THE IMPACT OF IN VITRO FERTILIZATION ON PATIENTS, PARENTS, AND PEDIATRICS

MARISA PACELLA, MD
FELLOW LECTURE
JANUARY 28, 2016
CASE

- Full term, singleton female
- CHOP NICU for hypoglycemia, hyperinsulinism
- Consulted CHOP Genetics
  - History: born to a surrogate using IVF and a sperm donor
  - Exam: macrosomia, nevus flammeus, subtle hemihypertrophy
- Conclusion?
  - Beckwith Wiedemann syndrome
Know the types of assisted reproductive technologies and how they may influence pregnancy outcome.

Know the risk of congenital anomalies and chromosomal or genetic abnormalities associated with assisted reproductive technology.

Know the rationale, methods, and interpretation of screening for carrier status of genetic diseases and of first and second trimester screening for aneuploidy.

Know the potential fetal complications of multiple gestation.
ROAD MAP

IVF
- Infertility
- History
- Technique
- Epidemiology

Impact
- Parents
- Patients
- Pediatrics

Future
- Advances
HISTORY OF INFERTILITY

- Why did in vitro fertilization come about?
  - Infertility dates back to ancient times.
  - Infertility is the inability to conceive after 12 months, or 6 months if > 35 years of age.
Science has revealed a multitude of factors which influence a couple’s chances to conceive.
FEMALE INFERTILITY

**Infertility**

- **Ovarian**
  - Anovulation
  - Ovarian reserve

- **Tubal**
  - Scarring

- **Uterine**
  - Endometrosis
  - Fibroids

- **Cervical**
  - Cervicitis

- **Unexplained**
FEMALE INFERTILITY

- History taking may reveal risk factors toward one or the other etiology:
  - Age
  - Obesity
  - Menstrual history
  - Infection
  - Genetic
  - Lifestyle choices: smoking, drug use, and alcohol consumption

BUCK 1997
MALE INFERTILITY

- Infertility
  - Obstructive
    - Congenital absence of vas deferens
  - Non-obstructive
    - Impotence
    - Sperm count
    - Sperm motility
    - Morphology

PATEL 2011
Relevant history taking is similar in women and men:

- Infection
- Trauma
- Genetic
- Lifestyle choices: smoking, marijuana use, and alcohol consumption
- Anabolic steroid use

PATEL 2011, TOURNAYE 2011
The couple’s infertility factors are important in influencing:

- IVF methods used
- Prognosis
- Complications
ROADMAP

• Infertility
• History
• Technique
• Epidemiology
HISTORY

1790: Artificial Insemination

1827: Identification of the Ovum

1884: Donor Insemination
1884
Donor Insemination

1978
1st Live Birth from In Vitro Fertilization
HISTORY

1978  1st Live Birth from IVF

1981  1st American Live Birth

1985  Intracytoplasmic Sperm Injection

1990  Preimplantation Genetic Diagnosis

1996  CDC Surveillance
WHAT EXACTLY IS 'IN VITRO FERTILIZATION'?

Assisted Reproductive Technology (ART) - any artificial methods of aiding in conception

- Includes IVF, intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT)
- Does not include intrauterine insemination (IUI) or ovulation stimulation without IVF.

In Vitro Fertilization (IVF) - an ART that involves retrieving eggs from a woman’s ovaries and allowing fertilization to occur outside her body. A resulting embryo or embryos are then transferred into the woman’s uterus.
IVF CYCLE

1. **Ovulation Stimulation**
   - Downregulation of natural cycle
   - FSH, LH injections
   - Monitor for response

2. **Egg Retrieval**
   - HCG injection
   - Transvaginal retrieval
   - Concentrated sperm sample added to retrieved eggs

3. **Fertilization**
   - Fertilized egg undergoes cleavage into 8-cell embryo

4. **Embryo Culture**
   - Selected embryos are transferred to the uterus in hopes of implantation

5. **Ovulation Stimulation**

6. **Egg Retrieval**

7. **Embryo Transfer**

8. **Fertilization**
HOW IVF WORKS

3D animation of IVF
1978
1st Live Birth from In Vitro Fertilization

1981
1st American Live Birth

1985
Intracytoplasmic Sperm Injection

1990
Preimplantation Genetic Diagnosis
INTRACYTOPLASMIC SPERM INJECTION

- ICSI revolutionized management of male factor infertility.
The goal of PGD is to help couples who are carriers for genetic disorders conceive unaffected children.

