Assisted Reproductive Technologies and Perinatal Morbidity: Interrogating the Association

Kurt Barnhart, M.D., MSCE.
William Shippen Jr Professor of Obstetrics and Gynecology and Epidemiology
Perelman School of Medicine
University of Pennsylvania

No disclosures

Objectives:
1) To understand the risks of children born with assisted conception
2) To assess the quality of evidence to support risk
3) To be familiar with new studies assessing behavior and development of children born after ART

Background

- First successful IVF in the UK in 1978
- 200,000 cycles in US in 2008 alone
  - 61,00 live birth deliveries
- Dramatic increase in success rates
- Demand for IVF continues to rise

www.cdc.gov/ART/2008
IVF Health Risk

- 563,000 Hits in Google in 0.2 seconds

- Do IVF kids face more health risks?
  - MSNBC July 2003

- IVF health risks pinpointed
  - Bioed on line 2004

- More Health Risks Found in IVF Babies - Scientist Suggests IVF Children Should be Monitored into Adulthood
  - LifeSiteNews.com 2007

- Picture Emerging on Genetic Risks of IVF
  - New York Times 2009

Is it fair to lump all “infertility treatments” together?
- Does the public know the difference?
- Do other medical disciplines know the difference?
- Do “regulators” know the difference?

Diagnosis in Patients Undergoing IVF in the United States

*Total does not equal 100% due to rounding.

2002 SART/CDC Report (Published December 2005)
What is ART

- Assisted Reproductive Technology
  - Intracervical Insemination
  - Intrauterine Insemination
  - Ovulation induction
  - Superovulation
  - IVF

IVF-ET

- Ovarian stimulation
- Egg retrieval
- Laboratory
  - Environment
  - Culture media
  - Atmosphere
  - Technique(s)
- Embryo transfer
- Luteal support
- Environment at implantation

Micromanipulation of the Embryo

- ICSI
- Assisted Hatching
- Blastomere biopsy
  - Preimplantation diagnosis
- Gamete freezing
Oocyte retrieval
What are the Risks?

- Perinatal outcomes
- Maternal outcomes
- Congenital abnormalities
- Genetic abnormality
- Developmental delay
  - Autism

- What is relative risk, absolute risk
- What should we do about it?
**Preterm Delivery**

Jackson et al., Perinatal Outcomes in Singletons Following In Vitro Fertilization: A Meta Analysis

*Obstet Gynecol* 103:551-563, 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Preterm</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>250/327</td>
<td>26/307</td>
<td>1.22 (1.05, 1.42)</td>
<td>0.011</td>
</tr>
<tr>
<td>IVF</td>
<td>28/289</td>
<td>1.07 (0.87, 1.32)</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

**Low Birth Weight**

Jackson et al Obstet Gynecol 103:531-563, 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Low Birth Weight</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>250/327</td>
<td>26/307</td>
<td>1.22 (1.05, 1.42)</td>
<td>0.011</td>
</tr>
<tr>
<td>IVF</td>
<td>28/289</td>
<td>1.07 (0.87, 1.32)</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

**Small for Gestational Age**

Jackson et al Obstet Gynecol 103:531-563, 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Small for Gestational Age</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>250/327</td>
<td>26/307</td>
<td>1.22 (1.05, 1.42)</td>
<td>0.011</td>
</tr>
<tr>
<td>IVF</td>
<td>28/289</td>
<td>1.07 (0.87, 1.32)</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>
Perinatal Mortality
Jackson et al Obstet Gynecol 103:551-563, 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>IVF</th>
<th>Non-IVF</th>
<th>Significance</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected</td>
<td>124/118</td>
<td>124/118</td>
<td>N/A</td>
<td>1.0 (0.75, 1.34)</td>
</tr>
<tr>
<td>Matched select</td>
<td>69/69</td>
<td>69/69</td>
<td>N/A</td>
<td>1.0 (0.75, 1.34)</td>
</tr>
<tr>
<td>Randomization similarity</td>
<td>69/69</td>
<td>69/69</td>
<td>N/A</td>
<td>1.0 (0.75, 1.34)</td>
</tr>
<tr>
<td>Allocation</td>
<td>124/118</td>
<td>124/118</td>
<td>N/A</td>
<td>1.0 (0.75, 1.34)</td>
</tr>
<tr>
<td>Randomization</td>
<td>69/69</td>
<td>69/69</td>
<td>N/A</td>
<td>1.0 (0.75, 1.34)</td>
</tr>
<tr>
<td>Allocation</td>
<td>124/118</td>
<td>124/118</td>
<td>N/A</td>
<td>1.0 (0.75, 1.34)</td>
</tr>
</tbody>
</table>

