Evaluation of exclusion prenatal and exclusion preimplantation genetic diagnosis for Huntington’s disease in the Netherlands


Individuals at 50% risk of Huntington’s disease (HD) who prefer not to know their carrier status, might opt for exclusion prenatal diagnosis (ePND) or exclusion preimplantation genetic diagnosis (ePGD). This study aims to provide a better understanding of couples’ motives for choosing ePND or ePND, and surveys couples’ experiences in order to make recommendations for the improvement of counselling for exclusion testing. This qualitative retrospective interview study focussed on couples who underwent ePND or ePGD for HD in the period 1996–2010. Seventeen couples were included of which 13 had experienced ePND and 6 ePGD. Mean time-interval since exclusion-testing was 3.9 years. Couples’ moral reservations regarding termination of pregnancy (TOP) or discarding healthy embryos were counterbalanced by the wish to protect their future child against HD. Seven couples had terminated a total of 11 pregnancies with a 50% HD risk, none showed regret. ePGD was used by couples who wanted to avoid (another) TOP. ePND and ePGD are acceptable reproductive options for a specific group of counsellees. To guarantee sound standards of care, it is imperative that candidate couples be given in-depth non-directive counselling about all possible scenarios, and adequate professional and psychological support prior to, during and after ePND/ePGD.

Conflict of interest

The authors report no conflict of interest.
Huntington’s disease (HD) is a progressive incurable late-onset neurogenetic disorder with autosomal dominant inheritance (1, 2), caused by CAG (trinucleotide) repeat expansions in the Huntington (HTT) gene (3). Since the discovery of the gene defect in 1993, the uptake of both presymptomatic testing (PT) and prenatal diagnosis (PND) has remained unexpectedly low (4–9). Apparently, the majority of individuals at 50% risk prefer not to be informed about their carrier-status. However, to prevent HD in their offspring, exclusion PND (ePND) (usually by chorionic villus sampling) can be considered (10). Detection of one of either HTT alleles of the affected grandparent is associated with a 50% HD risk for the foetus, similar to the at-risk parent. Although termination of pregnancy (TOP) at 50% HD-risk is initially considered, this remains a moral dilemma. There are reports of couples continuing their pregnancy after receiving a 50% HD-risk result (11, 12).

Exclusion preimplantation genetic diagnosis (ePGD) has become an alternative since 2002 (13). Non-carrier IVF-embryos are selected prior to transfer into the uterus, thus avoiding the chance of TOP of a non-carrier foetus (13–15). However, in the Netherlands ePGD is prohibited by law because: (i) roughly half of the couples at risk will ‘unnecessarily’ undergo an invasive IVF/PGD treatment; (ii) discarding embryos with a 50% risk of not being an HD-carrier is considered unethical (16, 17). Dutch couples requesting ePGD are referred to Brussels (Belgium) for treatment.

ePND and ePGD have been applied for more than two decades (6, 8, 13–15, 18, 19). In the Netherlands exclusion-testing is applied in 15% of prenatal tests for HD (20); other countries showed a variety from 0% (Germany, Switzerland, Austria and Greece) to 48% (UK) (7, 21–24). This qualitative study among couples who have undergone exclusion-testing aims: (i) to create a better understanding of the motives of couples opting for ePND or ePGD, (ii) to study the acceptability of ePGD among candidates and (iii) to investigate experiences of couples with ePND and ePGD. The findings should enable recommendations for future counselling.

Participants and methods

Dutch couples who intentionally underwent ePND or ePGD between 1996 and 2010 were approached to participate in this interview study. Persons who were incapable of giving consent or responding to the interview questions were excluded. For this study we used the method of ‘purposive sampling’ (25). The size of the study group is determined by saturation, i.e. the point at which no new themes are observed, which usually occurs after about 12 interviews (26). The study protocol was approved by the Medical Ethical Committee of the Maastricht University Medical Centre and the Leiden University Medical Centre.

Recruitment of couples

Eligible ePND couples were selected from the database of the DNA laboratory in Leiden, where DNA analysis for HD is centrally performed. Couples were informed by the clinical geneticists involved, received written information after a positive response, and were included after returning the informed consent form.

Couples who applied for ePGD in Maastricht University Medical Centre and who had started ePGD in the Free University Hospital in Brussels were approached (by C.E.M.D.S.). Further inclusion procedure was identical to the ePND couples.

