Original Article


We aimed to study reproductive behaviour of couples opting for prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PGD) for Huntington’s disease (HD). In the Netherlands, exclusion PND is available for persons at 50% risk, whereas exclusion PGD is not allowed. All 162 couples who underwent PND or PGD for HD between 1998 and 2008 and referrals for exclusion PGD to Belgium were included. Couples’ reproductive information was collected until December 2010; 132 couples (81.5%) underwent PND in 262 pregnancies, 54 (33.3%) started PGD, and 25 used both. Sixteen percent of PND couples used exclusion PND and 6% used exclusion PGD. The outcomes were 76.5% of PND couples delivered ≥1 unaffected child(ren) after PND, and 44.4% of PGD couples delivered ≥1 PGD child(ren) (mean 2.5 cycles/couple). Couples opting for PGD secondarily (after a previous pregnancy) had more frequently terminated a pregnancy for HD (87.0%; p = 0.015). At-risk or HD expansion carrier males were underrepresented in the group of couples primarily opting for PGD (25%) and overrepresented in the secondary PGD group (64%). We conclude that couples reconsider their choices in every subsequent pregnancy based on their previous experience, personal beliefs and the gender of the at-risk partner.

Conflicting of interest
The authors report no conflict of interest.

Huntington’s disease (HD) is a severe progressive autosomal dominant neurodegenerative disorder characterized by chorea and hypokinesia, dementia, and psychiatric disorders (1). Currently, there is no curative treatment available (2, 3). The mean age at onset is between 35 and 44 years. The median duration of illness is 17 years. HD is caused by an expanded CAG repeat in the HTT gene on chromosome 4 (4p16.3) (4). Up to 26 CAG repeats are considered normal, 27–35 repeats are within the intermediate range, and 36–39 CAG repeats are associated with reduced penetrance, whereas full penetrance is observed from 40 repeats onwards.
Since the introduction of direct testing for HD in 1993, an estimated 24% of at-risk persons in the Netherlands opted for a pre-symptomatic test (PT) (5–7). Reproductive decisions are among the most frequently mentioned reasons for performing PT (5, 8, 9).

HD expansion carriers may want to avoid transmission of the disease to their offspring. They have various reproductive options, such as a spontaneous pregnancy with prenatal diagnosis (PND) and termination of pregnancy (TOP) in case of a foetus with the CAG expansion, or pre-implantation genetic diagnosis (PGD) (10). In PGD, one or two blastomeres of each embryo, obtained by in vitro fertilization (IVF), are biopsied and analysed for the presence of the CAG expansion, and/or the presence of genetically linked markers associated with the CAG expansion (11–13).

For individuals with 50% HD risk, who do not want to know their own status, exclusion testing using PND or PGD is a possibility. Linked markers are used to establish the origin of the HTT allele present in the foetus (11, 12). The detection of an HTT allele from the affected grandparent is associated with a 50% HD risk, identical to the at-risk parent. In this case, the pregnancy will be terminated or the PGD embryo will be discarded. In the Netherlands, exclusion PND (ePND) is applied since 1989 (5). However, exclusion PGD (ePGD) is prohibited for the following reasons: roughly half of the couples at risk will ‘unnecessarily’ undergo an invasive IVF/PGD treatment and discarding embryos with a 50% risk of not being an HD carrier is considered unethical (14, 15).

This retrospective cohort study surveys the complete reproductive behaviour of a cohort of all HD expansion carriers and at-risk persons opting for PND and PGD in the Netherlands from 1998 to 2008. The efficacy of PND and PGD is illustrated by comparing the cumulative outcomes of PND and PGD, and the uptake was estimated.

Materials and methods
Organization of PND and PGD in the Netherlands
PND for HD has been available in the Netherlands since 1987 (5). Chorionic villus sampling or amniocentesis can take place in one of eight centres for PND. All samples for PND analyses are examined at the Leiden University Medical Centre (LUMC). In 1995, the Maastricht University Medical Centre (MUMC) started the only licenced PGD centre in the Netherlands.

In 1999, the first PGD cycle for HD was performed. IVF treatment necessary for PGD, and biopsy of the embryo, can also take place in two IVF centres in Utrecht and Groningen, in which case blastomeres are transported to Maastricht for PGD analysis. At first, only direct testing was offered (16). Since 2006 ePGD for HD is prohibited by law (13, 15). Couples requesting ePGD may be referred to the PGD centre in Brussels.

