
Center for
Reproductive
Medicine

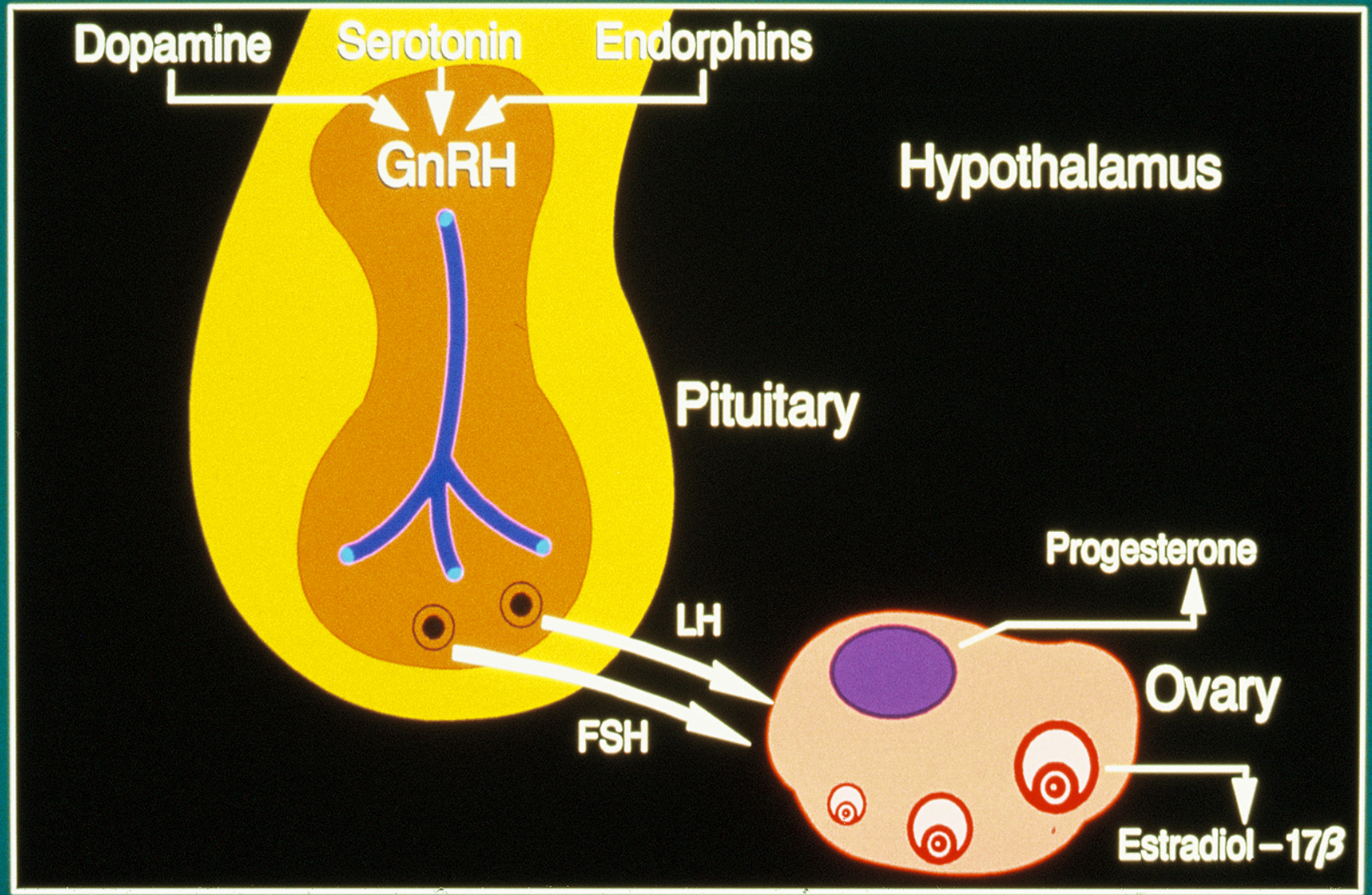
An IVF cycle typically includes the following steps or procedures:

- Medications to grow multiple eggs
- Retrieval of eggs from the ovary or ovaries
- Insemination of eggs with sperm
- Culture of any resulting fertilized eggs (embryos)
- Placement (“transfer”) of one or more embryo(s) into the uterus
- Support of the uterine lining with hormones to permit and sustain pregnancy

Medications for IVF Treatment

- The success of IVF largely depends on growing multiple eggs at once
- Injections of the natural hormones FSH and/or LH (gonadotropins) are used for this purpose
- Additional medications are used to prevent premature ovulation
- An overly vigorous ovarian response can occur, or conversely an inadequate response

Hypothalamic–Pituitary–Ovarian Axis



Gonadotropins

- Menopur
- Bravelle
- Follistim
- Gonal-F

FSH/LH

hp FSH

r FSH

Gonadotropin Side Effects

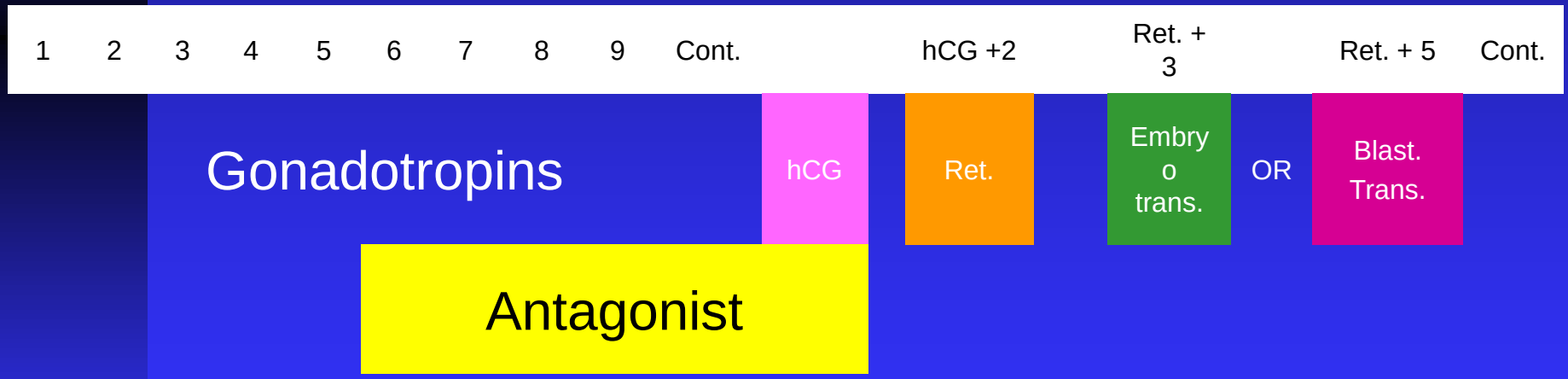
- Breast fullness/tenderness
- Pelvic discomfort
- Headache
- Ovarian cyst formation
- Nausea
- Intermenstrual bleeding
- Diarrhea
- Flatulence
- Changes in libido
- Emotional lability

