TRA: impacte en la salud fetal

Eduard Gratacós

BCNatal – Centre de Medicina Maternofetal i Neonatologia de Barcelona
Fetal I+D - Fetal and Perinatal Research Center
Hospital Clínic i Hospital Sant Joan de Déu - Universitat de Barcelona
gratacos@fetalmedicinebarcelona.org  www.fetalmedicinebarcelona.org
THE PROCESS OF REPRODUCTION

SPONTANEOUS SUCCESS RATE
Reproduction
Pregnancy
Childhood
Rest of life

90%
90%
90%

“SUB-OPTIMAL” FERTILITY
PARENTAL AGE
MATERNAL HEALTH

Maternal-Fetal Recognition
Fetal development
Uterine quiescence

The main obstetrical syndromes
Fetal growth restriction
Preeclampsia
Preterm delivery
Fetal death
Fetal Defects

Pregnancy complications

Fetal programming
Fetal Defects

Pregnancy complications

Fetal programming
PREVALENCE OF CONGENITAL MALFORMATIONS

- Pregnancy: 4%
- Childhood: 4%
- Rest of life: 8%
ART and fetal malformations

Crude association

RR 1.15-1.40

Corrected for age, maternal factors and previous fertility

RR 1.00-1.05

Controls

ART

Hansen 2004
Rimm 2005
Mc Donald 2005
Kallen 2005,2010
Davies 2012

Controls

ART

Kallen 2005
Zhu 2006
Rimm 2011
Davies 2012
ART and multiple pregnancy

USA 2010: ART were 20% of all twins and 33% of all 3+ pregnancies

(1997-2012: 36% twins and 77% 3+)

conditionally

RR for monozygotic twins

<table>
<thead>
<tr>
<th>RR</th>
<th>Normal</th>
<th>ICSI</th>
<th>Bl. Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0%</td>
<td>0.5%</td>
<td>0.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>1.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR 2.25 | RR 4.25

Vatthela 2009

MMWR Surveill Summ 2013
Fetal Defects

Pregnancy complications

Fetal programming
ART and preterm birth: crude comparisons

<table>
<thead>
<tr>
<th>Author</th>
<th>IVF</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivennes et al., 1993 [20]</td>
<td>1/162</td>
<td>15/5,096</td>
</tr>
<tr>
<td>Westergaard et al., 1999 [27]</td>
<td>94/1,298</td>
<td>98/1,298</td>
</tr>
<tr>
<td>Bergh et al., 1999 [28]</td>
<td>85/3,298</td>
<td>10,435/1,490,667</td>
</tr>
<tr>
<td>Dhont et al., 1999 [29]</td>
<td>82/3,048</td>
<td>24/3,048</td>
</tr>
<tr>
<td>Perri et al., 2001 [30]</td>
<td>7/95</td>
<td>8/190</td>
</tr>
<tr>
<td>Buckett et al., 2005 [32]</td>
<td>13/268</td>
<td>4/338</td>
</tr>
<tr>
<td>Wisborg et al., 2010 [33]</td>
<td>10/730</td>
<td>100/16,464</td>
</tr>
<tr>
<td>This study</td>
<td>9/613</td>
<td>428/39,503</td>
</tr>
<tr>
<td>Summary odds ratio</td>
<td>2.19 (95% CI 1.29–3.73)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>OI</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivennes et al., 1993 [20]</td>
<td>6/263</td>
<td>15/5,096</td>
</tr>
<tr>
<td>Ombelet et al., 2006 [15]</td>
<td>152/12,021</td>
<td>47/12,021</td>
</tr>
<tr>
<td>Wisborg et al., 2010 [33]</td>
<td>5/877</td>
<td>100/16,464</td>
</tr>
<tr>
<td>This study</td>
<td>16/639</td>
<td>428/39,503</td>
</tr>
<tr>
<td>Summary odds ratio</td>
<td>2.74 (95% CI 1.52–4.93)</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 7.** Forest plot of ORs from previous reports and current study for the risk of delivery before 34 weeks’ gestation in pregnancies conceived by IVF and after OI compared to SCPs.
ART and preterm birth: adjusted comparisons

n=850 - Adjusted OR
Non-significant differences among infertile patients

Valenzuela 2014
Fetal Defects

Pregnancy complications

Fetal programming
Apreciados Sres/Sras,

Me permito escribirles para formularles una consulta sobre nuestro hijo. Nació en la maternidad tras haber sido llevado el embarazo de mi mujer en dicho hospital, durante el embarazo le detectaron un ligero retraso en el crecimiento intrauterino que fue controlado y llegaron a proponernos incluirlo en un estudio con resonancia magnética cerebral intrauterina, pero finalmente lo descartaron por presentación podática.

