Measuring the effects of genetic testing: studies on thrombophilia, sickle cell trait, recurrent miscarriage and male subfertility
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Citation for published version (APA):
Vansenne, F. (2011). Measuring the effects of genetic testing: studies on thrombophilia, sickle cell trait, recurrent miscarriage and male subfertility
Chapter 10

Disclosure of a genetic abnormality in patients with recurrent miscarriage or male subfertility – estimated and perceived risks and influence on reproductive choices

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ABSTRACT

Objective
To evaluate risks as estimated and perceived by patients with recurrent miscarriage or male subfertility and their reproductive choices after disclosure of an abnormal genetic test result.

Design
Longitudinal prospective index-control questionnaire study with one year follow-up.

Setting
Seven of the eight clinical genetics departments of academic medical centers and their referring gynaecologists and urologists.

Participants
Carriers of a genetic abnormality and controls in whom no genetic abnormalities were found.

Interventions
Three questionnaires: one completed just before disclosure of genetic test result (baseline), a second 3 months after disclosure, and a third after 12 months.

Outcome measures
Estimated risks for outcomes like the occurrence of another miscarriage, birth of a child with major congenital malformations, having a stillborn child and passing on reproductive problems. Perceived risks for these outcomes compared to the general population. Obstetric outcomes: pregnancies and outcomes of pregnancies, as well as any prenatal diagnostics performed (ultrasound, chorionic villus sample (CVS), amniocentesis) and its outcomes. Ideas about termination of pregnancy and changes in views about having children.

Results
Disclosure of the genetic abnormality lead to significantly higher estimated risks in carriers of a genetic abnormality on the outcomes compared to controls. Both carriers and controls overestimated their risks compared to their actual risks. After disclosure of the abnormality carriers significantly more often would consider termination of pregnancy compared to controls (67% versus 42%, p=0.01) and more often changed their views; they more often wanted having less children than originally planned or wanted to refrain from having children at all (32% versus 9%, p<0.01), which was positively correlated to the estimated risks.

Conclusions
Disclosure of a genetic abnormality leads to higher risk perception for several adverse obstetrical outcomes and possibly inappropriate reproductive decisions. Emphasizing the actual risks could lead to more realistic expectations in carriers and thus to better – well informed - choices about reproductive options.
INTRODUCTION

Couples with recurrent miscarriage and men with poor semen quality may undergo genetic testing as part of the diagnostic work-up. In couples with recurrent miscarriage one of the partners may carry a balanced structural chromosome abnormality. If so, their offspring is at risk for unbalanced structural chromosome abnormalities leading to severe mental retardation and/or congenital malformations. The prevalence of a parental structural chromosome abnormality in this situation is estimated between 3% and 6%. Clinical guidelines recommend parental karyotyping in couples with recurrent miscarriage and subsequent invasive (PND) when such a chromosomal abnormality is found (a carrier couple). In case of an unbalanced fetal karyotype, termination of the pregnancy can be considered after careful and thorough counseling.

Genetic testing in men with poor semen quality is generally performed if the total sperm count is < 1 million spermatozoa per ejaculate. Men undergo karyotyping and are evaluated for deletions on the Y-chromosome before starting with Intra Cytoplasmatic Sperm Injection (ICSI) treatment. A genetic cause is found in 10% to 15% of cases. Men with a chromosomal abnormality have an increased risk of unbalanced chromosomal offspring after ICSI treatment. In case of Y-deletions, all sons conceived by ICSI will inherit the same deletion with possible consequences for their reproductive chances.

Here we investigate to what extent disclosure of a genetic abnormality influences reproductive choices of carriers, as it may well be that a person’s perception of the consequences of his/her genetic abnormality influence decisions on management options, such as the choice for invasive prenatal diagnosis (PND) in future pregnancies, or change his/her ideas about termination of pregnancy. In addition we evaluated possible differences between carriers and noncarriers in estimated risks of various outcomes associated with obstetric outcomes, like the risk of another miscarriage and the risk of having a child with major congenital malformations. We also evaluated how these risks were perceived relative to the risk of the general population by carriers and noncarriers.

