where does the aging process start?

- Endocrine mechanisms
- Ovarian reserve
- Oocyte quality
- Implantation

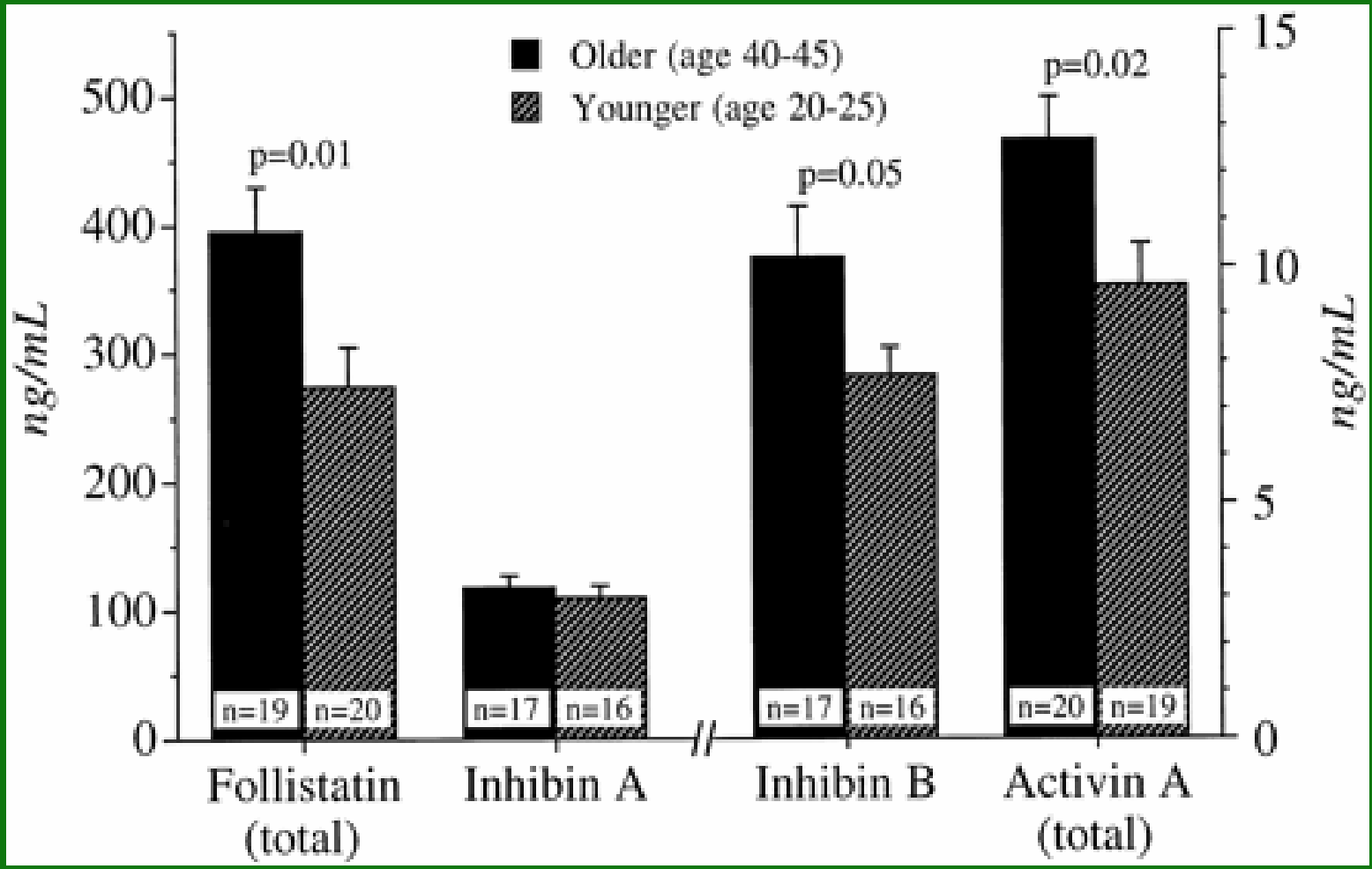
Changes

- **Already 10 years before menopause slight changes in menstrual cyclicity can be discerned.**
  - » Follicular phase shortens and hence does the menstrual cycle.
- A progressive **rise in FSH** secretion has been described throughout reproductive life and accelerates approximately a decade before menopause and therefore coincides with a phase of accelerated follicle depletion.



