



The Biological Clock and Fertility Diagnostic Testing

Richard J. Paulson, MD
University of Southern California
USC Fertility
Los Angeles, CA

Identified or perceived conflict of interest has been resolved in accordance with ACCME guidelines.

Keck School of Medicine of USC

1

Disclosures

- Nothing to disclose

2

The Biological Clock
and Fertility Diagnostic Testing

Learning Objectives

- To describe the biological clock in human reproduction
- To counsel patients about ovarian reserve testing
- To advise patients regarding fertility preservation

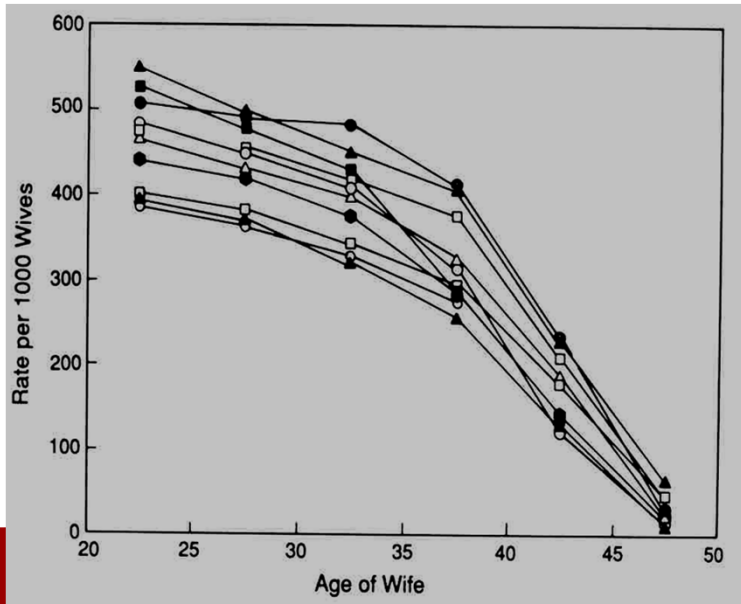
3

What is the biological clock?

4

The Biological Clock
and Fertility Diagnostic Testing

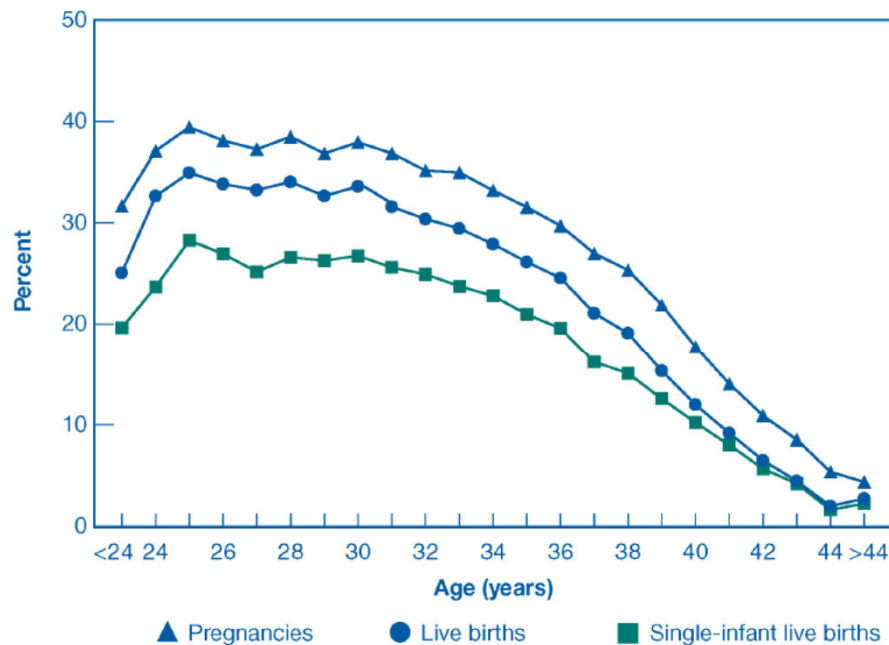
Fertility and Age: Natural Populations



- Marital fertility rates in natural populations (no contraception) as a function of age of wife

Menken et al, Science 1986;23:1389.

