Advanced Maternal Age
Management of Pregnancy in
Women over 40

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Maternal-Fetal Medicine

I have nothing to disclose.

OUTLINE

• Maternal age statistics and trends
• Assisted reproductive technologies (ART)
• Aneuploidy & Miscarriage Risk
• Underlying health problems
• Perinatal morbidity
• Management

Age
Infertility
Medical Co-Morbidities
Assisted Reproductive Technology
Multiple Gestations
MATERNAL AGE – STATISTICS AND TRENDS

What percent of births in the United States would you estimate are in women over age 40?

A. < 5%
B. 5 – 10%
C. 10 – 15%
D. > 15%

US Birth Rates Among Women ≥ 35

Total # of Births in US 1997 2013

<table>
<thead>
<tr>
<th>Age</th>
<th>1997</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44 Years</td>
<td>3,880,894</td>
<td>3,932,181</td>
</tr>
<tr>
<td># of Births (%)</td>
<td>76.6 (93%)</td>
<td>109,484 (2.8)</td>
</tr>
<tr>
<td>45-49 Years</td>
<td>3,333 (0.09)</td>
<td>7,495 (0.19)</td>
</tr>
<tr>
<td>≥ 50 Years</td>
<td>144 (0.004)</td>
<td>677 (0.017)</td>
</tr>
</tbody>
</table>


Infertility

By age 40 it is ~ 5% per cycle
At age 30, a woman’s chance of conception is ~ 20% per cycle

Data from multiple non-contracepting communities over many decades

Practice Committee Committee Opinion No 589 Fertil Steril 2014

Births Resulting from ART Procedures
National Vital Statistics Data 2011

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Number of Births</th>
<th>Number of Known ART-Births</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35</td>
<td>2,273,953</td>
<td>19,285</td>
<td>0.85</td>
</tr>
<tr>
<td>35-37</td>
<td>228,392</td>
<td>7,949</td>
<td>3.48</td>
</tr>
<tr>
<td>38-40</td>
<td>117,937</td>
<td>5,905</td>
<td>5.01</td>
</tr>
<tr>
<td>41-42</td>
<td>33,299</td>
<td>2,354</td>
<td>7.07</td>
</tr>
<tr>
<td>43-44</td>
<td>11,717</td>
<td>1,379</td>
<td>11.77</td>
</tr>
<tr>
<td>≥ 45</td>
<td>5,247</td>
<td>1,624</td>
<td>30.95</td>
</tr>
</tbody>
</table>

RISKS ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGIES

ART & Multiple Gestation

- 25 – 30% of ART pregnancies are twins
- 1.5 – 3% of ART pregnancies are triplets or more
- Monozygotic twinning: 1.7 – 2.5% (vs 0.5%)

ART is an independent risk factor for which of the following?

A. Birth defects
B. Cesarean section
C. Placenta previa
D. Pre-eclampsia
E. All of the above

---

**ART & Birth Defects**

**Singleton Births**

<table>
<thead>
<tr>
<th>Defect Type</th>
<th>Assisted Conception (N = 4333)</th>
<th>Spontaneous Conception (N = 295,220)</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Defect</td>
<td>361 (8.3)</td>
<td>16,989 (5.8)</td>
<td>1.30 (1.16 – 1.45)</td>
</tr>
<tr>
<td>Multiple Defects</td>
<td>95 (2.2)</td>
<td>4,690 (1.6)</td>
<td>1.24 (1.00 – 1.54)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>78 (1.8)</td>
<td>3,472 (1.2)</td>
<td>1.36 (1.08 – 1.72)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>130 (3.0)</td>
<td>4,776 (1.6)</td>
<td>1.50 (1.24 – 1.80)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>95 (2.2)</td>
<td>4,872 (1.7)</td>
<td>1.25 (1.01 – 1.55)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>34 (0.8)</td>
<td>1,832 (0.6)</td>
<td>1.18 (0.83 – 1.68)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>22 (0.5)</td>
<td>1,104 (0.4)</td>
<td>1.34 (0.86 – 2.07)</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>17 (0.4)</td>
<td>496 (0.2)</td>
<td>2.22 (1.35 – 3.63)</td>
</tr>
</tbody>
</table>

Adjusted for age, parity, fetal sex, year, race/ethnicity, country of birth, maternal conditions in pregnancy, maternal smoking during pregnancy, socioeconomic status and maternal and paternal occupation.