Premature Luteinization In Ovulation Induction

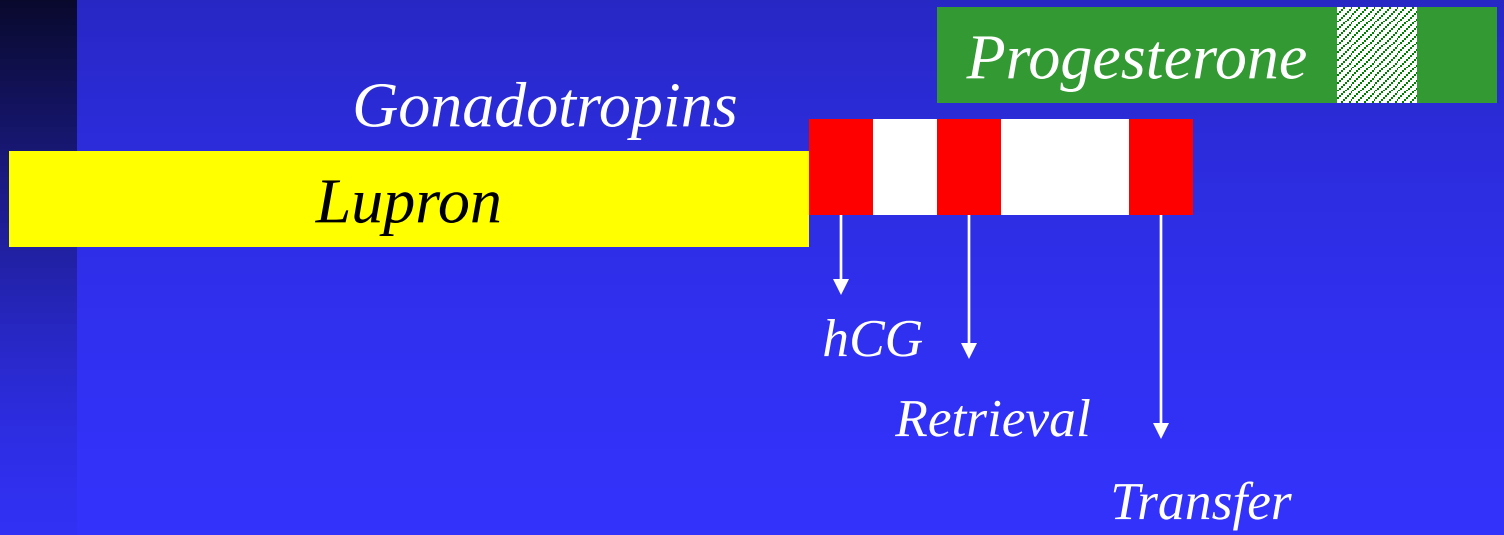
Early secretion of progesterone prior to ovulation

Medications Used In IVF Ovarian Stimulation To Block Premature Progesterone Release

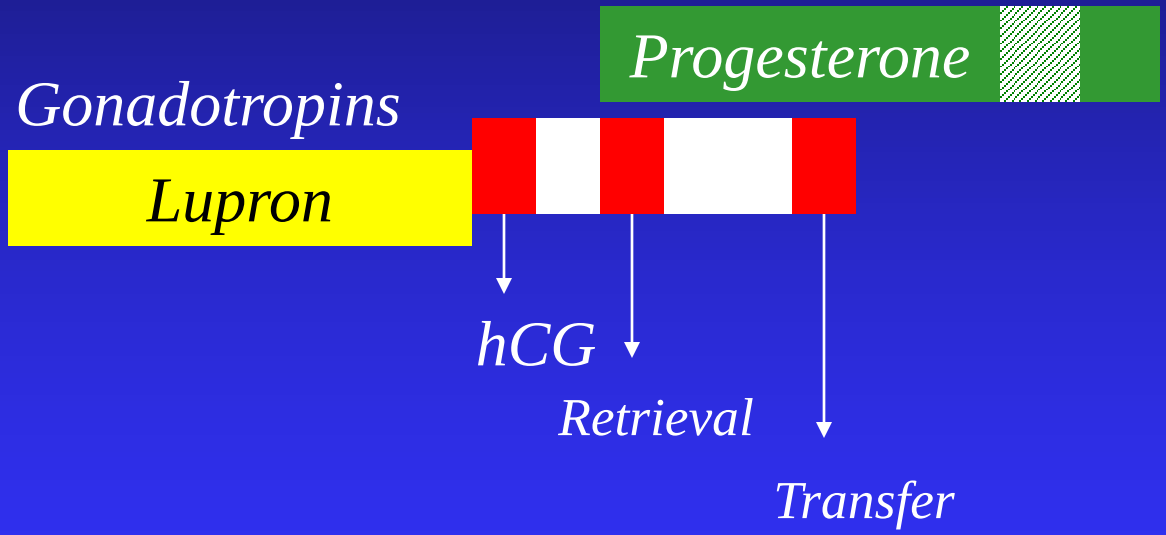
Ovarian Stimulation -GnRH Antagonist



Use Of GnRh Antagonist To Cause Down Regulation Of LH/FSH Prior To Stimulation



Use Of Lupron Flare For Poor Responders



Human Chorionic Gonadotropin (hCG)

- Placental Luteinizing Hormone-like protein
- 10x stronger than LH
- Effects:
  - Matures eggs (meiosis)
  - Stimulates progesterone secretion
  - Causes follicle release ~38-40 hours

Preparations of Human chorionic gonadotropin (hCG):

- Profasi®
- Novarel®
- Pregnyl®
- Ovidrel®

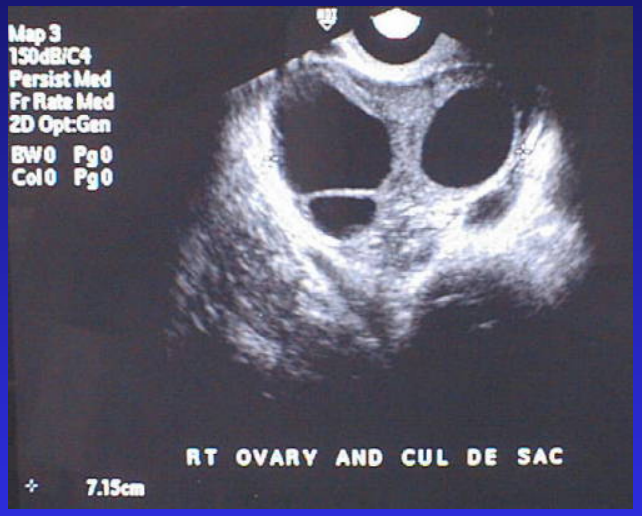
hCG Side Effects (in ~15 – 25 %)

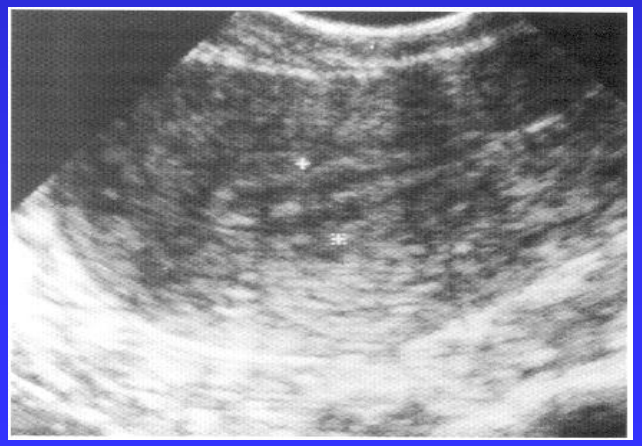
- Breast Tenderness/Fullness
- Mood Changes
- Water