Secondary Outcomes
Jackson et al Obstet Gynecol 103:551-563, 2004

FASTER Trial
• ART (OI 1200, IVF 550) vs unassisted conception (36,000)
  – Preterm labor 5.2% v 6.9%
  – Low birth weight 5.1% v 5.9%
  – Growth restriction 1.1% v 0.9%
  – No association aneuploidy or other fetal anomalies

Conflict with other studies?
• Prospective nature removed confounding?
• IVF group small in comparison to prior studies?
Shevell et al, for the FASTER Research Consortium
Obstet Gynecol 106:1039, 2005
Preterm Delivery and IVF

Singletons

- Risk of delivery <37 weeks is 70-100% increased with IVF
- Vast majority (90%) are uncomplicated
- Baseline rate in unassisted conceptions has been low (5-8%)
- Limited data to regarding clinical implications of PTD or SGA.
Assisted Reproductive Technologies and Perinatal Morbidity

- Issues of importance
  - Etiology
    - Is the association true (Bias? Confounding?)
    - If true, is it due to the underlying condition?
    - If true, is it due to procedures/methods of ART?
  - How can risk be reduced?
  - Goal is identify a modifiable practice, and change it, not eliminate ART

Is there perinatal morbidity associated with infertility?

Prolonged Time to Pregnancy is Associated with a Greater Risk of Adverse Outcomes

Kuopio University Hospital (Finland) between 1989 and 2007 (n=17,114)
Prolonged time to pregnancy is associated with a greater risk of adverse outcomes

"We conclude that subfertility, irrespective of treatment, is clearly associated with the risk of an adverse outcome during pregnancy. The common etiologic mechanisms associated with both subfertility and pregnancy complications need further investigation."


Adverse Obstetric and Perinatal Outcomes in Subfertile Women Conceiving Without ART

ART records linked to national birth registry in Australia 1999 - 2004

Health of Children Born After Ovulation Induction

"The OI children had poorer perinatal health and more episodes of long hospitalization than the control children."

"Either OI treatment or the reasons for the treatment increase the risk of health problems in early childhood."

"We conclude that subfertility, irrespective of treatment, is clearly associated with the risk of an adverse outcome during pregnancy. The common etiologic mechanisms associated with both subfertility and pregnancy complications need further investigation."


Adverse Obstetric and Perinatal Outcomes in Subfertile Women Conceiving Without ART

ART records linked to national birth registry in Australia 1999 - 2004

Health of Children Born After Ovulation Induction

"The OI children had poorer perinatal health and more episodes of long hospitalization than the control children."

"Either OI treatment or the reasons for the treatment increase the risk of health problems in early childhood."

"We conclude that subfertility, irrespective of treatment, is clearly associated with the risk of an adverse outcome during pregnancy. The common etiologic mechanisms associated with both subfertility and pregnancy complications need further investigation."


Adverse Obstetric and Perinatal Outcomes in Subfertile Women Conceiving Without ART

ART records linked to national birth registry in Australia 1999 - 2004

Health of Children Born After Ovulation Induction

"The OI children had poorer perinatal health and more episodes of long hospitalization than the control children."

"Either OI treatment or the reasons for the treatment increase the risk of health problems in early childhood."

"We conclude that subfertility, irrespective of treatment, is clearly associated with the risk of an adverse outcome during pregnancy. The common etiologic mechanisms associated with both subfertility and pregnancy complications need further investigation."

What about IVF?
- Can one isolate the aspects of IVF that may be associated with morbidity
- IVF is a complex set of procedures/techniques:
  - Usual suspects:
    - ICSI
    - Extended culture
    - Poor embryo quality?

