
Polycystic Ovary Disease: A Common Endocrine Disorder in Women

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Case Presentation – Jenn A.

- 23 Y. O. G0 P0 menarche age 13
- BMI 29. Hx of “weight problems”.
- Menses Q 60 -180 days. Start BCPS age 15.
- Moderate acne & hirsutism age 14-15
- Family Hx T2 diabetes and infertility



Polycystic Ovary Syndrome

- A Common Female Endocrine Dysfunction
 - Affects 1 of every 12 women in U.S.
- Key Features:
 - Oligo/Amenorrhea
 - Abnormal Androgen Production & Metabolism
- Probable Genetic Etiology
 - Conveys evolutionary “metabolic efficiency”
 - ? autosomal dominant/variable penetration
 - ? serine hyperphosphorylation defect

PCOS: A NEW PARADIGM

“ PCOS is a metabolic disorder affecting multiple body systems that requires comprehensive and long-term evaluation and management. ”

John Nestler, M.D. Fertility & Sterility November, 1998

How Do Women with PCOS Present?

- Irregular Menstual Periods
- Hirsutism
- Facial Acne
- Overweight
- Infertility
- Acanthosis Nigricans (café au lait spots)
- Sleep Apnea

PCOS: Diagnosis

- N.I.H. Definition (2 of 2)
 - Oligo/Anovulation
 - Cycles > 35 days apart or < 7 per year
 - Abnormal Androgen Production & Metabolism
 - Clinical (Hirsutism/Acne) or Lab (T, A, DHEA-S)
- ESHRE/ASRM Rotterdam 2003 (2 of 3)
 - Oligo/Anovulation
 - Androgen Excess
 - Polycystic Ovaries (12 or > follicles/ovary on U/S)

Rotterdam ESHRE/ASRM Group. Hum Reprod 2004;19:41-47.

Chang RJ. Am J Obstet Gynecol 2004;191:713-17.

PCOS: CVD Classification

- **Classic (75%)**
 - RD/NIH Criteria + Overweight (BMI > 25)
 - 40% Risk of IGT or T2DM by age 40 (5X controls)
 - Dyslipidemia in 70% of Classic PCOS (IR effect)
- **Ovulatory (Lean) (12.5%)**
 - Medium risk profile
- **Nonhyperandrogenic (12.5%)**
 - Lowest Risk

Assessment of Cardiovascular Risk in PCOS. JSEM May2010;95:5.

PCOS

YOUNG



**REPRODUCTIVE
AND
HYPERANDROGENIC
DYSFUNCTION**

LATER YEARS



**CARDIOMETABOLIC
DISORDERS**

PCOS: Evolutionary Benefits

- Metabolic “Thriftiness”
 - Maximal caloric conservation
 - ↑ Longevity in animal studies
 - Stress-induced ovulation (↓ LH P/F)
 - ↓ Rate of oocyte atresia (↑ Insulin levels)

PCOS: Clinical Consequences

- Endometrial Cancer (3x risk, up to 1/5)
- Spontaneous Abortion (? ↑ LH Effect)
- Gestational and Type 2 Diabetes (5-10x)
- Cardiovascular Disease (↑ LDL ↓ HDL)
- Hypertension
- Breast Cancer (3-4x risk in limited data)
- Ovarian Cancer

Evaluation of PCOS

- BMI, Waist Circumference, BP
- Baseline FSH, LH, TSH, Prolactin
- Testosterone, DHEA-S
- 17-OH Progesterone (Follicular a.m.)
- Fasting Glucose + Insulin/GTT
- Fasting Lipids & Chemistry Panel
- Transvaginal Ultrasound of Ovaries

RIGHT - 21 X 16

LEFT - 12 X 11

07/04/93
09:07:00
FROZEN
FQ 75 75
SC 06 06
FC FM FM
FR 10 10
SS
HR
DL
EE E2 E2
DR 45 45
CL 50 50
TX-03 03
RX 49 56

"String of Pearls" in PCOS

*WOMEN'S CARE FERTILITY CEN

Transvaginal Ultrasound of the Ovaries

PCOS: Insulin Resistance

- Demonstrated in 60 - 80% of PCOS
 - 95% in Obese PCOS (BMI > 30)
- Metabolic Effects:
 - Decreased Hepatic SHBG Production (↑ Free T)
 - Increased Ovarian Thecal Androgen Production
 - Increased Triglycerides and Adverse Lipid Profile
 - Obesity/Metabolic Syndrome
 - Hypertension
 - High Risk of T2 DM (25%)

Metabolic Syndrome: Diagnosis

- Three or more of the following:
 - Hypertension (130/85 or higher or on meds)
 - Elevated Triglycerides (>150 mg/dL or on meds)
 - Reduced HDL (Less than 50 mg/dL for women)
 - Waist circumference > 35 inches for women
 - Fasting Glucose >100 mg/dL or on meds