- Single-gene
- Sex-linked
PREIMPLANTATION GENETIC DIAGNOSIS & SCREENING

- PGS benefits women with either recurrent miscarriages or advanced maternal age as there is higher risk of aneuploidy.
The overall hope is that couples using PGS avoid the increased likelihood of miscarriage should that genetic material be unbalanced.

PGS also avoids the difficult dilemma that an abnormal amniocentesis may create of whether or not to terminate the pregnancy.
OBSTETRIC PRENATAL SCREENING

- Screening for carrier status in parents:
  - Hemoglobinopathy
  - Cystic fibrosis
  - Tay Sachs
  - SMA
Prenatal Screening

- Ultrasounds
  - Nuchal translucency may be seen on first trimester ultrasound.
  - Choroid plexus cyst may appear between 11 and 26 weeks gestation.
  - Other gross abnormalities (e.g. heart, abdominal wall, neural tube defects) may also be seen.

- Quad Screen
  - AFP, B-hCG, estriol, and inhibin A screen for trisomy 21, 18, 13, neural tube defects.

- Cell-free DNA
  - Screening test for aneuploidy, Rh incompatibility, gender, and specific disorders.

- Invasive testing
  - Amniocentesis, percutaneous umbilical blood sampling, chorionic villi sampling
1978 1st Live Birth from IVF
1981 1st American Live Birth
1985 ICSI
1990 PGD/PGS
1996 CDC surveillance
EPIDEMIOLOGY

CDC Surveillance - 2013
### 2013 ART CYCLE PROFILE

#### Type of ART and Procedural Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unstimulated</th>
<th>Used PGO</th>
<th>Used gestational carrier</th>
<th>&lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound factor (%)</td>
<td>99%</td>
<td>99%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vitrified embryos (%)</td>
<td>69%</td>
<td>69%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

#### Patient Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male factor</th>
<th>Female factors only</th>
<th>Other factor</th>
<th>Female &amp; male factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian stimulation failure</td>
<td>21%</td>
<td>12%</td>
<td>32%</td>
<td>17%</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome</td>
<td>16%</td>
<td>10%</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>50%</td>
<td>32%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Unknown factor</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

### 2013 ART SUCCESS RATES

#### Total number of cycles (includes 2,655 cycle(s) using frozen eggs)

<table>
<thead>
<tr>
<th>Type of Cycle</th>
<th>Fresh Embryos from Nondonor Eggs</th>
<th>Frozen Embryos from Nondonor Eggs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>Number of cycles: 40,683</td>
<td>Number of cycles: 21,827</td>
</tr>
<tr>
<td>35-37</td>
<td>Number of cycles: 19,853</td>
<td>Number of cycles: 10,324</td>
</tr>
<tr>
<td>38-40</td>
<td>Number of cycles: 16,061</td>
<td>Number of cycles: 7,713</td>
</tr>
<tr>
<td>41-42</td>
<td>Number of cycles: 9,588</td>
<td>Number of cycles: 3,005</td>
</tr>
<tr>
<td>43-44</td>
<td>Number of cycles: 4,835</td>
<td>Number of cycles: 1,209</td>
</tr>
<tr>
<td>&gt;44</td>
<td>Number of cycles: 4,179</td>
<td>Number of cycles: 732</td>
</tr>
</tbody>
</table>