Other Medications Possibly Used During The Cycle

- Oral contraceptive pills
- Other medications
  - Antibiotics
  - Low dose aspirin
  - Medrol (glucocorticoid)
  - Metformin
  - Progesterone

Monitoring Ovarian Stimulation

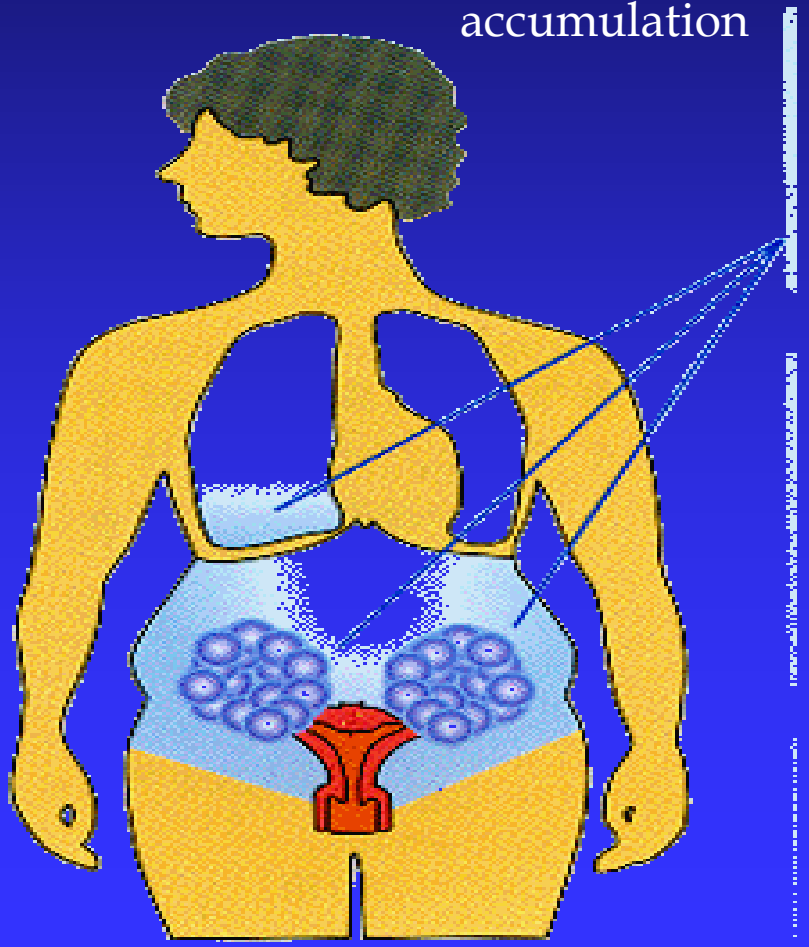




- Transvaginal ultrasound scanning:
  - No. & size of follicles
  - Pattern & thickness of endometrium
- Estrogen blood level

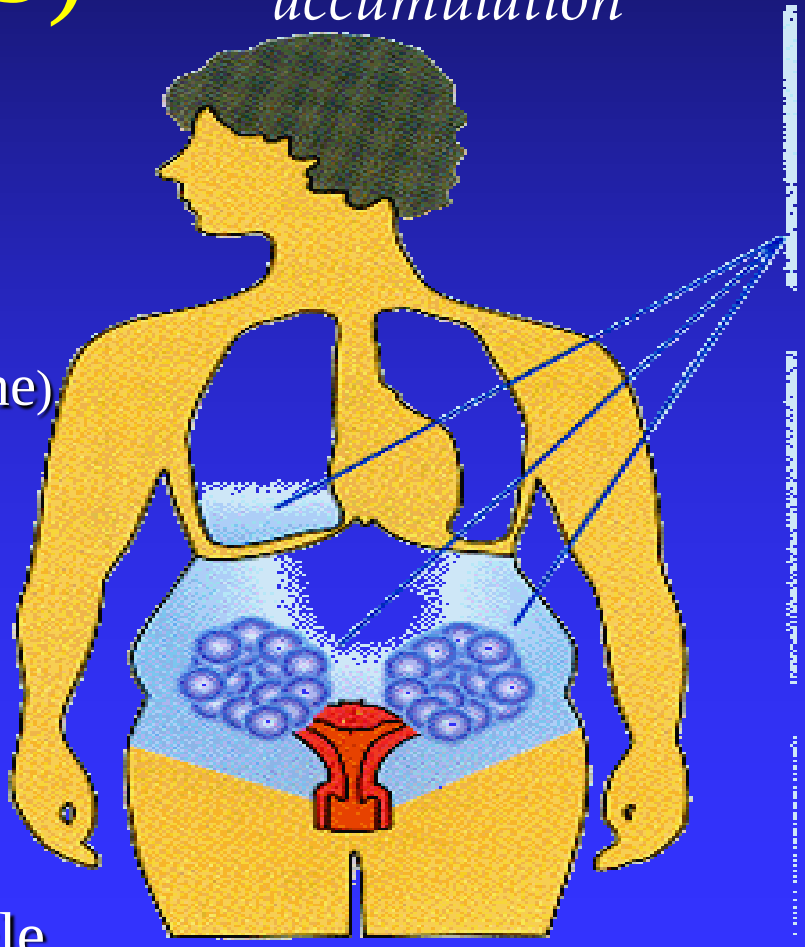
Complications: Ovarian Hyperstimulation Syndrome (OHSS)

- Mild: < 5%
  - (50% of pregnancy cycles)
  - Ovaries <5 cm
- Moderate: 1-2%
  - <10 cm
- Severe: << 1%
  - >10 cm
- Risk Factors
- Treatment



Severe Ovarian Hyperstimulation Syndrome (OHSS)

