Multiple gestation in Ovulation induction and ART: Prevention

Zeev Shoham

Dep. Of OB/GYN Kaplan Hospital, Rehovot, Israel
Multiple Gestation

From curiosity to epidemic
NEW DISCOVERY BRINGS HOPE TO THE
CHILDLESS—AND A MULTIPLE-BIRTH EPIDEMIC

The Fantastic Drug That
Causes Quintuplets

In an Auckland, New Zealand hos-
pital a wonder-struck mother wand-
ered along a row of incubators
and gazed down at her newborn
quintuplets. Two days after Mrs.
Shirley Ann Lawson’s four girls
and one boy were delivered in New
Zealand, another set of quintuplets
was born to Mrs. Karin Olsen in Falun,
Sweden. Both sets resulted from
fantastic new drugs which enable
better women to conceive—and
Septuplets following Ovulation induction; Miracle in Iowa?
Multiple Gestation

Rate

<table>
<thead>
<tr>
<th>Region</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>6.7/1000</td>
</tr>
<tr>
<td>U.S./Europe</td>
<td>11/1000</td>
</tr>
<tr>
<td>Africa</td>
<td>40/1000</td>
</tr>
<tr>
<td>Monozygous</td>
<td>3.5/1000</td>
</tr>
<tr>
<td>O.I./ART</td>
<td>37%</td>
</tr>
</tbody>
</table>
Complications

Maternal
- Miscarriages
- Hypertension
- Operation
- Postpartum hemorrhage
- Postpartum stress

Fetal
- IUGR
- Congenital anomalies
- Hydroamnios
- Birth asphyxia
- Neonatal death
Compliactions

Premature birth

<table>
<thead>
<tr>
<th>Average length of pregnancy</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton</td>
<td>39</td>
</tr>
<tr>
<td>Twins</td>
<td>35</td>
</tr>
<tr>
<td>Triplets</td>
<td>33</td>
</tr>
<tr>
<td>Quadruplets</td>
<td>29</td>
</tr>
</tbody>
</table>

13,206 Pregnant women

11,986 Singleton

1135 Twin

85 ≥ 3

Callahan et al, NEJM, 1994
ECONOMIC IMPACT OF MULTIPLE PREGNANCIES (1991)

- SINGLETON 9,845 US$
- TWINS 37,947 US$
- TRIPLETS 109,765 US$

Callahan et al, NEJM, 1994
Multiple birth rate in Ovulation Induction and ART

- Unacceptable high.
- Triplet and higher order is a major medical problem.
- Twins are also a medical problem.
- Can only be overcome by careful management of O.I. and reducing number of embryos transferred.
Twins born in Western Australia 1991

- 4 times more likely to be stillborn.
- 5 times more likely to die as neonates.
- 16 times more likely to weight less 1500g at birth.
- CP 8 times more often than a singleton.
- Required neonatal intensive care 8 times more often than singleton.
Multiple pregnancy

Prevention?
Multiple pregnancy rate related to the number of follicles $\geq 16$ mm on hCG day

<table>
<thead>
<tr>
<th>No. of follicles on day hCG</th>
<th>No. of cycles</th>
<th>No. of clinical pregnancy</th>
<th>Clinical pregnancy rate (%)</th>
<th>No. of birth</th>
<th>Birth rate (%)</th>
<th>No. of twins</th>
<th>Multiple birth rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 foll.</td>
<td>277</td>
<td>47</td>
<td>17.09</td>
<td>39</td>
<td>14.18</td>
<td>2</td>
<td>5.13</td>
</tr>
<tr>
<td>2 foll.</td>
<td>77</td>
<td>20</td>
<td>25.97</td>
<td>17</td>
<td>22.08</td>
<td>2</td>
<td>11.76</td>
</tr>
<tr>
<td>3 foll.</td>
<td>32</td>
<td>11</td>
<td>34.38</td>
<td>10</td>
<td>31.25</td>
<td>2</td>
<td>20.00</td>
</tr>
<tr>
<td>$&gt;3$ foll.</td>
<td>19</td>
<td>5</td>
<td>26.32</td>
<td>4</td>
<td>21.05</td>
<td>2</td>
<td>50.00</td>
</tr>
<tr>
<td>Overall</td>
<td>405</td>
<td>83</td>
<td>20.60</td>
<td>70</td>
<td>17.37</td>
<td>8</td>
<td>11.4</td>
</tr>
</tbody>
</table>
**FSH Administration Regimen**

