

Emerging Issues in Human Embryonic Stem Cell Research

November 7-8, 2006

Washington D.C.

Oocyte Procurement, Safety, and Use: Overview of the National Academies Workshop on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research

San Francisco, CA

September 27, 2006

Linda C. Giudice, MD, PhD, MSc

Chair, National Academies Committee on Assessing the Medical Risks of Human Oocyte
Donation for Stem Cell Research

Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Charge to the Committee

To assess the medical risks of human oocyte donation for human embryonic stem cell research.

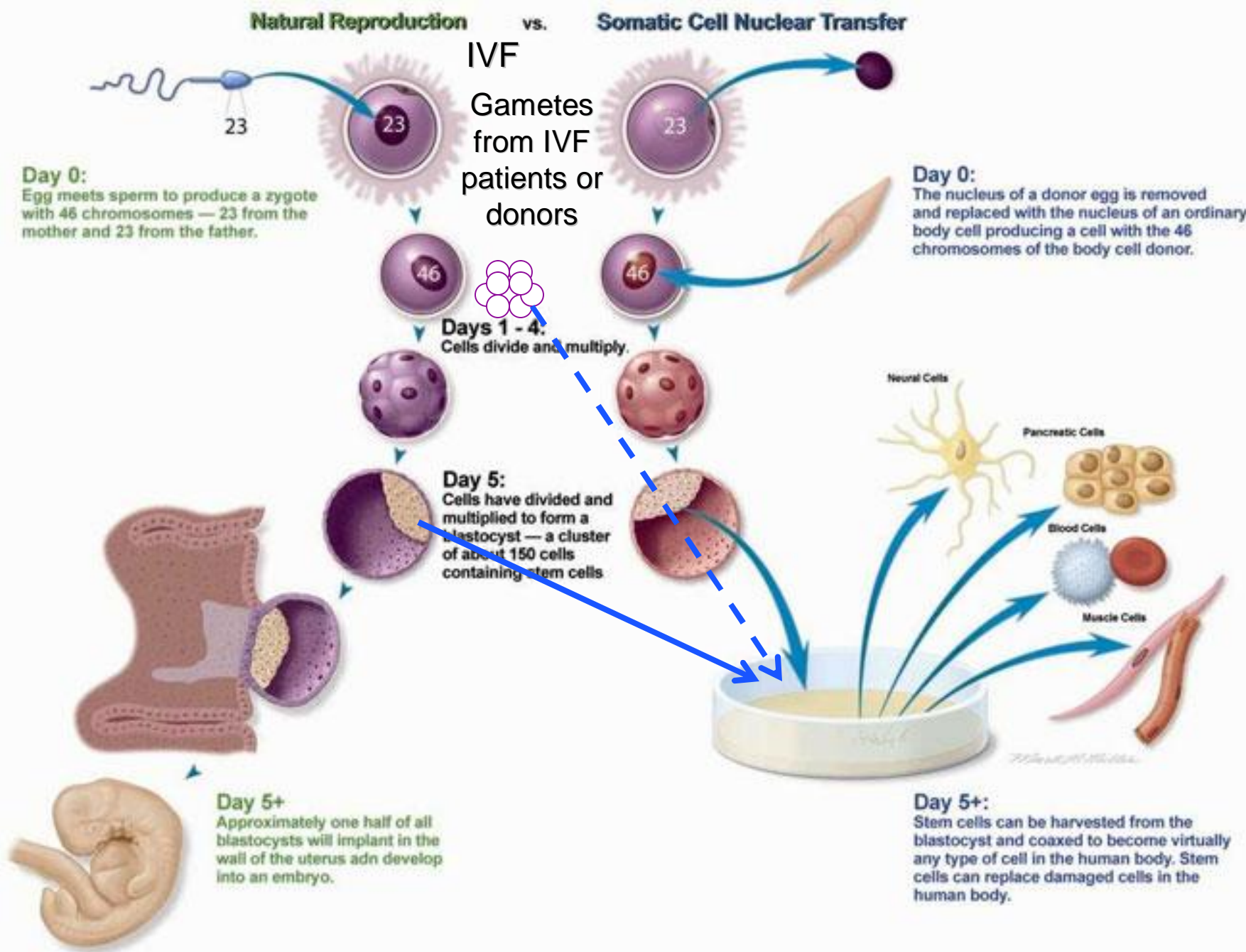
What we know.