METHODS

The CONGENO-study (CONsequences of GENOtyping in reproductive medicine) was a longitudinal prospective index-control questionnaire study in couples with recurrent miscarriage or male subfertility to whom parental chromosome analysis was offered. Data on a subset of the participants have been published before.

Study population

Couples with recurrent miscarriage or male subfertility in whom parental chromosome analysis was performed in both partners after recurrent miscarriage, or chromosome analysis in the male partner in case of male subfertility, were eligible to participate in the study. Between January 2006 and June 2009 all carrier couples in whom one of the partners were found to carry a chromosome abnormality (either a structural or numerical abnormality) or a (partial) interstitial deletion of the Y-chromosome were identified in the clinical genetics laboratories of seven academic hospitals in the Netherlands. For each carrier couple, a random subset of two noncarrier couples was formed by identifying the first two couples who tested negative after the carrier couple, matched for referring hospital and indication. These will be referred to as control couples. Matching was performed to obtain a sample balanced over time. Couples were excluded from the study if they had already received their genetic test result, had insufficient proficiency of the Dutch language, were pregnant at the time of the genetic test with a gestational age of more than 12 weeks, or if one of the partners of the couple had a serious or life threatening disease. For this study, we used only the partner carrying a genetic abnormality in carrier couples, and both partners of the control couples as controls.

Study procedure

After identification of an eligible carrier or control by the clinical genetics laboratory, the referring physician was contacted by the researchers to verify eligibility and to ask for consent to approach them. In case a control turned out to be non-eligible, a new control was selected. If a carrier or control was considered eligible, a first questionnaire including a letter explaining the purpose of the study and a written informed consent form was sent.

A few days after receiving the invitation and questionnaire the carrier or control was contacted by telephone by the researchers to be invited and to be provided with additional information...
when necessary. If they agreed, participants were asked to complete the first questionnaire individually at home. A stamped return envelope was included.

Most participants had a blood sample drawn for the genetic test six to eight weeks before being contacted and the appointment for disclosure of the genetic test result was scheduled one to three weeks after receiving the questionnaire. All invited participants were unaware of the results of genetic testing at the moment of returning the baseline questionnaire. Before study initiation, the Institutional Review Board (IRB) of the Academic Medical Center in Amsterdam had indicated that formal IRB approval was not needed for this study, according to legal requirements in the Netherlands.

All participants received a second questionnaire three months after disclosure of the genetic test results and a third set after 12 months. In case of non-response on the second or third questionnaire a reminder was sent after two weeks and participants were contacted by telephone after two more weeks of non-response.

**Questionnaires**

*Socio-demographics and obstetric history:* Participants were asked about their age, religion, education, occupation and obstetric history (baseline).

*Awareness of genetic test result.* Participants were asked to indicate if a genetic abnormality had been found in themselves or in their partner and, if so, which genetic abnormality. This was compared with the original test result by the researchers. In addition participants were asked if they thought this genetic abnormality was the cause of their recurrent miscarriage or male subfertility (second questionnaire at three months).

*Estimated and perceived risks on outcomes.* Participants were asked how they rated their personal risk of another miscarriage, a child with major congenital abnormalities, a stillborn child and the risk of passing on reproductive problems to their offspring. Participants marked these estimated risks on visual analog scales anchored at 0% and 100%. These estimated risks were compared to the actual risks based on data from the literature. Participants were also asked to indicate how they perceived their estimated risk for the respective outcomes relative to the risk for the general population (lower, comparable or higher) (included in all three questionnaires).

**Obstetric outcome**

During the follow-up period of 12 months obstetric information of the participants was recorded: pregnancies and outcomes of pregnancies, as well as any prenatal diagnostics performed (ultrasound, chorionic villus sample (CVS), amniocentesis) and its outcomes.