### Factor of IVF Associated with Perinatal Morbidity: Case/Control

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of medication</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>0.65 (0.13-3.27)</td>
<td></td>
</tr>
<tr>
<td>ICSI</td>
<td>0.25</td>
<td>1.40 (0.79-2.50)</td>
</tr>
<tr>
<td>AH</td>
<td>0.39</td>
<td>1.32 (0.70-2.48)</td>
</tr>
<tr>
<td>Embryo grade (best)</td>
<td>0.14</td>
<td>0.81 (0.60-1.07)</td>
</tr>
<tr>
<td>Embryo stage (best)</td>
<td>0.87</td>
<td>0.98 (0.79-1.22)</td>
</tr>
</tbody>
</table>

Chung and Barnhart et al, Fertil Steril, 2006

### Factor of IVF Associated with Perinatal Morbidity: Case/Control

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple gestation</td>
<td>&lt;0.0001*</td>
<td>11.94 (7.29-19.54)</td>
</tr>
<tr>
<td>Endometrial thickness on day of hCG</td>
<td>0.028*</td>
<td>0.89 (0.80-0.99)</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>0.026*</td>
<td>2.04 (1.09-3.83)</td>
</tr>
<tr>
<td>10-12 mm</td>
<td>0.568</td>
<td>1.19 (0.65-2.17)</td>
</tr>
<tr>
<td>&gt;12 mm</td>
<td>Reference group</td>
<td></td>
</tr>
</tbody>
</table>

Chung and Barnhart et al, Fertil Steril, 2006
To determine the association of adverse perinatal outcomes in patients undergoing frozen embryo transfer as compared to fresh embryo transfer in a cohort of patients at Penn Fertility Care.

Adverse Outcomes Associated with In-Vitro Fertilization: The Impact of the Intrauterine Environment in Fresh versus Frozen Embryo Transfer.

Suleena Kansal Kalra, MD, MSCE; Sarah J. Ratcliffe, PhD, Lauren Weissmann, MD; Clarisa R. Gracia, MD, MSCE, Christos Coutifaris, MD, PhD, Kurt T. Barnhart, MD, MSCE

Analysis of adverse outcomes in fresh versus frozen embryo transfers and twin gestation

Fresh vs Frozen/Thawed as a Model for Endocrine Milieu at Transfer

Ovarian Stimulation and Low Birth Weight in Newborns Conceived Through In Vitro Fertilization

Perinatal mortality after in vitro fertilization is lower with frozen embryo transfer

Suleena Kalra, MD, MSCE, Sarah J. Ratcliffe, PhD, Christos Coutifaris, MD, PhD, Thomas Molinaro, MD, MSCE, Kurt T. Barnhart, MD, MSCE

SART database 2004 – 2006

68,194 pregnancies (Fresh ET: n=44,721; FET: n=23,473)

Three analyses: 1)All good prognosis patients 2)Those with both a fresh and frozen transfer, 3) Those with egg donation
### Preterm Delivery in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer

<table>
<thead>
<tr>
<th>Preterm Delivery</th>
<th>Fresh ET</th>
<th>Frozen ET</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullterm</td>
<td>81.1%</td>
<td>81.7%</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>(32 - 37 wks)</td>
<td>16.7%</td>
<td>16.2%</td>
<td>1.05 (0.93-1.18)</td>
<td>p=0.50</td>
</tr>
<tr>
<td>Very Preterm</td>
<td>2.5%</td>
<td>2.7%</td>
<td>1.08 (0.72-1.64)</td>
<td>p=0.60</td>
</tr>
</tbody>
</table>

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, and implantation rate.

### Low Birthweight in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer

<table>
<thead>
<tr>
<th>Low Birthweight (&lt;2500 g)</th>
<th>Fresh ET</th>
<th>Frozen ET</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall LBW</td>
<td>10.0%</td>
<td>7.2%</td>
<td>1.44 (1.33-1.57)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Term LBW (&gt;37 weeks, &lt;2500 g)</td>
<td>2.5%</td>
<td>1.2%</td>
<td>2.10 (1.59-2.78)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Preterm LBW (&lt;37 weeks, &lt;2500 g)</td>
<td>34.1%</td>
<td>23.8%</td>
<td>1.46 (1.25-1.71)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, and implantation rate.

