Patients’ experiences of Preimplantation Genetic Diagnosis (PGD)

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ABSTRACT

The aim of the present study was to investigate the experiences and attitudes concerning preimplantation genetic diagnosis (PGD) among the couples that have undergone PGD in Sweden. PGD is an alternative to conventional prenatal diagnosis for couples with a high risk of having a child with genetic disease. Couples opting for PGD have to perform in vitro fertilisation, generated embryos are subjected to biopsy and diagnosis, and healthy embryos can be transferred to the female uterus. Hopefully a pregnancy will be established. However, PGD is a strategy that implies both physical and psychological stress, and it is not obvious that this is an easier alternative than prenatal diagnosis. A questionnaire was sent to 116 couples that had carried out at least one PGD treatment cycle. The response rate was 89%, thus almost all couples treated in Sweden since the start in 1995 was represented.

Results: The stress, both psychologically and physically, caused by the PGD treatment was evaluated somewhere between “As expected” and “More stressful than expected”. The stress experienced during the PGD treatments was not associated with the couples’ previous reproductive experiences. The most physical stressful event was the oocyte retrieval and the most psychologically stressful period was “waiting for a possibly/hopefully embryo transfer”.

The majority of couples that had performed prenatal diagnosis on a spontaneous pregnancy and experienced a PGD treatment reported that PGD was more physically stressful (54%), but that prenatal diagnosis was more psychologically stressful (51%). The couples reported the reproductive alternatives chosen after PGD closure, and couples performing PGD at the present rated future reproductive alternatives. Results indicated that oocyte- and sperm donations were a less attractive alternative than for example adoption. Participants in the study also had the opportunity to state for whom/which indications PGD should be an option.

Conclusion: The stress associated with performing PGD or prenatal diagnosis is extensive and none of the alternatives is an obvious choice. PGD was reported as more physical stressful, but prenatal diagnosis was more psychologically stressful. The reproductive pathways chosen after PGD closure was reported, and surprisingly sperm and oocyte donations were not attractive alternatives. The choice of reproductive alternatives might be influenced by the information and support provided by the healthcare personal. Knowledge about the experience of PGD treatments is of great importance for those that meet these couples for genetic and reproductive counselling, in order to give them proper care and to better meet their demand of information and support.

Keywords: preimplantation genetic diagnosis, couples experiences, reproductive alternatives, descriptive data report, statistical comparison
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>2</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>4</td>
</tr>
<tr>
<td><strong>Preimplantation Genetic Diagnosis (PGD)</strong></td>
<td>4</td>
</tr>
<tr>
<td>The procedure of PGD</td>
<td>5</td>
</tr>
<tr>
<td>Previous studies</td>
<td>6</td>
</tr>
<tr>
<td>The patients</td>
<td>8</td>
</tr>
<tr>
<td>PGD in Sweden</td>
<td>8</td>
</tr>
<tr>
<td>Aim</td>
<td>9</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>10</td>
</tr>
<tr>
<td>Design</td>
<td>10</td>
</tr>
<tr>
<td>Participants</td>
<td>10</td>
</tr>
<tr>
<td>Procedure</td>
<td>10</td>
</tr>
<tr>
<td>Instruments</td>
<td>10</td>
</tr>
<tr>
<td>Statistical analyses</td>
<td>12</td>
</tr>
<tr>
<td>Ethical considerations</td>
<td>13</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>14</td>
</tr>
<tr>
<td>Descriptive data</td>
<td>14</td>
</tr>
<tr>
<td>Reproductive history</td>
<td>15</td>
</tr>
<tr>
<td>Reasons for choosing PGD</td>
<td>17</td>
</tr>
<tr>
<td>The experience of PGD</td>
<td>18</td>
</tr>
<tr>
<td>The stress of PGD compared to expectations</td>
<td>18</td>
</tr>
<tr>
<td>Most stressful period/event during the PGD treatment</td>
<td>19</td>
</tr>
<tr>
<td>PGD versus prenatal diagnosis</td>
<td>20</td>
</tr>
<tr>
<td>Reproductive alternatives</td>
<td>21</td>
</tr>
<tr>
<td>When PGD no longer is an alternative</td>
<td>21</td>
</tr>
<tr>
<td>When PGD is a current choice</td>
<td>23</td>
</tr>
<tr>
<td>Who should be offered PGD?</td>
<td>25</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td>26</td>
</tr>
<tr>
<td>The experience of PGD</td>
<td>27</td>
</tr>
<tr>
<td>Most stressful PGD event</td>
<td>28</td>
</tr>
<tr>
<td>PGD versus prenatal diagnosis</td>
<td>28</td>
</tr>
<tr>
<td>Proceedings after PGD</td>
<td>29</td>
</tr>
<tr>
<td>PGD as the present choice</td>
<td>30</td>
</tr>
<tr>
<td>Who should be offered PGD?</td>
<td>30</td>
</tr>
<tr>
<td>Methodological discussion</td>
<td>31</td>
</tr>
<tr>
<td>Conclusion</td>
<td>32</td>
</tr>
<tr>
<td><strong>Acknowledgement</strong></td>
<td>32</td>
</tr>
<tr>
<td>References</td>
<td>33</td>
</tr>
</tbody>
</table>
INTRODUCTION

Preimplantation genetic diagnosis (PGD)

Couples at risk of having a child with a severe genetic disorder are usually offered prenatal diagnosis, if there is a diagnostic test available for the particular disorder. If the foetus is diagnosed as affected, the pregnancy can be terminated. The prenatal diagnosis is performed on amniotic or chorionvilli samples that are taken earliest at week 14 or 10 respectively. In case of a termination these will be performed rather late in the pregnancy, which will have psychological consequences for the couple. The risk of carrying an affected foetus depends on the inheritance pattern of the specific disease. For autosomal dominant inheritance pattern the risk is 50%, which means that in theory half of the pregnancies would be terminated.