**Chronic Low Dose (CLD):** S. Franks et al.

- Days 7: 75 IU
- Days 14: 75 IU
- Days 21: 112.5 IU
- Days 28: 150 IU

**Step Down (SD):** B. Fauser et al.

- Days 7: 150 IU
- Days 14: 112.5 IU
- Days 21: 75 IU

**Sequential (SE):** J.N. Hugues et al.

- Days 6: 75 IU
- Days 12: 112.5 IU
- Days 12: 150 IU
- Days 12: 75 IU

- Foll. ≥ 10 mm
- Foll. ≥ 14 mm

hCG
How to minimize the risk of multiple birth

- Strict criteria for hCH administration.
- Replacing hCG with rec-LH or GnRH-a

Optimize Follicular Development?
The use of different doses of rec-LH
How to minimize the risk of multiple birth and still achieve a good pregnancy rate/started stimulation?

- Adjust the No. of embryos transferred depending on risk factors for multiple gestation.
  - Age.

- A good freezing program
Complications

Embryo reduction

Miscarriage 4-5 %
Premature labor 75 %

Traumatic experience
Conclusion

Identify groups who will benefit from having one blastocyst only.

We have to adopt a strategy where we try to retrieve as many oocytes as possible, replace one blastocyst and freeze the others.
How to minimize the risk of multiple birth

Optimize Follicular Development?

- Strict criteria for hCG administration.
## Multiple pregnancy rate related to the number of follicles $\geq 16$ mm on hCG day

<table>
<thead>
<tr>
<th>No. of follicles on day hCG</th>
<th>No. of cycles</th>
<th>No. of clinical pregnancy</th>
<th>Clinical pregnancy rate (%)</th>
<th>No. of birth</th>
<th>Birth rate (%)</th>
<th>No. of twins</th>
<th>Multiple birth rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 foll.</td>
<td>277</td>
<td>47</td>
<td>17.09</td>
<td>39</td>
<td>14.18</td>
<td>2</td>
<td>5.13</td>
</tr>
<tr>
<td>2 foll.</td>
<td>77</td>
<td>20</td>
<td>25.97</td>
<td>17</td>
<td>22.08</td>
<td>2</td>
<td>11.76</td>
</tr>
<tr>
<td>3 foll.</td>
<td>32</td>
<td>11</td>
<td>34.38</td>
<td>10</td>
<td>31.25</td>
<td>2</td>
<td>20.00</td>
</tr>
<tr>
<td>$&gt;3$ foll.</td>
<td>19</td>
<td>5</td>
<td>26.32</td>
<td>4</td>
<td>21.05</td>
<td>2</td>
<td>50.00</td>
</tr>
<tr>
<td>Overall</td>
<td>405</td>
<td>83</td>
<td>20.60</td>
<td>70</td>
<td>17.37</td>
<td>8</td>
<td>11.4</td>
</tr>
</tbody>
</table>
FSH Administration Regimen

**Chronic Low Dose (CLD):** S. Franks et al.

<table>
<thead>
<tr>
<th>Days</th>
<th>7 IU</th>
<th>7 IU</th>
<th>112.5 IU</th>
<th>150 IU</th>
</tr>
</thead>
</table>

**Step Down (SD):** B. Fauser et al.

- 150 IU
- 112.5 IU
- 75 IU

Foll. $\geq 10$ mm

**Sequential (SE):** J.N. Hugues et al.

<table>
<thead>
<tr>
<th>Days</th>
<th>75 IU</th>
<th>112.5 IU</th>
<th>150 IU</th>
<th>75 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Foll. $\geq 14$ mm
How to minimize the risk of multiple birth

Replacing hCG with rec-LH or GnRH-a
Spontaneous LH surge

Endogenous surge triggered by GnRH-a

Periovulatory phase (hrs)

hCG
The use of rec-LH to facilitate monofollicular development

European r-hLH Research Group
To assess the efficacy of two doses of r-hLH

225 450

Given at the late follicular phase to FSH treated PCOS patients if ≥ 4 foll. 8-13 mm
17 PCOS patients enrolled

Placebo : 5 patients
r-hLH 225 IU/day : 4 patients
r-hLH 450 IU/day : 8 patients
PRIOR TO STUDY:

patients received FSH stimulation.
If met following criteria:

