Elective
Single Embryo Transfer (eSET)

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Disclosures

- Industry
  - Research Funding/Consulting
    - Auxogyn
    - Bayer
    - LabCorp
    - Ziva
  - Shareholder in: Advanced Reproductive Care
- Professional Organizations
  - ASRM: Past President
  - FIGO: Chair, Committee on Reproductive Medicine
  - ICMART: Chair
  - IFFS: Board of Directors
  - WERF: President

- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies
Learning Objectives

• To apply knowledge of ART procedure outcomes to laboratory and clinical decision making
• To explain actions that can be implemented to reduce the multiple birth rate
• To identify challenges associated with implementation of elective SET and reduction of the multiple birth rate
Many Causes of Multiple Births

- Number of embryos transferred
  - eSET vs. DET vs. >DET
- Reproductive potential of embryos
  - Quality
  - Stage at transfer
  - Screened vs. unscreened embryos
  - Fresh vs. frozen cycle
- Elective fetal reduction
- Societal factors
  - Health system
    - Access limitations
    - Patient cost/fertility coverage
    - Quality of clinical and laboratory care
    - Other factors (e.g. reporting, competition)
  - Social values
    - Religious
    - Effectiveness vs. safety

Access to ART
Access to ART Treatment According to Funding

- Free access or Reimbursed
- Non-reimbursed developed (Japan): 890
- Non-reimbursed developed (USA): 357
- Non-reimbursed developing (LA): 150
- Non-reimbursed developing (Egypt): 113

ART cycles per 1,000,000 habitants

Courtesy Fernando Zegers, MD and ICMART
Relationship Between Access to ART And Number of Embryos Transferred
Effectiveness of ART
Delivery Rates per Aspiration According to Region (IVF & ICSI) 2008

Delivery Rates per Aspiration According to Region (IVF & ICSI) 2008

North America
Latin America
Middle East
Europe
Australia & New Zealand
Asia

Fresh cycles Cumulative
ARS Question 1: With good antenatal care, risk for abnormal outcomes in singleton and twin pregnancies are:

1. Similar maternal and higher fetal
2. Similar maternal and fetal
3. Higher maternal and similar fetal
4. Higher maternal and higher fetal
5. None of the above
Safety of ART
### Risks of Multifetal Gestation

<table>
<thead>
<tr>
<th>NUMBER</th>
<th>FETAL LOSS (%)</th>
<th>AVERAGE DELIVERY</th>
<th>MORTALITY (%)</th>
<th>MORBIDITY (%)</th>
<th>2008 Data</th>
<th>Courtesy Mark Evans, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>90%</td>
<td>26</td>
<td>20%</td>
<td>30% per fetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50%</td>
<td>28</td>
<td>15%</td>
<td>25% per fetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>25%</td>
<td>29</td>
<td>6%</td>
<td>15% per fetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>32</td>
<td>3%</td>
<td>5% per fetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8%</td>
<td>35</td>
<td>2%</td>
<td>3% per fetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3%</td>
<td>39</td>
<td>1%</td>
<td>2% per fetus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Percentage of Transfers With 1-2 Embryos By Region 1998 & 2008
Delivery Rate per Retrieval and Twin Pregnancies By Region 1998 & 2008
Proportions of All Liveborn Children Resulting from ART in the US That Were Members of Multiple Births

![Graph showing the proportions of liveborn children resulting from ART in the US that were members of multiple births from 2000 to 2008. The graph includes lines for multiple births, twin births, and triplet+ births.](image)

ASRM Practice Committee eSET. 2011.
Conclusions Regarding Global Access, Effectiveness and Safety
Conclusions

- **Access**
  - Much *lower* than needed worldwide
  - Even in most developed countries

- **Effectiveness**
  - Highest in US, stabilized at
    - Fresh LBR/Retrieval ~ 35%
    - FET LBR/Transfer ~ 25%
    - Donor Egg LBR/Transfer ~ 55%