**Termination of pregnancy**

Participants were asked about their ideas about termination of pregnancy, whether they would ever consider it or not and, if they did, under which circumstances. Participants could also indicate and motivate any changes in ideas about termination of pregnancy during the follow-up period (asked in all three questionnaires).

**Changes in views about having children**

Participants were asked about any changes in their views about having children, such as considering to have less children than originally planned or refraining from having children at all. They could also indicate what the main reason was for this change of view (asked in all three questionnaires).

**Analysis**

In the analysis we focused on the effect of disclosure of the abnormal genetic test result in carriers and compared their responses with those of the control group. We performed subgroup analyses, stratifying for gender or type of fertility problem (recurrent miscarriage or male subfertility).

T-tests were performed to test for significant differences between carriers and controls and between recurrent miscarriage and male subfertility on estimated risks were tested with t-tests. Differences between carriers and controls on the rating of their perceived risk against the general population were tested with χ² tests. Differences between carriers and controls in choices for termination of pregnancy or changes in views about having children were tested with χ² tests.
RESULTS

For this study 800 eligible participants were identified: 66 carriers and 220 controls in the recurrent miscarriage group, and 98 carriers and 416 controls in the male subfertility group (Figure 1). Of all eligible carriers 41 had to be excluded. Overall 362 participants (48%) returned the first questionnaire, of which 36 were carriers with recurrent miscarriage and 48 carriers with male subfertility. In total 174 participants (65%) completed the follow-up questionnaires, 57 with recurrent miscarriage (18 carriers and 39 controls) and 117 with male subfertility (23 carriers and 94 controls).

Socio-demographics and obstetric history

In the carrier group a higher percentage of men was included compared to the control group (74% versus 50%, p<0.01) (Table 1). This is because of a relatively high contribution of male subfertility (where in all cases the man was the carrier of the genetic abnormality) versus recurrent miscarriage (where either man or women could be carrier). The control group consisted of both men and women. The mean age of the carrier group was 35.4 years versus 35.2 years in the control group (p=0.74). There were no differences between the carrier and the control group in nationality, education or religious affiliation. There were no statistically significant differences between carrier couples and control couples with regard to obstetric history (Table 1).

Figure 1 RM: Recurrent miscarriage; MSF: male subfertility
TABLE 1 Baseline characteristics and obstetric history of carriers and controls with recurrent miscarriage or male subfertility

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Carriers (n=85)</th>
<th>Controls (n=281)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>63 (74%)</td>
<td>141 (50%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women</td>
<td>22 (26%)</td>
<td>140 (50%)</td>
<td></td>
</tr>
<tr>
<td>Dutch nationality</td>
<td>77 (91%)</td>
<td>265 (94%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>35.4 (5.0)</td>
<td>35.2 (6.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>Primary</td>
<td>5 (6%)</td>
<td>9 (3%)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>48 (57%)</td>
<td>153 (55%)</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>28 (33%)</td>
<td>110 (40%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Religious affiliation</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>None</td>
<td>43 (54%)</td>
<td>168 (61%)</td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>22 (28%)</td>
<td>81 (30%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (18%)</td>
<td>25 (9%)</td>
<td></td>
</tr>
<tr>
<td>Obstetric history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since starting to conceive</td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>6 months – 1 year</td>
<td>7 (8%)</td>
<td>17 (13%)</td>
<td></td>
</tr>
<tr>
<td>1– 2 years</td>
<td>36 (43%)</td>
<td>56 (41%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>39 (47%)</td>
<td>60 (44%)</td>
<td></td>
</tr>
<tr>
<td>Median no. previous pregnancies (IQR)</td>
<td>0 (0-3)</td>
<td>1 (0-3)</td>
<td>0.71</td>
</tr>
<tr>
<td>Median no. previous miscarriages (IQR)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Median no. live born children (IQR)</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Genetic test result

Participants were asked in the second questionnaire (three months after disclosure) if they could recall the genetic test result. In the carrier group 85% of the participants (46 out of 54) were aware that a genetic abnormality had been found. Five of the remaining eight carriers stated no genetic abnormality had been found, two carriers did not know and one male carrier answered that the genetic abnormality was found in his female partner. Carriers were also asked to specify the type of genetic abnormality. This was done correctly by 64% of carriers (34 out of 53). Ten carriers did not answer the question and ten carriers gave an incomplete or incorrect answer (e.g. they only indicated ‘translocation’ but not between which chromosomes).

