Risk of congenital anomalies in children born after IVF / ICSI: what to tell your patient?

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Ob/Gyn “Shterev Hospital”, Sofia

Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations.

Congenital anomalies can be defined as structural or functional anomalies (for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or may only be detected later in infancy, such as hearing defects.
Sir,—In analysing further data from the register of in-vitro fertilisation (IVF) and gamete intrafallopian transfer (GIFT) pregnancies in Australia and New Zealand, we found more infants than expected with two types of congenital malformation—namely, spina bifida and transposition of the great vessels.
Infants conceived with use of intracytoplasmic sperm injection or in vitro fertilization have twice as high a risk of a major birth defect as naturally conceived infants.

## Congenital anomalies
### ART vs. Non ART infants

Reported meta-analyses on birth defects and assisted reproductive technologies

<table>
<thead>
<tr>
<th>Early meta-analyses</th>
<th>Number of articles</th>
<th>Number ART Infants</th>
<th>Pooled estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimm et al (2004)</td>
<td>19</td>
<td>35,578</td>
<td>1.29 (1.01 – 1.67)</td>
</tr>
<tr>
<td>Hansen et al (2005)</td>
<td>25</td>
<td>28,638</td>
<td>1.29 (1.21 – 1.37)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recent meta-analyses</th>
<th>Number of articles</th>
<th>Number ART Infants</th>
<th>Pooled estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wen et al (2012)</td>
<td>46</td>
<td>124,468</td>
<td>1.37 (1.26 – 1.48)</td>
</tr>
<tr>
<td>Hansen et al (2013)</td>
<td>45</td>
<td>92,671</td>
<td>1.32 (1.24 – 1.42)</td>
</tr>
</tbody>
</table>

**ARTs increase risk of birth defects by about 30%**
## Congenital anomalies

### Effect of type of ART

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
<th>Controls</th>
<th>IVF RR (95% CI)</th>
<th>ICSI RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>6163</td>
<td>308974</td>
<td>1.07 (0.90-1.26)</td>
<td>1.57 (1.30-1.90)</td>
</tr>
</tbody>
</table>

**ICSI: increases risk of birth defects**  
**IVF: Does not increase risk of birth defects**

The Fetal Medicine Foundation


• **IVF:** 46 890
• **ICSI:** 27 754
• **RR:** 1.05 (95% CI 0.91-1.20)

No difference in congenital anomalies between IVF and ICSI
### Congenital anomalies

#### Effect of type of ART

<table>
<thead>
<tr>
<th>OR (95% CI) for severe malformations after IVF:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fresh ejaculated ICSI                      0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>• Fresh IVF                                  1.00 reference</td>
</tr>
<tr>
<td>• Cryopreserved ejaculated ICSI               1.01 (0.76-1.33)</td>
</tr>
<tr>
<td>• Fresh ejaculated ICSI                      1.00 reference</td>
</tr>
<tr>
<td>• Cryopreserved ejaculated ICSI               0.75 (0.53-1.06)</td>
</tr>
<tr>
<td>• Cryopreserved IVF                          1.00 reference</td>
</tr>
<tr>
<td>• Fresh epididymal ICSI                      1.07 (0.41-2.92)</td>
</tr>
<tr>
<td>• Fresh testicular ICSI                      1.00 reference</td>
</tr>
<tr>
<td>• Fresh non-ejaculated ICSI                   1.13 (0.72-1.87)</td>
</tr>
<tr>
<td>• Fresh ejaculated ICSI                      1.00 reference</td>
</tr>
<tr>
<td>• Cryopreserved non-ejaculated ICSI           0.95 (0.30-2.99)</td>
</tr>
<tr>
<td>• Fresh non-ejaculated ICSI                   1.00 reference</td>
</tr>
</tbody>
</table>

### Congenital malformations in infants after IVF:
- Central nervous system
- Cardiovascular system
- Urogenital system
- Limb reduction defects

**No difference between different types of IVF**

Heisey et al. Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments. Birth Defects Res A Clin Mol Teratol 2015

Singletons
• ART: 4 064
• Other ART: 9 589
• Controls: 1 090 154

RR = 1.43; 95% CI (1.19–1.72)

Twins and higher order multiples
• ART: 3 056
• Other ART: 2 301
• Controls: 28 008

RR = 1.26; 95% CI (1.01–1.57)
## Maternal factors and the risk of birth defects after IVF / ICSI

<table>
<thead>
<tr>
<th>Conception</th>
<th>n</th>
<th>Age ≥35 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF:</td>
<td>2211</td>
<td>34.4%</td>
</tr>
<tr>
<td>ICSI:</td>
<td>1399</td>
<td>30.3%</td>
</tr>
<tr>
<td>Controls:</td>
<td>301060</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th>RCOG</th>
<th>ACOG</th>
<th>SOGC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnion</td>
<td>1%</td>
<td>0.3-0.5%</td>
<td>0.2-1.5%</td>
</tr>
<tr>
<td>CVS</td>
<td>1-2%</td>
<td>0.3-0.5%</td>
<td>0.2-1.5%</td>
</tr>
</tbody>
</table>