- **Safety**
  - Much *improved*, BUT
  - Triplet rate needs further reduction by DET
  - Twin rate reduction requires SET
“Twin Pregnancy, Contrary to Consensus, is a Desirable Outcome in Infertility”

• Most risk assessments after fertility treatment use spontaneous conceptions
• IVF twins have 40% lower outcome risks
• Correct outcome is born children, not pregnancy
• Two children born with twins effectively halves the risk for babies and mothers
• For infertile women who want more than one child, twin pregnancies are favorable and cost-effective and should be encouraged

How To Meet
The Challenge
1. Reduce the Number of Embryos Transferred

- Fewer embryos can be transferred to obtain equivalent pregnancy rates
- Multiple pregnancy rates can be reduced
- **Expert** physician knowledge and experience is needed
- **Individualized** patient decision making and treatment is required
## LBR by Number of Embryos Transferred, Age and Presence of Embryos to Cryopreserve

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Embryos Transferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29(-)</td>
<td>2 3 4 5</td>
</tr>
<tr>
<td>(+)</td>
<td>42.7 41.1</td>
</tr>
<tr>
<td>30-34(-)</td>
<td>36.0 41.5</td>
</tr>
<tr>
<td>(+)</td>
<td>24.7 33.0 37.6*</td>
</tr>
<tr>
<td>35-39(-)</td>
<td>5.1 7.7 13.8* 19.6*</td>
</tr>
<tr>
<td>(+)</td>
<td>- 18.8 17.5 24.0</td>
</tr>
</tbody>
</table>

(-) = NO embryos to cryopreserve (Poorer prognosis)

(+) = Extra embryos to cryopreserve (Good prognosis)

Relationship of Multiple Gestation and Age

- Risk decreases with age (1)
  - Still high through age 40
- Multiple birth with DET (+ Cryo = TOP)
  - < 35 40%
  - 35-37 33%
  - 38-40 28%
- Maternal risk increases with age
- Blastocyst lower rate, similar IR and PR (2)
- Single blast PR late 30’s ~ 50% (1)

1. SART/ASRM Practice Committees. eSET. 2011.
2. Don’t Transfer Two Blastocysts!

- Cumulative live birth rates
  - not very different
  - with Blastocyst eSBT vs. DBT
- Twin rates
  - extremely high
- Monozygotic twins
  - more frequent
- Increased risks
  - Blastocyst compared with cleavage stage
  - e.g. imprinting disorders
  - Increased proportion abnormal babies
## Blastocyst Transfer
### RCT of eSBT vs. eDBT

<table>
<thead>
<tr>
<th></th>
<th>IR</th>
<th>PR</th>
<th>Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>eSBT</td>
<td>61%</td>
<td>61%</td>
<td>0%</td>
</tr>
<tr>
<td>eDBT</td>
<td>56%</td>
<td>76%</td>
<td>47%</td>
</tr>
</tbody>
</table>

n=48

ARS Question 2: Which of the following is the most effective way to reduce the twin rate?

- Reduce the average number of embryos transferred
- Perform more frozen/thaw embryo transfers
- Perform PGS on all patients
- Perform PGS on selected patients
- Do more elective single embryo transfers
3. Increase Use of eSET

• It is the only way to reduce the twin rate

• Live birth rates are reduced only slightly, if at all
“As many babies as you want, but one at a time”

“eSET should be considered for every patient, every time, but is not the best treatment for every patient every time”

Adamson, 2012
ART Outcomes in Relation to Number of Embryos Transferred

Fig. 1. ART Outcomes in US: Relationship with SART/ASRM Guidelines for Number of Embryos to Transfer

- %Twin/Preg
- %Triplet+/Preg
- %Multiples/Delivery

Data derived from http://www.cdc.gov/ART/ARTReports.htm
Dashed lines indicated years at which SART/ASRM guidelines were introduced (1998) and subsequently revised (1999, 2004, 2006 and 2008).
Multiple births are expressed per delivery; twin and triplet+ pregnancies are expressed per clinical pregnancy.

