REI 101:
REVIEW & REFRESHER COURSE

Advances in reproductive medicine & IVF nursing practice,
and strategies to improve reproductive potential & outcomes

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Table of Contents

	Page
Purpose & Learning Objectives	1
Educational Grantors	2
Faculty Affiliations	3
Financial Disclosure Information	4
Disclosure of Unlabeled/Investigational Uses	6
Co-chair & Faculty Biographies	7

Abstracts and Presentations

A History of IVF & Mainstreaming of Reproductive Technology ***Daniel B. Shapiro, MD***	12
Menstrual Cycle Characteristics and Reproductive Strategies ***Kaylen M. Silverberg, MD***	33
The Infertility Work-up ***Carol B. Lesser, MSN, NP-C***	54
Optimizing Stimulation Protocols ***Kaylen M. Silverberg, MD***	75
Genetics and ART ***Lauren J. Isley, MS, LCGC***	108
Navigating Gamete Donation in Clinical Practice ***Maria M. Jackson, RN, MA***	120
Confronting Compassion Fatigue & Burnout ***Carol B. Lesser, MSN, NP-C***	145

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Purpose

The REI Nursing 101: A Review & Refresher Course provides nurses new to practice, as well as those experienced nurses who may require reinforcement, with an overview of key concepts in reproductive endocrinology and infertility. This overview helps develop and strengthen a foundation that will be critical to clinical practice, and especially to advancing the sophisticated educational concepts on which the StartART (Scientific & Therapeutic Approaches to Assisted Reproductive Technology) Congress presentations, including late-breaking information, cutting-edge techniques, and best practices to improve ART outcomes.

Learning Objectives

After attending this activity, the attendee should be able to:

- Describe the history of IVF, identifying the milestones that are responsible for advances in the field
- Identify the complex of menstrual cycle characteristics, according to the menstruation, follicular, ovulation and the luteal phases
- Review considerations for optimizing stimulation protocols
- Evaluate the causes of female and male infertility
- Describe the infertility work-up
- Indicate available treatment options including OI, IVF/ET, and donor gametes
- Understand the side effects of infertility treatment
- Define the development and management of an early pregnancy
- Assess the psychological aspects of infertility
- Discuss basic genetic concepts
- Recognize common genetic tests in the ART setting
- Evaluate common genetics issues that may arise in the ART setting and when referrals are appropriate
- Define compassion fatigue and burnout in the field of fertility nursing and its signs and symptoms

Educational Grantors

This activity is supported by educational grants from:

EMD Serono, Inc., an affiliate of Merck KGaA, Darmstadt, Germany

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REI 101 Faculty

Lauren J. Isley, MS, LCGC
Genetic Counselor
Generate Life Sciences
Los Angeles, CA

Maria M. Jackson, RN, MA
Third Party Nurse Coordinator
Institute for Reproductive
Medicine and Science
Cooperman Barnabas Medical Center
Livingston, NJ

Carol B. Lesser, MSN, NP-C
Nurse Practitioner
Boston IVF
Waltham, MA

Daniel B. Shapiro, MD
Medical Director
Reproductive Biology Associates
Atlanta, GA

Kaylen M. Silverberg, MD
Medical Director, Managing Partner
Texas Fertility Center
Austin, TX

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The faculty, discussants, and Executive, Curriculum, and CNE Committees have disclosed the following:

Lauren J. Isley, MS, LCGC
Full-time employee of Generate Life Sciences, a company providing donor gamete services

Maria M. Jackson, RN, MA
Has no relationships to disclose

Carol B. Lesser, MSN, NP-C
Has no relationships to disclose

Daniel B. Shapiro, MD
Is a consultant to: Organon
Owner/Founder of MyEggbank-NA
Holds stock in Prelude Fertility

Kaylen M. Silverberg, MD
Has received research grants from Baxter
Has received consulting fees from Baxter, Seikagaku, Serono
Has served as a speaker for AbbVie, Myovant
Is a co-founder and member of board of directors: Ovation Fertility

Disclosure Information (cont.)

Executive Committee, CNE Committee, Curriculum Committee Members

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Shannon L. DeVita, MSN, RN, CNL, DNP
University of San Diego
San Diego, CA

Michele Nichols, PharmD
Pharmacy Consultant
Private Practice
Raritan, NJ

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The learners are advised that some sections in this continuing nursing education activity may contain references to devices and/or protocols or clinical strategies that are unlabeled, investigational, or unapproved by the FDA. Healthcare professionals should note that the use of information presented that is outside of current approved labeling is considered experimental and are advised to consult current prescribing information. All faculty members have agreed to disclose any unlabeled/unapproved uses of drugs or products referenced in their presentation.

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Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

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Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

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Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Daniel B. Shapiro, MD
Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Kaylen M. Silverberg, MD
Has agreed to disclose any unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies referenced in his presentation

Co-Chair Biography

Maria M. Jackson, RN, MA, is the Third Party Nurse Coordinator at the Institute for Reproductive Medicine and Science at Cooper Barnabas Medical Center in Livingston, New Jersey. Ms. Jackson received her nursing diploma from Bellevue School of Nursing in New York, and then completed a degree in psychology from Upsala College. Four years later, she matriculated a master's degree in counselor education from Kean University, where her thesis was entitled 'Gender Differences and the Perception of Infertility.'

Ms. Jackson began her nursing career in both education and research. She joined the American Cancer Society as a support group facilitator; however 4 years later, chose a shift in nursing focus, and initiated a fulfilling career in reproductive medicine. She segued from cancer support group facilitator to infertility support group facilitator as IVF/GIFT Egg Donation Nurse Coordinator at the Diamond Institute. She has served as a chair of the Nurses Professional Group (NPG) of the American Society for Reproductive Medicine and is an Emeritus Advisor to the NPG Board.

A recipient of several prestigious awards for academic achievement, lectures and abstracts, Ms. Jackson is perhaps most proud of the 2001 American Infertility Association Family Building Award. She is a sought-after presenter, and has authored papers, abstracts, book chapters and training manuals, all contributing to the education and inspiration of nurses in the fertility field.

Co-Chair Biography

Carol B. Lesser, MSN, NP-C, is a women's health nurse practitioner at Boston IVF in Brookline, Massachusetts. She earned her undergraduate degree in psychology from Cornell University in Ithaca, New York, and matriculated a nursing degree from the State University of New York at Stony Brook, followed by a Master's of Science degree in Ob/Gyn Clinical Nursing from Boston College.

Ms. Lesser has been providing infertility services to couples in the Boston area for more than 3 decades. She began her nursing career as an Ob/Gyn Nurse Practitioner at Harvard Community Health Plan in Cambridge, Massachusetts. However, for more than 20 years, she has been a nurse practitioner at Boston IVF, one of New England's leading infertility treatment centers. Ms. Lesser is NAACOG certified as an Ob/Gyn Nurse Practitioner and is NCC certified in reproductive endocrinology and infertility.

A former board member of Resolve of the Bay State and a member of the American Society for Reproductive Medicine (ASRM) and the New England Fertility Society, Ms. Lesser was the 2006 recipient of the Jean Purdy Visionary Award for Excellence in Reproductive Nursing and a recipient of Resolve's 2009 Hope Award for Service. She has delivered presentations on many topics in reproductive medicine, and speaks frequently to IVF nursing groups across the US. Ms. Lesser is the author of journal articles, ASRM abstracts, online newsletters, and content for continuing education activities. She is currently the editor for the ASRM nursing supplement to *Sexuality, Reproduction and Menopause*. Her areas of interest include ovarian decline in later reproductive years, patient friendly techniques for administering *in vitro* fertilization medications, polycystic ovarian syndrome, and ovarian hyperstimulation.

Faculty Biography

Lauren J. Isley, MS, CGC, is a Medical Science Liaison at Generate Life Sciences, the parent company of California Cryobank, Donor Egg Bank USA, and CBR. She received her Bachelor's Degree from the University of Missouri in Columbia, Missouri and received her Master's Degree in Genetic Counseling from Wayne State University in Detroit, Michigan.

Following graduation, she was hired by Genesis Genetics (now Cooper Genomics) in Detroit, Michigan as a genetic counselor and established her reputation for excellence there in helping individuals and couples to understand and make informed decisions based on preimplantation genetic screening and diagnosis. In 2013, Ms. Isley transitioned from Genesis Genetics to a position at California Cryobank, where she counseled gamete donors and recipients. She joined Counsyl (now Myriad Genetics) in 2016 as a clinical laboratory genetic counselor. In 2019, Lauren then rejoined California Cryobank, now part of the parent company Generate Life Sciences, in a different role as a Medical Science Liaison. Ms. Isley works directly with reproductive healthcare providers to provide education and support regarding gamete donor screening and newborn stem cell banking.

She is an active member of the American Society of Reproductive Medicine, where she is the current Chair of the Genetic Counselor Professional Group. Ms. Isley also sits on the Executive Board of the Society for Assisted Reproductive Technology. Ms. Isley is also the former chair of the National Society of Genetic Counselor's Special Interest Group on Assisted Reproductive Technologies/Infertility. Ms. Isley has authored several publications in *Fertility and Sterility* and other journals regarding genetic evaluation of gamete donors, management of inherited risks in donors and donor-conceived offspring, and genetic counseling scope of practice in ART. She also has served as faculty at several national conferences and has presented abstracts at reproductive medicine and genetics meetings.

Faculty Biography

Daniel B. Shapiro, MD, is the Medical Director and a partner in Reproductive Biology Associates (RBA) in Atlanta. A graduate of Bowdoin College in Brunswick, Maine, Dr. Shapiro received his medical degree from Emory University School of Medicine in Atlanta, following which he served as a Chief Resident in Obstetrics and Gynecology at Pennsylvania Hospital in Philadelphia. He then completed a fellowship in Reproductive Endocrinology and Infertility at the University of Connecticut School of Medicine in Farmington, and was appointed as junior faculty of the University of Connecticut affiliated hospitals.

Dr. Shapiro co-founded the nation's largest frozen egg bank, located at RBA. Since 2007, the egg bank completed ~7000 embryo transfers resulting in 3800 deliveries of 4200 babies.

He is board certified in Obstetrics and Gynecology, as well as Reproductive Endocrinology. He is a member of the American Society of Reproductive Medicine, the Society of Reproductive Endocrinologists, and the Thomas Bond Society.

Dr. Shapiro is well published in clinical reproductive endocrinology, including in estrogen bio-synthesis. He also is recognized for his research focus on GnRH antagonists and their applications in fertility medicine.

Faculty Biography

Kaylen M. Silverberg, MD, is a Founding Partner, Managing Partner, and Medical Director of the Texas Fertility Center. He is also Medical Director and a Co-Founder of Ovation Fertility, and serves on the Ovation Board of Directors. He was educated at Vanderbilt University in Nashville, Tennessee, where he majored in finance and molecular biology. He pursued his medical studies at Baylor College of Medicine in Houston, followed by an internship and residency at Vanderbilt University Medical Center, where he served as Chief Resident. Dr. Silverberg then completed a fellowship in reproductive endocrinology/infertility at the University of Texas Health Science Center in San Antonio. He is certified by the American Board of Obstetrics and Gynecology, as well as the Subspecialty Board of Reproductive Endocrinology/Infertility.

Dr. Silverberg is actively involved in clinical research in infertility. In addition, he is a member of several corporate boards and medical advisory boards. He also serves as a consultant, including to members of Congress on issues relating to healthcare economics and policy.

Dr. Silverberg has been honored with numerous recognitions, including for papers presented at infertility meetings. He was also honored by the American Fertility Association with their national 'Family Building Award'.

Active in several professional organizations and societies, Dr. Silverberg is a member of the American College of Obstetrics and Gynecology, the American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, and the American Association of Gynecologic Laparoscopists. In addition to his extensive contributions to the peer-reviewed literature, Dr. Silverberg also serves as a reviewer for several respected clinical journals, including *Obstetrics & Gynecology*, *Fertility & Sterility*, and *The Journal of Gynecologic Surgery*.

History of IVF

Daniel B. Shapiro, MD

Human understanding of the link between sexual intercourse and reproduction dates back to the beginning of written human history. Though the ancients did not understand any scientific details, they knew that physical union between male and female were needed to conceive and that human semen either contained something needed to make a baby or the whole baby in miniature.

Classical views of reproduction persisted from the time of ancient Athens to the 17th century. The age of enlightenment brought new technologies, notably microscopy, which made it possible to see sperm and in the early part of the 19th century, eggs. The early 20th century brought advancements in biochemistry and identification of hormones of the hypothalamic-pituitary-gonadal axis, which provided the road-map for ovarian stimulation.

All the advancements needed to make IVF possible were in place by the mid-1970s: adequate imaging, hormonal management, vaginal ultrasound, culture technique and a favorable public perception of fertility medicine. Once established as acceptable, the field of fertility medicine exploded in the 1980s and 1990s. IVF births now account for over 1% of American deliveries. IVF is also the gateway for application of genetic screening technologies now and will be the future access point for patients who require genetic therapies on their embryos to ensure healthy live births.

A History of IVF:
The Mainstreaming of Reproductive Technology

Daniel Shapiro, MD
RBA and MyEggBank-NA

Disclosure Information

- Consultant to Organon
- Owner/Founder-MyEggbank-NA
- Stockholder in Prelude Fertility
- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- Outline the key developments in fertility medicine
- Review reaction of western society to reproductive technologies
- Anticipate where IVF medicine will take human reproduction

Concern About Fertility is *OLD*

Sarah presents Hagar to Abraham
Van der Werff, 1699

Sarah, herself infertile, asks Hagar to be her surrogate to produce an heir for Abraham. Abraham accepts (Hagar hadn't much choice) and Ishmael is born.

Sarah got pregnant anyway…

Abraham, Sarah and the Angel
Jan Provost, 1590

An angel of G-D tells Sarah and Abraham that they will bear a son. He's 100 and she's 90. Did the Almighty broker an egg donation?!

Isaac (Yitzchak in Hebrew) means 'he will laugh'…because Abraham and Sarah thought it laughable that she could become pregnant!

Biblical Begetting

- Biological basis for reproduction was known to result from sexual intercourse…but what was actually happening was a bit of a mystery to the besot who begot

Early Concepts of Reproductive Science

- Hippocrates- around 400 BC (Greek)
  - Considered the possibility that both men and women contributed 'seed' and that it mixed in the uterus
  - All female medical conditions were the result of either suppressed menstruation or excessive bleeding
  - Diseases of the woman emanate from hysteron (uterus)…hence the word "hysterical"

Source: *Hippocrates' Woman: Reading the Female Body in Ancient Greece; King H, Routledge, London 1998.*

More Classical Medicine…

- Aristotle (Greek) about 300 BC
  - Believed it was all about the male
  - Woman was vessel to carry the seed planted by the male…which contained an entire tiny baby (homunculus)
  - Women were imperfect men, who were 'colder' than men and were unable to provide enough heat to warm blood into semen

Source: *Hippocrates' Woman: Reading the Female Body in Ancient Greece; King H, Routledge, London 1998.*

The classical view of reproductive physiology lasted about 2000 years…until enlightenment scientists (17th and 18th century) called the teachings of Hippocrates and Aristotle into question

Science Enters the Picture

- William Harvey
  - English, '*omne vivum ex ovo' (everything from the egg)-1651*
- Johannes van Horne/Jan Swammerdam
  - Dutch anatomists in 1650s
  - Recognized the importance of ovarian follicles in reproduction
- Regnier de Graaf
  - Dutch-1650s first described the development of ovarian follicles (now called Graffian follicles in his honor)
  - Postulated that the follicle contains the egg (still unseen though)

Important Dates in Early Reproductive Science

- 1677 Antonii van Leeuwenhoek (Dutch)
  - First to examine semen under a microscope
  - Confirmed the presence of sperm
- 1827 Karl Ernst von Baer (Estonian/Russian)
  - Observed mammalian eggs under the microscope
  - Described the principles of embryologic development
- 1876 Oscar Hertwig (German)
  - Confirmed that sperm/egg union caused fertilization
  - Documented meiosis and role of nucleus as a genetic vector

What Technologies Make *In-vitro* Fertilization Possible?

• Microscopy	1600s
• Incubation/Culture media	Ancient/1880s
• Anesthesia	1840s
• Endocrine regulation/Assessment	1920s to 1980s
• Gray Scale Ultrasound	1973

Reproductive Medicine Begins…

J. Marion Sims-1855; chief of staff at Woman's Hospital in NYC (now St Luke's-Roosevelt)

'Father of modern GYN'
performed 55 IUIs over 2 year period; only one pregnancy which ended in miscarriage

Investigational methods were highly unethical-he worked on surgical technique by operating on enslaved African women without anesthesia

First Donor Insemination

Dr Pancoast…tsk…tsk…tsk

Diagnosed azospermia in husband (from gonorrheal obstruction)

Asked best looking medical student in his charge to provide a sperm sample and then surreptitiously placed it in the wife while she was chloroformed and the other students watched

Husband was informed of the truth when the baby boy was born

Truth was published by a med student who was probably the donor…25 years later

The guilt-ridden medical student's name?

Addison Davis HARD, MD

(I did not make this up…)

He wrote a letter to the journal MEDICAL WORLD *in 1909 detailing the event and defending it as a means of 'race uplifting' whose net effect would be to improve human beings by using the best seed available.*

PBS Documentary , 'Test Tube Babies', 2003.

The Dark Ages

- 1873- Harvard Medical School Professor Edward Clarke, MD publishes 'Sex in Education' arguing that higher education in women contributes to their infertility
- 1932- Aldous Huxley publishes 'Brave New World' with a dystopian future filled with 'test tube babies'
- 1949- Pope Pius XII condemns attempts to fertilize human eggs in-vitro as sacrilege
- 1954-Illinois courts declare donor sperm babies to be legally illegitimate (later overturned)

More Resistance to Reproductive Science

- 1968 -Pope Paul VI issues *Humanae Vitae* which explicitly forbids Catholics from using the Pill and requires that procreation be the result of sexual intercourse
- 1971-Nobel Laureate James Watson (discoverer of DNA's double helix), speaking at the American Bioethics Conference condemns IVF research as it '*necessitates infanticide'.* Robert Edwards gets a standing ovation when he argues against Watson's position.
- 1972 - The AMA urges a moratorium on ***ALL*** IVF research

IVF Origins

- 1934 -Harvard researcher Gregory Pincus succeeds with IVF using rabbit eggs and suggests this would help infertile women. He is denied tenure at Harvard as a result.
- 1937 - John Rock, MD writes an anonymous editorial for NEJM suggesting IVF would be 'a boon for the barren woman with closed tubes!'

PBS Documentary 'Test Tube Babies', 2003.