5

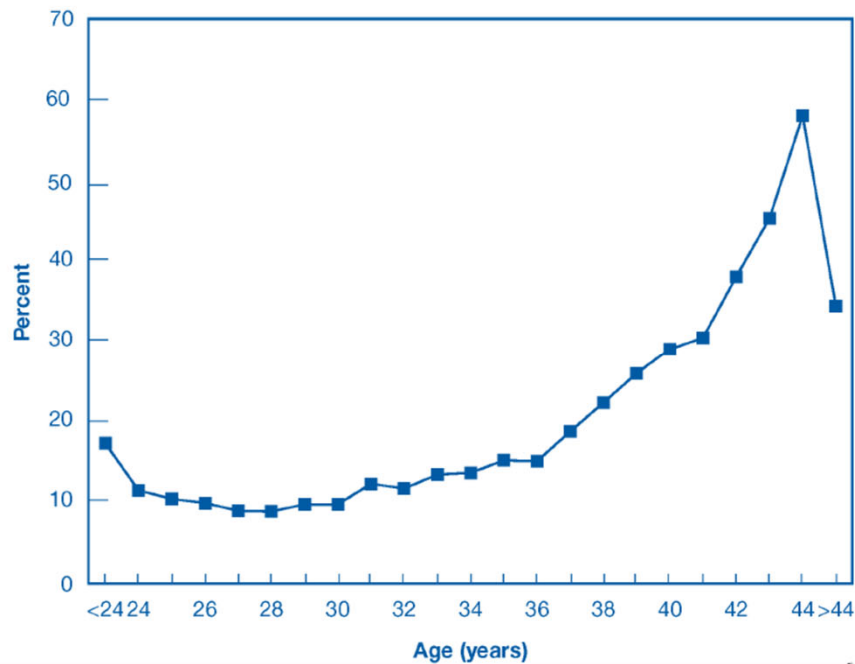


Fertility and Age:
IVF cycles

CDC, 2016

6

The Biological Clock
and Fertility Diagnostic Testing

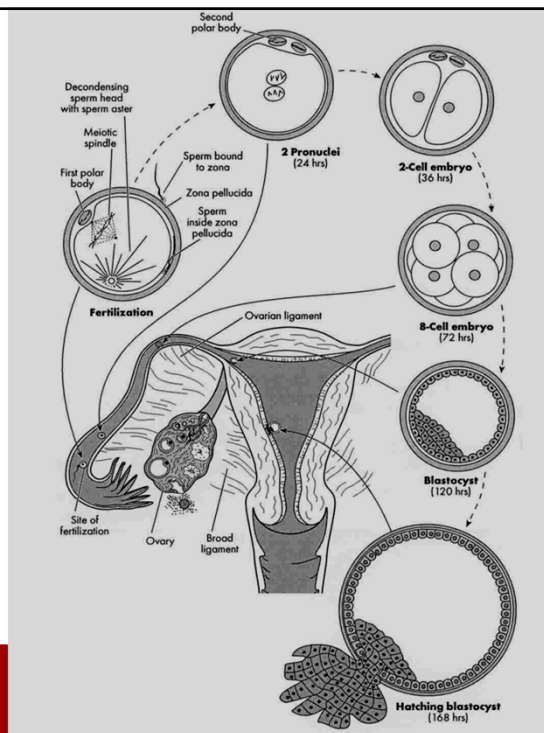


Fertility and Age:
Miscarriage rates

CDC, 2016

7

Reproduction in vivo



8

The Biological Clock and Fertility Diagnostic Testing

What is needed for normal fertility?

- 1) Oocytes
- 2) Sperm
- 3) Transport – uterus and Fallopian Tubes

9

Work-up of Infertility: 3 Steps

- 1) Oocytes
 - Ovulation
 - Egg quality
- 2) Sperm
 - Semen analysis
 - Concentration, motility, morphology
- 3) Transport - Hysterosalpingogram
 - Uterus
 - Tubes

