Subfertile men with constitutive chromosome abnormalities do not necessarily refrain from intracytoplasmic sperm injection treatment: a follow-up study on 75 Dutch patients


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A follow-up study was performed to investigate the impact of the detection of a chromosome abnormality in infertile men who are candidates for intracytoplasmic sperm injection (ICSI) treatment. In this collaborative study between clinical genetics centres and fertility clinics in the Netherlands, 75 ICSI couples of which the male partners had a chromosome abnormality were included. All couples were extensively counselled on the risk of having a chromosomally unbalanced child. Forty-two out of 75 couples chose to proceed with the ICSI treatment. So far, treatment has resulted in a pregnancy in 11 cases. Four of them opted to have invasive prenatal diagnosis. Despite the genetic risks related to a chromosome abnormality in infertile men, a small majority (56%) of the couples did not refrain from the ICSI treatment.

Key words: chromosome abnormality/follow-up/intracytoplasmic sperm injection (ICSI)/male infertility/oligoasthenoteratozoospermia (OAT)

Introduction

The majority of cases of male infertility remain unexplained (Chandley, 1995). There is evidence, however, that genetic factors such as chromosome abnormalities and deletions of the Y-chromosome are involved in up to 20% of these cases (Chandley, 1995; Reijo et al., 1996; Tuerlings et al., 1998).

Some of the chromosome abnormalities found in infertile men can also be found in fertile men. These men have a chance of transmitting such an abnormality to their children. For example, carriers of balanced translocations can produce offspring with either a normal, a chromosomally balanced or a chromosomally unbalanced karyotype. In the latter case this can result in an early developmental embryonic arrest, a spontaneous abortion, a still birth or birth of a child with a combination of (multiple) congenital anomalies and psychomotor retardation. The risk of producing such unbalanced offspring depends on which chromosomes are involved and on the extent of the chromosomal imbalance (Stengel-Rutkowski et al., 1988; Daniel et al., 1989). Since infertile men may now take advantage of intracytoplasmic sperm injection (ICSI) to reproduce, it is assumed that the risk of producing unbalanced offspring for these men is at least as high as it is for fertile men with the same chromosome abnormality. In addition, infertile men could pass on other yet unknown genetic factors causing infertility to their offspring via the ICSI procedure. Couples asking for this treatment must be counselled carefully on the genetic risks of this technique (In’t Veld et al., 1997; Pauer et al., 1997; Wilkins-Haug et al., 1997; Tuerlings et al., 1998).

The aim of the study was to assess the impact of the finding of a chromosome abnormality on the couple’s decision whether or not to proceed with the ICSI procedure.

Materials and methods

Chromosome analysis in peripheral blood is performed routinely in all male candidates prior to ICSI treatment in the Netherlands. In a recent study, in which the results of karyotyping 1792 males of ICSI couples were presented, 72 were found to have a constitutive chromosome abnormality (Tuerlings et al., 1998). These 72 men were the initial subjects of the present study, of which 15 were excluded because of azoospermia. In cases of azoospermia, non-ejaculated spermatozoa would have to be used for ICSI, a method that is not allowed in the Netherlands due to a national moratorium. The remaining 57 couples, as well as 18 more recently diagnosed patients (male ICSI candidates) with a chromosome abnormality, were included in this study. These 75 couples were counselled on the potential risks, prior to ICSI treatment. Since no risk figures are available from the literature for the ICSI population, couples were informed about the increased risk without a precise estimate being given. Where risk figures were available from fertile men with the same chromosome abnormality, these figures were discussed with the couple but it was emphasized that the risks could be higher for offspring after ICSI treatment. With regard to a possible chromosome abnormality in the child, the difference between sex chromosome and autosomal abnormalities was discussed in that unbalanced sex chromosome abnormalities usually have a much milder phenotype than unbalanced autosomal abnormalities, especially with regard to psychomotor development (Linden et al., 1996). Invasive prenatal diagnosis and extensive ultrasound investigation were offered to all couples.

We determined: (i) whether the ICSI couples chose to proceed with the ICSI treatment; (ii) whether ICSI had resulted in a pregnancy;
and (iii) where a pregnancy was achieved, whether they had opted for invasive prenatal diagnosis. We did not collect data on the individuals’ motivation or reasons for refraining from ICSI treatment, or for proceeding and opting for prenatal diagnosis. If no prenatal karyotyping had been performed, we investigated whether postnatal karyotyping had been carried out. Results of prenatal and postnatal karyotyping were recorded. The number of treatment cycles performed in order to achieve a pregnancy was not recorded.

Results
The karyotypes of infertile men are categorized in Table I. The patient sample was divided into a group with sex chromosome abnormalities (SCA) and one with autosomal chromosome abnormalities (ACA) because the potential chromosome abnormalities in the offspring of the first group have a relatively mild phenotype, whereas those in the offspring of the second group can be much more severe. This difference might influence the decision of proceeding with ICSI for couples of either group. There were 29 SCA and 46 ACA, 19 of which were Robertsonian translocations.

In cases of SCA, 17 (59%) of the couples proceeded with ICSI treatment, 10 (34%) refrained from the treatment and two (7%) had not yet decided. There were five pregnancies as a result of ICSI and there was one spontaneous pregnancy. In one case prenatal diagnosis was performed and in an other case we had no information on this, but in any case this was not performed in the Netherlands.

