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Chromosomal abnormalities in azoospermic and non-azoospermic infertile men: numbers needed to be screened to prevent adverse pregnancy outcomes

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STUDY QUESTION: How many infertile men who wish to conceive need to be screened for chromosomal abnormalities to prevent one miscarriage or the birth of one child with congenital anomalies (CAs)?

SUMMARY ANSWER: In azoospermic men, the prevalence of chromosomal abnormalities is 15.2% and the number needed to be screened (NNS; minimum—maximum estimate) for a miscarriage is 80–88 and for a child with CAs is 790–3951. The prevalence of chromosomal abnormalities in non-azoospermic men is 2.3% and the NNS are 315–347 and 2543–12 723, respectively.

WHAT IS KNOWN ALREADY: Guidelines advise the screening of infertile men for chromosomal abnormalities to prevent miscarriages and children with congenital anomalies, but no studies have been published on the effectiveness of this screening strategy.


PARTICIPANTS, SETTING, METHODS: Men with azoospermia and men eligible for ICSI treatment visiting a university hospital fertility clinic in The Netherlands who underwent chromosomal analysis between 1994 and 2007 were identified retrospectively in a registry. Only cases of which at least one sperm analysis was available were included. Data were collected by chart review, with a follow-up of pregnancies and their outcomes until 2010. The chromosomal abnormalities were categorized according to their risk of unbalanced offspring, i.e. miscarriage and/or child with CAs. Multi-level analysis was used to estimate the impact of chromosomal abnormalities on the outcome of pregnancies in the different subgroups of our cohort. NNS for miscarriages and children with CAs were calculated based on data from our cohort and data published in the literature.

MAIN RESULTS AND THE ROLE OF CHANCE: A chromosomal abnormality was found in 12 of 79 men with azoospermia (15.2%) and in 26 of 1144 non-azoospermic men (2.3%). The chromosomal abnormalities were categorized based on the literature, into abnormalities with and abnormalities without increased risk for miscarriage and/or child with CAs. In our study group, there was no statistically significant difference between the subgroups with and without increased risk respectively, regarding the frequency of children born with CAs (1/20; 5.0% versus 2/14; 14.3%) or unaffected liveborn children (9/20; 45.0% versus 9/14; 64.3%). The prevalence of chromosomal abnormalities with a theoretically increased risk of unbalanced progeny was 1.0% in non-azoospermic men and 3.8% in men with azoospermia. For the calculation of the NNS, the risk of an adverse pregnancy outcome in our cohort was compared with the incidence ranges of miscarriage and children with CAs in the general population. The number of azoospermic men that needs to be screened to prevent one miscarriage (80–88) or one child with CAs (790–3951) was considerably lower compared with the NNS in the non-azoospermic group (315–347 and 2543–12 723, respectively).
Introduction

The prevalence of chromosomal abnormalities and submicroscopic deletions of the Y chromosome azoospermia factor (AZF) region is increased in infertile men (summarized by O’Flynn O’Brien et al., 2010). Because of this increased prevalence, guidelines recommend screening for these genetic abnormalities before ICSI treatment in case of (severe) male infertility (NVOG, 1999; Crosignani and Rubin, 2000; Foresta et al., 2002; NICE, 2004; AUA and ASRM, 2006). However, these guidelines are not based on clinical data and cost-effectiveness studies. So far, no studies have been published on the prevalence of adverse pregnancy outcomes in large cohorts of infertile men with genetic abnormalities.

The detection of a chromosomal abnormality in men with poor sperm quality allows clinicians to counsel the couple, not only regarding their chance of achieving a viable pregnancy with or without assisted reproductive technology (ART), but also on recurrent miscarriages or the risk of a child with congenital anomalies (CAs). The association between the latter two and balanced chromosomal rearrangements in particular, is well established (Tharapel et al., 1985; Egozcue et al., 2000; Suzumori and Sugura-Ogasawara, 2010). The risk for a couple of having a child with an unbalanced karyotype depends on the segregation behaviour of the derivative chromosomes during meiosis and the size and nature of the translocated or inverted chromosome segments.