#### Outcomes per Cycle

<table>
<thead>
<tr>
<th>Cycle Type</th>
<th>Percentage of cycles resulting in term, normal weight singleton live births (%)</th>
<th>Percentage of cycles resulting in singleton live births (%)</th>
<th>Percentage of cycles resulting in twin live births (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>23.8 (13.5)</td>
<td>28.2 (16.7)</td>
<td>11.3 (2.5)</td>
</tr>
<tr>
<td>35-37</td>
<td>22.9 (15.2)</td>
<td>24.8 (16.7)</td>
<td>10.3 (1.8)</td>
</tr>
<tr>
<td>38-40</td>
<td>26.2 (16.7)</td>
<td>26.2 (16.7)</td>
<td>11.3 (2.5)</td>
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<tr>
<td>&gt;44</td>
<td>30.2 (16.7)</td>
<td>30.2 (16.7)</td>
<td>11.3 (2.5)</td>
</tr>
</tbody>
</table>

#### Current Services & Profile

<table>
<thead>
<tr>
<th>Percentage of clinics that allow &quot;cycling&quot;</th>
<th>Number of reporting clinics: 467</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor eggs 92%</td>
<td>Fresh Embryos</td>
</tr>
<tr>
<td>Donor embryos 69%</td>
<td>Frozen Embryos</td>
</tr>
<tr>
<td>Single women 96%</td>
<td>Number of clinics: 467</td>
</tr>
</tbody>
</table>

### EPIDEMIOLOGY

- National Summary for 2013
### 2010 ART CYCLE PROFILE

<table>
<thead>
<tr>
<th>Type of ART</th>
<th>Procedural Factors</th>
<th>Patient Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>IVF</td>
<td>&gt;99%</td>
<td>Tubal factor</td>
</tr>
<tr>
<td></td>
<td>With ICSI</td>
<td>Other factor</td>
</tr>
<tr>
<td>PIVF</td>
<td>&lt;1%</td>
<td>Ovulatory dysfunction</td>
</tr>
<tr>
<td>ZIFT</td>
<td>&lt;1%</td>
<td>Unknown factor</td>
</tr>
<tr>
<td>Combination</td>
<td>&lt;1%</td>
<td>Diminished ovarian reserve</td>
</tr>
<tr>
<td></td>
<td>Used gestational carrier</td>
<td>15%</td>
</tr>
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<td></td>
<td>Used PGD</td>
<td>Female factors only</td>
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<td></td>
<td>With eSET</td>
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<td>Unstimulated</td>
<td>Ovulatory dysfunction</td>
</tr>
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<td></td>
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<td>Male factor</td>
<td>Endometriosis</td>
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<td></td>
<td>Other factor</td>
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<td></td>
<td>Unknown factor</td>
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*Note: The percentages and factors may vary depending on the specific context or dataset.*
2013 ART SUCCESS RATES

Total number of cycles: 190,773 (includes 2,655 cycle[s] using frozen eggs)

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<td>19,853</td>
<td>18,061</td>
<td>9,588</td>
<td>4,823</td>
<td>1,379</td>
</tr>
<tr>
<td>Age of Woman</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of cancelations (%)</td>
<td>5.6</td>
<td>8.9</td>
<td>12.3</td>
<td>15.6</td>
<td>18.3</td>
<td>23.9</td>
</tr>
<tr>
<td>Average number of embryos transferred</td>
<td>1.4</td>
<td>2.0</td>
<td>2.3</td>
<td>2.7</td>
<td>2.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Percentage of embryos transferred resulting in implantation (%)</td>
<td>39.9</td>
<td>30.8</td>
<td>20.0</td>
<td>10.7</td>
<td>5.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Percentage of elective single embryo transfers (eSET) (%)</td>
<td>21.4</td>
<td>12.6</td>
<td>5.1</td>
<td>1.8</td>
<td>0.6</td>
<td>0.8</td>
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<tr>
<td>Outcomes per Cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of cycles resulting in term, normal weight &amp; singleton live births (%)</td>
<td>23.8</td>
<td>18.6</td>
<td>13.7</td>
<td>7.8</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Percentage of cycles resulting in singleton live births (%)</td>
<td>23.2</td>
<td>22.2</td>
<td>16.7</td>
<td>9.6</td>
<td>4.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Percentage of cycles resulting in twin live births (%)</td>
<td>11.3</td>
<td>8.0</td>
<td>4.2</td>
<td>1.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Percentage of cycles resulting in live births (%)</td>
<td>39.9</td>
<td>31.6</td>
<td>21.1</td>
<td>11.1</td>
<td>5.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Percentage of cycles resulting in pregnancies (%)</td>
<td>45.9</td>
<td>38.0</td>
<td>28.6</td>
<td>18.8</td>
<td>10.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Outcomes per Transfer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of transfers</td>
<td>33,750</td>
<td>15,941</td>
<td>13,456</td>
<td>6,588</td>
<td>3,086</td>
<td>750</td>
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<tr>
<td>Percentage of transfers resulting in term, normal weight &amp; singleton live births (%)</td>
<td>28.2</td>
<td>24.4</td>
<td>18.4</td>
<td>11.4</td>
<td>6.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Percentage of transfers resulting in singleton live births (%)</td>
<td>33.5</td>
<td>28.9</td>
<td>22.5</td>
<td>14.0</td>
<td>7.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Percentage of transfers resulting in twin live births (%)</td>
<td>13.4</td>
<td>10.0</td>
<td>5.5</td>
<td>2.2</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Percentage of transfers resulting in live births (%)</td>
<td>47.4</td>
<td>39.3</td>
<td>28.4</td>
<td>16.2</td>
<td>8.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Percentage of transfers resulting in pregnancies (%)</td>
<td>54.5</td>
<td>47.3</td>
<td>38.3</td>
<td>27.3</td>
<td>15.9</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Frozen Embryos from Nondonor Eggs