First Human IVF

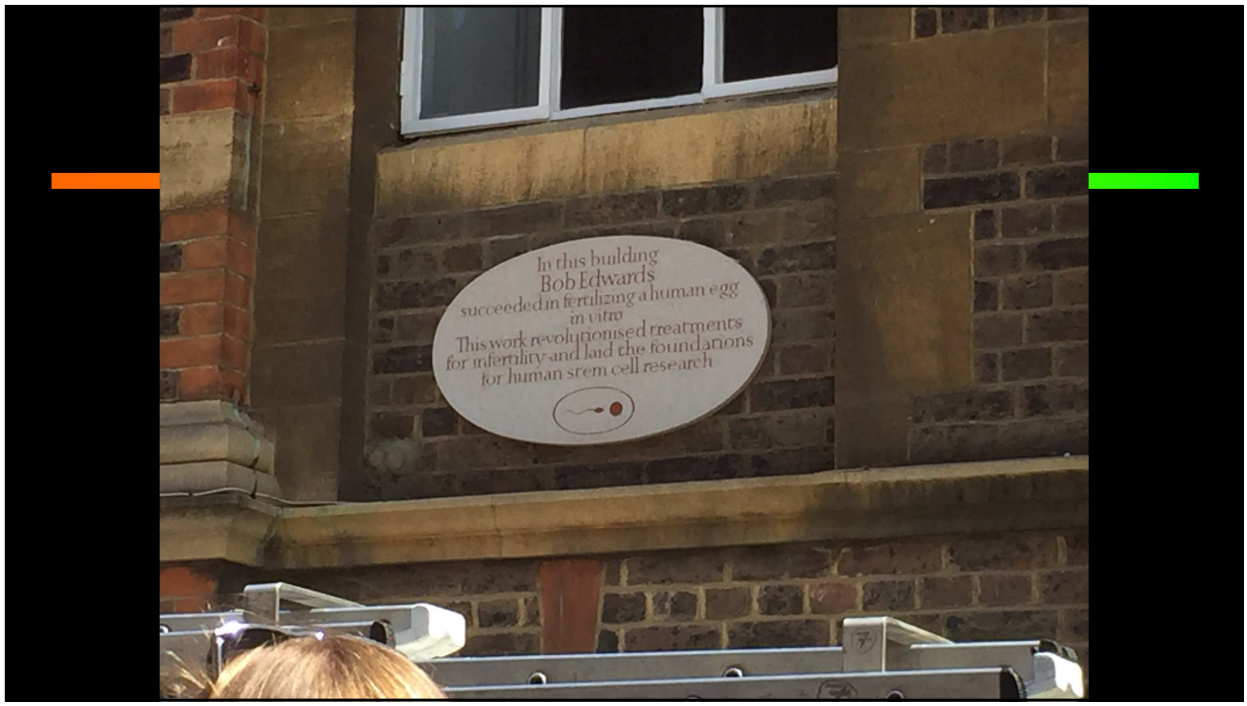
- 1938-John Rock hires Pincus' research assistant Miriam Menkin and begins collecting human ova with the intent to fertilize them in-vitro.
- 1944- Six years, 800 eggs and 138 attempts at insemination later, Rock and Menkin succeed in fertilizing 4 eggs in-vitro. No attempt was made to replace them into a patient.
- 1951- Landrum Shettles, MD duplicates Rock and Menkin's work at Columbia-Presbyterian in NYC

Sir Robert G. Edwards

British physiologist

Attempted fertilization *in-vitro* but was unsuccessful until partnering with Howard And Georgeanna Jones at Johns Hopkins in 1965

Returned to England and in 1968 collaborates with Dr. Patrick Steptoe, a British gynecologist interested in helping Edwards achieve a live birth from IVF



1973

"All the News That's Fit to Print"

The New York Times

LATE CITY EDITION

Weather: Partly sunny, mild today; fair tonight. Sunny, mild tomorrow. Temp. range: today 45-59; Monday 35-54. Full U.S. report on Page 76.

VOL. CXXII . No. 42,003 NEW YORK, TUESDAY, JANUARY 23, 1973 15 CENTS

LYNDON JOHNSON, 36TH PRESIDENT, IS DEAD; WAS ARCHITECT OF 'GREAT SOCIETY' PROGRAM

High Court Rules Abortions Legal the First 3 Months

State Bans Ruled Out Until Last 10 Weeks

National Guidelines Set by 7-to-2 Vote

By WARREN WEAVER Jr.

WASHINGTON, Jan. 22 — The Supreme Court overruled today all state laws that prohibit or restrict a woman's right to obtain an abortion during her first three months of pregnancy. The vote was 7 to 2.

In a historic resolution of s

Cardinals Shocked —Reaction Mixed

By LAWRENCE VAN GELDER

Reaction to the Supreme Court decision on abortion fragmented yesterday along predictable lines, as leaders of the Roman Catholic Church assailed the ruling while birth control and women's rights activists praised it.

In the forefront of Catholic reaction were Cardinal Cooke

3.7 MILLION CARS RECALLED BY G.M. TO CORRECT FLAW

Shields Will Be Installed to Prevent Entry of Gravel Into Steering System

By JERRY M. FLINT

DETROIT, Jan. 22 — The General Motors Corporation recalling today 3.7 million 1971 and 1972 cars, its full-size Chevrolet, Pontiac, Buick and

KISSINGER IN PARIS; CEREMONIAL SITE CHOSEN FOR TALKS

Use of Conference Center Indicates Both Sides View Truce Round as Vital

By FLORA LEWIS

PARIS, Jan. 22 — Henry A. Kissinger arrived here tonight and it was announced that his talks tomorrow with Le Duc Tho of North Vietnam would

NATION IS SHOCKED

Citizens Join Leaders in Voicing Sorrow and Paying Tribute

By ROBERT D. McFADDEN

Shock, sorrow and the sense of a historic leader lost were the mourning themes of public officials and private citizens across the nation last night as word spread that Lyndon Baines Johnson was dead.

From the White House and the halls of Congress where he had served, and in cities and

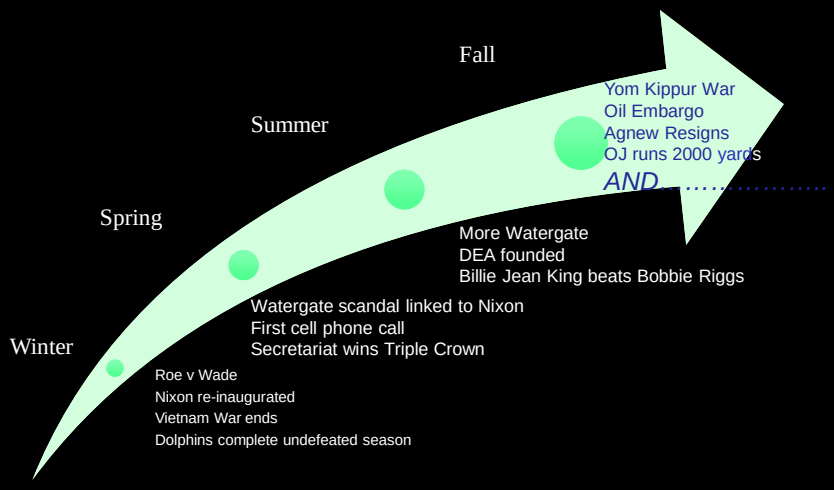
STRICKEN AT HOME

Apparent Heart Attack Comes as Country Mourns Truman

SAN ANTONIO, Tex., Jan. 22 —Lyndon Baines Johnson, 36th President of the United States, died today of an apparent heart attack suffered at his ranch in Johnson City, Tex.

The 64-year-old Mr. Johnson, whose history of heart illness began in 1955, was pronounced dead on arrival at 4:33 P.M. central time at San Antonio In-

1973 was a very busy year…



First Attempt with IVF in the US

Doris and John Del Zio; September 1973

Under the care of Drs Shettles and Sweeny at Columbia Presbyterian, eggs were collected by surgery after ovarian stimulation, mixed with sperm and placed in an incubator.

A colleague of Shettles notified superiors of the attempt at which point the petri dish was taken out of the incubator and brought to Hospital administration, effectively ending the Del Zio's chance of success.

The Del Zios sued and went to trial the same week Louise Brown was born in 1978. They won but were awarded only 50,000.

1975

- Steptoe and Edwards achieve an IVF pregnancy but it proves to be ectopic.
- US government task force concludes that all federal IVF and fetal tissue research grants must be approved by a National Ethics Advisory Board; but no board is formed until 1978.

1977

- Howard and Georgeanna Jones retire from Hopkins and resume their work in Norfolk at Eastern Virginia Medical School.
- Steptoe and Edwards meet Lesley Brown in England and suggest an attempt at IVF to bypass her blocked fallopian tubes.
- November 12, 1977- A single 8 cell embryo derived from a laparoscopic retrieval is implanted into Lesley Brown.

1978

July 25, 1978

Louise Brown born in Oldham, England.

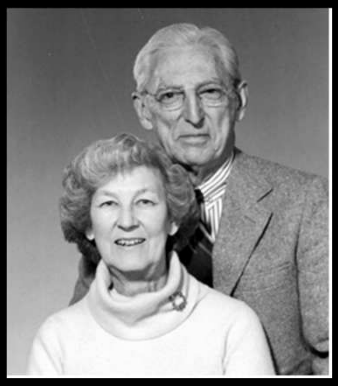
A media circus ensues…

Despite the world-wide fascination and delight with Louise Brown….

Her parents receive several bags of hate mail

Louise Brown: My Life as the World's First Test-Tube Baby
Bristol Books , 2015, London.

1981



Howard and Georgeanna Jones

Founders of the Jones Institute in Norfolk and responsible for the first IVF clinic in the US and the first IVF baby in the States (Elizabeth Carr)

Elizabeth Carr

At Birth, 1981

At ASRM Annual Meeting, Baltimore, 2015

1984
Orwellian IVF

- Agonist down-regulation comes into use causing a decline in IVF cycle cancellations and a concomitant rise in pregnancy rates
- First frozen embryo baby (Australia)
- First donor egg babies (Australia and US)

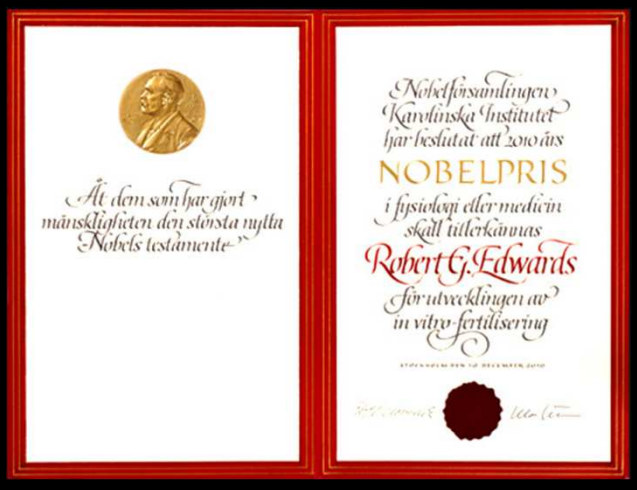
Turning Points in IVF Since 1984

- 1986-First Baby from Egg Freezing (Chen; Australia)
- 1987-Vaginal Probe Ultrasound Egg retrievals
- 1987-Partial Zona Dissection (precursor to ICSI) (Cohen et.al)
- 1989/90- PGD; Embryo biopsy for X-linked diseases (Handyside *et al.*)
- 1992- ICSI (Palermo *et al.*)
- 1994- PGS

More Turning Points

- 1997-first frozen donor egg baby (US)
- 1999-GnRH antagonists approved
- 2000-vitrification of blastocyst with delivery reported
- 2005-vitrification modification makes process easier
- 2007-First frozen donor egg bank based on vitrification
- 2010-clinical application of comparative genomic hybridization
- 2015-Marriage Equality in US

2010
Nobel Prize in Medicine
Robert Edwards



Social Objections to IVF

- Arise from traditional social norms and religious teaching
- Are more common in patriarchal societies
- Emanate from debate over abortion and the concept of 'ensoulment'
- Include arguments based on access to care and social class

>1% Of All US Babies are the Result of IVF

- Social and political barriers to IVF remain but are less profound than they were prior to Roe v Wade
  - Embryos can be discarded, tested, used for stem cell research etc.
  - Hospital boards embrace REI now but kept it on the down low in the past
- Criticisms continue however
  - Multiple birth rates
  - Cost of care
  - Potential for abuse/objectification

The Threat to Reproductive Medicine

- Roe struck down 5-4 (6-3 on the question of the Mississippi Ban)
  - First time in US history a constitutional right has been rescinded.
  - Three Trump appointees, two of whom were approved under politically charged circumstances, created the new majority
- Abortion fully illegal in 3 States with 3 states making it illegal from conception
  - IMPERILS FERTILITY MEDICINE!

  WHAT TO DO WITH ALL THE EMBRYOS IN STATES WITH BANS?
- Many states with abortion restrictions about to be enacted
  - Ghost laws, Trigger Laws, New restrictions coming in as many as 30 States

Food for Thought

- Study of human embryonic genetics requires access to an IVF lab
- The genetic revolution is underway and IVF medicine is at the forefront of genetic technology
- Gene splicing and gene therapy is already possible
- The overturning of ROE in June imperils all of the above?

Conclusions

- IVF is the result of
  - Intense human desire for children
  - Hundreds of years of scientific advancement
  - Ethical fluidity
- Social attitudes have lagged behind scientific advance but eventually catch up
- Organized religion has a hard time reconciling IVF with theology and is currently working to end REPRODUCTIVE FREEDOM.
- Genetic science will likely influence our thinking about ethics in reproduction over the next few decades

Menstrual Cycle Characteristics

Kaylen M. Silverberg, MD

The human menstrual cycle is the result of a very complex series of events that involve multiple organs, multiple hormones, and – above all else – appropriate, timely communication between them all. The cycle starts at a time when the endometrium is shedding due to a lack of hormonal support. In response to this dearth of (primarily) estradiol and progesterone, the hypothalamus sends a signal to the pituitary gland. The messenger for this signal is a small decapeptide called gonadotropin releasing hormone (GnRH). When released with the appropriate amplitude and the appropriate frequency, the pulses of GnRH stimulate cells in the anterior pituitary to secrete follicle stimulating hormone (FSH).

FSH travels through the circulatory system to the granulosa cells of the ovarian follicles, causing them to grow and secrete increasing amounts of estradiol (E_2). As the serum E_2 level rises, it exerts a negative feedback effect on the hypothalamus, causing it to diminish the amount of GnRH secretion. This decrease results in uni-follicular development, serving as a natural barrier to prevent multiple gestation. As the single (dominant) follicle continues to grow and develop in response to lower levels of GnRH, the follicle makes ever increasing amounts of E_2. This E_2 acts to increase endometrial development, causing a thickening of the uterine lining.

When the serum estradiol reaches a sustained, elevated level (that is different between women and even in different cycles within the same woman), the hypothalamus changes the way it secretes GnRH. Rather than the high frequency, low amplitude pulsations that lead to FSH secretion, the pulses change to high amplitude, low frequency – resulting in a surge of luteinizing hormone (LH). The LH surge causes 3 things to happen within the developing follicle: luteinization of the granulosa cells so that they begin to make progesterone (P_4) in addition to estradiol, a decrease in oocyte maturation inhibitor so that the egg can resume meiosis, and eventually, ovulation.

Ovulation is the process by which the egg extrudes from the follicle. Once this happens, and in response to the LH surge, the follicle becomes the P_4 secreting corpus luteum. P_4 causes a specific sequence of events to occur within the endometrium, preparing the lining for implantation. If implantation fails to occur, the corpus luteum dies within 12-14 days, resulting in a huge decrease in both E_2 and P_4 production. This precipitous fall in both E_2 and P_4 causes sloughing of the endometrium. The hypothalamus detects this hormonal fall and again starts to secrete GnRH – and the next menstrual cycle begins.

Many different etiologies can cause derangements in the menstrual cycle. The primary cause is a disruption in the signaling between the hypothalamus and the pituitary – leading to abnormal follicular development and the irregular production of E_2. Other common causes include:

- Polycystic ovarian syndrome
- Hypothyroidism
- Hyperprolactinemia
- Hyperandrogenism (via either testosterone or DHEA-S)
- Alterations in body weight

The evaluation of menstrual cycle irregularities should include:

- A transvaginal sonogram
- Lab work
    - Day 3 FSH, E2, AMH
    - TSH, Prolactin
    - If indicated: Testosterone, DHEA-S, 17 OH P4/17 OH Pregnenolone, 2-hour glucose tolerance test (GTT)

The treatment of menstrual cycle derangement depends on the individual patient's needs and goals. For those not seeking pregnancy, hormonal therapy – usually with an oral contraceptive pill – will usually provide regular, predictable menses, as well as protection against endometrial hyperplasia and cancer. For those women desiring pregnancy, primary therapy usually includes treatment with either clomiphene citrate or letrozole. The drugs effectively induce ovulation and therefore a resumption of regular menstrual cycles.

Menstrual Cycle Characteristics

Kaylen M. Silverberg, MD

Texas Fertility Center
Ovation Fertility
Austin, TX
San Antonio, TX

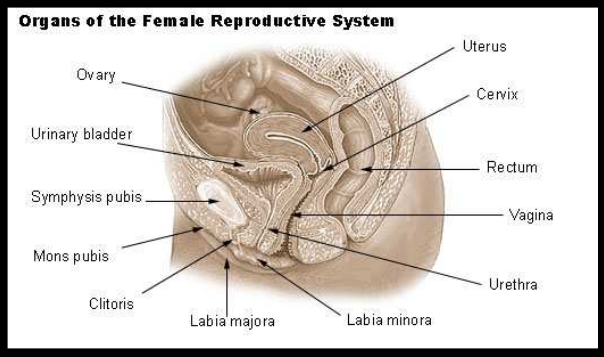
Disclosure Information

- Has received research grants from Baxter
- Has received consulting fees from Baxter, Seikagaku, Serono
- Has served as a speaker for AbbVie, Myovant
- Is a co-founder and member of board of directors: Ovation Fertility
- I will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- Identify the parts of the female reproductive system and the role these organs play in human reproduction
- Explain the process of folliculogenesis and the hormonal feedback mechanism that drives this process
- Discuss factors that can influence the menstrual cycle and strategies to improve reproductive efficiency

Female Anatomy



Uterus
- Contains and nourishes the fetus during pregnancy
- Contracts during labor resulting in childbirth
- The endometrium develops every month and sloughs if pregnancy does not occur

Fallopian tubes
- Transport the ovum from the ovary to the uterus and the sperm from the vagina
- Site of fertilization

Ovaries
- Storage and development of ova (eggs)
- Production and secretion of estrogen & progesterone

The Menstrual Cycle in 2 Minutes

Hormones of Ovulation

Hypothalamus

GnRH

(+)

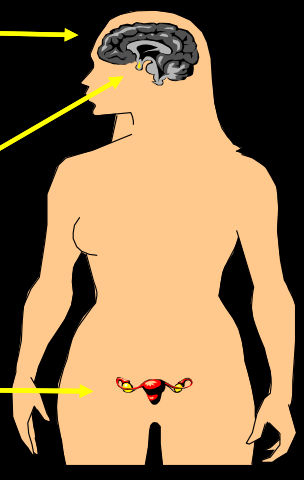
Pituitary Gland

LH / FSH

(+)

Ovary

Estrogen

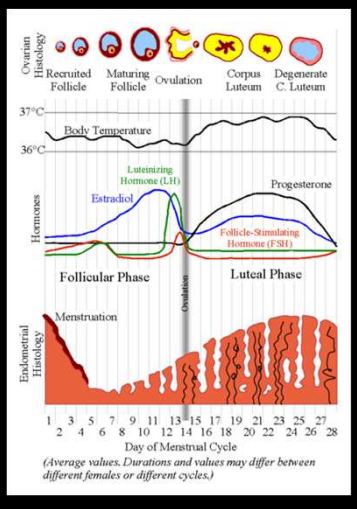


Menstrual Cycle vs. Menstrual Cycles

- There are actually 2 cycles occurring simultaneously:
  - Ovarian cycle
    - Follicular development, estradiol production, ovulation, progesterone production
  - Uterine cycle
    - Thickening in response to estradiol, stabilization and protein secretion in response to progesterone
    - Sloughing and regeneration if pregnancy fails to result
    - Maintenance of pregnancy
  - For successful pregnancy to result, these cycles must be SYNCHRONIZED

Menstrual Cycle

Phase	Cycle Days
Menstrual	1-4
Follicular (ovary) Proliferative (uterine)	5-13
Ovulation	~14
Luteal (ovary) Secretory (uterine)	15-28



Two Cell Two Gonadotropin Theory

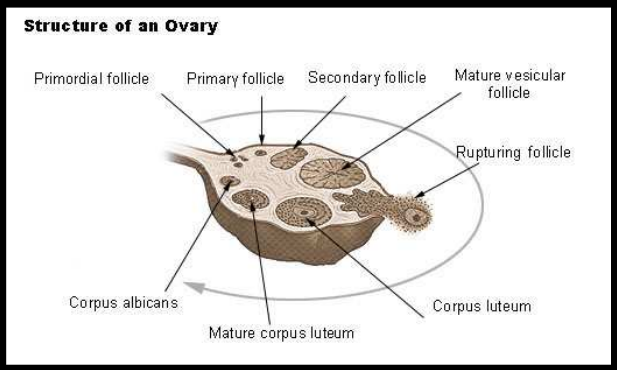
FSH

- Causes recruitment of the follicles
- Stimulates granulosa cells (the estrogen-secreting cells within the Graafian follicle)
- Responsible for selecting the dominant follicle