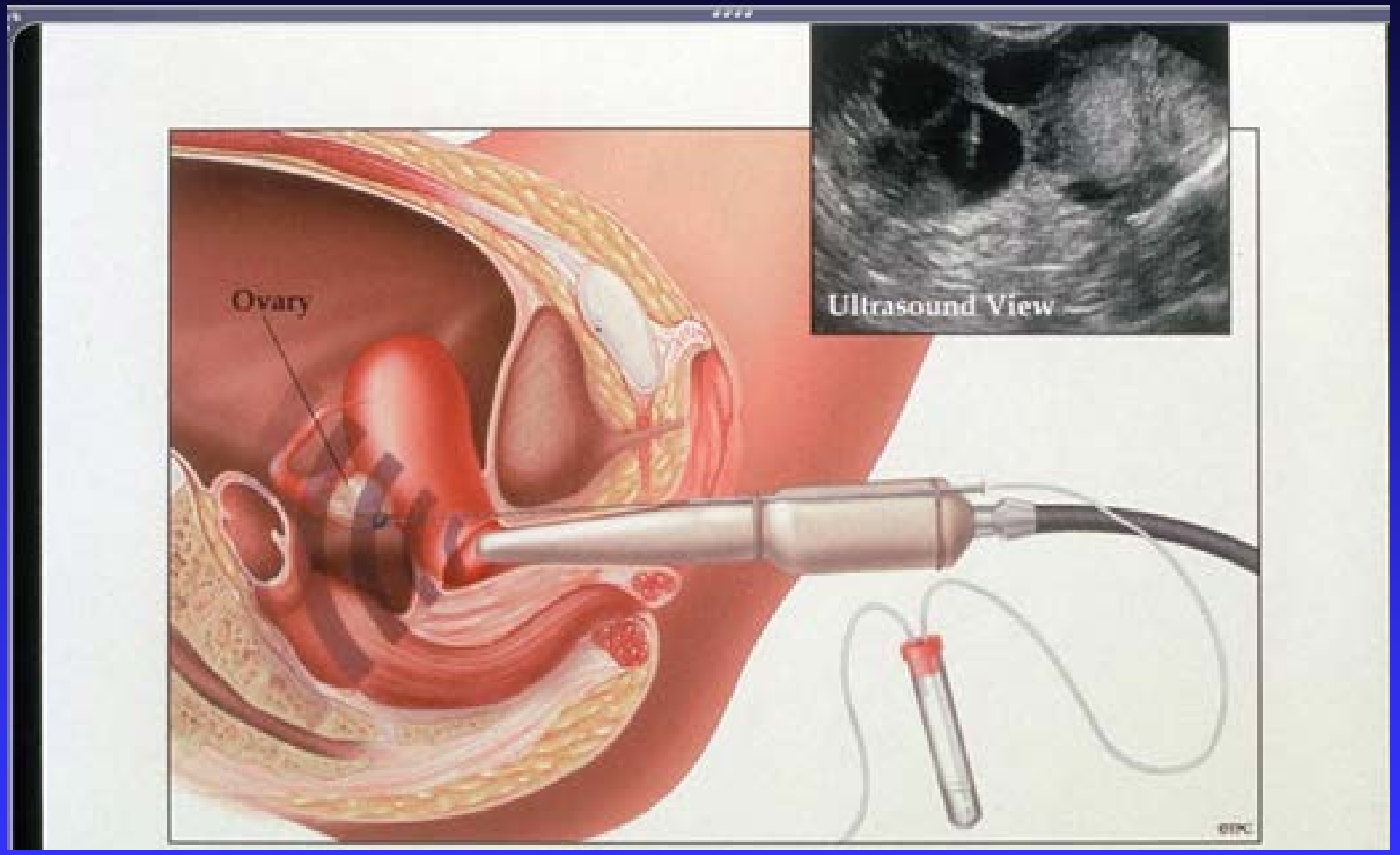
- Prevention
  - High protein diet
  - Hydration
  - Medications(e.g cabergoline)
- Treatment
  - Cryopreservation of all embryos
  - Coasting
  - Lupron Trigger
  - Cancellation of IVF Cycle



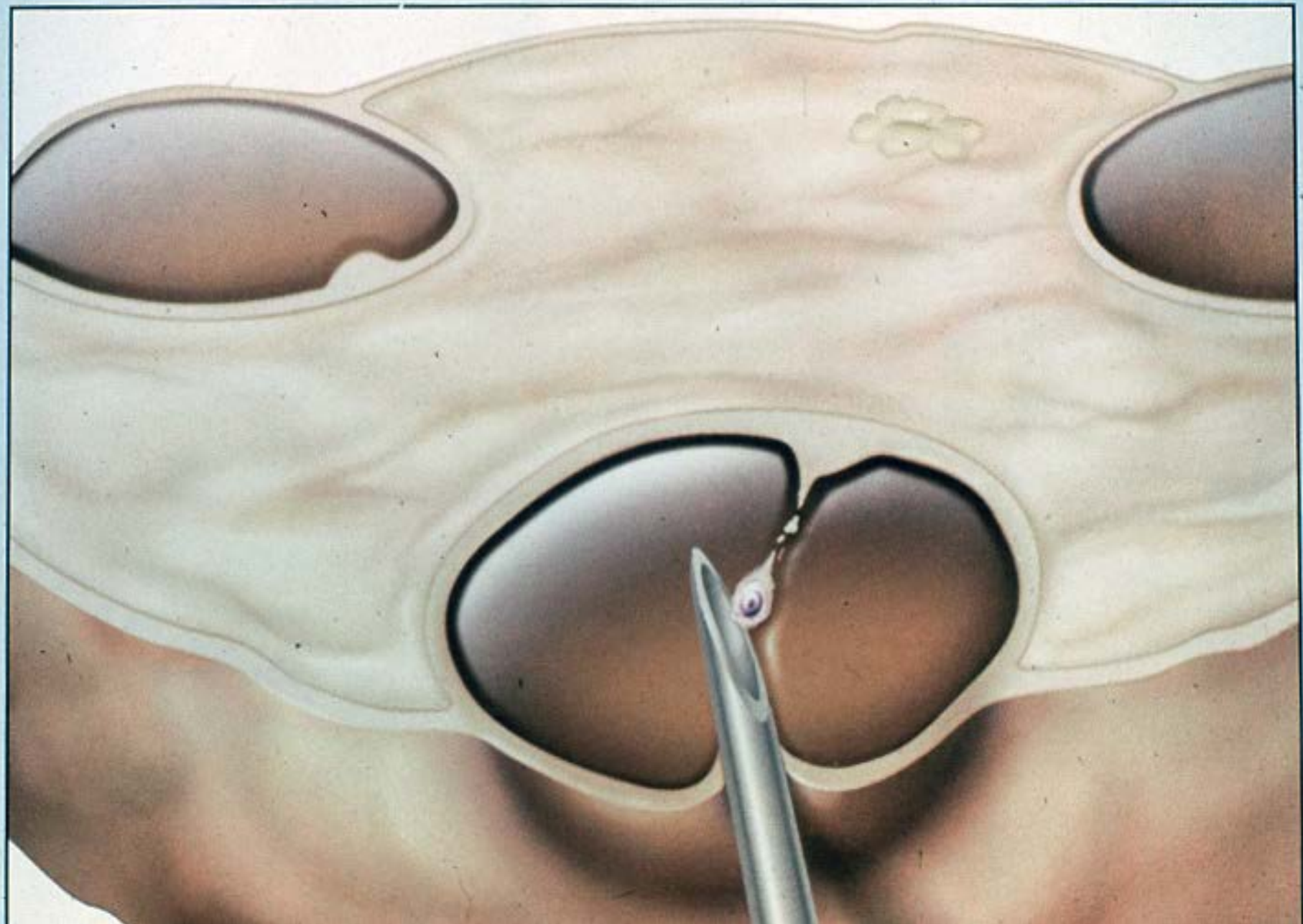
In Vitro Procedures

Transvaginal Egg Retrieval

- Eggs are removed from the ovary with a needle under ultrasound guidance
- Anesthesia is provided to make this comfortable
- Injury and infection are rare but possible
- Bleeding
- Tissue damage/trauma
- Anesthesia complications
- Failure to recover eggs