<table>
<thead>
<tr>
<th>Number of cycles</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
<th>43-44</th>
<th>&gt;44</th>
</tr>
</thead>
</table>

- 199,773 cycles (up from 147,260)
- 54,323 live-births (up from 47,090)
- 67,996 children (up from 61,564)

CDC 2015, ASRM 2013
SUCCESS RATES & COST

Success Rates

- **< 35 years**: 30-35%
- **35-37 years**: 25%
- **38-40 years**: 15-20%
- **> 40 years**: 6-10%
IVF SUMMARY

What?
Artificial manipulation of female and male gamete

When?
First successful in 1978, but hundreds of years in the making

Who?
Hundreds of thousands of couples (plus single women, same-sex couples)
IVF SUMMARY

Why?
Infertility, avoidance of hereditary disorders, desire for family

Where?
Almost 500 reproductive endocrinology infertility clinics in the U.S.

How?
Superovulation → Egg retrieval → In vitro fertilization → Embryo culture → Embryo transfer
IMPACT

IVF
- Infertility
- History
- Technique
- Epidemiology

Impact
- Parents
- Patients
- Pediatrics
IMPACT ON PARENTS

Benefits
- Overcome infertility
- Delay childbearing
- Select against hereditary disorders
- Create a family

Risks
- Expensive
- Emotional costs
- Physical risks to the mother
PHYSICAL RISKS TO THE MOTHER

- Inherent risks of IVF:
  - Exogenous hormone exposure

- Obstetric complications:
  - Pregnancy
  - Delivery
INHERENT RISKS OF IVF

- Hormone exposure leads to potential complications including ovarian hyperstimulation syndrome (OHSS), long-term cancer risks, and multiple gestation.
Ovarian hyperstimulation syndrome (OHSS) occurs when oocytes are overproduced through ovulation stimulation and then released, leading to vascular instability.

- Especially seen in younger women and women with polycystic ovarian syndrome (PCOS)
- Milder symptoms: abdominal discomfort, nausea
- Severe symptoms: significant weight gain, distention, pain, hemodynamic instability, oliguria, electrolyte imbalance, respiratory difficulty, blood clots, renal failure
INHERENT RISKS OF IVF

- Many studies have looked at the association between fertility treatments and subsequent development of breast, uterine, or ovarian cancers in women.

- The consensus among both large cohort and meta-analysis articles is that there is currently no increased risk of these cancers due to fertility drugs.

OBSTETRIC COMPLICATIONS OF IVF

- Fertility drugs increase the chance of having **multiples**, which is considered a high-risk pregnancy due to the risks to both the mother and the fetuses.
Reproductive endocrinology and infertility specialists (REI), especially those within academic settings, adhere to ethical guidelines regarding limits to the number of transferred embryos.