What we do not know.

What we need to know.

Goals of Today....

- What is the process to procure human oocytes?
- What is the magnitude of the resource?
- What are the risks involved?
- How good are the data?
- What are some of the solutions?



Adapted from <http://www.kcchamber.com/>

ASSISTED REPRODUCTIVE TECHNOLOGIES

- *multiple therapies to achieve a pregnancy*
- *opportunity to participate in hESC and SCNT research*
- *the promise of cures for chronic diseases*

Participants:

patients
sperm donors
egg donors
surrogates
 genetic
 gestational

IVF-ET = in vitro fertilization/embryo transfer
Oocyte donation/IVF
PGD = pre-implantation genetic diagnosis
Embryo, gamete cryopreservation “banking”

Old Paradigm

some donation of embryos
and eggs for other individuals/
couples or research.

New paradigm:

couples/individuals undergoing
ART procedures solely to
donate gametes or embryos for
research

for family members
for \$
altruistically

ART Cycles in the U.S. - 2003

122,872 ART cycles

437 ART clinics in the US in 2003

399 programs reported

35,785 live births

48,756 babies

4,525 miscarriage, stillbirth or induced AB

91,032 cycles (74.3%) - fresh embryos, non-donor egg

17,517 cycles (14%) - frozen embryos, non-donor egg

9,845 cycles (8.0%) - fresh donor egg

4,578 cycles (3.4%) - frozen donor egg

11,349 cycles were discontinued before the egg retrieval
for poor oocyte production >> medical complications.

The Procurement Process

History, physical, consents, diagnostic testing



- history and physical exam
- extensive family history
- psychological screening

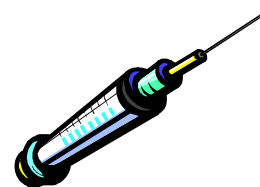
informed consent



procedures, medications
risks, benefits,
alternatives
disposition of
embryos and gametes