LH

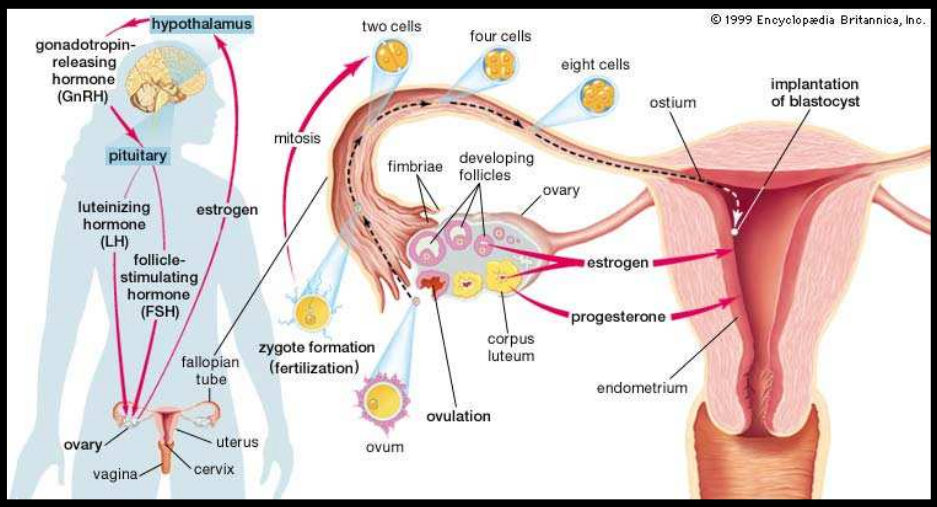
- Stimulates theca cells to produce androgens which are then aromatized to estrogens by granulosa cells under the influence of FSH stimulation

Folliculogenesis



- Follicle:
  Small fluid-filled sac in the ovary
  1. Primordial follicle
  2. Primary follicle
  3. Preantral follicle
  4. Antral follicle

Fertilization and Embryo Development



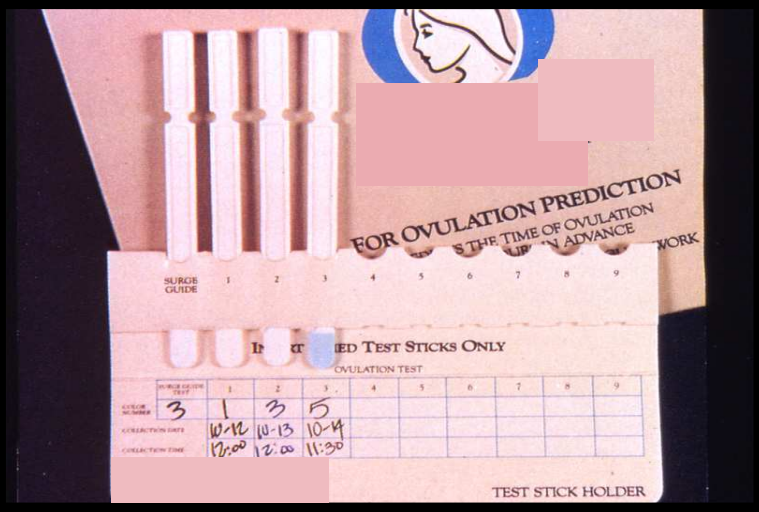
Ovulatory Dysfunction

- Incidence:40% of infertile women
- Signs/Symptoms
  - Oligomenorrhea/polymenorrhea
  - Dysfunctional uterine bleeding
  - Short luteal phase
- Causes:
  - PCOS
  - Thyroid disease
  - Pituitary tumor
  - Hyperandrogenism
  - Hyperprolactinemia
  - Extremes in wt loss/exercise
  - Obesity
  - Miscommunication between the hypothalamus and the pituitary

Documentation of Ovulation

- Basal body temperature (BBT)
- Luteal progesterone
- Ovulation prediction kit/LH detection
- Serial transvaginal sonography

Ovulation Prediction Kit



Ovulation Prediction Kit

Hormonal Issues and Ovulatory Dysfunction

- Ovulatory dysfunction: menstrual cycles are out of the normal range (25-35 days)
- Initial work-up should include measurements of TSH, prolactin, Day 3 FSH, E2, AMH, 2 hour GTT (if evidence of PCOS)
- If evidence of hyperandrogenism, add:
  - Testosterone, DHEAS, 17-OHP

Miscommunication Between the Hypothalamus and the Pituitary

- Responsible for most causes of ovulatory dysfunction
- Disordered GnRH signals from hypothalamus to pituitary leads to irregular FSH and LH production causing irregular follicle growth, suboptimal LH surges and anovulation

Polycystic Ovarian Syndrome

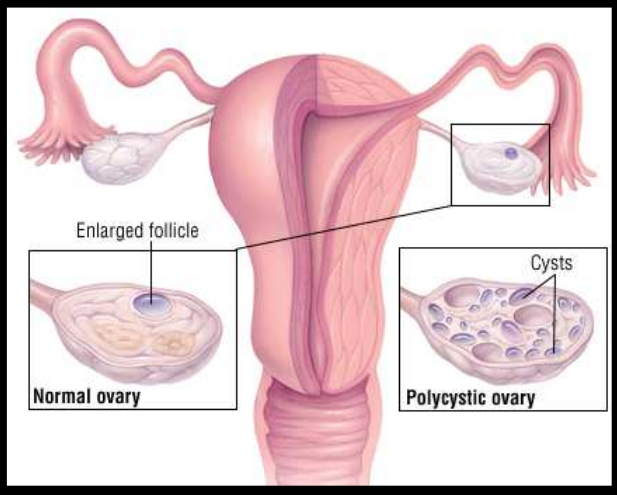
- Affects 5-20% of women. Most common endocrine disorder of reproductive age women.
- Diagnosis:
  - Chronic anovulation
  - Frequently accompanied by hyperandrogenism and/or hirsutism
  - Polycystic appearing ovaries on ultrasound
  - Presence of metabolic syndrome
- Lack of ovulation results in continuous exposure of the endometrium to estrogen causing excessive thickening of the uterine lining
- Metabolic syndrome is common in women with PCOS:
  - Abdominal obesity
  - Cholesterol abnormalities
  - Hypertension
  - Insulin resistance
  - Associated with an increased risk of insulin-dependent diabetes and heart disease

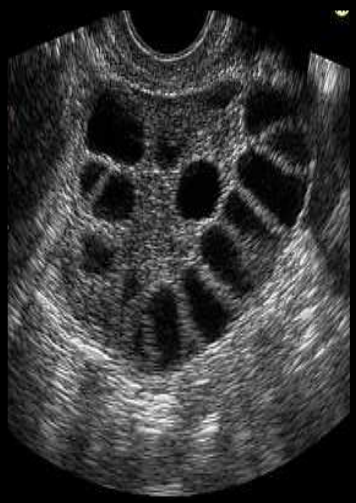
PCOS Diagnosis

- Rotterdam criteria (2 of the following)
  - Anovulation
  - Hyperandrogenism
  - Polycystic ovarian morphology
  - Metabolic syndrome (2 hour GTT)

Rotterdam ESHRE/ASRM Consensus workshop group. Fertil Steril.2004;81:19-25.

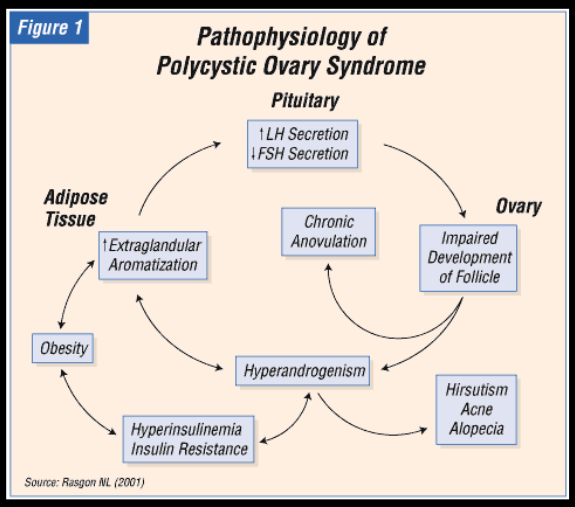
Polycystic Ovarian Syndrome (PCOS)





Treatment of PCOS

- Ovulation induction with clomiphene (CC)
  - If unsuccessful with CC, oral letrozole may be used
- Medications that increase the body's sensitivity to insulin, such as metformin if +metabolic syndrome
- Gonadotropins can be used when CC and/or letrozole do not result in ovulation or pregnancy



Hypothyroidism

- Diagnosis: TSH level
- Both hypo and hyperthyroidism can interfere with ovulation
- Causes: Hashimoto's (autoimmune) thyroiditis, iodine deficiency
- Frequently hereditary
- Cause of weight gain – but NOT all weight gain…
- Treatment: Thyroxine

Hyperprolactinemia

- Prolactin: hormone secreted by anterior pituitary
- Responsible for inducing lactation
- Most common cause is pituitary adenoma
  - Micro
  - Macro
  - MRI to distinguish
  - Prolactin level/2x100% = likelihood of tumor
  - Other causes: Chest wall trauma, hypothyroidism, shingles, Cushing's syndrome
- Treatment is medical – dopamine agonists

Transvaginal Ultrasound

- Basic evaluation of ovaries, uterus, and maybe even the tubes
- AFC, ovarian size/volume, masses/cysts
- Fibroids/polyps/developmental abnormalities
- Hydrosalpinges

Hyperandrogenism

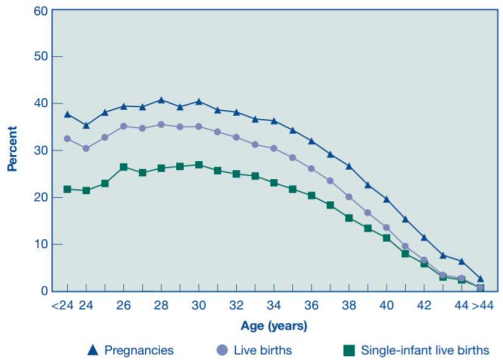
- DHEAS- Adrenal
- Testosterone – Ovary
- Congenital Adrenal Hyperplasia
  - Due to defect in cortisol pathway leading to excessive androgen secretion

Other Causes of Ovulatory Dysfunction: Age: Effect on Fertility

- Women are most fertile in their 20s
- Fertility gradually declines in the 30s, particularly after age 35
- Age related loss of fertility results from the gradual decline in quality and quantity of eggs

Pregnancy Rates by Patient Age

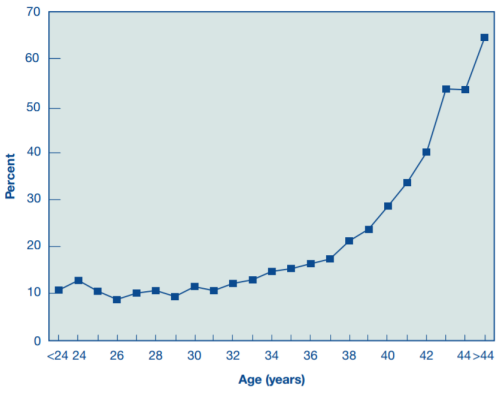
Figure 15
Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Pregnancies, Live Births, and Single-Infant Live Births, by Age of Woman,* 2015



* For consistency, all percentages are based on cycles started.

Miscarriage and Age

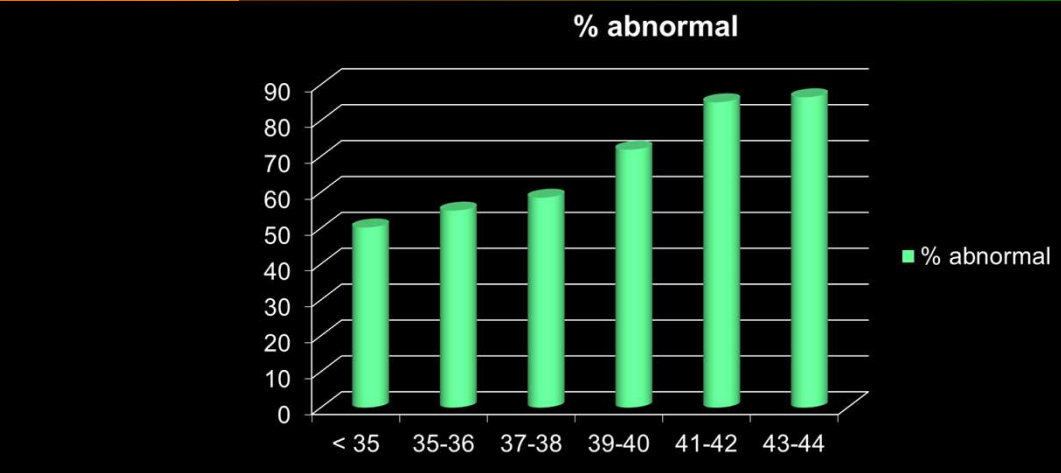
Figure 17
Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Miscarriage, by Age of Woman, 2015



Egg Quality

- Pregnancy rates decline/miscarriage rates increase with advancing maternal age
- Frequency of genetic abnormalities (aneuploidy) increases with advancing maternal age
- As quality declines, spindle apparatus is more prone to breakage, leading to aneuploid embryos
- Most aneuploid embryos fail to implant or miscarry

Incidence of Aneuploidy Increases with Maternal Age

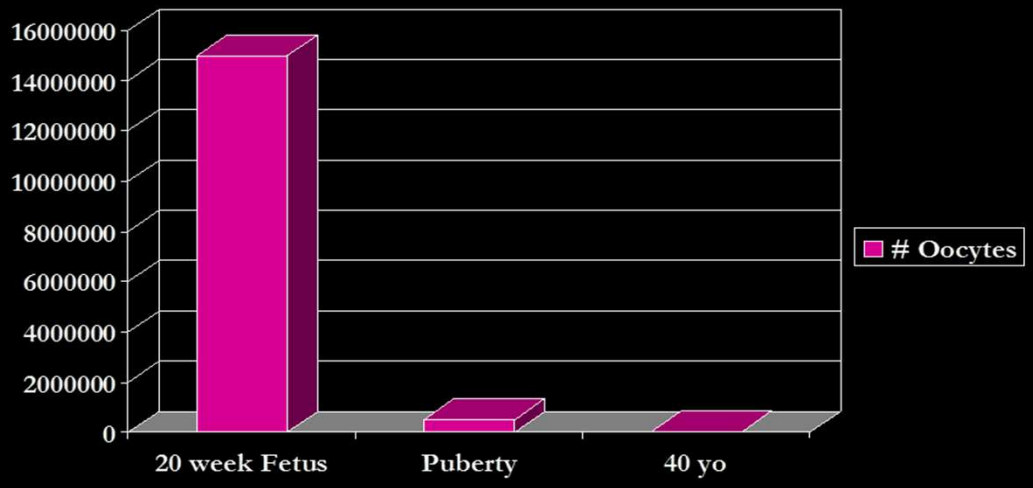


Courtesy, Genesis Genetics – n=3518 embryos tested by aCGH

Egg Quantity

- Diminished ovarian reserve (DOR): decreasing number of egg-containing follicles
- DOR is usually age related
  - Natural loss of eggs (atresia)
- High levels of FSH or estrogen/low levels of AMH indicate low ovarian reserve
- Low antral follicle count (AFC)

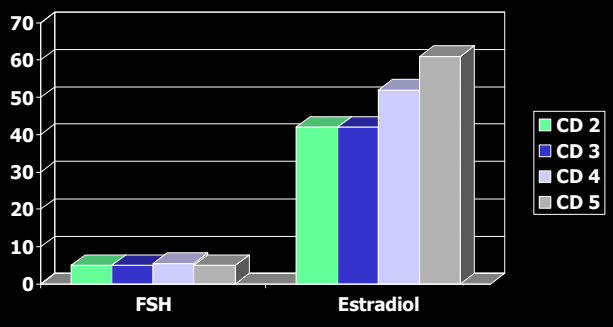
Oocyte Attrition



Ovarian Reserve Tests
CD 3 FSH, Estradiol, AMH

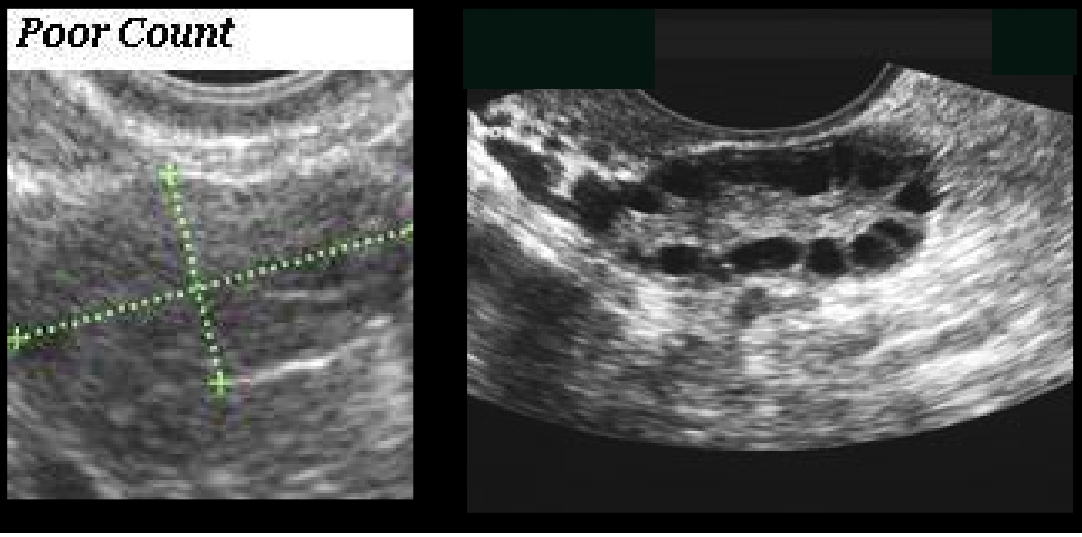
- Normal
  - FSH <15, preferably <12
  - Estradiol 20-50
  - AMH >0.7, preferably >1.0
- FSH levels increase with decreasing reserve
  - The higher the level, the lower the reserve
  - Levels > 18 mIU/mL suggests a very low chance of pregnancy with IVF
- AMH levels decrease with decreasing reserve
  - Difficult assay to perform so need to be familiar with the lab you use

Basal FSH & E2 Variability



Hansen et al *Hum Reprod* 1996;11:486.

Antral Follicle Count



Smoking Decreases IVF Success

- Increased medication requirements
- Lower peak estradiol levels
- Fewer eggs retrieved
- More cancelled cycles
- Lower implantation rates
- Increased risk of failed fertilization
- Twice the number of cycles to achieve pregnancy

Pfeifer S, Fritz M, Goldberg J, et al; *Fertil Steril*. 2012;98(6):1400-1406.

Body Weight: Outcome

	Normal	Overweight	Obese	Obese	Morbidly Obese
BMI	18.5-24.9	25-29.9	30-34.9	35-39.5	>40
Clin Preg	1.00	0.91	0.67	0.56	0.50
Spon Ab	1.00	0.63	0.97	0.75	1.44
Live Birth	1.00	1.06	0.23	0.66	0.51

1721 women, 1st cycle of IVF.
Shah DK, et. al. *Obstet Gynecol* 118:63-70, 2011.

Conclusions

- Irregular menstrual bleeding is usually caused by ovulatory dysfunction
- Cause is usually easy to determine
- Workup:
  - Transvaginal sonogram (AFC, organ measurements)
  - Day 3 FSH, E2, AMH, TSH, Prl
  - IF indicated:
    - 2 hr GTT
    - DS, T, 17OH P4/pregnenolone
    - Pituitary MRI

The Infertility Work-up

Carol B. Lesser, MSN, NP-C

Reproductive endocrinology infertility (REI) nurses working in centers and practices that provide assisted reproductive technology require an understanding of the infertility work-up for their female, male and transgender patients. The current REI nursing role focuses on patient education and patient preparation for testing and treatments, so understanding the foundations of the infertility work-up is imperative. Competency in this arena can serve to optimize patient support throughout the fertility journey.