In a previous study, we found a low prevalence of chromosomal abnormalities in a cohort of 1223 men who were azoospermic or eligible for ICSI treatment (3.1%) (Dul et al., 2010). There was a significant difference in the prevalence of chromosomal abnormalities between azoospermic men (15.2%) and non-azoospermic men (2.3%) (Dul et al., 2012). The question whether or not to perform chromosomal analysis in infertile men not only depends on the prevalence of chromosomal abnormalities, but also on the consequences of these abnormalities. To explore the consequences, we addressed two questions in the present study: (i) Was ART performed in couples in which the male partner carried a chromosomal abnormality and what were the outcomes? (ii) Does the detected chromosomal abnormality have clinical relevance for the pregnancy of the couple and what would be the consequences if the abnormality had remained undetected? The aim of this study was to assess, by answering these questions for azoospermic and non-azoospermic men separately, the efficiency of screening infertile men for chromosomal abnormalities in terms of estimating

Materials and Methods

Our cohort consisted of men with azoospermia or eligibility for ICSI treatment who visited the fertility clinic of the University Medical Center Groningen between November 1994 and October 2007. Azoospermia and non-azoospermia were determined based on the first sperm analysis in our centre, as described in detail previously (Dul et al., 2010). In 1223 men, the results of chromosomal analysis were available. Data on ART, ART related and spontaneous pregnancies (with a follow-up until 2010) and their outcomes were collected by chart review. In the study period, only ART with ejaculated sperm was offered in our centre.

No ethical board approval is required for retrospective chart review and collection of anonymized data in The Netherlands. Infertile couples attending our clinic are informed at intake about possible use of their anonymized data for research purposes, and a ‘no objection procedure’ is followed. Only patients who had not objected participated in this study.

Chromosomal analysis

Chromosomal analysis was performed on cultured peripheral lymphocytes. Five GTG-banded metaphase spreads with a minimal banding resolution of 550 were analysed per patient. In case of numerical mosaics, 100 metaphases were examined by conventional microscopic screening or FISH. When structural chromosomal aberrations were present, the evaluation was extended to additional molecular cytogenetic analysis by FISH or array comparative genomic hybridization, whenever appropriate. Chromosomal heteromorphisms as defined in the International System for Human Cytogenetic Nomenclature 2009 were not considered chromosomal abnormalities (Shaffer et al., 2009).

Classification of consequences

For each abnormality found, we performed a literature search for the risk of transmitting a chromosomal imbalance to the progeny. The estimation of the risk of unbalanced offspring is based on family history, and on published data on the expected segregation pattern of the translocation chromosomes and viability of the respective deletions and duplications (Stengel-Rutkowski et al., 1988; Schinzel, 2001; Feenstra et al., 2006). Based on these publications, we categorized the detected chromosomal abnormalities into the following categories: Chromosomal abnormality that does not increase the risk for miscarriage or the birth of a child with CA.

Key words: chromosomal abnormalities / miscarriage / congenital anomalies / male infertility
the risk of miscarriage (M); Chromosomal abnormality that increases the risk of both miscarriage and a child with CAs (M and CA). The incidences of miscarriages and of children with CA were compared between the latter two categories combined (M + M and CA) versus the NI group.

Calculation of NNS and statistical analysis

The NNS represents the number of subjects to be tested to detect one with a chromosomal abnormality that increases the risk for adverse pregnancy outcomes. For calculating NNS, the absolute difference in the risk of an adverse event in the study group and the risk in a reference population is calculated and the inverse of this risk difference is given as the NNS.

In order to calculate the NNS to prevent one miscarriage in infertile men, we first determined the incidence of miscarriage in the couples with a male karyotype known to be associated with an increased risk of miscarriage. However, not all miscarriages in this group will be due to an unbalanced karyotype and thus a correction needs to be made. This correction was based on the consistently reported incidence of clinically recognizable miscarriage in general population studies (12–15%) (summarized in Regan and Rai, 2000). Thus, the minimum NNS can be calculated as 1 divided by the prevalence of chromosomal abnormalities known to be associated with an increased miscarriage risk times the incidence of miscarriages in the study group minus the minimal reported general population incidence of 12%. The maximum NNS will be 1 divided by the prevalence times the incidence of miscarriages in the study group minus the maximal reported population incidence of 15% (see Table I).