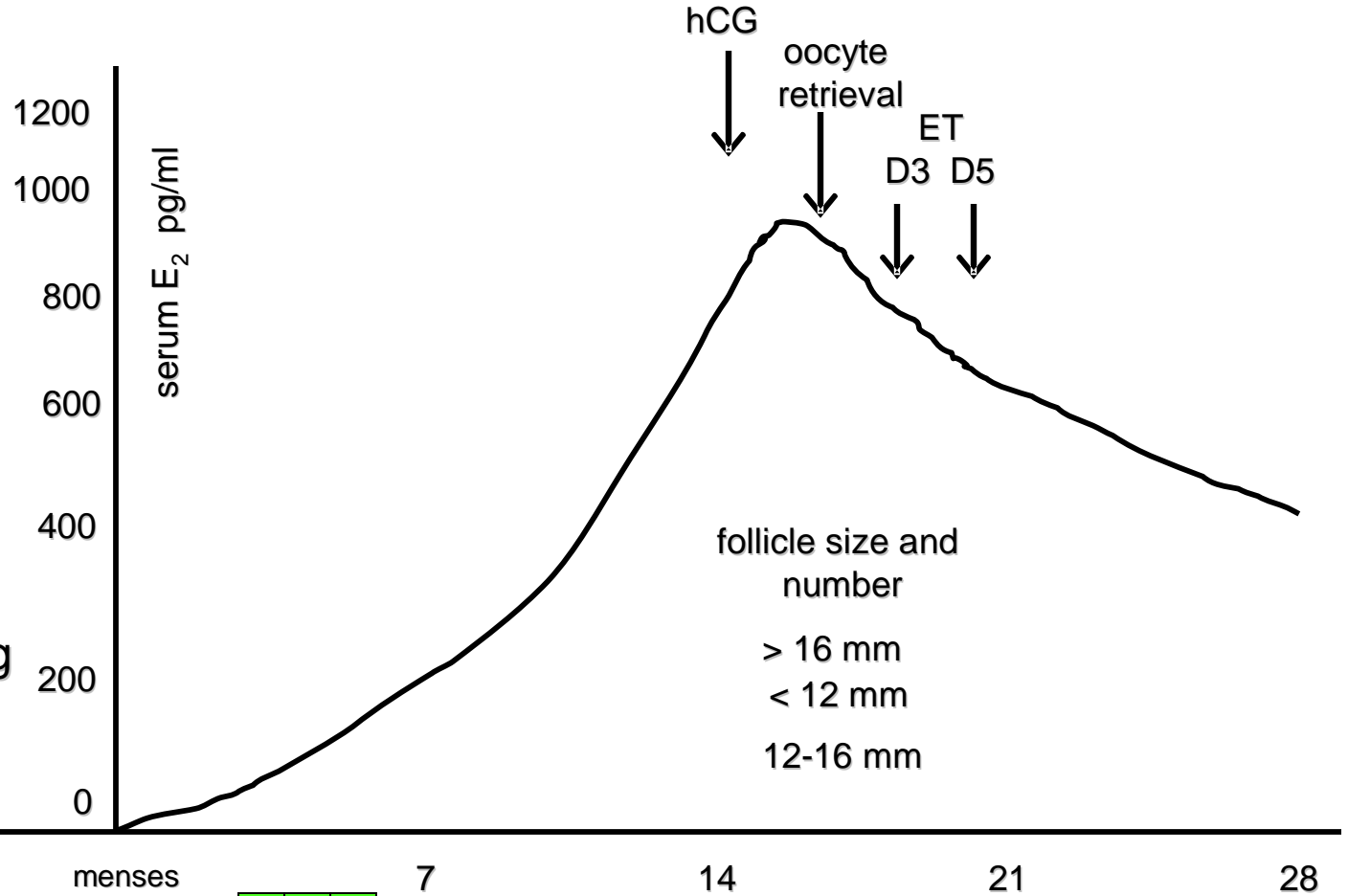
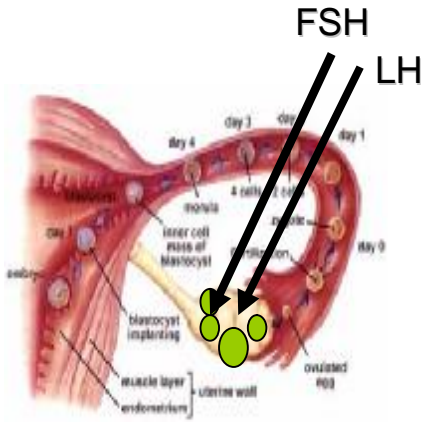
- female -
 - hormonal testing
 - anatomic testing
- male
 - semen analysis



- infectious disease testing (HIV, HTLV I, II, Hepatitis B,C, RPR)

