AAB 2014
Annual Meeting and Educational Conference

International Perspective on IVF

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Professor, ACF, Stanford University
Associate Clinical Professor, University of California San Francisco
Disclosures

- **Industry**
  - Advanced Reproductive Care (ARC): Founder and CEO

- **Professional Organizations**
  - ASRM: Past President
  - FIGO: Chair, Reproductive Medicine Committee
  - ICMART: Int’l Committee Monitoring ART
  - IFFS: Executive Committee
  - WERF: President
  - WHO: Co-chair, Reproductive Committee

- **Funded Research Studies/Consultant**
  - Auxogyn
  - Bayer
  - LabCorp
ICMART is an NGO in official relations with WHO.

David Adamson: USA
Fernando Zegers: Chile
Elizabeth Sullivan: Australia
Karl Nygren: Sweden
Osamu Ishihara: Japan
Ragaa Mansour: Egypt
Jacques de Mouzon: France
Manish Banker: India
Silke Dyer: South Africa
The International Committee Monitoring Assisted Reproductive Technologies (ICMART)

- An independent, **international** non-profit organization
- Taken a **leading** role in
- Development, collection and dissemination of **worldwide data on ART**
- Provides information on **access, effectiveness and safety**
- To health professionals, health authorities and the public
Data Collection on Outcomes and Adverse Effects Helps

- **Patients** make informed decisions
- Medical Profession and Laboratory Professionals in providing optimal patient care
- **Public Health** Authorities developing health care delivery and reimbursement policies
- The **Public** in understanding ART better

www.icmartivf.org
Different Levels and Purposes of ART Data Collection

• **Individual centers**
  - Monitoring own procedures
  - Research
  - Information for patients
  - Basis for publication

• **National and regional registries**
  - Summarize total experience of all ART clinics

[www.icmartivf.org](http://www.icmartivf.org)
Different Levels and Purposes of ART Data Collection

• **International data collection programs**
  – Generally multicenter *epidemiologic* studies rather than a multinational registry program
  – International data collection and analysis for *research* studies primarily serves to identify rare but very important events

• **International registry**
  – Describe the worldwide use of ART
  – Access, effectiveness, safety
  – Identify *similarities, differences and trends*
Access to Reproductive Health Care

Millennium Development Goal 5b
“Universal access to reproductive health”

- Inter American Court of Human Rights 2012
  - Costa Rica’s ban of ART violates human rights and discriminates against poor
  - Reparations include access to ART through public health systems
  - Costa Rica government resisting
Data Collection Methodology

- National collection and analysis of clinic result summaries
  - Inexpensive and simple
  - Each center gives a yearly summary report
  - Disadvantage is that it is less informative

- Centralized data collection from all cycles started in all centers within one country
  - More difficult and expensive
  - Requires a uniform data system
  - Opportunities for research on multiple factors influencing selected outcomes of interest

www.icmartivf.org
ICMART World Reports on ART


www.icmartivf.org
• Zegers-Hochschild F, Adamson GD, Nygren KG, de Mouzon J, Ishihara O. Worldwide differences in access to assisted reproduction technology (ART) influence providers/consumers decisions on the number of embryos transferred, affecting the proportion of multiple births. Fertil Steril 2009; 92(3), S1: S80-S81
ICMART/WHO Glossary

- Developed in cooperation with the World Health Organization (WHO)
- Facilitates dissemination of ART data through a set of agreed-upon definitions
- Provides a conceptual framework for further international terminology and data development for ART
- Being revised 2014

NEW!! The ICMART Tool Box for ART Data Collection

The ICMART Tool Box for ART Data Collection is a package to facilitate the monitoring and data collection of ART cycles and outcomes.
Pending ICMART Publications

  - New data collection program
  - Directly online
  - Developed by ICMART with Uppsala University
ART World Report 2009

 Registers : Regional Organisations

EUROPE : ESHRE : Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Rep, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, Ukraine, UK

AUSTRALIA - NEW ZEALAND : Australia, New Zealand

LATIN AMERICA : Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru, Uruguay, Venezuela

NORTH AMERICA : Canada, USA

Middle-East : Egypt, Lebanon, Palestinian territory

 Registers : National Level :

Israel, Japan, Korea, South Africa

Individual clinics: Cameroon, Togo, Tunisia
<table>
<thead>
<tr>
<th>Region</th>
<th>Participating (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>4</td>
</tr>
<tr>
<td>America, Latin</td>
<td>11</td>
</tr>
<tr>
<td>America, North</td>
<td>2</td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
</tr>
<tr>
<td>Australia-NZ</td>
<td>2</td>
</tr>
<tr>
<td>Europe</td>
<td>34</td>
</tr>
<tr>
<td>Middle East</td>
<td>3</td>
</tr>
<tr>
<td>Israel</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59</strong></td>
</tr>
</tbody>
</table>
Access to ART
Number of Countries and Cycles Reported to ICMART

2008: 1,059,000 cycles
+ 21,000
2% increase
ARS Question 1: Which country performs the most IVF cycles in the world?