Mean follicular fluid concentrations for older subjects (40-45) and younger control (20-25)

From Klein et al. JCE 85, 4518-25,2000



Older subjects had significantly higher concentrations of total follistatin and activin A

No significant difference in concentrations of Inhibin A and B

From Klein et al. JCE 85, 4518-25,2000

- ***Seifer et al. J Clinical Endocrinol Metab 81, 736-9, 1996***
- Luteinized granulosa cells from women with elevated day 3 FSH levels
  - produce less steroids,
  - are less viable in culture,
  - have a reduced mitotic index
  - produce decreased quantities of IGF-I and IGF-II

Follicular/oocyte development and oocyte quality

- In the human oocytes enter meiosis early in fetal life (~ 12 weeks).
- Oocytes progress to the diplotene stage of meiosis I (GV stage).
- Oocytes stay in this state until just before they resume ovulation
- This event is gonadotropin-dependent and triggered off by the mid-cycle LH surge

Data on apoptosis in the oocyte

- Does apoptosis play a role in relation to «the age factor » in the human oocyte?
- Maturation rates in vitro of oocytes was lowest in the age group 41 to 50.
- The rate of apoptosis in immature oocytes in vitro was also higher in this group.

Wu et al. Fertil Steril 74, 1137-41, 2000

Data from IAC

- ***Campana et al.***
  Hum Reprod, 11,732-736, 1996
  - review of 1115 cycles of IUI (332 couples).
  - outcome was affected by the woman's age (>39 years old) and by total motile sperm count
  - No pregnancy after the age of 44

Data from IAD

- ***Kang BM and Wu TC***
  Obstet Gynecol 88, 93-8, 1996
  The cumulative probability of pregnancy after 7 cycles was
  88% for women 35 years old or younger compared to 65% and 42% in women 35-40 and over 40 years old

Data from IVF cycles

- **«Embryo quality and developmental potential is compromised by age»**

  Ziebe S., Loft A., Petersen J.H. et al. Acta Obstet Gynecol Scand 80, 169-174, 2001

  – Decrease

  » in number of oocyte recovery (1 oocyte per 2.3 years)

  » Number cleaved oocytes (1oocyte per 3.7 years)

  - Due to decreased number of retrieved oocytes

Results II

- The percentage of fragmented oocytes increased 3% per year of age
- The number of transferred embryos decreased significantly from 2.1 at the age of 25 to 1.8 at the age of 40.
- In the selected subgroup of «good quality embryos» implantation rates decreased significantly with age
- The decrease in the ongoing pregnancy rate was almost linear (~ 1.5 per year)

Effects of maternal age on the oocyte developmental competence

- Meiotic incompetence (effects on fertilisation)
- Errors in meiosis (genetic abnormalities)
- Cytoplasmatic deficiencies (anomalies at different stages of development (before or after fertilisation)

» ***Armstrong DT Theriogenology 55, 1303-22, 2001***

Data from oocyte donation

- ***Borini et al. Fertil Steril 65, 94-7,*** 1996

  Retrospective data analysis of cases where recipients of different ages shared oocytes from a single donor

- 114 women undergoing a cycle of oocyte donation
- Group A : = or <39 / Group B : 40 to 49
- Pregnancy rates of 47,3% and 24,5% respectively
- Abortion rates 14,8% and 7% respectively

Implantation and age

- Still matter of some controversy even if the «oocyte factor» seems determinant.
- The lack of knowledge of all the physiological variables that determine a successful nidation makes the analysis of the uterine receptivity difficult.

Is assisted hatching useful ?

- ***Schoolcraft WB, et al J Assist reprod Genet 12, 581-4, 1995***
  - delivery rate per oocyte retrieval was significantly higher in the assisted hatching group.
  - It seems to improve implantation and term pregnancy rates in women age 40 and over.