Procedure

A semi-structured interview was developed concerning the reproductive decision-making process and addressed (i) reasons to opt for exclusion testing, (ii) motives contributing to the choice for ePND or ePGD and factors contributing to a possible shift in reproductive behaviour, (iii) moral considerations with respect to ePND and ePGD, (iv) future prospects connected with the possible impact of HD and the way it affects couples’ present life and (v) reflection on reproductive decisions and experiences and on the acceptability of ePGD.

All interviews were held by the principal investigator (M.C.V.R.). Psychological follow-up was offered if needed.

Data preparation and analysis

All interviews were recorded, transcribed verbatim and anonymized. Interviews were analysed using the phenomenological hermeneutical research approach (27). By repeatedly listening to the interviews and iterative reading of the transcripts (M.C.V.R. and A.T.), the personal and motivational contexts were identified. Reported motives, and aspects contributing to choices were categorized until no new key themes were detected. Later, all interviews were reviewed to look for any additional significant statements. To assess reliability of coding, two interviews were independently coded by two other members of the research team (E.K.B. and C.E.M.D.S.). Differences in coding were minimal.

Results

Eighteen out of 28 couples consented and were interviewed between February and April 2012. Twelve couples had experienced only ePND with various outcomes (Table 1). Four couples opted for ePGD from the start. Two couples continued with ePGD after one or two TOPs after ePND. Response of ePND couples was 58% (14/24) and of ePGD couples was 100%. One at-risk female was excluded because she did not meet the inclusion criteria.

Of the 10 couples who did not respond or declined to respond, 8 males and 2 females were at risk. Non-participating couples showed similar outcomes of ePND compared with the participating couples.
At the time of the interview, the at-risk individuals’ genetic status was still undisclosed. Three at-risk partners did not attend the interview because they did not want confrontation with HD. Differences in age and time intervals since the last ePND or ePGD between both groups are not statistically significant and may result from the fact that ePGD was only performed in the second half of the inclusion period (Table 1). Reproductive history and outcome per couple are summarized in Tables 2 and 3. None of the couples made use of the psychological follow-up.

Reasons to opt for exclusion-testing

All at-risk persons insisted on not wanting to know their own HD-carrier status. They feared that HD might control their lives \((n = 8)\), deprive them from hope \((n = 8)\) or stigmatize them \((n = 5)\). The wish ‘not to know’ was generally respected by their partners. Additionally, all couples intended to prevent the birth of an HD-carrier child \((n = 17)\) and cited one or more various underlying motives as follows: to avoid passing HD on to a child \((n = 12)\), to eradicate HD (from the family/world) \((n = 4)\), the anticipated inability of the partner to cope with a double loss (first the partner then a child) \((n = 4)\), the inability to justify having taken the risk of transmitting HD to their future child \((n = 4)\).

Motives contributing to the choice for ePND or ePGD

Most couples \((13/17)\) were informed about both options prior to reproductive decision making. Four couples were not aware of ePGD, one of them was counselled in 1997, before the introduction of ePGD \((13)\). The remaining three couples were counselled in 2003–2006. The most prominent considerations were the artificial aspect of ePGD vs natural conception in ePND, the objections against TOP (ePND) and the limited success rates (ePGD) (see Table 4). Couples expressed emotional reasons as well as moral objections against TOP. Alternative reproductive options which were considered varied from refraining from having children \((n = 6)\), adoption \((n = 6)\), just taking or accepting the risk \((n = 2)\) or the use of donor gametes \((n = 2)\). Five ePND couples had considered ePGD as an alternative. Two ePGD couples and two ePND couples had considered direct PND without prior PT. But the wish not to know the carrier status of the at-risk parent prevailed.