1. United States
2. United Kingdom
3. China
4. Japan
5. Unknown
### Main Contributors 2009 (> 40,000 cycles)

<table>
<thead>
<tr>
<th>Country</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>211,942</td>
</tr>
<tr>
<td>USA</td>
<td>135,405</td>
</tr>
<tr>
<td>France</td>
<td>80,919</td>
</tr>
<tr>
<td>Germany</td>
<td>68,487</td>
</tr>
<tr>
<td>Australia</td>
<td>63,041</td>
</tr>
<tr>
<td>UK</td>
<td>54,069</td>
</tr>
<tr>
<td>Spain</td>
<td>53,717</td>
</tr>
<tr>
<td>Italy</td>
<td>48,930</td>
</tr>
<tr>
<td>Russia</td>
<td>40,834</td>
</tr>
</tbody>
</table>

**Total**: 1,080,479

70% of the total contributions come from Japan, USA, and France.
ICMART World Coverage 2009

- **59 countries** (25 in 1991, 57 in 2008)
  - Almost all Europe, Americas, Australia-NZ
  - Missing countries: Africa, Middle-East, Asia
  - But 4 new African countries (Cameroon, South Africa, Tunisia, Togo): hope for future?

- **2,237 clinics**: approximately 80% of clinics
  - 27 countries with full coverage

- Estimate of the overall coverage
  - 63% - 70% of World activity
In 2004, decrease of 40,000 German cycles because of law changing IVF funding.
Regional Contribution of ART Cycles to the World Report 2009

N = 1,080,479

Middle East  4%
Latin America  3%
Australia & New Zealand  6%

Corresponds to aspiration cycles in IVF, ICSI & GIFT and transfer cycles in FET & OD.
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$34,200 – 50,856</td>
<td>France (11.0%)</td>
<td>84.0</td>
<td>16.0</td>
<td>1062</td>
</tr>
<tr>
<td></td>
<td>Denmark (10.8)</td>
<td>84.0</td>
<td>16.0</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>Sweden (9.2%)</td>
<td>81.2</td>
<td>18.8</td>
<td>1341</td>
</tr>
<tr>
<td></td>
<td>UK (8.2%)</td>
<td>87.4</td>
<td>12.6</td>
<td>623</td>
</tr>
<tr>
<td></td>
<td>Australia (8.7%)</td>
<td>67.2</td>
<td>32.8</td>
<td>1739</td>
</tr>
<tr>
<td></td>
<td>Japan (8.1%)</td>
<td>82.2</td>
<td>17.8</td>
<td>890</td>
</tr>
<tr>
<td>$43,000</td>
<td>USA (15.2%)</td>
<td>45.8</td>
<td>54.2</td>
<td>357</td>
</tr>
<tr>
<td>$3,350 – 8,894</td>
<td>Argentina (10.1%)</td>
<td>45.5</td>
<td>54.5</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>Brazil (7.5%)</td>
<td>47.7</td>
<td>52.1</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mexico (6.6%)</td>
<td>43.3</td>
<td>56.7</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Chile (5.3%)</td>
<td>47.3</td>
<td>52.7</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Peru (4.4%)</td>
<td>42.9</td>
<td>57.1</td>
<td>26</td>
</tr>
<tr>
<td>$1,512</td>
<td>Egypt (6.3%)</td>
<td>40.7</td>
<td>59.3</td>
<td>114</td>
</tr>
<tr>
<td>$20,863</td>
<td>Israel (8.0%)</td>
<td>65.3</td>
<td>34.7</td>
<td>3541</td>
</tr>
</tbody>
</table>
### Access to ART (2004) According to Demographic Factors & Fertility Rate