### Preterm Delivery in Twin Live Births Following Fresh vs. Frozen Embryo Transfer

<table>
<thead>
<tr>
<th>Preterm Delivery</th>
<th>Fresh ET</th>
<th>Frozen ET</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullterm</td>
<td>23.3%</td>
<td>23.7%</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>(32 - 37 wks)</td>
<td>62.4%</td>
<td>63.1%</td>
<td>1.00 (0.87-1.16)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Very Preterm</td>
<td>15.7%</td>
<td>13.8%</td>
<td>1.09 (0.80-1.49)</td>
<td>p=0.60</td>
</tr>
</tbody>
</table>

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, and implantation rate.

**For adjusted analysis, preterm and very preterm delivery combined**

Kalra et al: OBGYN 2011
Low Birthweight in Twin Live Births Following Fresh vs. Frozen Embryo Transfer

<table>
<thead>
<tr>
<th></th>
<th>Fresh ET</th>
<th>Frozen ET</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall LBW ((&lt;2500 , \mathrm{g}))</td>
<td>69.9% (7,924/11,339)</td>
<td>61.5% (1,912/3,111)</td>
<td>1.46 (1.34-1.58)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.36 (1.22-1.52)</td>
<td>p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term LBW ((&gt;37 , \mathrm{wk}, ,&lt;2500 , \mathrm{g}))</td>
<td>32.7% (873/2,670)</td>
<td>26.1% (192/737)</td>
<td>1.38 (1.15-1.66)</td>
<td>p = 0.001</td>
</tr>
<tr>
<td></td>
<td>1.73 (1.31-2.29)</td>
<td>p=0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm LBW ((&lt;37 , \mathrm{wk}, ,&lt;2500 , \mathrm{g}))</td>
<td>77.6% (5,536/7,132)</td>
<td>67.2% (1,324/1,971)</td>
<td>1.69 (1.52-1.89)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.59 (1.38-1.84)</td>
<td>p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, and implantation rate

Preterm Delivery and Low Birthweight in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer in Same Patient at Different Times: Paired Cycle Analysis

<table>
<thead>
<tr>
<th></th>
<th>Fresh ET</th>
<th>Frozen ET</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullterm</td>
<td>81.1% (550/678)</td>
<td>82.2% (555/675)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Preterm Delivery (32 - 37 wks)</td>
<td>14.8% (101/678)</td>
<td>15.9% (107/675)</td>
<td>1.03 (0.73-1.46)</td>
<td>p=0.49</td>
</tr>
<tr>
<td></td>
<td>1.86 (0.73-4.71)</td>
<td>p=0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Preterm ((&lt;32 , \mathrm{wks}))</td>
<td>4.0% (27/678)</td>
<td>1.9% (13/675)</td>
<td>2.44 (1.14-5.20)</td>
<td>p&lt;0.02</td>
</tr>
</tbody>
</table>

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, and implantation rate

Preterm Delivery and Low Birthweight in Singleton Live Births Following Fresh vs. Frozen Embryo Transfer in Donor Recipients

<table>
<thead>
<tr>
<th></th>
<th>Fresh ET</th>
<th>Frozen ET</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullterm</td>
<td>76.6% (4,328/5,648)</td>
<td>75.7% (2,361/3,120)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Preterm Delivery (32 - 37 wks)</td>
<td>19.3% (1,091/5,648)</td>
<td>20.7% (646/3,120)</td>
<td>0.93 (0.83-1.03)</td>
<td>p = 0.16</td>
</tr>
<tr>
<td></td>
<td>0.96 (0.84-1.09)</td>
<td>p=0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Preterm ((&lt;32 wks))</td>
<td>4.1% (229/5,648)</td>
<td>3.6% (113/3,120)</td>
<td>1.08 (0.86-1.36)</td>
<td>** p=0.48</td>
</tr>
<tr>
<td>Overall LBW ((&lt;2500 , \mathrm{g}))</td>
<td>11.5% (644/5,595)</td>
<td>11.3% (346/3,072)</td>
<td>1.03 (0.90-1.18)</td>
<td>p=0.65</td>
</tr>
<tr>
<td></td>
<td>0.99 (0.82-1.20)</td>
<td>p=0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term LBW ((&gt;37 , \mathrm{wk}, &lt;2500 , \mathrm{g}))</td>
<td>2.4% (93/4,286)</td>
<td>1.7% (39/2,325)</td>
<td>1.30 (0.89-1.89)</td>
<td>p=0.17</td>
</tr>
<tr>
<td></td>
<td>1.41 (0.82-2.42)</td>
<td>p=0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm LBW ((&lt;37 , \mathrm{wk}, &lt;2500 , \mathrm{g}))</td>
<td>32.7% (352/1,078)</td>
<td>33.1% (211/638)</td>
<td>0.98 (0.80-1.21)</td>
<td>p=0.87</td>
</tr>
<tr>
<td></td>
<td>0.94 (0.71-1.24)</td>
<td>p=0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for reporting year, patient age, parity, infertility diagnosis, number of embryos transferred, number of prior ART cycles, prior miscarriage, reduction in fetal heart, multiple pregnancy, and implantation rate

