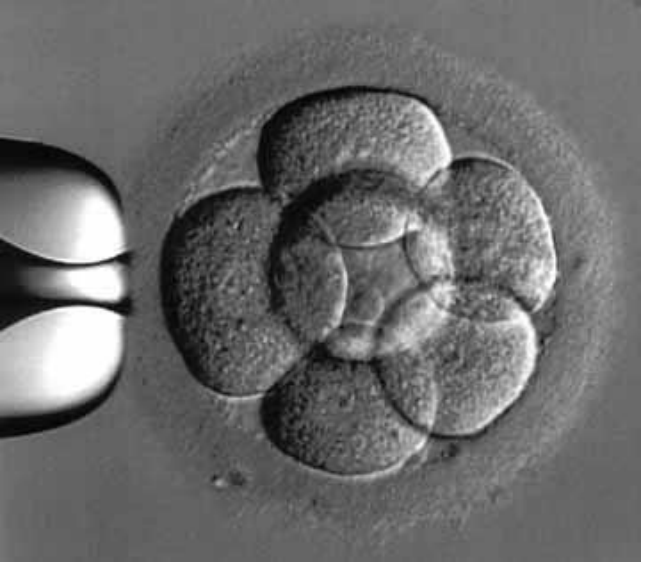


EASTERN WASHINGTON WOMEN'S HEALTH CONFERENCE OCTOBER 11, 2019

Infertility Evaluation & Management

Christopher Herndon, M.D.
Reproductive Endocrinology & Infertility

UW Medicine

DISCLOSURES

None

OBJECTIVES

At the conclusion of this presentation, attendees should be able to:

1. Describe the natural history of conception, ovarian aging, and infertility

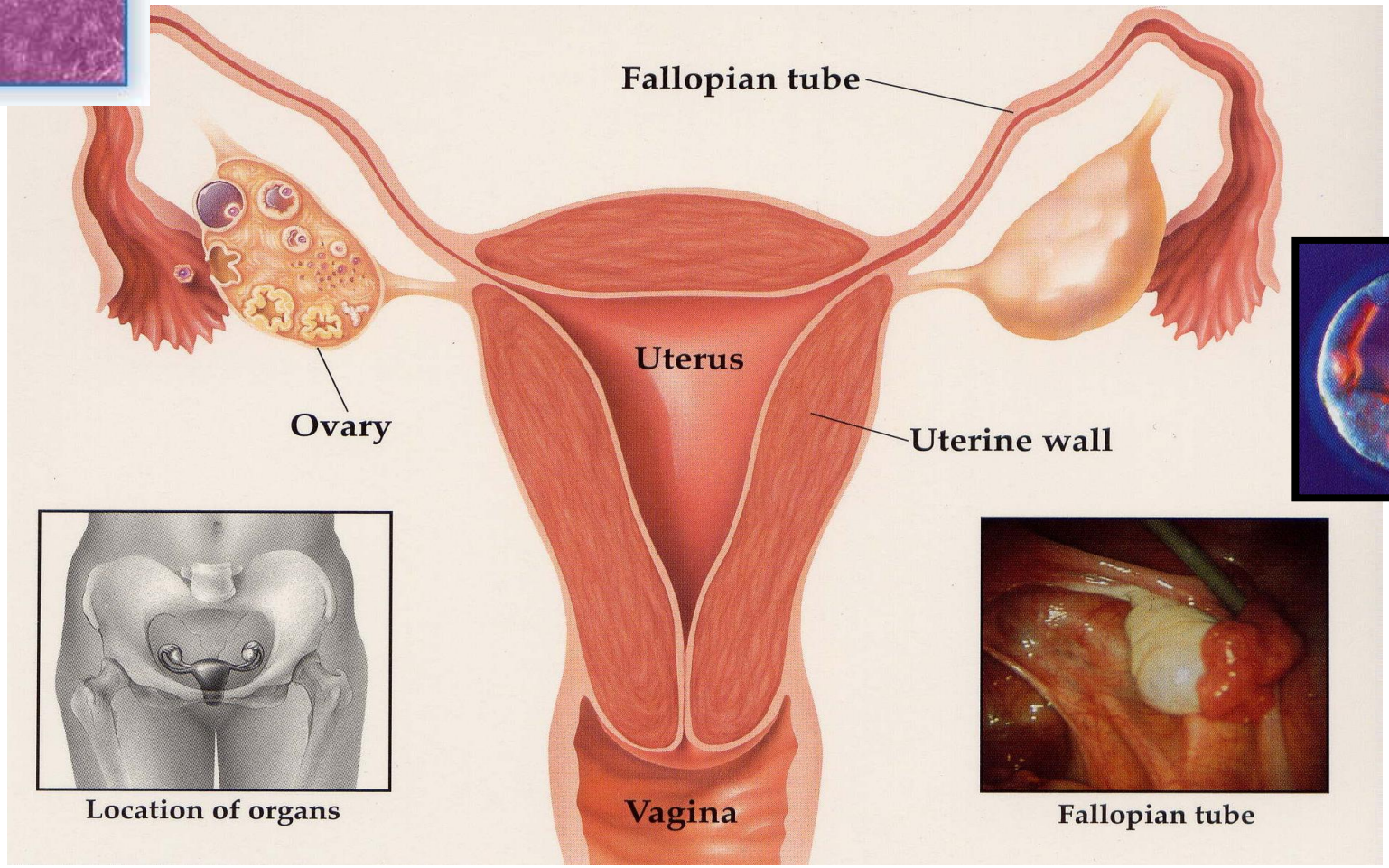
2. Review an office-based and systematic approach for the diagnostic evaluation of infertility

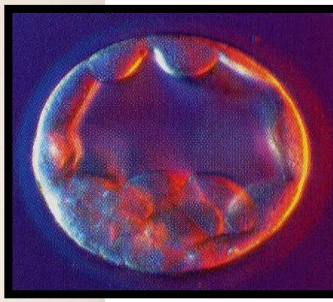
3. Review treatment options including ovulation induction, intrauterine insemination, and assisted reproductive technologies as well as options for fertility preservation.

INFERTILITY

- **8-15% of couples** in a given population are infertile
- Infertility defined as failure to achieve a successful pregnancy **after 12 months** or more of **regular unprotected intercourse**
- **6 months in women over age 35 years**
- Earlier evaluation may be justified based on history and clinical context

A SYSTEMATIC APPROACH





Location of organs

Fallopian tube

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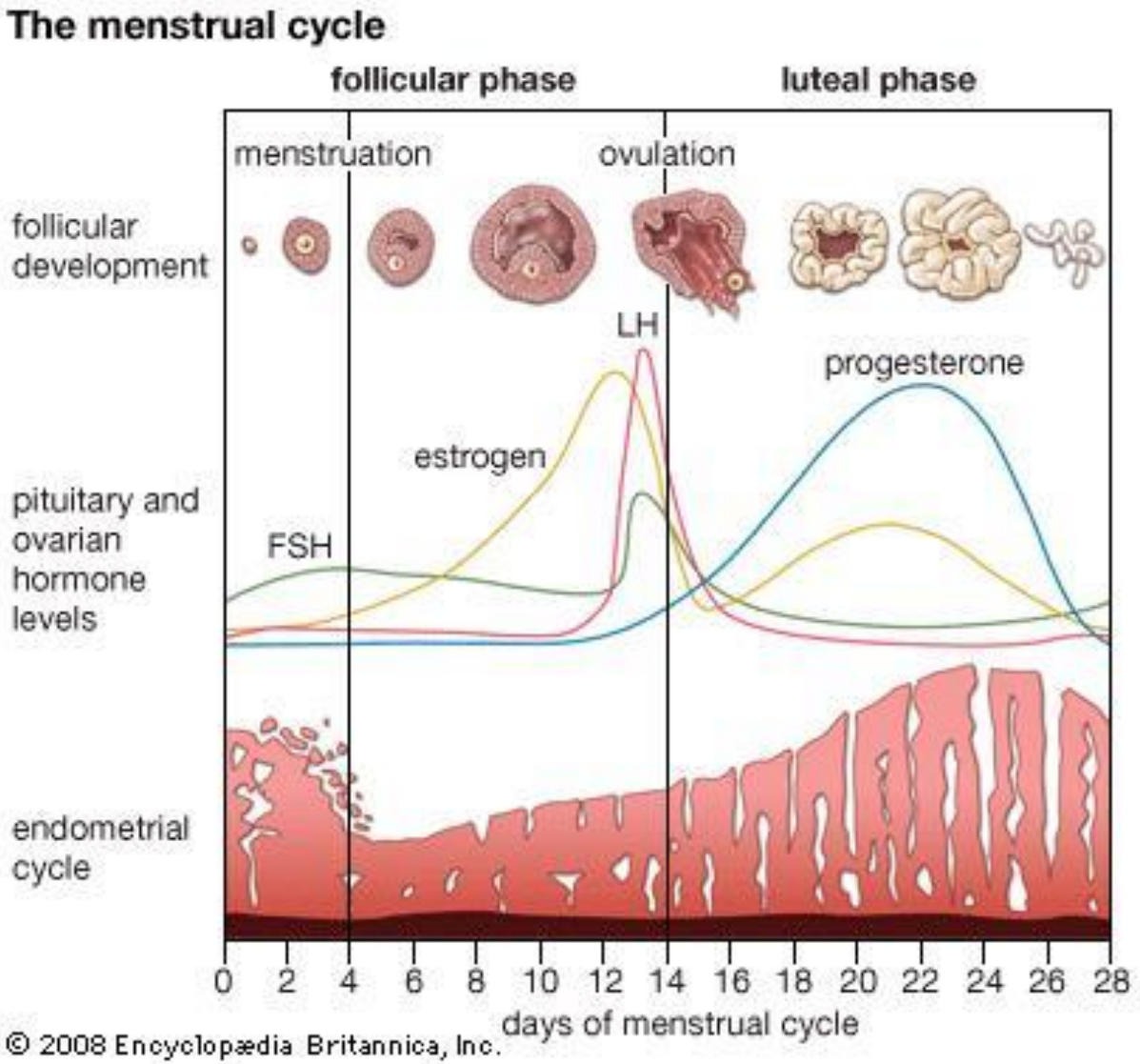
THE MENSTRUAL CYCLE



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OVULATORY ASSESSMENT
HOW & WHEN TO CHECK

- Menstrual diaries
- Basal body temperature (progesterone thermogenic rise ~0.5 deg F)
- LH ovulation predictor kits (~24 hrs prior to ovulation)
- Follicular monitoring ultrasound
- Luteal progesterone
  - Check 1 week before expected menses
  - ≥ 3 ng/mL
  - Variation in serum concentration

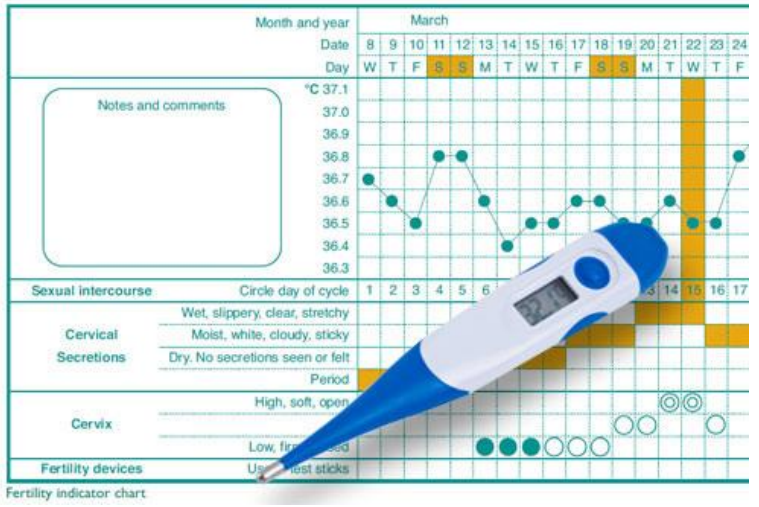
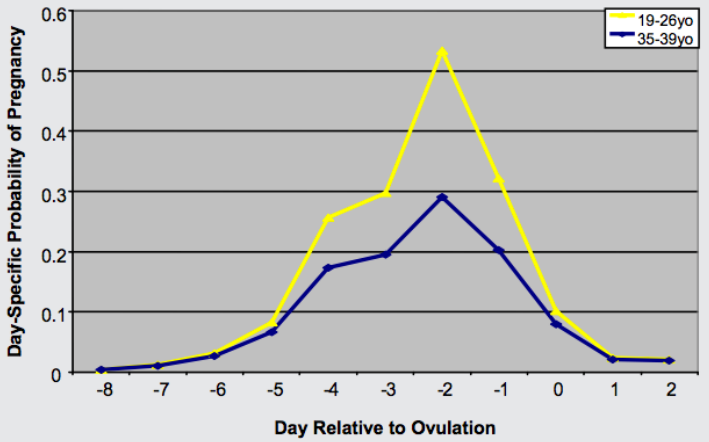


FIGURE 3



Probability of pregnancy by cycle day, involving recurrent intercourse, by age. Data from Stanford and Dunson 2007 (16).

Practice Committee. Optimizing natural fertility. Fertil Steril 2013.