Patients
Those included were all HD expansion carriers and at-risk persons who had performed PND in one or more pregnancies and HD expansion carriers or at-risk persons who started PGD between 1998 and 2008. The databases of PND analyses (LUMC) and PGD referrals and treatments (MUMC and UZ Brussels) were combined in order to match identical individuals. Information on the age of both partners and the gender of the HD expansion carrier or at-risk person was collected from the patients’ files of the centres for PND throughout the country and the PGD centre in Maastricht. The date of PT was registered. We collected detailed information on reproductive history and all consecutive pregnancies and PGD cycles until December 2010.

Definitions
Each natural conception with or without PND and each PGD cycle started was defined as an attempt to have a child. All possible attempts recorded are listed in Box 1. All reproductive attempts and their outcomes were ordered chronologically, including pregnancies preceding the first PND or PGD attempt (miscarriage and untested child).

Box 1: Decision-making process with respect to conception, diagnosis, and outcome of all attempts

1. Spontaneous conception
   a. Pregnancy without prenatal diagnosis
      i. Pregnancy loss
      ii. Pregnancy termination
      iii. Birth of ≥1 child
   b. Pregnancy with prenatal diagnosis
      i. Pregnancy loss
      ii. Pregnancy termination
      iii. Normal pregnancy and child unaffected with HD
      iv. Continued pregnancy of HD carrier or at-risk foetus

2. IVF and PGD treatment cycle
   a. No pregnancy
   b. Pregnancy after PGD
      i. Pregnancy loss
      ii. Pregnancy termination
      iii. Birth of ≥1 child unaffected with HD

Primary or secondary reproductive choices
We distinguished couples primarily opting for PND or PGD with no previous pregnancy and couples who started PND or PGD secondarily, after a history of PGD or PND, or an untested pregnancy. Every PND attempt involves many possible outcomes depending on the test result and the course of the pregnancy after PND (Box 1). We assumed that the experience of PND and its variation of possible outcomes contributed to the choice of the following attempt (17). For this reason, couples repeatedly using PND were included in the secondary PND group (after the first attempt). In contrast, the most likely PGD outcome is ‘pregnant yes/no’, and
the chance of an adverse effect resulting in TOP for HD due to misdiagnosis after PGD is very limited (18). Moreover, successive PGD use is, as a rule, only offered after a PGD treatment has resulted in the birth of a child after a maximum of three to four cycles. Because of these biases, the couples repeatedly using PGD were regarded as a separate group.

Outcome and uptake of PND and PGD

To compare the efficacy of both PND and PGD, the cumulative outcome after (repeated) PND or PGD attempts per couple was monitored. The uptake of PND and PGD among HD expansion carriers of reproductive age (arbitrarily set at females ≤40 years, and males ≤50 years) was estimated. Details on the calculation of uptake are described elsewhere (19).

Data were analysed in coded form. According to the Dutch law governing the rights and duties of patients and medical practitioners (WGBO) (20), all couples involved implicitly consent to their anonymous data being used for scientific research. Approval of the Medical Ethics Committee of the MUMC was obtained.

Statistics

Comparisons of differences regarding the gender of the partner at risk or HD carrier, and couples’ reproductive histories (frequencies between groups) were performed by $\chi^2$ tests (corrected for continuity). Continuous data (age at certain moments and time intervals) were compared using a $t$-test.

All reported $p$ values are two-sided and results were considered statistically significant if $p \leq 0.05$. The analyses were conducted with SPSS for Windows version 17.

Results

A total of 162 couples were included in the study. The index cases were 89 female and 73 male HD expansion carriers or persons at 50% risk. More females than males had performed a PT prior to their first PND or PGD attempt (85.4% vs 69.9%, $p = 0.017$).

One hundred and eight couples exclusively used PND in one or more pregnancies, 29 couples exclusively had one or more PGD cycles, and 25 couples used both PND and PGD. Two couples used PND to check for misdiagnosis in a PGD pregnancy.

An overview of all 458 recorded attempts by the 162 couples is listed in Table 1. The mean number of attempts per couple was 2.8 (range 1–9). A total of 137 couples had 322 spontaneous conceptions. In all, 132 couples (81.5%) opted for PND in 262 pregnancies. The majority were direct tests (84.1%), whereas in 12.9% of couples ePND was performed and in 3% exclusion-definitive testing.