Ninety-four percent of carriers (44 out of 46) indicated they thought the genetic abnormality found was the cause of the recurrent miscarriage or male subfertility.

In the control group, 189 out of 213 participants answered correctly that no genetic abnormalities had been found (89%), seven controls did believe an abnormality was found, of which four in themselves and three in their partner; 17 controls stated that they could not recall the genetic test result.

Estimated risks

Estimated risks for a number of outcomes are displayed in Table 2, combined with the actual risks. Both carriers and controls overestimated their risk in the follow-up questionnaires, compared to their actual risks. There were no differences in estimated risks between groups before disclosure at baseline, except for the risk of having a child with major congenital malformations which the carrier group estimated as higher than the control group (mean 26% versus 19%, p=0.03).

After disclosure of the genetic test result, both carriers and controls kept overestimating their risks on the various outcomes. Carriers estimated their risks significantly higher after disclosure compared to controls, especially in the recurrent miscarriage group. This applied in all outcomes except for ‘having a stillborn child’. The individual estimated risks for all risk outcomes were highly correlated in both carriers and controls (p<0.01). Correlations ranged between 0.178 and 0.749.
Perceived risks

All participants were asked how they perceived their estimated risks relative to those of the general population. Carriers rated their risk for almost all outcomes as much higher than the general population. This was the case for the perceived risk of another miscarriage at three months follow-up ($\chi^2 (2)=42.20$, $p<0.01$, $r^2=0.51$, $0.44$ vs. $0.03$) and recurrent miscarriage and male subfertility compared to the control group ($\chi^2 (2)=49.40$, $p<0.01$, $r^2=0.51$, $0.44$ vs. $0.03$). The number of pregnancies and miscarriages did not differ significantly between carrier and control couples in both the recurrent miscarriage and male subfertility group.

TABLE 3 Obstetric outcome after 12 months follow-up in couples with recurrent miscarriage or male subfertility

<table>
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<th>Procedure</th>
<th>No. of pregnancies (%</th>
<th>p-value</th>
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<tr>
<td>Ultrasound</td>
<td>8 (75%)</td>
<td></td>
</tr>
<tr>
<td>Chorionic villus sampling</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td>Nuchal translucency</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>'Combinatietest'</td>
<td>2 (5%)</td>
<td></td>
</tr>
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</table>

Obstetric follow-up

At 12 months follow-up, 12 out of 18 carrier couples from the recurrent miscarriage group had become pregnant (67%) and 16 out of 20 control couples (80%) ($p=0.47$) (Table 3). In the male subfertility group the pregnancy rate was 30% for carrier couples and 40% for the control couples ($p=0.60$). The number of pregnancies and miscarriages did not differ significantly between carrier and control couples in both the recurrent miscarriage and male subfertility group.

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When prenatal diagnosis was performed, this was most often through ultrasound (in 92% of pregnancies). Only 3 carriers in the recurrent miscarriage group opted for invasive prenatal diagnosis; in all cases an amniocentesis was performed. In two cases the same balanced translocation was found as in the parent, in one case a normal karyotype was found. The most frequently reported reason for having prenatal diagnosis in the recurrent miscarriage...
group was being carrier of a genetic abnormality (7 out of 9). In the carrier group with male subfertility this was mentioned once (1 out of 3).