ASRM Practice Committee. Multiple Gestation. 2011.
## 1 Fresh + 1 Frozen Embryo vs 2 Fresh Embryo Transfer

<table>
<thead>
<tr>
<th></th>
<th>eSET N = 350</th>
<th>DET N = 353</th>
<th>Adj. OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live birth</strong></td>
<td>38%</td>
<td>42%</td>
<td><strong>0.85 (0.62, 1.15)</strong></td>
</tr>
<tr>
<td><strong>Multiple live birth</strong></td>
<td>1%</td>
<td>32%</td>
<td><strong>0.02 (0.00, 0.13)</strong></td>
</tr>
</tbody>
</table>

McLernon. BMJ 2010. 341:c6945
Single Embryo Transfer (SET): The Swedish Experience
IVF/ICSI 1997-2004
ART Outcomes in Sweden and the US, 2006

<table>
<thead>
<tr>
<th>Country</th>
<th>% per Embryo Transfer</th>
<th>% per Live Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Live Birth Rate</td>
<td>Singleton Birth Rate</td>
</tr>
<tr>
<td>Sweden</td>
<td>27.2</td>
<td>25.6</td>
</tr>
<tr>
<td>US</td>
<td>35.4</td>
<td>24.6</td>
</tr>
</tbody>
</table>

ASRM Practice Committee. Multiple Gestation. 2011.
Dramatic Decrease in Annual Number of Multiple Births in Japan

Ishihara. MHLW and JSOG data.
LBR/Fresh Nondonor Transfer <35 + Extra Embryo by Number of Embryos Transferred

Figure 61

*Cycles involving the transfer of one embryo were not included because of the small number of cycles where one embryo was transferred and extra embryos were set aside for future use.

http://www.cdc.gov/art/ART2006/sect5_fig49-64.htm#f61
eSET should be considered seriously for good prognosis patients, assuming the availability of effective cryopreservation protocols that will help to maximize cumulative pregnancy rates.
4. Follow SART/ASRM Guidelines (At Least!)

Number of Embryos to Transfer (2008)

<table>
<thead>
<tr>
<th>Day 3</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable*</td>
<td>1-2</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>All Others</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 5</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable*</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>All Others</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

1st cycle, good embryos, # to cryo, or prior IVF success
Updated (2009) SART/ASRM Guidelines on Number of Embryos Transferred

• Based on 2007 ASRM and SART data
• Poor prognosis patients
  – No more than one additional embryo
• Frozen embryo transfer cycles
  – number of good quality thawed embryos transferred
  – not exceed the recommended number of fresh embryos

Clinicians have a professional and ethical obligation to optimize the chance of a singleton birth for prospective parents whose preferences and choices may be clouded by feelings of desperation to achieve a pregnancy.
5. Use New Technologies To Reduce The Number of Embryos Transferred

- **Embryo cryopreservation**
  - Vitrification
- **Blastocyst transfer**
  - Selected patients
- **Assessment of embryo quality**
  - PGD/S
  - Complete Genomic Hybridization (CGH)
  - Metabolomics
  - Proteomics
  - Time lapse photography
Risk of Multiple Gestation With Cryopreserved Embryos

- **Reduced** compared with fresh transfer (1)
- Decisions regarding eSET should consider
  - Prognosis
  - Embryo quality
  - Individual program pregnancy rates (2)

