Non-reproductive heritable disorders in infertile couples and their first degree relatives

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The genetic safety of intracytoplasmic sperm injection (ICSI) remains a matter of continuing debate. One source of concern is the limited knowledge about the general genetic constitution and background of patients who need sophisticated reproductive technology to procreate. It has been postulated that such individuals could be carriers of genetic lesions that might result in an increased prevalence of heritable disorders among their offspring. To investigate this issue, we determined the frequency of potentially heritable non-reproductive diseases in 621 infertile couples and their first degree relatives. A total of 1302 fertile couples who underwent genetic counselling prior to prenatal diagnosis served as controls. The infertile patients had a slightly higher prevalence of potentially heritable non-reproductive disorders (‘significant genetic risk factors’) than the controls (1.9 versus 0.9%; P = 0.015). In contrast, such diseases were less prevalent in their families than in the fertile couples’ families. Our data do not support the hypothesis that their familial genetic background predisposes children born after ICSI to malformations or other non-reproductive genetic diseases. Key words: family history/heritable disease/infertility/intracytoplasmic sperm injection

Introduction

Genetic factors play a prominent role in the pathogenesis of male factor infertility (De Braekeleer and Dao, 1991; Lilford et al., 1994; Reijo et al., 1995; Meschede and Horst, 1997). Children conceived by intracytoplasmic sperm injection (ICSI; van Steirteghem et al., 1996) might therefore be at increased risk for later fertility problems. It has been postulated that severely subfertile couples could also carry and transmit genetic aberrations that jeopardize the general physical or developmental health of their offspring (Cummings and Jequier, 1994; Engel et al., 1996; Kurinczuk and Bower, 1997; Rappaport et al., 1998). While most follow-up studies of children born after ICSI have been reassuring in this regard (Bonduelle et al., 1996a,b; 1998; Palermo et al., 1996; Wennerholm et al., 1996; Sutcliffe et al., 1999), two recent publications raised the possibility of increased rates of major malformations or mild developmental delays (Kurinczuk and Bower, 1997; Bowen et al., 1998).

It has been demonstrated that genetic counselling of infertile couples considering ICSI uncovers monogenic and multifactorial disorders that are risk factors to the health of the patients’ children (Bonduelle et al., 1996a,b; Pauer et al., 1997). However, these studies did not differentiate between potentially heritable late-manifesting diseases and disorders already symptomatic in infancy or childhood. In our experience it is mainly the latter category of diseases that are a source of concern for prospective parents. Also, no rigorous distinction was made between heritable disorders in the infertile patients themselves and in their close relatives. Most importantly, so far no study has included a fertile control group that enables an assessment of the prevalence of non-reproductive genetic diseases in infertile couples or their families. Only an increased rate would indicate that children conceived by ICSI are at particular risk for heritable disorders through their specific familial background.

To address these issues, we have undertaken a prospective study of more than 600 infertile couples enrolled for ICSI treatment at our institution. A cohort of 1302 fertile couples considering prenatal diagnosis was recruited as controls.

Materials and methods

Patients and controls

All infertile patients undergoing pre-ICSI genetic counselling at our institution over a 4 year period were eligible for the study. A total of 731 couples was originally enrolled; 88 of them planned to have ICSI treatment elsewhere. To ensure a homogeneous study group of consecutive cases treated in a single institution these couples were excluded from the analysis. Of the remaining 643 couples, 22 had previously undergone genetic counselling. They were also excluded to obtain a cohort of genetically uncharacterized cases. A total of 621 infertile couples remained for the study.

The control group was recruited from 1356 consecutive couples undergoing genetic counselling at our institution prior to planned prenatal diagnosis. They considered an amniocentesis or chorionic villus biopsy either for advanced maternal age (>35 years at the expected date of confinement) or abnormal results upon α-fetoprotein or triple serum marker screening (Falk, 1995). None of the control subjects had received genetic counselling before, nor did they seek prenatal diagnosis for reasons of a known genetic disorder in themselves or in their families. A total of 54 of the original 1356 couples were excluded from the control group due to a history of fertility problems in the past, leaving 1302 couples for comparison with the ICSI group.
Documented medical and family history
For both the infertile and the fertile couples a complete medical, reproductive and family history was taken. The family history comprised first and second degree relatives and was documented in a pedigree drawn for each person counselled. During the first 21 months of the study a detailed dysmorphological examination was performed in the ICSI group to find indicators of syndromal type of disorders. It entailed a complete physical examination with particular emphasis on malformations and minor dysmorphisms (Aase, 1990). To standardize the procedure the examiner used a documentation sheet where all positive and negative findings in 28 distinct body areas (e.g. skull, scalp hair, eyes, external ear, nose, oral cavity etc.) were noted. When an interim analysis showed that the yield of relevant findings was extremely low, the laborious and time-consuming dysmorphological examination was cancelled from the study protocol.