Factors contributing to a shift in reproductive decisions

The wish to avoid (another) TOP for 50% HD-risk was the main reason against ePND \((n = 6)\). One couple shifted towards exclusion-definitive testing after the birth of an HD-free child, i.e. direct testing of the foetus after identification of a 50%-risk allele \((9)\). Two couples decided to refrain from having more children after having had one child, because they did not want ‘to tempt fate anymore’ \((C11)\). One couple stopped using ePND for future pregnancies after three miscarriages and one TOP \((C14)\). After the next miscarriage she said: ‘I
Table 3. Reproductive history of couples attending the interview

<table>
<thead>
<tr>
<th></th>
<th>ePND (n = 11)</th>
<th>ePGD (n = 4)</th>
<th>ePND and ePGD (n = 2)</th>
<th>Total (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion-PND n (couples)</td>
<td>23 (11)</td>
<td>3 (2)</td>
<td>26 (13)</td>
<td></td>
</tr>
<tr>
<td>TOP 50%-risk allele n (couples)</td>
<td>8 (5)</td>
<td>3 (2)</td>
<td>11 (7)</td>
<td></td>
</tr>
<tr>
<td>Miscarriage (50%-risk allele)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child HD risk excluded</td>
<td>13 (9)</td>
<td>13 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child (50%-risk allele)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion-PGD</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Cycles started</td>
<td>8 (4)</td>
<td>6 (2)</td>
<td>14 (6)</td>
<td></td>
</tr>
<tr>
<td>PGD child</td>
<td>4 (4)</td>
<td>0</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Second or third trimester</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>pregnancy after PGD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not pregnant after PGD</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Untested pregnancy</td>
<td>2 (1)a</td>
<td></td>
<td>2 (1)</td>
<td></td>
</tr>
</tbody>
</table>

ePND, exclusion prenatal diagnosis; ePGD, exclusion pre-implantation genetic diagnosis; TOP, termination of pregnancy.
aUntested child and ongoing pregnancy of the same couple.

Table 4. Advantages and disadvantages of ePND or ePGD considered by couples in their decision-making process

<table>
<thead>
<tr>
<th>Exclusion prenatal diagnosis</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Exclusion preimplantation genetic diagnosis</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural pregnancy</td>
<td>TOP (late-onset) HD TOP healthy child (50%)Emotional barrier TOP</td>
<td>No need for TOP</td>
<td>Hormones and artificial character PGD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High chances (50% favourable result)</td>
<td>If continued to direct test, carrier-status revealed chances of double bad news</td>
<td>Carrier status at-risk partner remains undisclosed</td>
<td>Limited pregnancy rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy/no hospital visits</td>
<td>Having to decide for TOP or continuation of pregnancy</td>
<td>Laboratory selects between embryos; couple not involved in selection process</td>
<td>Physical and practical burden (duration PGD/hospital visits)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chance continuing at-risk pregnancy</td>
<td>PGD Belgium: distance, cultural and financial aspectsa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stress until PND result</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOP, termination of pregnancy.
aePGD treatment in Belgium is not or in most cases only partially covered by Dutch health insurance companies.

knew I would always have the feeling: would the child have it or not? I would have always had that sense of unease’ (C14). Two couples shifted from ePND to ePGD, in order to avoid another TOP. After ePGD had failed, one of the latter decided to have children without testing. They thought they could explain to their children that they had done everything in their power to prevent transmitting HD (C15). One couple continued their at-risk pregnancy through a combination of circumstances (C12). Their first 50%-risk allele pregnancy turned out to be a missed abortion at the moment of preparation for TOP. In one phone call the PND-result, again 50%-risk allele, was reported together with the notification of the gynaecologist that the hospital would not provide another exclusion-test in any future pregnancy. The couple felt they had no choice but to continue their already advanced pregnancy.

Moral considerations

Protection of the unborn life is one of the moral concerns in ePND and ePGD. Most couples experienced a conflict between the value of the foetus or embryo and the at-risk partner’s right not to know. Four female partners explicitly considered the status of the foetus to be of less importance than their at-risk partner’s well-being. Therefore, violation of his well-being due to an unfavourable test result would be unacceptable and TOP acceptable. This can be illustrated by a conflict one couple had after their first ePND showed a high-risk allele. The female partner wanted a direct test to prevent the chance of TOP of a healthy foetus: ‘At that moment he [the at-risk husband] really showed his fears, really showed his grief. Then we said to each other, we will talk about it tomorrow . . .’ . Subsequently, the husband offered to do a direct test, but the woman decided
van Rij et al.

to terminate the pregnancy without further testing, because she finally understood her husband’s profound fears and she did not want to risk a ‘double loss’ of her husband being an HD-carrier, and terminating an affected pregnancy at the same time (C07).