1. Wright. MMWR Surveill Summ 2008;57:1-23
2. SART/ASRM Practice Committees. eSET. 2011.
ET Cycles in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>FER</th>
<th>ICSI</th>
<th>IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>10711</td>
<td>21067</td>
<td>24447</td>
</tr>
<tr>
<td>2001</td>
<td>11883</td>
<td>23058</td>
<td>25143</td>
</tr>
<tr>
<td>2002</td>
<td>14729</td>
<td>25866</td>
<td>26708</td>
</tr>
<tr>
<td>2003</td>
<td>19545</td>
<td>27895</td>
<td>27857</td>
</tr>
<tr>
<td>2004</td>
<td>24342</td>
<td>29946</td>
<td>29090</td>
</tr>
<tr>
<td>2005</td>
<td>28701</td>
<td>30983</td>
<td>29232</td>
</tr>
<tr>
<td>2006</td>
<td>35784</td>
<td>32509</td>
<td>29361</td>
</tr>
<tr>
<td>2007</td>
<td>43452</td>
<td>34032</td>
<td>27729</td>
</tr>
<tr>
<td>2008</td>
<td>56494</td>
<td>34425</td>
<td>28609</td>
</tr>
<tr>
<td>2009</td>
<td>71161</td>
<td>35168</td>
<td>28073</td>
</tr>
</tbody>
</table>

JSOG data
Improve Embryo Quality

- Improve quality of embryos transferred
  - Time-lapse imaging
  - Assessment of embryo morphology and growth dynamics (1)
  - Blastocyst transfer in selected patients
  - Preimplantation Genetic Screening (PGS) (yet to be validated) (2-4)
  - Better technologies to assess embryos: e.g. CGH, proteomics, metabolomics, algorithms, time lapse photography etc. (yet to be validated) (5,6)

ARS Question 3: Day 5 blastocyst transfer has better outcomes than day 3 cleavage stage stage transfers.

- True
- False
6. Assess Objectively the Benefits and Disadvantages of New Technologies
e.g. Cleavage vs. Blastocyst Transfer & PGS

• Live Birth Rate
  – Blastocyst > Day 3: OR 1.35 (95% CI 1.05-1.74)
  – Especially for
    • Good prognosis patients
    • Equal number of embryos transferred (including SET)
    • Randomization on Day 3 (ability to select patients for blast culture)

• Rates of Embryo Cryopreservation
  – Blastocyst < Day 3: OR 0.45 (95% CI 0.36-0.56)

• Failure to Transfer Any Embryos
  – Failure Blastocyst > Day 3: OR 2.85 (95% CI 1.97-4.11)
  – Good prognosis Pts: OR 1.50 (95% CI 0.79-2.84)

• “Emerging evidence that in selected patients blastocyst culture may be applicable for SET.”
Outcome Issues: CD 3 Cleavage vs. CD 5 Blast Transfer

• ? Effects of longer durations of culture
  – Epigenetic issues
  – Some literature creates concern
  – Some literature is reassuring

• Adverse neonatal outcomes vs. natural
  – CD 3 OR, 1.11 (95% CI, 1.02-1.21)
  – CD 5 OR, 1.53 (95% CI, 1.23-1.90)

• Clinical significance unclear (1)

SART/ASRM Practice Committees. eSET. 2011.
ASRM Practice Committee. Multiple Gestation. 2011.
Cleavage vs. Blastocyst Transfer: Live Birth per Couple (Favors Blastocyst)