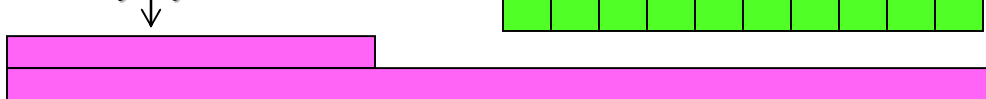
The Procurement Process

A Typical IVF Cycle



initial consult
testing
consenting
injection teaching

Daily or twice daily injections

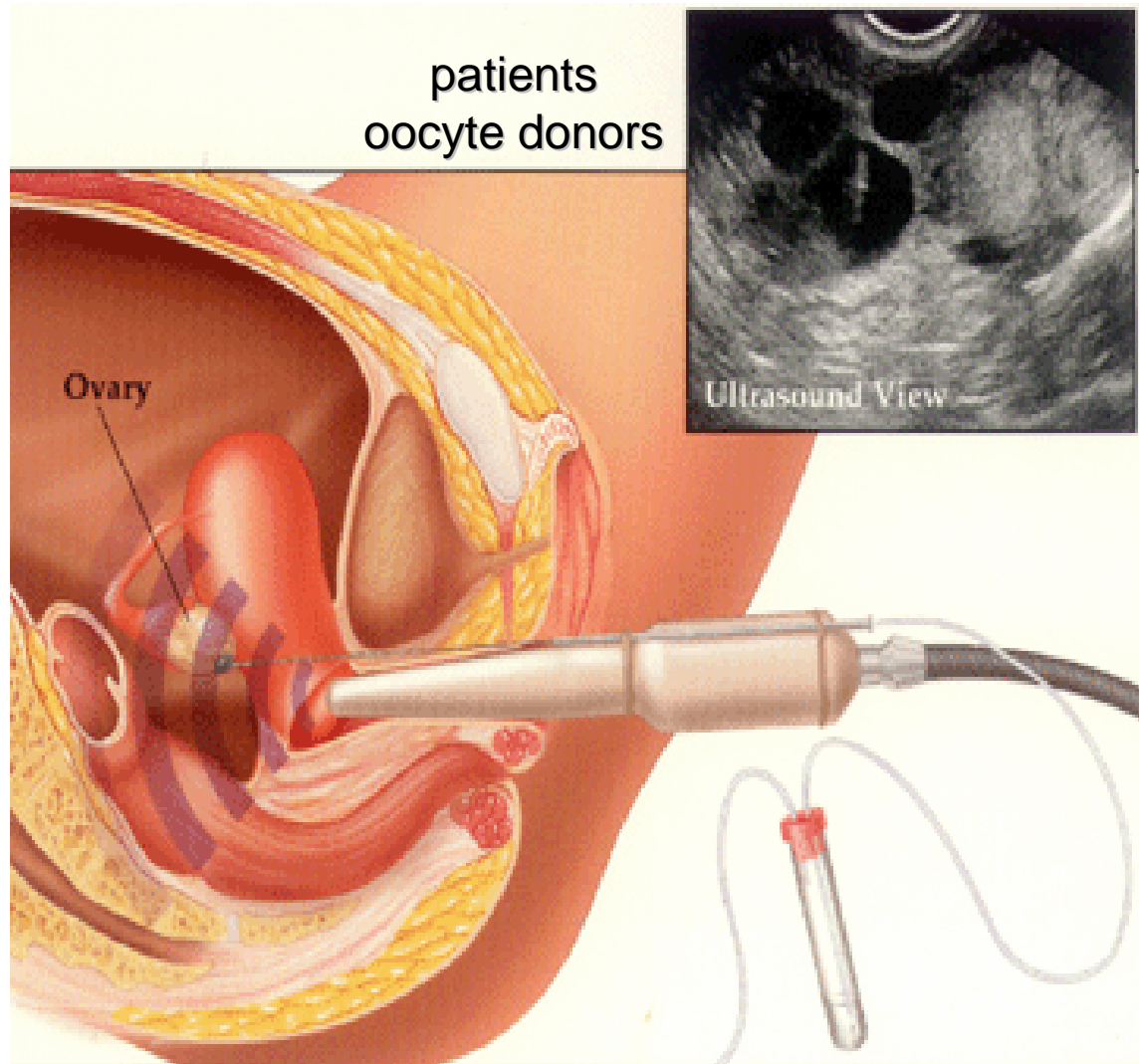