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>France</td>
<td>39.7</td>
<td>1.88</td>
<td>0.6</td>
<td>1062</td>
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<tr>
<td>Sweden</td>
<td>41.5</td>
<td>1.67</td>
<td>0.4</td>
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<tr>
<td>Denmark</td>
<td>40.2</td>
<td>1.76</td>
<td>0.2</td>
<td>2008</td>
</tr>
<tr>
<td>UK</td>
<td>39.8</td>
<td>1.70</td>
<td>0.4</td>
<td>623</td>
</tr>
<tr>
<td>Japan</td>
<td>44.3</td>
<td>1.29</td>
<td>0.1</td>
<td>890</td>
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<tr>
<td>USA</td>
<td>37.4</td>
<td>2.04</td>
<td>1.0</td>
<td>357</td>
</tr>
<tr>
<td>Argentina</td>
<td>29.9</td>
<td>2.35</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td>Brazil</td>
<td>27.7</td>
<td>2.35</td>
<td>1.3</td>
<td>56</td>
</tr>
<tr>
<td>Chile</td>
<td>30.8</td>
<td>2.00</td>
<td>1.0</td>
<td>73</td>
</tr>
<tr>
<td>Mexico</td>
<td>25.5</td>
<td>2.40</td>
<td>1.0</td>
<td>34</td>
</tr>
<tr>
<td>Peru</td>
<td>24.8</td>
<td>2.70</td>
<td>1.1</td>
<td>26</td>
</tr>
<tr>
<td>Egypt</td>
<td>23.8</td>
<td>2.91</td>
<td>1.8</td>
<td>114</td>
</tr>
<tr>
<td>Israel</td>
<td>29.0</td>
<td>3.17</td>
<td>1.7</td>
<td>3541</td>
</tr>
</tbody>
</table>

Zegers. ICMART. 2012.

US Census Bureau/International Data Base (IDB) / UN Statistics Division / ICMART
Total ART Treatment Costs as a Percentage of Total Healthcare Expenditure (USD 2006)

Note:
Total healthcare expenditure was sourced from The World Bank, World Development Indicators database (24).

Profile of Procedures and Patients
Global Results
2009

- 1,080,479 initiated cycles, 195,873 deliveries

- 731,703 aspirations
  - 200,713 IVF*
  - 432,545 ICSI**
  - 334 GIFT

- 242,519 Thaws
- 10,695 PGD/PGS
- 44,671 Egg donations

Delivery Rate
- 22.6%
- 18.7%
- 9.5%
- 33.1%

*Not counted: Japan IVF aspirations for freezing only 22,924; Israel retrieval sum of IVF & ICSI 21,862; Australia 35,875; NZ 2,895.
**Not counted: Japan: ICSI aspirations for freezing only 32,424.
Trends in Procedure Distribution: Retrievals, FET, Egg Donation

[Bar chart showing trends from 1991 to 2008 for ED, Thawings, and Fresh asp]
Trends in Procedure Distribution: IVF vs. ICSI per Aspiration
Procedure Distribution According to Region 2009

*Excluding Israel*
Women’s Age ≥ 40 yrs

%
Women Age ≥40 By Region 2006 (IVF + ICSI)
ARS Question 2: The United States has the highest IVF pregnancy rates in the world.

- True
- False
Effectiveness of ART
ART 2007 Global Cumulative (Fresh + Frozen) Delivery Rate Per Retrieval

<table>
<thead>
<tr>
<th>Year</th>
<th>Cumulative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>23.9</td>
</tr>
<tr>
<td>2006</td>
<td>25.2</td>
</tr>
<tr>
<td>2007</td>
<td>25.8</td>
</tr>
</tbody>
</table>
Delivery Rates per Retrieval According to Region

IVF & ICSI 2009

%-

N Amer: 34.4%
S Amer: 23.9%
Mid East: 21.4%
Eur: 19.2%
ANZ: 19.9%
Asia: 11.2%

Yellow bars represent Fresh cycles, and pink bars represent Cumulative.
Numbers of Autologous ART Treatment Cycles, Procedures and Outcomes in 2003

Cumulative/ Overall embryo cycles

<table>
<thead>
<tr>
<th>Variable</th>
<th>United States</th>
<th>Canada</th>
<th>United Kingdom</th>
<th>Scandinavia</th>
<th>Japan</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative delivery rate with at least one live birth (%)</td>
<td>37.7</td>
<td>31.6</td>
<td>28.5</td>
<td>26.3</td>
<td>20.2</td>
<td>28.7</td>
</tr>
<tr>
<td>Overall multiple birth delivery rate (%)</td>
<td>32.9</td>
<td>30.3</td>
<td>24.2</td>
<td>17.3</td>
<td>16.0</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Cost Per Live Birth in 2003 for Autologous ART Treatment Cycles