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EVALUATION OF ANOVULATION

- Amenorrhea / oligomenorrhea
- Primary vs. secondary differential
- Endocrinologic vs. structural
- hCG
- TSH, prolactin

HYPERPROLACTINEMIA

- Elevations in prolactin suppress GnRH pulsatility
- Prolactin secretion under inhibitory suppression by dopaminergic neurons
- Broad differential but most common: **medication-induced** (e.g. antipsychotic dopamine blockade agents) or a **secreting pituitary adenoma**.
- **Microadenoma <10 mm**– suppression (dopamine agonists, bromocriptine or cabergoline) is needed only to achieve ovulation for conception or if hypoestrogenic
- **Macroadenoma (≥ 10 mm)** based on prolactin levels, headaches, bitemporal hemianopia, order cranial MRI to evaluate; need suppression to prevent further extension (the sella is a small space) and impairment of visual pathways

EVALUATION OF OVULATORY DISORDERS

World Health Organization Classification:

- **Class I** (low FSH/LH, low estradiol)
- **Class II** (~normalish FSH/LH/estradiol)
- **Class III** (high FSH/LH, low estradiol)

I. HYPOTHALAMIC PITUITARY DISORDERS

- Congential (Kallman's associated with anosmia, idiopathic IHH), acquired (tumor, infiltrative disease, iatrogenic, Sheehan's syndrome.
- Typically FSH > LH usually less than 5 mIU/mL; E2 < 50 pg/mL
- MRI of pituitary
  If acquired, must consider other HP axes (e.g. corticotrophic, thyrotropic)
- Functional hypothalamic amenorrhea / female athletic triad' - 1) menstrual dysfunction, 2) negative energy balance, and 3) decreased bone-mineral density
- Screen for eating disorders
- DEXA (use Z score in younger women)
- HRT, Ca, Vit D, exercise

II. POLYCYSTIC OVARY SYNDROME

- 5-10% of adult female population
- Common syndrome with a very wide spectrum of presentations
- Prevalence relatively stable across ethnic and racial populations; although may present differently
- Although PCOS is associated with hyperandrogenism and infertility early in life, it is a harbinger of a lifelong condition that can lead to serious sequelae such as **diabetes mellitus, hyperlipidemia, endometrial hyperplasia/carcinoma, central obesity, and sleep apnea**

PRECONCEPTUAL MANAGEMENT

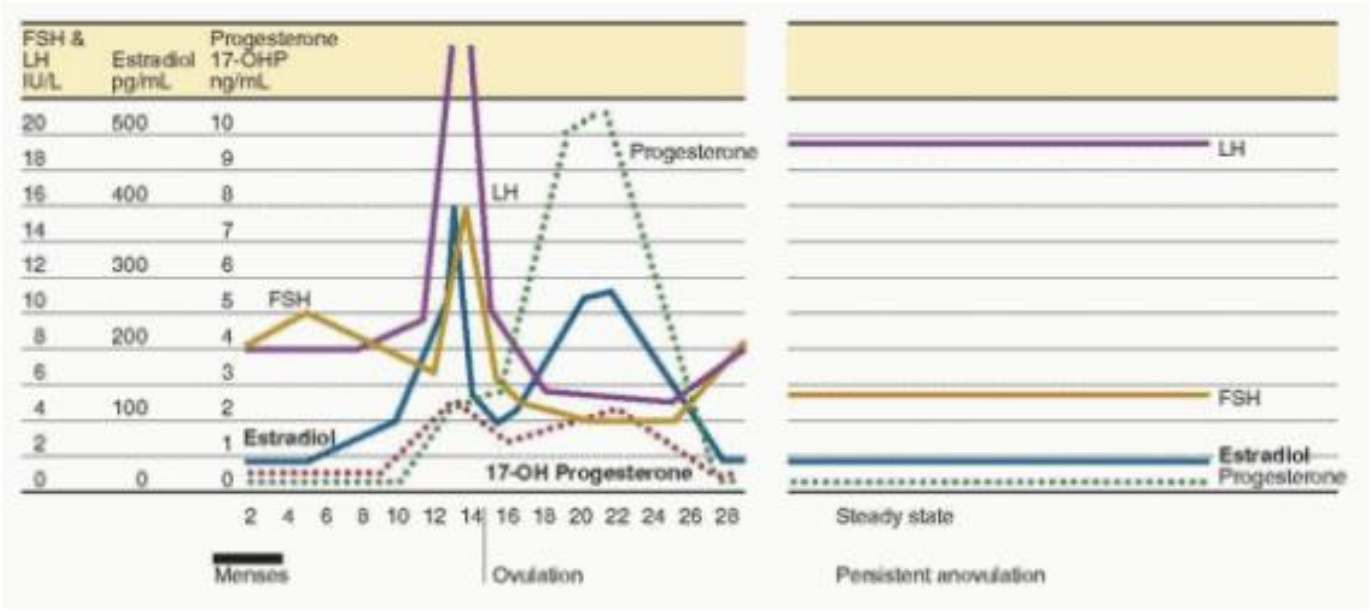
Optimize metabolic status prior to conception

Preconceptual consultation for risks with elevated BMI, diabetes, hypertension

Strategies

- Don’t leave the patient to her own devices!
- See at least every 6 weeks
- Active follow up for ‘weigh-ins’; address and expect recidivism and plateaus
- Can increase medication or utilize alternatives
- Encourage fitness if weight loss is not easily achieved

OVULATION INDUCTION FOR PCOS



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HOW TO GIVE LETROZOLE OR CLOMIPHENE

Letrozole

- Not necessary to start with menses
- Confirm lack of pregnancy (Pregnancy category X)
- Start with 2.5mg daily for 5 days
- If mid-luteal P <3ng/ml, increase dose
- May check with ultrasound for follicle growth but not done in PPCOSII trial
- Higher livebirth rate but off label

Clomiphene

- Not necessary to start with menses
- Confirm lack of pregnancy (Pregnancy category X)
- Start with 50mg daily for 5 days
- If mid-luteal P <3ng/ml, increase dose
- May check with ultrasound for follicle growth but not done in PPCOSII trial

CLOMIPHENE CITRATE / LETROZOLE
SIDE EFFECTS, CONTRAINDICATIONS, AND RISKS

Ovulation Rates for CC

- 50 % ovulate at 50mg dose
- 20% ovulate at 100mg dose
- 8 – 10% ovulate at 150mg dose

Side Effects

Vasomotor 15%
Abdominal pain 5.5%
Nausea and vomiting 2.2%
Headaches 1.3%
Visual 2%

Contraindications

- Pregnancy, hypersensitivity

Risks and Complications

- 5 – 8% Twins <1% triplets
- OHSS (uncommon)

OVULATION INDUCTION IN PCOS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2007 VOL. 356 NO. 6

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Huiman X. Barnhart, Ph.D., William D. Schlaff, M.D., Bruce R. Carr, M.D., Michael P. Diamond, M.D., Sandra A. Carson, M.D., Michael P. Steinkampf, M.D., Christos Coutifaris, M.D., Ph.D., Peter G. McGovern, M.D., Nicholas A. Cataldo, M.D., Gabriella G. Gosman, M.D., John E. Nestler, M.D., Linda C. Giudice, M.D., Ph.D., Phyllis C. Leppert, M.D., Ph.D., and Evan R. Myers, M.D., M.P.H., for the Cooperative Multicenter Reproductive Medicine Network*

ABSTRACT

BACKGROUND

The polycystic ovary syndrome is a common cause of infertility. Clomiphene and insulin sensitizers are used alone and in combination to induce ovulation, but it is unknown whether one approach is superior.

METHODS

We randomly assigned 626 infertile women with the polycystic ovary syndrome to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of metformin and clomiphene for up to 6 months. Medication was discontinued when pregnancy was confirmed, and subjects were followed until delivery.

RESULTS

The live-birth rate was 22.5% (47 of 209 subjects) in the clomiphene group, 7.2% (15 of 208) in the metformin group, and 26.8% (56 of 209) in the combination-therapy group ($P<0.001$ for metformin vs. both clomiphene and combination therapy; $P=0.31$ for clomiphene vs. combination therapy). Among pregnancies, the rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group. The rates of first-trimester pregnancy loss did not differ significantly among the groups. However, the conception rate among subjects who ovulated was significantly lower in the metformin group (21.7%) than in either the clomiphene group (39.5%, $P=0.002$) or the combination-therapy group (46.0%, $P<0.001$). With the exception of pregnancy complications, adverse-event rates were similar in all groups, though gastrointestinal side effects were more frequent, and vasomotor and ovulatory symptoms less frequent, in the metformin group than in the clomiphene group.

CONCLUSIONS

Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication. (ClinicalTrials.gov number, NCT00068861.)

From Pennsylvania State University College of Medicine, Hershey (R.S.L.); Duke University Medical Center, Durham, NC (H.X.B., E.R.M.); University of Colorado, Denver (W.D.S.); University of Texas Southwestern Medical Center, Dallas (B.R.C.); Wayne State University, Detroit (M.P.D.); Baylor College of Medicine, Houston (S.A.C.); University of Alabama, Birmingham (M.P.S.); University of Pennsylvania School of Medicine, Philadelphia (C.C.); University of Medicine and Dentistry of New Jersey, Newark (P.G.M.); Stanford University, Stanford, CA (N.A.C.); University of Pittsburgh, Pittsburgh (G.G.G.); Virginia Commonwealth University School of Medicine, Richmond (J.E.N.); University of California at San Francisco, San Francisco (L.C.G.); and the National Institute of Child Health and Human Development, Bethesda, MD (P.C.L.). Address reprint requests to Dr. Legro at the Department of Obstetrics and Gynecology, Pennsylvania State University College of Medicine, M.S. Hershey Medical Center, 500 University Dr., H103, Hershey, PA 17033, or at rsl1@psu.edu.

*Other members of the Cooperative Multicenter Reproductive Medicine Network are listed in the Appendix.

N Engl J Med 2007;356:551-66.

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PCOS OVULATION INDUCTION

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network*

ABSTRACT

BACKGROUND

Clomiphene is the current first-line infertility treatment in women with the polycystic ovary syndrome, but aromatase inhibitors, including letrozole, might result in better pregnancy outcomes.

METHODS

In this double-blind, multicenter trial, we randomly assigned 750 women, in a 1:1 ratio, to receive letrozole or clomiphene for up to five treatment cycles, with visits to determine ovulation and pregnancy, followed by tracking of pregnancies. The polycystic ovary syndrome was defined according to modified Rotterdam criteria (anovulation with either hyperandrogenism or polycystic ovaries). Participants were 18 to 40 years of age, had at least one patent fallopian tube and a normal uterine cavity, and had a male partner with a sperm concentration of at least 14 million per milliliter; the women and their partners agreed to have regular intercourse with the intent of conception during the study. The primary outcome was live birth during the treatment period.

RESULTS

Women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5%] vs. 72 of 376 [19.1%], P=0.007; rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group (P=0.65). The cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], P<0.001). There were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin pregnancy (3.4% and 7.4%, respectively). Clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness. Rates of other adverse events were similar in the two treatment groups.

CONCLUSIONS

As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others; ClinicalTrials.gov number, NCT00719186.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Legro at the Department of Obstetrics and Gynecology, Penn State College of Medicine, M.S. Hershey Medical Center, 500 University Dr., H103, Hershey PA, 17033, or at rsl1@psu.edu.

*Additional members of the National Institute of Child Health and Human Development (NICHD) Reproductive Medicine Network are listed in the Supplementary Appendix, available at NEJM.org.

This article was updated on October 9, 2014, at NEJM.org.

N Engl J Med 2014;371:119-29.
DOI: 10.1056/NEJMoa1313517

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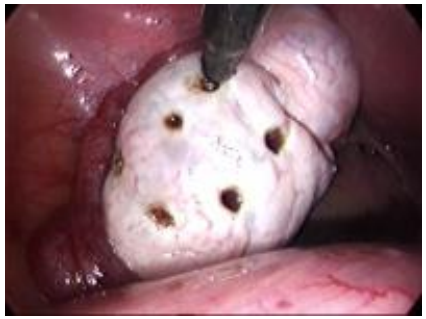
CLOMIPHENE / LETROZOLE RESISTANT PCOS

- Gonadotropin-based ovulation induction
  - High risks of multiple gestation, ovarian hyperstimulation syndrome (OHSS), cycle cancellation
  - Traditional long low dose gonadotropins vs. sequential protocols

CLOMIPHENE / LETROZOLE RESISTANT PCOS

- Historical paper on 75 women who underwent bilateral wedge resections
- Nearly 90% of whom began to have spontaneous menstrual cycles and 65% of those seeking fertility conceived (Stein, Cohen and Elson 1948)

- Laparoscopic ovarian drilling
  - Ovulation rates ~70-90%
  - Cautery or laser
  - 3-6 sites per ovary at depth 4 to 10mm
  - Risk for adhesions / decline of ovarian reserve – uncertain impact