Ovary
Ultrasound View

Transvaginal Oocyte Retrieval Procedure



In Vitro Fertilization and Embryo Culture

- Sperm and eggs are placed together in specialized conditions (culture media, controlled temperature, humidity and light) in hopes of fertilization
- Culture medium is designed to permit normal fertilization and early embryo development
- Embryo development in the lab helps distinguish embryos with more potential from those with less or none

Semen Preparation

Lab staff analyzing sperm

Micromanipulation

- Intracytoplasmic Sperm Injection (ICSI)
- Assisted Hatching

Intracytoplasmic Sperm Injection (ICSI)

- ICSI is used to increase the chance of fertilization when fertilization rates are anticipated to be lower than normal
- Overall fertilization rates with ICSI of mature eggs are higher than for standard IVF insemination
- ICSI will not improve oocyte defects

Adverse Outcomes of ICSI

- **1.4% increase in inherited abnormalities – related to severity of sperm factor**
- **Men with very low sperm count (< 5 million) are at higher risk of carrying genetic abnormalities that could be passed on to offspring**
- **In some cases male offspring at risk for low sperm count/infertility – Y chromosome microdeletion**

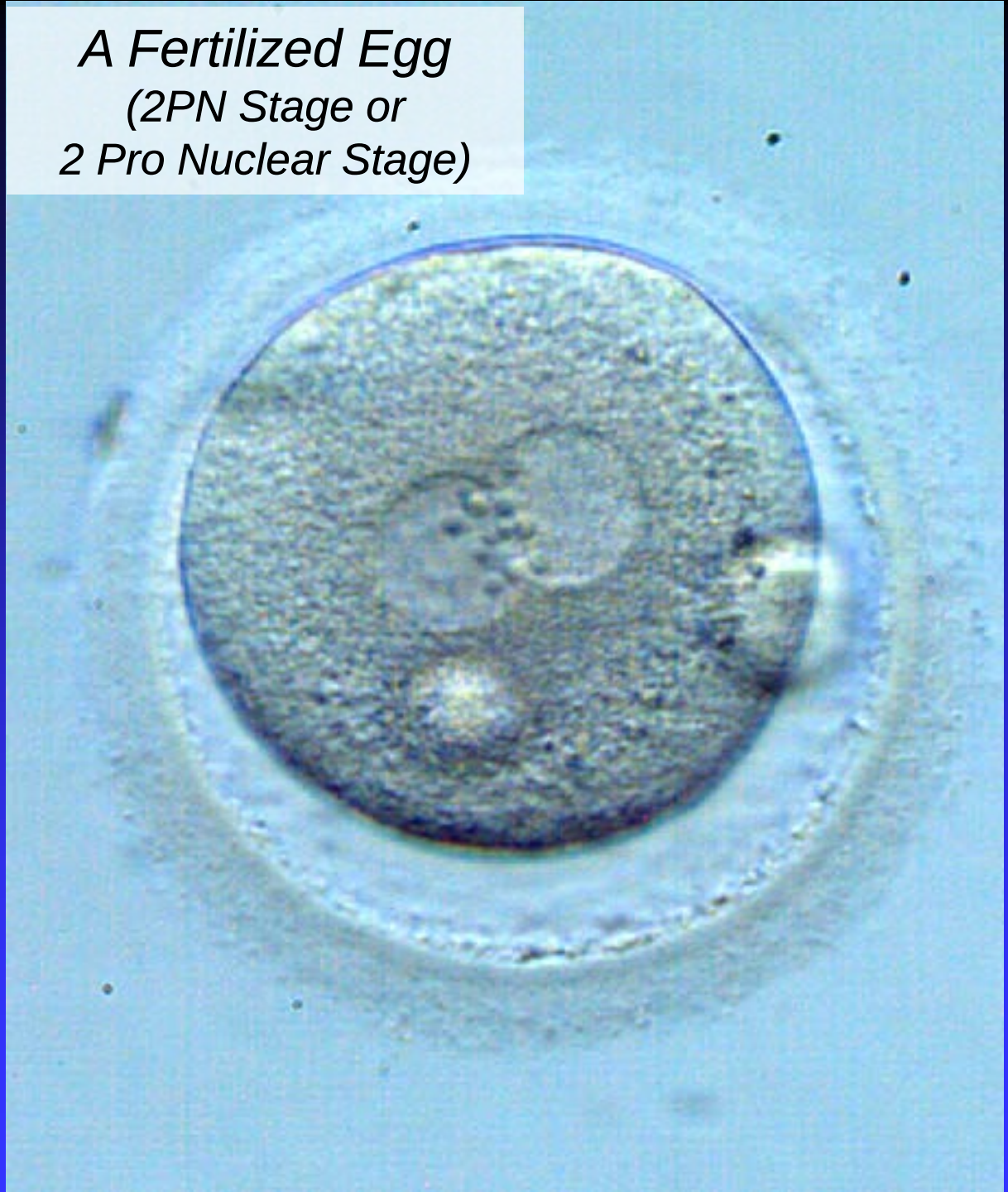
Assisted Hatching

- Assisted Hatching involves making a hole in the outer shell (zona pellucida) that surrounds the embryo
- Hatching may make it easier for embryos to escape from the shell (egg wall) which surrounds them

Embryo Development

A Fertilized Egg

(2PN Stage or
2 Pro Nuclear Stage)



2 Cell Embryo

4 Cell Embryo
(typically day 2 post retrieval)

8 Cell Embryo
(typically day 3)

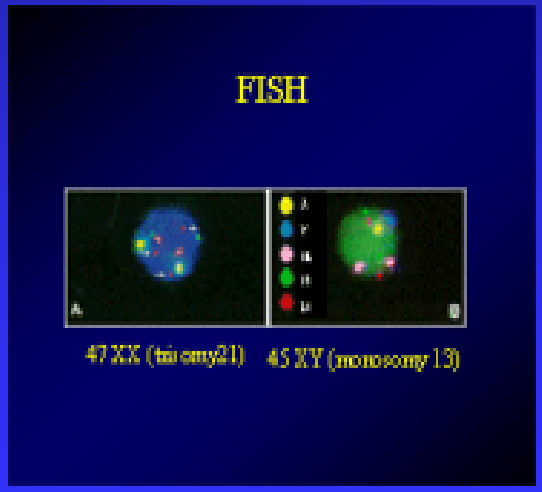
A Blastocyst
(day 5 or day 6)

Potential Embryo Problems

- Laboratory problems
- Natural disaster
  - Hurricanes
  - Floods
  - Power outage
- No fertilization
- Abnormal fertilization/failure to grow

PGD (Pre-implantation Genetic Diagnosis)

- Testing an embryo when inherited risk is known
- Biopsy at the blastocyst stage
  - Cells subjected to the genetic test
  - Identifies which embryo(s) to transfer
- Types of test:
  - CGH for whole chromosome analysis
    - Blastocyst must be frozen after biopsy with embryo transferred in subsequent cycle
    - 1% chance of error



PGS (Pre-implantation Genetic Screening)

- No pre-existing known abnormality in the parents
- Screening for chromosome copy number
- Benefit most notable in women of advanced maternal age, recurrent pregnancy loss and unexplained IVF failures

Embryo Transfer

- After a few days of development, the best appearing embryos are selected for transfer
- The number chosen influences the pregnancy rate and the multiple pregnancy rate
- A woman's age and the appearance of the developing embryo have the greatest influences on pregnancy outcome
- Embryos are placed in the uterine cavity with a thin tube
- Excess embryos of sufficient quality that are not transferred can be frozen

Blastocyst Transfer

- Highly specialized sequential culture media which supports embryonic growth after 72 hours in tissue culture
- These nutrients are required for continued development *in vitro*

Blastocyst Transfer

- Allows for self selection of “robust” embryos in extended culture and optimal in patients under the age of 38 years.
- Reduced number blastocyst transfer with higher implantation rate
- Theoretically more mature blastocyst for cryopreservation (but decreased number)
- Some risk as ~5% will not continue to grow
- Increased cost – time/media

Is Blastocyst Culture For Everyone?

