Recurrent Pregnancy Loss: To Offer Chromosome Testing to all Couples/Individuals or only Selectively

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CEO, ASRM

Best of ESHRE/ASRM 2019 Debate

Couples diagnosed with recurrent pregnancy loss should be routinely offered chromosome analysis for identification of etiologic chromosome abnormalities

Pro: Richard Reindollar, MD USA
Con: Mariette Goddijn, MD, PhD The Netherlands

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Counsel couples/individuals with recurrent pregnancy loss about the chance to carry a balanced chromosomal rearrangement.
2. Discuss what the unbalanced state of a chromosomal rearrangement could cause.
3. Order appropriately chromosome testing in these couples.
DISCLOSURE

- I have no commercial or financial relationships related to this talk to disclose.

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RECURRENT PREGNANCY LOSS

ESHRE Guideline 2017

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[Recommendations]

Parental karyotyping is not routinely recommended in couples with RPL. It could be carried out after individual assessment of risk.
Supporting a “Pro” case for offering parental chromosome screening to all couples with recurrent pregnancy loss, even those at low risk

- Structural chromosome abnormalities occur in couples with recurrent pregnancy loss, even in those at low risk.
- Couples who carry a chromosome translocation, even at low risk, have the right to know the cause of their miscarriages.
- Children with various phenotypes, ranging from normal to abnormal, are the possible outcomes of parental chromosome abnormalities.
- The unexpected delivery of one child with an unbalanced chromosome state and associated defects is too many.
- While 83% will have normal child, 50% of pregnancies will miscarry.
- Couples/individuals have the ethical right of autonomy to make decisions about their care and the right to understand the cause of their pregnancy losses.
- Management options are also available through donor gametes and adoption. PGT can be performed in at risk embryos for the transfer of an euploid embryo.
- Nondirective counseling is the fundamental principle of genetic counseling.

Spontaneous abortion: Magnitude of the Problem

- Spontaneous abortion: 15 – 20% of clinically recognized pregnancies
- Recurrent Pregnancy Loss: 2 or more first trimester clinically recognized pregnancy losses occurs in 1 – 2% of couples attempting pregnancy

Chromosomal Abnormalities 2000 Random Spontaneous Abortions (up to 60% ABN)

- Trisomy 52.0%
- Triploidy 19.0%
- Monosomy X 14.6%
- Other 14.4%

Incidence of Human Aneuploidy

- Arrested development before blastocyst (63% of unbalanced)
- Spontaneous miscarriages (50 - 65%)
- Stillborn, 20 weeks (20%)
- Stillborn, term (6%)
- Liveborn term (0.5 - 1%)

Random spontaneous abortions (usually chromosomally abnormal) are a common human phenomenon - “The Natural Selection Process”

- to be contrasted with recurrent pregnancy loss caused by parental chromosome abnormalities.

Recurrent Abortion
-Etiologies for 100 Couples-

<table>
<thead>
<tr>
<th>Identified Non-Genetic</th>
<th>Unidentified</th>
<th>Identified Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>37%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Recurrent Abortion
-Easily Identified Genetic Etiologies-

Tho, Byrd, McDonough: Fert Steril, 32:389, 1979

- Balanced translocation (11)
- Sex chromosome aneuploidy (1)
- Ring chromosome
- Large para/pericentric inversion

Chance of Structural Chromosome abnormality carrier state:

- 0.2% of general population (balanced translocation)
- 2 – 5% of recurrent spontaneous pregnancy loss couples, are carriers for a major balanced chromosome abnormality (MCA)
  - Tharapel AT, B J Obstet Gynaecol, 1985, 79 studies of 8208 women and 7834 men combined, 2.9% MCA
  - Clifford K, Hum Reprod, 1995: 500 couples, 3.6% MCA
  - Franssen MTM (Goddijn), BMJ, 2006: 11,971 couples with RPL screened, 382 carrier couples with structural chromosome abnormality, 3.2% MCA
  - Ozawa N, Fertil Steril, 2008: 114 couples, 4.9% MCA

Chromosome Translocations: Outcome (Robertsonian)

Parents 14 14/21 21
Gametes 14 21 or 14 21 or 14 21 or 14 21
Fetus Normal Normal Carrier Abnormal Trisomy 14 Abnormal Trisomy 21
Chromosome Translocations: Outcome (Reciprocal)

