NOTES FROM ASRM 2015

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Grand Rounds November 11, 2015

KU School of Medicine
Wichita
The University of Kansas
Objectives

• Counsel patients about the risks and benefits of various methods of invasive fetal testing...preimplantation genetic diagnosis (CREOG 7.III.C.8.d)

• Discuss effects of maternal and paternal obesity on fertility and the health of offspring.

• Describe (some of) the legal implications surrounding fertility treatment

• Describe symptomatic cesarean scar defect and potential indications for treatment.
To: 37607

- JAMIEDUBAUT766
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Answer:

- Day 5 trophectoderm biopsy
Background

PGS
- Euploid: AMA
- DOR
- RPL
- eSET

PGD
- w/o Disease: SGD, Mito Dz, HLA-type
- Translocation
  - Sex linked
PGS Utility

- Good prognosis
  - 2 RCTs higher pregnancy rates/cycle
  - 1 RCT equivalent pregnancy rate/cycle with euploid SET vs morphologic DET

- Poor prognosis
  - Observational studies, higher implantation & pregnancy rate/embryo transferred
  - Many don’t make it to biopsy/transfer
    - Fewer eggs, more aneuploidy

PGS Limitations

• False negatives
  • Confirm euploid by prenatal genetic testing

• False positives
  • Some due to mosaicism
  • Evidence that mosaic embryo sequester aneuploid cells to trophectoderm
    • Placental mosaicism associated w/ IUGR
  • Blast biopsy is of trophectoderm
Further Evidence Against the Use of PGS in Poor Prognosis Patients: Report of Normal Births After Transfer of Embryos Reported as Aneuploid

- Poor prognosis patients
- Formal center policy
- If no euploid embryos available for transfer, offered to transfer embryos w/ PGS results consistent w/ lethal monosomies

8 couples qualified → 5 chose to transfer → 3 pregnancies & deliveries of euploid infants

Gleicher et al. ASRM 2015 O-151
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Periconception Medicine and Biology in Relation to Human Health

- Weight
- Poor nutrition
- Stress
- Infection
- Smoking
- Alcohol
- Environmental toxins
- Assisted reproduction

Robert Norman, MD University of Adelaide
What periconception factors affect

- DNA
- Epigenome
- Mitochondria
- Metabolism
- Placentation
  - Microarray differences in endometrium of obese women
- Organ development
- Gametes->embryo->fetus
Transgenerational effects

• Maternal smoking affects gonad formation in the fetus
  • Reduced eggs/sperm
  • Higher testicular cancer

• Nutrition
  • See next slides
Female BMI

- Female BMI affects fertility
  - Menses affected too, but doesn’t explain entire effect on fertility
- Increased odds of infertility
  - Underweight (BMI <20)
  - Overweight (BMI 25-29)
  - Obese (BMI 30-34)
  - Very obese (BMI 35+)
Female BMI

- Central fat distribution lower pregnancy rates w/ DI than peripheral fat distribution (same BMI)
- Increased rates of PCOS w/ increasing BMI
- IVF success rates decreased
  - Overweight, obese, very obese
  - Repeated study 10 years later, differences not as marked
    - Better embryology “rescue” bad embryos?
Gambia – seasonality

• Neonatal weight and head circumference corresponded with mother’s season of conception/birth
• Epigenetics/methylation of neonate’s genome affected by wet/dry season of conception
Paternal BMI/diet

- Swedish study: grandfather’s prepubertal food availability related to grandson’s CV & DM related health
- Netherlands: undernourished fathers had more obese children
- Paternal obesity, independent of environment, related to increased body fat and mass in prepubertal children
Paternal BMI & IVF

- University of Adelaide (presenter) 2011
- N=305
- Controlled for maternal BMI

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
<th>Morbid Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>41%</td>
<td>26%</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>D5 ontime blasts</td>
<td>29%</td>
<td>28%</td>
<td>20%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Bakos et al. Fertility and Sterility 2011.
Mouse model

- Obesity affects
  - Ovulation rate
  - Fetal weight
  - Oocyte fat content
  - Mitochondrial activity
  - Liposome rafts
  - Spindle formation
Next steps?

• Multidisciplinary approach
  • Researchers
  • Doctors
  • Nurses
  • Dieticians
  • Media including internet resources
Find out more about the fertility factors

Age
For women
For men

Weight
For women
For men

Smoking
For women
For men

Alcohol
For women
For men

Timing
For women
For men

Other Factors
For women
For men
Reproductivefacts.org

Patient Fact Sheets and Booklets

ASRM offers patient education in three languages:

En Español

In English

在中国

Edad y Fertilidad

Age and Fertility

年龄和生育能力
Welcome to the SART Patient Predictor. SART has developed this predictor based on nearly 500,000 cycles of therapy to more than 320,000 women throughout the United States since 2006. This calculator is meant to help you understand your chances of having a live birth, based on your personal situation. The answers to the following questions influence the likelihood that the IVF treatment will be successful. Some of the answers you may know — like your height and weight. Other answers — such as the diagnosis of the cause of infertility — will depend on whether or not you have been seen by a physician, and may change during your course of treatment. The calculations from this Patient Predictor assume that you have not had prior IVF treatment.