In order to calculate the NNS to prevent one child with CA, we used a different strategy as the number of pregnancies in the couples with a male chromosomal abnormality with an increased risk for a child with CA was too small to reliably determine the incidence of children with CA. Instead, we used the (theoretical) risk estimation for male carriers of a balanced chromosomal abnormality with a known increased risk of viable offspring with an unbalanced karyotype. In general, these risk figures may vary from as low as 1% to well above 20%, depending on the particular translocation, but the majority have a risk far below 5% (Gardner and Sutherland, 2004). We conservatively estimated the risk of a child with CA to be increased by 1–5% for the carriers of a translocation with an assumed increased risk for CA. The estimated risk of 1–5% is the extra risk due to the paternal chromosomal abnormality and is added to the population risk of 3% of a child with CA. The minimum NNS for a child with CA thus will be 1 divided by the prevalence of chromosomal abnormalities related to an increased risk for CA times 5% and the maximum NNS as 1 divided by the prevalence times 1% (see Table I).

Since the prevalence of chromosomal abnormalities in men with azoospermia was significantly higher than in men with non-azoospermia, we calculated the NNS for both subgroups separately.

Table I Calculation of NNS for miscarriage (M) and for a child with CA.

<table>
<thead>
<tr>
<th>Formula number needed to screen</th>
<th>1: [prevalence of chromosomal abnormalities with increased risk (incidence of adverse pregnancy outcome in study cohort—incidence in reference population)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input parameters</td>
<td>Prevalence of chromosomal abnormalities with increased risk of congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>Infertile men</td>
</tr>
<tr>
<td></td>
<td>Azoospermic men</td>
</tr>
<tr>
<td></td>
<td>Non-azoospermic men</td>
</tr>
<tr>
<td>Theoretical incidence of child with congenital anomalies in men with a chromosomal abnormality with increased risk of a child with congenital anomalies</td>
<td>4–8%</td>
</tr>
<tr>
<td>Incidence of child with congenital anomalies in general population</td>
<td>3%</td>
</tr>
<tr>
<td>Prevalence of chromosomal abnormalities with increased risk for miscarriage</td>
<td>Infertile men</td>
</tr>
<tr>
<td></td>
<td>Azoospermic men</td>
</tr>
<tr>
<td></td>
<td>Non-azoospermic men</td>
</tr>
<tr>
<td>Incidence of miscarriage in men with a chromosomal abnormality with increased risk for M</td>
<td>45%</td>
</tr>
<tr>
<td>Incidence of miscarriage in reference population</td>
<td>12–15%</td>
</tr>
<tr>
<td>Number needed to screen for congenital anomalies</td>
<td>Infertile men</td>
</tr>
<tr>
<td></td>
<td>to 1/[(11/1223 × 0.04–0.03)]</td>
</tr>
<tr>
<td>Azoospermic men</td>
<td>1/[2/79 × (0.08 – 0.03)] to 1/[2/79 × (0.04 – 0.03)]</td>
</tr>
<tr>
<td>Non-azoospermic men</td>
<td>1/[(9/1144 × 0.08 – 0.03)] to 1/[(9/1144 × 0.04–0.03)]</td>
</tr>
<tr>
<td>Number needed to screen for miscarriage</td>
<td>Infertile men</td>
</tr>
<tr>
<td></td>
<td>to 1/[14/1223 × (0.45 – 0.15)]</td>
</tr>
<tr>
<td>Azoospermic men</td>
<td>1/[(3/79 × (0.45 – 0.12)] to 1/[(3/79 × (0.45 – 0.15)]</td>
</tr>
<tr>
<td>Non-azoospermic men</td>
<td>1/[(11/1144 × (0.45 – 0.12)] to 1/[(11/1144 × (0.45 – 0.15)]</td>
</tr>
</tbody>
</table>

Results

A chromosomal abnormality was detected in 38 of the 1223 men. The chromosomal abnormalities found are listed per sperm concentration category in Table II. In this table, the detected abnormalities are categorized according to their presumed consequences for progeny.