Preimplantation genetic diagnosis (PGD) can, for some couples, be an attractive alternative to conventional prenatal diagnosis (Sermon et al. 2004b). In PGD, the genetic diagnosis is performed before the embryo is implanted in the uterus. This means that the couple can begin the pregnancy knowing that the foetus does not have the particular disease. In order to perform PGD, the oocytes have to be fertilized by *in vitro* fertilization. The female is treated with hormones so that more than one oocyte is mature at the same time. On average, ten oocytes are picked out from the women and fertilized *in vitro* with the sperms from her male partner. On day three after fertilization the embryo consists of 6-10 cells. At that point, one or two cells can be removed without harming the embryo and these cells can be used to diagnose the embryo for the specific genetic disease. The embryo is incubated in 37°C until the analysis is ready, usually within 24 hours. Embryos diagnosed as healthy can be considered for embryo transfer, and one or two are transferred to the female uterus on day 4. Hopefully, a pregnancy will be established. However, an *in vitro* fertilization treatment is a stressful treatment both physically and psychologically, and there is no guarantee of getting pregnant. The pregnancy rate is about 25% at the most (Harper et al. 2005), and many patients go through more than one treatment without success. In some cases, none of the embryos are healthy, and therefore no embryo can be transferred to the female after the treatment. In these cases, the treatment was all for nothing and there is no hope at all of getting pregnant.

PGD is offered all around the world today and the indications are chromosomal aberrations or monogenic disorders. PGD has also been developed for HLA typing of preembryos in order to identify a potential donator to an affected sibling. This application has been regarded
controversial and is not offered in Sweden today. PGD-AS (screening for aneuploid embryos) is another application with the aim to improve the success rate of IVF treatments. Couples with repeated IVF failures, repeated miscarriages or female with advanced age are the target for this approach. The reason for the IVF failures has been speculated about, and one reason could be a high degree of aneuploid embryos. PGD has also been performed for sexing of embryos for social reasons.

The procedure of PGD

In order to perform PGD, different steps have to be taken.

1) Genetic Counselling. The couple has to be informed of the different reproductive alternatives that are applicable for them, and pros and cons are considered. The procedure of PGD is described together with the risks and success prognoses. If PGD still is the choice for the couple, the laboratory investigation can be initiated. However, one has to consider if the genetic disease is fulfilling the present criteria’s for PGD indications in Sweden. Today in Sweden, there is no law regulating PGD and its indications. There is a parliamentary proposal from 1994/1995, saying that PGD is only to be applied for “Couples with a high risk of having children with severe, progressive, inherited disease that will lead to an early death and for which no cure or treatment is available”. This text has been difficult to interpret as regard to the term “early death”. In addition, there are very severe diseases that do not lead to an early death.

2) Laboratory Investigation. Before initiating a PGD treatment, the genetic test has to be designed and evaluated. Almost every family is unique regarding the genetic aberration, thus each couple requires a specific designed test. This test has to be evaluated on samples from the couple and often also from an affected relative. This investigation is often complicated and time consuming.

3) In vitro fertilisation and embryo biopsy. The couple is referred to the IVF clinic in order to evaluate and design the IVF treatment for the couple. Regarding IVF treatments in Sweden in general, the woman has to be below a specific age in order to be treated. This age limit is different for different IVF laboratories, but usually somewhere between 38-40 years. Some private clinics do not restrict the treatments based on the age of the woman at all. In the case of PGD, the restrictions have been liberal regarding the age of the woman so far. This is because that the majority of these couples is not performing PGD because of infertility, but
have to perform IVF in order to perform the diagnosis. As soon as the genetic laboratory investigation is concluded, the PGD/IVF treatment cycle can be initiated. The woman is treated with hormones for about a month. Oocytes are retrieved and fertilized with sperms from the man, and on day three after fertilization, the embryo biopsy is conducted. A small hole is made in the zona pellucida, using a weak acid that is aspirated from a needle, and one or two blastomeres are aspirated out from the pre-embryo.

4) **The Genetic Test.** Two blastomeres are removed from the pre-embryo and are used for the diagnostic test. The test has a time constrain (about 24 hours) and a high demand for accuracy. The remainder of the embryos are in culture until early day 4. If healthy embryos are identified, one or two are transferred back to the woman.

**Previous studies**

There are only a few studies performed today that investigate the patients experience of the PGD treatment and the consequences (Chamayou et al. 1998; Katz et al. 2002; Lavery et al. 2002).

Conventional prenatal diagnosis, by amniocentesis or chorionvilli samples, is well established all over the world. A large number of genetic disorders can be tested for with high accuracy. The disadvantage of conventional prenatal diagnosis is that if the foetus is diagnosed as affected, the couple has to consider the termination of a desired pregnancy. A termination of a pregnancy is often associated with emotional trauma (Iles and Gath 1993; Hunfeld et al. 1997). The grief can be compared to the sorrow of loosing a child during the neonatal period (Kenyon et al. 1988), and many couples who have experienced repeated abortions choose to give up further attempts to get pregnant (Chamayou et al. 1998). For these couples, PGD could be an attractive alternative. Previous experience of termination of pregnancies is the reason for opting for PGD in 15% of the cases (Harper et al. 2005). Objection to abortion/termination of pregnancy is the reason in 29% of the cases. This objection could be based on religious, moral or psychological issues, and the relative significance of these different issues are probably dependent on cultural and religious differences.

With PGD, the risk of having to terminate a desired pregnancy can be avoided, as the diagnosis is performed before the pregnancy is established. This is often the strongest
argument for wanting PGD (Snowdon and Green 1997; Chamayou et al. 1998; Lavery et al. 2002). However, PGD exhibits some drawbacks and is not always an obviously attractive alternative to amniocentesis or chorionvilli sampling. The chance of becoming pregnant after one attempt with PGD is only 15-20% (Sermon et al. 2004a). This low success rate is to some extent related to the risk of identifying only affected embryos at the PGD cycle. For some couples the risk for this is rather high, and is even increased if the woman does not produce a large number of oocytes. Another reason for the low success rate is that IVF treatment by itself has a low success rate, about 30%. In order to perform PGD the couple has to go through IVF, which is a physically and psychologically stressful treatment (Weaver et al. 1997; Olivius et al. 2004). Previous results indicate that many couples with infertility terminate their IVF attempts even though more IVF treatments were planned (Olivius et al. 2004). Thus, for PGD couples that are fertile and have the chance of becoming spontaneously pregnant, the requirement of IVF in order to perform PGD can be an obstacle.