Metabolic Syndrome: What We Know

- Occurs in 1/6 (16%) of the general population and 60% of obese men and women.
- 10% of people with NGT, 40% with IGT, 85% with T2 DM.
- Prevalence 24% higher in women (40% by age 60) and increases with age.
- Conveys a high risk of T2 DM and cardiovascular disease.
- Significant increased risk with PCOS

Metabolic Syndrome: Treatment

- Lifestyle: Diet, Exercise, Weight Loss
- Correction of Problems: HTN, DM, Lipids
- Regular monitoring/follow-up
- ? Low-dose aspirin

PCOS: Cardiovascular Disease

- Dyslipidemia
- Hypertension
- Impaired Glucose Tolerance/Type2DM
- Metabolic Syndrome
- Frequent Positive FH CVD before age 55
- Carotid-IMT (10-15% over controls)
- Carotid Artery Calcification
- Multivessel CVD (32% vs. 25%)

Assessment of Cardiovascular Risk in PCOS. JSEM May2010;95:5.

PCOS: Treatment Options

- Anovulation: Cyclic Progestins, BCPs
 - Prevent D.U.B., Endometrial CA
- Acne/Hirsutism: BCPs, Spironolactone
- Contraception: Low-Androgenic BCPS
- Fertility: Clomiphene, FSH/hMG
- Weight Loss: Low Calorie ADA Diet
- Role of Metformin & Thiazolidinediones

PCOS: Positive Effects of Insulin Sensitizing Agents

- ↑ SHBG (↑ Androgen Binding)
- ↓ Testosterone and Androstenedione
- ↓ Triglycerides and LDL
- Regulation of Menstrual Cycles (30%)
- Weight Loss (Slow)
- Increased Sensitivity to Clomiphene
- ? Decreased Risk of Miscarriage

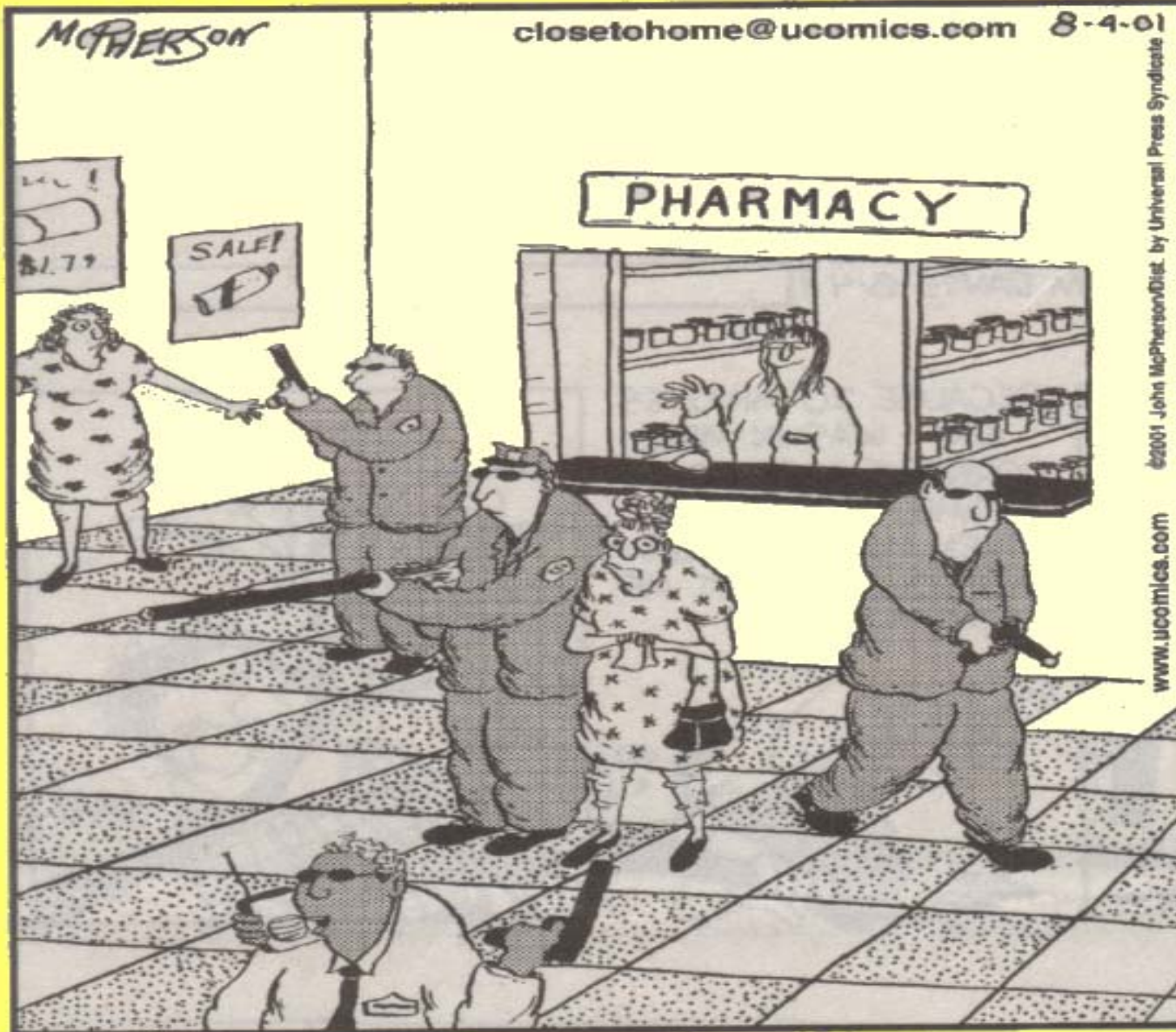
PCOS: Who to Treat with Metformin in 2015