- Blastocyst Culture is optimal for those under the age of 38.
- In patients over the age of 38 or with diminished ovarian reserve, transfer may be performed on Day #3 as embryos from these patients may not tolerate extended culture conditions.
- We have noted an improvement in pregnancy outcomes for patients in this category.

Elective Single Embryo Transfer

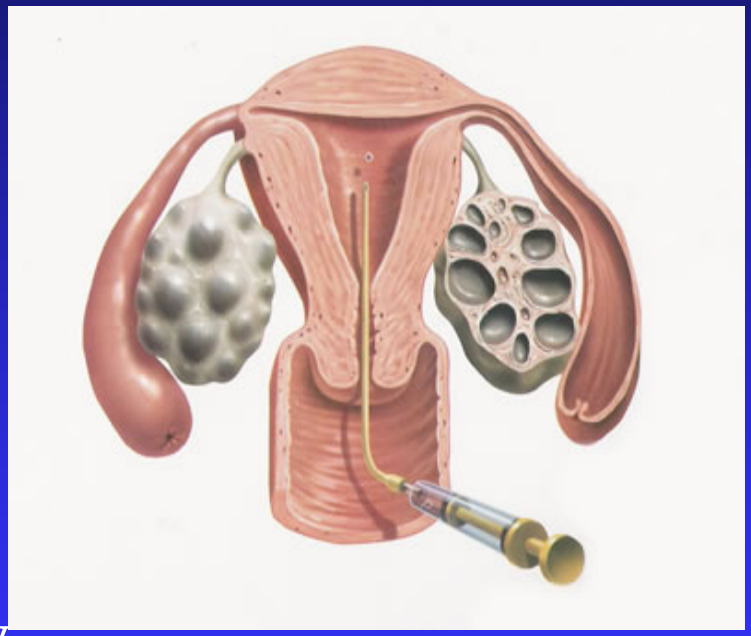
High quality blastocyst embryos available

Almost guarantees a singleton pregnancy

Lower risk of maternal complications in pregnancy

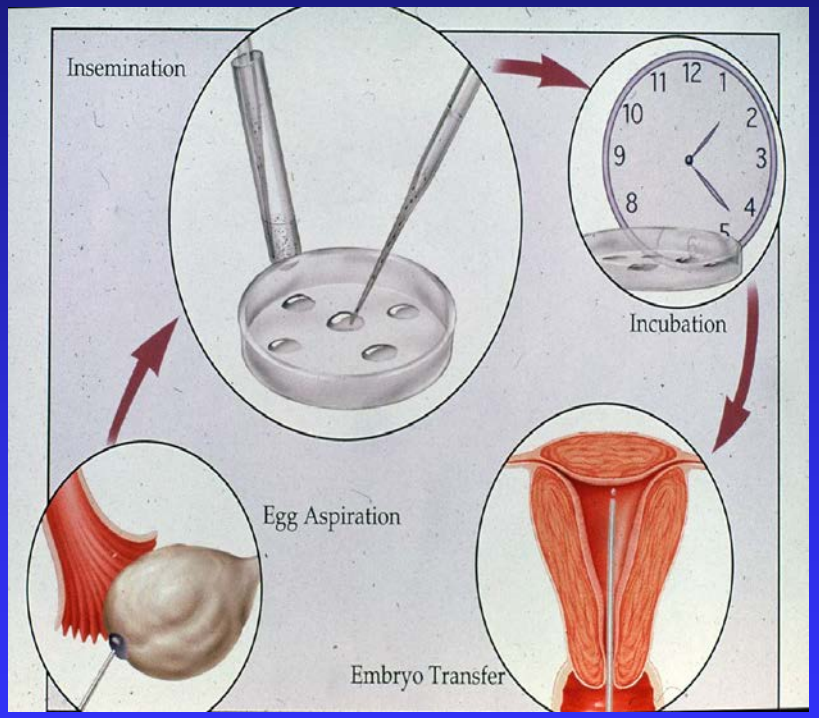
Lower risk of premature delivery

Allows other embryos to be frozen and used in the future



Hormonal Support of Uterine Lining

- Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support
- Progesterone, given by intramuscular or vaginal route, is routinely given for this purpose



Potential Risks of Transfer

- Infection

Indications for Cryopreservation

- To reduce the risks of multiple gestation
- To preserve fertility potential in the face of certain necessary medical procedures (e.g., cancer treatment)
- To increase the chance of having one or more pregnancies from a single cycle of ovarian stimulation
- If the risks for OHSS or other stimulation related complication are high, then all embryos may be frozen to be used safely in the future