1 amp FSH (LH) daily or 2x/day

GnRH agonist (sc) daily

The Procurement Process

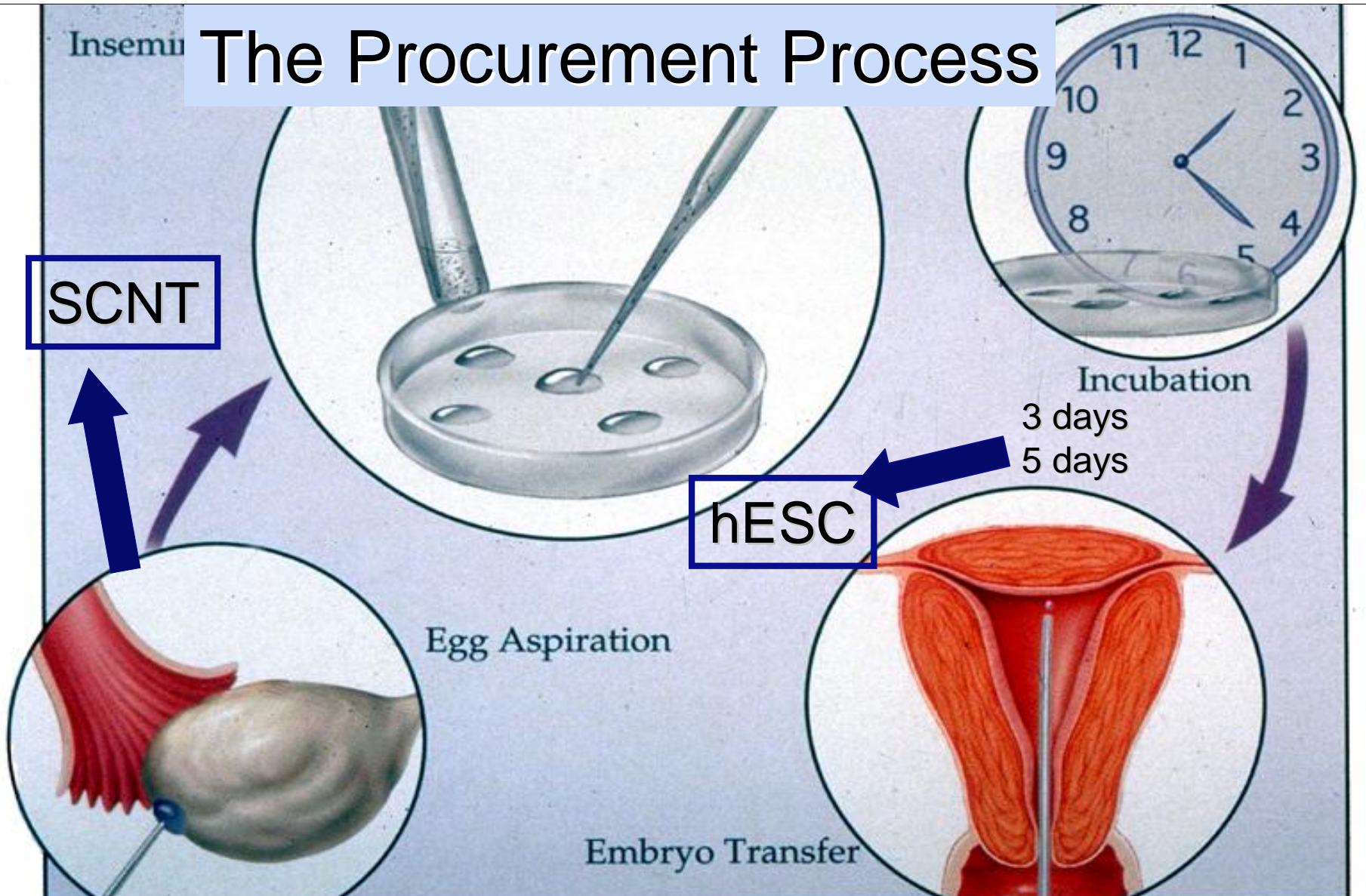
Oocyte retrieval



The procedure is performed under light anesthesia (primarily conscious sedation).