The need to test for ovarian reserve FSH

- ***Scott et al. Fertil Steril 1989***
- Large retrospective study on 758 IVF cycles
- Pregnancy rates decreased as basal FSH previous to treatment increased
- FSH threshold <15 IU
- Ages were equivalent in the 2 groups (mean 35 years)
- FSH provides better predictive values for pregnancy and cancellation rates

The need to test for ovarian reserve

- **Ovarian volume**
- Reported to be better than basal FSH to predict ovarian response to gonadotrophins
  - ***Syrop et al. Fertil Steril 64, 1167-71, 1995***
  - ***Sharara et al. Hum Reprod 14,183-5,1999***
- **Basal antral follicular counts**
- No good threshold
  - ***Pellicier et al. Fertil Steril 70, 671-5, 1998***

Risk of miscarriage and age

- Fetal loss is the possible destiny of 13% of clinical pregnancies.
- At 42 more than half of pregnancies result in fetal loss.
- The risk of spontaneous abortion is 8.9% in the age group 20-24 and 74% in those aged 45 or more
  - ***Andersen et al. BMJ 320,1780-1712, 2000***

Age	35-37	38-43 with EB	38-43 without EB	>43 with EB
Cycles	284	102	179	65
Abbandoned cycles	49	22	47	36
N eggs collection	235	80	132	29
N transfers	177	48	92	15
N clinical pregnancies	66	20	20	1
% pregnancies	37	42	22	7
Implantation rate %	23	25	11	5
Number of miscarriages	8	3	2	0

Gianaroli et al.. 1999

Evidence for declining fecundity in older men

- *Hum Reprod 15 ,1703-1708, 2000 Ford et al.*
- *All couples in the Avon Health District expecting a baby between April 91 and December 92 were eligible.*
- *Questionnaires were completed at 18 weeks.*
- *Of 12 106 couples 70,7% had planned the pregnancy and 99.5% stated the time to conception*

Male fertility declines with age? II

- *Specific and non specific fertility factors*
- *Parity, paternity, cohabitation, oral contraception.*
- *Educational achievements, housing, cigarette smoking, alcohol consumption, obesity.*

Results I

- Of the 8515 planned pregnancies
- 74% were conceived at 6 months,
  14% in the second 6 months
  12% after more than a year.
- after adjustment for variables (including age of the mother)
  the likehood of conception within 6 or 12 months was lower in older men

Results II

- Adjusted odd ratios for conception in ≤12 months compared to men ≤ 25 years old were
  0.62 (30-34 y)
  0.50 (35-39y)
  0.51 (≥ 40y)
- There is a larger decline in male fecundity with advancing age than previously reported

Male fertility declines with age? I

- ***No***
- Retrospective analysis for 558 oocyte donation cycles (441 couples) in an oocyte donation program
  - Am J Obstet Gynecol 2001
    - » Paulson RJ, Milligan RC, Sokol RZ »
      - Negative correlation between male age and total sperm count
      - No association between male age and fertilisation rates, pregnancy or live birth rates

Male fertility declines with age? II

- ***Yes***
  - ASRM 2000, San Diego California
  - 2 groups communicated data suggesting the effect of the male partner's age
    - » Kentucky Center for Reproductive Medicine Retrospective study on 800 sperm samples showed a decrease of TFSF (total functional sperm fraction) from 107.1 million to 35.5 million from the age of 20 to 50 years old

Male fertility declines with age? III

- French group found a negative correlation between the fertilisation rate and the age of the husband on a oocyte donor program
- Fertilisation rate for men less than 39 years old was 60,2 % and only 51,3% for men over 39.

A review of the literature

- Kidd SA, Askenazi B and Wrombek AJ
  - Fertil Steril 2001 75(2), 237-48
  - The weight of the evidence suggests that increased male age is associated with a decline in semen volume, sperm motility and sperm morphology but not with sperm concentration.

Daddy's time bomb?

- «*Mom may have her biological clock but dad may be harboring a time bomb*»
- Study on 90 000 Israeli children found that advancing paternal age accounts for 1 out of every four schizophrenia cases.
- The older the man was at the time of conception the higher the risk after the age of 40.
- The age of the mother did not matter

Harlap et al. Arch Gen Psy, May 2001