Figure 3. Forest plot of comparison: 1 Live birth rate, outcome: 1.1 Live birth per couple.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Day 5/6 Events</th>
<th>Total</th>
<th>Day 2/3 Events</th>
<th>Total</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugnon 2010</td>
<td>22</td>
<td>55</td>
<td>21</td>
<td>52</td>
<td>7.8%</td>
<td>0.98 [0.46, 2.12]</td>
</tr>
<tr>
<td>Devreker 2000</td>
<td>3</td>
<td>11</td>
<td>1</td>
<td>12</td>
<td>1.0%</td>
<td>3.53 [0.43, 29.14]</td>
</tr>
<tr>
<td>Elgindy 2011</td>
<td>52</td>
<td>100</td>
<td>35</td>
<td>100</td>
<td>14.8%</td>
<td>1.99 [1.14, 3.48]</td>
</tr>
<tr>
<td>Emiliani 2003</td>
<td>33</td>
<td>82</td>
<td>41</td>
<td>89</td>
<td>12.6%</td>
<td>0.79 [0.43, 1.44]</td>
</tr>
<tr>
<td>Frattarelli 2003</td>
<td>15</td>
<td>29</td>
<td>8</td>
<td>28</td>
<td>4.2%</td>
<td>2.57 [0.90, 7.35]</td>
</tr>
<tr>
<td>Levitas 2004</td>
<td>3</td>
<td>23</td>
<td>3</td>
<td>31</td>
<td>1.6%</td>
<td>1.40 [0.26, 7.65]</td>
</tr>
<tr>
<td>Levron 2002</td>
<td>8</td>
<td>46</td>
<td>15</td>
<td>44</td>
<td>5.2%</td>
<td>0.42 [0.16, 1.08]</td>
</tr>
<tr>
<td>Livingstone 2002</td>
<td>14</td>
<td>30</td>
<td>11</td>
<td>29</td>
<td>4.4%</td>
<td>1.42 [0.51, 3.96]</td>
</tr>
<tr>
<td>Papanikolaou 2005</td>
<td>38</td>
<td>80</td>
<td>23</td>
<td>84</td>
<td>11.6%</td>
<td>2.35 [1.25, 4.43]</td>
</tr>
<tr>
<td>Papanikolaou 2006</td>
<td>56</td>
<td>175</td>
<td>38</td>
<td>176</td>
<td>20.7%</td>
<td>1.70 [1.06, 2.72]</td>
</tr>
<tr>
<td>Rienzi 2002</td>
<td>24</td>
<td>50</td>
<td>24</td>
<td>48</td>
<td>7.4%</td>
<td>0.92 [0.42, 2.03]</td>
</tr>
<tr>
<td>Van der Auwera 2002</td>
<td>24</td>
<td>70</td>
<td>17</td>
<td>66</td>
<td>8.6%</td>
<td>1.49 [0.72, 3.10]</td>
</tr>
</tbody>
</table>

Total (95% CI)             | 751            | 759   | 100.0%         | 1.40  [1.13, 1.74] |

Total events               | 292            | 237   |

Heterogeneity: Chi² = 18.43, df = 11 (P = 0.07); I² = 40%
Test for overall effect: Z = 3.07 (P = 0.002)
Cleavage vs. Blastocyst Transfer: Cumulative Pregnancy Rate From Fresh and Frozen Transfers (Favors Cleavage Stage)

Figure 5. Forest plot of comparison: Cumulative pregnancy rate from fresh and frozen transfers.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Day 5/6 Events</th>
<th>Day 5/6 Total</th>
<th>Day 2/3 Events</th>
<th>Day 2/3 Total</th>
<th>Weight</th>
<th>Peto Odds Ratio (Non-event)</th>
<th>Peto Odds Ratio (Non-event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugnon 2010 (1)</td>
<td>24</td>
<td>55</td>
<td>25</td>
<td>52</td>
<td>21.5%</td>
<td>1.19 [0.56, 2.55]</td>
<td></td>
</tr>
<tr>
<td>Emiliani 2003</td>
<td>43</td>
<td>99</td>
<td>56</td>
<td>94</td>
<td>39.0%</td>
<td>1.90 [1.08, 3.34]</td>
<td></td>
</tr>
<tr>
<td>Rienzi 2002</td>
<td>31</td>
<td>50</td>
<td>41</td>
<td>48</td>
<td>15.5%</td>
<td>3.28 [1.35, 8.02]</td>
<td></td>
</tr>
<tr>
<td>Van der Auwera 2002</td>
<td>24</td>
<td>66</td>
<td>22</td>
<td>63</td>
<td>24.0%</td>
<td>0.94 [0.46, 1.93]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>270</strong></td>
<td><strong>257</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td>1.58 [1.11, 2.25]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 122, 144

Heterogeneity: Chi² = 5.54, df = 3 (P = 0.14); I² = 46%

Test for overall effect: Z = 2.55 (P = 0.01)

(1) Study had policy of single embryo transfer

Cleavage vs. Blastocyst. Cochrane 2012 Jul 11;7:CD002118
Cleavage vs. Blastocyst Transfer: Multiple Pregnancy Rate/Couple (P=NS)