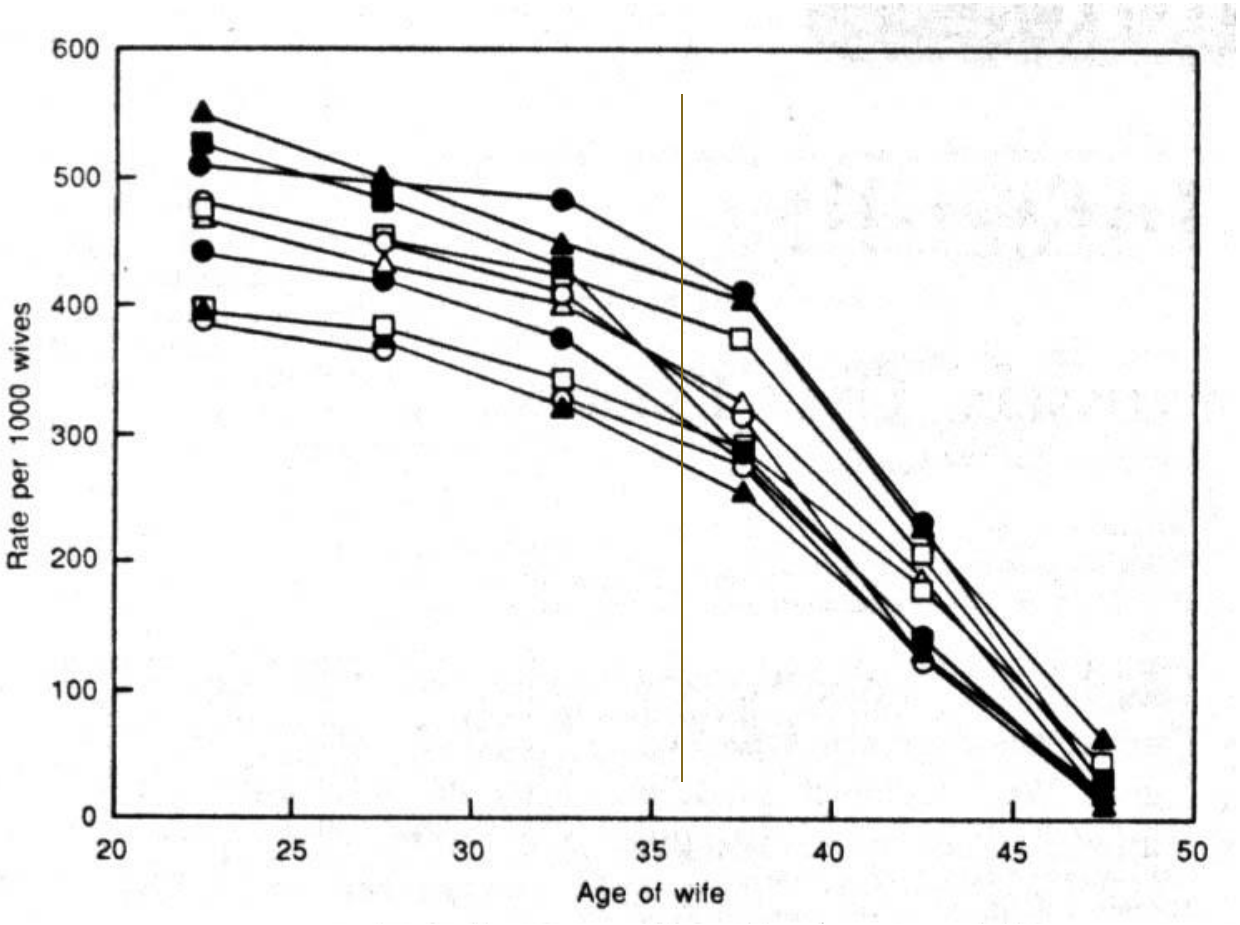


III. PREMATURE OVARIAN INSUFFICIENCY

- Onset menopause before age 40
- FSH /LH / Estradiol & AMH
- Most common idiopathic
- Mosaic Turner Syndrome (check karyotype)
- Fragile X pre-mutation (6% check # CGG repeats FMR1 on X chromosome)
- Autoimmune 5-9% (anti-adrenal and anti-21 hydroxylase antibodies, TSH)

- HRT (increased cardiovascular risk, bone density depletion)
- Donor ovum recipient IVF

AGE DECLINE IN FECUNDITY



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Menken et al. Science 1986

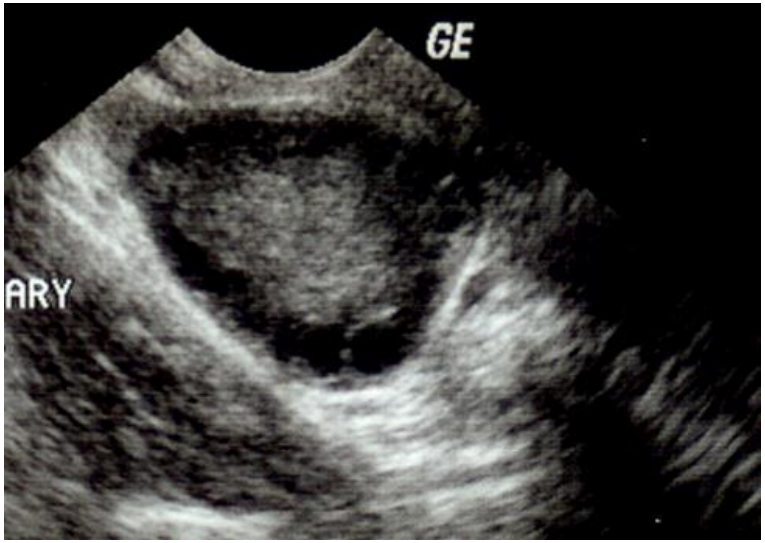
ASSESSMENT OF OVARIAN RESERVE

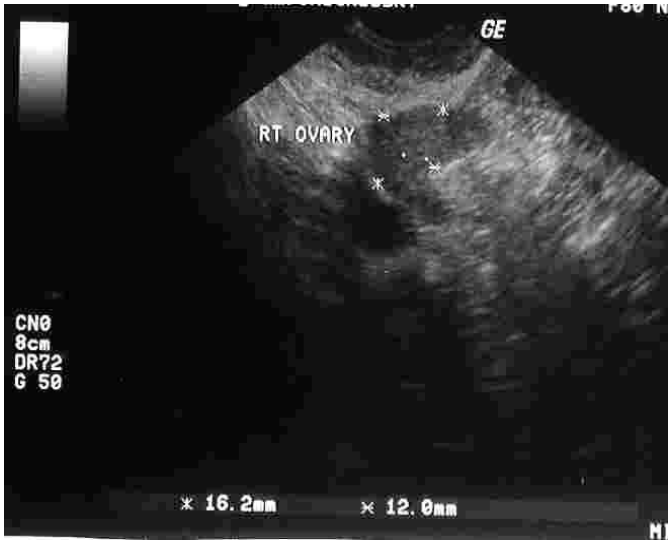
- **Quantity**
  - Day 3 FSH / estradiol / CCCT
  - Anti-mullerian hormone (AMH)
  - Antral follicle counts (AFC)

- **Quality**
  - Female age
  - No clinical tests or morphological grading of oocytes

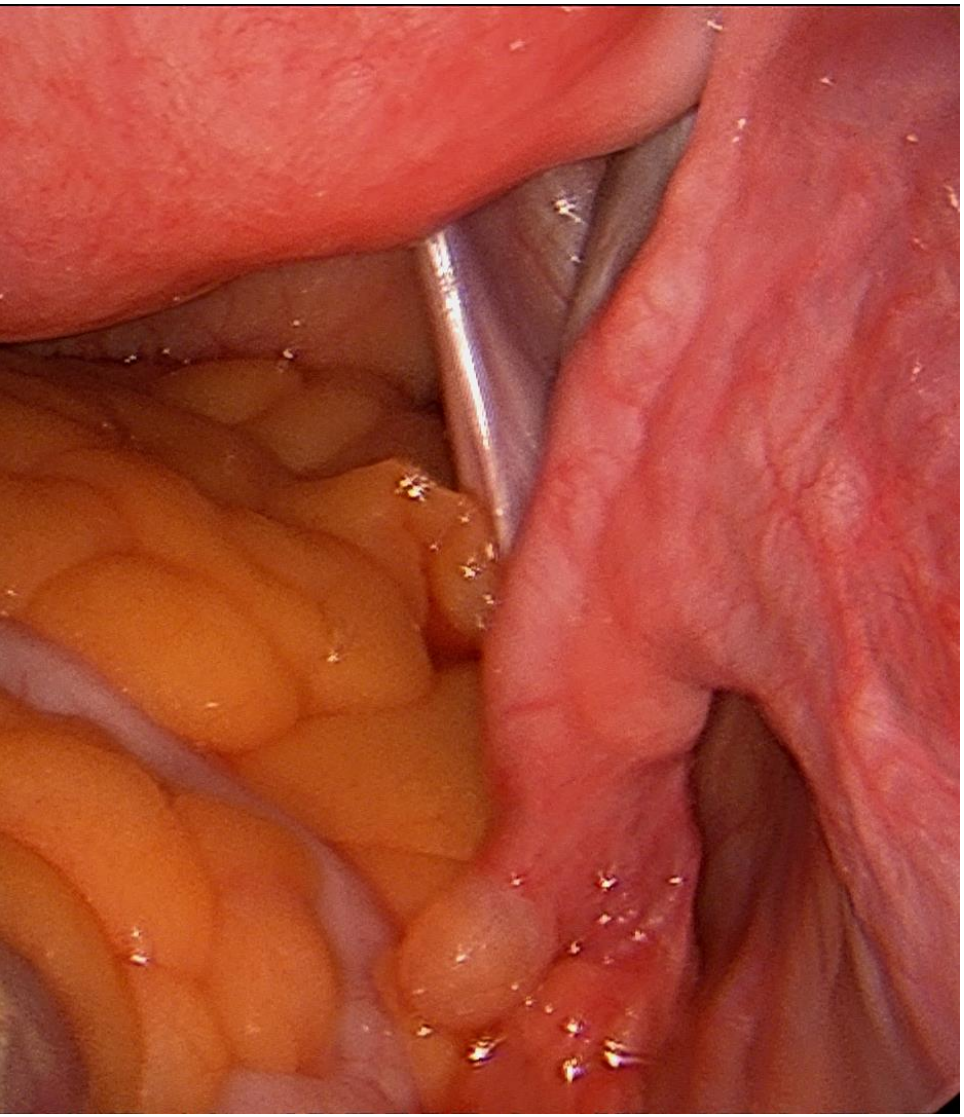
- **Ovarian reserve is not a direct marker of reproductive potential**

  - may predict response to treatment and to an extent prognosis (ASRM 2015)



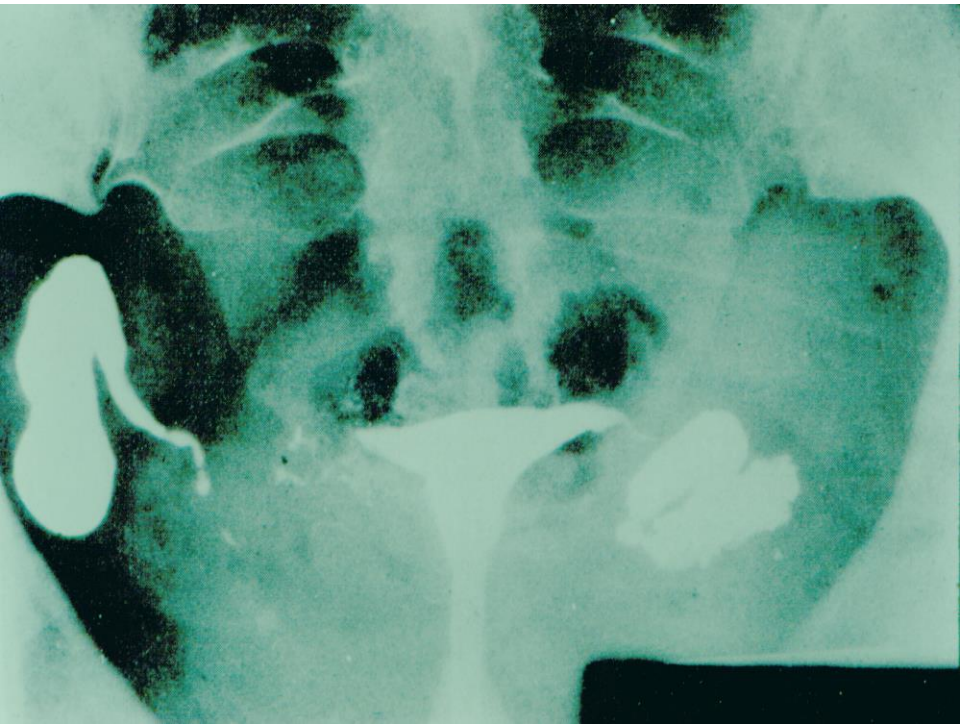


TUBAL / PERITONEAL FACTOR



- ~30-40% infertility
- Risk factors: exposure to untreated STIs; pelvic infections; surgeries; endometriosis
- Risk factors alone not sufficient to screen for tubal factor
- Endometriosis: distorted anatomy but also has effects on folliculogensis, ovum transport, fertilization, implantation
- Role of surgery for endo

HYSTEROSALPINGOGRAM



- Hysterosalpingogram is traditional and standard method for evaluating tubal patency
- 94% NPV
- 38% PPV (Coppus et al. 2007)
- May have some therapeutic benefit
- Chromopertubation at time of surgery

ROLE OF TUBAL SURGERY

Role of tubal surgery in the era of assisted reproductive technology: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

This document reviews surgical options for achieving patency in obstructed fallopian tubes and the factors that must be considered when deciding between surgical repair and IVF. This document replaces the document of the same name, last published in 2012 (Fertil Steril 2012;97:539–45). (Fertil Steril® 2015;103:e37-43. ©2015 by American Society for Reproductive Medicine.)

Key Words: Fallopian tube, hydrosalpinx, sterilization reversal, tubal disease, infertility

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

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/asrmpraccom-tubal-surgery/

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TABLE 1

Comparison of pregnancy rates and outcomes after various techniques.