- Obese (BMI>30) PCOS patients
 - Adults
 - Adolescents (who can be compliant)
- Insulin resistant patients
 - Fasting Insulin > 12-20 or G/I ratio < 4.5
- Patients who need menses regulation and fail BCPs/Progestins
- Young patients (age <30) desiring fertility
- Patients with impaired glucose tolerance (IGT) or Type 2 D.M.

PCOS: Management Summary

- Tailor treatment to life stage
- Induce regular menses
- Identify & treat endocrinopathies
- Identify & treat insulin resistance
- Monitor BP, Lipids, DM, Liver Function, Cancer risk

CLOSE TO HOME

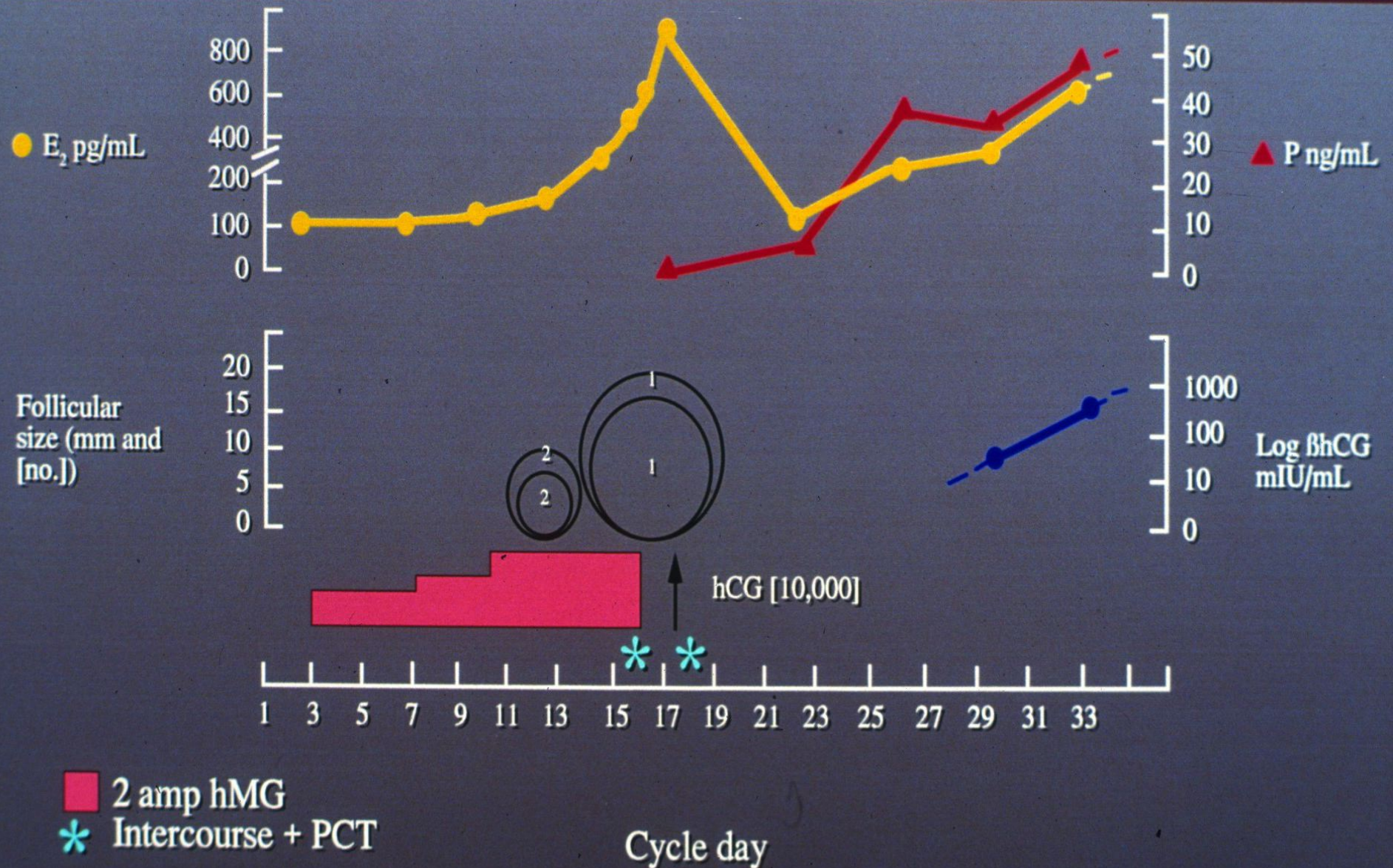


With prescription drug prices rising exponentially, many drugstores now provide armed escorts to assure that customers reach their cars safely.