Cleavage vs. Blastocyst Transfer: Miscarriage Rate per Couple (\(P=\text{NS}\))

Cleavage vs. Blastocyst.
Cochrane 2013.
Cleavage vs. Blastocyst Transfer: Embryo Freezing per Couple (Favors Cleavage)

OR=2.88
P=0.00001

Cleavage vs. Blastocyst.
Cochrane 2013.
Cleavage vs. Blastocyst Transfer: Failure to Transfer Embryos (Favors Cleavage)

Cleavage vs. Blastocyst.

Cochrane 2013.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Day 3/6  n/N</th>
<th>Day 2/3 n/N</th>
<th>Odds Ratio (Non-transfer)</th>
<th>Odds Ratio (Non-transfer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardner 1998</td>
<td>24/5</td>
<td>0/47</td>
<td>0.18 [0.05, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Burgum 2003</td>
<td>0/61</td>
<td>0/57</td>
<td>0.0 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Cowan 2000</td>
<td>0/100</td>
<td>0/101</td>
<td>0.0 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Donderer 2000</td>
<td>0/11</td>
<td>0/12</td>
<td>0.0 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Emiliari 2003</td>
<td>10/99</td>
<td>1/94</td>
<td>0.10 [0.01, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Frattari 2003</td>
<td>32/9</td>
<td>3/28</td>
<td>1.28 [0.48, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Hrdlickova 2004</td>
<td>46/4</td>
<td>3/80</td>
<td>0.58 [0.18, 2.11]</td>
<td></td>
</tr>
<tr>
<td>Kavli 2002</td>
<td>9/80</td>
<td>0/82</td>
<td>0.05 [0.00, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Kolbitskis 2004</td>
<td>36/526</td>
<td>16/234</td>
<td>0.39 [0.21, 0.72]</td>
<td></td>
</tr>
<tr>
<td>Lovato 2004</td>
<td>6/23</td>
<td>2/21</td>
<td>0.20 [0.04, 0.88]</td>
<td></td>
</tr>
<tr>
<td>Lovato 2002</td>
<td>3/46</td>
<td>0/44</td>
<td>0.14 [0.01, 2.78]</td>
<td></td>
</tr>
<tr>
<td>Motta 1990 A %B</td>
<td>60/88</td>
<td>1/58</td>
<td>0.15 [0.02, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Papanicolaou 2005</td>
<td>0/80</td>
<td>0/94</td>
<td>0.0 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Papanicolaou 2006</td>
<td>11/175</td>
<td>8/176</td>
<td>0.71 [0.28, 1.81]</td>
<td></td>
</tr>
<tr>
<td>Renzi 2003</td>
<td>0/50</td>
<td>0/50</td>
<td>0.0 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Van der Auwera 2002</td>
<td>18/70</td>
<td>6/66</td>
<td>0.29 [0.11, 0.80]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1217 1242

OR = 0.35

P = 0.00001
PGS for Aneuploidy: Advanced Maternal Age LBR Per Woman Randomized (Favors Control)

Figure 3. Forest plot of comparison: advanced maternal age, outcome: live birth rate per woman randomised.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PGS group</th>
<th>Control group</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Debrock 2010</td>
<td>6</td>
<td>44</td>
<td>10</td>
</tr>
<tr>
<td>Hardarson 2008</td>
<td>3</td>
<td>56</td>
<td>10</td>
</tr>
<tr>
<td>Mastenbroek 2007</td>
<td>49</td>
<td>206</td>
<td>71</td>
</tr>
<tr>
<td>Scholecraft 2009</td>
<td>16</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Staessen 2004</td>
<td>21</td>
<td>199</td>
<td>29</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>537</strong></td>
<td><strong>525</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>95</strong></td>
<td><strong>136</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.38, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 3.35 (P = 0.0008)

PGS for Aneuploidy: Advanced Maternal Age Miscarriage Rate (P=NS)