Studies	No. patients	Pregnancy (%)[a]	SAB (%)[a]	Ectopic (%)[a]	Ongoing (%)[a]
Microsurgical (n = 5)	175	58.9 (51.2–75)	6.8 (0–56)	12.6 (0–25)	47.4 (37.5–5)
Hysteroscopic (n = 4)	133	48.9 (29–71.4)	13.8 (0–6.7)	9.2 (0–5.9)	48.9 (29–57)
Fluoroscopic (n = 9)	482	21.4 (6.3–55)	17.5 (2.1–7.8)	12.6 (0–7.8)	15.6 (8.7–40)

Note: Reproduced from Honore et al. (1). SAB = spontaneous abortion.
[a] Values are median (range).

Practice Committee of the ASRM. Tubal surgery. Fertil Steril 2015.

- Patients with extensive adhesions, peritubal adhesions, massively dilated tubes are poor prognosis

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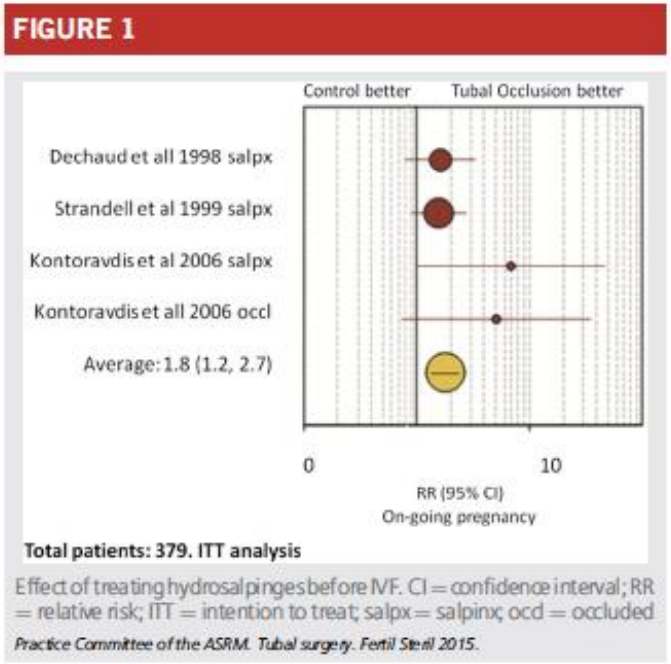
REMOVAL OF HYDROSALPINX

- 50% lower pregnancy rates from IVF and higher SAB in presence of hydrosalpinx (Zeyneloglu et al. 1998, Camus et al 1999)
- Greatest impact from hydrosalpinges visible on ultrasound (Strandell et al. 1999; de Wit et al. 1998)
- Standard of care to remove or ligate hydrosalpinx before IVF



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TUBAL REVERSAL

- 42- 69 % pregnancy rates (van Seeters et al. 2017)
- 4 – 8 % ectopic rate

- Open mini-lap vs. laparoscopic vs. robotic-assisted approaches

- Age, tubal length (4 cm), adhesive disease

- Full fertility evaluation in planning

Human Reproduction Update, Vol.23, No.3 pp. 358–370, 2017
Advanced Access publication on February 22, 2017 doi:10.1093/humupd/dmx003

human reproduction update

Tubal anastomosis after previous sterilization: a systematic review

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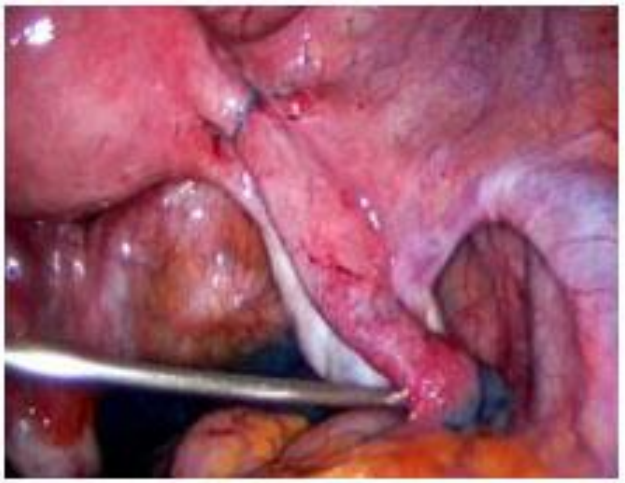


UTERINE FACTOR ASSESSMENT

TABLE 1

Diagnostic accuracy parameters of HSG, TVS, and SHG for polypoid lesions of the uterine cavity.

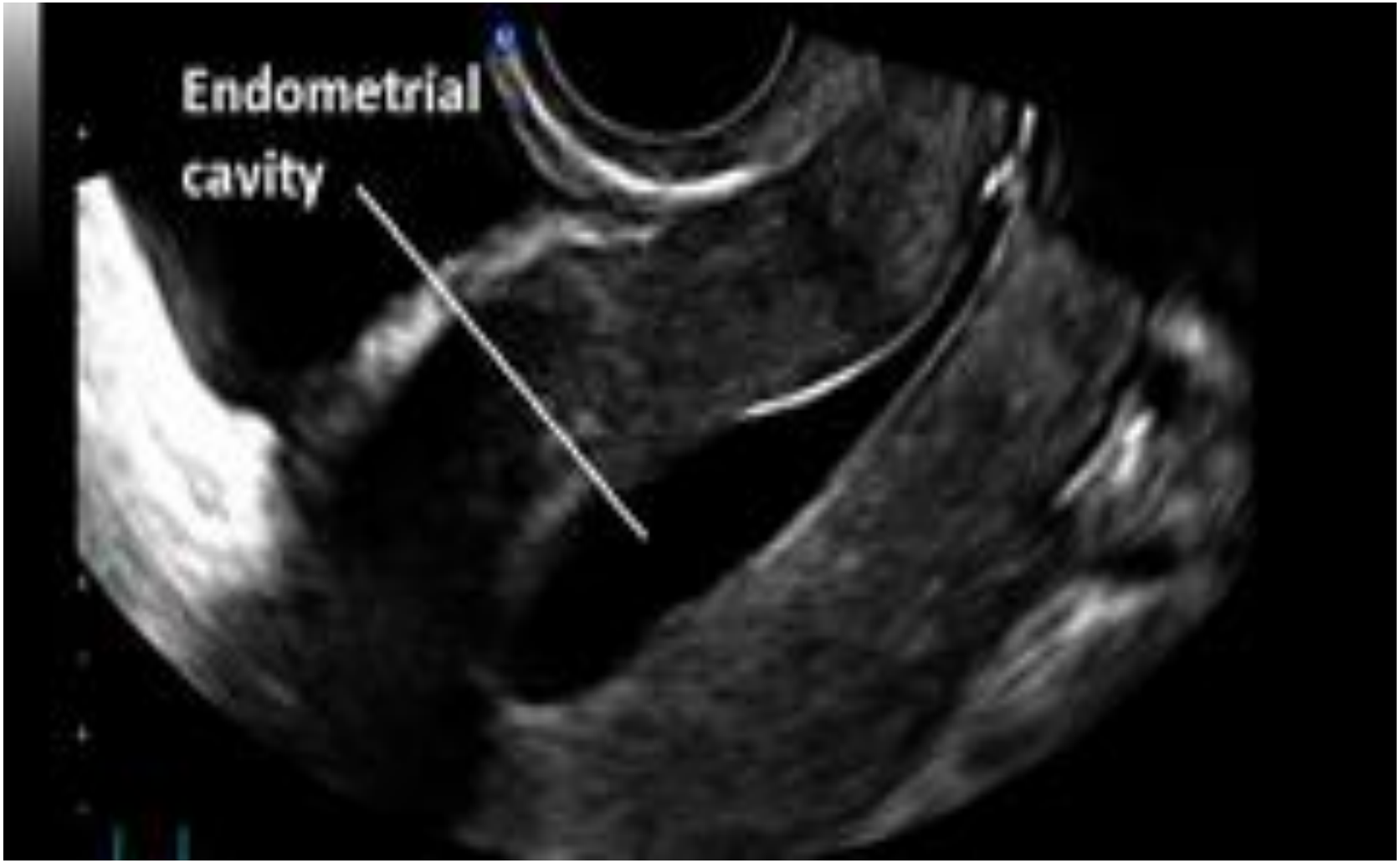
Examination	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
HSG	50.0 (17.4–82.6)	82.5 (69.6–90.8)	28.6 (9.6–58.0)	92.2 (80.3–97.5)
TVS	75.0 (35.6–95.5)	96.5 (86.8–99.4)	75.0 (35.6–95.5)	96.5 (86.8–99.4)
SHG	100 (59.8–100)	100 (92.1–100)	100 (59.8–100)	100 (92.1–100)

Note: The numbers in parentheses are the limits of the 95% confidence interval. HSG = hysterosalpingography; SHG = sonohysterography; TVS = transvaginal sonography; PPV = positive predictive value; NPV = negative predictive value.

Soares. Diagnostic accuracy. Fertil Steril 2000.

- Uterine factors (polyps, leiomyomas, synecha) are a rare primary cause but can be contributory
- Endometrial assay receptivity tests

UTERINE FACTOR ASSESSMENT



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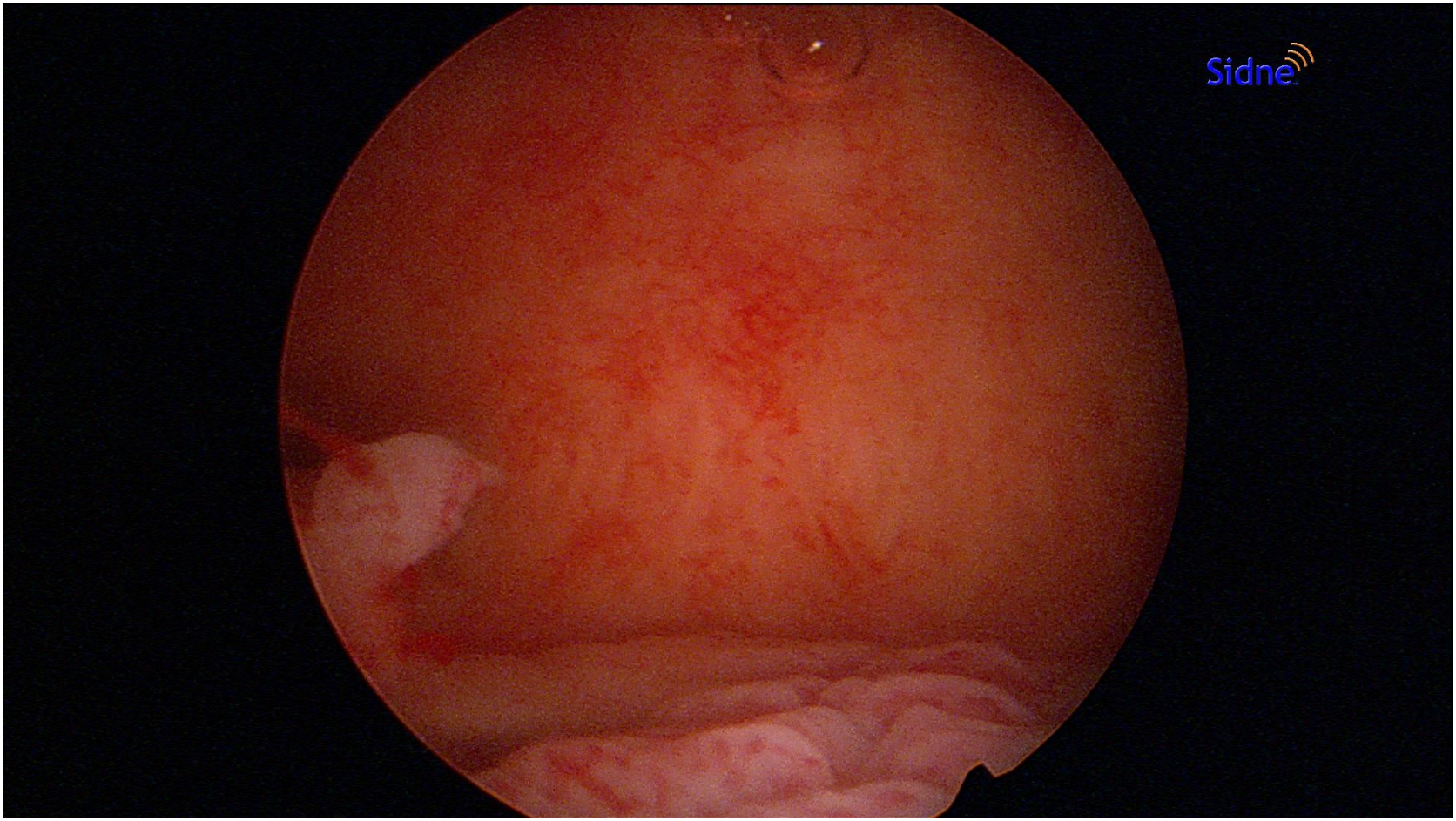
Saline-infusion sonography