Couples who have experienced both prenatal diagnosis with termination of pregnancies and PGD treatments can compare the level of stress these events create. One recent study (Lavery et al., 2002) showed that 40% of the couples that had experienced both these alternatives, considered PGD less stressful than prenatal diagnosis, while 35% regarded PGD as more stressful. The remaining 25% did not take a stand in this question. The majority (77%) of the couples in the Lavary study (2002) planning for more children opted for PGD, while the remaining couples chose to try for a spontaneous pregnancy and either use prenatal diagnosis (15%) or avoid testing at all (8%).

There is an ongoing discussion about restrictions regarding the use of PGD. What patients should or could be offered PGD? What indications are acceptable for PGD? There are concerns regarding PGD and the risk that this technique will be misused for the selection of embryos with desired features like gender, intelligence etc. In a study by Katz et al., (2002) couples referred for PGD (monogenic diseases) or aneuploidy screening and couples going through IVF due to infertility, were asked about their opinion regarding this issue. All groups stated that PGD was a highly acceptable treatment. They were not worried that PGD would be misused for testing non-disease-related features and strongly emphasized the importance of patients’ autonomy. The couple should have the right to decide about their own embryos, for example which embryos to transfer.
The patients

The majority of the couples are treated due to the women or the man being a balanced carrier of structural chromosomal aberrations. These patients have a high risk of having offspring with unbalanced chromosomal aberrations. These unbalances may result in the birth of an affected child (the risk is 10-15%) with mental retardation and dysmorphic features. An unbalance may also result in a spontaneous termination of the pregnancy, and many of these patients suffer from repeated miscarriages and fertility problems. This implies the need for IVF in order to get pregnant. For these couples, PGD is an attractive alternative, and maybe the only possibility to have biological children. Carriers of monogenic disorders like myotonic dystrophy and beta-thalassemia are usually fertile and do not have the need of IVF in order to get pregnant. On the other hand, they have 25-50% risk of having an affected child.

Monogenic disorders can be inherited following different inheritance patterns. For autosomal dominant disorders, either the woman or the man suffers from the specific disorder and these couples have a 50% risk of having an affected child. In autosomal recessive diseases, both the woman and the man in the couple is a healthy carrier of the disease, and the couple has a 25% risk of having an affected child. In X-linked diseases, the woman is a healthy carrier and the couple has a 25% risk of having an affected child (only boys will be affected). Couples treated with PGD for monogenic disorders have often experienced the birth of an affected child or have performed prenatal diagnosis and terminated affected pregnancies.

PGD in Sweden

About 125 patients have been treated with PGD, and concluded one treatment cycle, in Sweden today. PGD is offered at two centres in Sweden, in Stockholm and in Gothenburg. The Stockholm PGD centre is collaboration between the Fertility Unit and the Unit for Clinical genetics at the Karolinska University Hospital. The first PGD treatment cycles were performed in 1996, and the number of patients is increasing each year. In Stockholm, about 90 couples have been treated with PGD until May 2005, and 24 pregnancies have been established with 13 children born and 9 ongoing pregnancies. PGD has been developed for patients with structural chromosomal aberrations, and a number of monogenic diseases (myotonic dystrophy, Duchennes muscular dystrophy, beta-thalassemia, cystic fibrosis, and the list of monogenic disorders is expanding continuously). At the Unit for Reproductive medicine at Sahlgrenska University Hospital in Gothenburg, PGD has been performed since 1995. Until May 2005, about 33 couples have been treated there, with eight pregnancies
established and six children born. The majority of these couples have a high risk of having boys affected with X-linked diseases. Gender determination of the embryos, and selective transfer of female embryos is an easy and straightforward strategy for X-linked diseases. Patients with balanced chromosomal aberrations have been treated as well.

The knowledge of how these patients experiences the PGD treatment and what alternatives they consider are still unexplored. Couples with high risk of having children with severe genetic disease are in a difficult reproductive situation. None of the possible alternatives is easy or obvious, and there are pros and cons for each of them. There are different reasons for choosing PGD. Religious, moral or psychological objections against abortions could be one reason. Another reason is infertility problems and the need for IVF in any case. Many PGD patients have experienced repeated miscarriages and regard PGD as a possibility to avoid that.

**Aim**
The aim of the present study was to investigate the experiences and attitudes concerning PGD and other reproductive options among the patients who have undergone PGD in Sweden. The following specific research questions were posed

1. What are the main reasons for opting for PGD?
2. How stressful is PGD treatment compared to expectations based on information provided by health personal?
3. Do couples with different reproductive histories differ with regard to their experience of PGD treatment?
4. How stressful is PGD treatment compared to prenatal diagnosis and possible termination of pregnancy?
5. What reproductive alternatives are considered when PGD no longer is an option?
6. Do couples with different reproductive history differ regarding what reproductive alterative they proceeded with?
7. What are the future reproductive alternatives considered by couples presently performing PGD?
8. Do couples with different reproductive history differ with regard to consideration of future reproductive alternatives?
9. What attitudes do PGD patients have regarding what couples should be offered PGD?
METHOD

Design
A postal survey to the entire population of PGD patients in Sweden, resulting in a descriptive data report with some statistical analyses of comparisons.