Superovulation and ovulation induction (SO/OI) with intrauterine insemination (IUI), an alternative to IVF for some women, provides less control over number of eggs released and embryos formed.
OBSTETRIC COMPLICATIONS OF IVF

- Mothers of multiples have higher incidences of:
  1. gestational diabetes
  2. pregnancy induced hypertension
  3. peripartum hemorrhage
  4. caesarean section
  5. sick leave and hospitalization
  6. minor common complications: anemia, cholestasis, hyperemesis, reflux, constipation, dyspnea, dermatoses, back pain

NORWITZ 2005, KRAMER 2013, PINBORG 2005
Obstetric complications are not limited to those who are expecting multiples.

Meta-analysis of singleton pregnancies from IVF compared to naturally conceived (NC) singletons points to increased incidence of adverse maternal outcomes.

- Ante-partum hemorrhage
- Caesarian sections
- Fetal malpresentation
- Congenital anomalies
- Hypertension disorders of pregnancy
- Preterm rupture of membranes
- Preterm delivery
- Gestational diabetes
- Induction of labor
- SGA

PANDEY 2012, STOJNIC 2013
IMPACT

- Infertility
- History
- Technique
- Epidemiology

- Parents
- Patients
- Pediatrics
## IMPACT ON PATIENTS

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life</td>
<td>Perinatal complications</td>
</tr>
<tr>
<td>Desired by family</td>
<td></td>
</tr>
</tbody>
</table>
PERINATAL COMPLICATIONS OF IVF

- Twinning & Multiples
- Prematurity
- Birth defects
Just how many ART-associated births are multiples? And how many are preterm?

### 2010 - Live Births from Fresh Nondonor Embryos
- Singletons - 69.7%
- Twins - 28.8%
- Triplets or more - 1.5%

### 2013 - Live Births from Fresh Nondonor Embryos
- Singletons - 73.4%
- Twins - 25.7%
- Triplets or more - 0.9%

CDC 2010, 2015
MULTIPLES

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preterm</th>
<th>Low Birth Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletons</td>
<td>11.7%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Singletons from multiple-fetus pregnancy</td>
<td>16.7%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Twins</td>
<td>59.4%</td>
<td>56.3%</td>
</tr>
<tr>
<td>Triplets or more</td>
<td>96.1%</td>
<td>93.4%</td>
</tr>
</tbody>
</table>

CDC 2010
The number of fetuses is directly proportional to the risk of maternal, fetal, and neonatal complications. Fetal and neonatal complications include:

- fetal demise
- perinatal mortality
- infant mortality
- preterm birth
- intrauterine growth restriction (IUGR)
- low birth weight (<2,500 g)
- very low birth weight (<1,500 g)
- NICU admission
- length of stay
- major handicap, e.g. cerebral palsy
Increased placental abruption, vasa previa, and placenta previa in multiples is one of the reasons for fetal demise, perinatal mortality, and morbidity. The morbidities include emergent preterm delivery, anoxic brain injury, and severe anemia.
ART-associated twinning is not just dizygotic, but also monozygotic!

Therefore, along with the other risks to the fetuses associated with being a multiple, twin-twin transfusion does occur as well.

Twin-twin transfusion is the transfusion of blood from one twin (donor) to the other (recipient).

- Donor: anemia, growth restriction, oligohydramnios
- Recipient: polycythemia, polyhydramnios, congestive heart failure, hydrops
PREMATURITY

- Controlling for *maternal age*:
  - IVF-twins still have significantly greater risks of preterm birth and low birth weight compared to NC-twins.

- Controlling for poor *fertility* and non-IVF ART:
  - IVF singletons had greater risks than singletons born after poor fertility or non-IVF-ART alone.

- Controlling for *genetics*:
  - IVF singletons had greater risk than their non-IVF siblings.

- Again, IVF twins are impacted more so than IVF singletons, but both have significantly higher preterm birth rates.

*MCDONALD 2009, WISBORG 2010, PINBORG 2013, PINBORG 2004*
Prematurity-associated complications:
- Retinopathy of prematurity
- Bronchopulmonary dysplasia
- Cerebral palsy
- Necrotizing enterocolitis
- Intraventricular hemorrhage
Meta-analysis of birth defects linked to IVF does show a risk of 1.37 (95% CI: 1.26-1.48).