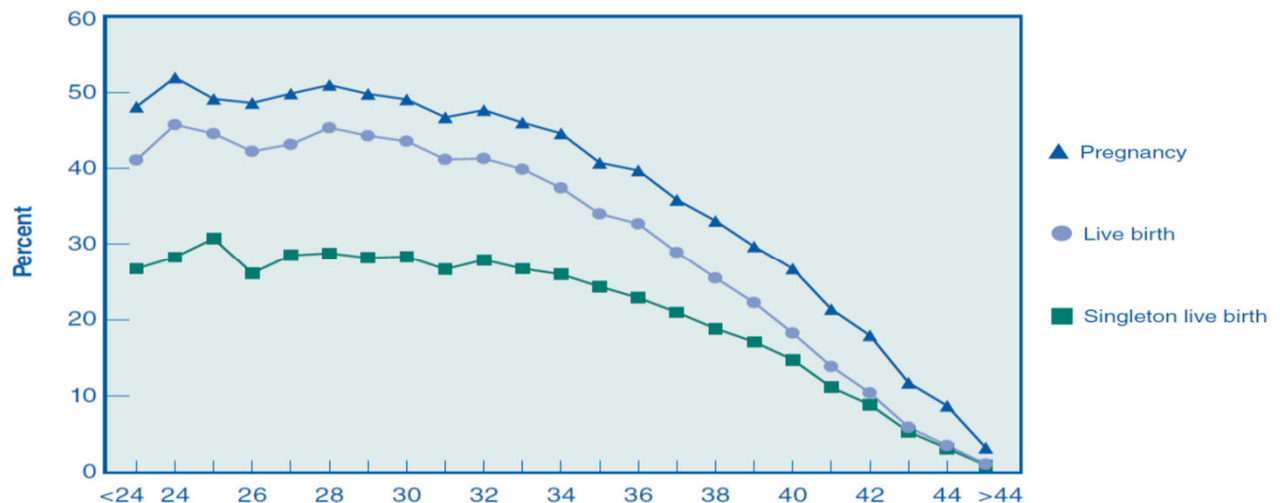
10

Infertility

- Definition:
 - 12 months of trying
 - “unprotected intercourse”
- Work-up
 - 6 months in women ≥ 35 years of age
 - Immediately if positive history:
 - Irregular periods
 - Suspected male infertility
 - Suspected uterine/tubal disease

11

AGE is Most Important in Reproduction



12

The Biological Clock
and Fertility Diagnostic Testing

Ovarian Reserve Testing: Predicting Fertility Potential?

- Who should get Ovarian Reserve Testing?
 - Women ≥ 35 years old after 6 months of trying
 - Women < 35 years old after 1 year of trying
 - Women at higher risk of \downarrow Ovarian Reserve
 - Women considering egg freezing

13

What tests should you order?

- AMH (anytime)
- FSH (+estradiol) on cycle day 3
- Antral Follicle Count
- Not recommended
 - Ovarian volume, Inhibin, Clomiphene Challenge Test, home fertility tests

14

- AMH (anytime)
 - Ideal ≥ 2.0 ng/mL
 - Bad < 0.5 ng/mL
- FSH (+estradiol) on cycle day 3
 - Bad ≥ 20 mIU/mL
 - Ideal < 10 mIU/mL
 - Estradiol must be < 100 pg/mL to have FSH be valid
- Antral Follicle Count
 - Ideal ≥ 20
 - Bad < 5

15

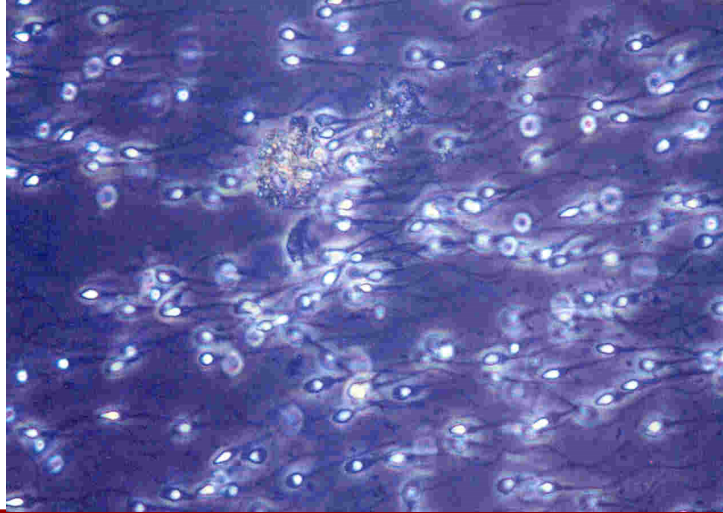
Work-up of Infertility: 3 Steps

- 1) Oocytes
 - Ovulation
 - Egg quality
- 2) Sperm
 - Semen analysis
 - Concentration, motility, morphology
- 3) Transport - Hysterosalpingogram
 - Uterus
 - Tubes