UTERINE FACTOR ASSESSMENT



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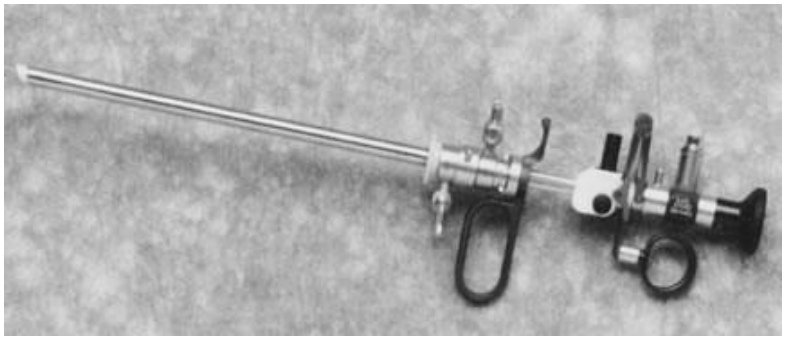
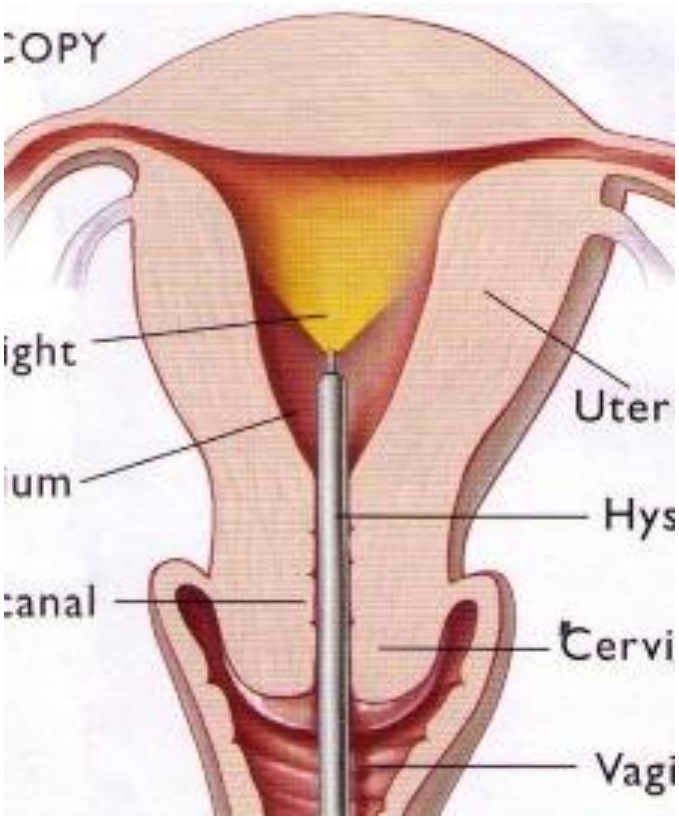
Hysteroscopy

HYSTEROSCOPY

- Complications & how to manage and prevention
- Uterine perforation
- Hypo-osmolality
  - Hyponatremia
  - Measure lytes, EKG changes (widened QRS, T wave inversion, ST elevation), examine pt, pulmonary edema
  - Note careful slow correction with hypertonic saline with Lasix 20-40mg IVF
- 2000 mL (isotonic solution)
  1000 mL (hypotonic solutions)
  500 mL (hyperviscosity solutions)
  [ACOG 2018]





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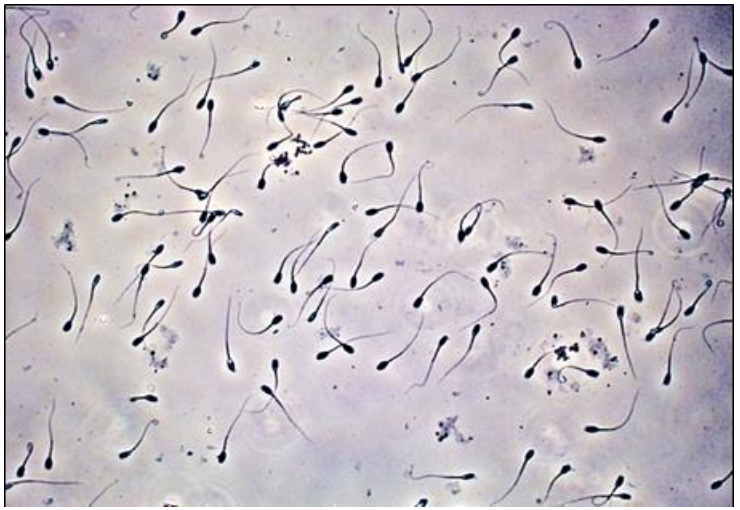
MALE FACTOR ASSESSMENT

When to check semen analysis (ALWAYS!)

World Health Organization 2010

- Volume > 1.5 ml
- Concentration > 15 Mil/mL
- Motility > 40%
- Progressive motility > 40%
- Strict morphology > 4%



Total Motile Count (> 39 Mil)

Always repeat if abnormal

What if the evaluation is negative??

UNEXPLAINED INFERTILITY

- 15-30% of couples
- Etiology yet to be identified
- Subtle impairments -
  - Oocyte maturation and competence; impaired oocyte pickup and transport; sperm-ovum interactions, compromised implantation
- Goals of Therapy
  - ↑↑ number of eggs, ↑↑ sperm in the fallopian tubes, optimize endocrine environment
- Clomiphene / Letrozole + IUI; Gonadotropin injection + IUI (~20%)

Advantages and disadvantages

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility

M.P. Diamond, R.S. Legro, C. Coutifaris, R. Alvero, R.D. Robinson, P. Casson, G.M. Christman, J. Ager, H. Huang, K.R. Hansen, V. Baker, R. Usadi, A. Seungdamrong, G.W. Bates, R.M. Rosen, D. Haisenleder, S.A. Krawetz, K. Barnhart, J.C. Trussell, D. Ohl, Y. Jin, N. Santoro, E. Eisenberg, and H. Zhang, for the NICHD Reproductive Medicine Network*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Diamond at the Department of Obstetrics and Gynecology, Georgia Regents University, 1120 15th St., Rm. BA-7313, Augusta, GA 30912, or at michael.diamond@gru.edu.

*A complete list of investigators in the National Institute of Child Health and Human Development (NICHD) Reproductive Medicine Network is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on September 24, 2015, at NEJM.org.

N Engl J Med 2015;373:1230-40.
DOI: 10.1056/NEJMoa1414827

ABSTRACT

BACKGROUND

The standard therapy for women with unexplained infertility is gonadotropin or clomiphene citrate. Ovarian stimulation with letrozole has been proposed to reduce multiple gestations while maintaining live birth rates.

METHODS

We enrolled couples with unexplained infertility in a multicenter, randomized trial. Ovulatory women 18 to 40 years of age with at least one patent fallopian tube were randomly assigned to ovarian stimulation (up to four cycles) with gonadotropin (301 women), clomiphene (300), or letrozole (299). The primary outcome was the rate of multiple gestations among women with clinical pregnancies.

RESULTS

After treatment with gonadotropin, clomiphene, or letrozole, clinical pregnancies occurred in 35.5%, 28.3%, and 22.4% of cycles, and live birth in 32.2%, 23.3%, and 18.7%, respectively; pregnancy rates with letrozole were significantly lower than the rates with standard therapy (gonadotropin or clomiphene) (P=0.003) or gonadotropin alone (P<0.001) but not with clomiphene alone (P=0.10). Among ongoing pregnancies with fetal heart activity, the multiple gestation rate with letrozole (9 of 67 pregnancies, 13%) did not differ significantly from the rate with gonadotropin or clomiphene (42 of 192, 22%; P=0.15) or clomiphene alone (8 of 85, 9%; P=0.44) but was lower than the rate with gonadotropin alone (34 of 107, 32%; P=0.006). All multiple gestations in the clomiphene and letrozole groups were twins, whereas gonadotropin treatment resulted in 24 twin and 10 triplet gestations. There were no significant differences among groups in the frequencies of congenital anomalies or major fetal and neonatal complications.

CONCLUSIONS

In women with unexplained infertility, ovarian stimulation with letrozole resulted in a significantly lower frequency of multiple gestation but also a lower frequency of live birth, as compared with gonadotropin but not as compared with clomiphene. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT01044862.)

FASTT TRIAL

INFERTILITY

A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial

Richard H. Reindollar, M.D.,[a] *Meredith M. Regan, Sc.D.,*[b] *Peter J. Neumann, Sc.D.,*[c] *Bat-Sheva Levine, M.D.,*[c] *Kim L. Thornton, M.D.,*[d] *Michael M. Alper, M.D.,*[d] *and Marlene B. Goldman, Sc.D.*[e]

[a] Department of Obstetrics and Gynecology, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; [b] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [c] Center for the Evaluation of Value and Risk in Health, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; [d] Department of Obstetrics, Gynecology and Reproductive Biology, Division of Reproductive Endocrinology and Infertility, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Boston IVF, Waltham, Massachusetts; and [e] Departments of Obstetrics and Gynecology and Community and Family Medicine, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Objective: To determine the value of gonadotropin/intrauterine insemination (FSH/IUI) therapy for infertile women aged 21–39 years.
Design: Randomized controlled trial.
Setting: Academic medical center associated with a private infertility center.
Patient(s): Couples with unexplained infertility.
Intervention(s): Couples were randomized to receive either conventional treatment (n = 247) with three cycles of clomiphene citrate (CC)/IUI, three cycles of FSH/IUI, and up to six cycles of IVF or an accelerated treatment (n = 256) that omitted the three cycles of FSH/IUI.
Main Outcome Measure(s): The time it took to establish a pregnancy that led to a live birth and cost-effectiveness, defined as the ratio of the sum of all health insurance charges between randomization and delivery divided by the number of couples delivering at least one live-born baby.
Result(s): An increased rate of pregnancy was observed in the accelerated arm (hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.00–1.56) compared with the conventional arm. Median time to pregnancy was 8 and 11 months in the accelerated and conventional arms, respectively. Per cycle pregnancy rates for CC/IUI, FSH/IUI, and IVF were 7.6%, 9.8%, and 30.7%, respectively. Average charges per delivery were $9,800 lower (95% CI, $25,100 lower to $3,900 higher) in the accelerated arm compared to conventional treatment. The observed incremental difference was a savings of $2,624 per couple for accelerated treatment and 0.06 more deliveries.
Conclusion(s): A randomized clinical trial demonstrated that FSH/IUI treatment was of no added value. (Fertil Steril® 2010;94:888–99. ©2010 by American Society for Reproductive Medicine.)

Key Words: Unexplained infertility, FASTT Trial, intrauterine insemination, in vitro fertilization

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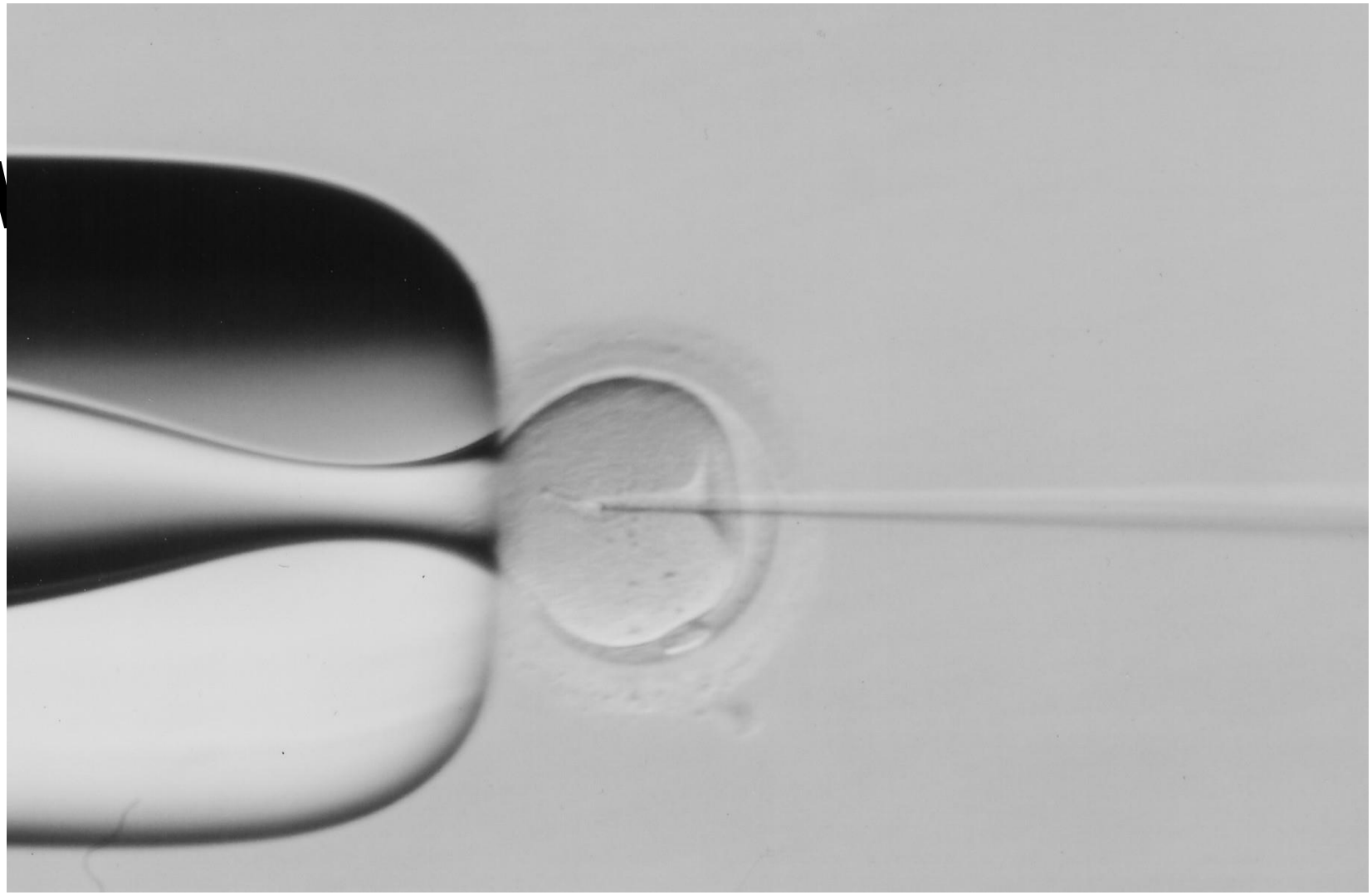
IN VITRO FERTILIZATION