Participants
A questionnaire was sent to all couples that had been treated with PGD in Sweden until May 2005, and was addressed to the couple. If the couple had separated, i.e. had different addresses, the questionnaire was sent to the individual who was the carrier of the disorder. In total, 125 couples had carried out at least one treatment cycle and the questionnaire was sent to 116 of them (90 treated in Stockholm and 26 treated in Gothenburg). Nine couples were excluded due to the fact that they were patients from other countries (N=6), or that the couple had separated and it was considered insensitive to approach these specific couples (N=3). In total, 103 couples chose to participate in the study and returned the questionnaire, which give a response rate of 89%. The questionnaire was most frequently completed by the couple together (57%), or by the woman (38%) and in a few cases by the man (3%).

Procedure
A questionnaire was sent together with a letter describing the aim of the study and an inquiry for participating. The questionnaires were coded and the coding list was kept in a locked space, only available for the person responsible for practically performing the study. A reminder was sent to the couples that had not returned the questionnaire within 20 days. Due to the fact that the questionnaire and the first reminder were sent during the summer, a second reminder was sent after another eight weeks to those that still had not answered.

Instruments
Due to the lack of standardised instruments focusing the issues relevant for the present study, a study-specific instrument was constructed by a team of researchers based on clinical experience and previous studies (see attachment 1). The questionnaire consisted of 20 questions that could be grouped in three parts.
1) Background information about the couple
• Who answered the questionnaire (The couple together, The woman, The man)?
• The number of PGD treatments performed.
• Whether the PGD treatment ever resulted in a pregnancy (At least once, Never).
• The genetic reason for performing PGD (Chromosomal aberration, Monogenic disorder)
• The age of the woman and the man respectively. They were reporting an age interval at the last PGD treatment (a) <29 years, b) 30-38 years, or c) <38 years).
• Education of the woman and the man respectively (Primary school, Secondary school, Graduate school).
• Carrier status (The woman, The man, Both).
• The reproductive history of the couple, i.e. if they previously had experienced the birth of a healthy or an affected child, prenatal diagnosis and termination of an affected pregnancy, miscarriages, or infertility (Yes, No).
• Patients were also requested to report what year these events occurred, and the number of miscarriages.
• The couple’s main reason for performing PGD, except the risk of having an affected child (Previous experience of terminations of desired pregnancy, Objections to termination, Need of IVF, Repeated miscarriages, Other reason). When more than one option was applicable, couples were requested to indicate their primary and secondary reason. Couples that had stated “Objection to termination” as a reason, were asked to indicate whether this objection was based on one or several of issues (Religious, Moral, Psychological, Other).

2) Patients experience during PGD treatment
• The experience of physical strain (pain, fatigue, distress, discomfort) and psychological strain (anxiety, depression, stress, disappointment) compared to expectations (Easier than expected, As expected, More stressful than expected, Much more stressful than expected).
• The psychologically most stressful event/period, and the physiologically most stressful event/period during PGD treatment. Patients were requested to choose one of several listed events/periods (see figure 6 for options).
• Couples that had experienced both prenatal diagnosis and PGD were asked to compare these events regarding psychological and physical stress (PGD more stressful, Equally stressful, Prenatal diagnosis more stressful).
3) **Options and choices regarding reproductive alternatives**

- Current plans for more PGD treatments (Yes, No). Couples who answered “No” were requested to report the reason or reasons for closing that opportunity (see figure 12 for options).
- Couples who had terminated PGD were asked to report what reproductive alternatives they had tried, regarding their wish for children (Yes, No) (see figure 13 for options).
- Couples currently performing and planning for PGD were asked to rate their future reproductive alternatives (First choice, Second choice, Third choice, Fourth choice) (see figure 14 for options).
- Would the couple encourage other couples in the same situation to try PGD as a way of having children (Yes, No)?
- Patient attitudes concerning under what circumstances PGD should be available to couples. Participants were requested to consider the following five scenarios and state whether PGD should be offered as an option. 1) Couples with high risk of having a child with severe genetic disease that often results in an early death. 2) Couples with high risk of having a child with some kind of handicap 3) Couples that have an affected child, and by PGD want to select an embryo with the matching HLA type in order to have a child that can be a bone marrow donor 4) Couples wishing to chose non-disease features 5) Women with advanced maternal age, with an 1% risk of having a child with Down’s syndrome 6) No opinion/do not know.

In addition, there were several opportunities for the couple to add personal comments to the different questions in the questionnaire. Many of the couples did specify or comment the stated alternative, and many described the personal experiences in their own words.

**Statistical analyses**

All data was first transferred manually to an excel file, and then imported to SPSS format. All entries were checked and confirmed. All personal comments added to the different questions in the questionnaire were rewritten into a Word file and sorted according to the questions. Statistical analysis with Mann-Whitney test was performed when comparing two subgroups of participants. When more than two subgroups were compared, the Kruskal-Wallis test was used. These are non-parametric methods comparing ordinal values. In order to analyse
differences regarding reproductive options between different subgroups, the data in question were transformed; first choice were rated 4, second choice rated 3 and second choice rated 2 and finally fourth choice rated 1. Chi2 test could not be used as the number of entries in each group was too few.

**Ethical considerations**

The present research study was approved by the Karolinska Institute, Ethical committee, region Stockholm. The study was also approved by Magnus Nordenskjöld, Verksamhetschef, Clinical genetics, Karolinska University Hospital, and Associate Professor Inger Bryman, Verksamhetschef, Gynecology and Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg.

This is a study that implies a low risk for the participants. The questions asked in the questionnaire could though awake unpleasant memories for the couple, and in that way upset the couple. However, one can choose not to participate, and to throw the questionnaire away. A letter was sent attached to the questionnaire in which the aim of the study was described and that the participation is voluntarily. If they had questions regarding the questionnaire, the name of a contact person was included in the letter, together with telephone number and E-mail address. When the questionnaire was returned and answered, approval of participant was assumed. All collected data have been treated confidentially. No individuals or couples can be distinguished in the report, in which results are only shown for different groups.
RESULTS

Descriptive data

In total, 103 couples out of 116 chose to participate in the study and returned the questionnaire, which gave a response rate of 89%. The questionnaire was most frequently answered by the couple together (57%), or by the woman (38%) and in a minority of cases by the man (3%). The number of PGD treatments performed per couple varied from 1 to 6, but 89% had performed 1-3 treatments (figure 1).