16

The Biological Clock
and Fertility Diagnostic Testing

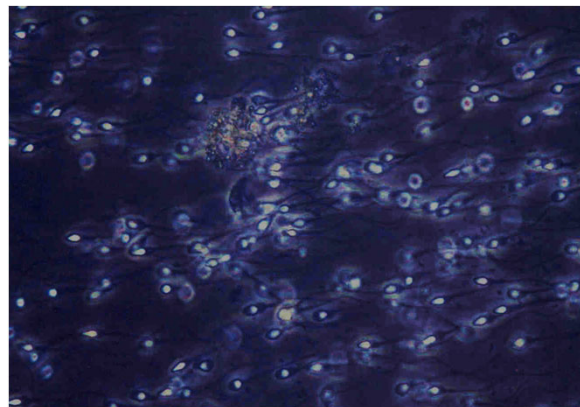
Sperm



17

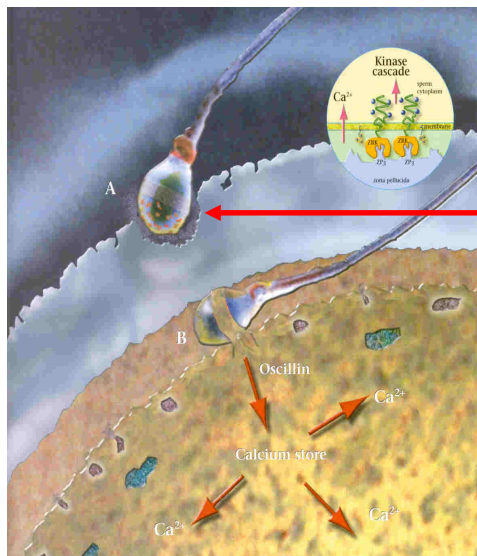
Sperm: Semen Analysis

- Correlates with sperm function
 - Ability to fertilize
- Fixed time of abstinence
 - >2 days, <7 days
 - Volume (≥ 1.5 mL)
 - Concentration ($\geq 15 \times 10^6/\text{mL}$)
 - Motility ($\geq 40\%$)
 - Morphology ($\geq 4\%$)



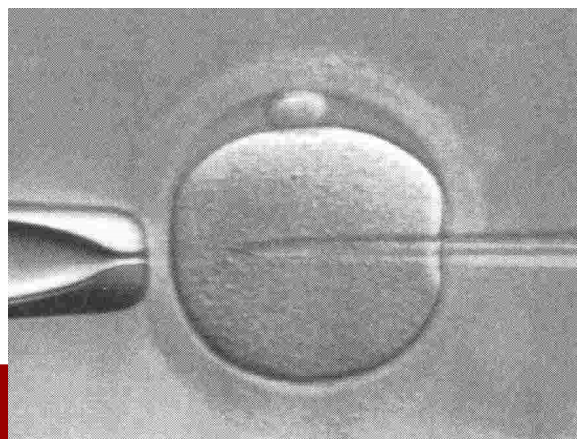
18

The Biological Clock
and Fertility Diagnostic Testing



Fertilization

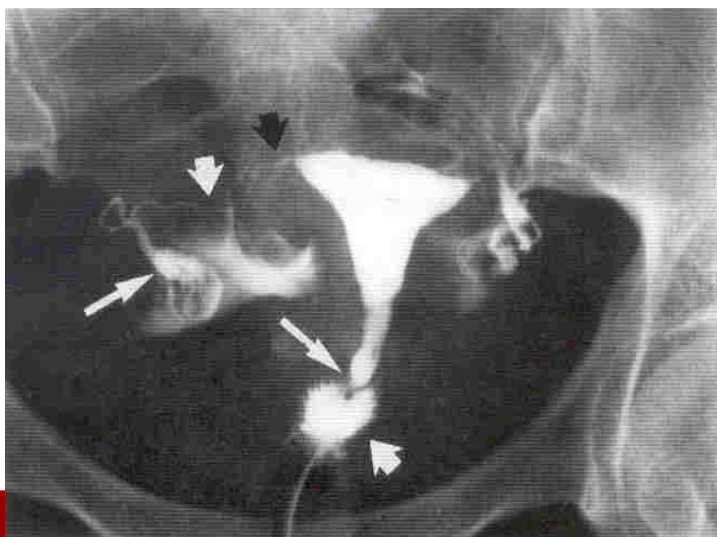
Sperm binds to specific protein in zona pellucida



Sperm can be injected directly into cytoplasm

19

Hysterosalpingogram (HSG)