Moral objections against TOP for a late-onset disease like HD, and the 50% chance of terminating a healthy foetus, formed an obstacle for two couples (C01, C02). Another two described an emotional resistance to TOP (C08, C09). Twelve couples showed difficulty accepting the possibility that a healthy foetus is terminated, but after careful consideration they found it morally acceptable given the circumstances: ‘It was absolutely clear that we wanted to prevent the birth of a child who could get Huntington’s … As much as possible we realised that this could mean that we would do something really bad, but we were determined to do it’ (C16). Only one couple expressed neither moral objection nor emotional resistance against TOP after exclusion testing (C03).

When asked, eight couples specifically commented on the moral status of the 5-day embryo (ePGD). Two couples had difficulty to accept discarding healthy embryos: one considered ePGD ‘the least bad of two options’ (C02), the other couple would have preferred non-disclosure PGD to prevent discarding healthy embryos (C05).

Five couples (including C02) consider the PGD embryo to be of less value than a foetus at 12–16 weeks’ pregnancy, whereas two couples (C03, C11) valued them equally. One female included the chance of selection in the moral discussion: ‘PND only involves a chance of TOP while PGD always involves a selection’ (C4).

All couples had to reconcile their responsibility towards their future child and the strong wish not to know their own genetic status. One at-risk male: ‘The burden you would give to a child if you pass on HD is greater, or we thought it was greater, than the termination of a healthy pregnancy’ (C12). One couple felt a duty towards their child to prevent the transmission of HD at any cost. In their opinion discarding healthy embryos outweighed the cost and the health benefits to society by reducing the incidence of HD (C08).

Finally, nine couples objected strongly against the political involvement in their personal reproductive decision making; they believed that people who have not experienced HD cannot judge whether ePND or ePGD is acceptable or not.

The impact of the HD risk on couples’ present life and their future prospects

When asked about the future prospects of the couple/family, and the role of HD in their future, the majority of couples (n = 10) expressed a preference to live for the moment and not look far ahead. Seven couples also pointed out that the partner without HD-risk could be struck by a car or get cancer.

Two at-risk females planned to have their children early in life (C01, C15). Two couples tried to save money for the future of their child and partner (C01, C16). Three at-risk persons were worried about leaving behind their spouse and child(ren). One male partner mentioned risk avoiding behaviour because he might become a single parent in the future (C02). Five couples were concerned about the increasing need for care if the at-risk partner fell ill. Three men elaborated on the possible impact of HD on their child: ‘Even if I get ill, the child can also learn a lot from that, as long as the stability remains’ (C07). ‘It [having a father with HD] didn’t affect me negatively, I think. I think I just had a different outlook on the world really early because of that, that’s true’ (C06).

Reconsidering reproductive choices

All four couples who had only used ePGD (resulting in an ePGD-child) would use it again if they had to start all over. For one of the two couples who shifted from ePND to ePGD, the latter was less burdensome than expected, and resulted in pregnancy. However, this couple still believed chances were in favour of ePND, and it could have turned out right (C05). The other couple felt more positive about ePGD. For them the disappointment after an ePGD-cycle without pregnancy was much less burdensome than after TOP (C15). They would never use ePND again because of the terrible grief they experienced after TOP. Others also described TOP as an emotional and painful event. Shame and fear of incomprehension prevented one woman from sharing the experience with her best friends (C14). Without exception, all couples (n = 7) felt they ‘did the right thing’ at that moment, and expressed no regrets. Six out of seven couples would opt for ePND again, while only four had reached their goal of having a healthy child.

In contrast, only one of six couples who had ≥1 child after ePND (and no TOP) would try ePND again without hesitation. One at-risk female would now prefer to first perform PT herself. If she proved to be an HD-carrier, she would refrain from having children (C04). Two couples disagreed about opting for ePND again or not having children (C13, C18). Three couples, who had never heard of ePGD prior to the interview liked to know more about ePGD because it seemed to be an attractive alternative, avoiding the chance of TOP (C12, C14, C16).

Discussion

In exclusion-testing, couples have to weigh up a number of moral dilemmas concerning the conflicting interests of the future child and the at-risk person. Moreover, in the process of ePND and ePGD, couples are exposed to considerable emotional strain. Nevertheless, this study showed that both options were acceptable for all couples involved.