Laboratory procedures
In the infertile group, a set of laboratory procedures was performed to test for known genetic causes of infertility such as chromosomal abnormalities, Y chromosomal microdeletions, and mutations in the cystic fibrosis CFTR gene. These data have been presented elsewhere (Meschede et al., 1998a, 2000). For some cases from the infertile and the fertile cohorts, chromosome or DNA analysis was needed to define genetic risks indicated by the medical or family history. Only the results of these tests are taken into account here.

Definitions
To make the genetic data amenable to quantitative analysis, we devised the term ‘significant genetic risk factor’. When the family history or the patients’ personal medical history indicated a risk of at least 0.5% that their child would be born with a specific ‘major’ congenital or early manifesting disorder, this was classified as a significant genetic risk factor (SGRF). Major disorders are defined as requiring surgical correction, necessitating continuous medical treatment for compensation, or conveying a permanent functional or cosmetic handicap.

Some examples may illustrate this classification system. Cleft lip or palate has a recurrence risk of 3–5% in the offspring of an affected parent (Harper, 1993). Given this magnitude of the recurrence risk, the congenital nature of the disorder, and the necessity of surgical correction cleft lip or palate in a patient from one of the study cohorts would qualify as SGRF. Cleft lip or palate in a third degree relative (calculated from the perspective of hypothetical offspring) would not be an SGRF as the recurrence risk amounts to only 0.3%. Also, Huntington’s disease in a patient from one of the study cohorts would not be an SGRF as defined above. While the recurrence risk would be 50% for all children of this patient, Huntington’s disease is a late-manifesting disorder usually not causing morbidity before adulthood. Atopic allergy in a patient from one of the study cohorts would also not qualify as SGRF despite its high recurrence risk, because it would not represent a major disorder.

Statistics
Statistical testing for differences between the infertile and fertile cohorts was performed with the \( \chi^2 \) test. A\( \ P \) value of \( < 0.05 \) was considered as statistically significant.

Results
Baseline characteristics of the infertile group
Male factor infertility was the most common indication for ICSI (60.7%), followed by combined male and female factor infertility (37.0%). Female factor infertility as the sole indication for ICSI was rare (1.8%), as was unexplained infertility (0.5%). The mean duration of primary or secondary involuntary childlessness was 4.8 years. In 79.7% neither of the partners had ever attained a clinical pregnancy. Patients from 11.1% of the couples had liveborn children from the present or a past partnership. Mean (±SD) age was 34.5 (±5.3) years for the men and 31.6 (±4.0) years for the women. The majority of the couples (87.6%) were of German ancestry.

Baseline characteristics of the fertile group
The reasons for genetic counselling were advanced maternal age in 60.6%, increased risk for Down’s syndrome indicated by triple serum marker screening in 28.1%, increased risk for a neural tube defect indicated by elevated maternal serum \( \alpha \)-fetoprotein in 5.4%, and any combination of these in 5.9%. A total of 59.1% of the women were 35 years or older at the time of counselling. Mean (±SD) age was 35.7 (±6.0) years for the men and 34.0 (±4.9) years for the women. Gestational age at the time of counselling ranged from 7–30th post-menstrual week (mean 15.2 weeks). Both partners were of German ancestry in 88.8% of cases.

Significant genetic risk factors
Of the 1242 patients in the ICSI cohort 23 (1.9%) had non-reproductive diseases that fulfilled the criteria for a ‘significant genetic risk factor’. The corresponding rate in the fertile control group was 0.9% \( (n = 23; \ P = 0.015; \chi^2 \) test). Details are given in Table I. In the infertile group 13 men and 10 women were affected, in the fertile group 12 men and 11 women.

The registration of SGRF in the patients’ families was confined to their parents, full siblings and biological children, since medical data reported by the patients counselled were regarded as reliable only for these first degree relatives. Eight couples from the fertile and 19 couples from the infertile group were excluded from the analysis due to incompleteness of their family data, e.g. due to adoption. The fertile couples had more siblings (2.48 versus 2.26 for the males, 2.54 versus 2.37 for the females) and more children (1.22 versus 0.16 per couple) than the infertile ones. The larger average family size of the fertile couples was taken into account by calculating the rate of SGRF per first degree relative. Table II summarizes the results. The prevalence of SGRF among first degree relatives was 1.4 times higher in the fertile than in the infertile group, a difference that did not reach statistical significance (fertile couples: one SGRF per 134 relatives; infertile couples: one SGRF per 186 relatives; \( P = 0.147 \)).