- No difference in overall risk with or without ICSI
- No predominance in type of birth defect.

### Birth Defects

<table>
<thead>
<tr>
<th>System</th>
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<tbody>
<tr>
<td>Nervous system</td>
<td>15</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>17</td>
</tr>
<tr>
<td>Digestive system</td>
<td>19</td>
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<tr>
<td>Circulatory system</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>18</td>
</tr>
<tr>
<td>Eye, ear, face, and neck</td>
<td>15</td>
</tr>
</tbody>
</table>
IMPACT

• Infertility
• History
• Technique
• Epidemiology

Parents
• Patients
• Pediatrics
Overall, the children are healthy and do well long-term.
Limited long-term follow-up data suggest that there is an increase in the incidence of
- asthma
- raised blood pressure, elevated fasting glucose, increase in total body fat composition,
  advancement of bone age and potentially subclinical thyroid disorder

Why? Whether these potential associations are related to the IVF treatment, the adverse obstetric outcomes associated with IVF treatment, or are related to the genetic origin of the children is yet to be determined.

KÄLLÉN 2013, HART 2013
Many theories have been proposed for how IVF may affect children in the long-term.

- Will the chemicals and radiation from IVF affect the embryo? Might cryopreservation damage a thawed embryo’s DNA?
Cancer Risk in Children and Young Adults Conceived by In Vitro Fertilization. *Pediatrics* 2010

**Objectives:** “Studies...so far have found no statistically significant...risk of cancer....”

**Methods:** Compare 26,692 IVF children born in 1982-2005 -vs- children in the Swedish Cancer Register

**Results:** 53 cases of cancer in children who were born after IVF versus 38 expected cases (OR=1.42, 95%CI=1.09-1.87)

- 18 Hematologic
- 17 CNS/eye
- 12 Solid tumor
- 6 Langerhans histiocytosis

**Conclusions:** Moderately increased risk for cancer.
Along with the concern for carcinogenic effects, IVF is being studied for potential epigenetic effects.

Whereas carcinogenic effects are caused by changes to the DNA sequence itself, epigenetic effects are changes in gene expression.

Epigenetics has its basis in the Barker Hypothesis, which states that a number of adult diseases have their origin in fetal life.

E.g. Obesity, Diabetes mellitus, Hypertension, Cardiovascular disease
Imprinting is an epigenetic modification of a gene where that only one parental allele is expressed.

- For example, the hypermethylation of maternal allele H19 is associated with Beckwith-Wiedemann syndrome, whereas hypomethylation is associated with Silver-Russell syndrome.
IMPRINTING

- Beckwith-Wiedemann syndrome
- Silver-Russell syndrome
- Prader-Willi syndrome
- Angelman syndrome
- Wilm’s tumor
- Retinoblastoma
- Osteosarcoma
- Rhabdomyosarcoma
- Beckwith-Wiedemann syndrome
Is there any long-term effect on neurodevelopmental outcomes?

- Autism
- Intellectual disability
- Mental/psychological health
- Behavior/socio-emotional health
- ADHD

SANDIN 2013, CEDARS 2013, KÄLLÉN 2011, HART 2013, WAGENAAR 2009
NEURODEVELOPMENTAL OUTCOMES

- Is there any long-term effect on neurodevelopmental outcomes?
  - Autism NO
  - Intellectual disability
  - Mental/psychological health
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  - ADHD

SANDIN 2013, CEDARS 2013, KÄLLÉN 2011, HART 2013, WAGENAAR 2009
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- Autism: NO
- Intellectual disability: YES, but not really
- Mental/psychological health: NO
- Behavior/socio-emotional health: NO
- ADHD: YES, slightly

SANDIN 2013, CEDARS 2013, KÄLLÉN 2011, HART 2013, WAGENAAR 2009
Physicians should inform oncology patients about their options for fertility preservation and future reproduction prior to chemotherapy, surgery, or radiation.