The content of this presentation reviews the tests involved in the female, male, and transgender work-up with an emphasis on ovarian reserve, ovulatory dysfunction, uterine cavity and fallopian tube assessment, as well as the semen analysis. Adjunct tests that screen for genetic disease, infectious diseases, as well as other risk factors that could affect achieving a healthy pregnancy are reviewed.

The intent of this presentation is to provide sufficient information to REI nurses so that they are able and confident to guide their patients through the process of initial testing, interpretation of the results, and implications of the findings. The content aims to help REI nurses better function in their roles while contributing to increased proficiency and the quality of care delivered.

The Infertility Work-up

Carol Lesser, MSN, NP-C

Boston IVF
Waltham, MA

Disclosure Information

- Has no relationships to disclose
- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- At the conclusion of this presentation participants should be able to:
  - Explain the key tests in the female and male infertility evaluation
  - Prepare patients for their initial testing
  - Gain competency in interpreting test results for patients

Female Infertility Work-up and Testing

Starts with a thorough history and exam

Patient History

- Age/length of time trying to conceive
- Gynecologic
  - Menstrual history
  - Surgical history
- Obstetrical history
- Medical history including medications, BMI
- Family history
- Lifestyle: diet, smoking, ETOH

Infertility Evaluation

- Ovulation/ovarian reserve
- Uterus
- Fallopian tubes
- Sperm
- Preconception testing

Hormone Evaluation

- “Day 3” estradiol, FSH, AMH
- TSH, PRL, LH
- Antral follicle count (AFC, BAF)
- Androgens when indicated
- POF patient: Fragile X, karyotype

Ovarian Reserve Testing

- “Day 3” Estradiol, FSH
- Anti-Müllerian hormone level (AMH)
- Antral Follicle Count (AFC)

Day 3 Levels

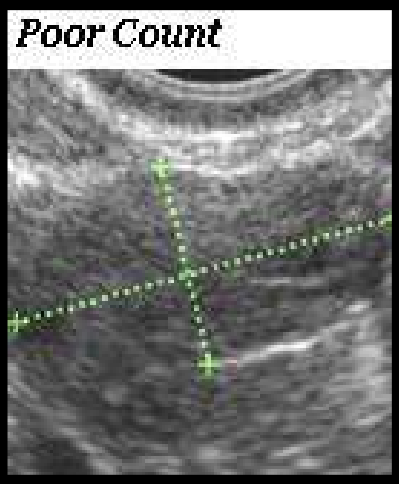
February 2022

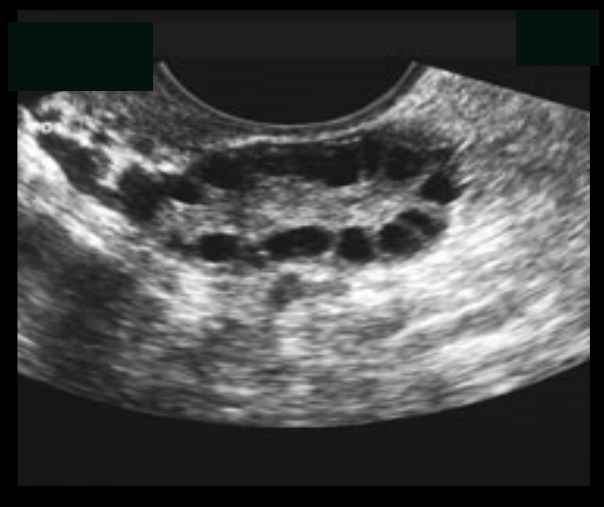
- E2 407
- FSH 6.0

March 2022

- E2 25
- FSH 35.9

Antral Follicle Count





Ovulation Assessment

- Menstrual history
- LH, Progesterone
- TVUS may be indicated

Other Testing

- Infectious disease screening
- Blood type and RH
- CBC, Rubella, VZV
- Genetic carrier screening
- Gyn and Pap up-to-date

Patient Exam

- BMI
- Vital signs
- Thyroid
- Androgen excess
- General exam
- Pelvic exam

Uterine Cavity Evaluation

- Hysterosalpingogram (HSG)
- HyCoSy (FemVue)
- Saline infusion sonogram SIS or SHG
- 3D ultrasound
- Office hysteroscopy
- Diagnostic or operative hysteroscopy
- Pelvic MRI

Hysterosalpingogram (HSG)

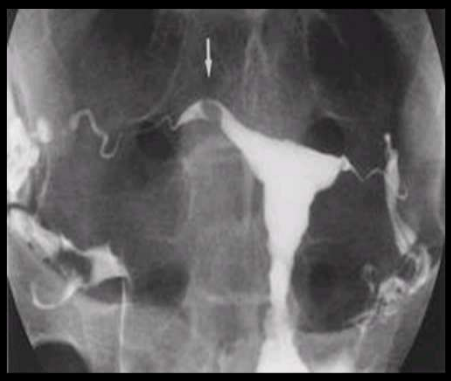
- Assess uterine cavity for shape and filling defects
- Check for tubal patency

Hysterosalpingogram (HSG)

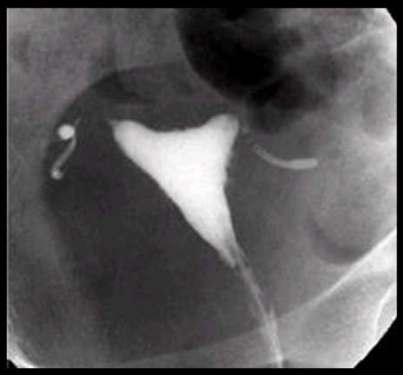
- Performed in the follicular phase
- Absolute contraindications: pregnancy, pelvic infection, allergy to iodine
  - Pregnancy test should be done prior to x-ray
- Risk of infection following HSG in those patients with confirmed distally blocked tubes
- Prophylactic antibiotics should be given to women with known tubal disease (doxycycline 100 mg po BID x 5 days or) prior to or day of test. D/C if normal. Azithromycin 1 gm ok.

Assessing Tubal Patency

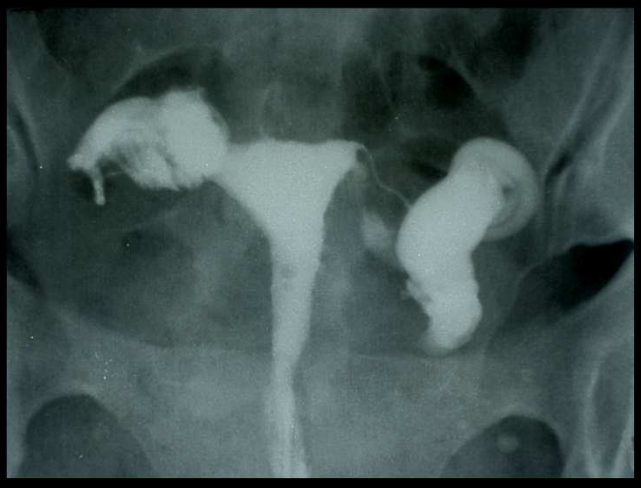
Normal HSG



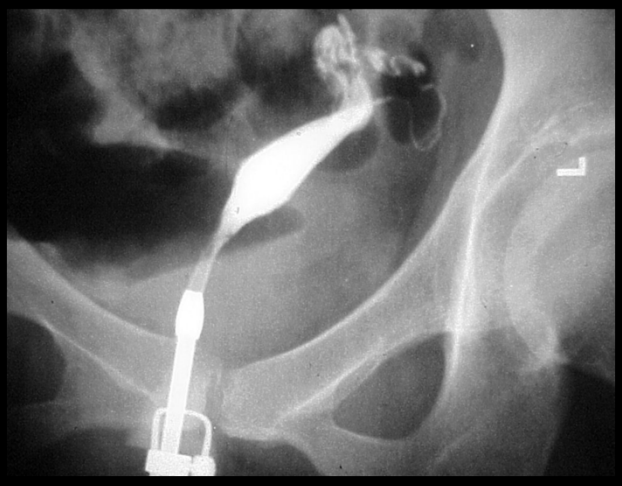
Tubal Obstruction



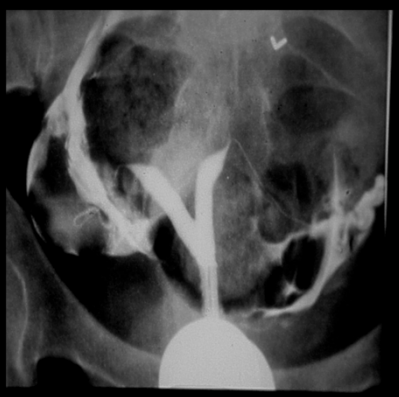
HSG: What is the Diagnosis?

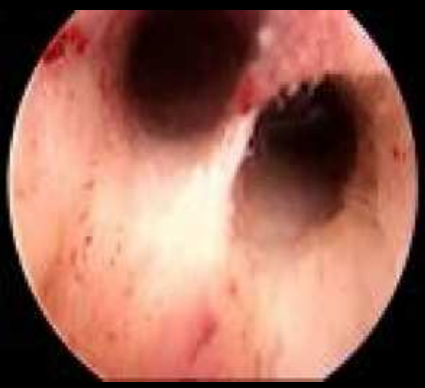


HSG: Unicornuate Uterus



HSG: Septate Uterus





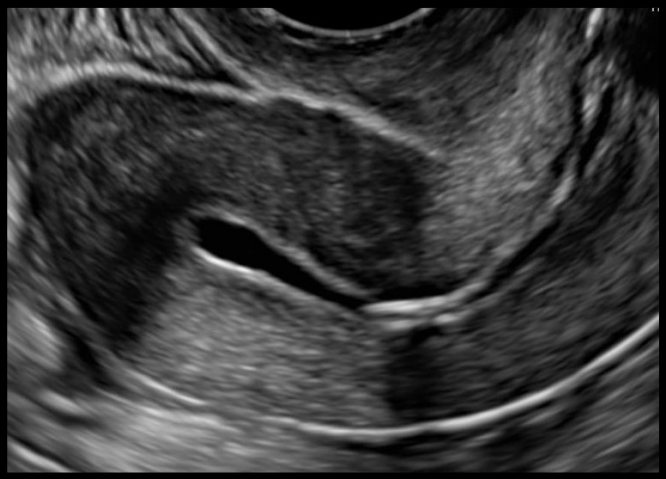
Tubal Patency Evaluation

- HSG
- HyCoSy
- Laparoscopy with chromotubation

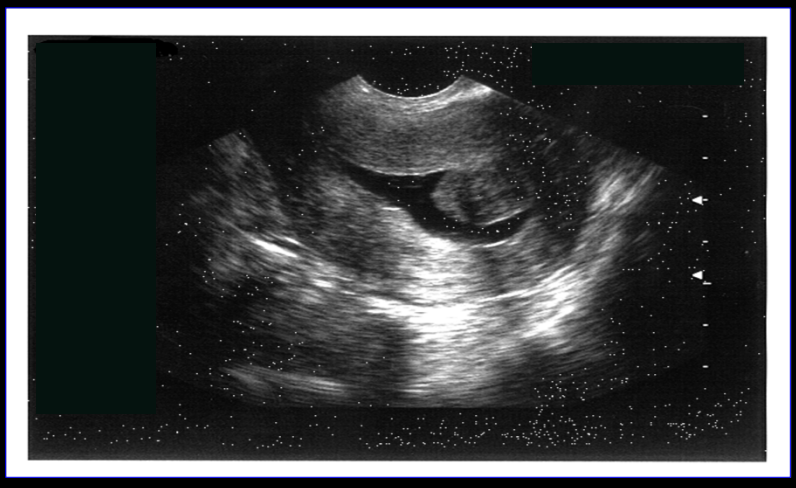
HyCoSy

- Hysterosalpingo Contrast Sonography
- In-office sonography
- Cavity check for filling defects
- Tubal patency assessment
- Same timing as SIS or HSG

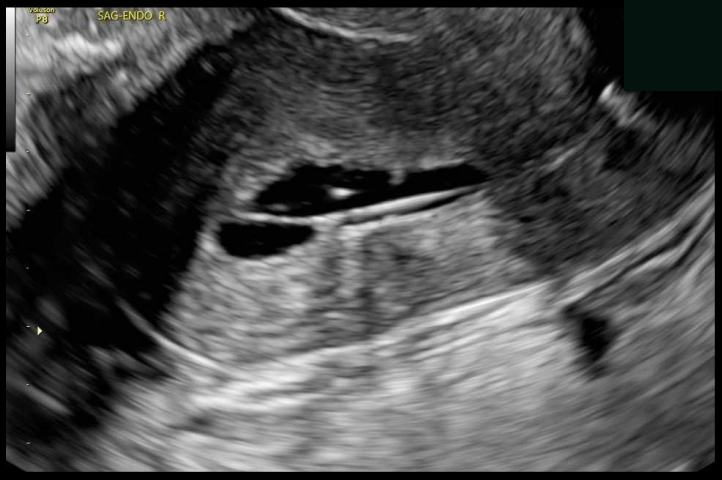
Sonohysterogram (SIS or SHG)



Sonohysterogram Filling Defect

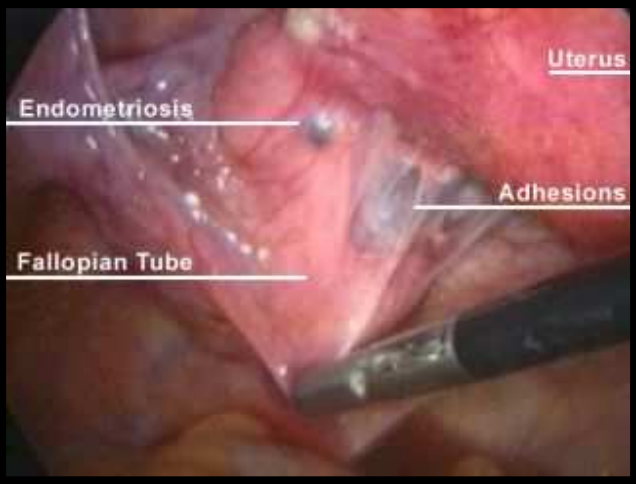


SIS Filling Defect



Laparoscopy

- Surgical procedure
- Diagnose & treat endometriosis
- Remove adhesions
- Address tubal factor
- Remove or reduce septums, fibroids
- Not routine



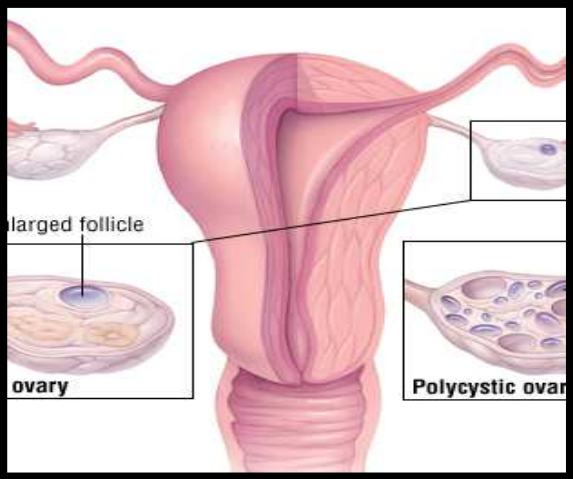
Pelvic Ultrasound (TVUS)

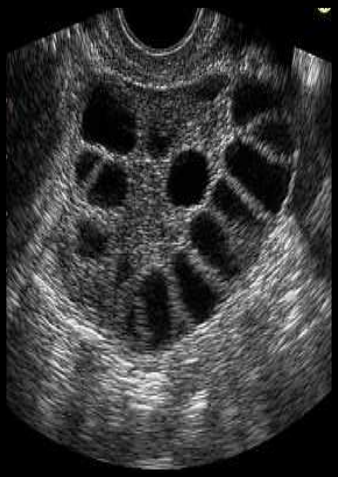
- Uterus
  - Fibroids
- Ovaries
  - Antral follicle count (AFC) (BAF)
  - Assess follicular development
  - Cysts
- Pregnancy monitoring

Endometrial Biopsy

- Not a standard test for most patients
- May be indicated in anovulatory patients to r/o hyperplasia/EIN (endometrial intraepithelial neoplasia)
- Helpful to r/o chronic endometritis
- Checks for presence of CD-138, plasma cells

Polycystic Ovary Syndrome (PCOS)





Male Infertility Work-up and Testing

- Starts with a thorough history and exam

Evaluation of the Male

- Sexual history
- Urologic history
- Surgical history
- Medical history including STDs, febrile illness
- Family history
- Medications including anabolic steroids
- Toxic exposure

Semen Analysis

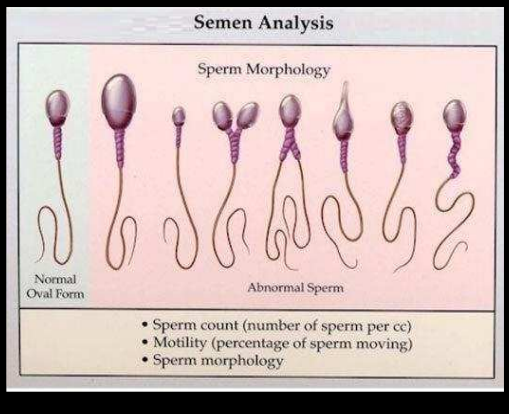
- Volume 2-5ml
- Count >20 mil/ml
- Motility >50%
- Morphology: abstinence affect
  - WHO vs Strict Kruger/>4
- Progression >2 (scale 1-4)
- Presence of RBC/WBC

Male Infertility Work-Up

- Blood work
  - Hormonal evaluation when indicated
  - Infectious disease screening
  - Genetic screening
- Referral to reproductive urologist as needed
  - Scrotal ultrasound as indicated
  - Advanced sperm assessment as indicated

Semen Analysis

Morphology



Semen Analysis Concerns

Advanced Maternal Age (Additional Testing)

- PCP medical clearance
- MFM obstetrical clearance
- Additional screening including EKG, GTT, mammogram

Transgender Considerations

- Inclusive care
- Use of pronouns
- Staff training, all departments
- Customize patient forms
- Humility

Fertility Preservation Patients

- Cancer patients: fast track to retrieval - testing optional
- Non-cancer patients: emphasis on ovarian reserve testing and counseling

REI Nurses

- Your role is vital to patient's ability to navigate through testing and treatment
- You are the bridge that connects patients to the complex web of information vital to their fertility journey

Optimizing Stimulation Protocols

Kaylen M. Silverberg, MD

ART really is an art. Ovarian stimulation involves a thorough understanding of the inner workings of the hypothalamic-pituitary-ovarian (H-P-O) axis and then, figuring out ways to manipulate it using some of the gonadotropins at our disposal. Unfortunately, clinicians are unable to change the physiology of the ovary or create gametes yet.

Currently, we are limited by the fact that women are born with a finite egg supply, determined *in utero* and utilized over decades. These eggs are arrested in development whilst they await their turn to enter the pool of developing follicles and fulfill their destiny. Following puberty, and maturation of the H-P-O axis, developing follicles get a chance to complete their journey of maturation and enter the race for ovulation. As one can see, the efficiency of this whole process is abysmal with only a fraction of the 5 million eggs that populate the ovaries ever having a chance to ovulate as a mature egg and getting a chance to be fertilized. Understanding how to manipulate this process to our advantage and maximize the yield of mature oocytes in a woman desiring to preserve her future fertility or achieve a pregnancy is critical to improving ART outcomes. Using all of the key gonadotropins and hormones (or antagonists/blockers), this presentation will review the use of FSH, LH (hCG), HCG, GnRH agonists and antagonists, estrogen and OCP pre-treatment, oral agents like estrogen receptor modulators or aromatase inhibitors and different ways of tricking Mother Nature to improve the odds.

