Pre-pregnancy Medical Risk Assessment of Older Women Seeking Assisted Reproduction

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Case

- 38 year old woman, G0P0

PMH:
- Complex CHD (Ebstein’s), multiple ORs ➔ heart TxP in 2005
- Seizure disorder, peripheral neuropathy
- Psychiatric issues
- VTE events around time of TxP, A/C x 6 months
- Hypothyroidism

Good function now

Meds: azathioprine, tacrolimus, levetiracetam, gabapentin, topiramate, mirtazapine, duloxetine, olanzapine, ramipril, atorvastatin, ASA, levothyroxine, folate
Case

- Pregnancy strongly discouraged by Cardiologist and Obstetrician

  - Requesting **ovarian stimulation** for egg retrieval, to pursue a **surrogate pregnancy**

  - Is this safe? Appropriate? What are the risks?
Objectives

At the conclusion of this session the learner will be able to:

1. Define infertility and discuss its prevalence
2. Review maternal/pregnancy risks with increasing maternal age
3. Outline available ART techniques
4. Discuss the risks of ART procedures
5. Present an approach to the pre-ART assessment of older women
“Physicians should obtain a complete medical evaluation before deciding to attempt transfer of embryos to any woman over age 50…

embryo transfer should be strongly discouraged or denied to any woman over age 50 with underlying issues … and discouraged in [all] women over age 55”

American Society for Reproductive Medicine
Committee Opinion
August 2013
NICE Guideline (UK)

- In women aged **under 40** years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination … offer 3 full cycles of IVF

- In women aged **40–42 years** … offer 1 full cycle of IVF
What is Infertility?

- Infertility refers to the failure to conceive a child after ~1 year of regular, unprotected sexual intercourse

- Infertility is a common problem (CDC)
  - 7.4% of married couples of reproductive age are infertile (US)
  - 12% (1:8) women of reproductive age have impaired fecundity (difficulty achieving pregnancy or carrying a child to term)
  - 1.2% of men of reproductive age reported ever having an infertility problem (US)
  - the prevalence of infertility rises significantly with increasing maternal age
Causes of Infertility
US (2011)

Male factor
- Reduced ovarian reserve
- Multiple male & female factor
- Other
- Tubal factor
- Ovulatory dysfunction
- Unknown
- Multiple female factor
- Endometriosis
- Uterine Factor

Annual fertility rate per 100 women not using contraception


Infertility

Infertility has been an increasing problem in most countries over the last 30-40 years. Delayed childbearing, later age at first marriage, are factors contributing to this trend.

Options for achieving pregnancy through assisted reproduction (ART) have become progressively more effective and available. First successful human in vitro fertilization (IVF) resulting in a live birth occurred in the UK in 1978. Now ~3.5 million babies have been born worldwide following IVF, ~1% of all current births (US) and up to 4% in some European countries (ESHRE, 2009).

Costs remain high and government subsidy is variable, limiting uptake in developing countries.

Figure 1: Estimates of the direct cost of one fresh ART treatment cycle (euro 2006). (1) Henne et al., 2008; (2) Chambers et al., 2009; (3) Statistics in Brief.

Figure 2: % of annual disposable income vs. Gross cost of a standard cycle as a % of disposable income. Net cost of a standard cycle as a % of disposable income after government subsidization.
Risks of Increasing Maternal Age

- Women who undergo ART are older than the overall obstetric population

- Maternal risks increase with age (>35):
  - GDM
  - Preeclampsia
  - VTE

- Pregnancy risks also increase with age:
  - PTD
  - SGA and LGA
  - Fetal loss
  - Cesarean delivery

## Maternal Risks of Increasing Maternal Age

### Pregnancy outcome at extremely advanced maternal age

Am J Obstet Gynecol 2010;203:558.e1-7

Age \( \geq 45 \), single centre, 2000-8, \( n=177 \) (vs age 20-29)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age 20-29</th>
<th>Age ( \geq 45 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>cHTN</td>
<td>0.1%</td>
<td>6.8%</td>
</tr>
<tr>
<td>DM</td>
<td>0.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>0.7%</td>
<td>10.7%</td>
</tr>
<tr>
<td>gHTN</td>
<td>2.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>GDM</td>
<td>1.4%</td>
<td>17.0%</td>
</tr>
<tr>
<td>Cesarean</td>
<td>15.7%</td>
<td>78.5%</td>
</tr>
<tr>
<td>Previa</td>
<td>0.2%</td>
<td>5.6%</td>
</tr>
<tr>
<td>PPH</td>
<td>1.0%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>
What is ART

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  - sperm donation,
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What is ART

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  - ovulation induction (OI) therapy,
  - testicular sperm extraction (TESE),
  - intracytoplasmic sperm injection (ICSE),
  - in-vitro fertilization (IVF) with fresh or frozen embryo transfers
  - +/- PGD
IVF – since 1978
Outcomes of IVF – USA, 2011
Success Rates (Live Birth)

* ~ 152,000 cycles, ICSI in 67%


‘Nondonor eggs = 84%’
Outcomes of IVF – Multiple Gestation

2011 Canada: 30 % Multiple Gestation (CARTR)


Multiple gestation ~ 40%
What ‘additional’ risks are there with ART

- Intentional ovarian hyperstimulation
- Estrogen levels as high or higher than 3rd trimester
  - Risk of VTE, esp first-trimester

*BMJ* 2013;346:e8632
What ‘additional’ risks are there with ART

“For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months post-resolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C)” [NNT~ 39]

ACCP, 2012

For other women – who would otherwise merit antepartum anticoagulation – LMWH may be started along with ovarian stimulation

- Very high E2 levels
- Thrombosis risk > 1%, higher in older women with additional risk factors, often at unusual sites (UE, IJ, etc)

Other Maternal Risks of IVF

- Use of donor oocytes
- Increased risk of preeclampsia (OR 4.0, risk ≥ 25%)
- Multiple gestation – rates 30-50% \(\Rightarrow\) eSET
- Attendant increased risks: HTN/Preeclampsia, VTE, GDM, bed rest, PTL, C-section, PPH
- Preeclampsia (OR 1.6-2.2)
- Placenta previa (OR 2.9) – risk of APH, c-section and PPH

Figure 2. Effect of a Woman’s Age on the Rate of Live Births per IVF Embryo Transfer.

Medical Assessment and Management prior to ART

- Will she be able to tolerate ART and pregnancy?
  - assume OHSS (if ovaries stimulated): up to 5% severe
  - assume multiple gestation: up to 30-50% unless SET
  - assume preeclampsia: risk > 25%

- Clinical assessment may be supplemented by:
  - EKG
  - +/- Exercise stress test or PFTs
  - +/- Echocardiogram
  - Thrombophilia testing?

- If NO, consider whether egg retrieval for surrogacy would be tolerated

As prior to any high-risk pregnancy
Summary

- Consider whether the given pregnant woman would be appropriate/safe to undertake spontaneous pregnancy.

- Then consider the additional risks of ART:
  - Increased risk of preeclampsia ➔ low-dose ASA
    - esp. if using donor oocytes
  - Increased risk of VTE ➔ liberal use of LMWH
  - Intentional ovarian hyperstimulation ➔ encourage safer protocols
    - risk of OHSS
  - Significant possibility of multiple gestation ➔ encourage SET

- Detailed ‘pre-ART’ evaluation
  - as you might do prior to any high-risk pregnancy

- Consider whether egg retrieval alone might be an option
  ➢ Surrogacy (rules & availability vary significantly by country)

- Discuss and provide info regarding adoption with highest risk women
Thank you for your attention!