Of all couples opting for PND, 47.0% had ≥1 TOP for HD, and 76.5% had delivered ≥1 child free from HD. Twelve couples (9.1%) continued their pregnancy with an HD expansion or 50% risk allele. Two withdrew without obtaining the PND result (Table 1).

Fifty-four couples started PGD cycles. Three of these (5.6%) used ePGD. Four couples continued PGD treatment after interruption with a spontaneous pregnancy. A total of 136 PGD cycles were performed (mean 2.5 cycles per couple). In 44.4% (24/54) of the PGD couples 26 ongoing pregnancies resulted in the birth of 33 PGD children. Of the total group ($n = 162$), 23 couples (14.2%) had ≥1 miscarriages in spontaneous pregnancies (without PND). Three couples had a TOP without PND (1.9%), and 21 couples (13.0%) had ≥1 ongoing pregnancies without PND.

Patterns in the use of PND and PGD

Figure 1 shows a summary of the reproductive choices of all 162 couples who used PND and/or PGD during the period of study. Of these couples, 99 opted for PND in their first pregnancy, 28 couples primarily opted for PGD. Thirty-five couples had ≥1 pregnancies before their first PND or PGD attempt, resulting in ≥1 miscarriages (14 couples) or live-born untested child(ren) (21 couples).

In the primary PND as well as in the primary PGD groups, more females were at risk/HD expansion carriers (75% and 57%, respectively), whereas in the primary non-PND/PGD groups the majority of at-risk/HD expansion carriers were male (71% and 57%, respectively) ($\chi^2$: $p = 0.01$) (Table 2).

Thirty-four of the 99 primary PND couples stopped using a form of testing after their first attempt (Fig. 1). The majority of these couples (25/34) had one healthy child after PND. Twenty-three of these 34 couples were CAG expansion carriers, 11 were at 50% risk; four of the latter were shown to be non-HD expansion carriers during or after their first attempt. Six pregnancies in the primary PND group were continued after showing either an HD expansion in the foetus ($n = 4$) or a 50% risk allele ($n = 1$), or without obtaining the PND result ($n = 1$). Three of these 34 couples had affected pregnancies terminated.

Of the 65 couples who continued their attempts after primary PND, 9 opted for PGD for their next pregnancies and 56 again opted for PND.

For 14 of the 28 couples in the primary PGD group, PGD treatment (1–4 cycles/attempts) resulted in the birth of at least one PGD baby: five of these couples started a second PGD treatment, whereas nine stopped using PGD after delivery. After PGD treatment did not result in a pregnancy, three couples had a spontaneous pregnancy with PND, while for 11 couples no PND attempts were registered.

In the primary non-PND/PGD groups, 21 couples had 27 children untested for HD as well as 4 miscarriages, and 14 couples had 18 miscarriages in all.

Secondary choices

A total of 99 couples opted for PND secondarily (Fig. 1); 14 of those 99 continued to use PGD
afterwards. For a comparison of the secondary PND and secondary PGD groups, these 14 couples were regarded as belonging to the PGD group, because PGD was their last choice.

The cumulative reproductive history of both secondary PND (n = 75) and secondary PGD (n = 28) groups is listed and compared in Table 3. Significantly more female HD expansion carriers (80%) opted secondarily for PND compared with PGD (20%), while male expansion carriers showed a 50:50 distribution between the PND and PGD groups (p = 0.009). The reproductive history of the secondary PND and PGD groups showed an equal distribution of couples with previous pregnancies, miscarriages and proportion
PND and PGD for Huntington’s disease

Fig. 1. Summary of reproductive choices of the 162 couples opting for prenatal diagnosis (PND) or pre-implantation genetic diagnosis (PGD) or both. Note: The numbers represent couples. The numbers between brackets represent the 14 couples continuing to PGD secondarily.

of pregnancies with PND (Table 3). However, the couples with a history of PND in the secondary PND group had a TOP for HD significantly less frequently (32/58, 55.2%) than the couples in the PGD group (20/23, 87.0%) (p = 0.015). The couples opting for PND secondarily more frequently had ≥1 child (54/75, 72.0%) compared with couples starting PGD secondarily (13/28, 46.4%) (p = 0.029). The proportion of children born after PND or untested did not differ significantly between these groups.

Finally, after using PGD, 9 of the 28 couples continued to use PND (once more) (Fig. 1).