Table III summarizes the ART procedures and outcomes of pregnancies in our cohort of couples with a male chromosomal abnormality. In 21 of 26 couples with non-azoospermia, ART was started and 17 conceived. In two couples, a spontaneous pregnancy occurred. Azoospermic men with a gonosomal abnormality (n = 10) could not be offered ART in our clinic and these couples did not conceive. The remaining two azoospermic men [one with a reciprocal translocation (3:16) and one with a Robertsonian translocation (13;14)] in combination with an inversion of chromosome 5 showed some spermatozoa in subsequent sperm analyses and ICSI treatment was started. The first couple did not conceive, but the latter did, which resulted in the birth of a healthy child.
<table>
<thead>
<tr>
<th>Abnormality type per concentration category</th>
<th>Chromosomal abnormality</th>
<th>Prevalence per concentration category</th>
<th>Consequences for offspring&lt;br&gt;a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azoospermia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonosomal</td>
<td>47.XXY (4 cases)</td>
<td>15.2% (12/79)</td>
<td>NI</td>
</tr>
<tr>
<td>Translocation</td>
<td>47.XYY (2 cases)</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td>Inversion</td>
<td>45.XY,der(1;14)(q44;q11.2)</td>
<td>M and CA</td>
<td></td>
</tr>
<tr>
<td>Translocation and inversion</td>
<td>45.XY,inv(11)(q21q23.3)</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td><strong>0–1 million/ml</strong></td>
<td></td>
<td>3.1% (10/319)</td>
<td></td>
</tr>
<tr>
<td>Gonosomal</td>
<td>47.XXY</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td>Translocation</td>
<td>46.XY,t(1;14)(q44;q11.2)</td>
<td>M and CA</td>
<td></td>
</tr>
<tr>
<td>Inversion</td>
<td>46.XY,inv(11)(q21q23.3)</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td><strong>1–5 million/ml</strong></td>
<td></td>
<td>1.2% (3/251)</td>
<td></td>
</tr>
<tr>
<td>Gonosomal</td>
<td>47.XYY</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td>Inversion</td>
<td>46.XY,inv(10)(p11.2q21.2)</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td><strong>5–10 million/ml</strong></td>
<td></td>
<td>1.4% (3/211)</td>
<td></td>
</tr>
<tr>
<td>Translocation</td>
<td>46.XY,t(4:5)(q32;q14)</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td><strong>10–20 million/ml</strong></td>
<td></td>
<td>3.1% (6/191)</td>
<td></td>
</tr>
<tr>
<td>Gonosomal</td>
<td>Mos 45.X [4]/46.XY [26]</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td>Translocation</td>
<td>45.XY,der(13;14)(q10q10)</td>
<td>M and CA</td>
<td></td>
</tr>
<tr>
<td><strong>&gt;20 million/ml</strong></td>
<td></td>
<td>2.3% (4/172)</td>
<td></td>
</tr>
<tr>
<td>Translocation</td>
<td>46.XY,t(2;9)(q37.3;q12)</td>
<td>M and CA</td>
<td></td>
</tr>
<tr>
<td>Inversion</td>
<td>46.XY,inv(2)(p12q14.2)</td>
<td>M and CA</td>
<td></td>
</tr>
</tbody>
</table>

[n] represents number of cells within mosaic with that karyotype.

*a*: NI: Chromosomal abnormality without increased risk for miscarriage or a child with congenital anomalies; M: Chromosomal abnormality with increased risk of miscarriage only; M and CA: Chromosomal abnormality with increased risk of miscarriage and child with congenital anomalies.
that theoretically increases the risk of a child with CA by 1–5%.

Of the 1223 men in our cohort carried a chromosomal abnormality could not be related to the paternal chromosomal abnormality. Eleven type, but the other child had a normal karyotype, and the anomalies chromosomal abnormality, in which a child with CA was born to not significantly from the incidence in 38 infertile couples with a male children with CA was 3.1% (38/1211). This incidence did not differ signifi-

For our entire cohort of 1223 infertile men, the incidence of chil-

Table III Pregnancy outcomes in 38 couples in which the male partner had a chromosomal abnormality, categorized to its association with miscarriage and offspring with CAs.

<table>
<thead>
<tr>
<th>Total</th>
<th>% NI</th>
<th>% M + M and CA</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of couples</td>
<td>38</td>
<td>24</td>
<td>14 (3 + 11)</td>
</tr>
<tr>
<td>Of which treated</td>
<td>23</td>
<td>60.5</td>
<td>12</td>
</tr>
<tr>
<td>Total number of pregnancies (include spontaneous)</td>
<td>31</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Number of gestational sacs</td>
<td>34</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Live born normal (% per gestational sac)</td>
<td>18/34</td>
<td>52.9</td>
<td>9/14</td>
</tr>
<tr>
<td>Live born abnormal (% per gestational sac)</td>
<td>2/34</td>
<td>5.9</td>
<td>1/14</td>
</tr>
<tr>
<td>Miscarriage (% per gestational sac)</td>
<td>11/34</td>
<td>32.4</td>
<td>2/14</td>
</tr>
<tr>
<td>Ectopic pregnancy (% per gestational sac)</td>
<td>1/34</td>
<td>2.9</td>
<td>1/14</td>
</tr>
<tr>
<td>Unknown outcome of pregnancy (% per gestational sac)</td>
<td>2/34</td>
<td>5.9</td>
<td>1/14</td>
</tr>
<tr>
<td>At least one normal live born (% per treated couple)</td>
<td>12/23</td>
<td>52.2</td>
<td>6/12</td>
</tr>
</tbody>
</table>