Figure 1. The number of PGD treatments performed for each couple.

The reason for performing PGD was one in the couple being a carrier of a balanced chromosomal aberration (59%) or of a monogenic disease (39%). In two cases the reason was increased risk for aneuploidy in the foetus due to unknown factors. In most cases (70%), the woman was the carrier. PGD for autosomal recessive disorders (both the woman and the man are carriers) represents only 3% of the couples. The age and education distribution is shown in figure 2 and table 1. About one third of couples reported that the PGD treatment ever had resulted in a pregnancy.
Table 1. Level of education.

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Data regarding education level in the Swedish population is taken from www.scb.se

Reproductive history

The aspects of the reproductive history of the patients’ included in the present study is shown in figure 3. About 1/4 of the patients had experienced the birth of an affected child. Many of the couples had carried out prenatal diagnosis on previous pregnancies (37%) and terminated affected pregnancies (25%). Miscarriages were common in this group of patients, and 46% had experienced at least one. However, the term repeated miscarriages usually refers to three or more, which was the case for 24% of the patients. The majority of these patients are carriers of balanced chromosomal aberrations and it is known that they have a high risk for spontaneous abortions due to unbalanced foetuses. The number of miscarriages reported was one to eleven. In addition, one-fourth of the patients reported that they had fertility problems, continuously or during some periods.
Figure 3. The previous experiences of different reproductive events. Each couple could report more than one event. Based on information regarding year and comments, it was possible to separate the birth of healthy child with or without PGD, and prenatal diagnosis of spontaneous pregnancy versus PGD pregnancy.
**Reasons for choosing PGD**

We asked the patients what their primary reason was, except the high genetic risk, for opting for PGD (figure 5). For many couples, the need of *in vitro* fertilization in order to become pregnant was the main reason to opt for PGD (28%) or the fact that the previous pregnancies resulted in spontaneous abortion (23%). Other primary reason for the couples was objection to termination of pregnancies (23%), the previous experience of terminations of pregnancy (18%), or other reasons (9%). Some of the couples defined “other reasons” and issues included were the previous birth of an affected child that need a lot of attention, the previous birth and the death of an affected child, or wishing to stop the inheritance of the disease in the family. In total, 36% of the couples ranked “objection to abortion” as a reason for performing PGD, and this was for psychological, moral or religious reasons (figure 6). Among the couples that objected abortion, 60% stated psychological reasons, 21% moral reasons, 6% religious reasons and 12% stated other reasons.

![Figure 5. Reasons, except the genetic risk, for opting for PGD.](image)

![Figure 6. Couples that had marked “Objection to termination” as a reason, were asked to specify what this objection was based on, religious, moral, psychological or other issues.](image)
The experience of PGD

The stress of PGD compared to expectations

The couples were requested to evaluate the PGD treatment both regarding the physical and psychological aspects. Only 6% of the couples found the treatment much more physical stressful than expected, and remaining couples were distributed equally between the other three alternatives. In contrast, 18% of couples reported that the psychological stress was much more stressful than expected and another 32% stated it was more stressful than expected (figure 7).

![The PGD treatment](image)

Figure 7. The couple’s experience of the actual PGD treatment compared to expectations

The couples were asked if they would recommend PGD to other individuals in the same situation, and almost all of them would (96%).

Previous reproductive experiences might influence how stressful the PGD treatment is considered as compared to expectations. Therefore we performed statistical analyses in order to investigate if some subgroups of couples had experienced the physical and psychological stress of the PGD treatment significantly different compared to remaining couples.
• A successful PGD treatment resulting in a pregnancy might influence the perception of the treatment. However, no significant different could be shown between couples with PGD pregnancies established (N=30) as compared to the couples that so far had failed (N=73), regarding the experienced stress during the PGD treatment as compared to expectations, neither physically nor psychologically.

• No significant difference could be detected between the couples that performed PGD because of chromosomal aberrations (N=61) as compared to couples that performed PGD due to monogenic disorder (N=40), regarding the experienced stress during the PGD treatment as compared to expectations. As these groups often have different reproductive histories, they might have different expectations of the PGD treatment.

• The couples that had experienced the birth of an affected child or/and that had terminated pregnancies due to an affected foetus (N=46) might be more motivated to go through PGD and therefore tolerate the stress of the treatment in a better way. These couples were compared to the ones without this experience (N=56), but there was no significant difference regarding the rating of how stressful the PGD treatment was considered as compared to expectations.

• Previous experience of repeated miscarriages or infertility might motivate a PGD treatment and might influence the perception of the stress it causes. However, the couples with these experiences (N=66) did not regard the PGD treatment less stressful then the rest of the couples (N=36).

**Most stressful period/event during the PGD treatment**

![Most stressful physical moment](image)

Figure 8. Couples were asked for the most physical stressful moment, one alternative per couple.
The oocyte retrieval (OPU) procedure was reported to be the most physically stressful event (55%), but also the hormone treatment was regarded highly stressful (21%) (figure 8). The PGD events/periods associated with the most psychological stress was ”waiting for a possible embryo transfer” (38%) and ”waiting for the pregnancy test” (29%) (figure 9).

**PGD versus prenatal diagnosis**

Among couples with experience of both PGD and prenatal diagnosis of spontaneously conceived pregnancies (N=38, 37%), the opinion seems to be that PGD is more physically stressful then prenatal diagnosis. However, prenatal diagnosis is more psychologically stressful than PGD or as stressful as PGD (figure 10 and 11).
Reproductive alternatives

When PGD no longer is an alternative

We asked the patients if they were planning or wishing for further PGD treatments. Many patients (N=66, 64%) had finished and closed for further treatments. Among these couples, the reasons for closing was either 1) PGD resulted in a pregnancy (21%), 2) Have no strength for another treatment (14%), 3) Not meaningful/low chance of success (24%), 4) Wish to try other reproductive alternatives (5%), or other reasons (38%). Some couples defined what “other reasons” included, and issues mentioned were achieved spontaneous pregnancy, becoming to old for PGD/IVF, or that they did not get another treatment paid by the local healthcare.