Total PND and PGD use and outcome

The total number of 175 PND or PGD pregnancies resulted in the birth of 183 children (Table 4). PND was applied in 149 of 175 (85.1%) spontaneous pregnancies; 12 of 149 (8.1%) pregnancies were continued with an HD expansion or 50% risk allele. Additionally, two pregnancies were continued without being informed of the test result. A total of 14.9% of pregnancies resulted from PGD treatment. Of all 183 live-born children, 5.5% were HD expansion carriers, 2.2% have a 50% HD risk, and 92.3% are free from HD. For 39 couples (24.1%), PND and/or PGD did not lead to childbirth.

Figure 2 shows the cumulative outcome of all 262 PND attempts of the 132 couples performing PND. The outcome of each attempt was ordered chronologically as first, second, and third attempt until the birth of a child. After the birth of a child, any following attempt was considered another first attempt to conceive a child. The attempts resulted in 135 ongoing pregnancies (52%) and the birth of a child without HD, and 110 pregnancies (42%) were terminated or lost.

Figure 3 shows the cumulative outcome of each of the 136 PGD cycles (attempts) performed by 54 couples. For couples who continued PGD cycles after the birth of a PGD child, any following attempt was considered a new first attempt. The majority of the 26 ongoing pregnancies (19% per cycle) resulted from the first or second PGD cycles. The proportion of favourable outcome (in terms of a live-born child with a reduced HD risk) after PND was relatively high compared with PGD (Fig. 4).

Uptake of PND and PGD

Couples in our study performed their PT on average 1.8 years before their first attempt to have a child (range 11.5 prior to first attempt to 6.0 years after first attempt). Therefore, the 11-year period starting from October 1996 is the closest way to approximate the moment of PT of our study group. In this period, 1414 pre-symptomatic tests were performed in the Netherlands on 587 males (42%) and 827 females (58%). Of the 962 individuals of reproductive age, a total of 406 (199 males <50 years and 207 females <40 years) showed CAG repeats ≥36. Additionally, five untested individuals of reproductive age indirectly turned out to be HD expansion carriers after an unfavourable outcome of PND. In our study population, 162 couples performed PND and/or PGD. Of these couples, 26 did not undergo PT (as of December 2010). Of the remaining 136 couples, 5 took their PT abroad (n = 2) or were diagnostically tested (n = 3), possibly because they had mild HD features. These five couples were excluded from the calculation. The estimated
Table 3. Characteristics and cumulative reproductive history of couples opting secondarily for PGD vs repeatedly or secondarily for PND

<table>
<thead>
<tr>
<th></th>
<th>PND N = 75</th>
<th></th>
<th>PGD N = 28</th>
<th></th>
<th>Difference between groups&lt;sup&gt;b&lt;/sup&gt; (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (couples)</td>
<td>SD</td>
<td>n (couples)</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Male carrier (%)</td>
<td>18 (50%)</td>
<td>18 (50%)</td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Female carrier (%)</td>
<td>36 (80%)</td>
<td>9 (20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male at risk</td>
<td>15 (100%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Female at risk</td>
<td>6 (85.7%)</td>
<td>1 (14.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean male age at PT (n)</td>
<td>32.0 (18)</td>
<td>7.45</td>
<td>30.8 (18)</td>
<td>5.28</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean female age at PT (n)</td>
<td>25.78 (36)</td>
<td>0.84</td>
<td>27.06 (9)</td>
<td>4.90</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total pregnancies</td>
<td>148 (73)</td>
<td></td>
<td>57 (28)</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Miscarriage (no PND)</td>
<td>19 (13)</td>
<td></td>
<td>10 (10)</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Total pregnancies with PND</td>
<td>104 (58)</td>
<td></td>
<td>37 (23)</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>TOP for HD</td>
<td>53 (32)</td>
<td></td>
<td>27 (20)</td>
<td></td>
<td>0.015&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total pregnancy loss after PND&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7 (6)</td>
<td></td>
<td>0 (0)</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>PGD started</td>
<td>2 (2)</td>
<td></td>
<td>4 (4)</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Total children</td>
<td>64 (54)</td>
<td></td>
<td>14 (13)</td>
<td></td>
<td>0.029&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children with no HD PND</td>
<td>39 (37)</td>
<td></td>
<td>7 (7)</td>
<td></td>
<td>n.s.&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>PGD child</td>
<td>0 (0)</td>
<td></td>
<td>3 (3)</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Untested children</td>
<td>23 (17)</td>
<td></td>
<td>4 (4)</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Continued affected</td>
<td>2 (2)</td>
<td></td>
<td>0 (0)</td>
<td></td>
<td>n.a.</td>
</tr>
</tbody>
</table>

HD, Huntington's disease; n.a., not applicable; n.s., not significant; PGD, pre-implantation genetic diagnosis; PND, prenatal diagnosis; PT, pre-symptomatic test.