Insemin

The Procurement Process



SCNT

hESC

Incubation

3 days
5 days

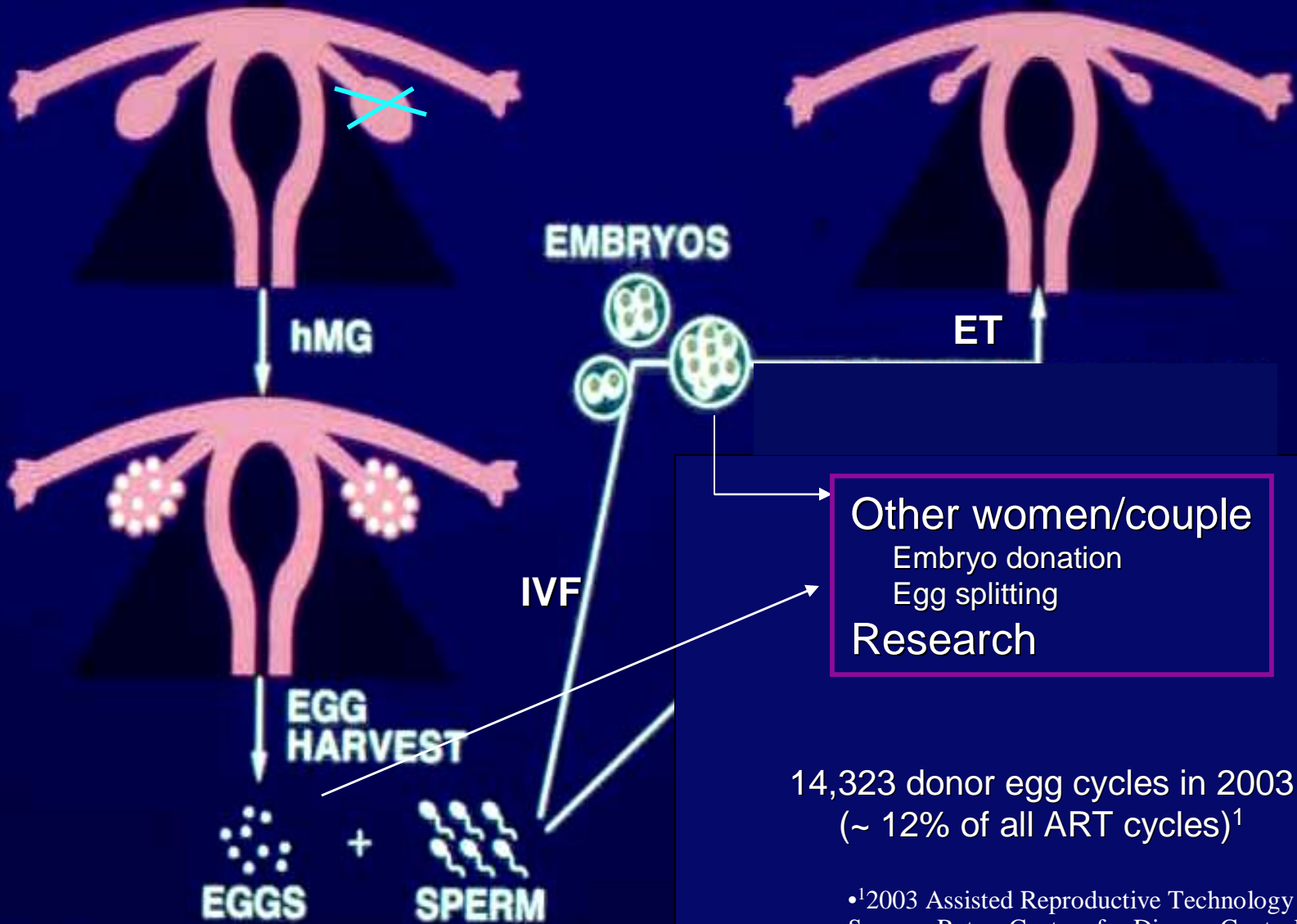
Egg Aspiration

Embryo Transfer

DONOR OOCYTE PROGRAM

DONOR

RECIPIENT



Other women/couple
Embryo donation
Egg splitting
Research

14,323 donor egg cycles in 2003
(~ 12% of all ART cycles)¹

¹2003 Assisted Reproductive Technology
Success Rates, Centers for Disease Control

What Are the Risks?

Acute Risks

- OHSS
- Surgical
- Anesthetic
- Psychological

Chronic Risks

- Breast, ovarian, endometrial cancer
- Future Fertility

Ovarian Hyperstimulation Syndrome (OHSS)

Marcelle Cedars, M.D.

- Exaggeration of a *desired* response
- Increased size of the ovaries
- Gastrointestinal symptoms
- Increased vascular permeability
 - accumulation of intra-abdominal fluid
 - intravascular volume depletion
 - hemoconcentration
 - activation of vasoconstrictor and anti-natiuretic factors

Ovarian Hyperstimulation Syndrome (OHSS)

Enlargement of the ovaries due to ovarian stimulation with gonadotropins and administration of hCG (Rizk and Aboulghar – 1999).

- **Minimum** - most women undergoing ovarian stimulation have some degree - enlarged ovaries, some lower abdominal discomfort.
- **Moderate**
 - discomfort, abdominal ascites
 - nausea/vomiting
 - normal hematologic profile
- **Severe** (100-200/100,000 (0.1-0.2%))
 - Grade A – outpatient treatment
 - dyspnea, nausea/vomiting, enlarged ovaries, marked ascites, normal biochemical profile
 - Grade B – hospital admission
 - severe, oliguria, hemoconcentration, elevated creatinine and abnormal liver function tests
 - Grade C - hospital admission
 - serious complications:
 - thromboembolic events ((0.7/1,000,000 - 2.4/10,000) - data include pregnant women who are at higher risk.
 - renal failure (1.4%)

Ovarian Hyperstimulation Syndrome (OHSS)

Additional Classification

Early OHSS

- 2-7 days after hCG
- more applicable to ovum donation population

Late OHSS

- 12-17 days after hCG
- occurs primarily in women who are pregnant - not the ovum donation population
- 4-12 fold higher prevalence than the early form

Surgical Risks

Ana Murphy, M.D.