Figure 11. Twenty-one of the 103 couples included in the study (20%) had experienced both PGD and prenatal diagnosis of spontaneous pregnancies that resulted in termination of the pregnancy. They compared the stress these two event causes, both physically and psychologically.

Figure 12. The couples that had closed for further PGD treatments (N=66, 64%) stated the reason for the closure.
Figure 13. Sixty-six out of 103 couples had concluded their PGD attempts. How did these 66 couples proceed regarding the wish and desire for children? Couples can have proceeded and tried more than one way, i.e., the height of the staple does not refer to number of couples, but rather number of choices.

These couples had closed for PGD many years ago or more recently. How did these 66 couples proceed regarding their wish and desire for children? Many couples had tried several options (figure 13).

Statistical analysis was performed in order to evaluate if some subgroups among couples had proceeded significantly different regarding reproductive alternatives compared to remaining couples. Mann-Whitney test was used to compare the following subgroups: 1) Couples for whom PGD was performed due to chromosomal aberrations versus remaining couples, 2) Couples with experience of miscarriages versus remaining couples, 3) Couples with infertility problems versus remaining couples. 4) Statistical analysis (Kruskal-Wallis Test) was also performed as whether the age of the woman had influenced the reproductive choices made after PGD attempts. The patients had reported in which age-interval they were in at the last PGD treatment, and the three groups were compared: a) <29 years, b) 30-38 years or c) 38 and above. 5) Another factor that was analysed was if the reproductive alternatives were influenced by whether the woman or the man or both were carriers of the disorder.

1. The couples performing PGD because of chromosomal aberrations were significantly more likely to have tried to become pregnant and excluding prenatal diagnosis in case of pregnancy, compared to those performing PGD for monogenic disorders. ($Z=-2.126$ $p=0.033$). Descriptive results show that 10 out of 41 couples performing PGD for chromosomal aberrations had proceeded in this way, while none of the carriers of monogenic disorders (24 couples) had chosen that alternative.
2. Couples with previous experiences of miscarriages had also tried to become pregnant without including prenatal diagnosis significantly more often compared to the other couples (Z=-3.280, p=0.001). Thirty couples out of 66 that had closed for PGD had experienced miscarriages, and ten of them (1/3) had tried to become pregnant without including prenatal diagnosis. None of the couples without experience of miscarriages had tried that alternative.

3. Couples with infertility problems were significantly more likely to have chosen adoption than remaining couples (Z=-2.322, p=0.020). For couples with infertility problems, 7 out of 16 have opted for adoption (44%), while 8 out of 50 couples (16%) without these problems opted for adoption.

4. The age of the woman at the couple’s last PGD treatment was not significantly associated with the reproductive choices made.

5. As expected, sperm donation was significantly more often chosen as a reproductive alternative when the man was the carrier (p=0.002).

**When PGD is a current choice**

Preimplantation genetic diagnosis was still a current alternative for 32 (31%) of the patients. They were asked to rate the reproductive alternatives that could be an option in their future plans. Results are shown in figure 14. PGD seems to be the first choice for the majority of these patients (84%). However, 19% of the couples for which PGD still was an option were trying to achieve a spontaneous pregnancy. Adoption seems to be a second, third or fourth choice for about 22% of these patients. Oocyte- or sperm donation was only mentioned as a possible option by 8 of the couples. Three couples were considering staying childless if PGD was not successful.
Figure 14. PGD is still a possible reproductive alternative for 32 of the couples. They were asked to rate the different reproductive alternatives as first, second, third choice for the future plans regarding reproduction.

Did previous reproductive history influence rating of the future reproductive alternatives? Subgroups that were compared (Mann-Whitney test) were: 1) Couples for whom PGD was performed due to chromosomal aberrations (N=17) versus remaining couples (N=15), 2) Couples with experience of miscarriages (N=14) versus remaining couples (N=18), 3) Couples with infertility problems (N=9) versus remaining couples (N=23). Kruskall-Wallis test was used to compare 4) Couples including women of different ages at the last PGD treatment (a) <29 years, N=6, b) 30-38 years N=24, c) >38 years N=2), and 5) Couples with different carrier status (female carrier N=24, male carrier N=7, both carriers N=1).

1. There were no significant differences between the ratings of reproductive alternative by carriers of chromosomal aberrations and carriers of monogenic disorders.
2. There were no significant differences between couples with experience of miscarriages and the other couples.
3. There were no significant differences between couples with infertility problems versus the other couples.
4. The age of the woman did not have an influence of the couples’ ratings of future reproductive alternatives.
5. As expected, oocyte donation was a significantly higher rated reproductive alternative when the woman was the carrier than when the man was the carrier (p=0.027). Similarly, sperm donation was a more highly rated reproductive alternative when the man was the carrier as compared to if the woman was the carrier (p=0.000).

Who should be offered PGD?
We gave six alternative scenarios and asked the patients to mark if PGD should be offered as an option in these cases. The risk of having a child with severe genetic disease was accepted as a PGD indication by almost all. The risk of having a child with a handicap was accepted as a reason by 68% of the patients, and PGD in order to choose a child with HLA match to an affected sib was accepted by 42%. Only 6 persons indicated that PGD should be applicable in order to select children with non-disease features (e.g. gender). PGD for women of advanced maternal age (1% risk of Downs syndrome) was accepted by 22% of the couples (figure 15).