The Assisted Reproductive Technologies (ART)

- **In Vitro Fertilization (IVF)**
- **Intracytoplasmic Sperm Injection (IVF/ICSI)**
- **Donor Oocyte IVF**
- **Frozen Embryo Thaw and Transfer**
- **Cryopreservation/In Vitro Maturation of Oocytes**

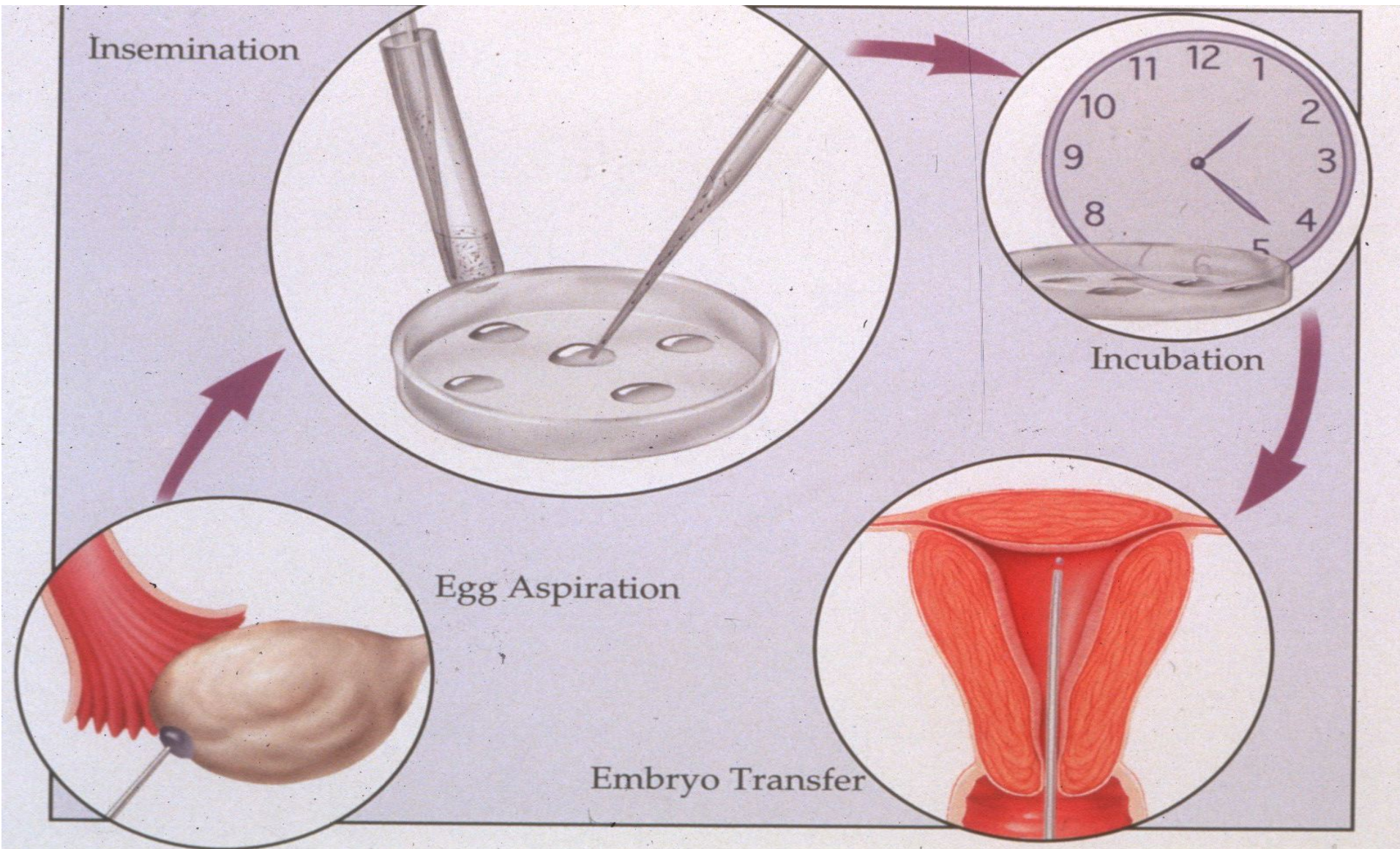
An hMG-hCG Cycle



Adapted from Navot and Rosenwaks, 1987.