Figure 9. Forest plot of comparison: 1 advanced maternal age, outcome: 1.7 miscarriage rate per woman randomised.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PGS group Events</th>
<th>PGS group Total</th>
<th>Control group Events</th>
<th>Control group Total</th>
<th>Weight</th>
<th>Odds Ratio M.H, Fixed, 95% CI</th>
<th>Odds Ratio M.H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debrock 2010</td>
<td>2</td>
<td>44</td>
<td>5</td>
<td>50</td>
<td>8.0%</td>
<td>0.43 [0.08, 2.33]</td>
<td></td>
</tr>
<tr>
<td>Hardarson 2008</td>
<td>7</td>
<td>56</td>
<td>6</td>
<td>53</td>
<td>9.7%</td>
<td>1.12 [0.35, 3.58]</td>
<td></td>
</tr>
<tr>
<td>Mastenbroek 2007</td>
<td>37</td>
<td>206</td>
<td>36</td>
<td>202</td>
<td>53.6%</td>
<td>1.01 [0.61, 1.68]</td>
<td></td>
</tr>
<tr>
<td>Schoolcraft 2009</td>
<td>5</td>
<td>32</td>
<td>7</td>
<td>30</td>
<td>11.0%</td>
<td>0.61 [0.17, 2.18]</td>
<td></td>
</tr>
<tr>
<td>Staessen 2004</td>
<td>7</td>
<td>199</td>
<td>10</td>
<td>190</td>
<td>17.7%</td>
<td>0.68 [0.24, 1.76]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>537</strong></td>
<td><strong>525</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td>0.87 [0.59, 1.27]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>58</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.80, df = 4 (P = 0.77); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.73 (P = 0.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## PGS for Aneuploidy:
### Good Prognosis
Clinical Pregnancy Rate (Favors Control)

**Figure 12. Forest plot of comparison: 3 good prognosis patients, outcome: 3.5 clinical pregnancy rate per woman randomised.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PGS group</th>
<th>Control group</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.5.1 biopsy at cleavage stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer 2009</td>
<td>11</td>
<td>23</td>
<td>0.46 [0.14, 1.49]</td>
</tr>
<tr>
<td>Staessen 2008</td>
<td>37</td>
<td>120</td>
<td>0.77 [0.45, 1.32]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>48</td>
<td>60</td>
<td>0.70 [0.43, 1.15]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>48</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); ℓ² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.41 (P = 0.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.5.2 biopsy at blastocyst stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jansen 2008</td>
<td>22</td>
<td>55</td>
<td>0.47 [0.21, 1.04]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>55</td>
<td>46</td>
<td>0.47 [0.21, 1.04]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>22</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.86 (P = 0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>198</td>
<td>190</td>
<td>0.63 [0.42, 0.95]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>70</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); ℓ² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.18 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroups differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PGS for Aneuploidy: Good Prognosis Live Birth Rate (P=NS*)

**PGS for Aneuploidy:**
Good Prognosis Miscarriage Rate (P=NS)

### Figure 13. Forest plot of comparison: 3 good prognosis patients, outcome: 3.7 miscarriage rate per woman randomised.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PGS group Events</th>
<th>Control group Events</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.7.1 biopsy at cleavage stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer 2009</td>
<td>5</td>
<td>23</td>
<td>6.39 [0.68, 59.65]</td>
<td></td>
</tr>
<tr>
<td>Staessen 2008</td>
<td>10</td>
<td>120</td>
<td>0.64 [0.27, 1.48]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>143</strong></td>
<td><strong>144</strong></td>
<td><strong>0.94 [0.45, 1.97]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>15</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.65, df = 1 (P = 0.06); I² = 73%</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.16 (P = 0.87)</td>
<td></td>
</tr>
</tbody>
</table>

| **3.7.2 biopsy at blastocyst stage** | | | | |
| Jansen 2008       | 5                | 55                   | 4.50 [0.51, 39.99]          |                         |
| **Subtotal (95% CI)** | **55**          | **46**               | **4.50 [0.51, 39.99]**      |                         |
| Total events      | 5                | 1                    |                             |                             |
| Heterogeneity: Not applicable | | | Test for overall effect: Z = 1.35 (P = 0.18) |