<sup>a</sup>Cumulative reproductive history before the last registered PGD or PND attempt.

<sup>b</sup>Frequencies: chi square corrected for continuity calculated per couple, continuous data compared by two-tailed t-test.

<sup>c</sup>Numbers are too small for statistics.

<sup>d</sup>Couples with ≥1 TOP for HD per couples performing PND.

<sup>e</sup>Miscarriage after PND, late pregnancy loss after PND.

<sup>f</sup>Couples without child vs with child (PND, PGD, or ongoing affected, untested).

<sup>g</sup>Couples with ≥1 child after PND compared with couples with ≥1 child.

<sup>h</sup>Prenatal test showed 39 and 45 repeats, respectively.

Table 4. Ongoing pregnancies and live-born children after the use of PND or PGD

<table>
<thead>
<tr>
<th></th>
<th>PND</th>
<th></th>
<th>PGD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continued HD</td>
<td></td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>expansion/50%</td>
<td></td>
<td>PND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>risk allele /</td>
<td></td>
<td>No PND</td>
<td>Control PND</td>
</tr>
<tr>
<td></td>
<td>without PND result</td>
<td></td>
<td>Total PND</td>
<td>Total PND</td>
</tr>
<tr>
<td></td>
<td>No HD</td>
<td></td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>135</td>
<td>77.1%</td>
<td>85.1%</td>
<td>26</td>
</tr>
<tr>
<td>Singletons</td>
<td>134</td>
<td>14</td>
<td>148</td>
<td>18</td>
</tr>
<tr>
<td>Twins</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Triplets</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Children</td>
<td>136</td>
<td>74.3%</td>
<td>82.0%</td>
<td>31</td>
</tr>
<tr>
<td>HD risk after birth</td>
<td>100%</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>≤1%</td>
<td>136</td>
<td>136</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18.0%</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

HD, Huntington's disease; PGD, pre-implantation genetic diagnosis; PND, prenatal diagnosis.

uptake of PND and/or PGD was 32% (131/411) of pre-symptomatic HD expansion carriers of reproductive age. The age at the moment of PT for males and females not opting for PND or PGD was significantly higher (34.2 and 29.4 years, respectively) compared with the age at PT of couples opting for PND or PGD in our study population (males 31.4 years and females 26.6 years; age differences: males p = 0.02 and females p = 0.0003).

Discussion

This retrospective cohort study provides a complete overview of PND and PGD use among HD expansion carriers and at-risk persons who applied for PND or PGD in the Netherlands in the period 1998–2008. In the period under review, 81.5% of 162 couples opted for PND in 262 pregnancies, and 52% of which resulted in the birth of children without HD. PGD was performed by 33% of couples, showing a live-birth rate of 19% per
started cycle. However, couples may have undertaken more PND/PGD attempts after the collection of data ceased.

The introduction of PGD for HD in the Netherlands in 1999 does not seem to have reduced the use of PND in terms of absolute figures. We assume that PGD has attracted a separate group of individuals who selectively opt for PGD. The majority of couples who opt for PND or PGD do stick to their primary choice, even when a large number of treatments are needed. Consecutive failure of PGD or TOP after PND, however, may lead to a shift from PND to PGD or vice versa. Couples secondarily opting for PND more frequently had a child compared with couples secondarily opting for PGD. For some, a successful previous PND might have strengthened the preference to use PND again, and for some the practical obstacle of having a child when going through PGD might have contributed to a preference for PND (17).

The male/female (M/F) ratio of HD expansion carriers or at-risk persons in our total study population was 45:55, comparable with that found in the literature (5, 7, 21, 22). However, for several groups, the M/F ratio was distorted. Male HD expansion carriers/at-risk persons were overrepresented (71.4%) in the group with an untested child prior to PND or PGD compared with the other primary groups. Differences might be explained by M/F differences in responsibility towards family life and caretaking, or a more reluctant attitude of males towards PT(22). A paradoxical shift was observed from the primary PGD group, which consisted of 75% female HD expansion carriers/at-risk persons, to the secondary PGD group, in which 36% carrier/at-risk persons were females (p = 0.013). It may be speculated that at-risk males, when making their primary choice, may underestimate the impact of PND and overestimate the impact of PGD. The impact of PND resulting in TOP may also be correlated with the gender of the at-risk partner. After experiencing PND and TOP, these males may be prompted to change their point of view and shift towards PGD.