In Vitro Fertilization (IVF)

- Daily S/C or IM FSH/hMG injection
- Follicular monitoring with serum estradiol and transvaginal ultrasound
- HCG given to trigger ovulation (LH surge)
- Transvaginal oocyte retrieval and insemination
- Embryo culture and transcervical embryo transfer
- Embryo cryopreservation for future F.E.T.
- Pregnancy rate of 40-50 % per cycle



©TTC

In IVF, eggs are harvested from the woman's ovary and fertilized in the laboratory with sperm. The embryos are then transferred into the uterus.

IVF Embryo Culture and Transfer

Intracytoplasmic Sperm Injection (ICSI)

- Standard IVF Stimulation and oocyte retrieval
- Injection of a single sperm into each oocyte
- Embryo culture and transcervical embryo transfer
- Currently used in almost 50% of IVF cycles for treatment of male factor and unexplained causes
- Pregnancy rate of 40-50 % per cycle

Intracytoplasmic Sperm Injection (ICSI)



Future Directions in ART

- The “-omics” Revolution
- Preimplantation genetic diagnosis (PGD)
 - with transgenic therapy ?
- Nuclear and/or cytoplasmic oocyte transfer
- Embryonic Stem Cell Line Development
- Gamete Stem Cell Development

Future Directions in ART (Con't)

- Embryo Cloning - Reproductive/Therapeutic
- Adult Cell Gamete Cloning - sperm/oocyte
- Adult Somatic Cell Cloning

The “-omics” Revolution in Infertility

- Genomics: The branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes.
- Proteomics: The set of proteins expressed by the genetic material of an organism under a given set of environmental conditions.

The “-omics” Revolution in Infertility

- Metabolomics: The systematic study of the unique chemical fingerprints that specific cellular processes leave behind.
- Embryomics: The identification, characterization and study of the diverse cell types which arise during embryogenesis.

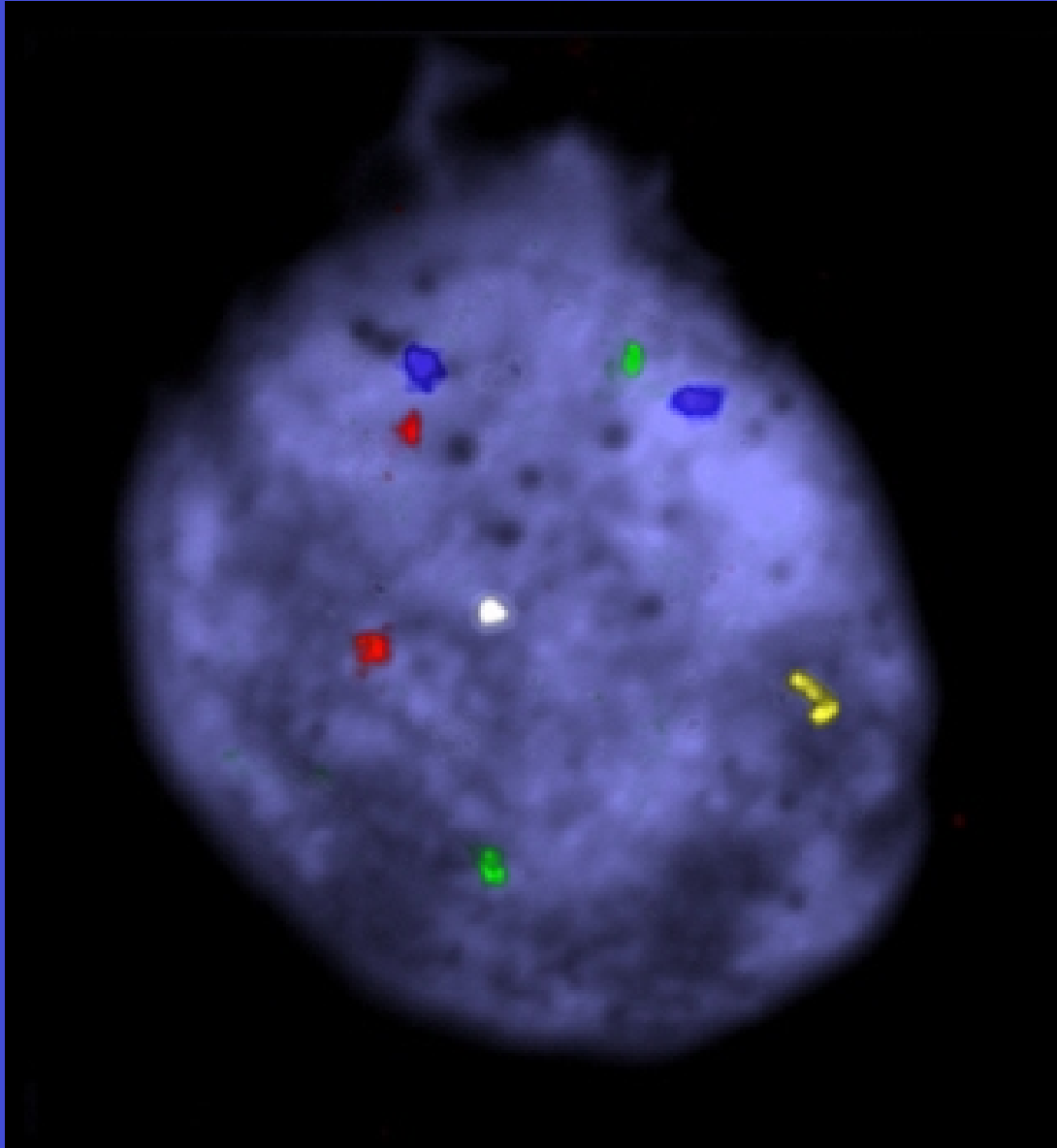
Preimplantation Genetic Diagnosis (PGD)