Safety of ART
Transfers of 1-2 Embryos per Region (%) 1998 vs. 2009
Delivery Rate (Fresh) and Twin Pregnancies per Region 1998 vs. 2009

Twins 2009: 20.4%
Triplet Pregnancies per Region
1998 vs. 2009

North America
Latin America
Europe
A-NZ
Asia
Middle-East

%
Results and Percentage of Transfers With ≥ 4 Embryos 2008

Relation between transfers ≥ 4 and:

- Delivery rate: $r = -0.30; \ p < 0.05$
- Twin rate: $r = 0.41; \ p < 0.01$
- Triplet rate: $r = 0.58; \ p < 0.001$
Cumulative Delivery Rate and Number of Embryos Transferred
Relationship Between Access to ART And Number of Embryos Transferred
Single Embryo Transfer (SET): The Swedish Experience IVF/ICSI 1997-2004

Ishihara. JSOG data
Number of Transferred Embryos (IVF&ICSI: 2007)

Ishihara. ESHRE, SART and JSOG data
No Reduction of PR/ET with Frozen-Thawed ET After the Transition to SET

Ishihara. JSOG data.
ARS Question 3: The biggest potential reduction in multiple births would result from fertility professionals:

1. Encouraging women to have babies at a younger age
2. Performing elective single embryo transfer on all women less than 40
3. Always limiting the number of embryos transferred to 2
4. Reducing the number of multiples resulting from controlled ovarian stimulation (COS)
5. None of the above
Multiple Births From IVF, COS, Natural United States 2006

SART. Personal Communication. 2009.
Conclusions
Conclusions

- **1,080,479 cycles** reported (+2.0%)
  - Estimate ~1.6 million worldwide
- **243,927 babies** born (-6.0%)
  - Estimate 400,000 Worldwide
- 67.1% ICSI (-2.0%);
- 20.3% women>40 (-0.4%)
- Mean number of transferred embryos: **1.97** (-0.11)
- **Delivery Rate per Aspiration**
  - 19.5 % (-1.3%)
  - 25.7% cumulative (+1.0%)
- **Wide differences** in availability, practice and results
Results: Global Estimated Prevalence of IVF Babies Among Reporting Countries 2012

Total Babies Born in USA and Europe

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Europe</td>
<td>262,897</td>
<td>303,974</td>
</tr>
<tr>
<td>Germany</td>
<td>Europe</td>
<td>270,145</td>
<td>315,210</td>
</tr>
<tr>
<td>Spain</td>
<td>Europe</td>
<td>155,544</td>
<td>243,236</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Europe</td>
<td>188,724</td>
<td>211,215</td>
</tr>
<tr>
<td>United States</td>
<td>North America</td>
<td>642,420</td>
<td>799,708</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>2012 Cumulative Live Birth Lower Boundary</th>
<th>2012 Cumulative Live Birth Upper Boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>1,776,874</td>
<td>2,216,220</td>
</tr>
<tr>
<td>North America</td>
<td>696,920</td>
<td>863,727</td>
</tr>
</tbody>
</table>
Cumulative Total Number of Babies Born Globally

- Since the birth of Louise Brown on July 25, 1978, at least 3.3 million and as many as 4.1 million babies have been born after IVF in countries reporting to ICMART.

- It is likely that 1-2 million additional babies were born during the same period in countries not reporting to ICMART, and in particular in China.

- The number of babies born after IVF has increased rapidly in most parts of the world, with the possible exception of Africa, the Middle East and South East Asia, although this observation is potentially driven by lack of ART registration and reporting.

- ART has established itself as an important technology for fulfilling the dreams of millions of families worldwide.
Conclusions

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

• **Effectiveness**
  – *Highest in USA*, stabilized at
    • Fresh LBR/Retrieval ~ 35%
    • FET LBR/Transfer ~ 30%
    • Donor Egg LBR/Transfer ~ 55%
  – *? Impact blastocyst and PGS/other screening*

• **Safety**
  – Much improved, BUT
  – Triplet rate needs further reduction by DET
  – *Twin rate reduction requires SET*
New ICMART Challenges

- Increase coverage
  - Geographically
    - China: Ministry of Health
    - Asia: Reps, Organizations
    - Africa: Organizations, ICMART role
  - Professional organizations
    - ICMART is an NGO with WHO
    - ASPIRE, ESHRE, ASRM
- Funding
  - Professional organizations
  - Industry
- Data Collection
  - Technology: Blastocysts/screened embryos
  - Protocols: Cryopreservation all embryos
  - Cross border reproductive care
Thank You!