Optimizing Stimulation Protocols

Kaylen M. Silverberg, MD
Medical Director, Managing Partner
Texas Fertility Center
Austin & San Antonio, Texas

Disclosure Information

- Has received research grants from Baxter
- Has received consulting fees from Baxter, Seikagaku, Serono
- Has served as a speaker for AbbVie, Myovant
- Is a co-founder and member of board of directors: Ovation Fertility
- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, or therapeutic strategies

Learning Objectives

- Explore the rationale for ovarian stimulation
- Discuss, compare and critically evaluate the different medical options for ovarian stimulation
- Review the published effectiveness (of lack thereof) of popular supplements for male and female infertility
- Examine the mechanism of action by which effective supplements may affect fertility

Agenda

- Purpose of ovarian stimulation
- Medications
  - Clomiphene
  - Letrozole
  - Metformin
  - OCPs
  - GnRH agonists and antagonists
  - FSH vs. hMG
  - Growth Hormone
  - DHEA
  - Other Adjuncts

What are the Purposes of Stimulation?

- To obtain a greater number of oocytes by:
  - Expand the number of embryos
  - Improve likelihood of at least 1 euploid
  - Increase chances for pregnancy
  - Enhance possibility of embryo banking

Inherent Inefficiency of IVF

- 12 oocytes (12)
- 75% fertilization (9)
- 40-60% blast utilization rate (3-5)
- 30-50% euploid (1-3)
  - Therefore, it takes about 9-12 eggs (depending on patient age) to produce 1 euploid blastocyst

Clomiphene Citrate

- Oral medication – 50 mg
- 2 isomers
  - Estrogen agonist
  - Estrogen antagonist
- Basically works by fooling hypothalamus and pituitary
- Results in increased FSH (and LH) secretion

Clomiphene Citrate (cont.)

- Give x 5 days (3-7 vs. 5-9…)
- Monitor for ovulation
  - LH kit
  - Sonography
  - P4 levels
- If no ovulation, progesterone withdrawal (+/-) and increase dose next cycle
- Can go up to 250 mg/day x 5-10 days

Clomiphene Citrate (cont.)

- Ovulation rates up to 80%
- Pregnancy rates 8-12%/cycle; cumulative rates of 55-60% in 6 cycles
- Life table analysis: 95% of those who will conceive on CC do so within 6 cycles
- Multiple pregnancy risk: 5-8%
- Adverse effects: hot flashes, vaginal dryness, headache, mood swings, scotomata

Letrozole

- 3rd generation aromatase inhibitor
- Oral medication 2.5-10 mg/day x 5 days
- Blocks peripheral conversion of androgen to estrogen
- Releases the hypothalamus and pituitary from negative feedback induced by estrogen
  - FSH increases
  - Increase in follicular development

Letrozole (cont.)

- Initially proposed as alternative to clomiphene[1]
- Optimal dosage not determined
- Similar results to clomiphene[2]
  - 75% ovulation
  - Similar pregnancy rates (8-15%/cycle)
  - Similar miscarriage rates

[1] Mitwally, Casper. Fertil Steril 2001;75:305-9.
[2] Badawy, et al. Fertil Steril 2007.

Letrozole Toxicity

- Question of fetal toxicity previously limited use
  - Skeletal & cardiac abnormalities[1]
    - Biljan (n=150 study patient deliveries vs. 36,000 control deliveries)
    - Other studies suggest no problems
      - Tulandi (n=911)[2]
      - Forman (n=94 letrozole conceptions vs. 242 clomid conceptions vs. 94 spontaneous conceptions)[3]

[1]Biljan et al. Fertil Steril 2005.
[2]Tulandi et al. Fertil Steril 2006.
[3]Forman et al. J Obstet Gynecol Canada 2007.

Metformin

- Oral biguanide
- Works by:
  - decreasing insulin levels, increasing insulin sensitivity
  - decreasing androgens (free and total)
  - decreasing LH
  - increasing SHBG
- Effective vs. hyperglycemia; does NOT cause hypoglycemia in euglycemic patients

Metformin in the PCO IVF Patient

- Prospective randomized trial
- n=101
- Metformin 850 BID vs. placebo
- Higher ongoing pregnancy rates
  - 38.5% vs. 16.3% ($p<0.05$)
- Significantly lower OHSS
  - 3.8% vs. 20.4% ($p<0.05$)

Tang et al. Hum Reprod 2006;21:1416.

Metformin (cont.)

- Dosage 1500-2000 mg/day
- Restoration of ovulation in 78-96% of patients[1]
- Enhances effect of clomiphene[2]
- Although Metformin with or without clomiphene improves clinical pregnancy rates, NO evidence of increased live birth rate in Cochrane Collaboration (2010)[3]

[1] Homburg, Insler. *Hum Reprod Update*. 2002;8(5):449-62.
[2] Vandermolen D, et al. *Fertil Steril*. 2001;75:310-15.
[3] Tang, et al. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003053.

OCPs? How About Before IVF?

- Decreased incidence of cysts
- Greater number of oocytes
- Higher E2 levels
- Possibly faster stimulation with less gonadotropin
- Higher fertilization rates
- BUT – can suppress ovarian response, especially in poor responders…

GnRH: Agonists vs. Antagonists

- Antagonist
  - Block receptors rapidly
  - Competitive inhibition
  - Immediate suppression
  - Rapidly reversible
  - "Turn off light switch"
- Agonist
  - 4-6 day "flare"
  - Down regulation of receptor
  - Slow suppression due to desensitization of pituitary
  - Slowly reversible
  - Light bulb "burns out"

GnRH Agonists

- Significantly lower cancellation rates
  - Block spontaneous LH surges
- Enhanced scheduling flexibility
- Greater # oocytes
- More embryos
- Higher pregnancy rates (2x)[1]

[1] Hughes et al. *Fertil Steril* 1992;58:888.

GnRH Antagonists

- Theoretic advantages:
  - Shorter duration of treatment
  - Fewer injections, less discomfort
  - Lower dose of gonadotropins
  - Lower cycle cost
  - Lower incidence of OHSS
  - Rapid pituitary recovery

Agonist vs. Antagonist: Data

- Cochrane review (2002)[1]
  - 5 studies
  - Lower delivery rates with antagonist 0.79 (CI 0.63-0.99)
  - 5% absolute treatment effect, so for every 20 couples treated, there will be one more pregnancy with agonist
- Cochrane review (2006)[2]
  - 27 studies
  - Significantly lower pregnancy/delivery rates with antagonist ($p<0.05$)

[1] Al-Inany et al, *Hum Reprod.* 2002;17:874.
[2] Al-Inany et al, *Cochrane Database Syst Rev*. 2006;19:3.

GnRH Antagonists in Donors

- No differences in pregnancy rates in 2 trials
  - 1 prospective, randomized (n=148)[1]
  - 1 retrospective (n=1036)[2]

[1] Prapas et al. *Hum Reprod* 2005;20:1516.
[2] Scott et al. 2008 UCLA IVF Course, unpublished data

So, is There a Problem with GnRH Antagonists?

- Agonists appear to be superior in fresh IVF cycles
- Appears to be no difference in donor cycles
- NO difference in FET cycles
- Suggests a potential effect on the endometrium – never clearly demonstrated

So, Why did Antagonist Cycles Become So Popular?

- Fewer injections
- Potentially less ovarian suppression
- Shift to FET
  - Caused pregnancy rates to improve
  - Etiology?

Recombinant FSH-only Protocols

- Oocyte development can occur in absence of LH
- Excessive LH may cause oocyte atresia
- Estradiol production is limited
- Endogenous LH appears to be adequate for oocyte development
- The real ?: Do we make normal patients hypogonadal with GnRH-a or –ant??
  - Probably NOT
- Therefore, recombinant FSH alone works fine due to continued endogenous LH secretion

Do We Need to Give LH in Addition to FSH?

- Difficult question to answer as studies vary in design, protocol, dosing
- May need if GnRH-a and OCPs suppress endogenous LH to hypothalamic levels
- Since data suggest this doesn't happen, probably no LH needed

- So, why do >80% of cycles in US use LH?

Meta-analysis #1: FSH vs. hMG

- 5 RCT, > 2000 women, non-inferiority design
- Clinical pregnancy rate higher with hMG (CI 1.03-1.44)
- No difference in live birth rate
- Non-inferiority demonstrated

Van Wely et al *Fertil Steril* 2003;23:1086.

Meta-analysis #2: FSH vs. hMG

- 7 RCT
- 2159 women
- Higher birth rates for hMG

Coomarasamy et al *Hum Reprod* 2008;80:310.

Meta-analysis #3: FSH vs. hMG

- 42 RCT
- 9606 women
- No difference in:
  - Birth rates (rFSH vs. uFSH or hpFSH)
  - OHSS incidence
- Small but statistically significant difference in :
  - Birth rates (rFSH vs. uhMG*)

Van Wely M, et al *Cochrane Summaries 2012:12;12.*

Meta-analysis #4: FSH vs. hMG

- 70 studies (all prospective, controlled)
- Results:
  - FSH alone: higher # retrieved oocytes
  - No difference in # MII oocytes
  - Combo: greater number of embryos and higher implantation rate
  - Higher pregnancy rate with combo ONLY in GnRH agonist cycles

Santi D et al *Endocrine Abstracts* 2017;49:1107.

Supplements

- FDA status
  - Approved
  - Exempt
- Usually sold over the counter – or over the internet (no prescription required)

Male Infertility

Male Fertility Supplements

- 90 unique ingredients have been evaluated
- 5 most commonly prescribed:
  - Vitamin E
  - Vitamin C
  - Zinc
  - Folic acid
  - Selenium

Kuchakulla M, et al. Urology. Vol 136, Feb, 2020:133-41.

Male Fertility Supplements

- 5 ingredients with the most supportive data:
  - Vitamin E
  - Vitamin C
  - Zinc
  - L carnitine
  - CoQ10
- Only 17% of ingredients had published data demonstrating positive effect
- Evolution 60 and Conception XR had the highest scores

Kuchakulla M, et al. Urology. Vol 136, Feb, 2020:133-41.

Male Fertility Supplements – Critical Evaluation

- 41 RCTs or meta-analyses
- 18 ingredients had reported efficacy
- 11 had at least 2 RCTs or 1 RCT and 1 meta analysis supporting efficacy:
  - Vitamin B12 25 µg
  - Folic Acid 400 µg
  - L arginine 1.4 g
  - L carnitine 1.0 g
  - N-Acetyl Cysteine 600 mg
  - Vitamin C 0.5 g
  - Zinc 50 mg
  - Tribulus Terrestris 250 mg
  - Alpha Tocopherol 20 mg
  - EPA + DHA 0.48 g
  - CoQ10 200 mg

Garolla A, et al. Nutrients. 2020 12:1472.

Popular Male Fertility Supplements with No Published Data Supporting Efficacy

- Nettle DE
- Glucosamine
- Vitamin D
- Niacin
- Biotin
- Manganese

Garolla A, et al. Nutrients. 2020 12:1472.

Meta-analysis Evaluating Medications and Supplements to Improve Spontaneous Pregnancy Rates in Idiopathic Male Infertility

- Evaluated all RCTs from 1990-2021
  - 65 studies, 7541 men
- Drugs/supplements studied:
  - Medications
    - FSH, testosterone, clomiphene, letrozole
  - Supplements
    - Trace elements (selenium, zinc)
    - Vitamins (C,D,E, folic acid)
    - Energy supplements
      - Carnitine, CoQ10, fatty acids
  - Other
    - DHA, probiotics

Li J, et al. Engineering. Accessed August, 2021 online.

Mechanisms of Action for Male Supplements

- Act as antioxidants to protect sperm from damage from ROS
  - Zinc, selenium, carnitine, Vits C/E, CoQ10
- Regulation of mitochondrial bioenergetics
  - CoQ10 enhances energy production for sperm motility
  - Carnitine also enhances energy production

Li J, et al. Engineering. Accessed August, 2021 online.

Meta-analysis Evaluating Medications and Supplements to Improve Spontaneous Pregnancy Rates in Idiopathic Male Infertility

- Findings:
  - Compared to placebo, carnitine plus vitamins increased SPR 3.7x
  - FSH and fatty acids significantly increased sperm concentration
  - SERMs (clomiphene) plus CoQ10 significantly increased sperm motility and normal morphology

Li J, et al. Engineering. Accessed August, 2021 online.

Female Infertility

Egg Quantity vs. Egg Quality

- Many supplements have been demonstrated to increase egg quantity
- None definitively improve egg quality (difficult to assess)
- IMPORTANT that patients know the difference

Folic Acid

- 400 µg/day increases follicular fluid levels of folate and decreases homocysteine
- Folic acid is critical for DNA synthesis, methylation, and protein synthesis
- Proven to reduce the risk of neural tube defects
- Not proven to enhance LBR

Growth Hormone for IVF- Early Meta-analyses

- Cochrane Review
- 6 PR trials
- No effect on stimulation parameters
- Higher live birth rates (CI 1.06-18.01)[1]
- Women >40: PR study
- Higher E2, delivery rate 22% vs. 4% ($p<0.05$)[2]
- Expensive, availability, safety?
- Not effective for poor responders

[1] Harper et al. Cochrane Database System Rev.2003, issue 3.
[2] Tesarik et al. *Hum Reprod* 2005;20:2536.

Growth Hormone for IVF- Australian LIGHT Study

- <41 years of age
- Previous poor response (< 6 oocytes in previous IVF cycle)
- FSH <15
- Pros, randomized
  - A: 12 IU GH starting stim day*
  - B: Placebo
- GH treated patients:
  - higher likelihood of TVOR (95.4% vs. 78.5%; 5 vs. 4 oocytes)
  - NO difference in embryonic development, likelihood of ET, pregnancy (14.5 vs. 13.7%)

[1]*Norman R, et al. Reprod Biomed Online. 38:908-15. 2019.

Growth Hormone for IVF- Latest Meta-analyses

- 12 RCTs, 1139 patients – 2020[1]
- Higher number of retrieved oocytes than placebo
- More embryos available for ET
- NO increase in LBR, no diff in SAb rate

- 15 RCTs, 1448 patients - 2020[2]
  - Higher LBR (OR 1.74; CI 1.19-2.54), # oocytes, reduced cycle cxl, gonadotropin dose
  - No difference in miscarriage rate

[1] Cozzolino et al Fertil Steril 114;97-109. 2020.
[2] Yang P , et al. Reprod Biol and Endocrin18;76. 2020.

DHEA

- Adrenal androgen – precursor for estradiol production
- Mechanism of action to improve fertility unknown
- Possibilities:
  - Increases IGF-1 expression, sensitizing granulosa cells to exogenous FSH
  - Increases intrafollicular androgen causing an increase in AMH expression and Inhibin B production (related to DHEA duration)[1]
  - Improves embryo ploidy
  - Promotes pre-antral follicle growth, suppresses apoptosis
- 2010 survey reported that >25% of IVF specialists used DHEA for poor responders[2]

[1] De Macedo et al.2018.
[2] Nardo L, et al Upsala J Med Sci. 125. 2020.

Vitamin D3

- Included in 30% of supplements
- Involved in AMH secretion, so potentially relevant
- NO effect on IVF outcome

Cozzolino M, et al. Fertil Steril 2020.114:1014-25.

DHEA

- P, R trial, n=33 (51 cycles) [1]
- 75 mg/d DHEA
- Delivery 23% vs. 4% (controls, p<0.05)

- "We would like to present how insufficient the current evidence of acceptable quality is to warrant a conclusion that DHEA supplementation is an effective treatment for women with diminished ovarian reserve. More studies needed…"[2]

[1] Wiser, et al. Hum Reprod.2010;25:2496.
[b]2Yakin and Urman Hum Reprod Online, May 18,2011.

DHEA – Review Articles and Meta-analysis

- Extensive review article by Malasevskaia, et al highlighted poor study design and conflicting data[1]
- Meta-analysis (6 RCTs, 745 patients)[2] demonstrated:
  - Significant increase in clinical pregnancy rate (OR =1.45, CI 1.04-2.03, p<0.05)
  - Significant increase in LBR (OR=2.7, CI 1.24-5.85, p=0.01)
  - No effect on miscarriage rate (OR=0.43, CI 0.03-6.7, p=0.55)

[1] Malasevskaia I, et al. J Mid East and N Africa Sciences. 7(04); 6-18. 2018.
[2] Liu Y, et al. Gynecol Endocrinology; 178-83.2018.

Heparin

- Blocks formation of thrombi at implantation site by inhibiting Factor X
- Conflicting data from meta analyses due to poor statistical methodology, small sample sizes
- Some studies DO suggest improvement in LBR, but data remain inconclusive

Akhtar M, et al. Fertil Steril. 103:33-4. 2015 .

Aspirin

- Inhibits platelet aggregation, improves blood flow to the ovaries and uterus
- Meta-analysis did not show improved LBR in IVF[1]
- Cochrane review – 13 RCTs[2]
  - No improvement in pregnancy rates or LBR

As an aside…

- Latest Cochrane review for RPL patients showed no benefit of ASA with or without low molecular weight heparin (enoxaparin, LMWH) in patients with or without thrombophilia[3]

[1] Gelbaya T, et al. Hum Reprod Update 13:357-64. 2007.
[2] Siristatidis C, et al. Cochrane DatabaseSyst Rev 2011;CD004832.
[3] DeJong P, et al. Cochrane Database Syst Rev 2014;CD004734I.

Sildenafil

- Vasodilator, improving blood flow to uterus
- Very poor quality data
- Small studies suggest occasional benefit but large, retrospective study demonstrated no improvement in endometrial thickness, endometrial blood flow, or LBR

Check J, et al. Clin Exp Obstet Gynecol 31:99-102. 2004.

Steroids

- Very difficult to assess due to multiple small studies using different drugs, different dosing regimens, different combinations, etc.
- Multiple proposed MOAs, all pointing to reduction in intrauterine inflammation
- Cochrane review of 14 RCTs:
  - No benefit of glucocorticoids on LBR, and SAb rates when used in unselected IVF/ICSI patients[1]
- Some evidence that prednisolone (with LMWH) may improve LBR in patients with one or more failed IVF cycles[2]

[1] Boomsma C, et al. Cochrane Database Syst Rev 2012;CD005996

[2] Fawzy M, et al. Arch Gynecol Obstet289:677-80. 2014

Intralipids

- Fatty emulsion of egg yolk, phospholipids, glycerine, soy bean oil, water
- Double blind, RCT of 296 RPL patients with elevated NK cells showed no difference in CPR
- Second study terminated early as control group did better than treatment group
- No substantive evidence demonstrating efficacy

Nardo L, et al. Upsala J Med Sci. 125;2:144-51. 2020.

IV Immunoglobulin (IVIG)

- Very poor data due to poor study design, multiple small uncontrolled trials
- Only 2 studies were RCT looking at RIF patients undergoing IVF
- No difference between study and control patients in terms of CPR or LBR
- No substantive data supporting its use

Li et al. Am J Reprod Immunol 70;434-47. 2013.

Myo-inositol

- Most common ingredient in female supplements
- Daily use of 4 mg reduces gonadotropin requirements; lower doses ineffective
- Most supplements do not contain enough to be effective

Lagana A, et al. Arch Gynecol Obstet 2018;298:675-84.

CoQ-10

- Free radical scavenger
- Meta-analysis, but only included 1 RCT of CoQ 10
- Significant improvement in CPR vs. control (poor responders) (OR 2.2, CI (1.08-4.58)*
- Significant reduction in cycle cancellation rate (OR 0.33, CI 0.15-0.74)

* Zhang et al. Hum Reprod Update 26 (2):247-63. 2020.

IVF Lab Supplements/Techniques

Embryo Glue

- It is hyaluronan - NOT glue
- Glycoprotein that raises viscosity in uterine cavity
- Cochrane review of 17 RCTs, 2898 patients*:
  - Moderate quality evidence for an improvement in LBR
  - Increased risk of twins

*Bonetkoe S, et al. Cochrane Database 2014;CD007421.