Parents may act to preserve fertility of oncology patients who are minors if the child assents and the intervention is likely to provide net benefits to the child.
FUTURE ADVANCES

IVF
- History
- Technique
- Epidemiology

Impact
- Parents
- Patients
- Pediatrics

Future
- Advances
Reproductive Endocrinology and Infertility specialists (REI) share many of the same concerns as do the obstetricians, neonatologists, and pediatricians.

1. Hormone exposure is dangerous for the mother.
2. Hormone exposure is necessary for stimulating and collecting multiple eggs.
3. Multiple eggs are needed to increase the chances of successful implantation and to cryopreserve embryos for future attempts.
4. Repeating the process due to failed implantation or pregnancy is costly.
5. Transferring multiple embryos increases the likelihood of multiple gestations.
6. Multiple gestations have risks of obstetric complications to the mother and risks of preterm delivery and other fetal complications to the babies.
How do we retrieve, fertilize, and transfer less embryos and yet still succeed in producing a viable pregnancy?
FUTURE ADVANCES

- **Elective single-embryo transfer (eSET)**
  - Most appropriate for women with a good prognosis:
    - Age < 35 years, quality embryos available, using donor eggs, history of successful IVF, or attempting first or second IVF treatment.

- Reduces twinning *significantly* from 30% with double-embryo transfer in this population to 1-2%.
  - Thus, reducing prematurity and other complications.

- More cost efficient when taking to account the long-term morbidities of double embryo transfer.

SART 2012, DE SUTTER 2002
FUTURE ADVANCES

- Blastocyst transfer
  1. synchronization between embryo and endometrium
  2. time to observe and select most viable embryos
  3. higher implantation rates
  4. potential decrease in embryo number for transfer
FUTURE ADVANCES

- **Time-lapsed image analysis** - a camera attached to the embryo incubator takes high-resolution photographs of the developing embryos every 5 minutes; then, embryologists watch the time-lapsed imaging to gain additional parameters for choosing usable blastocysts.
  - Morphology
  - Kinetics
Can embryos be genetically modified for families carrying genetic disorders? Can we do more than just PGS to ensure a healthy embryo is transferred?
FUTURE ADVANCES

Three-parent in vitro fertilization:

To prevent inherited mitochondrial diseases, this technique combines maternal and paternal nuclear material with a third set of mtDNA from an unaffected donor.

1. Pronuclear transfer
2. Spindle transfer
Does the future hold ‘Designer’ babies?
CONCLUSIONS

- With the help of IVF, couples may overcome infertility and also screen for inherited genetic disorders.
- Most children do well long-term; however, couples should be informed of the increased risks of obstetric and neonatal complications in both singleton and multiple gestation.
- It is unclear whether complications are directly due to the technology or indirectly due to its ability to overcome infertility obstacles.
- Prevention of multiple gestation through IVF advances may help in the reduction of complications, especially prematurity and its sequelae.
After in vitro fertilization using 2 embryos, 1 male and 1 female (determined by sex determination of the blastocysts), a 39-year-old mother becomes pregnant. On ultrasound, twin pregnancy is documented at 10 weeks gestation. The woman delivers vaginally at term. The twin female babies are similar sized and their examinations show no anomalies.

Of the following, the placental configuration MOST likely to be found in this situation is:

- a. Dichorionic, diamniotic: fused placenta
- b. Dichorionic diamniotic: separate placentas
- c. Dichorionic, monoamniotic
- d. Monochorionic, diamniotic
- e. Monochorionic, monoamniotic
A 37 year old, gravida 2 (with 1 miscarriage) woman who is 8 week pregnant discusses with her obstetrician her interest in evaluating the pregnancy for possible aneuploidy. She has a first cousin with trisomy 21, but no other significant family history.

Of the following, the MOST appropriate test to recommend at this time is:

a. amniocentesis
b. cell-free fetal DNA
c. chorionic villus sampling
d. maternal serum concentration of unconjugated estriol
e. ultrasound with nuchal translucency measurement
THANK YOU

- Dr. Karen Berkowitz
- Dr. Kuzma
- Dr. Skuby
- Dr. Sandelich
QUESTIONS


REFERENCES