Termination of pregnancy
At baseline, no differences between carriers and controls concerning ideas about termination of pregnancy were found. In the carrier group 56% answered that they would consider termination of pregnancy, in specific circumstances, (46 out of 82) versus 52% in the control (142 out of 275; $\chi^2(2)=3.2$, $p=0.21$). At three months follow-up more carriers (30 out of 45, 67%) would consider termination of pregnancy compared to controls (62 out of 149, 42%; $\chi^2(2)=9.0$, $p=0.01$). In the carrier group at three months follow-up 11 out of 53 participants (21%) stated that their ideas about termination of pregnancy had changed since the baseline questionnaire, meaning they would now consider termination of pregnancy. Of those carriers, 91% indicated their ideas had changed because of the genetic abnormality found (10 out of 11).

At 12 months follow-up still more carriers considered termination of pregnancy compared to controls (62% versus 38%, $\chi^2(2)=6.2$, $p=0.04$). In carriers we found a positive correlation between ideas about termination of pregnancy at three and 12 months follow-up (Spearman's rho =0.37, $p=0.04$), but not compared to baseline. In controls there was a positive correlation between ideas about termination of pregnancy at baseline and three months follow-up (Spearman's rho = 0.43, $p<0.01$).

Changes in views about having children
At three months carriers had significantly more often changed their views about having children since baseline, compared to controls. At three months 17 out of 53 carriers had changed their views about having children (32%), compared to 19 out of 213 controls (9%), $\chi^2(1)=19.5$, $p<0.01$; they indicated they considered having less children than they originally wanted or refraining from having children at all. 15 out of those 17 carriers changed their view because of the genetic abnormality (88%). No differences were found between carriers and controls at 12 months follow-up. There was a high correlation between estimated risk on two outcomes and changes in views about having children in carriers: carriers with higher estimated risks more often changed their views about having children ($p=0.05$ for a child with congenital malformations, $r=0.274$; $p=0.02$ for a stillborn child, $r=0.314$).

DISCUSSION
In this study in patients being tested for a genetic abnormality we found that disclosure of the abnormality leads to significantly higher estimated risks in carriers on different outcomes such as the risk of another miscarriage and the risk of having a child with major congenital abnormality, compared to controls. Both carriers and controls overestimated their risks compared to their actual risks. After disclosure of the abnormality carriers significantly more often would consider termination of pregnancy compared to controls (67% versus 42%, $p=0.01$) and more often changed their views about having children (32% versus 9%, $p<0.01$), which was positively correlated to estimated risks.

The strengths of this study are that estimated and perceived risks and reproductive choices were measured in all included participants at the same moment before disclosure of the genetic test result (baseline) and twice after disclosure during a one year follow-up. This was studied in carriers and compared with controls in whom no genetic abnormality had been found. Secondly, the study was conducted in seven of the eight academic hospitals in the Netherlands, including a representative sample of patients undergoing genetic testing at outpatient clinics of gynecology because of reproductive problems.

Several potential limitations of our study should be considered. Only one telephone call to include eligible participants could be made, since time between identification of carrier couples in the laboratory and previously planned appointments for disclosure of the genetic test result was limited, and participants had to have their baseline questionnaire returned before disclosure of their genetic test result. We have no data on non-responders and their reason for not participating. It is therefore possible that a form of selection bias occurred where participants who felt more attracted to the subject of the study were more willing to participate. Nevertheless, comparing the patient characteristics in our study to those of a large earlier study in couples with recurrent miscarriage, it seems that the participants in our study offer a good representation of the clinic based population. Two-thirds of participants completed the follow-up questionnaires. This might also have led to a selection bias, if more anxious people were lost to follow-up because they did not want to be confronted with questions about the genetic test or potentially unsuccessful fertility treatments. Overall the number of carriers who completed the follow-up questionnaires was relatively small, so results could not always be quantified, but are used to qualify the results.
Although research on the psychological effects of genetic testing is growing there has been relatively little attention for the influence of genetic testing on behavior, such as uptake of health-related behaviors, use of health services or reproductive choices.\textsuperscript{15-17} The association between receiving genetic risk-information and patients’ willingness to change behaviour is unclear, but could be strong, since genetic information has an effect on different perspectives of life because of its hereditary character. Health-related behavior is an important outcome parameter in genetic evaluation studies, as it might be a good indicator for the effect of genetic testing.\textsuperscript{18}