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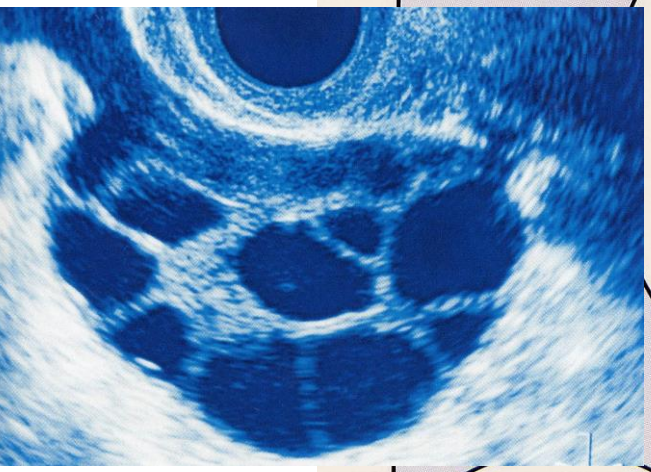
IN VITRO FERTILIZATION



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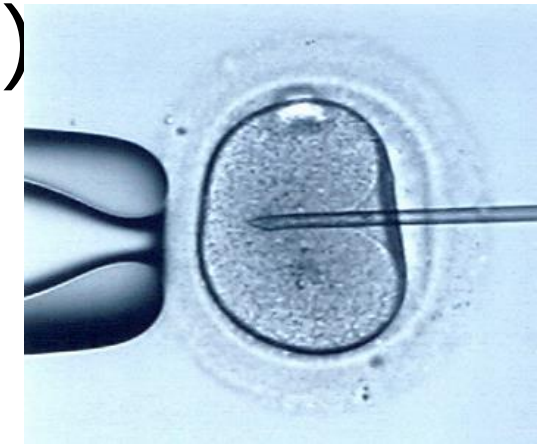
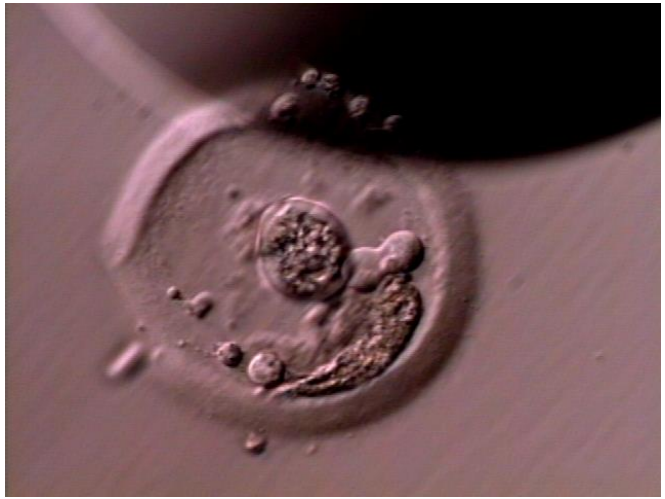
IVF LABORATORY PRIMER

Fertilization: conventional microdroplet vs. intracytoplasmic sperm injection (ICSI)



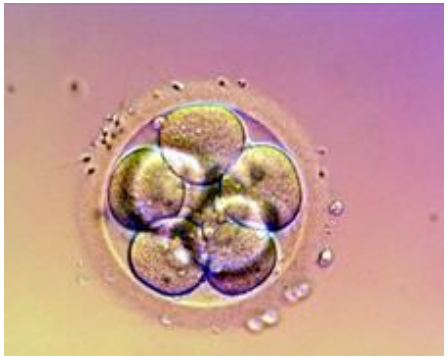
+/- assisted hatching



DURATION OF EMBRYO CULTURE

Day 2-3 Transfer (cleavage or tubal stage)

- minimize duration in vitro culture
- transfer more than one embryo



Day 5-7 Transfer (blastocyst)

- select out “best” embryos
- transfer fewer embryos

ASRM EMBRYO TRANSFER GUIDELINES

TABLE 1

Recommended limits on the numbers of embryos to transfer.

	Age (y)			
Prognosis	**< 35**	**35–37**	**38–40**	**41–42**
Cleavage-stage embryos[a]				
Favorable[b]	1–2	2	3	5
All others	2	3	4	5
Blastocysts[a]				
Favorable[b]	1	2	2	3
All others	2	2	3	3

[a] See text for more complete explanations. Justification for transferring one additional embryo more than the recommended limit should be clearly documented in the patient's medical record.
[b] Favorable — first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle.

Practice Committee. Pharmacogenetic approach to male infertility. Fertil Steril 2013.

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PREIMPLANTATION GENETIC TESTING (PGS OR PGT-A)

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Embryo Transfer

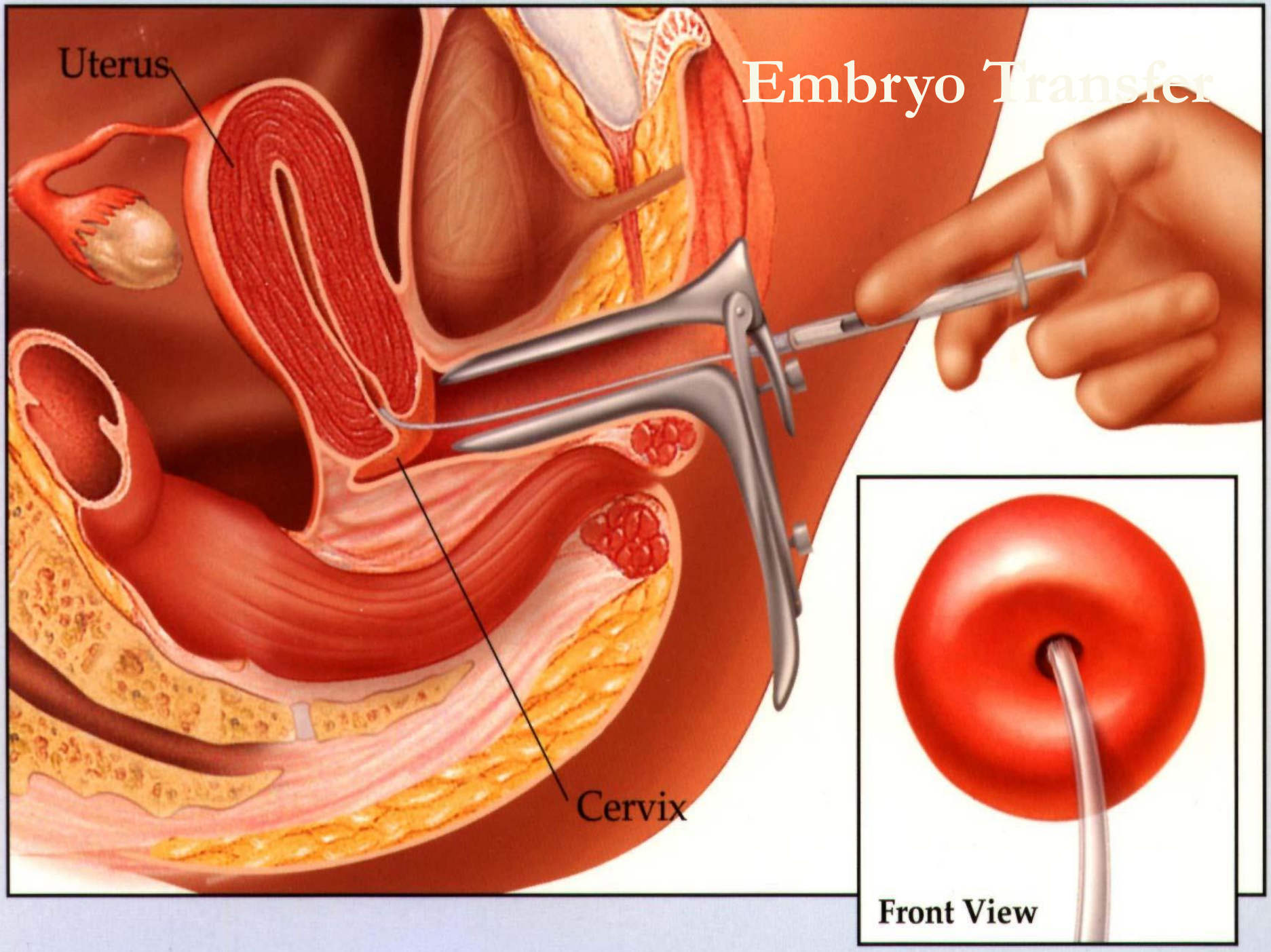
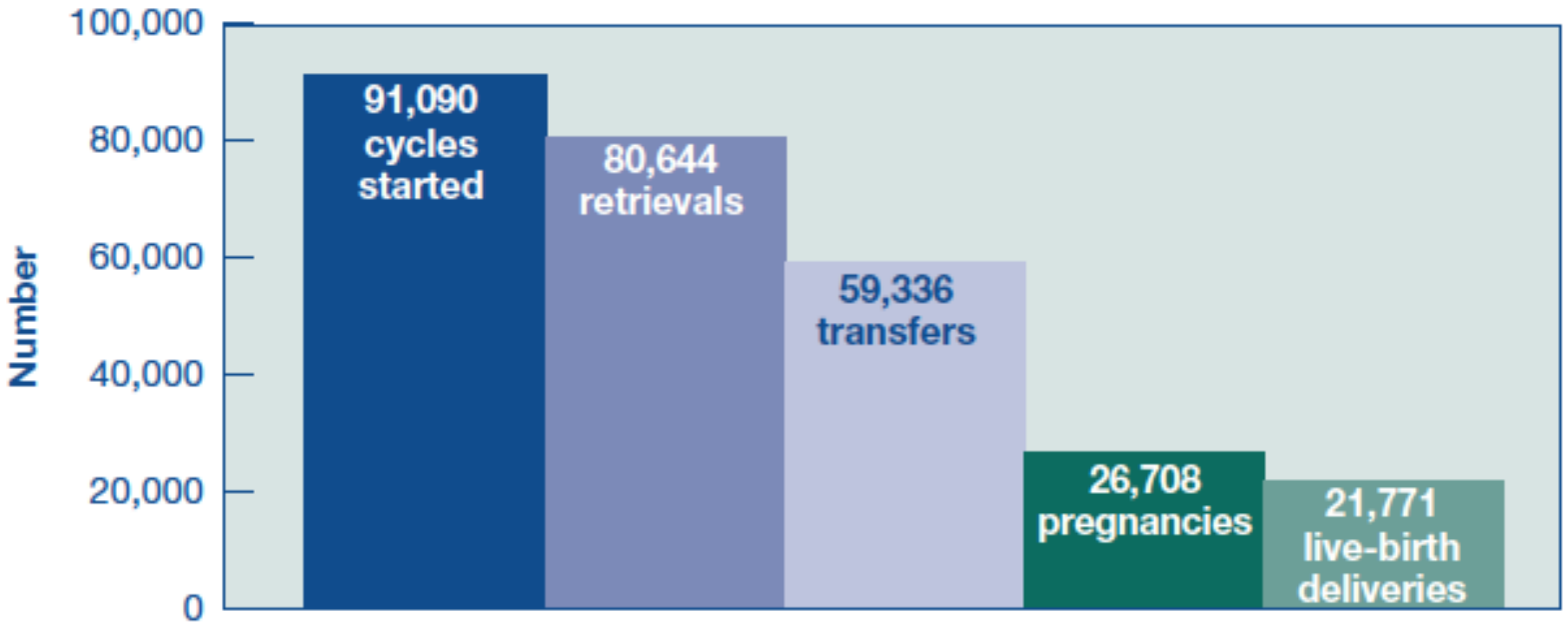


Figure 7
Outcomes of ART Cycles Using Fresh Nondonor Eggs or Embryos, by Stage, 2015



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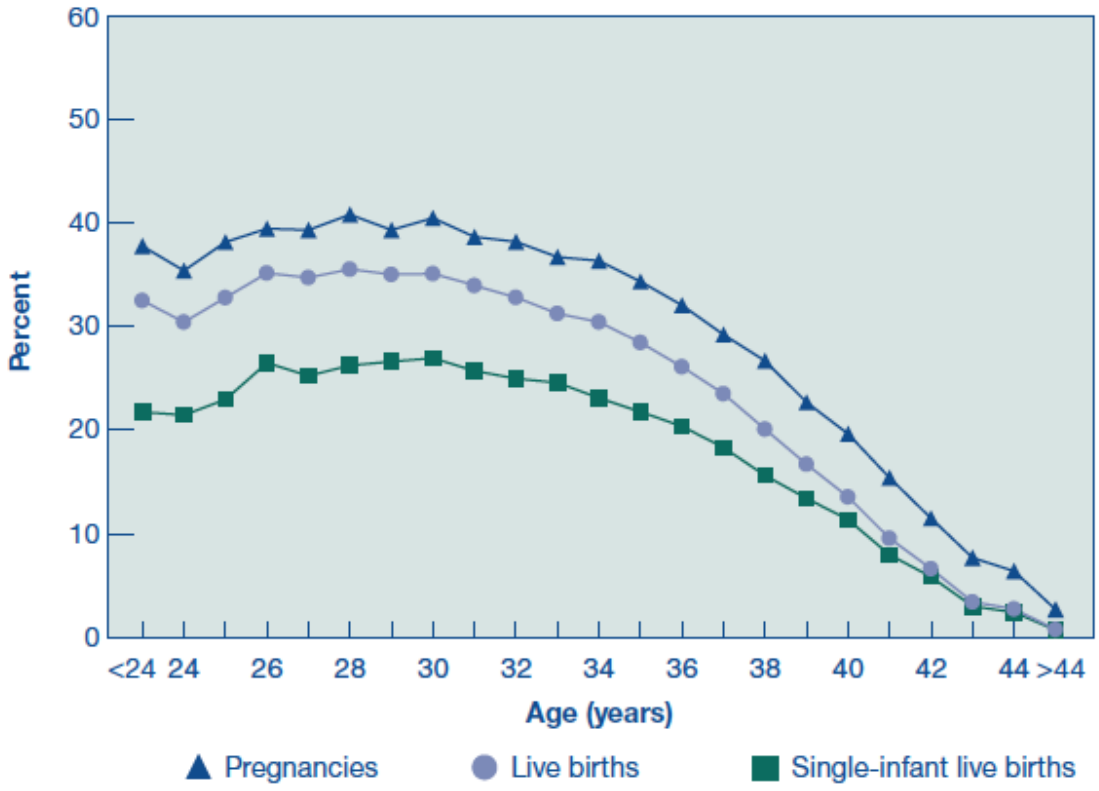
CDC 2015

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.