**Background and Reproductive History**

**How old are you?**

Please Select

**How tall are you?**

[ ] feet  [ ] inches  [ ] feet  [ ] meters

**How much do you weigh?**

[ ] lbs  [ ] kgs

**How many prior pregnancies have you had?**

[ ]

**How many prior full-term (≥ 37 weeks) births have you had?**

[ ]
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21st century families: ART and Law

- Unique area of medicine b/c ART treats more than 1 person, creates new separate legal entity
- Doctors make babies, lawyers make families
- Cutting edge legal issues
  - Frozen Embryos
  - Egg freezing
  - 3rd parties
  - Access to (in)fertility treatment

Susan Crockin JD Washington DC
Legal fundamentals

- No international ART law
- Little Federal US law
- State law decides: Parentage, Tort, Contract based on
  - Genetics
  - Intent
  - Gestation
IVF Embryos

• 1st US frozen embryo case 1992 (Davis vs Davis, divorce)
  • Absent Pt-clinic agreement, constitutional right NOT to procreate trumped right to procreate, embryos discarded

• Since 1st case, 20+ higher court decisions
  • Generally follow prior agreements
  • Usually right NOT to procreate trumps right to procreate regardless of agreement
  • But 3 lower court decisions have awarded “last chance” divorcing embryos to women as cancer survivors

• Important (separate, carefully worded, comply w/ state)
  • Informed consent to treat
  • Disposition of embryos agreement
Egg Freezing

• Fertility preservation
  • Imminent medical need
    • Oncofertility: time pressures, >1 specialty
  • Future/speculative need ("social/elective")
    • Marketing/media attention
    • Apple & Facebook covering cost for employees
    • Medical risks, human costs, technology will continue to improve, so legal concerns/vulnerability for practices who promote this
  • Law students of today who think their new employers should cover it will be lawyers armed to litigate when things don’t go the way they expected.
Egg Freezing

• Donor
  • Anonymity: non-existent, don’t overpromise
    • Lawyers/investigators can find
  • Donor payments are taxable income; she contracted to undergo pain and suffering
  • Anti-Trust Class action law suit
Third-party ART

• Balancing genetics, intent, gestation
• Known donor/surrogacy most complex b/c can be hard to nail down intent
• KS: Fatherhood assigned when lesbian couple applied for public assistance, done without doctor’s involvement, violating state law.
• Sherri Shepherd surrogacy case
  • Midway through pregnancy, Shepherd walked out on marriage and surrogacy. (Egg donor) (gestational carrier had been sent letter for child support)
  • Intent to parent > non-genetics/non-parentage
Access

• Medically “infertile” need/right to treatment
• Legal rationales to expand non-discriminatory family building treatment and coverage to those in their reproductive years who cannot otherwise achieve pregnancy and biological parenthood
  • Oncofertility, genetic disorders, same-sex couples
• A Constitutional right to “build a family”?
Cross Border Surrogacy

• Babies born in the US are US citizens
• But are they residents of states qualifying for coverage under ACA?
  • Loophole vs. insurance fraud
• 2 cases ACA coverage issued then rescinded
• Incentive for multiples
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What Does it Take? The Number of Mature (MII) Oocytes Needed to “Bank” on Success

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>25-34 (n=22)</th>
<th>35-37 (n=39)</th>
<th>38-40 (n=74)</th>
<th>41-42 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB/MII</td>
<td>13%</td>
<td>10%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>No. MII to achieve BB</td>
<td>8</td>
<td>10</td>
<td>14</td>
<td>50</td>
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</tbody>
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KN Goldman et al. ASRM 2015 O-231
Management of C-section Scar Disorder

• Uterine isthmocele incidence 0.3%-19.4%, depends on definition
  • Diverticulum or triangular anechoic area at site of previous cesarean section scar, w/ associated myometrial thinning
    • CEM: don’t measure on SHG, artificially thins
    • EOF: always measure on SHG, more sensitive test

• Pathology
  • Chronic inflammation, fibrosis, necrosis, endometriosis
Management of C-section Scar Disorder

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Management of C-section Scar Disorder

- Risk factors
  - Maternal age <30
  - retroverted uterus
  - labor >5 hours
  - dilation at c/s >5cm
  - lower station at delivery
  - pitocin use
  - incision closer to cervical os
  - exclusion of endometrium during repair
  - single layer closure
  - delayed absorption of sutures (vicryl)
  - more ischemic closure
    - However, no factor has shown significance to suggest altering practice
Management of C-section Scar Disorder

- **Symptoms**
  - AUB – esp. prolonged spotting after period
  - Pelvic pain(?)
  - Dysmenorrhea
  - Secondary infertility
    - Endometrial fluid in cavity
    - Distortion of cavity interfering with IVF
  - Ectopic pregnancy

- **Treatment options**
  - Medical
  - Surgical
    - Transvaginal
    - Hysteroscopic resection
    - Laparoscopic resection (+/- Robot)
    - Hysterectomy
Management of C-section Scar Disorder

• Charles E. Miller; Advocate Lutheran General Hospital
  • Laparoscopic resection
    • Exposure of lower uterine segment
    • Hysteroscopy to delineate defect
    • Resect defect
    • Repair in layers
    • [https://www.aagl.org/master-course/sasaki-master-course/](https://www.aagl.org/master-course/sasaki-master-course/)
  • Reported outcomes for first 17 cases
    • 7 have had at least 3 cycles to attempt pregnancy
    • 5 pregnancies including spontaneous and IVF

• Emilio O. Fernandez; Unit of Reproductive Medicine, Santiago, Chile
  • Hysteroscopic resection
    • Remove superior and inferior edges of defect until muscular layer seen
    • Places the wall of the edges in continuity with those of the cervical canal so there is no longer an outpouching for blood to stagnate
QUESTIONS?

Thank you!

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