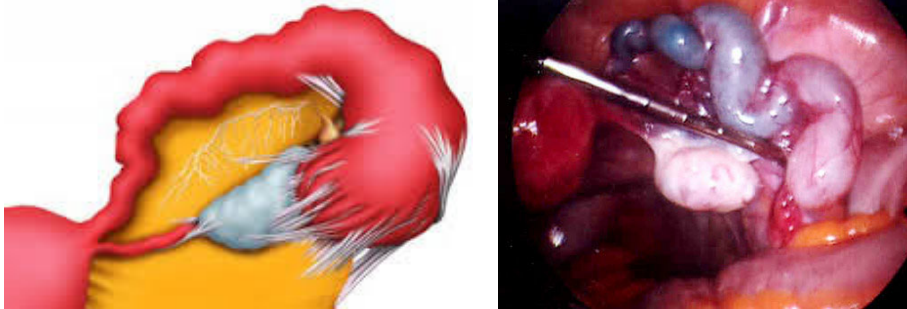


20

The Biological Clock
and Fertility Diagnostic Testing

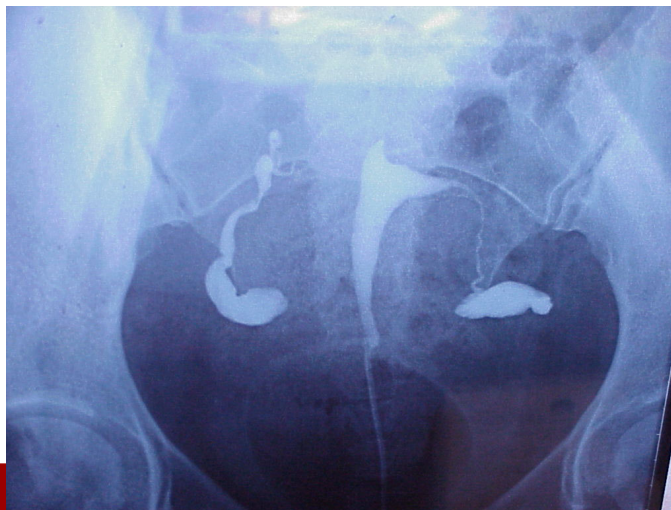
Fallopian Tube Dysfunction

- Blockage, scarring
 - Infection, prior surgery, endometriosis



21

Bilateral Tubal Block (hydrosalpinges)

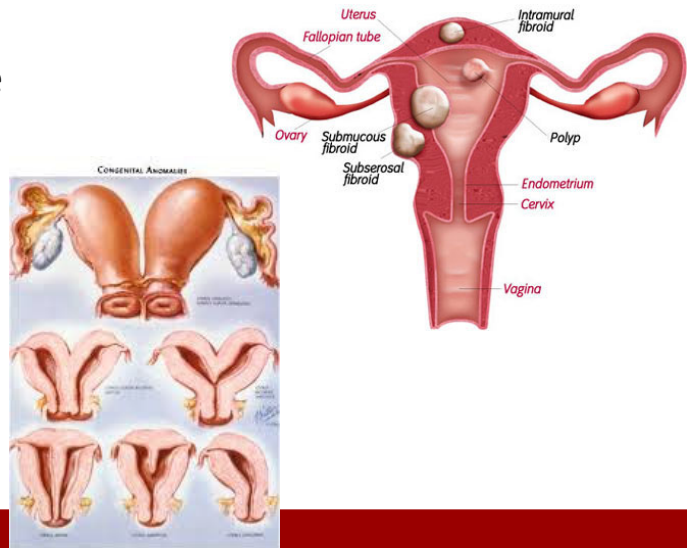


22

The Biological Clock
and Fertility Diagnostic Testing

Uterine Abnormalities

- Uterine cavity – size/shape
 - Developmental anomalies
 - Acquired anomalies: polyps, fibroids, scarring



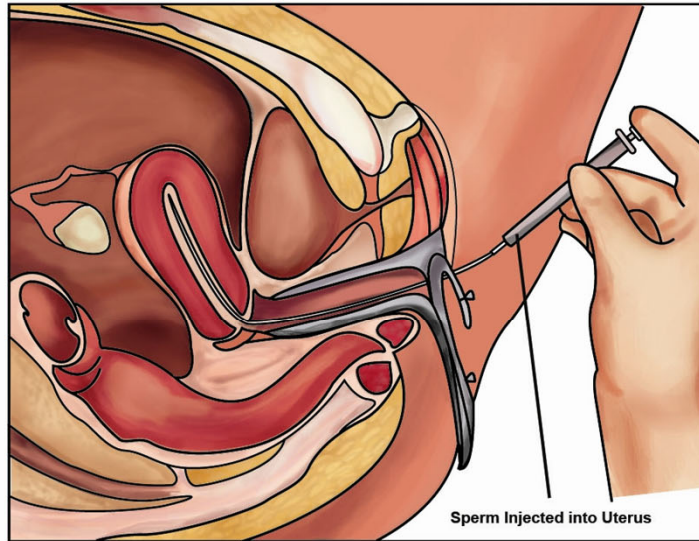
23

Simple Fertility Treatment

- Ovulation induction
 - Oral medications that increase FSH
 - Clomiphene = receptor antagonist
 - Letrozole = aromatase inhibitor
 - FSH injections
- Intra-uterine insemination (IUI)
 - Improves sperm transport
 - Often combined with fertility meds

