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

Dopamine → Serotonin → Endorphins → GnRH → Hypothalamus

Pituitary:
- LH
- FSH

Ovary:
- Progesterone
- Estradiol – 17β
Gonadotropins

- Menopur: $FSH/LH$
- Bravelle: $hp\ FSH$
- Follistim: $r\ FSH$
- Gonal-F: $FSH/LH$
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

Gonadotropins

Lupron

Progesterone

hCG

Retrieval

Transfer
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**

Interstitial fluid accumulation
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
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
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?

Live Birth Rates for ART Cycles
Fresh vs Frozen Embryos by Age of Woman
How Do Miscarriage Rates Vary Among IVF Patients Of Different Ages?

Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Miscarriage, by Age of Woman, 2012

- Age (years) vs. Percent
- <24, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44
- Percent: 0, 10, 20, 30, 40, 50, 60, 70
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

Live births per transfer (%)
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Absolute Risk (%) in IVF-conceived Pregnancies</th>
<th>Relative Risk (vs. non IVF-conceived Pregnancies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ecclampsia</td>
<td>10.3%</td>
<td>1.6 (1.20 – 2.0)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>2.4%</td>
<td>2.9 (1.5 – 5.4)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>2.2%</td>
<td>2.4 (1.1 – 5.2)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>6.8%</td>
<td>2.0 (1.4 – 3.0)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>26.7%</td>
<td>2.1 (1.7 – 2.6)</td>
</tr>
</tbody>
</table>
# Potential Risks in Singleton IVF Pregnancies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Absolute Risk (%) in IVF Pregnancies</th>
<th>Relative Risk (vs. non-IVF Pregnancies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>11.5%</td>
<td>2.0 (1.7 – 2.2)</td>
</tr>
<tr>
<td>Low birth weight (&lt; 2500g)</td>
<td>9.5%</td>
<td>1.8 (1.4 – 2.2)</td>
</tr>
<tr>
<td>Very low birth weight (&lt; 1500g)</td>
<td>2.5%</td>
<td>2.7 (2.3 – 3.1)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>14.6%</td>
<td>1.6 (1.3 – 2.0)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>17.8%</td>
<td>1.6 (1.3 – 2.0)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.2%</td>
<td>2.6 (1.8 – 3.6)</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>0.6%</td>
<td>2.0 (1.2 – 3.4)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>0.4%</td>
<td>2.8 (1.3 – 5.8)</td>
</tr>
<tr>
<td>Genetic risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-imprinting disorder</td>
<td>0.03%</td>
<td>17.8 (1.8 – 432.9)</td>
</tr>
<tr>
<td>-major birth defect</td>
<td>4.3%</td>
<td>(1.5 (1.3 – 1.8)</td>
</tr>
<tr>
<td>-chromosomal abnormalities (after ICSI):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-of a sex chromosome</td>
<td>0.6%</td>
<td>3.0</td>
</tr>
<tr>
<td>-of another chromosome</td>
<td>4.6%</td>
<td>5.7</td>
</tr>
</tbody>
</table>
Multiple Gestation Risks

Obstetrical Risks

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

<table>
<thead>
<tr>
<th></th>
<th>Singleton</th>
<th>Twin</th>
<th>Triplet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Av. Wks at Birth</strong></td>
<td>39 wks</td>
<td>36 wks</td>
<td>32 wks</td>
</tr>
<tr>
<td><strong>% Very Premature</strong></td>
<td>1.7%</td>
<td>14%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Av. Birth Weight (lbs)</strong></td>
<td>7.4</td>
<td>5.3</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>% Severe Handicap</strong></td>
<td>1.9%</td>
<td>3.4%</td>
<td>5.7%</td>
</tr>
<tr>
<td><strong>% Infant Mortality</strong></td>
<td>1.1%</td>
<td>6.6%</td>
<td>19%</td>
</tr>
</tbody>
</table>
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.
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