NI: Chromosomal abnormality without increased risk for miscarriage or a child with congenital anomalies; M + M and CA: Sum of categories M: Chromosomal abnormality with increased risk of miscarriage only, and M and CA: Chromosomal abnormality with increased risk of miscarriage and child with congenital anomalies.

difference was not statistically significant. If ART was performed, the chance for a couple of conceiving at least one normal live born was comparable in both groups (6/12; 47.4% and 6/11; 54.5%, respectively).

Six couples had one or more miscarriages. The incidence of miscar-

Six couples had one or more miscarriages. The incidence of miscar-

Discussion

The aim of this study was to assess the efficiency of screening infertile men for genetic abnormalities in terms of estimating the risk of an adverse pregnancy outcome (i.e. a child with CAs or a miscarriage). These data are urgently needed as a basis for evidence-based guidelines on screening. Our findings are based on a large cohort of 1223 infertile men of whom 38 (3.1%) carried a chromosomal abnormality.

This relatively low prevalence is in agreement with reports from the literature. However, no data are published on pregnancy outcomes in large cohorts of infertile men with chromosomal abnormalities.

We collected these data and calculated the NNS for adverse preg-

The NNS in infertile men for a miscarriage is 265–291. In men with azoospermia the NNS is 80–88 and in non-azoospermic men, 315–347 (Fig. 1).

The most important consequence of genetic abnormalities in men with a procreative wish is the increased risk of a child with CA due to an unbalanced chromosomal abnormality. In the general population, the risk of a child with any CA is estimated to be 2–3%. Most gonosomal abnormalities may cause infertility in the offspring, but no other CA. The risk of CA is increased in translocations and some pericentric inversions, and the precise risk estimation is based on which chromosomes are involved and the breakpoints of the chromosomal anomaly. Worldwide published data on this risk estimation are used to counsel the couple on their specific risk. The estimation can be very precise when the abnormality is relatively common. However, for most abnormalities, no data for calculating the risk are available. We did not find a significant difference in the incidence of children with CA born to infertile men with and without chromosomal abnormalities. This is probably caused by the small number of pregnancies in our study in the men with chromosomal abnormalities.

For the calculation of an NNS, we therefore used the theoretical risk of a child with CA in these men, based on the literature. Because in the study period only ART with ejaculated sperm could be offered in our clinic, only the couples with non-azoospermia have undergone ART and conceived. Based on the data obtained in our study, the NNS for a child with CA is 2543–12723 in men with non-azoospermia. If ICSI with surgically retrieved sperm is performed in azoospermic men with genetic abnormalities, the risk for
the offspring is expected to remain low since most genetic abnormalities found in azoospermic men are not associated with miscarriage or children with CA. If we extrapolate the results of this study to men with azoospermia, the NNS for a child with CA in azoospermic men would be 790–3951.

Another consequence of chromosomal abnormalities can be an increased risk (in reviews varying from 49 to 83%) of miscarriages, especially in translocations and pericentric inversions (Franssen et al., 2006; Stephenson and Sierra, 2006; Suzumori and Sugiuura-Ogasawara, 2010). In our study, ART treatment of non-azoospermic men with chromosomal anomalies did not result in significantly more miscarriages (32.4%), when compared with men with a normal karyotype (25.1%). Based on our data, the NNS for miscarriage in infertile men is 265–291 (80–88 for azoospermic men and 315–347 for non-azoospermic men). In non-azoospermic men, it might be more cost-effective to limit screening for chromosomal abnormalities to those with a history of more than one miscarriage. In recurrent miscarriage, the risk that one of the partners of a couple is a carrier of a translocation or inversion is 4–6% (Goddijn and Leschot, 2000), while in our study the prevalence of chromosomal abnormalities with an increased risk of miscarriages was only 1.0% for the male partner with non-azoospermia. A higher prevalence of structural chromosomal abnormalities, as in couples with recurrent miscarriages, might lower the NNS substantially. The low prevalence of translocations and inversions among infertile men indicates that male infertility alone is not the most effective selection criterion for genetic screening. It remains to be established whether a positive history for recurrent miscarriage or a positive family history for recurrent miscarriage or children with CA decreases the NNS significantly in non-azoospermic infertile men. Research on the impact of recurrent miscarriages in relatives on the NNS might be hampered by non-disclosure of miscarriages, which may be culturally determined.