Figure 15. The couples were given five different scenarios (summarised in the figure), and asked if PGD should/could be applicable / offered for these indications.
DISCUSSION

In Sweden, the first PGD attempts were performed in 1995, and since then the 103 couples included in this study have been going through in total 223 treatment cycles. PGD is a technically advanced method that demands the combined expertise of molecular genetics, embryology and reproductive medicine. During the last 10 years, the technique has been improved, both regarding accuracy and efficacy, and the number of patients is increasing for each year. As PGD providers we meet the couples before and during the PGD treatment, but so far no comprehensive study has been carried out in order to investigate the couples’ experiences of PGD. The aim of the present study was to investigate the experiences and attitudes concerning PGD and other reproductive options among the patients who have performed PGD in Sweden.

A questionnaire was sent to 116 couples that had carried out at least one PGD treatment cycle. This represents almost all couples that have been treated in Sweden since the start in 1995. The response rate was 89%, and only 13 couples failed to return the questionnaire. Three of these couples had separated and the questionnaire was addressed to the carrier partner that in these cases was the man. Another three couples were from foreign countries and might have difficulties with the Swedish languish, and thus difficulties understanding the questionnaire.

For most of the couples, the woman was the carrier of the disease. Among those that performed PGD for monogenic disorders, the woman was the carrier in 32 out of 38 couples. This can partly be explained by the fact that monogenic disorders include X-linked diseases, in which the woman always is the carrier. However, also in the group that performed PGD for chromosomal aberrations there was an excess of female carriers, 35 as compared to 25 male carriers. The reason for this is more difficult to interpret, and this discrepancy has not been reported by the ESHRE (European Society of Human Reproduction) collection data set (Harper et al. 2005). ESHRE has established a consortium to which almost all European PGD centres as well as some Australian and American PGD centres are reporting information about PGD treatments and cycles performed. The gathered information is reported yearly in an international journal.
The level of education for the male and female respectively is shown in table 1. The couples performing PGD seem to have a higher level of education as compared to the Swedish population in general (www.scb.se). Many of the PGD couples have actively searched information about PGD themselves and asked for the possibility to be treated by this alternative. Maybe this ability and initiative ness is correlated to the education level of the patient.

Reasons for opting for PGD, except for the genetic risk of having an affected child, are either 1) Experience of previous termination 2) Objection to abortion/termination of pregnancy 3) Need of IVF 4) Repeated miscarriages. The distribution between these alternatives is comparable to the data generated from the ESHRE data collections of PGD treatments performed between 2000-2001 and 2002 (Harper et al. 2005). In the present study, experience of previous termination is the major reason for 17.5% of the couples (ESHRE data collection 8-15%), objection to abortion is the major reason for 23% of the couples (ESHRE data collection 19-29%), need of IVF was the main reason for 28% of the couples (ESHRE data collection III-IV: 22-30%). In the present study, objection to termination of pregnancy was a reason for PGD, and this objection was either because of psychological moral, or religious reasons, in that specific order. Religious reasons seems to be a less important reason in Sweden today, but could be of greater importance in other countries and cultures.

**The experience of PGD**

The stress, both psychologically and physically, caused by the PGD treatment was evaluated, and the mean value was somewhere between “As expected” and “More stressful than expected”. In a previous study, 41% of the couples found the treatment extremely stressful (Lavery et al. 2002), while in the present study a much more physical and psychological stress than expected was less common reported (6% and 18% respectively). One might suspect that some previous experiences would make the couples highly motivated to seek reproductive alternatives like PGD, in order to get a healthy child. However, the results from the present study indicate that the stress experienced during the PGD treatments was not associated with the couples’ previous reproductive experiences. When comparing different subgroups with the remaining couples, no significant differences could be detected. The subgroup of couples that had given birth to affected children or carried out prenatal diagnosis and terminated affected pregnancies did not rate the PGD experience more or less stressful as compared to the couples.
without this experience. Almost half of the couples reported that they had experienced miscarriages, and one fourth had experienced repeated miscarriages (3 or more). Couples with 3 or more miscarriages were, almost exclusively, carriers of balanced chromosomal aberrations (24 out of 25 couples). Carriers of balanced chromosomal aberrations have an increased risk of repeated miscarriages, due to chromosomal unbalance in the foetus. For these couples PGD is an alternative that minimises the risk for miscarriages. Neither repeated miscarriages nor infertility was associated with a more or less stressful PGD experience.

Thirty couples had a successful PGD treatment resulting in a pregnancy. This positive experience might influence the perception of the PGD treatment. However, no significant difference was detected regarding experienced stress of the PGD treatment between couples that succeeded and those that did not. The perception of the actual treatment is not dependent of the outcome of the treatment.

**Most stressful PGD event**

The most physical stressful event was the oocyte retrieval, followed by hormone treatment and the most psychologically stressful period was “waiting for a possibly/ hopefully embryo transfer”, followed by “waiting for the pregnancy test”. In the study by Lavery et al. 2002, the most stressful event during PGD reported was the time waiting for the pregnancy result followed by time waiting before the treatment.

**PGD versus prenatal diagnosis**

Our experience is that the majority of PGD couples that become pregnant after a PGD cycle choose to carry out a conformational prenatal diagnosis. These couples do have the experience of both PGD and prenatal diagnosis. However, in these cases the prenatal test is performed on a pregnancy that most likely is a healthy one, and the psychological stress probably is less pronounced. Because of this, only couples with experience of prenatal diagnosis of a spontaneous pregnancy were included in the analysis regarding this issue. The majority of couples that had performed prenatal diagnosis on a spontaneous pregnancy and experienced a PGD treatment reported that PGD was more physically stressful (54%), but that prenatal diagnosis was more psychologically stressful (51%). In a previous study, 35% found PGD more stressful and 40% of couples found PGD less stressful than prenatal diagnosis (Lavery et al., 2002). In that study, stress was not defined as physical or psychological and
results are therefore not straightforward to compare. However, in that study, 77% of the couples would opt for further PGD if considering a child. It seems that neither PGD nor prenatal diagnosis are optimal tools in the efforts of having a healthy child. None of the alternatives offer an easy treatment, and there are pros and cons that have to be evaluated by the couple. However, the majority of couples (96%) in the present study would recommend PGD to other couples in the same situation. Some couples commented that it was worth going through PGD even if it did not succeed. In these cases they had given it a try anyway, and could proceed with other reproductive alternatives.