** For adjusted analysis, preterm and very preterm delivery combined

Kalra et al: OBGYN 2011
Summary

In large database isolating on aspect of IVF

Risk of Preterm labor minimal

Risk of low birthweight apparent in:
  • Term and preterm singletons
  • Term and preterm twins

Risk is Higher in the same women who conceives with both

Risk is not apparent in women who use donor egg, where
Preparation of the endometrium is the same in fresh and Transfer.

Placenta an issue?

What about other (modifiable) aspects of IVF?

Extended Embryo Culture?
Preterm Delivery and Low Birthweight in Live Births Following Cleavage Stage versus Blastocyst Embryo Transfer

Unpublished data

Association of Adverse Perinatal Outcome and Extended Embryo Culture in Sub-Populations of Singleton Births

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Extended Culture</th>
<th>Blastocyst Culture</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Delivery (PTD)</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>1.30 (1.26 – 2.35)</td>
</tr>
<tr>
<td>Low Birth Weight (LBW)</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>7.31 (7.10-7.53)</td>
</tr>
</tbody>
</table>

Blastocyst transfer RR for twins: RR 1.30 (1.26 – 2.35)

If twins: PTD; RR 4.18 (4.10-4.28), p<0.001
LBW; RR 7.31 (7.10-7.53), p<0.001

Therefore Blast transfer increase morbidity in TWO ways

Unpublished data

“California octuplets case dismays fertility experts”

- Suleman said her fertility specialist told her about risks for the children. But she did not want to have only one or two embryos implanted. “Of course not, I wanted them all transferred.”
**Multiple Births**

*U.S. National Birth Statistics*

![Graph showing multiple births over time](image)

CDC. National Vital Statistics Reports, 56(6), Dec 5, 2007

---

**What do we know about children beyond the perinatal Period?**

---

**Childhood Development**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowen, Lancet 1998</td>
<td>89 ICSI, 84 IVF and 80 conceived without medical assistance in a prospective cohort study in Australia</td>
<td>17% of ICSI children experienced developmental delay vs 2% and 1% in IVF &amp; unassisted.</td>
</tr>
<tr>
<td>Stromberg, Lancet 2002</td>
<td>Swedish, Population based retrospective matched cohort of 5680 IVF conceived children and 11360 naturally conceived infants</td>
<td>2.0 (0.7-5.4)</td>
</tr>
</tbody>
</table>

Systematic review in Human Repro update: 1) only 23 of 115 good quality, 2) Cannot conclude negative association, 3) Need to study greater number of older kids.
Altered behavior: Is there a link?

- One study noted prevalence of Autism spectrum disorder to be 3.4% (instead of 1.5%) (Bonduelle Hum Reprod. 2005 Feb; 20(2):413-9)
- Animal data?
  - Mice derived from extended culture
    - 1) alteration in anxiety (open quadrant maze, elevated zero maze)
    - 2) impaired spatial memory (water maze, ability to find platform)
  - This data was quoted in NY Times


Maternal Report of Diagnoses and Interventions

<table>
<thead>
<tr>
<th>Maternal Report of</th>
<th>Unassisted</th>
<th>IVF</th>
<th>Relative Risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>early intervention services</td>
<td>8.4%</td>
<td>12.6%</td>
<td>1.5 (0.7-3.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>special education use</td>
<td>1.9%</td>
<td>4.0%</td>
<td>1.6 (0.8-3.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>developmental delay</td>
<td>2.9%</td>
<td>4.2%</td>
<td>1.4 (0.3-6.3)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Unpublished data