> 4 follicles with diameter $\geq 8$ mm and $\leq 13$ mm
Endometrium thickness $\geq 8$ mm

When at least one follicle of $\geq 18$ mm and $\leq 3$ follicles of $\geq 11$ mm $\Rightarrow$ hCG 5’000 IU
Mean total number of follicles at baseline (≥ 8-13 mm) and on day of hCG (≥ 14 mm)

Placebo
- ≥ 8-13 mm: 14
- >11: 5.6
- >14: 3.8

225 IU r-hLH
- ≥ 8-13 mm: 9.75
- >11: 2.25
- >14: 1.25

450 IU r-hLH
- ≥ 8-13 mm: 8.88
- >11: 3.75
- >14: 1.5
Summary

- This study supports the ‘hypothesis’: by adding high dose of LH during the late follicular phase, atresia of growing follicles can be induced.
Challenge of ART

Avoid multiple pregnancy without significantly lowering the overall pregnancy rate.
How to minimize the risk of multiple birth and still achieve a good pregnancy rate/started stimulation?

- Adjust the No. of embryos transferred depending on risk factors for multiple gestation.
- Age.
- Embryo quality
- No. of previous IVF cycles
- A good freezing program
Reason for transfer of one embryo

Women wish
Risk of OHSS
Diabetes Mellitus
Uterine malformations
Cervical incompetence

## Retrospective Study

<table>
<thead>
<tr>
<th></th>
<th>Selection of 1 Embryo available</th>
<th>1 Embryo available</th>
<th>2 Embryos available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Cycles</strong></td>
<td>74</td>
<td>94</td>
<td>742</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>34 (24-42)</td>
<td></td>
<td>34 (23-42)</td>
</tr>
<tr>
<td><strong>Preg. rate</strong></td>
<td>29.7%</td>
<td>20.2%</td>
<td>29.4%</td>
</tr>
<tr>
<td><strong>Twins</strong></td>
<td></td>
<td></td>
<td>23.9%</td>
</tr>
</tbody>
</table>
# Embryo development

## Pregnancy rate

<table>
<thead>
<tr>
<th>4-5 cells on day 2</th>
<th>2-3 cells on day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.8%</td>
<td>9.7%</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6-8 cells on day 3</th>
<th>45.5%</th>
</tr>
</thead>
</table>
# Embryo Grading - Pregnancy rate

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fragmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No Fragmentation</td>
</tr>
<tr>
<td>II</td>
<td>&lt;20% Fragmentation</td>
</tr>
<tr>
<td>III</td>
<td>&lt;50% Fragmentation</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;50% Fragmentation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade I-II</th>
<th>Grade III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.8% - 26.7%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

\[ P < 0.05 \]
<table>
<thead>
<tr>
<th>Age</th>
<th>Pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35</td>
<td>32.8%</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>18.8%</td>
</tr>
</tbody>
</table>
Best Pregnancy Rate with no Multiple Gestation

Age < 35

4 to 5 cells on day 2

Grade I or II

45.5%
Top quality embryo

4 or 5 blastomeres on day 2
7 blastomeres on day 3
Absence of multinucleated blastomeres
<20% fragments on day 2 or 3

Gerris et al. Hum Reprod. 1999
**Prospective randomized study**

<table>
<thead>
<tr>
<th></th>
<th>1 Trans.</th>
<th>2 Best.</th>
<th>2 Trans.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles</td>
<td>26</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>Ong. Preg.</td>
<td>10 (38%)</td>
<td>20 (74%)</td>
<td>22 (42%)</td>
</tr>
<tr>
<td>Mult. Preg.</td>
<td>1 (10%)</td>
<td>6 (30%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Impl. rate</td>
<td>11/26 (42%)</td>
<td>26/54 (48%)</td>
<td>33/106 (31%)</td>
</tr>
</tbody>
</table>

Gerris et al. Hum Reprod. 1999
Blastocyst transfer

Published data of 2 blastocysts indicate a clinical pregnancy rate of 87% and twin rate of 61%.

No studies of elective 1 blastocyst transfer have been performed.

Conclusion

Identify groups who will benefit from having one blastocyst only.

We have to adopt a strategy where we try to retrieve as many oocytes as possible, replace one blastocyst and freeze the others.
Physician obligations are:

- Do no harm.
- Assessing the balance between risk and benefit.
A major challenge for every physician is to balance the immediate gain of a pregnancy against the potential long term negative impact of multiple gestation.