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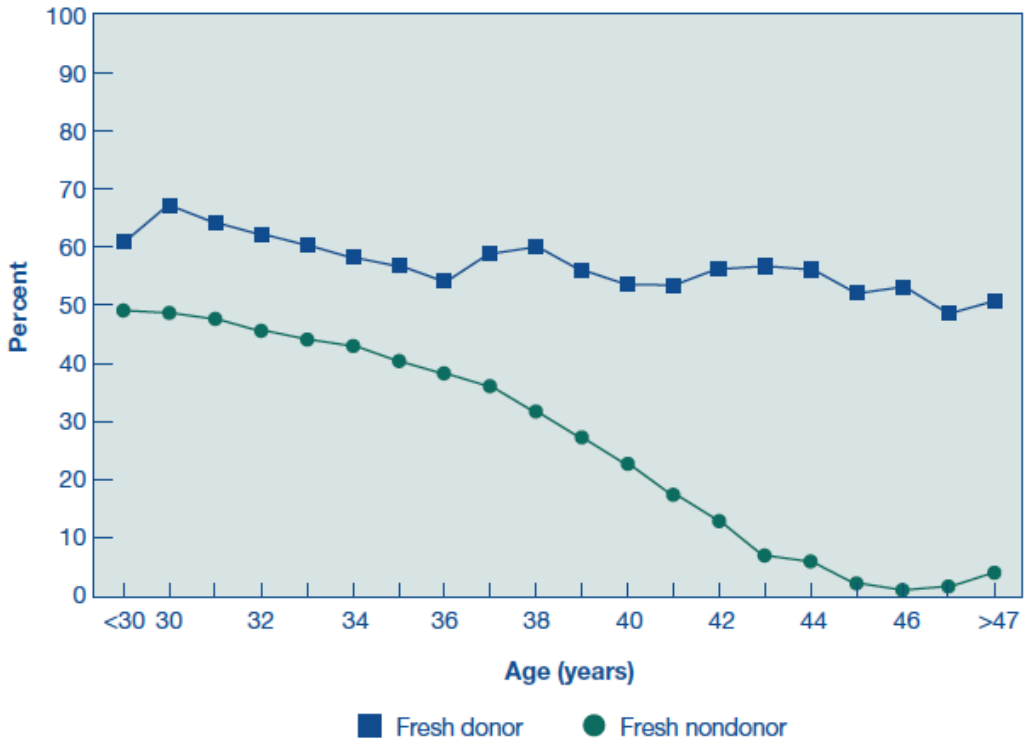
CDC 2015

Figure 41
Percentages of Transfers Using Fresh Embryos from Donor or Nondonor Eggs That Resulted in Live Births, by Age of Woman, 2015



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CDC 2015

PREGNANCY RISKS ASSOCIATED WITH ART

Potential Risks in having a single child through IVF

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
Placenta previa	2.4%	2.9 (1.5--5.4)
Placental abruption	2.2%	2.4 (1.1--5.2)
Gestational diabetes	6.8%	2.0 (1.4--3.0)
Cesarean delivery *	26.7%	2.1 (1.7--2.6)

NOTE: The Absolute Risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF compared to the risk in non-IVF pregnancies. For instance, a relative risk of 2.0 means that twice as many IVF pregnancies have this risk as non-IVF pregnancies. The numbers in parentheses show the range in which the actual Relative Risk lies. * Please note that most experts believe the rate of Cesarean delivery to be well above the 26.7% rate quoted here.

Reference: Reddy, U. M., R. J. Wapner, R. W. Rebar and R. J. Tasca, 2007 Infertility, assisted reproductive technology, and adverse pregnancy outcomes: executive summary of a National Institute of Child Health and Human Development workshop. Obstet Gynecol 109: 967-977.

s in Singleton IVF Pregnancies

	Absolute Risk (%) in IVF Pregnancies	Relative Risk (vs. non-IVF Pregnancies)
Preterm birth	11.5%	2.0 (1.7–2.2)
Low birth weight (less than 2500 grams)	9.5%	1.8 (1.4–2.2)
Very low birth weight (less than 1500 grams)	2.5%	2.7 (2.3–3.1)
Small for gestational age	14.6%	1.6 (1.3–2.0)
NICU (intensive care) admission	17.8%	1.6 (1.3–2.0)
Stillbirth	1.2%	2.6 (1.8–3.6)
Neonatal mortality	0.6%	2.0 (1.2–3.4)
Cerebral palsy	0.4%	2.8 (1.3–5.8)
Autism	0.1%	0.38 (0.51–0.98)
Genetic risks		
-imprinting disorder	0.03%	17.8 (1.8--432.9)
-major birth defect	4.3%	1.5 (1.3–1.8)
-chromosomal abnormalities (after ICSI):		
-of a sex chromosome	0.6%	3.0
-of another chromosome	0.4%	5.7

In this table, the Absolute Risk is the percent of IVF pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies. For example, a relative risk of 2.0 means that twice as many IVF pregnancies have this risk as compared to non-IVF pregnancies. The numbers in parentheses show the range in which the actual Relative Risk lies.

References

Lidegaard, O., A. Pinborg and A. N. Andersen, 2005 Hum Reprod 20: 950-954.
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Wijers, C.H., van Rooijm I. A., Rassouli, R., Wijnen, M. H., Broens, P. M., Sloots, C. E., Brunner, H. G., De Blaauw, I., Roeleveld, N., 2015 Epidem. 26(2):169-76
Seggers, J., de Walle H., E., Bergman, J.E., Groen, H., Hadders-Algra, M., Bos, M.E., Hoek, A., Haadsma, M. L., 2015 Fert and Steril 103(4):1001-1010
Kissin, D.M., Zhang, Y., Boulet, S.L., Foutain, C., Bearman, P., Schieve, L., Yeargin-Allsopp, M., Jamieson, D.J., 2015 Hum Reprod 30(2):454-65.

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RISKS TO ART

Conventional risks

Ovarian hyperstimulation syndrome (OHSS)

Multiple gestation

Increased risks for congenital abnormalities (esp with ICSI)

Increased risk for imprinting disorders

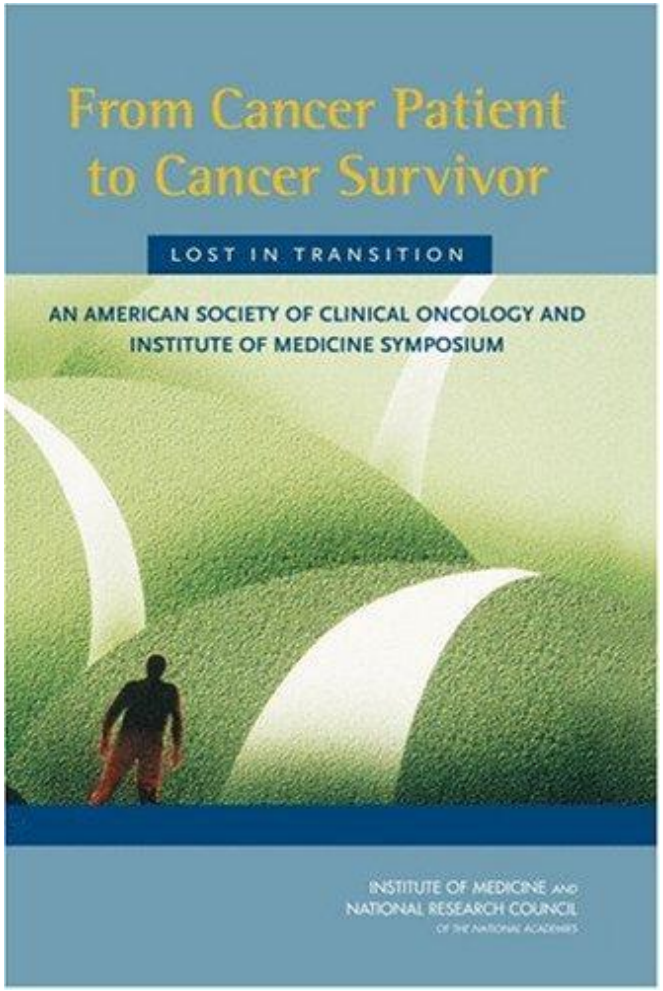
Unknowns

WHO ARE CANDIDATES FOR FERTILITY PRESERVATION?

- Reproductive age patients with a new diagnosis of cancer or other systemic disease anticipating gonadotoxic treatment
- BRCA mutation carriers / Turner's Syndrome
- Women desiring elective fertility preservation (e.g. egg freezing)

CANCER & FERTILITY

- > 125,000 women under age 50 with cancer (SEER 2006)
- 450,000 reproductive age survivors (Jemal 2007)
- 75% at diagnosis desire children (Schover 2009)



IMPACT OF CANCER THERAPY ON OVARIAN FUNCTION

- Gonadotoxic chemotherapy
- Radiation treatment
- Bone marrow transplantation

- > 5 year delay in childbearing with tamoxifen

Table 4
Gonadotoxic impact of chemotherapeutic agents.

High risk of inducing amenorrhea
- Cyclophosphamide
- Ifosphamide
- Melphalan
- Busulfan
- Nitrogen mustard
- Procarbazine
- Chlorambucil

Intermediate risk
- Cisplatin
- Adriamycin

Low risk
- Bleomycin
- Actinomycin D
- Vincristine
- Methotrexate
- 5-Fluorouracil

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BARRIERS TO ACCESS

Barriers to oncology referral (Quinn J Clin Oncol 2009)

- Lack of knowledge
- Insufficient time
- Perceptions that patients cannot delay treatment
- Perceptions that patients not interested because they did not initiate discussion

Cost & perceptions of resources, logistics, medical complexity

ELECTIVE OOCYTE CRYOPRESERVATION

- Age of a woman's first birth in United States is rising (Mathews 2016, NCHS 2008)
- Increase in women pursuing postgraduate education and in professional workforce

- Women who delay childbearing may face infertility by time ready to begin childbearing
- Option for unpartnered women not desiring use of donor sperm