- **Goal: Identify Genetically Abnormal Embryos**
- **IVF/ICSI + Embryo Culture**
- **Blastomere Biopsy of 8-cell Embryo**
- **FISH/PCR Genetic Studies (X,21,single gene,etc)**
- **Transfer of Normal Blastocysts/Frozen Embryos**

PGD 8-cell Blastomere Biopsy



PGD FISH - Normal Embryo

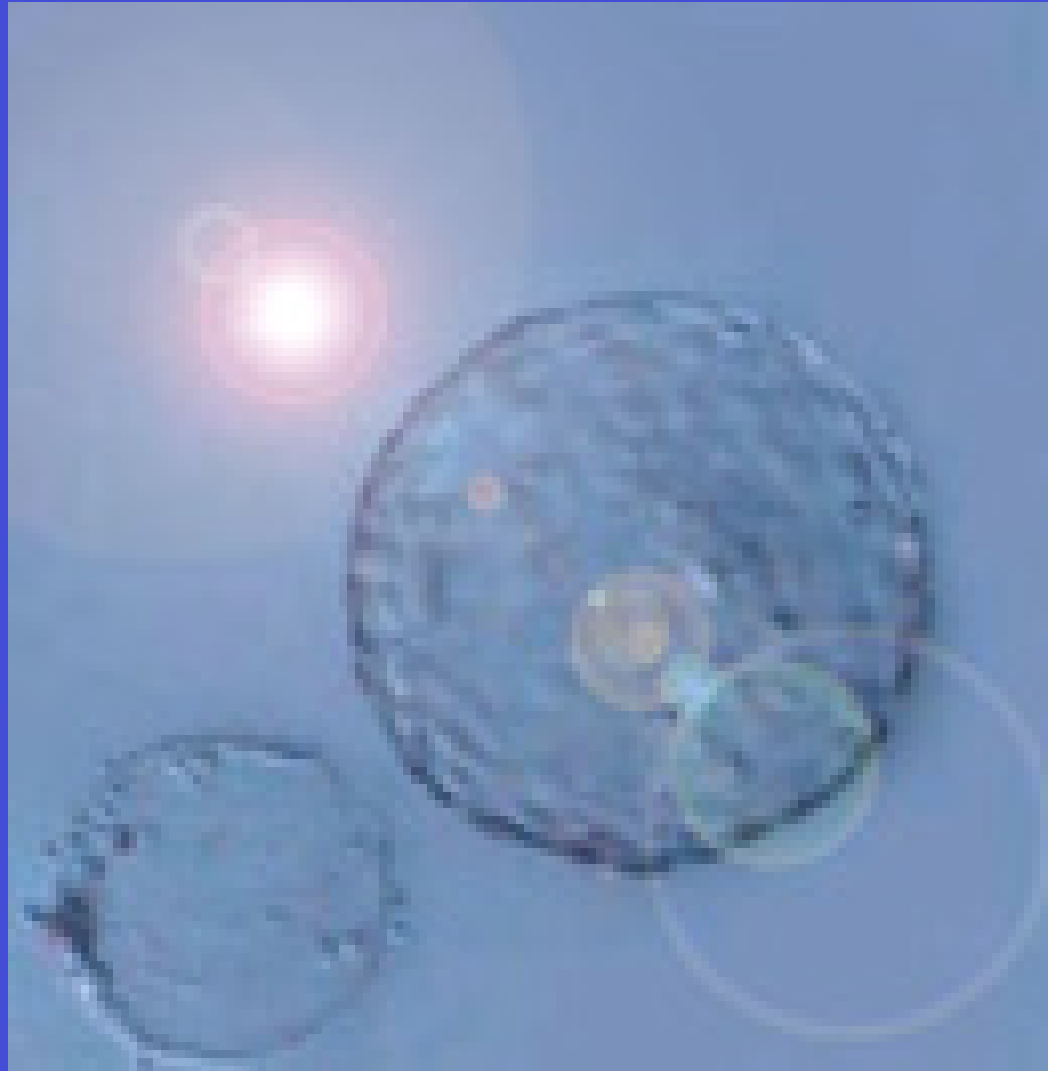


White= Y
Yellow= X