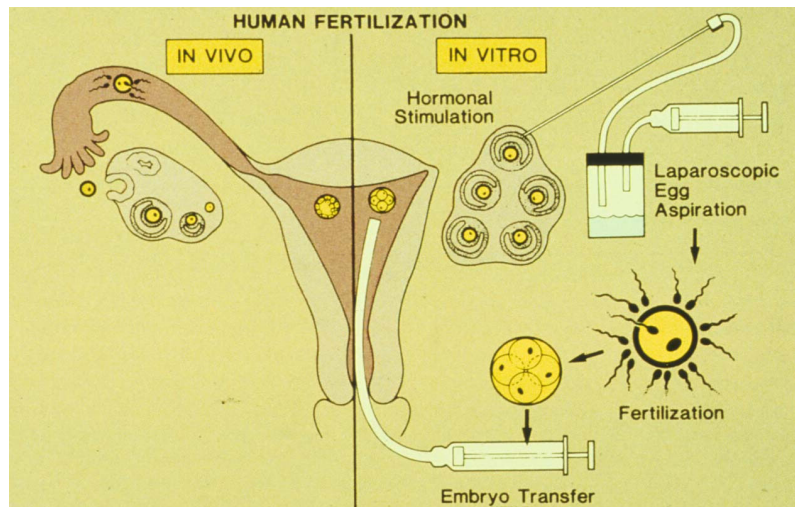
24

The Biological Clock
and Fertility Diagnostic Testing



25

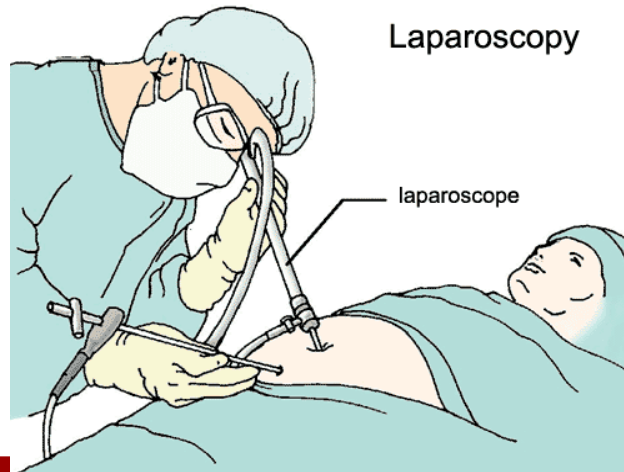
Complex Fertility Treatment: IVF



26

The Biological Clock
and Fertility Diagnostic Testing

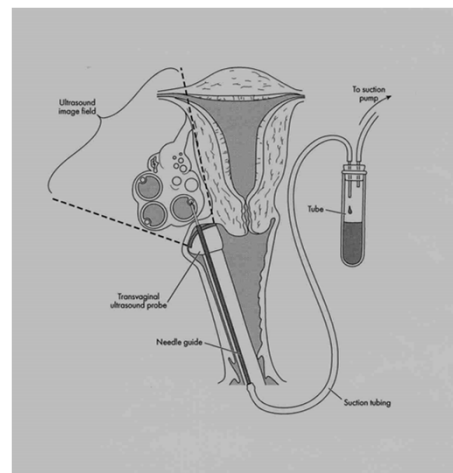
Egg Retrieval – HOW?



27

Follicle Aspiration for Egg Retrieval

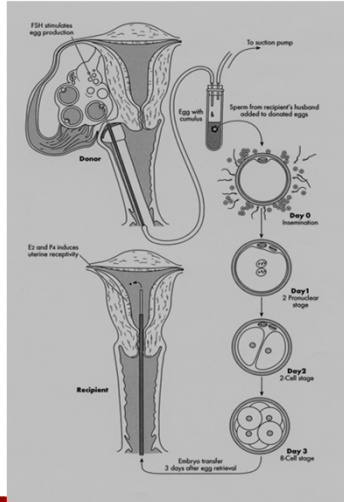
- Ultrasound-guided
- Most common method
- Conscious sedation
- Office procedure



28

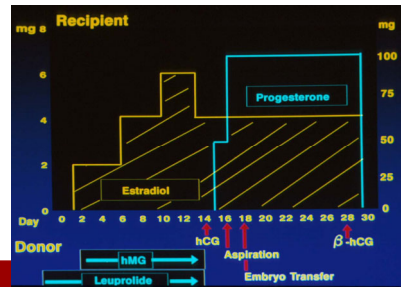
The Biological Clock
and Fertility Diagnostic Testing