FERTILITY PRESERVATION OPTIONS

1. Expectant management

2. Embryo cryopreservation through IVF (*embryo banking*)

3. Oocyte cryopreservation (*egg freezing*)

4. Ovarian tissue cryopreservation and transplantation

5. Initiating attempts at pregnancy

EXPECTANT MANGEMENT

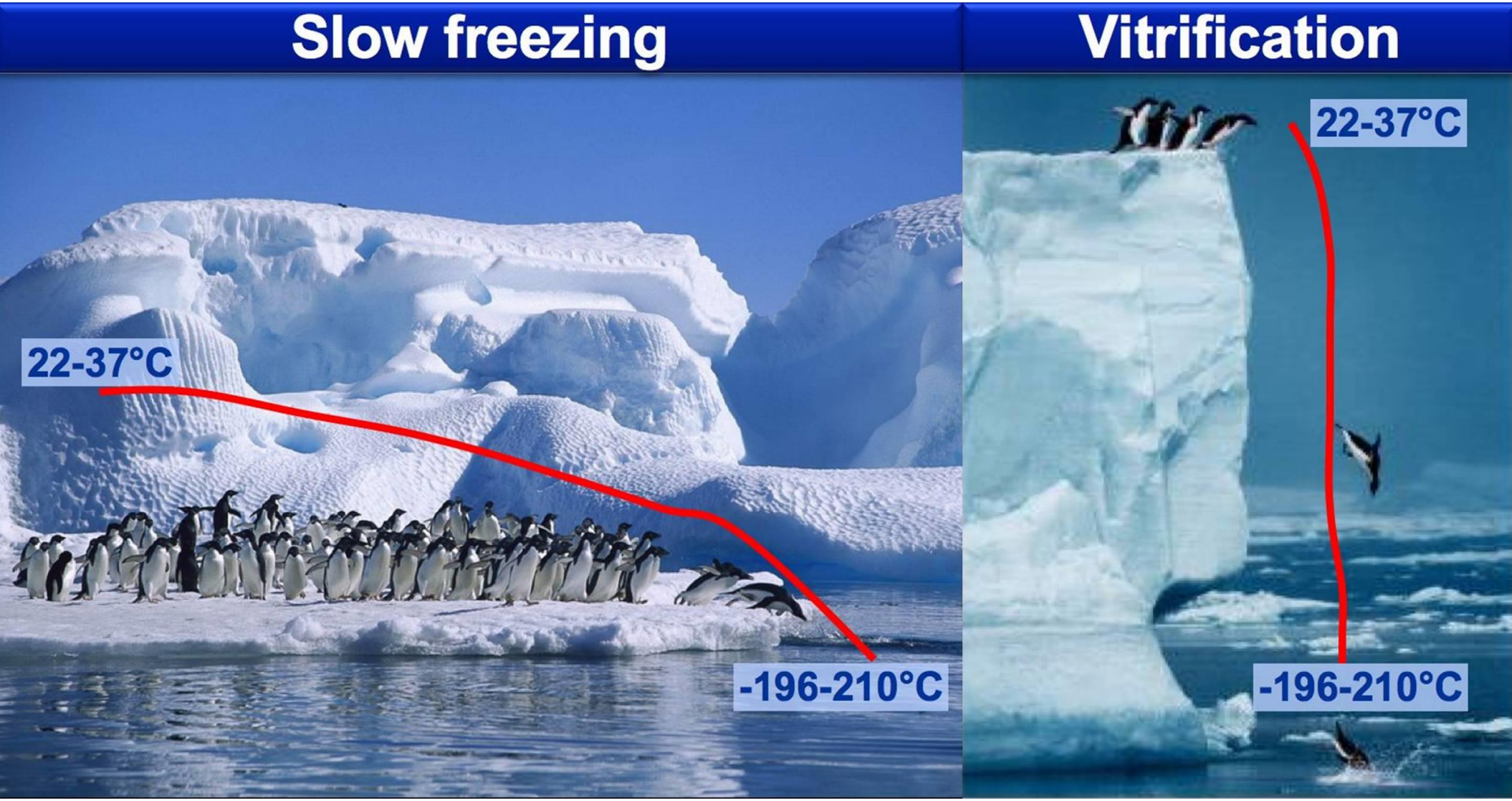
- Rate of follicular decline varies individually but trends conserved across ages
- No therapeutic modality available that slows decline of follicular atresia and reproductive senescence
- No clinical tests or assays available to assess egg quality beyond predicted by age
- Ovarian reserve tests such as AMH are imperfect and limited utility – **not measures of reproductive potential** (ASRM 2012)

OOCYTE CRYOPRESERVATION

First live birth in 1986 (Chen 1986)

Meiotic spindles of mature oocytes exquisitely sensitive to freeze thaw-process

Recovery rates using slow freeze process historically poor until advent of vitrification



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OOCYTE CRYOPRESERVATION

Studies in donor oocytes and early series reported excellent recovery rates (Cobo 2008, Grifo & Noyes 2010, Trokoudes 2011, Rienzi 2017)

No apparent increase in congenital anomalies, aneuploidy or adverse perinatal outcomes (Chian 2008, Cobo 2014, Grifo & Noyes 2009, Ho 2017)

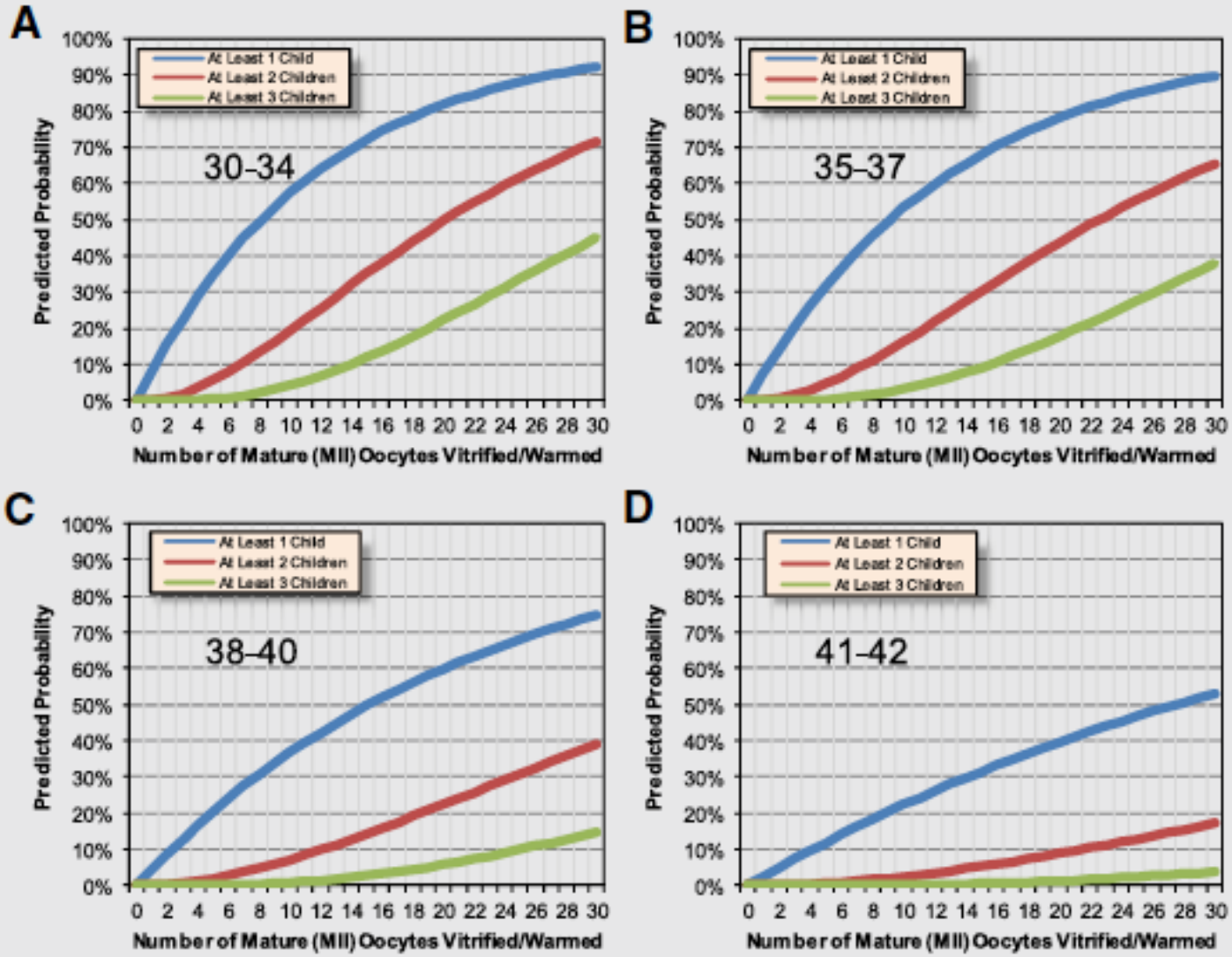
ASRM lifted label of ‘experimental’ in 2013

Reported pregnancy outcomes are limited; no large cohort studies or studies on child development (Schattman 2015, Argyle 2016)

WHAT IS THE OPTIMAL NUMBER?

- Relatively few patients who have electively have returned to use their oocytes (Hodes-Wertz 2013, Schattman 2015)
- Difficult to find an appropriate population to counsel patients on optimal number
- Studies report clinical pregnancy rates of 3.3-8.2% per oocyte (Chang 2013, Doyle 2015)
- Patients are heterogeneous in age, ovarian reserve and response (Munne 2012)
- Modeling but with limited data to support (Doyle 2015, Goldman 2017)

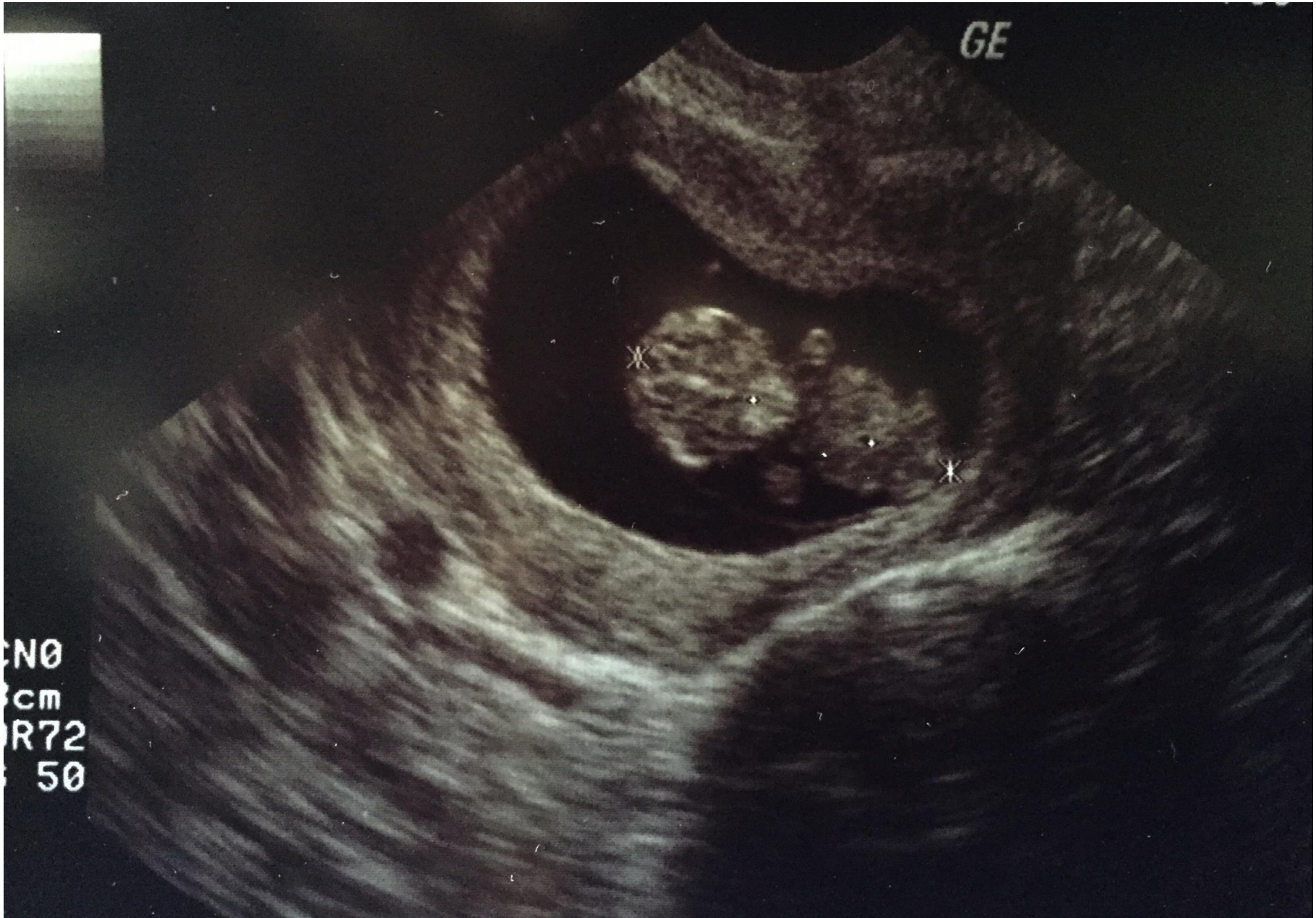
FIGURE 1



Predicted probabilities of having at least one, two, and three live-born children according to the number of mature oocytes cryopreserved for elective fertility preservation, according to age at oocyte retrieval and the associated oocyte to live-born child efficiency estimates: (**A**) 30–34 years, 8.2% efficiency; (**B**) 35–37 years, 7.3% efficiency; (**C**) 38–40 years, 4.5% efficiency; (**D**) 41–42 years, 2.5% efficiency.

Doyle. Autologous vitrified oocyte IVF outcomes. Fertil Steril 2016.

INITIATING ATTEMPTS AT PREGNANCY



FOR YOUR PATIENTS

Counseling on reproductive aging and age-related fertility decline

Empowerment of patient for reproductive choice and autonomy

Decisions are complex; referral to fertility center for individualized counseling

DISPARITIES IN ACCESS TO CARE

- 7 - 15% prevalence in global reproductive age population (Nachtigall 2006)
- ~ 80-100 million people worldwide (Boivin et al. 2007)

- **< 1% globally has access to effective infertility care** (Ombelet 2009)

- 6.7 million in US (Chandra et al. NSFG 2015)
- **~74% of US infertile population cannot access IVF** (Chambers 2009)

MANAGEMENT OF INFERTILITY IN LOW RESOURCE SETTINGS

- Acknowledge impact of the disease
  - Frustration, feelings of hopelessness
  - Resource and infrastructure limitations
- Understand sociocultural and educational barriers (Nachtigall et al. 2009, Becker et al. 2006)
- Access & referral barriers

INITIAL APPROACH & MANAGEMENT

- Health literacy
- Health maintenance & screening
- Structured basic evaluation
- Ovulatory, Tubal **AND** Male Factors
- Present full treatment options

"Navigating through an imperfect world"

THANK YOU!

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