Feelings of responsibility when planning a family underlie one of the most frequently cited motives for
PT, and decision making about PND or PGD for HD (28–32). However, at-risk individuals in this study have to reconcile this responsibility and their wish not to discover their own genetic status. On the one hand they talk of their responsibility towards future children, and are willing to sacrifice their moral reservations about TOP or discarding healthy embryos. On the other hand they live for the moment, do not look too far ahead, and keep hoping (33). This observation suggests that, like in other studies at-risk couples avoided, minimized, or denied the potential future impact of HD on themselves and their (future) children (34). Exposure to an affected parent is difficult for children (35, 36) especially if they are confronted with HD very early in life (37). Therefore, ‘the reasonable welfare principle’ or the ‘high risk of serious harm standard’ stating that it is wrong to expose future children to high risks of serious suffering is widely accepted (38, 39). Consequently, in our opinion it is the counsellor’s challenge to carefully draw the couple’s attention to this issue so that it can be included in the couples’ considerations.

Physicians involved in assisted reproductive technologies like IVF/PGD have a shared responsibility towards the child brought into the world by their actions (39, 40). However, physicians may be too reluctant to offer ePND or ePGD, since there are, after all, many children in HD-families who seem to cope reasonably well. Moreover, adaptive coping skills on the part of the unaffected parent may have protective effects (37). The chance of a child being exposed to HD after exclusion testing is actually limited compared to HD-carrier couples opting for direct PND or PGD. Hence, a case-by-case approach, with special attention to the effects of the symptoms of HD upon the future child’s welfare, would be preferable (40, 41).

In this paper, we focussed on the variables most relevant to exclusion testing; other factors contributing to couples’ reproductive choices are described in the literature (5, 15, 29, 30, 42–45).

For all couples the wish ‘not to know’ was the starting point for further decisions regarding family planning. The right not to know is part of the right to self-determination, protecting the at-risk person against potentially harmful information (46, 47). It is of the utmost importance that partners reach a state of mutual understanding and respect for the at-risk partner’s right not to know prior to exclusion testing. This is especially true if the male is at risk, because his wife will be exposed to the physical burden and emotional stress of ePND or ePGD to preserve her husband’s right not to know.

Study limitations

The participating couples experiencing ePND seemed a fair reflection of the total ePND group in respect of the odds of ePND results (50:50 distribution). However, a selection bias of another kind (impact of ePND and outcome, or gender of at-risk carrier) cannot be ruled out. In ePGD-couples a successful outcome resulting in the birth of a PGD-child was overrepresented. This skewing was not the result of a response bias (100% response of ePGD-couples), but was solely the result of chance (individual fortune). The positive outcomes of ePGD couples might have biased their experiences. Differences in response between the ePND and ePGD groups might have been centre specific (ranging from 0% to 100%). The concept of cognitive dissonance might explain the more positive presentation of couples’ experiences later (48).

Implications for practice

Accurate communication of and honouring agreements are essential issues to be considered. A multidisciplinary team, with a positive attitude towards ePND/ePGD, should be able to guide eligible couples through the moral and emotional complexities. The following topics should be explored during reproductive counselling: the emotional implications of ePND or ePGD regarding the procedures themselves and the possibility of TOP after ePND, the moral status of the embryo or foetus and values in relation to TOP, the interests of all those involved (future child, at-risk parent, partner), a discussion of all (reproductive) options available, anticipating the future about the possible impact of HD on the future child, and the strategies to limit the psychological repercussions for future children, e.g. by not postponing procreation (41). Finally, the mutual agreement of both partners and respect for the at-risk partner’s right not to know are conditions for the successful application of ePND or ePGD.

Conclusion

Both ePND and ePGD for HD are acceptable reproductive options for a specific group of counsellees. Couples carefully consider all moral dilemmas involved, and cope with the considerable emotional strain reasonably well. Candidate couples should receive comprehensive and timely non-directive counselling in respect of all the possible scenarios and adequate professional and psychological support prior to, during and after the test/treatment.

Acknowledgements

The authors would particularly like to thank all couples who participated in the interviews and to express their gratitude to the following colleagues for approaching their clients and informing them about this study: Dr. I. van der Burgt, MD, PhD; Dr. M. C. van Maarle, MD, PhD; Dr. A. A. Maat-Kievit, MD, PhD; Mr. R. P. Stulp(BAS); Dr. C. C. Verschuuren-Beremelms, MD; and Prof. Dr. I. Liebers.

References

van Rij et al.