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**Multiple Births**

<table>
<thead>
<tr>
<th>Defect Type</th>
<th>Assisted Conception (N = 1,830)</th>
<th>Spontaneous Conception (N = 7,591)</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Defect</td>
<td>152 (8.3)</td>
<td>557 (7.3)</td>
<td>1.16 (0.91 – 1.49)</td>
</tr>
<tr>
<td>Multiple Defects</td>
<td>55 (3.0)</td>
<td>188 (2.5)</td>
<td>1.10 (0.73 – 1.64)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>30 (1.6)</td>
<td>142 (1.9)</td>
<td>0.99 (0.60 – 1.64)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>25 (1.4)</td>
<td>102 (1.3)</td>
<td>0.92 (0.54 – 1.57)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>50 (2.7)</td>
<td>173 (2.3)</td>
<td>1.10 (0.74 – 1.65)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>23 (1.3)</td>
<td>88 (1.2)</td>
<td>1.13 (0.59 – 2.26)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>10 (0.5)</td>
<td>42 (0.6)</td>
<td>1.08 (0.39 – 2.96)</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>16 (0.9)</td>
<td>50 (0.7)</td>
<td>1.39 (0.69 – 2.77)</td>
</tr>
</tbody>
</table>

Adjusted for age, parity, fetal sex, year, race/ethnicity, country of birth, maternal conditions in pregnancy, maternal smoking during pregnancy, socioeconomic status and maternal and paternal occupation.

---

*Hansen et al. NEJM 346:725-30, 2002*

*Davies et al. NEJM 366:1803-13, 2012*
ART & Perinatal Risk

### Table 2. Potential Adverse Outcomes in Singleton In Vitro Fertilization Pregancies

<table>
<thead>
<tr>
<th>Perinatal Risk</th>
<th>Absolute Risk (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal death</td>
<td>0.6</td>
<td>0.1–0.9</td>
</tr>
<tr>
<td>Low birthweight (less than 2,500 g)</td>
<td>2.1</td>
<td>1.8–2.3</td>
</tr>
<tr>
<td>Very low birthweight (less than 1,500 g)</td>
<td>3.3</td>
<td>2.7–3.9</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>3.4</td>
<td>2.9–3.9</td>
</tr>
<tr>
<td>NICU admission</td>
<td>4.8</td>
<td>2.1–5.0</td>
</tr>
<tr>
<td>Siblicide</td>
<td>2.3</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Neuronal mortality</td>
<td>0.5</td>
<td>0.1–0.9</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>0.4</td>
<td>0.2–0.8</td>
</tr>
</tbody>
</table>

### Risk of Chromosomal Abnormalities

#### Risk at Live Birth, According to Maternal Age

<table>
<thead>
<tr>
<th>Maternal Age at Delivery (years)</th>
<th>Risk of Down Syndrome</th>
<th>Risk of Any Chromosomal Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1/1667</td>
<td>1/526</td>
</tr>
<tr>
<td>35</td>
<td>1/378</td>
<td>1/192</td>
</tr>
<tr>
<td>40</td>
<td>1/106</td>
<td>1/66</td>
</tr>
<tr>
<td>45</td>
<td>1/30</td>
<td>1/21</td>
</tr>
</tbody>
</table>

Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. JAMA 1983;249:2034-8

### Aneuploidy & Miscarriage Risk

#### Risk of Spontaneous Abortion According to Maternal Age at Conception

ART Modifies Miscarriage Risk

Donor Oocytes Further Modify SAB Risk

UNDERLYING HEALTH PROBLEMS

- Infertility
- Multiple Gestations
- Assisted Reproductive Technology
- Medical Co-Morbidities
Risk of Death Increases with Age

Number of Deaths/100,000 US Females 2010


Percent of US Women With Obesity (BMI > 30) 2007

cdc.gov NHANES 2006-2007

Percent of US Females With Hypertension NHANES 1999-2008


Diabetes & Prediabetes Women ≥ 18, 2007-2010

cdc.gov NHANES 2007-2010

Adjusted for: race/ethnicity, diabetes, chronic kidney disease, alcohol use, OCP use, BMI

aOR = 3.3 (2.1 – 5.2)
aOR = 8.2 (5.0 – 13.3)
Chance of Being Diagnosed with Breast or Colon Cancer in the Next 10 Years

- Colon Cancer
- Breast Cancer


PERINATAL MORBIDITY

Age
Multiple Gestations
Infertility
Assisted Reproductive Technology
Medical Co-Morbidities

Perinatal Risk

Age (Years)
### Obstetrical Risks Associated with Increased Maternal Age

#### Non-Chromosomal Congenital Anomalies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio/Relative Risk</th>
<th>Maternal Age</th>
<th>Reference Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reefhuis</td>
<td>1.1 – 1.9</td>
<td>35-40</td>
<td>25-29</td>
</tr>
<tr>
<td>Loane</td>
<td>1 – 1.8</td>
<td>≥ 40</td>
<td>25-29</td>
</tr>
<tr>
<td>Cleary-Goldman</td>
<td>1.4 – 1.7</td>
<td>≥ 35</td>
<td>&lt; 35</td>
</tr>
</tbody>
</table>