Abnormal CBCL Scores

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Unassisted</th>
<th>IVF</th>
<th>p value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite (any abnormal behavior)</td>
<td>10.2%</td>
<td>12.5%</td>
<td>0.9</td>
<td>1.03 (0.4, 2.46)</td>
</tr>
<tr>
<td>Adjusted to maternal education, paternal age &amp; education</td>
<td>0.8</td>
<td>1.15 (0.3, 3.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral Domain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.7%</td>
<td>5.0%</td>
<td>0.3</td>
<td>0.46 (0.06, 3.42)</td>
</tr>
<tr>
<td>Somatic</td>
<td>4.2%</td>
<td>5.8%</td>
<td>1.0</td>
<td>1.07 (0.77, 1.48)</td>
</tr>
<tr>
<td>Attention</td>
<td>0.8%</td>
<td>1.3%</td>
<td>0.6</td>
<td>2.38 (0.26, 24.7)</td>
</tr>
<tr>
<td>Aggressive</td>
<td>0.3%</td>
<td>1.9%</td>
<td>0.6</td>
<td>2.55 (0.19, 31.3)</td>
</tr>
<tr>
<td>Emotional</td>
<td>2.0%</td>
<td>0.0%</td>
<td>0.5</td>
<td>*</td>
</tr>
<tr>
<td>Depressive</td>
<td>4.8%</td>
<td>1.0%</td>
<td>1.0</td>
<td>1.07 (0.3, 3.9)</td>
</tr>
</tbody>
</table>

*Unpublished data

Molinaro et al., Parental Report of Childhood Behavioral Disorders in Unassisted and In Vitro Fertilization Conceived Offspring With and Without IVF.
### Preliminary Results Full Dataset

#### Unadjusted Analysis

<table>
<thead>
<tr>
<th>Childhood Behavioral Diagnosis</th>
<th>+</th>
<th>-</th>
<th>TOTAL</th>
<th>Risk (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>infertility diagnosis, drugs, or procedure</td>
<td>606</td>
<td>29,861</td>
<td>30,467</td>
<td>1.98</td>
<td>1.13 (1.04, 1.23)</td>
</tr>
<tr>
<td>-</td>
<td>4,396</td>
<td>245,028</td>
<td>249,424</td>
<td>1.76</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>4,992</td>
<td>274,889</td>
<td></td>
<td>1.92</td>
<td>1.13 (1.05, 1.23)</td>
</tr>
</tbody>
</table>

Unpublished data

---

### Summary of What We Know

- **Short term consequences of ART are apparent**
  - It is clear that there is increased morbidity for children conceived with IVF:
    - “We” underestimate the complications that happen after we transfer care
    - Less than 50% of those who conceive with IVF have a full term infant without any complications
- **Disease process appears to be altered**
  - Low birth weight noted even when not premature
  - The presentation and outcome of women with preclampsia is altered.
- **Risk of congenital and chromosomal anomalies is associated with ICSI**

---

### Summary of What We Do Not Know

- **What are the clinical implications of the short term outcomes?**
- **Long term implications are unclear**
- **Do not know what about IVF confers risk**
  - Does ART result in abnormal placentation? OR Are factors associated abnormal implantation also associated with infertility (and need for IVF)?
- **Why does FET reduce morbidity?**
- **How does extended culture increase morbidity?**
**Action Plan**

- The subspecialty of REI needs to take the lead in addressing these issues
- Minimizing multiple pregnancy foremost goal
- Need to change the informed consent process
- Clear research priority
  - Basic science link should be included
  - What part of ART is associated with adverse outcome?
- Goal should be to identify modifiable treatment practices to reduce adverse outcome

**What We Cannot Do**

- Underestimate the magnitude of this issue in the eyes of the public
- “Blame it on the disease (or the patient)”
- Let another discipline (or the government) dictate standard of care
- Use unproven technology without careful consideration and full disclosure
- Dismiss the risk to our patients

**Conclusion**

- ART has allowed us to enter a Brave New World
- Practicing ART is a privilege, but also carries responsibility
- As scientists and physicians it is our responsibility to provide safe care
- The risks associated with ART are rare but cannot be minimized
- The evidence is still evolving. So let's........
  - Not to throw the baby out with the bathwater