Assisted Hatching

- Used for over 20 years
- Mechanical or chemical disruption of zona
- Designed to facilitate embryo hatching as well as paracrine effects between embryo and endometrium
- Meta-analysis of 36 RCTs, 6459 patients
  - No increase in LBR

Li D, et al. Sci Rep 6:31228, 2016.

Intentional Endometrial Injury ("Scratch")

- Theory is that injury promotes production or secretion of growth factors and other cytokines
- Obvious problem is that injury doesn't occur in same cycle as transfer; "injured" endometrium shed in preceding cycle…
- RCT demonstrated no benefit or improvement in LBR

Lensen S, et al. N Engl J Med 380:325-34.2019.

Conclusions

- Never ending search for anything to improve LBR with IVF
- Some medications for male fertility are beneficial:
  - FSH, clomiphene citrate

Conclusions: Male Fertility Supplements

- Over 90 supplements scientifically evaluated
- Good data support the use of up to 11 supplements
- Vitamins: B12, C, E?
- Others:
  - Folic acid, L-carnitine, L-arginine, N-acetyl cysteine, CoQ10, zinc, EPA+DHA, tocopherol
- Many popular supplements lack any supporting data
  - Glucosamine, Vit D, biotin, niacin

Conclusions: Female Fertility Supplements

- Proven Benefit: None at this time
- Unclear but potential benefit:
  - DHEA, CoQ10, growth hormone, LMWH, Prednisolone, myo-inositol
- Unlikely benefit:
  - Aspirin, sildenafil, glucocorticoids, intralipids, IVIg

Conclusions: Laboratory Techniques

- Proven benefit:
  - Embryo glue
- Unlikely benefit:
  - Assisted hatching
  - Intentional endometrial injury/“scratch”

Genetics and ART

Lauren J. Isley, MS, LCGC

Clinical genetics is an integral component of reproductive medicine. Carrier screening and preimplantation genetic testing (PGT) are commonly offered genetic tests in the assisted reproduction setting. Carrier screening can help determine if a couple may be at an increased risk for a genetic disorder in their future offspring, and provide them with the opportunity to explore alternative reproductive options as needed. PGT-M may be available to test the couple's embryos for a specific genetic disorder. In addition, PGT-A is an option to determine the chromosomal status of embryos prior to transfer. For intended parents using a gamete donor, consideration of that donor's carrier screening results and family medical history is an important component of donor selection. Clinicians should consider referring patients to a genetics specialist, such as a genetic counselor, to discuss family medical history and genetic test results in the reproductive medicine setting.

Genetics and ART

Lauren J. Isley, MS, CGC
Genetic Counselor
Medical Science Liaison, Generate Life Sciences
Los Angeles, CA

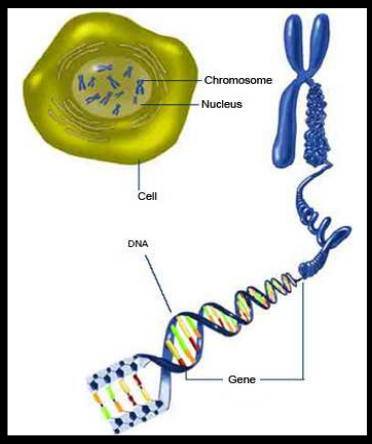
Disclosures

- Full-time employee of Generate Life Sciences, a company providing donor gamete services
- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- Discuss basic genetic concepts
- Recognize common genetic tests in the ART setting
- Evaluate common genetics issues that may arise in the ART setting and when referrals are appropriate
- Review current issues and topics in the field of clinical genetics

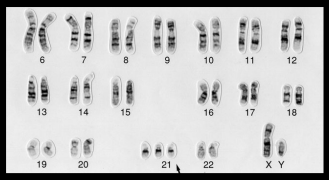
Genes and Chromosomes: Back to the Basics



- Humans have 46 chromosomes
  - "Euploid" vs. "aneuploid"
- Each human chromosome is consisted of a continuous DNA double helix
- Genes: Segments of DNA which code for protein or functional products
- 2 chromosome copies = 2 gene copies (the majority of the time)
- Mutations/copy number changes may cause genetic disease

Cytogenetic Disorders vs. Single Gene Disorders

- Refers to an abnormal number of chromosomes
- Trisomy 13, 18, 21
- Sex chromosome abnormalities
- Unbalanced translocations



- Refers to diseases caused by gene mutation(s)
  - Mutation: genetic change that is generally disease-causing
- Mutation may be in one or both genes
- Gene cannot produce functional product -> phenotype of disease
- Examples: Cystic fibrosis, Sickle cell anemia, Huntington disease

Patterns of Inheritance

- Autosomal recessive
  - Most recognized in ART setting
- Autosomal dominant
- X-linked (dominant and recessive)
- Multifactorial

Cross: Aa x Aa

	A	a
A	**AA**	**Aa**
a	**Aa**	**aa**

Multifactorial Genetics

- Complex interactions between a number of genetic and environmental factors
- Risk figures are empirically derived
  - Familial aggregation, twin studies, degree of relationship
- Type 1 diabetes, Alzheimer's disease (some rare exceptions) , mental illness, certain congenital malformations
- *"Can you test my embryos for…..?"*

Uhlmann W., Schuette J., Yashar B. (2009). A Guide to Genetic Counseling, 2nd edition. Wiley-Blackwell.

Genetic Testing in ART: Infertility Evaluations

- Karyotype analysis
  - Infertility/recurrent SAB
  - Rule out chromosome rearrangement or sex chromosome disorder (i.e. Klinefelter syndrome)
- Fragile X carrier screening
  - POF
- Cystic fibrosis
  - CBAVD in men
- Others
  - Thrombophilia panels, Y chromosome deletion, rare genetic syndromes, etc.

Shah, K. (2003). The genetic basis of infertility. *Reproduction*, 126(1), pp.13-25.

Genetic Testing in ART: Carrier Screening

- May include autosomal recessive or X-linked conditions
- Certain diseases recommended by ACOG/ACMG
  - Limited panels vs. expanded carrier screening panel
- Targeted mutation analysis vs. gene sequencing
  - Detection rate of test?

Committee Opinion No. 690 Summary. (2017). *Obstetrics & Gynecology*, 129(3), pp.595-596.
Committee Opinion No. 691 Summary. (2017). *Obstetrics & Gynecology*, 129(3), pp.597-599.

Detection Rates

- If an individual is a carrier of a disorder, what is the chance that the test will detect a mutation?
- Determining detection rate
  - Test methodology (genotyping vs. sequencing)
  - Patient's ethnicity

Test Methodologies

- Targeted mutation analysis (genotyping)
  ATGCGTAGTTCCAAATCTGTCGAGAAGTTT
- Full gene sequencing
  ATGCGTAGTTCCAAATCTGTCGAGAAGTTT
- Deletion/duplication analysis
  ATGCGTAGTTCC GAAGTTT
  OR
  ATGCGTAATGCGTAGTTCCAAATCTGTCGAGAAGTTT

Genetics in ART: Preimplantation Genetic Testing

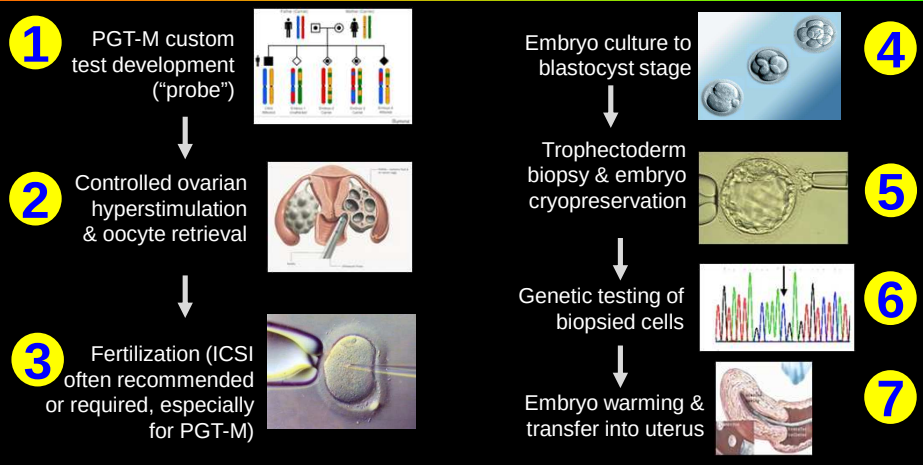
Old nomenclature

PGD (diagnosis): single gene disorders
PGS (screening) or CCS: aneuploidy

New nomenclature

PGT-M (monogenic): single gene disorders
PGT-SR (structural rearrangements): translocations, inversions, etc.
PGT-A (aneuploidy)

Overview of IVF/PGT Process



PGT-M: What is Required?

- Known variant/mutation
- Development of linkage-based test ("probe")
  - Patient's parents often need to pursue clinical genetic testing and provide additional DNA samples (cheek swabs) to the PGT laboratory
  - Typically takes ~2-3 months to complete once all necessary reports/samples are received by PGT lab

Complex Issues in PGT-M

- PGT-M for adult-onset conditions
- PGT-M for variants of uncertain significance
- PGT-M for diseases with reduced penetrance or mild presentation

ASRM PAGES

Use of preimplantation genetic testing for monogenic defects (PGT-M) for adult-onset conditions: an Ethics Committee opinion

Ethics Committee of the American Society for Reproductive Medicine

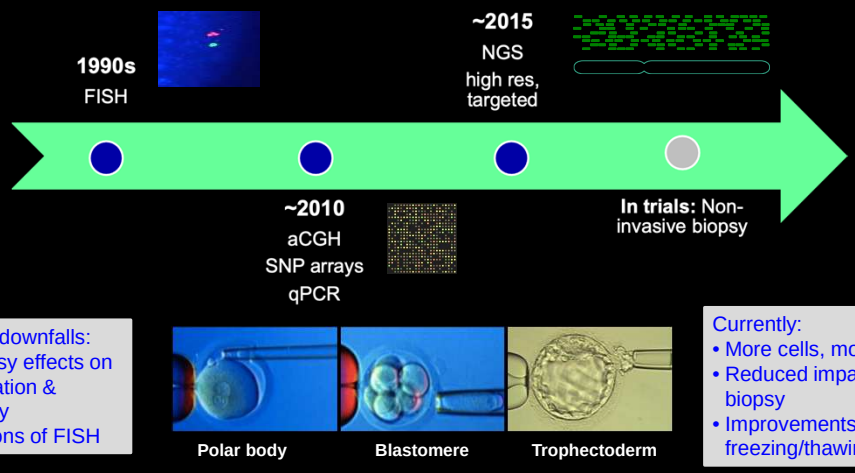
American Society for Reproductive Medicine, Birmingham, Alabama

Preimplantation genetic testing for monogenic diseases for adult-onset conditions is ethically permissible for a range of conditions including when the condition is serious and no safe, effective interventions are available. The Committee strongly recommends that a genetic counselor experienced with PGT-M counsel patients considering such procedures. This document replaces the document titled "Use of preimplantation genetic diagnosis for serious adult-onset conditions: a committee opinion," last published in Fertil Steril 2013;100:54-7. (Fertil Steril® 2018;109:989-92. ©2018 by American Society for Reproductive Medicine.)

Earn online CME credit related to this document at www.asrm.org/elearn

Discuss: You can discuss this article with its authors and with other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/31814-26069

Evolution of PGT-A Technologies

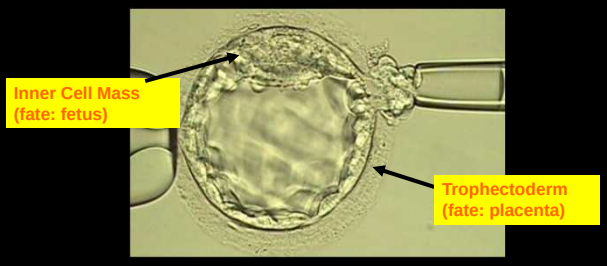


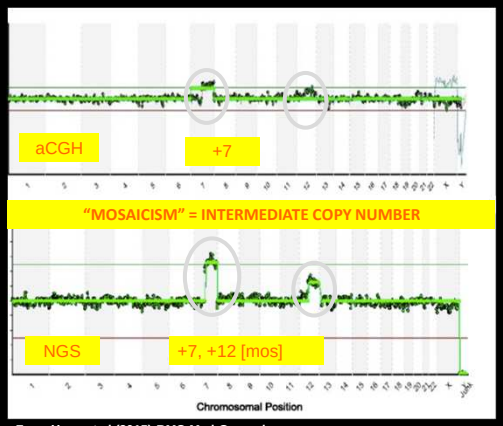
Previous downfalls:
- D3 biopsy effects on implantation & accuracy
- Limitations of FISH

Currently:
- More cells, more accurate
- Reduced impact of TE biopsy
- Improvements in freezing/thawing

Mosaicism in PGT-A

- Increased detection of mosaicism with TE biopsy and NGS
- ICM/TE concordance is high for euploid & aneuploidy but significantly lower for mosaic results

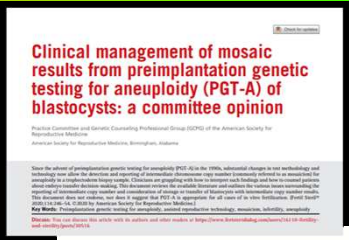




From Yang et al (2015) BMC Med Genomics

Mosaicism in PGT-A: Counseling Considerations

- PGDIS Position Statement on Transfer of Mosaic Embryos (2021)
  - Embryos with higher-level mosaicism may be associated with less favorable outcomes compared to lower-level mosaicism
  - A decision to transfer a mosaic embryo can be prioritized either on the level of mosaicism or type of mosaicism (whole chromosome vs. segmental changes)
- Current ASRM counseling recommendations state:
  - Patients considering transfer of a mosaic embryo should consult with a clinical genetics specialist, such as a genetic counselor
  - Counseling should include a discussion of the various possible explanations for mosaic PGT-A results and potential outcomes
  - A decision regarding transfer of an embryo with mosaic results is optimally made with ample time for careful consideration of the risks, benefits, and alternatives
  - Prenatal genetic counseling is strongly recommended
  - Postnatal evaluation should be considered



Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion

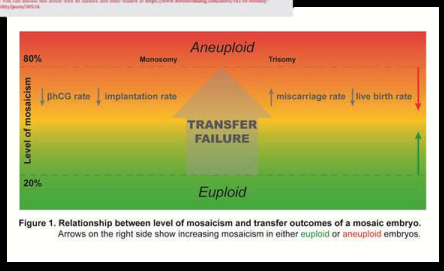
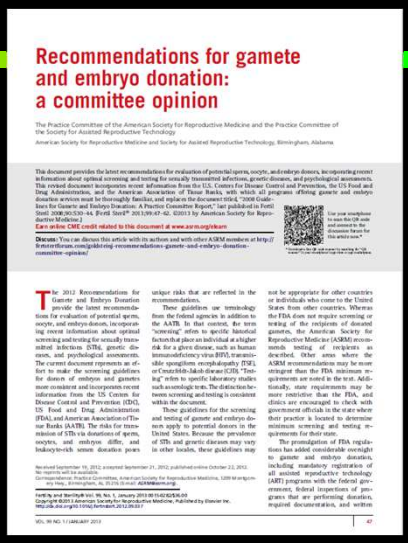


Figure 1. Relationship between level of mosaicism and transfer outcomes of a mosaic embryo. Arrows on the right side show increasing mosaicism in either euploid or aneuploid embryos.

PGDIS POSITION STATEMENT ON THE TRANSFER OF MOSAIC EMBRYOS 2021

Genetics in ART: Gamete Donation

- ASRM recommendations for gamete and embryo donation (updated 2021)
  - Includes exclusion criteria based on personal/family medical history and genetic testing results
- Standard donor evaluations
  - 3-generation personal/family medical history by trained genetics professional
  - Carrier screening
  - Other indicated genetic tests
- Evaluation of recipient



Recommendations for gamete and embryo donation: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology

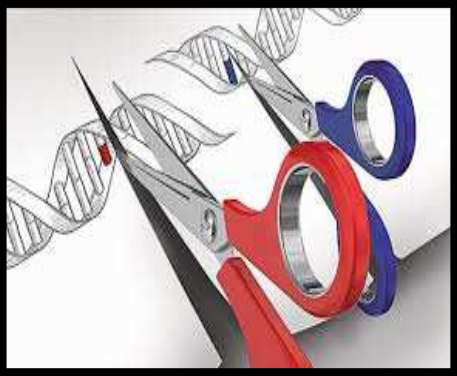
American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

When is a Genetics Referral Appropriate?

- Counseling about any of these genetics issues!
- Especially….
  - Positive carrier testing results
  - Abnormal karyotype (translocation; Klinefelter syndrome)
  - Personal/family/pregnancy history of birth defects, ID, significant medical issues, known genetic condition
  - Evaluation of a gamete donor and/or recipient
  - PGT patients

Hot Topics in ART Genetics

- Direct-to-consumer testing (DTC)
- PGT for polygenic (multifactorial) diseases
- Non-invasive PGT
- Mitochondrial transfer ("3-parent IVF")
- Germline genomic editing
- *In-vitro* gametogenesis



Navigating Gamete Donation in Clinical Practice

Maria M. Jackson, RN, MA

Gamete donation in clinical practice in the US dates back to the 1800s when an anonymous sperm donor was used to inseminate a woman whose husband was azoospermic. Since then, the number of people using both egg and sperm donors has increased significantly. Statistics tracking donor inseminations are difficult to determine and the numbers are estimated to be considerably higher than what is reported in the literature.

There are 4 distinct stakeholders involved in the practice of gamete donation and the implications for each are quite different. Donor conceived offspring are often referred to as the "forgotten stakeholders" because their long-term needs for information about their means of conception and their donor histories were often not considered. Moreover, scientific advances in the realm of genetics have changed the landscape and instances of inadvertent disclosure are becoming commonplace. The industry as a whole is largely unregulated therefore; responsibility for the ethical practice falls on clinics to educate donors and recipients regarding the numerous complex issues involved. Donor conceived offspring are asking for changes in the way gamete donation is practiced, forcing all the stakeholders to examine their rights and responsibilities within the framework of third party reproduction.