- Damage to internal organs due to oocyte retrieval procedure (0.1%)
- Severe intra-abdominal bleeding (0.2 - 0.3%)
- Infection:
 - 1993 9/1000 (no aseptic technique)
 - 2000 0/5000
- Torsion (0.13%) - late complication

Surgical risks increase in women with previous abdominal surgery pelvic adhesions, and previous pelvic inflammatory disease (PID).

Anesthetic Risks

Lawrence Tsen, M.D.

- i.v. anesthesia/conscious sedation primarily
 - anesthetic risks increase with increasing ASA scores
 - are highest in:
 - men
 - co-morbidities*
 - elderly
 - obesity*
 - inpatient
 - emergency
- * possible in oocyte donors
- minor and major morbidities - increased risk with increased BMI
 - death - extremely rare ($1/300,000 < \text{car accident}$)

Psychological Risks

Susan Klock, Ph.D.

- mood swings
- anxiety
- regret
- commodity
- travel and pain
- periods of vulnerability:
 - screening
 - during donation
 - post-donation
- no data on donors for research

Cancer Risks

Roberta Ness, Ph.D.

Ovarian, breast, and endometrial cancer

- Ovarian cancer - infertility increases the risk of ovarian cancer; NOT ovulation induction medications.
- No evidence that fertility drugs increase breast cancer risk.
- Uterine (i.e., endometrial) cancer - cannot conclude.
- Effects over time still need to be determined.

Future Fertility

Nicholas Cataldo, M.D.

- No convincing evidence that adhesions and anti-ovarian antibodies are increased with ovulation induction.
- Evidence does not support depletion of the follicle pool (and “early menopause”) with ovulation induction.
- The data are not compelling regarding increased risk of ovulation induction and oocyte retrieval on compromised future fertility.

Minimizing Risks

- Subject selection/careful history.
- Identifying who is at risk: trans-abdominal ultrasound to assess antral follicle count, uterine fibroids, ovarian endometriomas, etc.
- Exclude women with a history of severe endometriosis, PID, abdominal surgery with pelvic adhesions, thrombophilias, ovarian tumors, irregular menstrual bleeding, polycystic ovary syndrome.
- Avoid pregnancy - double contraception for ovum donors.
- Include genetic and sexually transmitted infection screening with standard screens.

Limitations of the Studies

- Studies are limited by relatively small numbers of subjects (except ovarian cancer studies).
- Data that we do have are on patients and not healthy volunteers (oocyte donor pool) who may have decreased/increased risks.
- Data are primarily on Caucasian women, middle-to-upper socioeconomic status.
- Despite > 20 years of IVF, a database on health outcomes of women (and men) undergoing these procedures has not been established. Thus, we cannot draw information about long-term risks from the > 1 million IVF cycles over the past 20 years in the U.S. and Canada.

Challenges for the Future

- Quantification of risk.
- Inclusion/exclusion criteria/complex matrix.
- Long-term outcomes - health outcomes of fertility, cancers, psychological issues, demographics.
- Should donors be women who have previously had a child or are nulliparous women suitable to donate for research?
- What is the optimal age of donors? Reproductive age (18-45 yo)? Reproductive *donor* age (21-34 yo)?
- How many times to donate?
- How much stimulation? Target # of eggs retrieved? E_2 ?
- Are donors with a chronic disease a good resource for oocytes?

Alternative Sources of Oocytes

- Immature oocytes from IVF retrievals (about 20% of eggs obtained are immature). These would need in vitro maturation (ivm).
- Failed-to-fertilize oocytes from IVF procedures.
- Ovarian cortex or wedge or antral follicle puncture from women undergoing pelvic surgery. Would likely need ivm.
- Cadaveric sources - issues of consents from families/next of kin at time of duress; advanced directive; how viable will the oocytes be after other organs are harvested? Will need ivm.
- Oocytes from fetal ovaries (need ivm).
- Oocyte generation from germ cells derived from hESCs.

Special Thanks to.....