In cases of ACA, 25 (54%) of the couples proceeded with ICSI treatment, 13 (28%) refrained from it and eight (18%) are still in doubt. Of the six pregnancies, prenatal diagnosis was performed in three cases and again in one case we have no information.

Thus, in total, 23 couples (31%) have decided to refrain from further ICSI treatment, whereas 42 couples (56%) have decided to proceed. Ten couples (13%) have not yet decided. Of the couples who underwent ICSI treatment, pregnancies have resulted in 11 cases so far. In four of these, the couples opted for invasive prenatal diagnosis. In these four cases, either a cytogenetically normal or a balanced karyotype was found in the fetus: 46,XX in the case of a male with an ACA, 45,XY,der(13;15) (q10;q10) and twice 45,XY,der(13;14) (q10;q10) in cases of male Robertsonian translocations. In one case of a male with an SCA, postnatal chromosome analysis in the child revealed a normal karyotype (46,XY).

Discussion
In the Netherlands, chromosome analysis of the male partner is performed in all infertile couples who want ICSI treatment. We have asked the question whether the increased risk of a karyotypically unbalanced offspring associated with a chromosome abnormality is sufficient reason for these couples to refrain from ICSI treatment and, if they do not refrain and a pregnancy results, whether they choose to have invasive prenatal diagnosis. To our knowledge, there are no published data addressing these questions.

Out of a total of 75 couples, 23 (31%) of them definitely refrained from ICSI treatment and 10 (13%) are still in doubt. We thought that the option of invasive prenatal diagnosis might be an important factor for the majority of couples (42) in deciding to proceed with ICSI treatment. This does not appear to be the case, as couples opted to have prenatal diagnosis in only four of the 11 pregnancies achieved. However, we are not aware in how many of these pregnancies detailed ultrasound investigation was performed and what the influence was of the availability of ultrasound investigation on the decision whether or not to have invasive prenatal diagnosis.

Although the phenotype of a child with an ACA is expected to be more severe than that of a child with an unbalanced SCA (as was discussed with the couples prior to ICSI), there are no major differences between couples with male SCA and with male ACA as to their decision to proceed with the treatment (59% versus 54% respectively). However, it appears that the number of pregnancies in the SCA group is higher (five in 17 couples) than in the ACA group (six in 25 couples). In a study by Montag et al. (1997) significantly lower fertilization, implantation and pregnancy rates were found in eight couples with a male constitutional chromosome abnormality than in controls.

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Table I. Follow-up data on couples with abnormal male karyotypes receiving intracytoplasmic sperm injection treatment (ICSI)

<table>
<thead>
<tr>
<th>Sex chromosome abnormalities</th>
<th>n</th>
<th>Proceed with ICSI treatment</th>
<th>No. of pregnancies</th>
<th>PND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal</td>
<td>75</td>
<td>42 (56)</td>
<td>11+1sp</td>
<td>4+2?</td>
</tr>
<tr>
<td>Structural (including mosaics)</td>
<td>10</td>
<td>5 (50)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>11</td>
<td>6 (54)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Numerical (including mosaics)</td>
<td>29</td>
<td>17 (59)</td>
<td>1+1sp</td>
<td>1+?</td>
</tr>
<tr>
<td>Subtotal</td>
<td>30</td>
<td>26 (87)</td>
<td>5+1sp</td>
<td>5+1?</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>1 (50)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>24</td>
<td>20 (83)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Robertsonian translocations</td>
<td>19</td>
<td>10 (53)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>46</td>
<td>25 (54)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Reciprocal translocations</td>
<td>12</td>
<td>3 (25)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>29</td>
<td>17 (59)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Supernumerary markers (including mosaics)</td>
<td>6</td>
<td>5 (83)</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal</td>
<td>30</td>
<td>26 (87)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Inversions</td>
<td>7</td>
<td>6 (86)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>24</td>
<td>20 (83)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>1 (50)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>26</td>
<td>21 (81)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>42 (56)</td>
<td>11+1sp</td>
<td>4+2?</td>
</tr>
</tbody>
</table>

PND = prenatal diagnosis, sp = spontaneous pregnancy.
by Montag et al. (one in eight couples) but still may be
decreased compared with that of controls. More couples from
the ACA group opted for prenatal diagnosis (three out of six
versus one out of five in the SCA group). The numbers are
too small to draw definitive conclusions.

All 75 couples with a karyotypically abnormal male had
been extensively counselled and informed about the increased
risk of having a chromosomally abnormal child. It should be
noted that we have no data on the interpretation by the potential
parents of the information given to them in counselling and
the meaning that the risk has for them. Thus, we cannot say
whether or not the couples felt that they were taking a great
risk. Either way, it appears that a small majority of the infertile
couples were prepared to bring about a pregnancy despite
having been counselled about an increased genetic risk. Once
a pregnancy was achieved, most of them were not prepared
to put the pregnancy at risk by carrying out prenatal diagnosis.
In our view, careful genetic counselling is needed before ICSI
is considered, in order to ensure that the couples are well
informed before they make a decision.

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