Gamete Donation in Clinical Practice

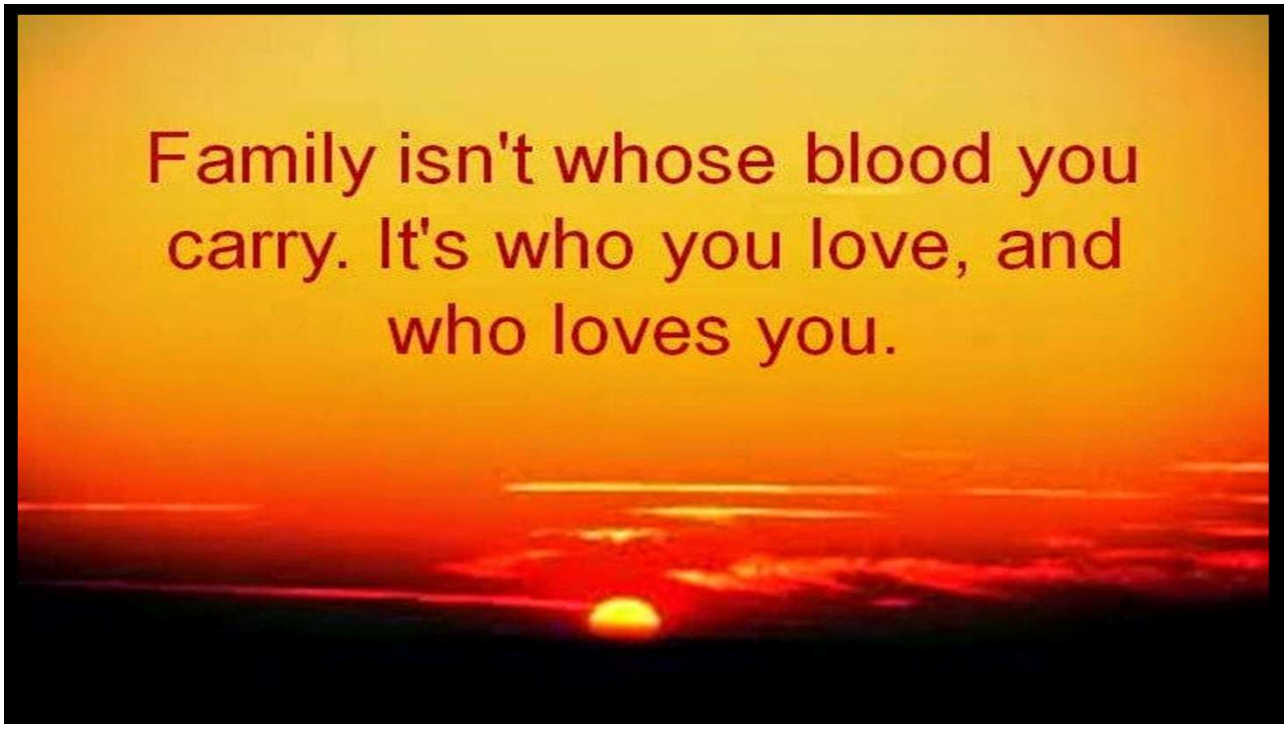
Maria M. Jackson MA, RN
Nurse Coordinator
Institute for Reproductive Medicine and Science
Livingston, NJ

Disclosures

- No financial relationships to disclose
- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- Review the history of donor insemination and oocyte donation
- List the indications for donor insemination and oocyte donation
- Describe the parties involved in gamete donation and the implications for each
- Evaluate the impact of at home DNA kits on the practice of gamete donation
- Explore outside influences that impact patient use and acceptance



Historical Perspectives: Donor Insemination

- Unofficial history claims that the first attempts to artificially inseminate a woman, were done by **Henry IV** (1425-1474), **King of Castile**, nicknamed *The Impotent*
- The first documented application of artificial insemination in a human was done in London in the 1770s by John Hunter, which has been called in medical history the “the founder of scientific surgery
- 1953 Dr. Jerome K. Sherman, an American pioneer in sperm freezing, introduced a simple method of preserving human sperm using glycerol
  - Resulted in the first successful human pregnancy with frozen spermatozoa

Ombelet w & Van Robays J. Facts Views Vis Obgyn 2015; 7(2): 137–143.

Historical Perspectives: US Donor Insemination

- In 1909, a letter was published in *Medical World* claiming the first human donor insemination had been performed at the Jefferson Medical College in Philadelphia in 1884 by Dr. William Pancoast.
- The woman had no abnormalities her husband was azoospermic due to a case of gonorrhea from “sowing his wild oats in his younger days.”
- Dr. Pancoast discussed the case with his medical students (including Addison Hard who wrote the letter) and it was suggested that semen should be collected from the "best looking" member of the class, and used to inseminate the woman.
- Dr. Pancoast agreed to the experiment, and did not inform either the woman or her husband.
- The woman was anesthetized, the procedure carried out and it wasn't until it became evident that the woman had actually conceived that her husband was informed; he was pleased. At his request, his wife was never told how she became pregnant.
- Hard's letter went on to say that, as a result of this medical school experiment, the wife gave birth to a son, who became the first known child by donor insemination (DI).

Gregoire AT & Mayer R. Fertil Steril 1965;16 (1): 130-134.

Historical Perspectives: Egg Donation

- The first birth using a donor egg was reported in 1984 from an egg fertilized *in vivo*
- An anonymous egg donor was inseminated, and then uterine lavage was performed at precisely the right time to recover the resulting embryo, which was transferred into the intended mother's uterus
- Until the late 1980s laparoscopy was used to to retrieve donor eggs not the transvaginal approach currently used

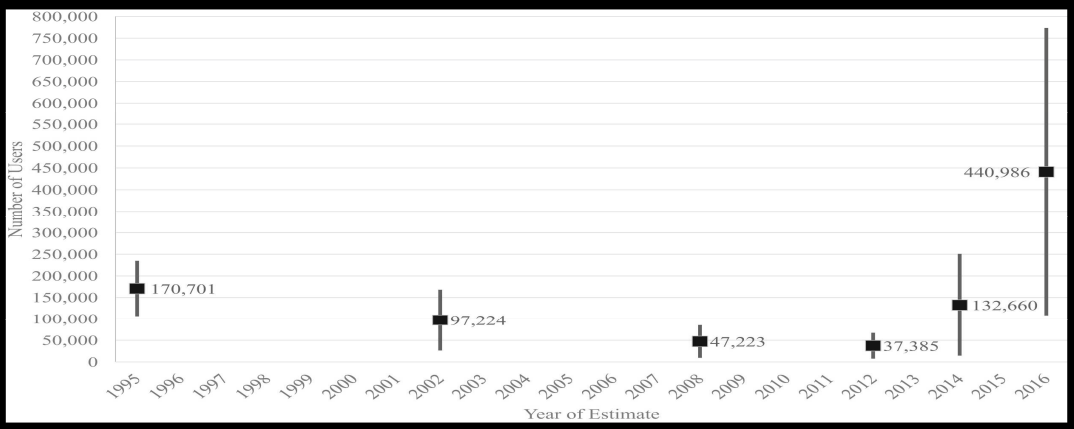
Bustillo M, Buster JE, Cohen SW, et al. JAMA 1984;251:889; Sauer MV. Fertil Steril 2018;110:981-987; Leeton J, Chan LK, Trounson A, Harman J. PJ. In Vitro Fert Embryo Transf 1986;3:379-382.

Donor Insemination Statistics

- The US government does not track DI therefore the actual number of donor conceived offspring is not known
  - Practice is shrouded in secrecy (still) so accurate estimates impossible to determine
  - 30,000 to 60,000 annual births from donated sperm has been the figure used in the literature
- National Survey of Family Growth include women of childbearing age (15–44)
  - In 2015–2017, **440,986** [95% CI: 108,458 – 773,513] were estimated to have used donor insemination
  - DI users were mostly White, urban, older, college-educated, and had high family incomes

Arocho R. et al. Fertil Steril. 2019 October ; 112(4): 718–723.

Estimated Number of Women Reporting Having Used Donated Sperm or Mixed Husband/Partner with Donor



Arocho R. et al. Fertil Steril. 2019 October ; 112(4): 718–723.

SART Data 2020: Donor Eggs

- Fresh
  - N: 1277
  - LBR: 44.6%
- Frozen
  - N: 2541
  - LBR: 41.1%
- Thawed Frozen Embryos
  - N: 13,649
  - LBR: 47.2%

https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2020#donor-fresh-egg

Indications for Donor Insemination

- Azoospermia, severe oligospermia, or other significant sperm or seminal fluid abnormalities
- Ejaculatory dysfunction
- IVF with ICSI is not elected or feasible
- Male partner has a significant genetic defect and the recipient also is known either to be affected or to be a carrier of it
- The recipient has previously produced an offspring affected by a condition and carrier status cannot be determined
- Male partner has an ineradicable sexually transmissible infection
- The female partner is Rh-negative and severely Rh-isoimmunized, and the male partner is Rh-positive
- Females without male partners

Fertil Steril. 2002(77):S5: 2-5.

Indications for Egg Donation

- Hypergonadotropic hypogonadism (Primary gonadal failure/Turners)
- Advanced reproductive age
- Diminished ovarian reserve
- Women who are known to be affected by or be the carrier of a significant genetic defect or who have a family history of a condition and whose carrier status cannot be determined
- Poor oocyte, and/or embryo quality
- Multiple failures in prior attempts to conceive by ART
- Single men/ same sex male couples

Practice Committee Volume 82, Supplement 1, 13-15 September 01, 2004.

Gamete Sources: Sperm

- Commercial sperm banks
  - Approximately 2 dozen in the US
  - Options
    - Non-identified (anonymous)
      - Open
      - ID disclosure
        - » Anonymous contact through the sperm bank
  - Approximately 1/3 of US sperm banks offer an open identity option
    - 2016 CA Cryo required all new donors to be either Open or ID disclosure
- Directed/Identified (known) donors

lamag.com/citythinkblog/sperm-bank-california-cryobank/

Gamete Sources: Eggs

- Clinic recruited
  - Costly, labor intensive, <10% of candidates are accepted
  - Covid has had a significant impact on recruitment
- Egg banks
  - Efficient, diverse inventories, multiple pricing options/guarantees, cycle synchronization unnecessary reducing the time to complete a cycle
- Agencies
  - Costly but useful when patients are looking for specific characteristics/ethnicities
  - Clinic is responsible for screening
- Identified/directed (known)

Gorrill M, Johnson L, Patton P, Burry K. Fertil Steril 2001; 75: 400-04.

Donor Sperm Screening

Donor sperm FDA requirements and ASRM recommendations (4–8).

Non-identified (anonymous) sperm donor	**FDA requirement** ✓ Donor physical exam ✓ Donor questionnaire ✓ Medical history ✓ Donor infectious laboratory tests at FDA-approved laboratory (including CMV and HTLV types I and II IgM and IgG on sperm source) within 7 days (before or after) of sperm acquisition ✓ 6-month quarantine with repeat infectious disease testing ✓ Must be ELIGIBLE to use tissue **ASRM recommendation (in addition to the FDA requirements)** ✓ Psychoeducational screening ✓ Genetic screening ✓ Infectious disease testing of recipient and recipient's sexually intimate partner(s)
Directed (known) sperm donor	**FDA requirement** ✓ Donor physical examination ✓ Donor questionnaire ✓ Donor infectious laboratory tests at FDA-approved laboratory (including CMV and HTLV types I and II IgM and IgG on sperm source) within 7 days of sperm acquisition ✓ Ineligible tissue can be used but with appropriate labeling and consent **ASRM recommendation (in addition to FDA requirements)** ✓ Psychological screening ✓ Genetic screening ✓ Infectious disease testing of recipient and recipient's sexually intimate partners ✓ Medical history ✓ Quarantine >35 days followed by repeat infectious disease testing ✓ Legal consultation; laws may vary by state

Note: ASRM = American Society for Reproductive Medicine; CMV = cytomegalovirus; FDA = U.S. Food and Drug Administration; HTLV = human T-cell lymphotropic virus; IgG = immunoglobulin G; IgM = immunoglobulin M.

ASRM. IVM: Gamete and embryo donation. Fertil Steril 2021.

Guidance regarding gamete and embryo donation *Fertil Steril* 2021; 115 (6):1395-1410.

Donor Egg Screening

Donor oocyte FDA requirements and ASRM recommendations (4, 5).

Oocyte donor	**FDA requirement** ✓ Donor physical examination[a] ✓ Donor questionnaire[b,c] ✓ Donor infectious laboratory tests at an FDA-approved laboratory 30 days before, or up to 7 days after[d] oocyte acquisition ✓ Non-identified (anonymous): must be ELIGIBLE to use tissue ✓ Directed (known): ineligible tissue may be used but with appropriate labeling and consent **ASRM recommendation (in addition to FDA requirements)** ✓ Psychoeducational counseling ✓ Genetic screening ✓ Medical history ✓ Infectious disease testing of recipient and recipient's sexually intimate partners ✓ Legal consultation, particularly for directed donation

Note: ASRM = American Society for Reproductive Medicine; FDA = U.S. Food and Drug Administration.

[a] https://www.fda.gov/media/73072/download.

[b] https://www.fda.gov/media/73072/download.

[c] https://www.fda.gov/media/96528/download.

[d] May not be resulted in time for fresh donation.

ASRM. IVM: Gamete and embryo donation. Fertil Steril 2021.

Guidance regarding gamete and embryo donation *Fertil Steril* 2021; 115 (6):1395-1410.

Parties Involved in Gamete Donation

- Multiple players are involved in the process and each has its own perspective
  - Clinic
  - Donor
  - Recipient
  - Offspring

ASRM Ethics Committee Opinion. Interests, obligations, and rights in gamete donation. Fertil Steril 2019;111:664–70.

Parties Involved in Gamete Donation

- Affected parties have, "distinct but, at times, competing interests"
  - These interests may give rise to rights and corresponding obligations
- Little consensus about how to balance conflicting interests or define the rights and responsibilities of donors, recipients, and programs
  - For this reason, it is especially important that programs are explicit about expectations regarding future information sharing and contact between donors and individuals born as a result of donation

Clinic Perspective

- Clinicians have an obligation to all the parties involved
  - Safety and well-being of the donor
  - Protecting the health of recipients
    - Ethically obligated to screen donors for infectious diseases and genetic risk factors
  - Protecting the health of the unborn child
- Obligation to do this in the most ethical way possible
  - Definition of "ethical" may be interpreted differently
    - Psychological screening over the phone once frowned upon now commonplace
    - Establish an age limit for recipient
- Must be done in a cost efficient manner
- Managing patient expectations in light of information available to them from social media and Dr. Google

Recipient's Perspective

- I can't believe I'm considering this option
- Who are the donors?
  - What's their motivation?
  - How are they screened?
  - Do you validate the information they provide?
  - Do you do background checks?
- What do my partner and I need to do?
- What are my chances of taking home a baby?

Recipient's Perspective: Managing Their Expectations

We are seeking a high-achiever egg-donor with high standardized test scores and some outstanding achievements and awards. You should be between 18 - 35 years old.

An ideal egg-donor would be a 21 year old Harvard student with A GPA, near-perfect SATs, and several awards in high school and university. She wants to be an egg-donor in order to help bring a child into the world with the same special gifts she has.

Your eggs will be fertilized with sperm from the husband, and the resulting embryos used to impregnate the wife, or a surrogate mother.

About us: We are a highly educated couple, but are unable to have children due to the wife's infertility. The husband is a highly accomplished scientist/mathematician and businessman. The wife has a good graduate-

- **The ideal donor would be**
  - **Pretty/handsome**
  - **Smart**
  - **Athletic**
  - **Musically talented**

HEALTH ›

Ivy League sperm: Do you have it?

MARCH 31, 2011 / 1:31 PM / CBS NEWS

https://www.cbsnews.com/pictures/ivy-league-sperm-do-you-have-it/4/

To become a sperm donor, a guy must have lots of fast-swimming, well-formed sperm. But that's not all he needs. Potential donors are also judged on their personality and intelligence. It helps if you're an Ivy Leaguer. The ideal sperm donor stands six feet tall and has blond or brown hair, blue or green eyes and a "medium" complexion. Dimples? They're a plus!

Recipient's Perspective: Managing Their Expectations

Majority would love twins…

- Aware of increased maternal risks
  - Feel technology is good so the risks are low
- Aware of increased risk of premature delivery
- Avoid having to do another cycle
- Avoid waiting lists
- Like the **idea** of twins

Ryan GL et al. *Fertil Steril* 2004;81(3):500–4.
Mendoza R et al. *J Reprod Infertil* 2018; 19(3):167–173.

Recipients Perspective: Age cutoffs

New technologies and cultural shifts have created a booming cohort of wrinkled moms and dads with newborn babies. So why do older parents make so many people uneasy? *By Lisa Miller*

- "Old parents face a version of the judgment implicit here: *They have no idea what they're in for*. More than that: *This is just not right*.
- A new child may be a blessed event, but when a 50-year-old decides to strap on the Baby Björn, that choice is seen as selfish and overwhelmingly prompts something like a moral gag reflex. "

Is this the new normal?

ART: Advanced Reproductive Age

ADVANTAGES

- Better prepared
- Less stressed
- Better positioned economically
- Higher levels of education
- Happier parents

DISADVANTAGES

- Goes beyond the "natural" age limits to reproduce
- Unable to meet the emotional, financial, and physical demands of raising a child
- Greater likelihood that the children will suffer the loss of one or both parents before reaching adulthood
- Medical/obstetrical risks
- Increased germline DNA mutations (older fathers)

Myrskyla M et al. Gynakologe 2017: 50(10):767-772.

Zweitel JE. *Fertil Steril* 2015:104:513-9.
Carslake et al. *Nature Research* 2019; 9:1-14.

Recipient's Perspective: Age Cutoffs

Why they're needed:

- Concerns for the mother's health
  - Careful screening required
  - Adequate counseling re: risks of complications
- Additional screening and clearances necessary
- SET strongly recommended
- Discouraged/denied in women 50 and over with underlying medical conditions & >55 regardless of health
- Each clinic determines what that age is

ASRM Ethics Committee Report: Oocyte or embryo donation to women of advanced age. Fertil Steril 2016; 106 (5): e3-7.

Are my Parents Too Old?

Meet the 57-year-old woman who gave birth: 'The whole thing was a bit surreal'

Barbara Higgins gave birth to a son at 57, nearly five years after she and her husband endured the death of their 13-year-old daughter.

"Actually in many ways I think it's easier," she said. "I don't have such big expectations. I'm not concerned about external judgments and factors. It's just us and Jack and our day-to-day life. So far, so good."

Having a baby at 50: Most of my friends are grandparents

19 May 2021

Claire Mear said going for scans as an older mum was "terrifying"

This week Naomi Campbell made the surprise announcement that she had become a mother for the first time at 50. It comes amid a rise in women having children later in life. According to the ONS, there were 2,390 babies born to mothers aged over 45 in England and Wales in 2019 - the latest figures available - a rise of almost half in 10 years.

BBC Radio 5 Live has been hearing from women who have had babies later in life.

https://www.bbc.com/news/57174993g

Recipient Psychoeducational Counseling

- Psychoeducational consultation with a qualified licensed mental health professional who has training and education in third-party reproduction is strongly recommended for all parties involved in gamete donation
- Covering potential emotional, moral, ethical, and social implications of using a gamete donor
- If a directed donor is used there should be separate consultations done.

- Long-term impact on the family
- Needs of donor-conceived persons
- Grief and loss
- Limitations of donor screening
- Transition to parenthood
- Disclosure
  - Planned
  - Inadvertent
- Challenges of anonymity and the implications for donor-conceived families because of:
  - Direct-to-consumer DNA testing
  - Technological advances
  - Social media, and the implications for donor-conceived families

Donor Perspective

- Donation is not a one time event
- Anonymity not guaranteed
- Implications are far reaching
- Ongoing communication is essential
  - Benefits recipient and offspring
  - May benefit the donor
- There may be frozen embryos resulting from their donation
  - Issues of consanguinity
- Possible donation of unused embryos to another recipient

Donor Perspective

- They may want contact with the recipient(s)/offspring
- They may have an interest in knowing the cycle outcome but are usually not told
- Have to be counseled about advances in genetics that may impact them
- Advised that laws and circumstances may change
- Promises of anonymity or future contact by offspring cannot be assured

Donor Psychoeducational Counseling

- Protects both the donor and recipient
- Issues are complex and changing
- Donors derive no benefit from medical treatment only financial
- Different risk/benefit decision
- Different ethical considerations

Offspring: Forgotten Part of the Equation?

Tough Questions

- What do we as a society owe donor-conceived children?
- Do recipient- parents have a duty to tell their donor-conceived child about his/her genetic origins?
- Should the identity of the donor be disclosed or remain anonymous?
- Does the child have a *right* to know their conception story and to receive information, including identifying information, about the donor?
- If a donor-conceived child has a right to know, who has the duty/responsibility to tell them about it?

Rights of the Offspring

- Focus for clinics is to "overcome" fertility issues of the recipient
  - Recipients get to experience pregnancy
  - Child genetically related to one of them
- Didn't anticipate the effects on offspring
  - Need to know where they come from
  - Knowledge is essential to forming their identity
- Clinics are complicit in the veil of secrecy that exists

Rights of the Offspring: International laws

- United Nations Convention on the Rights of the Child (2019)
  - Donor-conceived people requested international and national frameworks and laws that ensure their right to access information about their origins and to preserve relations with their genetic and social families
- Parliamentary Assembly of the Council of Europe (2019)
  - Approved Recommendation 2156 asking the Committee of Ministers to deliberate on the waiving of anonymity for all future human gamete donations in order to allow all children born through assisted reproductive technologies (ART) to know their origins

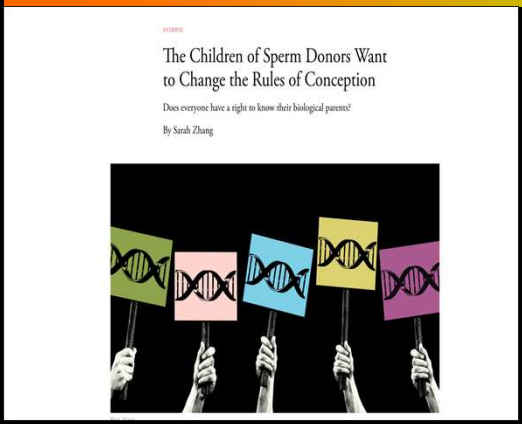
https://www.donorkinderen.com/united-nations-2019
http://assembly.coe.int/nw/xml/XRef/Xref-XML2HTML-EN.asp?fileid=27680

Why Disclose the Use of Donor Gametes?