Parents

Gametes

Normal  Unbalanced  Normal  Balanced  Unbalanced

11  11;22  22;11  22

Morin, F&S 2017:19
Robertsonian and Reciprocal Translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Robertsonian</th>
<th>Reciprocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cycles</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>No. Patients</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Age (M ± SD, years)</td>
<td>35.5 ± 3.7</td>
<td>34.0 ± 3.3</td>
</tr>
<tr>
<td>No. retrieved oocytes (M ± SD)</td>
<td>3.3 ± 4.3</td>
<td>3.7 ± 4.6</td>
</tr>
<tr>
<td>No. generated embryos</td>
<td>206</td>
<td>187</td>
</tr>
<tr>
<td>No. FISH analyzed embryos</td>
<td>175</td>
<td>154</td>
</tr>
<tr>
<td>No. FISH diagnosed embryos</td>
<td>175</td>
<td>154</td>
</tr>
<tr>
<td>FISH normal (%)</td>
<td>43 (25)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>FISH abnormal (%)</td>
<td>132 (75)</td>
<td>136 (88)</td>
</tr>
<tr>
<td>No. transferred embryos (M ± SD)</td>
<td>5.6 ± 0.9</td>
<td>5.4 ± 0.5</td>
</tr>
<tr>
<td>No. transferred cycles (%)</td>
<td>25 (93)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>No. clinical pregnancies (%)</td>
<td>13 (50)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>44.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Take-home baby rate per patient</td>
<td>41</td>
<td>4</td>
</tr>
</tbody>
</table>

Patients with an Altered Karyotype:
Robertsonian and Reciprocal Translocations

PGD Biopsy Results

- Reciprocal translocations: up to 82% embryos unbalanced
- Robertsonian translocations: 50 – 65% embryos abnormal
Selective chromosome analysis in couples with two or more miscarriages: case-control study. Franssen et al Goddijin, BMJ, 2005.

• Nested case-control study of 6 clinical genetics centers, Netherlands
• Couples referred for chromosome analysis after two or more miscarriages 1992 – 2000.
• 279 carrier couples - cases;
• 428 non-carrier couples - controls.

Factors that influence the probability of carrier status

| Low maternal age at second miscarriage |
| History of 3 or more miscarriages |
| History of two or more miscarriages in brother or sister of either partner |
| History of two or more miscarriages in the parents of either partner |

Conclusions of this study:
“Selective chromosome analysis in couples with two or more miscarriages - that is, withholding chromosome analysis from couples with a low probability of carrier status - would result in more appropriate referral policies, could decrease the annual number of chromosome analyses, and could therefore reduce the costs to the healthcare system.”

“Selective chromosome analysis could reduce the number of chromosome analyses by 18%.”

Table 1: Probability of carrier status in couples with two or more miscarriages, according to the multivariable logistic regression model (adapted from Franssen et al., 2005)

<table>
<thead>
<tr>
<th>Maternal age at second miscarriage</th>
<th>(R^2adj)</th>
<th>(R^2full)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19 miscarriages</td>
<td>2 miscarriages</td>
</tr>
<tr>
<td>&lt;23 years</td>
<td>10.2</td>
<td>7.3</td>
</tr>
<tr>
<td>25-35 years</td>
<td>10.0</td>
<td>7.2</td>
</tr>
<tr>
<td>36-46 years</td>
<td>5.6</td>
<td>4.1</td>
</tr>
<tr>
<td>37-48 years</td>
<td>5.2</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;59 years</td>
<td>4.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

All values are given in percentages.

Table adapted from Franssen et al., Hum Reprod, 2006.
Table 1. Probability of carrier status in couples with two or more miscarriages, according to the multivariable logistic regression model (modified from Fransoo et al. 2005).

<table>
<thead>
<tr>
<th>Maternal age at second miscarriage</th>
<th>(ΔM)_{1} (%)</th>
<th>(ΔM)_{2} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 years</td>
<td>10.2</td>
<td>7.3</td>
</tr>
<tr>
<td>25-33 years</td>
<td>10.0</td>
<td>7.2</td>
</tr>
<tr>
<td>34-38 years</td>
<td>5.8</td>
<td>4.1</td>
</tr>
<tr>
<td>39-49 years</td>
<td>3.2</td>
<td>2.2</td>
</tr>
<tr>
<td>≥50 years</td>
<td>2.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- ΔM_{1} = number of miscarriages in the couple, ΔM_{2} = number of miscarriages in the partner.
- Each row represents a two or more miscarriages in the couple and/or partner.

Couples initially referred for chromosome analysis after ≥ 2 pregnancy losses before 20 weeks were followed at least 24 months (mean 5.8 years):

- 278 carrier couples
- 427 non-carrier couples

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Carrier</th>
<th>Non-carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent miscarriage</td>
<td>120/247 (49%)</td>
<td>122/409 (30%) p&lt;0.01</td>
</tr>
<tr>
<td>≥ 1 healthy child</td>
<td>(39%)</td>
<td>(64%) ns</td>
</tr>
<tr>
<td>Unbalanced viable TAB</td>
<td>2 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Unbalanced live born</td>
<td>2 (0.4%)</td>
<td></td>
</tr>
</tbody>
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Autonomy-
A fundamental principle of ethics:

Autonomy is Latin for "self-rule". We have an obligation to respect the autonomy of other persons, which is to respect the decisions made by other people concerning their own lives. This is also called the principle of human dignity.
Case: What would you do?