Proceedings after PGD

The closure of the PGD treatments is determined either by the couple or by the PGD provider. The PGD provider could recommend the closure based on low success prognosis, i.e., bad response on the treatment. In the present study, 24% of the couples had closed PGD treatments because of bad prognosis, i.e., low chance of establishing a pregnancy. Other reasons for closure were successful PGD treatment and now they were satisfied (17%) or that they lacked the strength to go through another cycle (14%), or the wish to try other reproductive alternatives (5%).

Couples that had closed for PGD had tried other alternatives for having a child. Many had tried to get spontaneously pregnant with prenatal diagnosis if becoming pregnant. Adoption was the second most commonly reported alternative. Surprisingly, oocyte- and sperm donations were only used by a minority of the couples. Oocyte donation was introduced as a reproductive alternative in Sweden in 2003. Thus, for many of the couples in this study, oocyte donation was not an option by the time they were in the process of reproduction. Sperm donation has been a possible alternative all along, but was only used by three couples. Couples more frequently chose to adopt a child than to use sperm donation, and one might speculate about the reasons for that. If the man cannot be the biological father of the child, adoption may render more equality between the man and the woman.

After PGD closure, carriers of chromosomal aberration had tried to become pregnant without including prenatal diagnosis if pregnant, to a significant higher extent than the remaining couples. This was also true for the subgroup that had experienced miscarriages. In fact, these two subgroups are probably overlapping, as balanced carriers of chromosomal aberrations often suffer from repeated miscarriages. An explanation for the results could be that these
couples have experienced repeated miscarriages, and would not risk a current pregnancy by taking a chorionvilli or amniotic sample. In addition, if the specific pregnancy proceeds, there is a high chance that it is a balanced foetus. Infertility problems were reported by many couples, and after PGD closure these couples chose adoption to a higher extent than the remaining couples. The possibility to get spontaneously pregnant is not a feasible or possible alternative for these couples.

**PGD as the present choice**

Couples that were planning for further PGD treatment rated their future reproductive alternatives. Most of these couples opted for more PGD treatments as their first choice. Surprisingly, oocyte- and sperm donation were only mentioned as a second, third or fourth choice by eight couples. This is a less attractive alternative than adoption, and one may speculate regarding this. Oocyte donation might be a more attractive alternative than sperm donation as it renders the man and the woman more equality as compared to the situation with sperm donation. In oocyte donation, the man is the biological father and the woman will carry the child for nine months building a psychological and physical link to the child. However, this alternative is rather recent, and information and acceptance might turn this alternative more attractive in the future. The possibility to opt for this alternative is also dependent on the availability of oocyte donors in the future.

As a PGD provider, it is important to inform the couple about the reproductive alternatives. Several of the couples commented that accurate information about PGD in order to give realistic expectations was important. Others commented that information regarding other reproductive alternatives should be given in parallel with information about the PGD treatment, rather than as a secondary alternative after PGD closure. If PGD does not result in a child, it could be too late to proceed with other alternatives.

**Who should be offered PGD?**

Today in Sweden, there is no law regulating PGD and its indications. There is a parliamentary proposal from 1994/1995, saying that PGD is only to be applied for “Couples with a high risk of having children with severe, progressive, inherited disease that will lead to an early death and for which no cure or treatment available”. During the last years, a parliamentary
committee has been discussing questions regarding genetic integrity, including prenatal
diagnosis and PGD. The result of this work is now on a “review”, and a decision will be taken
during the first part of year 2006. It has even been discussed that a law regarding these issues
might be the result of the investigation. In the proposal, the term early death is removed, and
indication for PGD would be high risk for severe genetic disease.

The risk of having a child with severe genetic disease was accepted as a PGD indication of
almost all participants in the present study. This was not surprising as this is the situation for
all of the participating couples, and the reason for the PGD treatment. The risk of having a
child with a handicap was accepted by 68% of the couples, and the acceptance or not might be
influenced by how “handicap” personally is defined. PGD in order to choose a child with
HLA match to an affected sib was accepted by 42%. This application of PGD has been
debated in the media during the last years, as whether to be an acceptable treatment or not. In
Sweden, this application is not offered today, and the parliamentary proposition is not ready
to take a stand in that specific question yet. Only 6 persons state that PGD could be applicable
to non-disease features. PGD for women of advanced maternal age (1% risk of Downs
syndrome) was accepted by 22% of the couples. The risk of having a child with Down
syndrome is a risk of having a child with a handicap, which was accepted by 68%. The
reason to the low acceptance of Down syndrome as an indication is probably because of the
low risk, as compared to other PGD indications.

Methodological discussion
A strength with the study is that we have included all patients that have performed PGD in
Sweden, and achieved a very low drop out, which give good extern validity (representation).
One weakness of the study is that there is an excess of women answering the questionnaire,
which makes the opinions of the men less represented in the results. Another weakness is that
the patients were asked to respond to questions regarding PGD experiences retrospectively,
and for some couples the PGD event took place many years ago. Twenty-seven of the couples
performed their last PGD treatment before 2002. The instrument used in the study was
developed specific for this study and have not been evaluated regarding validity and
reliability. The results from this study were compared to other studies, and results seem to
correlate to some extent, which give some support for the instrument used.
Conclusion
Knowledge about the experience of PGD treatments is of great importance for those that meet these patients for genetic and reproductive counselling, in order to be able to give them proper care. From this knowledge we can improve the caretaking of this group of patients, and to better meet their demand of information and support.
Preimplantation genetic diagnosis has been an interesting topic in media during the recent years, and has been described as a very attractive alternative to prenatal diagnosis. In addition, the possibility to “design” a baby, the possibility to misuse this technique to create a child with desired features, has been put into focus. However, this is not possible. It is a small exclusive group of patients that really can benefit from a PGD treatment, in order to avoid severe genetic disease in a child.

ACKNOWLEDGEMENT
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REFERENCES


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