- Avoid secrets that can strain the family relationships
- Avoid inadvertent disclosure that can be far more damaging than planned disclosure
  - Especially true in light of advances in genetic testing
  - Expanded carrier panels
  - At-home DNA kits
- Every child's birth story is important to them
  - They don't necessarily care what it is
  - They'll want to hear it over and over again
- Knowing about the donor at an early age makes it a non-issue for the child
  - May be a much bigger issue for the parent

Hahn S, Craft-Rosenberg M. JOGGN 2002; 31: 283-93. Golombok S. Hum Reprod 1999; 13: 2342-47. Turner A, Coyle A. Hum Reprod 2000; 15: 2041-51.

What Donor Conceived Offspring are Saying



Uprooted author Peter Boni, who learned he was donor-conceived at age 49, lays out a "Donor-Conceived Bill of Rights" that demands, first and foremost, the end of anonymous donations and includes access to a donor's medical records, limits on the number of offspring per donor, and consequences for outright fertility fraud.

"Can you point to any federal law that protects the rights of the donor-conceived child?"

https://www.theatlantic.com/science/archive/2021/10/do-we-have-right-know-our-biological-parents/620405/

Donor Sibling Registry

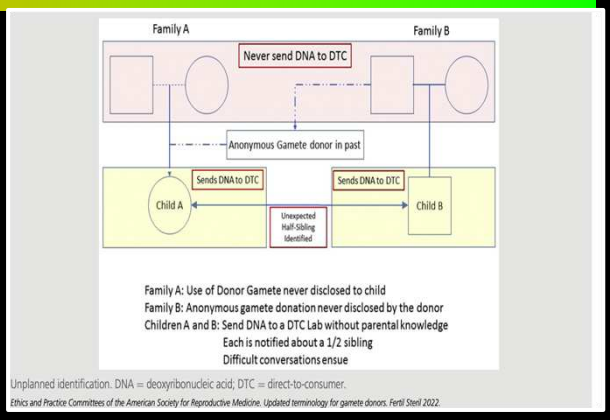
Who We Are

The Donor Sibling Registry (DSR) was created in September 2000 by Wendy Kramer and her son, Ryan. Certain that other donor offspring would have the same curiosity as Ryan about his genetic origins — yet also knowing that sadly, no public outlet existed for mutual consent contact between people born from anonymous sperm or egg donation — this site was started as the logical next step to making those connections.

In addition to the registered members, several thousand people check the site regularly. The DSR averages more than 17,000 unique visitors to the site each month and is a worldwide organization, matching people in Australia, Austria, Belgium, Bolivia, Brazil, Canada, Cayman Islands, Chile, China, Cyprus, Denmark, Dominican Republic, Estonia, Finland, France, Germany, Greece, Haiti, Hong Kong, Iceland, Ireland, Israel, Italy, Japan, Kenya, Liechtenstein, Luxembourg, Malta, Mexico, New Zealand, Norway, Philippines, Puerto Rico, Russia, S. Africa, S. Korea, Spain, Sweden, Switzerland, Taiwan

DNA Testing Kits: Changed the Landscape Irrevocably for all Parties Involved

- DNA testing is readily available for anyone who can afford it thanks to 23andMe and Ancestry.com
  - By the end of 2018 it was estimated that ~ 26 million individuals had taken an in-home DNA test
- Inadvertent disclosure of donor origins is becoming commonplace
- Donor anonymity is uncertain



Regalado, Antonio. "2017 was the year consumer DNA testing blew up." *MIT Technology Review* (Cambridge, MA) February 12, 2018. https://www.technologyreview.com/s/610233/2017-was-the-year-consumer-dna-testing-blew-up/.

Factors that Influence the Use of Donor Gametes

Religious Attitudes

- About a third of American adults say *in vitro* fertilization is morally acceptable, according to a Pew Research Study
- The conditions around IVF, mainly if donor sperm or eggs are used, can ignite debates, especially in faith circles
  - ”Children become products instead of gifts”
- Catholics, Evangelicals and Mormons are among those against using a sperm or egg donor
- Sunni Islam, the most dominant branch of the faith, is against using donors
- Increasing number of Muslims practicing Shiite Islam use donors, especially egg donors
- Chinese culture is strongly influenced by Confucianism, which accepts all forms of assisted reproduction that do not involve third parties

Pew Research Center, April 2, 2015. “The Future of World Religions: Population Growth Projections, 20102050”. http://www.pewforum.org/2015/04/02/religious projections20102050.
Salam HN & Salam NH. *FactS ViewS ViS ObgyN, 2016, 8 (1): 33-48*

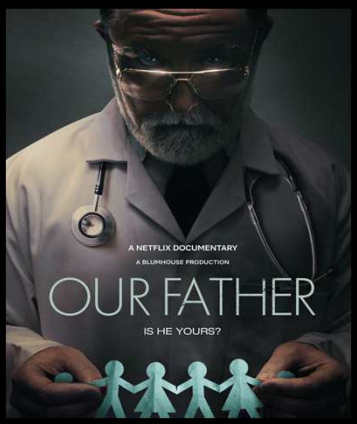
Media Influences

- The Center for Bioethics and Culture Network created two documentaries about egg donation:
  - *Maggie's Story* & *Eggsploitation*
- Women talk about serious medical problems they developed after egg donation and how they felt used and abused by the process
- They maintain that egg donation violates a woman's rights in four ways:
  - Coercing donors through ads "manipulative of young college-aged women"
  - Focusing only on women with certain racial, physical and intellectual characteristics
  - Not disclosing health risks needed for "informed consent"
  - Asking donors to remain anonymous

Q: Are we exploiting donors?

https://www.youtube.com/watch?v=jAMrwAGR3GA

Media Influences



- *Our Father* the Netflix documentary exposing Dr. Donald Cline, "the best infertility doctor in Indianapolis," who secretly fathered dozens of his patients' children — and was only caught when one of those children attempted to connect with her half-siblings
- Number of offspring was at 94 and counting when the film aired
- *Our Father*'s main focus is on highlighting the lack of legal recourse afforded to the siblings and their parents

Media Influences

"The sperm kings of America are exhausted.

People are fed up with sperm banks," said Kyle Gordy, 29. He invests in real estate but spends most of his time donating his sperm, free (except for the cost of travel), to women.

He also runs a nearly 11,000-member private Facebook group, Sperm Donation USA, which helps women connect with a roster of hundreds of approved donors. His donor sperm has sired **35** children, with five more on the way.

Donors are going direct to customers. They meet with prospective mothers-to-be in Airbnbs for an afternoon handoff; Facebook groups with tens of thousands of members have sprung up.

https://www.nytimes.com/2021/01/08/business/sperm-donors-facebook-groups.html

Third Party Regulation: Do we Need it?

"The USA has often been characterized as the 'wild west' of the reproductive industry given its relatively lax and sparse regulation of third-party and assisted-conception transactions. Unlike other nations which ban or strictly control practices such as surrogacy or gamete donation, the USA has no such federal legislation that regulates the rights and responsibilities of various players—from physicians and clinics to intended parents, donors and surrogates, and donor-conceived children — involved in third-party assisted reproduction in the USA."

"The permissive approach to assisted reproductive practices found in the USA fits within the dominant American cultural ideology of wariness about government interference in the 'private' sphere of the family. "

Markens S. J Law Biosci. 2016 Dec; 3(3): 666–672.

ASRM Guidelines

- Follow rigorous developmental process based on documented, verifiable systematic reviews of the scientific literature
- Summary statements include evidence-based recommendations intended to optimize patient care and guide medical practice
- A task force of topic experts with varying levels of experience develop the guidelines
- Reviewed every 5 years for currency or sooner if meaningful new data emerge

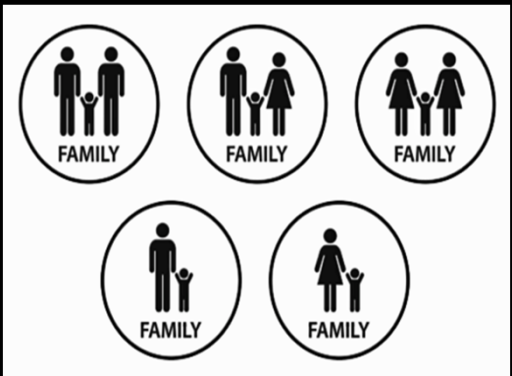
http://www.asrm.org/news-and-publications/practice-committee-documents/additional-documents/asrm-practice-documents/

Are ASRM Guidelines Necessary?

YES!

- We're confronted on a daily basis with challenging situations
- They provide a framework in a ***largely unregulated industry***
  - Some posit this is an attempt by ASRM to prevent further involvement by the Federal government in a largely unregulated industry
- Potential for abuse is great and ultimately the patient is the biggest loser
- Have no teeth but they provide a framework

In Summary: Family 2022



- There are multiple parties involved in gamete donation
- Interests of these parties may have competing agendas
- Clinicians are facilitators and educators
- The interests of the offspring must be considered

IRMS Reproductive Medicine

Confronting Compassion Fatigue & Burnout

Carol Lesser, MSN, NP-C

Fertility nurses are in the profession of creating life and helping patients navigate a deeply personal and emotional journey. While this career path can be deeply rewarding it is also inherently challenging and difficult, both intellectually and emotionally. The world of assisted reproductive technology (ART) is increasingly complex and calls upon the IVF nurse to understand many complex disciplines entwined in the IVF experience. This is even more challenging given that we learn our craft on the job, implying a steep learning curve to understand all of the components of IVF nursing.

The patient's experience, exacerbated by our current and protracted pandemic is intrinsically stressful and can place excess demands on the IVF nurse who has the majority of daily patient contact. The nurse is often overworked, can feel underappreciated, underprepared and overwhelmed with the demands and responsibilities of the job. Unfortunately, this can lead to compassion fatigue, burn out and staff turnover. This in turn leads to understaffing and higher than previously seen resignations and turnover. The COVID inspired "Great Resignation" means fewer nurses are willing to work in less than ideal work environments. While increasingly, individuals are looking for " more meaningful' work and certainly infertility nursing fits that bill, they are also interested in more flexible hours, virtual work when feasible, better wages and benefits that demonstrate appreciation for their service.

Our profession lends itself to a roller coaster of emotions, from moments of elation to times of disappointment and other times to grief, potentially placing us at risk of developing compassion fatigue. Compassion is intrinsic to nursing practice; therefore, none of us is immune to compassion fatigue. Fortunately understanding what puts us at risk for compassion fatigue can help prevent burnout and possibly worse, leaving our profession.

Recognizing the signs of compassion fatigue and understanding the universal nature of the mental health challenges of our particular filed can be useful. Sharing suggestions for how to navigate this common experience can offer nurses a foothold to incorporate the changes needed to improve the experience for both nurse and patient.

Strategies to mitigate compassion fatigue include creating open communication with co-workers and administrators to improve the work experience. This in turn should translate into better patient care and support. This includes valuing and promoting educational programs aimed at offering the nurse a deeper understanding of the foundational knowledge and principles of reproductive medicine and their role and responsibilities.

Our patients depend on our support and empathetic guidance. Before we can begin to take care of them, we must take care of ourselves. However, it also requires systemic changes that concretely and materially show appreciation for the challenging work IVF nurses with better staffing, compensation and recognition of the vital role IVF nurses play in the patient experience and success with ART, realizing that happy nurses make happy patients.

Confronting Compassion Fatigue & Burnout

Carol B. Lesser, MSN, NP-C
Boston IVF
Waltham, MA

Disclosure Information

- Has no relationships to disclose
- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- Define compassion fatigue and burnout in the field of fertility nursing and its signs and symptoms
- Discuss ways COVID-19 has worsened this issue
- Assess strategies to manage compassion fatigue in your work environment
- Recognize the unique contribution and critical role played by the IVF nurse and why this issue matters

Daily Awareness

"Every day, think as you wake up: Today I am fortunate to be alive. I have a precious human life. I am not going to waste it. I am going to use all my energies to develop myself, to expand my heart out to others, to achieve enlightenment for the benefit of all beings. I am going to have kind thoughts towards others; I am not going to get angry or think badly about others. I am going to benefit others as much as I can."

Tenzin Gyatso, the 14th Dalai Lama

Navigating Work with Compassion

"This is the real secret of life: to be completely engaged with what you are doing in the here and now. Instead of calling it work, realize it is play."

Alan Watts, theologian

Epicquotes, accessed 10/7/21.

Why We Choose This Work

Common reply: TO HELP OTHERS

- To help people through one of the hardest chapters in their lives
- I can think of no higher honor than helping people who place their trust in us to help them achieve the miracle of life
- To be of service to those who are determined to become parents
- Because I went through this and I understand

Challenges

- The increasing complexity of what the IVF nurse must learn
- The lack of formal training for this subspecialty
- The global pandemic and “the great resignation’s” effect on how we practice

Newer Challenges

- Increasingly, IVF is a team sport with the IVF nurse on the front line
  - Volume of phone calls/emails
  - EMR demands
  - Financial stressors
  - COVID has made direct contact less frequent with patients and other staff

Challenges We Face

- We often have to deliver bad news, sometimes repeatedly
- Patients ask us to explain why the cycle was not successful
- Our patients' stress can become our stress

Newer Challenges

- Patient turnover
- Staff turnover
- Both are affected by nursing job satisfaction
- Both can be impacted by improving the work environment for the nurse

"Happy nurses make happy patients"

The Patient Experience

- Increasing levels of anxiety and depression
- COVID has heightened these concerns
- Requires increased empathy

A Patient's Perspective

What I wish IVF nurses understood about their patients:

- "A simple kindness makes all the difference. The nurse who looked at me with a smile put me at ease. The nurse who gave an extra minute of patience to answer my questions calmed my racing mind."

A Patient's Perspective

- "Infertility challenges our beliefs, faith and hope in the normal workings of our body and can leave us feeling broken and defective. It forces us to ask why do bad things happen to good people."
- "It is empathy amidst the unknown. It's feeling the nurse is genuinely rooting for me. It's compassion amidst the chaos which makes the journey tolerable."

The Compassion Dilemma

- "Compassionate people are geniuses in the art of living, more necessary to the dignity, security, and joy of humanity than the discoverers of knowledge."[1]
- Compassion fatigue may be the result of being so preoccupied with helping those in distress, that it causes extreme tension resulting in secondary traumatic stress for the helper.[2]

Albert Einstein Quote. AZ Quotes website. http://www.azquotes.com/quote/606131.
Compassion Fatigue Awareness Project website. http://www.compassionfatigue.org/.

Compassion Fatigue Is Not New

- Compassion fatigue is defined as a loss of satisfaction related to doing one's job well or job-related distress that exceeds job satisfaction.
- Coined in 1992 to describe the in-hospital experience
- Now applied to broad settings

Compassion Fatigue: An Introduction. Gifts From Within website. http://www.giftfromwithin.org/html/What-is-Compassion-Fatigue-Dr-Charles-Figley.html.

Sheppard K. Am Nurs Today. 2016;11(1). https://www.americannursetoday.com/compassion-fatigue.

Signs and Symptoms of Compassion Fatigue

Signs and Symptoms

- Sadness and grief
- Nightmares
- Avoidance
- Somatic complaints
- Increased psychological arousal
- Changes in beliefs, expectations, assumptions
- Detachment
- Decreased intimacy

Key Triggers

Stressful situations in which nurses:

- Believe their actions would make no difference or never seemed to be enough
- Experience workplace issues such as high patient census, heavy patient load, high acuity, overtime, and additional work days
- Personally identify with the patients
- Miss serious patient symptoms
- Blame themselves for all problems

Beyond Compassion Fatigue

- Secondary traumatic stress describes the emotional distress that can occur when exposed to another person's traumatic experience
- Burnout is a negative emotional reaction related to workplace stressors

"Mental stress associated with compassion fatigue is a leading determinant of intent to leave the profession."

Theoretical framework: Structural Empowerment Theory (Kanter)

- The theory of structural empowerment suggest that empowering conditions give employees the ability to accomplish their work in a meaningful ways
- The absence of this structure creates a toxic work environment ripe for burn out

The Great Resignation

- While burnout manifests in individuals it originates in systems
- Burnout leads to resignation. Costly on many levels.
- Up to 47% of US health care workers plan to leave their positions by 2025

https://www.aamc.org/news-insights/medical-burnout-breaking-bad

How Do You Feel?

- Underappreciated
- Selfless
- Overworked
- Valued
- Stressed out
- Motivated

Solutions

- Must go beyond yoga, meditation and mindfulness
- Needs institutional solutions that truly support nurses
- Requires engaged and compassionate leaders

Biden-Harris Administration Awards $103 Million

American Rescue Plan Funds to Reduce Burnout and Promote Mental Health and Wellness Among Health Care Workforce

- January 2022
- National recognition of a worsening problem

https://www.hhs.gov/about/news/2022/01/20/accessed June 20, 2022

Compassion Fatigue

- Fertility nurses are in the business of trying to create life and help patients navigate a deeply personal and emotional road
- What we do is inherently complex, challenging, and difficult, both intellectually and emotionally
- Patients depend on our support and empathetic guidance
- Before you take care of them, you must take care of yourself

Lesson from Air Travel Protocol

- As caring professionals, we need to adopt the same life saving approach as on airplanes
- Put your oxygen mask on first before caring for others

Self-Care Is Not Selfish

- Create healthy boundaries
  - By using self-reflection and slowing your response when others invade personal boundaries, you can address the issues with professional and courteous responses
- Seek help from a mentor, supervisor, or charge nurse
  - Consider reducing overtime or changing job assignment
- Adopt replenishing strategies to promote physical, emotional, and spiritual well-being while making improvements to how the practice is organized

Workplace Support

- Increased staffing and pay
- Tangible displays of appreciation: a little goes a long way but more than ice cream breaks
- Intensive orientation tailored to your practice
- Initial emphasis on the basics and eventually training in IVF cycle co-management

It Takes a Village

- Develop and execute a formalized on-the-job training/mentorship programs from day one
- Refer complex cases to those more experienced
- Experienced nurses nearing retirement need to pass the baton of their knowledge and experience on to the newer fertility nurses

Don’t Take It Personally

- Never blame the victim
- Non-reactivity
- Don’t make assumptions
- Offer suggestions and solutions when possible
- Seek the support of a colleague or ask a colleague to intervene

Workplace Support

- Wellness programs embedded into fertility centers promote physical and psychological health
- Weekly mind/body programs
- Nutrition, yoga, acupuncture, and counseling services
- Team meetings to improve the collective experience
- Employee recognition programs, gift cards NOT ice cream
- Providing a relaxation refuge

Kindness

"Our prime purpose in this life is to help others. And if you can't help them, at least don't hurt them.…
This is my simple religion.
There is no need for temples;
no need for complicated philosophy.
Our own brain, our own heart is our temple; the philosophy is kindness.
Be kind whenever possible.
It is always possible."

Tenzin Gyatso, the 14th Dalai Lama

Kindness to Self

- Be kind to yourself
- Remember why you chose this profession
- Understand and clarify your personal boundaries
- Verbally express your needs
- Take positive action to make changes in your environment and work together

Summary

- Importance of networking and sharing our best experiences in the service of providing the best care possible to our patients
- Our work is intrinsically stressful. The challenge is how to work together to improve the experience for both nurse and patient.
- “Choose a job you love and you will never have to work a day in your life.”
  Confucius

Thank you for all that you do!