Committee Members

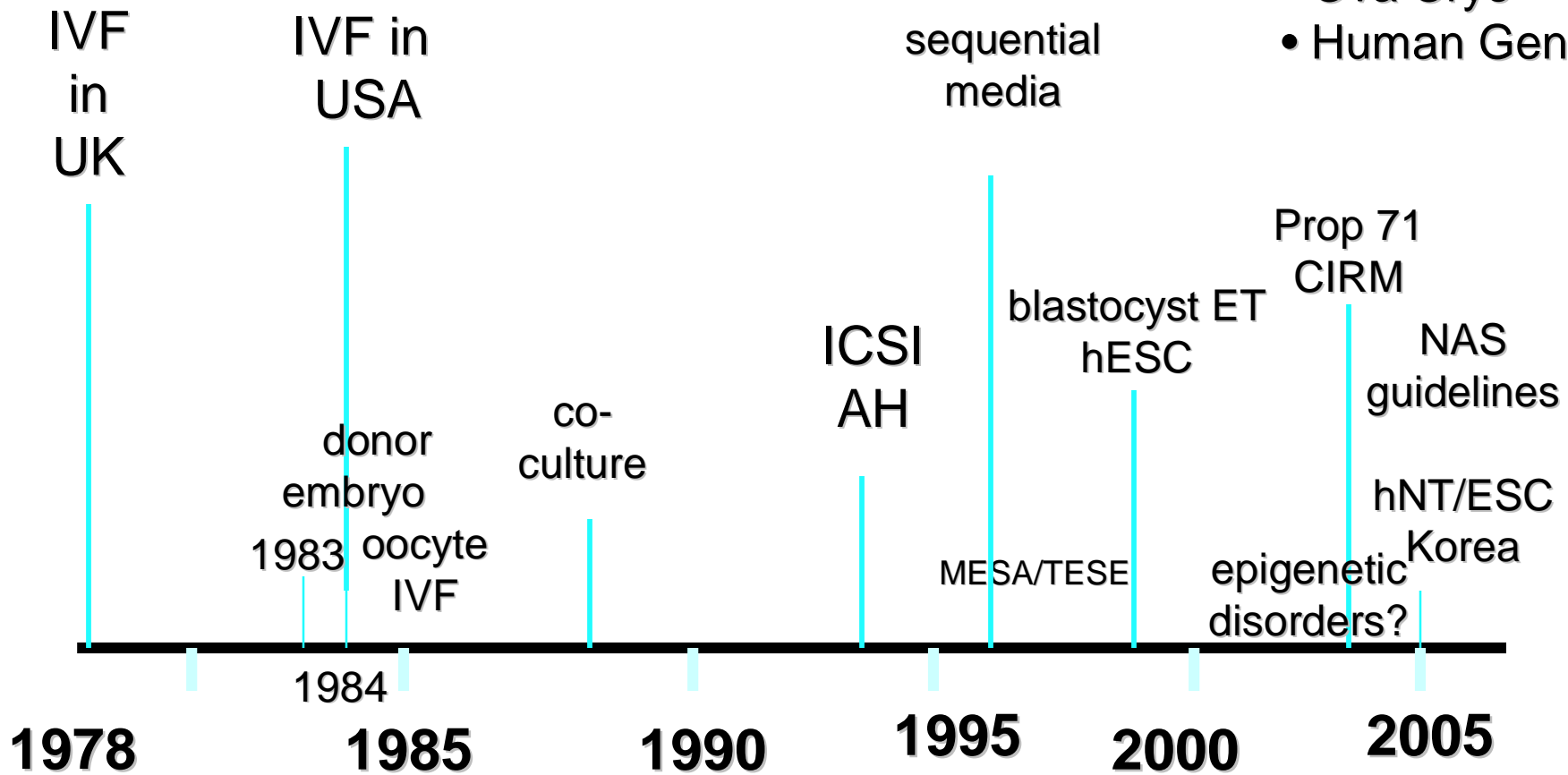
Marcelle Cedars
Ezra Davidson
Naihua Duan
Linda Giudice
Bernard Harlow
Susan Klock
Julia La Rosa
Catherine Racowsky
Zev Rosenwaks
Joe Leigh Simpson

NAS Staff

Andrew Pope
Frances Sharples
Eileen Santa
Amy Hass

ART Time Lines

- PGD
- Cytoplasmic transfer
- IVM
- Tissue Cryo
- Ova Cryo
- Human Genome



← Classical IVF →

• Gene R_x