Egg Donation: Synchronization



Donor:
Ovarian stimulation
(injectable FSH)

Recipient:
Uterine preparation
(estrogen and progesterone)



29

“Extending Reproductive Potential to Women Over 40”

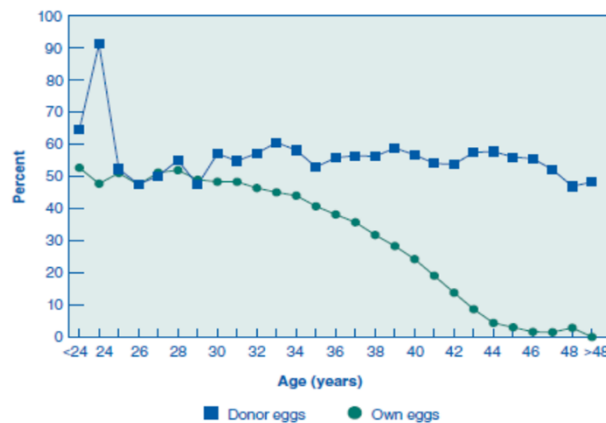
	Donor eggs under 40	Donor eggs over 40	IVF (own eggs) over 40
Transfers	14	8	26
Pregnancies	7/14 (50%)	6/8 (75%)	4/26 (16%)
Live births	7/14 (50%)	5/8 (63%)	2/26 (8%)

Sauer et al, NEJM 1990;323:1157.

30

The Biological Clock and Fertility Diagnostic Testing

Oocyte Donation Circumvents the Biological Clock



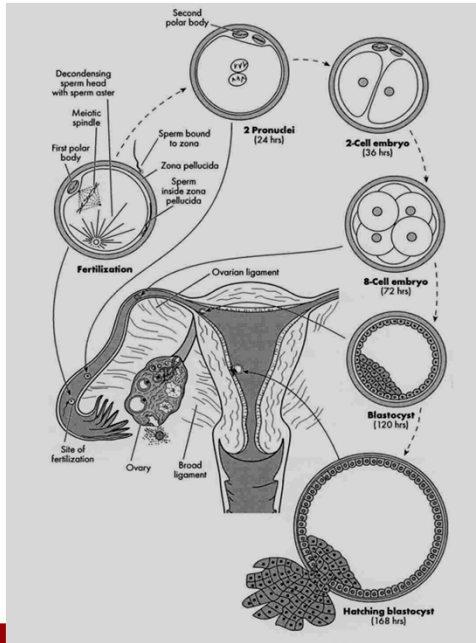
31

Question: Why do embryos derived from older oocytes implant at a lower rate than those from younger oocytes?

Answer: "Oocyte Quality"

32

The Biological Clock
and Fertility Diagnostic Testing



Embryo Development

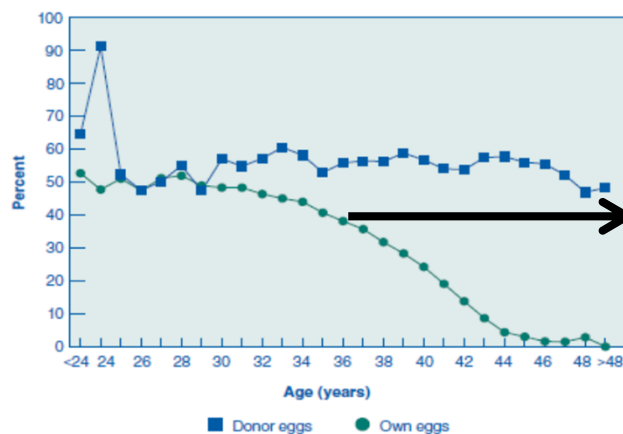
Oocyte quality =
Embryo Implantation

Older oocytes =
 ↑ chromosomal errors
 ↓ implantation
 ↑ miscarriages

Older cells =
 ↓ energy
 (mitochondria)
 ↓ telomere length

33

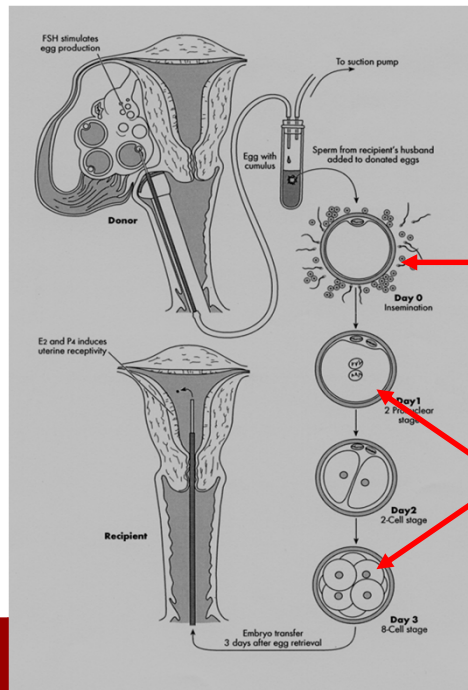
Is it possible to “pause” the biological clock?