King’s College hospital study
Singleton pregnancies with combined screening at 11-13 w

• Expectant management
• Livebirth n = 33,310; Miscarriage n = 404 (1.2%)
• Regression model to predict miscarriage

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.870</td>
<td>0.766-0.988</td>
</tr>
<tr>
<td>Delta nuchal translucency</td>
<td>1.778</td>
<td>1.496-2.114</td>
</tr>
<tr>
<td>Ductus venosus: reversed a-wave</td>
<td>2.208</td>
<td>1.508-3.232</td>
</tr>
<tr>
<td>Log10 PAPP-A MoM</td>
<td>0.356</td>
<td>0.233-0.543</td>
</tr>
</tbody>
</table>

CVS n = 2,396

Miscarriage

Observed: 44 (1.8%)
Expected: 45 (95% CI 32-58)

Danish study

- 147,987 singleton pregnancies
- All had first trimester combined screening
- Propensity score stratification

Miscarriage risk difference:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>-0.2%</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Stillbirth risk difference:

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<tr>
<th>Procedure</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>-0.3%</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

The Fetal Medicine Foundation

Screening for Down syndrome

1st trimester combined test

Trisomy 21

Cell-free DNA in maternal blood

Estimated DR 99.8% (920/923: 99.7%)
Estimated FPR 0.04% (25/54,359: 0.05%)
### Screening for trisomies

**Cell-free DNA in maternal blood**

<table>
<thead>
<tr>
<th>Trisomy</th>
<th>n=</th>
<th>DR</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>923</td>
<td>99.8% (99.2)</td>
<td>0.04% (0.09)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>290</td>
<td>97.6% (96.3)</td>
<td>0.05% (0.13)</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>212</td>
<td>96.5% (91.0)</td>
<td>0.02% (0.13)</td>
</tr>
</tbody>
</table>

*Mar Gil: Updated meta-analysis December 2016*

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Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies Ultrasound Obstet Gynecol 2015;45:249
Combined screening at 11-13 wks
(age, fetal NT, serum ß-hCG & PAPP-A)

High risk
\[ \geq 1:10 \]
Intermediate risk
Low risk
\[ <1:1000 \]

- cfDNA test
  - +ve
  - -ve

Invasive test
Nothing else

## Congenital anomalies

**ART: Type of defects**

### Increased risk of congenital defects in ART:

<table>
<thead>
<tr>
<th>Singletons</th>
<th>Multiples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ART:</strong> 9,653</td>
<td><strong>ART:</strong> 5,357</td>
</tr>
<tr>
<td><strong>Controls:</strong> 1,090,154</td>
<td><strong>Controls:</strong> 28,008</td>
</tr>
<tr>
<td><strong>RR = 1.43; 95% CI (1.19–1.72)</strong></td>
<td><strong>RR = 1.26; 95% CI (1.01–1.57)</strong></td>
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### Most commonly affected organs:
- Cardiovascular
- Genitourinary
- Musculoskeletal

### Most common defects:
- Hypospadias
- Omphalocele
- Neural tube defects

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*Heisey et al. Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments. Birth Defects Res A Clin Mol Teratol 2015*
Early detection of fetal defects

**11-13 weeks**

**Major defects**

- Acrania
- Holoprosencephaly
- Exomphalos
- Gastrochisis
- Megacystis
- Body stalk anomaly

Always detected 31%
Early detection of Open spina bifida

11-13 weeks

Spina bifida n=30

Brain stem diameter (mm)

CRL (mm)

Spina bifida n=30

Brain stem to occipital bone diameter (mm)

CRL (mm)

Brain stem

4th ventricle

Cisterna magna

Brain stem diameter (mm)

Brain stem to occipital bone diameter (mm)

Sphenoid bone

Brain stem

Occipital bone

Nicolaides et al., 1986

Chaoui et al., 2009; Lachman et al., 2011
Early detection of Major cardiac defects

11-13 weeks

Delta nuchal translucency (mm)

Risk of major cardiac defect (%)

0 2.0 4.0 6.0-2.0

0

20

40

60

80

100

Tricuspid regurgitation & DV reversed a-wave

Risk of major cardiac defect (%)

Delta nuchal translucency (mm)

Normal Doppler

TR

DVr

Detection rate

10%

53%

FPR 4%

58%

FPR 8%

75%

Cheleman 2011; Pereira 2011; Rembouskos 2012

History NT/TR/DV 4CV / Markers
Discordance for fetal abnormality

**Prevalence**  \( \text{DC : MC = 4 : 1} \)

- Defects in DC: 1 x singleton
- Defects in MC: 4 x singleton

Discordance for defects: MC=DC

**Management options**
- DC: 1 euploid and 1 trisomy 21
- DC: 1 euploid and 1 trisomy 18
- DC: 1 euploid and 1 anencephaly
- MC: 1 normal and 1 abnormal

**Timing of selective termination**
1. Increased risk of congenital defects in ART pregnancies

2. Equal risk of congenital defects between all types of ART pregnancies

3. Management of ART pregnancies:
   - Counselling with specialist in Reproductive medicine
   - Counselling with specialist in Fetal medicine

4. Need for randomized studies

Thank you