Actualmente está a punto de cumplir 4 años y presenta diversas alteraciones neurológicas:
- Trastorno específico del Lenguaje
- Retraso motriz
- Afectaciones sensoriales
- Retraso madurativo generalizado
- Carácter irritable con poca tolerancia a la frustración

Es posible que estas afectaciones tengan como origen el retraso de crecimiento intrauterino? ¿Qué otros problemas puede tener mi hijo en el futuro por culpa de dicho retraso?

Quedo a la espera de su respuesta.

Atentamente,

[Nombre], padre de [Nombre]
IMPACT OF ENVIRONMENT

OPPORTUNITY FOR CORRECTION

Fetus | Child | Young | Mature | Old
Direct risk factors:
- Growth restriction
- Prematurity
- Cardiac Malformations
- Infections
- Drugs

Indirect risk factors:
- Multiple pregnancy
- Maternal age
- Maternal diseases
- Obesity
- ART

Hediger 2013
Satchev, 2012
Figuera 2006-2011
Baschat 2009, 2011
Vohr 2004
Geva 2002-2011
1986 Barker (MRC Unit, Southampton, UK):
Coronary heart disease mortality rates
Background—Assisted reproductive technologies (ARTs) have been shown to be associated with general vascular dysfunction in late childhood. However, it is unknown whether cardiac remodeling is also present and if these changes already manifest in prenatal life. Our aim was to assess fetal and infant (6 months of age) cardiovascular function in ART pregnancies.

Methods and Results—This prospective cohort study included 100 fetuses conceived by ART and 100 control pregnancies. ART fetuses showed signs of cardiovascular remodeling, including a more globular heart with thicker myocardial walls, decreased longitudinal function (tricuspid ring displacement in controls: median, 6.5 mm [interquartile range, 6.1–7.1 mm]; tricuspid ring displacement in ART: 5.5 mm [interquartile range, 5.1–6.1]; P<0.001), impaired relaxation, and dilated atria (atrial area in controls, 1.46 cm² [interquartile range, 1.2–1.5 cm²]; atrial area in ART, 1.6 cm² [interquartile range, 1.3–1.8 cm²]; P<0.001). Additionally, ART infants showed persistence of most cardiac changes and a significant increase in blood pressure and aortic intima-media thickness (systolic blood pressure in controls, 74 mm Hg [interquartile range, 67–83 mm Hg]; systolic blood pressure in ART, 83 mm Hg [interquartile range, 75–94 mm Hg]; P<0.001; aortic intima-media thickness in controls, 0.52 mm [interquartile range, 0.45–0.56 mm]; aortic intima-media thickness in ART, 0.64 mm [interquartile range, 0.62–0.67]; P<0.001). We could not demonstrate that our findings were directly caused by ART because of their association with various confounding factors, including intrauterine growth restriction or factors related to the cause of infertility.

Conclusions—Children conceived by ART manifest cardiac and vascular remodeling that is present in fetal life and persists in postnatal life, suggesting opportunities for early detection and potential intervention. The underlying mechanisms and the effect of potential confounders such as growth restriction or prematurity remain to be elucidated. (Circulation. 2013;128:1442-1450.)

Key Words: fertilization in vitro • pediatrics • pregnancy • reproductive techniques, assisted • ventricular remodeling

Assisted reproductive technologies (ARTs), mainly standard in vitro fertilization or intracytoplasmic sperm injection, permit childbirth in many infertile couples and nowadays represent 1% to 4% of births in developed countries. Although these technologies are generally considered safe, the potential association of ART with poorer pregnancy outcomes has long been investigated. There is evidence that ART is associated with increased risk for adverse perinatal outcome and congenital malformations. This notwithstanding, it is not possible to separate ART-related risks from those secondary to the underlying reproductive pathology of the infertile couple. In this scenario, preliminary evidence has recently suggested that ART could be associated with long-term cardiovascular changes. Ceelen et al first suggested the presence of increased blood pressure in late childhood after ART conception. More recently, another study demonstrated the presence of signs of systemic and pulmonary vascular dysfunction in 12-year-old children conceived by ART. 

Editorial see p 1398
Clinical Perspective on p 1450
TRA: moderately worse pregnancy outcomes, but essentially due to worse starting conditions (age and infertility).

Only direct effect: increased twins.

Effects on cardiovascular risk that remain to be clarified.

TRA: indication to consider post-natal follow-up
TRA: peores resultados perinatales (discretamente), esencialmente por peores condiciones previas (edad e infertilidad).

Único efecto directo: aumento gestación múltiple.

Causalidad de efectos cardiovasculares pendiente aclarar.

TRA: indicación para valorar seguimiento post-natal