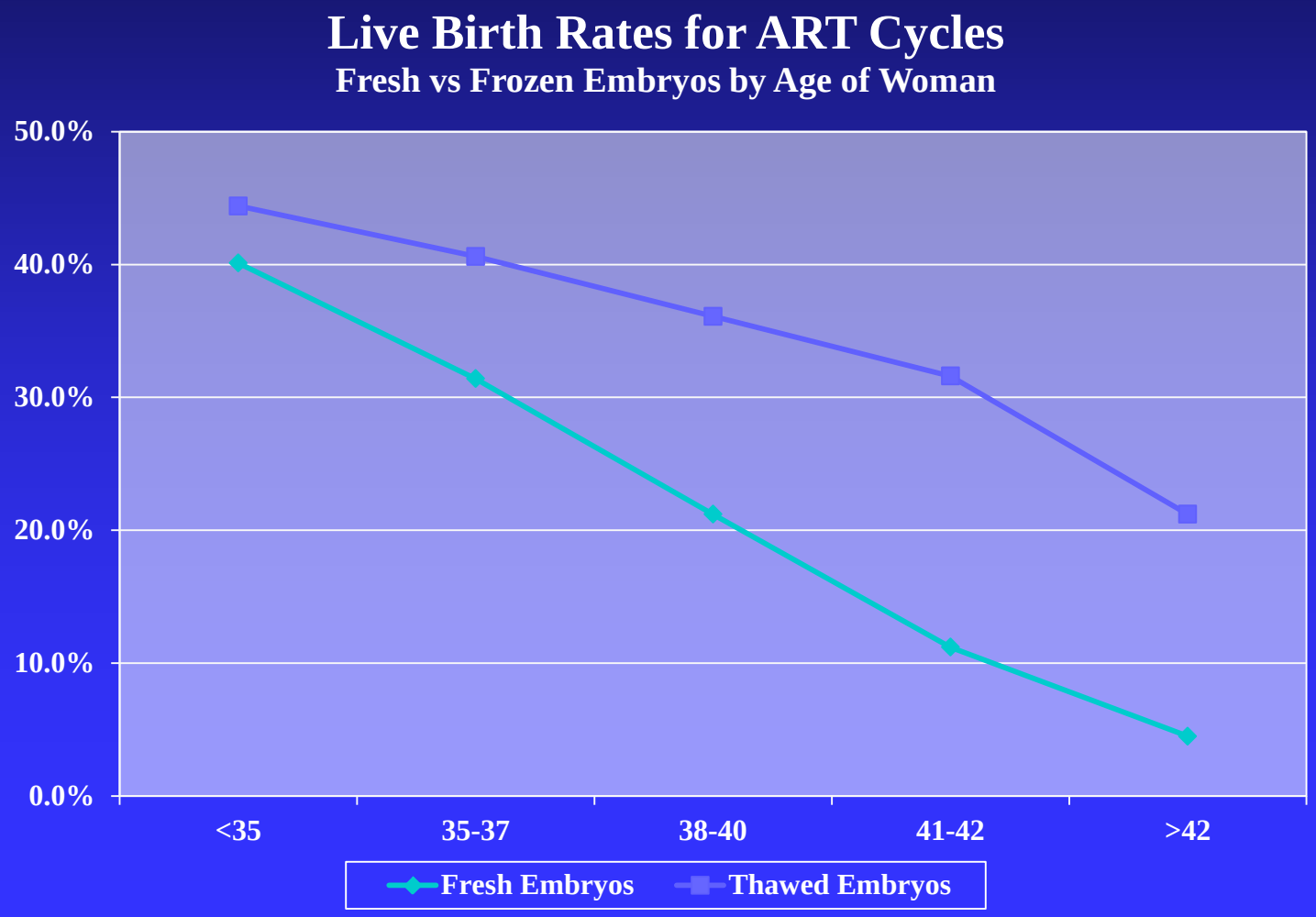
Cryopreservation of Embryos

- Slow freeze
- Rapid freeze
  - Vitrification

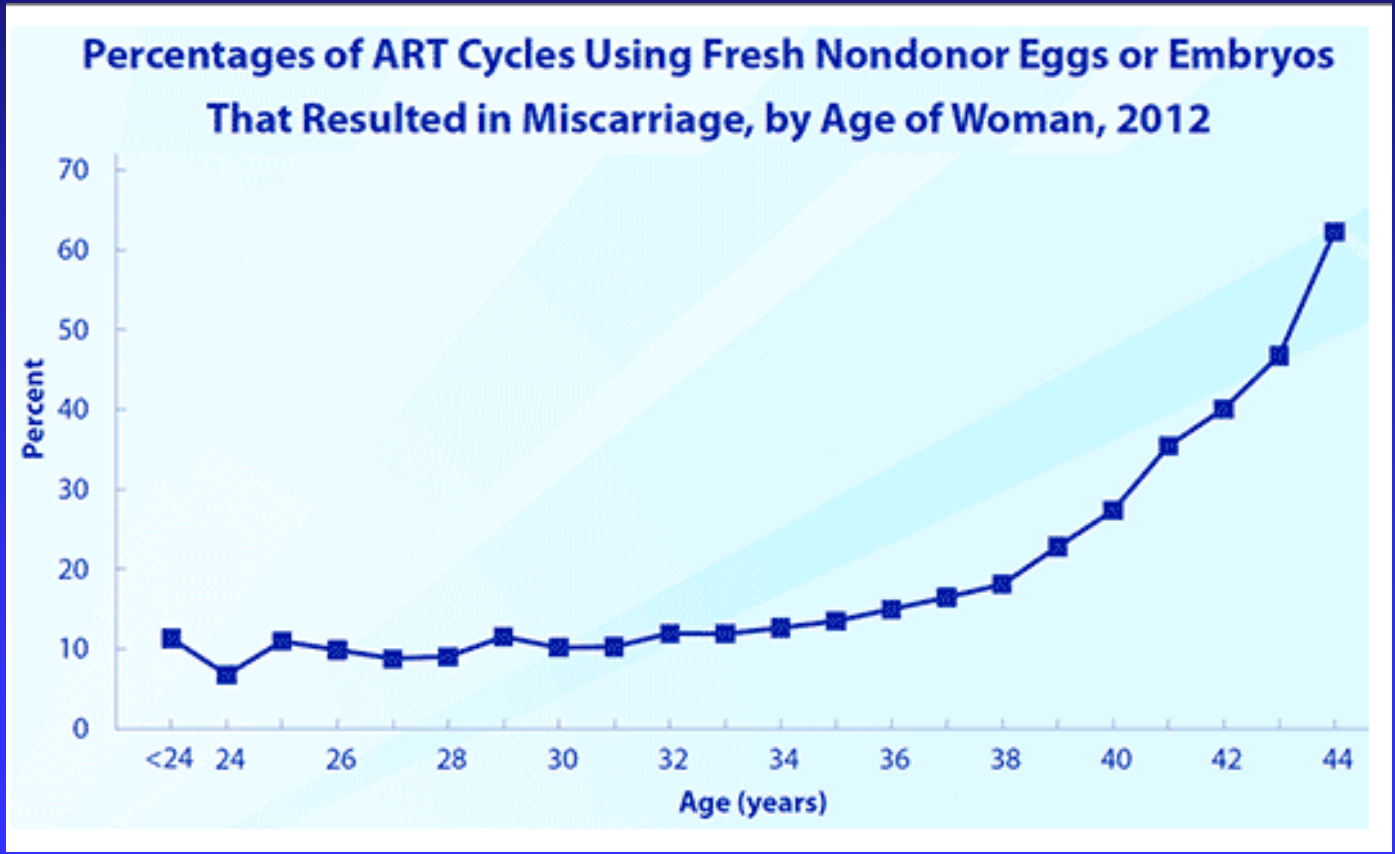
Embryo Storage Dewar

IVF Outcome Data

Do IVF Success Rates Differ by Age?



How Do Miscarriage Rates Vary Among IVF Patients Of Different Ages?