Most non-azoospermic men in our cohort with an increased risk of unbalanced progeny did not refrain from ART after counselling, and conceived. This did not result in a significantly higher incidence of miscarriages or offspring with CAs when compared with infertile men with a chromosomal abnormality without a known increased risk for adverse pregnancy outcome. This may indicate that screening for chromosomal abnormalities in non-azoospermic men does not decrease the incidence of adverse pregnancy outcomes.

Screening for chromosomal abnormalities, and also for AZF deletions, in men with poor sperm quality may serve another goal: it might give an explanation for the infertility, as in some chromosomal abnormalities (e.g. Klinefelter’s syndrome and Robertsonian translocations), and in AZF a and b deletions the association with infertility is well-known. A causative diagnosis may be helpful in the emotional coping process of the couple. Furthermore, in some countries, legislation prescribes testing for genetic causes in all infertile couples. This may include testing for cystic fibrosis-related and androgen receptor gene mutations, as well as other gene mutations and polymorphisms suspected to be involved in infertility (O’Flynn O’Brien et al., 2010).

Most guidelines advise the screening of infertile men for chromosomal abnormalities and AZF deletions and the performance of elaborate testing based on the clinical presentation. We explored the efficiency of the common policy of screening for chromosomal abnormalities and AZF deletions, in terms of finding the cause of the male infertility (Supplementary data, Table SI). We found that most genetic abnormalities detected in azoospermic men had a known association with infertility, while the majority of genetic abnormalities found in non-azoospermic men were chance findings (i.e. those occurring with a low frequency in the population and unrelated to the infertility of the couple). In our study, azoospermia was most frequent in men with gonosomal abnormalities (including AZF deletions) and Robertsonian translocations, while the majority of men with reciprocal...
translocations and inversions were non-azoospermic. This is in agreement with the literature (reviewed in O’Flynn et al., 2010).

For the development of evidence-based guidelines on the genetic screening of infertile men cost-effectiveness, analyses have to be performed that also consider the costs of adverse outcomes of pregnancies, and the costs of prevention of miscarriages and children with CAs by preimplantation genetic diagnosis and prenatal diagnosis. The current study provides data on the NNS for these adverse outcomes, to be used in future cost-effectiveness studies. The NNS in men with azoospermia for miscarriage (80–88) and for a child with CA (790–3951) are relatively low compared with men with non-azoospermia, in whom the NNS for miscarriage is 315–347 and the NNS for a child with CA is 2543–12723. The large difference in these NNS between men with azoospermia and non-azoospermia is caused by the significant difference in the prevalence of chromosomal abnormalities in these two groups of infertile men. The probability of finding a chromosomal abnormality is even higher in men with non-obstructive azoospermia compared with men with obstructive azoospermia (O’Flynn et al., 2010). As a consequence, the NNS in men with non-obstructive azoospermia will be substantially lower. Due to the retrospective design of our study, this subcategorization of azoospermia was not possible. Future studies should address this issue, to allow for a better risk estimate in obstructive and non-obstructive azoospermia.

Based on the NNS found in our study, we recommend performing chromosomal screening in all azoospermic men, because a relatively low number of men need to be screened to prevent adverse pregnancy outcomes. In non-azoospermic infertile men, screening might be limited to men with a history of recurrent miscarriage or with a positive family history for recurrent miscarriage or children with CAs. Future cost-effectiveness studies are needed to provide further evidence that will aid in the development of guidelines on screening infertile men for chromosomal abnormalities.

**Supplementary data**

Supplementary data are available at http://humrep.oxfordjournals.org/.

**Authors’ roles**

E.C.D. helped design the study, collected and analyzed the data and wrote the manuscript. J.v.E.-A. was responsible for the sperm analyses. H.G. supervised the statistical analysis. T.D. was responsible for the chromosomal analyses. J.A.L. was responsible for the design of the study. C.M.A.v.R.-A. helped design the study and provided the cytogenetic data. All authors revised the manuscript.

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**Conflict of interest**

None declared.

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