**Total (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>PGS group Total</th>
<th>Control group Total</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>198</strong></td>
<td><strong>190</strong></td>
<td>100.0%</td>
<td>1.17 [0.59, 2.30]</td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 5.68, df = 2 (P = 0.06); I² = 65%</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.45 (P = 0.65)</td>
</tr>
<tr>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Recognize Patient Choice, But Make It Informed Choice

- Majority of patients desire twins
- This is understandable
- BUT this is BEFORE they have to take care of twins, ESPECIALLY if the baby is not healthy
- Patients (and physicians) underestimate risks and family burden
  - Babies and Mothers
  - Short term
  - Long term
- Informed choice is essential
Factors Causing Multiple Births

- Patients’ sense of urgency
- Inadequate health care coverage
- Competition from marketplace pressures
- Different perspectives of multiple risk (1)
- Infertility specialists’ lack of involvement in follow-up care
- Focus on LBR/Cycle rather than cumulative LBR (2)
- Patients and physicians underestimate negative consequences of twin pregnancies (3-5)

Physician Attitudes

- Factors affecting patients’ attitudes towards single- and multiple embryo transfer (1)
  - Physicians’ attitudes matter
- Attitudes towards and management of single embryo transfer among Nordic IVF doctors (2)

Patient Education

• Increased patient education makes eSET more acceptable (1,2)
  – Preference for twins reduced by half
  – eSET became preferred option
  – Written patient education materials tripled eSET rate in 1 year
  – RCT of DVD vs. Written Brochure
    • eSET vs. DET
    • DVD significantly better

1. SART/ASRM Practice Committees. eSET. 2011.
Conclusions

- Elective SET should be offered to patients with a good prognosis and to recipients of embryos from donated eggs.
- IVF centers should promote eSET when appropriate through provider and patient education.
- Improvements in embryo selection should further increase the application of eSET.
8. Discuss Fetal Reduction

• A technology that is successful
  – Ethical issues
  – Personal and societal value issues
• Controversial for many
  – Know your patient’s perspective
• Be especially conservative if unacceptable to patient(s)
9. Reduce Multiple Births With COS/IUI, Not Just With ART

[Graph showing the comparison of natural and ART methods for reducing twins and high-order births]

10. Reduce Financial Disincentives

- Reduce risk of the cost of multiple cycles
- Educate patients (2)
  - Long term costs of twins
  - Especially if unwell
- **Insurance** coverage (2)
  - Reduces number of embryos transferred
- **Financial programs** (2)
  - Increase eSET 50%

2. SART/ASRM Practice Committees. eSET. 2011.
11. Reduce Drop-out Rates

- Patient drop-out rates are 37-68%
- A major unknown confounding variable on the overall success of eSET (1,2)
  - Cost
  - Physician-recommended
    - **Sweden:** 65% not pregnant did not pursue covered treatment (3)
      - Psychological – 26%
      - Poor Prognosis – 25%
      - Spontaneous pregnancy – 19%
      - Physical burden – 6%
      - Serious disease – 2%
      - Other – 7%

Emotional Support and Mind-Body Programs

The pain and burden of infertility is real.
12. Create Systematic Change To Reduce Multiple Births

- Professionals
  - Associations
    - Change guidelines
    - Change reporting of outcomes (e.g. % eSET, %eSBT, %DBT)
  - Individual physicians transfer fewer embryos/blastocysts
- Other stakeholders can initiate change
  - Professional colleagues (e.g. MFM)
  - March of Dimes
  - WHO
- Government can regulate
- Change perspectives
  - Patients
  - Society
Why Does Infertility Matter?
The FIGO Fertility Tool Box™

www.arcfertility.com/figo
Thank You!