Blue= 18
Red= 21
Green= 13

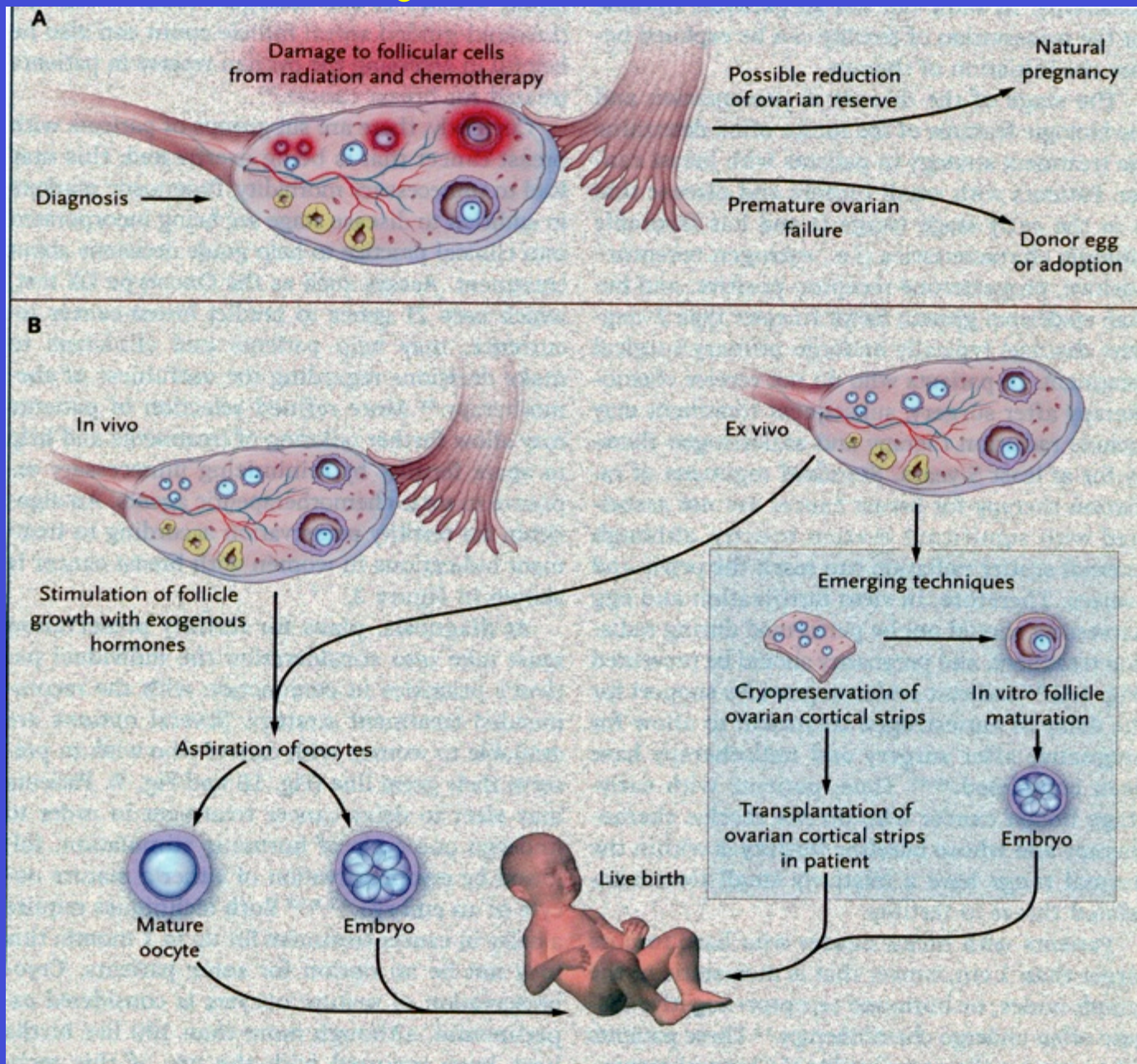
Oocyte Cryopreservation

- **Preservation of Oocytes Prior to Fertilization**
- **TV Retrieval of Stimulated Oocytes**
 - **Future: Unstimulated Oocytes with IVM**
- **Desiccation and Cryopreservation**
- **Delayed Thaw and IVF/ICSI Embryo Culture**
- **Transfer of Healthy Embryos**

