Short and Long-term Consequences of Multiple Births

Anja Pinborg
Professor, MD, DMSc

Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Denmark

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

- Describe short term consequences of multiple births
- Identify the advantages of single embryo transfer
- Summarize long-term consequences of multiple birth

DISCLOSURE

I have received research grants or been part of advisory boards for the following manufacturers of pharmaceuticals or medical devices:

- Ferring Pharmaceuticals
- Gedeon Richter
- Merck Serono
- Merck Sharp Dome
- Roche Diagnostics
• 7 million ART children born worldwide
  (de Geyter, ICMART/ESHRE 2018, Barcelona)

• 0.4-6.4% of the national ART birth cohorts in Europe
  (ESHRE/EIM data, De Geyter et al., HR 2018)

Multiple births after ART in Europe and USA

ART twin birth rate Europe 2014
Danish setting 5.7 million inhabitants

- 20 clinics (10 public and 10 private) performing >10,000 ART cycles per year
- Highest number of ART cycles per year per inhabitant in Europe
- Three reimbursed fresh cycles and all the added frozen cycles
- Partly reimbursement for medical drugs >1000 dollars
- Only public treatment for the 1. ART child and only in women <41 years
Single Embryo Transfer

Single embryo transfer > 90%
Singleton healthy child

Reduce national twin birth rate to 5-8% in Denmark

Danish Fertility Society
New guidelines (2015)

- Single embryo transfer is recommended
- Double embryo transfer can be performed, if the pregnancy chance is significantly reduced, though not if there is a medical contraindication to a twin pregnancy.
  - Female age ≥ 40 years
  - ≥ 4 previous embryo transfers
  - Low embryo quality

ART twin birth rates in Denmark

(www.fertilitetselskab.dk)
Twins that is what is in couples mind…….

“A nice chance to have two babies at once!”

“... to make up for lost time”

This is sometimes reality.............

<table>
<thead>
<tr>
<th>Twins (%)</th>
<th>Singletons (%)</th>
<th>AOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW &lt;2500 g</td>
<td>42 (55%)</td>
<td>11.8</td>
</tr>
<tr>
<td>BW &lt;1500 g</td>
<td>7.5 (10%)</td>
<td>5.4</td>
</tr>
<tr>
<td>PTB &lt;37 weeks</td>
<td>44 (59%)</td>
<td>9.9</td>
</tr>
<tr>
<td>VPTB &lt;32 weeks</td>
<td>8.5 (11%)</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Perinatal mortality risk 2-3 fold increased


Neonatal outcomes in IVF twin pregnancies (after DET) vs. two singleton pregnancies

(Sazonova et al., Fertil Steril 2013)
Neonatal and maternal outcomes in IVF twin pregnancies vs. two singleton pregnancies

Neurodevelopmental outcomes in twins vs. singletons

- Neurodevelopmental outcomes are poorer in twins
- RR 3.5-5.5 for cerebral palsy in twins vs. singletons with BW >2500 g
- Prevalence 2.4-12.6 per 1000 twins vs. 1.2-2.3 per 1000 singletons

Gestational age and birth weight are mediators not confounders

Cerebral palsy after assisted reproductive technology: a cohort study

- 211,660 live births in Western Australia 1994-2002
- Cerebral palsy
  - Prevalence after ART: 7.2 per 1000
  - Prevalence after natural conception: 2.5 per 1000
- Risk for cerebral palsy in ART vs. NC (twins + singletons)
  - (AOR 2.8 95%CI 1.6-4.0)
- Risk was doubled for ART singletons vs. NC singletons (AOR 2.0 95%CI 1.1-3.9), but stratified by gestational age odds were only increased <32 weeks

(Goldsmith et al. Dev Med Child Neurol 2017)
Cerebral palsy after assisted conception
(Hvidtjoern et al., Hum Reprod 2010)

- The risk of CP is increases after both IVF and OI
- The risk is strongly associated with multiplicity and preterm delivery
- Single embryo transfer is warranted to enhance long-term health in children born after ART

Maternal mortality and twin pregnancies
(Braat et al., Hum Reprod 2010; Santana et al., Obstet Gynecol 2016)

- Overall mortality was lower in the IVF female population
- 17 maternal deaths related to IVF pregnancy (42.5 per 100,000)
- 8/17 (47%) were related to twin pregnancy
- Venn et al., Hum Reprod 2001 also reported higher maternal mortality after IVF

Twin pregnancy and severe maternal outcomes
(Santana et al., Obstet Gynecol 2016 (WHO-survey))

RESULTS: Potentially life-threatening conditions, maternal near miss, severe maternal outcomes, and maternal deaths were 2.14 (1.99-2.30), 3.03 (2.39-3.85), 3.19 (2.58-3.94), and 3.97 (2.47-6.38) times higher, respectively, among twin pregnancies.

Our findings suggest increased maternal mortality and morbidity associated with twin pregnancy. Twin pregnancies should be regarded as a very high-risk condition, requiring close surveillance and specialized maternal care.
ART & "Vanishing twins" 1995-2001

Consequences of vanishing twins in IVF/ICSI pregnancies

- One in ten singletons is a survivor of a “vanishing twin” pregnancy in a double embryo transfer setting
- Survivors of a “vanishing twin” have higher perinatal risks
- The higher the gestational age at vanish the higher the risk

Adjusted odds ratio (95%CI)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight &lt;2500 gram</td>
<td>1.7 (1.2-2.2)</td>
</tr>
<tr>
<td>Birth weight &lt;1500 gram</td>
<td>2.1 (1.3-3.6)</td>
</tr>
<tr>
<td>Preterm birth &lt;37 weeks</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Preterm birth &lt;32 weeks</td>
<td>2.3 (1.4-4.0)</td>
</tr>
<tr>
<td>Small-for-gestational age</td>
<td>1.5 (1.0-2.3)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>3.6 (1.7-7.6)</td>
</tr>
</tbody>
</table>

*Adjusted for age, parity, ICSI
Long term health risks

Diseases later in life?
(Developmental Origins of Health and Disease; Barker hypothesis)

SGA predisposes for
- Cardiovascular diseases
- Diabetes
- Hypertonia
- Stroke

Multicenter RCT (Kina)
2157 ovulatory women

Birth rate
Freeze-all 48.7% and fresh 50.2%, RR 0.97 (95% CI 0.89-1.06) (P=0.5)

OHSS
Freeze-all 0.6% and fresh 2.0%, RR 0.32 (95% CI 0.14-0.74)

(Shi et al., NEJM 2018)
RCT with 782 ovulatory women (Vietnam)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Freeze-All vs. Fresh</th>
<th>RR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth rate</td>
<td>33.8% vs. 31.5%</td>
<td>1.07 (0.88-1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative birth rate</td>
<td>48.8% vs. 47.3%</td>
<td>1.03 (0.89-1.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-to-pregnancy</td>
<td>3.6 vs. 2.2 months</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>OHSS (moderate + severe)</td>
<td>0.8% vs. 1.0%</td>
<td>0.75 (0.17-3.33)</td>
<td></td>
</tr>
</tbody>
</table>

(Vuong et al., NEJM 2018)

The same pregnancy rate in Fresh and Frozen Embryo transfer in women with a regular menstrual cycle

(Siu et al., 2018 NEJM, Vuong et al., 2018 NEJM)

Take-home messages

- Multiple gestations are the most serious health risk factor for ART mothers and children
  - Also in women >40 years
  - Also in FET cycles
- Can be prevented by single embryo transfer and freezing of surplus embryos
- Single Embryo Transfer is almost for all
- We should maximize the use of single embryo transfer
Thank you