34

The Biological Clock and Fertility Diagnostic Testing

Fertility Preservation: Basic Concepts



Oocyte cryopreservation

Embryo cryopreservation

35

Embryo Cryopreservation

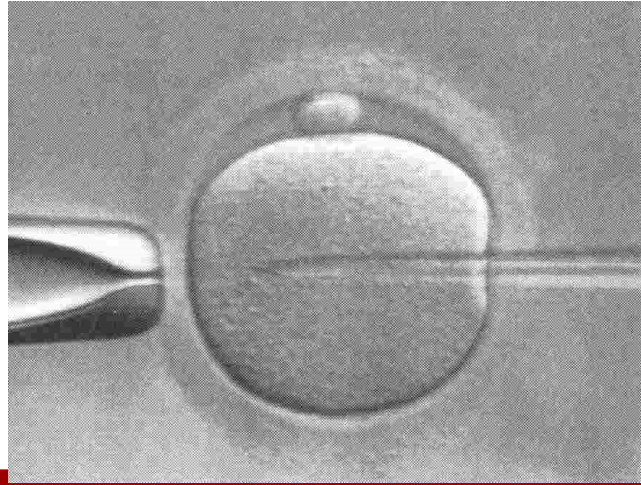
- First report:
1985, Australia
- First USA success:
1986, USC



36

The Biological Clock
and Fertility Diagnostic Testing

Fertilization After Egg Freezing: Intra-cytoplasmic Sperm Injection



37

Success rates:

Egg freezing = Embryo freezing

38

The Biological Clock
and Fertility Diagnostic Testing

Fertility Preservation

- Age of the egg is the most important
 - Pregnancy rates
 - Miscarriage rates

39

Oocyte Donation



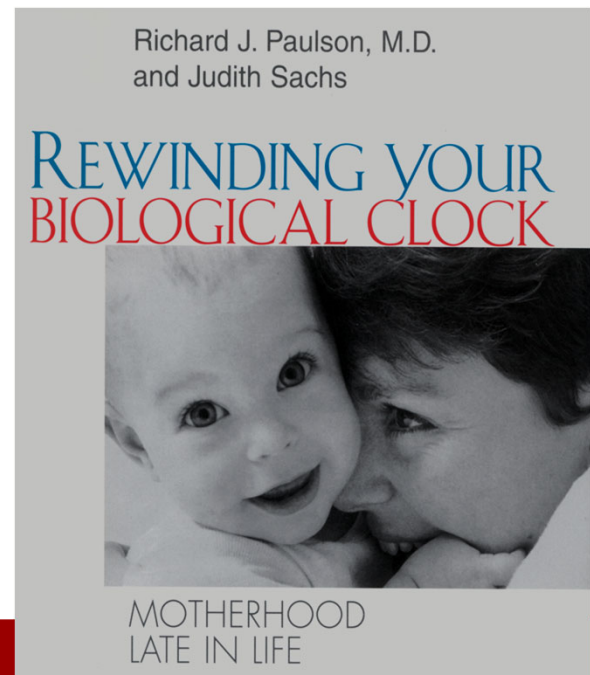
www.cdc.gov

40

The Biological Clock
and Fertility Diagnostic Testing

Oocyte Donation

- “Circumventing” the biological clock
- Pregnancy possible in anyone with a uterus
- Paved the way for surrogacy and fertility preservation



41

Fertility Awareness

Biological Clock:

- Real entity
- Age of Oocyte
 - Mitochondria
 - Aneuploidy
- Fertility preservation

42

The Biological Clock
and Fertility Diagnostic Testing

The Future

- Increased efficiency
- Singleton pregnancies
- Elimination of genetic disease
- Fertility preservation
- Artificial gametes from stem cell technology

43

References

- Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril*. 2015;103(3):e9–e17.
- Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility. *Fertil Steril*. 2017;107(1):15–282.
- Infertility workup for the women's health specialist. ACOG Committee Opinion No. 781. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2019;133:e377–84.
- Female age-related fertility decline. Committee Opinion No. 589. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and The Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril*. 2014;101(3):15–282.

44

The Biological Clock
and Fertility Diagnostic Testing