A 38 year old female and 39 year old male present with two miscarriages. No other miscarriages in family. Do you recommend testing?

Table 1. Probability of carrier status in couples with two or more miscarriages, according to the univariable logistic regression model (modified from Frisoni et al., 2007)

<table>
<thead>
<tr>
<th>Maternal age of second miscarriage</th>
<th>(PM ≤ 0.10%)</th>
<th>2 miscarriages</th>
<th>(PM &gt; 0.10%)</th>
<th>2 miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 years</td>
<td>(PM ≤ 0.10%)</td>
<td>10.2</td>
<td>7.3</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>(PM &gt; 0.10%)</td>
<td>10.0</td>
<td>7.2</td>
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</tr>
<tr>
<td>25-33 years</td>
<td>(PM ≤ 0.10%)</td>
<td>5.7</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>(PM &gt; 0.10%)</td>
<td>5.7</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>34-36 years</td>
<td>(PM ≤ 0.10%)</td>
<td>5.6</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>(PM &gt; 0.10%)</td>
<td>5.6</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>37-38 years</td>
<td>(PM ≤ 0.10%)</td>
<td>3.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(PM &gt; 0.10%)</td>
<td>3.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Note: PM = probability of carrier status; 2 miscarriages. Karyotyping can be notified to these couples.

Recommendations:
Parental karyotyping is not routinely recommended in couples with RPL. It could be carried out after individual assessment of risk.

ESHRE Guidelines 2017
Case: What would you do?

Case: 38 year old female and 39 year old male present with two miscarriages. No other miscarriages in family. Testing not recommended by ESHRE Guidelines.

The male partner has de novo 21/21 translocation

A Chromosome translocation Carrier: What are the options?

- Childless living or adoption
- Donor Gametes
- PGT
  - FISH
  - SNP microarray: 24 chromosome aneuploidy detection, 90%+ successful detection rates + improved ongoing pregnancy rates
  - Array CGH: similar results
### Supporting a "Pro" case for offering parental chromosome screening to all couples with recurrent pregnancy loss, even those at low risk

- Structural chromosome abnormalities occur in couples with recurrent pregnancy loss, even in those at low risk.
- Couples who carry a chromosome translocation, even at low risk, have the right to know the cause of their miscarriages.
- Children with various phenotypes, ranging from normal to abnormal, are the possible outcomes of parental chromosome abnormalities.
- The unexpected delivery of one child with an unbalanced chromosome state and associated defects is too many.
- While 83% will have normal child, 50% of pregnancies will miscarry.
- Couples/individuals have the ethical right of autonomy to make decisions about their care and the right to understand the cause of their pregnancy losses.
- Management options are also available through donor gametes and adoption. PGT can be performed in at risk embryos for the transfer of an euploid embryo.
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### REBUTTAL

### Rebuttal

Couples diagnosed with recurrent pregnancy loss should be routinely offered chromosome analysis for identification of etiologic chromosome abnormalities.
Rebuttal

Couples diagnosed with recurrent pregnancy loss should be routinely offered chromosome analysis for identification of etiologic chromosome abnormalities

Con Arguments

• 83% of Carrier Couples will have a healthy child (compared to 84% of controls).
• More carrier couples refrain from further pregnancies compared to non-carrier couples
• More carrier couples experience significant distress
• Not offering parental karyotyping to “low risk” individuals, can save health dollars (“selective chromosome analysis could reduce the number of chromosome analyses by 18%”)

Table 1. Probability of carrier status in couples with two or more miscarriages, according to the multivariable logistic regression model (modified from Fosse et al. 2006)

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<td>1.3</td>
<td>1.4</td>
</tr>
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<td>1.0</td>
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<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>36-44 years</td>
<td>1.0</td>
<td>1.2</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>1.0</td>
<td>1.2</td>
<td>1.3</td>
<td>1.4</td>
</tr>
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Carrier status: high probability (≥2%). Karyotyping can be withheld in these couples.

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**Con Arguments**
- 83% of Carrier Couples will have a healthy child (compared to 84% of controls).
- More carrier couples refrain from further pregnancies compared to non-carrier couples
- More carrier couples experience significant distress
- Not offering parental karyotyping to "low risk" individuals, can save health dollars ("selective chromosome analysis could reduce the number of chromosome analyses by 18%")
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