During the first 21 months of the study a systematic dysmorphological examination was performed for patients from the ICSI group. 190 men and 187 women underwent this procedure, corresponding to 30.4% of the infertile cohort. In no case was the diagnosis of SGRF made solely through this physical examination, which was therefore abandoned after an interim analysis.

Other genetic risk indicators
Apart from the personal medical and family history other indicators of genetic risk for children of the infertile couples
Non-reproductive heritable disorders

Table I. Diseases qualifying as ‘significant genetic risk factors’ among infertile patients, fertile controls and their first degree relatives. Disorders occurring in only a single patient, control or relative are not individually tabulated.

<table>
<thead>
<tr>
<th>Type of disorder</th>
<th>Affected infertile patients (n)</th>
<th>Affected fertile controls (n)</th>
<th>Affected first degree relatives of infertile patients (n)</th>
<th>Affected first degree relatives of fertile controls (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft lip/cleft palate</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4</td>
<td>7</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Congenital hip dislocation</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Deafness</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Diaphragmatic defect</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Myopathy</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Neural tube defect</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal and/or ureteral malformations</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Skin disorders (severe)</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Syndrome with multiple congenital anomalies</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Other disorders (one single case per disorder)</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>23</td>
<td>29</td>
<td>98</td>
</tr>
</tbody>
</table>

Table II. Frequency of diseases in patients’ first degree relatives qualifying as ‘significant genetic risk factors’ (SGRF).

<table>
<thead>
<tr>
<th></th>
<th>Infertile couples (n = 613ª)</th>
<th>Fertile couples (n = 1283ª)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First degree relatives (n)</td>
<td>SGRF in first degree relatives (n)</td>
</tr>
<tr>
<td>Parents</td>
<td>2452</td>
<td>3</td>
</tr>
<tr>
<td>Full siblings</td>
<td>2838</td>
<td>22</td>
</tr>
<tr>
<td>Children</td>
<td>97</td>
<td>4</td>
</tr>
<tr>
<td>All first degree relatives</td>
<td>5387</td>
<td>29</td>
</tr>
</tbody>
</table>

There were no significant differences between infertile and fertile couples; χ² test.

ªEight couples from the infertile group and 19 couples from the fertile group were excluded from this analysis due to incompleteness of their family data.

Discussion

Non-reproductive diseases that fulfilled the criteria for SGRF were more common in the infertile than the fertile study subjects. This could suggest that infertility is a manifestation of a systemic disease more often than currently recognized. While the concurrence of a fertility problem with a non-reproductive disease can be coincidental, such a constellation may indicate that a syndromal type of disorder is present. However, in our experience a routinely performed dysmorphological examination of infertile, but otherwise healthy patients is not an effective diagnostic tool.

While statistically significant, the difference between the two groups in the prevalence of SGRF (i.e. potentially heritable non-reproductive disorders) amounts to only 1%. It would thus be unjustified to label the infertile couples indistinctly as a high-risk group in genetic terms. However, for a minority of these patients a substantial recurrence risk for a potentially heritable disorder in their children had to be stated. Genetic counselling was a safeguard against these couples embarking on ICSI treatment without awareness of the attendant risks. Where genetic counselling is not part of the routine pre-ICSI protocol, the gynaecologist or andrologist in charge of the therapy should ensure that no potentially heritable disorders in the patients or their close relatives are overlooked.

There was no evidence for an increased prevalence of major congenital and potentially heritable disorders among close relatives of the infertile patients. In fact, such diseases were somewhat more common in the families of the fertile controls. The hospital- rather than population-based recruitment of the control group could have favoured the inclusion of couples with a positive family history for congenital major disorders,
even though the study protocol was designed to avoid this bias. It was usually not possible to verify the family history information provided by the patients counselled, e.g. through reviewing medical records of the affected relatives. However, this potential source of error applied equally to the infertile and the fertile group so that it should not have caused a systematic bias.

In summary, our study does not support the notion that the genetic background of ICSI children should make them generally prone to malformations or other non-reproductive genetic diseases. In that regard, our data are in concordance with those paediatric follow-up studies (Bonduelle et al., 1996a,b, 1998; Palermo et al., 1996; Wennerholm et al., 1996; Sutcliffe et al., 1999) which found normal malformation rates and regular psychomotor development of children born after ICSI.

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References


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