Although the absolute numbers of PND have considerably increased compared with the 11-year period studied by Maat-Kievit et al. (1987–1997) (5), the yearly use of PND has remained rather stable since 1996 (19). The use of ePND was reduced from 30% of couples (13/43) (5) to 16% in our study. The proportion of ePND was found to be around 30% in Australia (1994–2003) (23). European studies (1993–1998) showed a proportion of 10% of prenatal tests performed by exclusion testing in Belgium, 29% in France, 30% in Denmark, 42% in Italy and 48% in the UK (7, 24, 25). In Germany, Switzerland, Austria and Greece, no ePND was performed (25–27). The proportion of the use of PGD compared with that of PND in our study is quite low in comparison with Australia and France and comparable with the proportion of PGD use described in a Belgian study (13, 22, 23). This difference may be explained by a more liberal attitude towards TOP and the restrictions on the use of ePGD in the Netherlands. The proportion of ePGD by Dutch couples opting for PGD is low compared with the proportions of ePGD in Belgium (33%) and France (49%), most probably because of the restrictions on the application of ePGD (13, 15).
The 32% uptake of PND or PGD by HD carriers in the Netherlands nowadays is high compared with that in France, Canada, the United States, Germany, Austria, Switzerland, Greece, Australia, Northern Ireland and a diagnostic centre in Johannesburg (South Africa) (13, 21, 23, 25, 27–31) and to some extent comparable with the UK, Belgium and Denmark (7, 22, 24, 25). In our study population, the motives for performing a PT were not registered systematically. In other studies, only about 60–80% of individuals choose to perform PT for reproductive reasons (8, 9), and around 20–50% of individuals performing PT for reproductive reasons decide not to have children after testing HD positive (22, 32, 33). Therefore, we assume that the actual uptake among individuals with reproductive motives for PT will most probably be higher than 32%. Otherwise, there may be symptomatic individuals who reproduce. They are not included in these calculations, although their offspring shows a similar 50% HD risk.

Difficulties in calculating the absolute uptake of PT with respect to the at 50% HD-risk population complicate an accurate calculation and comparison of the uptake between countries (34).

We found that 44.4% (24/54) of the PGD couples delivered children without HD, whereas 52% of spontaneous pregnancies with PND resulted in the birth of a child without HD. However, if we look at the results of all attempts, we see that the outcome in terms of live-born children without HD after PND is relatively favourable compared with the success rate of PGD. If the first two PGD attempts were unsuccessful, a couple was less likely to conceive an ongoing pregnancy resulting in the birth of a child in a later PGD cycle (Fig. 3).

A direct and exclusively quantitative comparison between PND and PGD is probably not fair, as the psychological impact of both methods on partners may differ greatly. The artificial character of PGD and the time investment, the costs, the risks to mother and child, and the chance of misdiagnosis are frequently mentioned disadvantages of PGD (16, 22). By contrast, the physical and psychological consequences of an unfavourable outcome of PND resulting in TOP must not be underestimated (22). Although the chances are in favour of PND, some individuals have stated the negative impact of TOP to be much greater than the disappointment after a failed PGD cycle (35, 36). Another factor complicating PND is the chance of a continued HD expansion or 50% risk allele pregnancy. In our study, this occurred quite frequently (12 pregnancies) and it has previously been described by others (7, 22, 26, 37, 38). According to the international guidelines on PND, continuing an affected or at-risk pregnancy can be considered an early form of pre-symptomatic testing, and therefore it violates the future child’s right not to know (39). Specific details on these pregnancies are described elsewhere (19). The motives of these couples and the long-term consequences of this unfavourable outcome after PND will be subject to future study.

Conclusion

PND and PGD are well-accepted reproductive options in the Netherlands for HD. PND is used considerably more frequently than PGD. This study shows that only a minority of couples decide to change their reproductive strategy after a disappointing outcome of their primary choice. Although chances are in favour of PND, the psychological impact of both methods may differ greatly. To make a balanced choice between the available options, it is important for candidate couples to be well informed about the differences between PND, PGD and alternatives. We recommend repeated reproductive counselling prior to every attempt with an open approach to all available options.

References