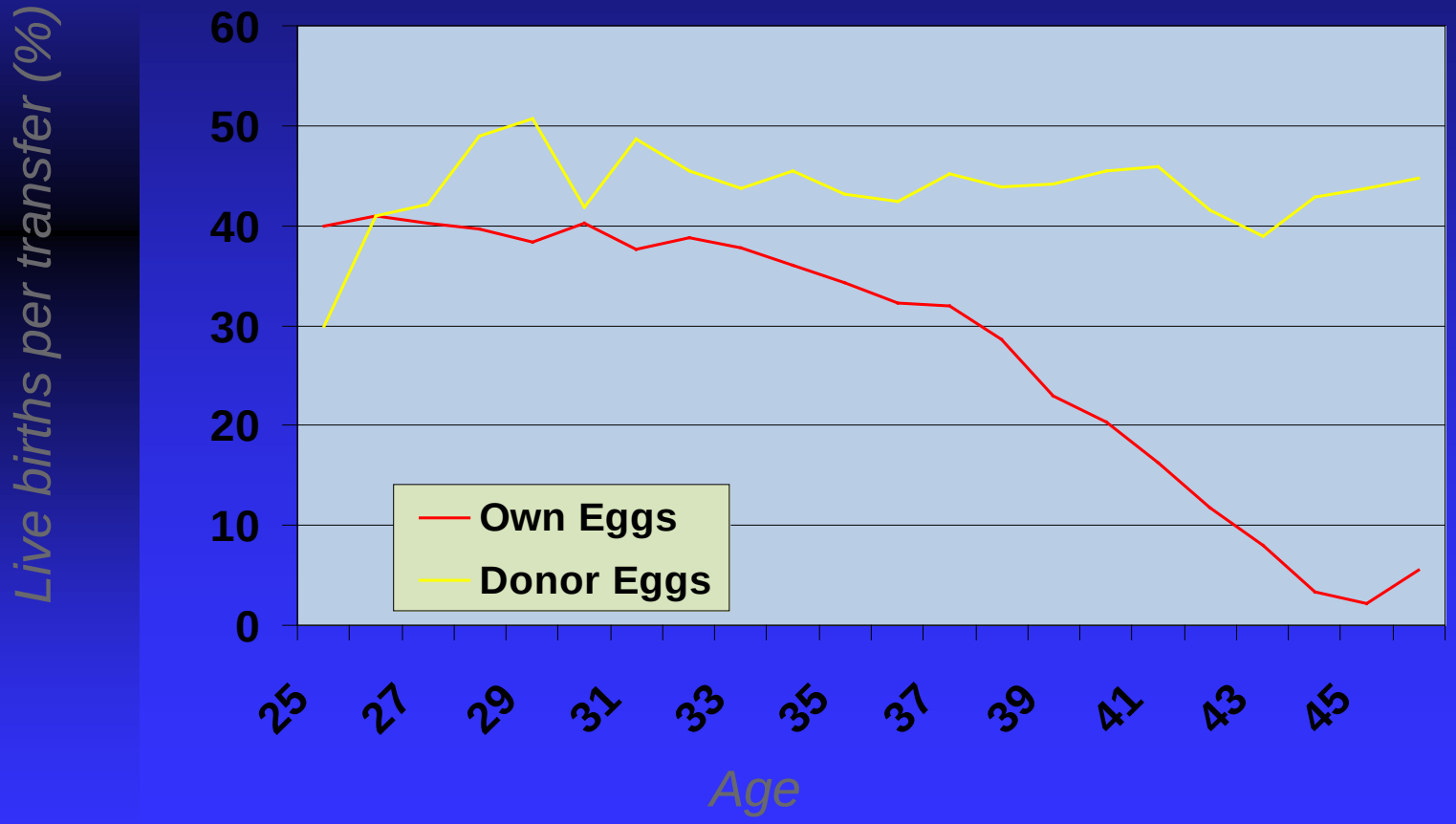
Donor Egg IVF

Age of egg donor
determines outcome

Pregnancy rates at CRM are between 60-70% per cycle

Donor Oocytes

Live Births per Transfer for Fresh Embryos From Own & Donor Eggs



Embryo Disposition

- Freezing extra healthy embryos provides additional chances for pregnancy without stimulation/egg retrieval required (bonus babies)
- Frozen embryos do not always survive the process of freezing and thawing
- Freezing of eggs before fertilization is currently much less successful than freezing of fertilized eggs (embryos)
- Ethical and legal dilemmas can arise when couples separate or divorce; disposition agreements are essential
- It is the responsibility of each couple with frozen embryos to remain in contact with the clinic on an annual basis

Storage – Options

- Thawed and transferred in future
- Donated
- Donated to research (not currently available)
- Discarded
- Must be transferred to a commercial storage facility if not used within two years

Risks to the Woman with IVF

- Ovarian Hyperstimulation Syndrome (OHSS) ~1%
- Risks of Pregnancy-related complications
- No scientific evidence supporting risk for cancer caused by ovarian stimulation

Potential Risks in Singleton IVF Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-ecclampsia	10.3%	1.6 (1.20 – 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)

Potential Risks 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 (< 2500g)	9.5%	1.8 (1.4 – 2.2)
Very low birth weight (< 1500g)	2.5%	2.7 (2.3 – 3.1)
Small for gestational age	14.6%	1.6 (1.3 – 2.0
NICU 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)
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	4.6%	5.7

Multiple Gestation Risks
Obstetrical Risks

- Preterm labor and delivery
- Intrauterine Growth Retardation
- Pregnancy-induced hypertension
- Gestational Diabetes

Multiple Pregnancy Complications

	Singleton	Twin	Triplet
Av. Wks at Birth	39 wks	36 wks	32 wks
% Very Premature	1.7%	14%	41%
Av. Birth Weight (lbs)	7.4	5.3	3.8
% Severe Handicap	1.9%	3.4%	5.7%
% Infant Mortality	1.1%	6.6%	19%

Risks to Offspring

- IVF babies may be at a slight increased risk for birth defects
- The risk for a multiple pregnancy is significantly higher for patients undergoing IVF, even when only one embryo is transferred
- Multiple pregnancies are the greatest risk for babies following IVF
- Some risk may also stem from the underlying infertile state, or from the IVF techniques, or both

Adverse Outcome in Infancy and Childhood

- Studies reassuring
- Possible slight increase in hospitalization and Genito-Urinary surgery (males)
- No increase in Cancer risk
- No increase in Neurologic dysfunction

Adverse Outcomes Of ART Twins

- 20 fold increase in twins with ART
- No difference in risks compared with spontaneously occurring twins
- But twins are at higher perinatal risks than singletons
- Vanishing twins pose a higher risk for the surviving fetus(es) than if the pregnancy had started as a singleton (or twin)
- Reduced twin pregnancies at higher risk than nonreduced twin pregnancies

Optimizing Natural Fertility

- Weight
  - Obesity—increases time to pregnancy two fold
  - Underweight—increases time to pregnancy four fold
- Toxins—decreases fertility
  - Smoking
  - Alcohol (>2 servings a day)
  - Caffeine (greater than 250 mg/day)

BMI

- Severe obesity—defined as a BMI >35
- Decreased fertility and implantation
- Six fold increase in miscarriages
- Increases the risk of obstetrics and neonatal complications
- Obesity in men: Abnormal seminal parameters and adversely affect male fertility.
- For the female patient with a BMI of greater than 40 undergoing IVF, the egg retrieval is at the hospital.

Fertility Preservation

- **Indications:** Any condition that will compromise your future fertility (e.g. cancer, premature menopause, genetic concerns)

- Cryopreservation
  - Sperm
  - Oocyte
  - Embryo

Falcone et al, 2007

Additional Resources

American Society of Reproductive Medicine
. www.asrm.org
American Congress of Obstetrics and Gynecology
. www.acog.org
Resolve – National Infertility Association
. www.resolve.org

Please Print/Sign the next page and submit to your nurse.

CRM

Certificate of Completion

In-Vitro Patient Education

We(I) acknowledge reading and understanding the In-Vitro Fertilization process and risks information outlined in the presentation.

_____ _____

Patient Signature Date

_____

Patient Name

_____ _____

Spouse/Partner Signature Date

_____

Spouse/Partner Name