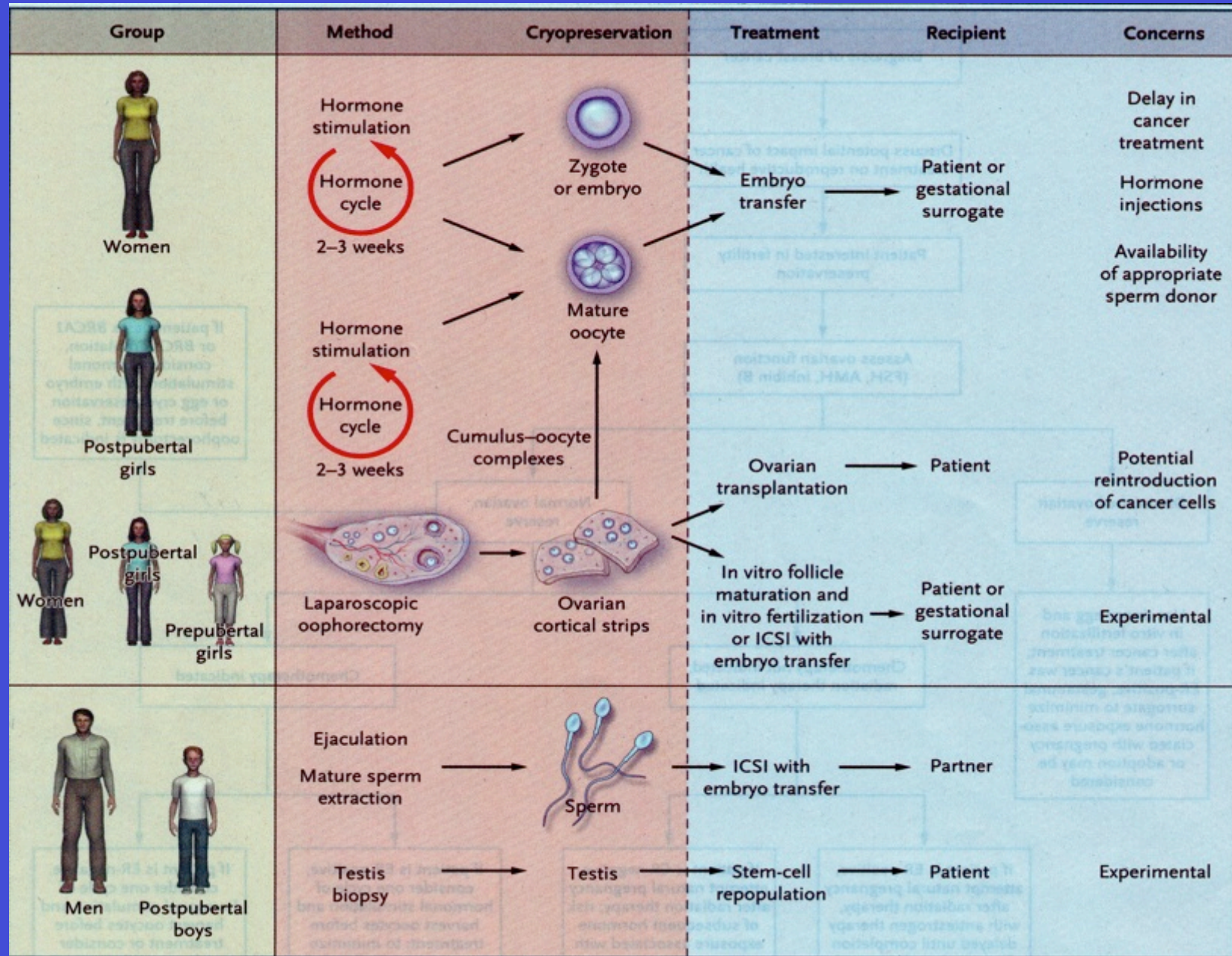
Oocyte Desiccation for Cryopreservation



Fertility Preservation



Fertility Preservation



IVF Treatment of Genetic Mitochondrial Disease

- **“Mitochondrial DNA Replacement Therapy”**
- **Performed by Donor Egg Nuclear Transfer**
- **1:200 incidence of pathogenic mtDNA mutation**
- **Recently approved by British Parliament**
- **Currently in active IRB-approved study at OHSU**

Stem Cell Gamete Production

A. Goal is cost-effective, ethically-acceptable source of sperm and oocytes

- Reduction of risks with donor gametes
- Alternative to somatic cell cloning

B. Potential treatment for cancer patients, age-related infertility, and severe male factor

C. Reduction of multiple gestation by SET

In Vitro Fertilization (IVF) - 2014

- SART Data: 61,740 IVF babies born in 2012 in U.S.
- IVF babies now constitute almost 2% of U.S. births
- Estimated 400,000 IVF babies born in 2012 in world
- IVF births now almost 4% of births in Europe
- Estimated 5,000,000 IVF births by Oct. 2013

- Who Knew ?????