#### Preterm Birth

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio/Relative Risk</th>
<th>Maternal Age</th>
<th>Reference Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary-Goldman (&lt; 37 wks)</td>
<td>1.0 – 1.4</td>
<td>≥ 35</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Yogev (&lt; 34 wks)</td>
<td>1.8</td>
<td>40-44</td>
<td>20-29</td>
</tr>
<tr>
<td>Luke (&lt; 32 wks)</td>
<td>1.6 – 2.1</td>
<td>≥ 40</td>
<td>30 – 34</td>
</tr>
</tbody>
</table>

#### Low Birth Weight

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio/Relative Risk</th>
<th>Maternal Age</th>
<th>Reference Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary-Goldman</td>
<td>1.1 – 1.6</td>
<td>≥ 35</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Yogev</td>
<td>0.8</td>
<td>40-44</td>
<td>20-29</td>
</tr>
<tr>
<td>Luke</td>
<td>9.2</td>
<td>NR</td>
<td>30-34</td>
</tr>
<tr>
<td>Yogev</td>
<td>0.7</td>
<td>≥ 45</td>
<td>20-29</td>
</tr>
<tr>
<td>Salihu</td>
<td>3.0</td>
<td>≥ 50</td>
<td>20-29</td>
</tr>
</tbody>
</table>

#### Pre-Eclampsia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio/Relative Risk</th>
<th>Maternal Age</th>
<th>Reference Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary-Goldman</td>
<td>0.9 – 1.1</td>
<td>≥ 35</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Yogev</td>
<td>NR</td>
<td>40-44</td>
<td>N/A</td>
</tr>
<tr>
<td>Yogev</td>
<td>1.3 – 1.6</td>
<td>≥ 45</td>
<td>N/A</td>
</tr>
<tr>
<td>Pare</td>
<td>aOR NS</td>
<td>&gt; 40</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Luke</td>
<td>1.04 – 4.6</td>
<td>≥ 40</td>
<td>30 – 34</td>
</tr>
<tr>
<td>Paulson</td>
<td>1.3</td>
<td>≥ 50</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Gestational Diabetes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio/Relative Risk</th>
<th>Maternal Age</th>
<th>Reference Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary-Goldman</td>
<td>1.8 – 2.4</td>
<td>≥ 35</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Yogev</td>
<td>10.2</td>
<td>NR</td>
<td>40-44</td>
</tr>
<tr>
<td>Yogev</td>
<td>17.0</td>
<td>NR</td>
<td>≥ 45</td>
</tr>
<tr>
<td>Paulson</td>
<td>17.5</td>
<td>NR</td>
<td>≥ 50</td>
</tr>
</tbody>
</table>

#### Placenta Previa

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio/Relative Risk</th>
<th>Maternal Age</th>
<th>Reference Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary-Goldman</td>
<td>1.8 – 2.8</td>
<td>≥ 35</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>Yogev</td>
<td>5.7</td>
<td>40-44</td>
<td>20-29</td>
</tr>
<tr>
<td>Yogev</td>
<td>13.4</td>
<td>≥ 45</td>
<td>20-29</td>
</tr>
<tr>
<td>Jacobsson</td>
<td>1.04 – 4.6</td>
<td>≥ 40</td>
<td>20-29</td>
</tr>
<tr>
<td>Salihu</td>
<td>16.7</td>
<td>NR</td>
<td>≥ 50</td>
</tr>
</tbody>
</table>
Mode of Delivery

Cesarean Section

<table>
<thead>
<tr>
<th>Age Group</th>
<th>35 – 40 Yrs</th>
<th>40 – 45 Yrs</th>
<th>45 – 50 Yrs</th>
<th>&gt; 50 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary-Goldman</td>
<td>31.4%</td>
<td>40.5% (aOR 2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogev</td>
<td>42.9% (RR 3.7)</td>
<td>78.5% (RR 31.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luke (primiparous)</td>
<td>43% (RR 1.96)</td>
<td>54.1% (RR 3.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobsson</td>
<td>23.5% (OR 2.8)</td>
<td>30.3% (OR 3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulitzki</td>
<td></td>
<td></td>
<td></td>
<td>39.4% (OR 7.3)</td>
</tr>
<tr>
<td>Paulson (singleton)</td>
<td></td>
<td></td>
<td></td>
<td>68%</td>
</tr>
</tbody>
</table>

Risk Factors for Cesarean Section

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥ 44</td>
<td>7.29</td>
<td>2.19, 16.7</td>
</tr>
<tr>
<td>Infertility treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Without egg donation</td>
<td>3.60</td>
<td>1.49, 8.83</td>
</tr>
<tr>
<td>With egg donation</td>
<td>19.5</td>
<td>6.08, 62.2</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiparity without previous cesarean delivery</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Primiparity</td>
<td>3.54</td>
<td>1.28, 9.81</td>
</tr>
<tr>
<td>Multiparity with previous cesarean delivery</td>
<td>17.1</td>
<td>3.18, 92.7</td>
</tr>
</tbody>
</table>

Krieg: Stanford University, 40 pregnancies in oocyte recipients compared to women ≥ 38 yrs who underwent autologous IVF cycles

- OR for C/S in oocyte recipients: 2.78 (1.44-5.36)
- Each 1 year increase in maternal age was associated with a 13% increase in the odds of C/S.