Most risks were overestimated by both carriers and controls at all points in time, compared to actual risks. The estimated risks at baseline have been discussed before and compared to the actual risks.\textsuperscript{10} Carriers highly overestimated their risks for a number of outcomes compared to controls after disclosure of their genetic abnormality. Earlier research has shown that in recurrent miscarriage, carriers have the same chance of having at least one healthy child compared to controls and the actual risk of severely handicapped offspring with unbalanced chromosomal abnormalities is very small.\textsuperscript{13} This shows that receiving an abnormal genetic test result has a negative influence on the perception of risk by carriers. This negative influence was still found one year after disclosure of the genetic abnormality, which might indicate a permanent effect. Overestimations of perceived risks have been reported before. In hereditary cancer, such as breast and ovarian cancer, patients also show an overestimation of perceived risks of getting cancer.\textsuperscript{17}

Perceived risks are positively correlated with anxiety.\textsuperscript{\textsuperscript{\textsuperscript{10}}} A higher perceived risk may lead to more anxiety in patients. More realistic perceptions of the possible risk could therefore lead to less anxiety in patients.\textsuperscript{13} On the other hand, it might also be that higher anxiety levels lead to higher perceived risks.\textsuperscript{12} Higher perceived risks have also been linked to a lack of knowledge about the disease, implicating that more information about the disease or condition could lead to more realistic perceived risks.\textsuperscript{19}

We also found that higher risk perceptions were correlated to changes in views about having children. Risk perception has been described as a significant motivator for the uptake of protective health-related behavior.\textsuperscript{20} Whether this is also true for reproductive behavior cannot be directly inferred from our study, but the opposite seems to take place. Inaccurate risk perceptions may lead to inappropriate decision making, which is of great concern if this leads to actions that cannot be made undone, such as a termination of pregnancy or refraining from having children. It seems therefore important that gynecologists emphasize the factual risks for carriers, stressing that chances of having at least one healthy child are not lower than in noncarriers and that the actual risk of unbalanced offspring is very small. Studies have shown that individuals, both patients and physicians, experience difficulty in understanding probability and relative risk data.\textsuperscript{21-23} This makes it even more important that gynecologists take time to explain risks, especially to carriers and maybe keep repeating these actual risks at different times.

Carriers indicated that after learning of the genetic abnormality they changed their views about termination of pregnancy, considering this more often after disclosure than before. Earlier studies on these issues reported conflicting results. One study found that couples at high risk of a child with cystic fibrosis postponed pregnancies or decided to have fewer children.\textsuperscript{24} Another study reported no differences between carriers of cystic fibrosis and noncarriers in reproductive behavior.\textsuperscript{25} We do not know whether the carriers in our study would actually terminate an affected pregnancy; it would be interesting to study if a change in intention also leads to a change in actual decision making.

Regarding the choices for prenatal diagnosis, most carriers opted for non-invasive procedures, such as an ultrasound, rather than invasive procedures. Our sample is too small to find statistically significant differences in the uptake of prenatal diagnosis between carriers and controls, but the overall uptake of invasive PND was low. Previous studies have shown that a substantial proportion of carriers refrain from invasive PND and that the key determinant regarding the uptake of invasive PND in women aged 35 years or older was their prior opinion regarding invasive PND, not the increased risk of a child with a chromosome abnormality.\textsuperscript{26,27} Although carriers perceive their risk of having a child with major congenital malformations as high, they do not act upon it by having invasive PND. It is very likely they feel that having an ultrasound is as effective as invasive PND in identifying abnormal offspring, but without the risk of inducing a miscarriage.
The implications of our findings for understanding health behavior based on risk perceptions are that gynaecologists need to realise that disclosure of a genetic abnormality leads to higher perceived risks and possibly to inappropriate reproductive decisions. Emphasizing the actual risks of different outcomes, such as another miscarriage or a child with congenital malformations could lead to more realistic expectations in carriers and thus to better – well informed - choices about reproductive options.

REFERENCES