Risk of Intrauterine Fetal Demise

At what gestational age do you offer induction of labor for women who are over 40 without other risk factors?

A. 39 – 40 weeks  
B. 40 – 41 weeks  
C. > 41 weeks  
D. 41 – 42 weeks

Hoffman et al. Pregnancy at or beyond age 40 years is associated with an increased risk of fetal death and other adverse outcomes. AJOG 2006.

Risk of IUFD

Odds of IUFD by GA compared to women < 35 years (N = 108,547)

<table>
<thead>
<tr>
<th>GA Period</th>
<th>35-39 Years aOR* (95% CI) N = 13,902</th>
<th>≥ 40 years aOR* (95% CI) N = 3,953</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 – 36 weeks</td>
<td>2.03 (1.54 – 2.69)</td>
<td>1.73 (1.05 – 2.83)</td>
</tr>
<tr>
<td>37 – 39 weeks</td>
<td>1.20 (0.85 – 1.70)</td>
<td>1.63 (0.97 – 2.75)</td>
</tr>
<tr>
<td>40 – 41 weeks</td>
<td>0.80 (0.44 – 1.45)</td>
<td><strong>2.28 (1.82 – 4.40)</strong></td>
</tr>
</tbody>
</table>

* Adjusted for race/ethnicity, parity, chronic hypertension, pre-eclampsia, diabetes

Hoffman et al. Pregnancy at or beyond age 40 years is associated with an increased risk of fetal death and other adverse outcomes. AJOG 2006.

IUFD Risk

Other Reported Risks

- Intensive care stay
- Myocardial infarction
- Pulmonary edema
- Venous thromboembolism
- Postpartum depression

Other Anecdotal Risks

- Anxiety
- Difficulty with breastfeeding

A BRIEF DIVERSION TO ADVANCED PATERNAL AGE
**Advanced Paternal Age**

**MANAGEMENT**

**TABLE 1**
Risk of Autosomal Dominant Genetic Syndromes With Increasing Paternal Age (53-55)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Relative Risk</th>
<th>Paternal Age (y)</th>
<th>Reference Age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
<td>9</td>
<td>45-49</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Pfeiffer</td>
<td>6</td>
<td>&gt;50</td>
<td>25-29</td>
</tr>
<tr>
<td>Thanatophoric dysplasia</td>
<td>3.2</td>
<td>≥35</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>2.5</td>
<td>&gt;35</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>1.4</td>
<td>≥35</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>

Possibly increased risk for other birth defects, autism-spectrum disorders

Salmeen, Zlatnik. The oldest gravidas: a review of pregnancy risks in women over 45. Obstetrical and Gynecological Survey 2011

**What I do...**

Without a lot of evidence

**Preconception Work-Up for Women ≥ 40**
(or ≥ 35 with risk factors)

- Hemoglobin A1c, fasting glucose
- TSH
- Mammogram
- EKG
- Lipids
- Serial BPs
- Cardiac Stress Test/Cardiology evaluation
First Trimester Care for Women ≥ 40

- Determine mode of conception
- Assess fetal number, chorionicity of multiples
- TSH (if not recently obtained)
- Early glucose testing
- If hypertensive: baseline pre-eclampsia labs
- Genetic counseling (adjust for oocyte-donor age)
- Consideration of aspirin prophylaxis

** Aspirin Prophylaxis **

- In “high-risk” women, aspirin prophylaxis may reduce the risk of pre-eclampsia by up to 17%
- I consider women over 40 to be “high risk” and offer aspirin

Prenatal Care for Women ≥ 40 (or ≥ 35 with risk factors)

- Detailed fetal anatomic survey
- Low-threshold for fetal echocardiogram
- Repeat glucose tolerance testing
- Evaluation of fetal growth in the third trimester
- Antenatal testing
- Labor planning, counseling regarding mode of delivery
- Labor induction 39-40 weeks

TAKE HOME POINTS

- Age-related risks are actually multifactorial
- IUFD increases with increasing maternal age. Induction for “post dates” may be appropriate after 39-40 weeks for women > 35 – 40 years.
- Age nor donor-oocyte recipient status are indications for cesarean delivery.
- Aspirin prophylaxis is indicated for women at high-risk for pre-eclampsia, including women over 40.
Questions?