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Reproductive options for prospective parents in families with Huntington's disease: clinical, psychological and ethical reflections

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BACKGROUND: Huntington's disease (HD) is an autosomal dominant neurodegenerative late onset disorder. This review of reproductive options aims to increase reproductive confidence and to prevent suffering in relation to family planning around HD and possibly other late onset neurodegenerative disorders.

METHODS: Selected relevant literature and own views and experiences as clinical geneticists, psychologists and ethicists have been used.

RESULTS: Possible options, with emphasis on prenatal diagnosis (PD) and preimplantation genetic diagnosis (PGD) to prevent the transmission of HD to the next generation, are described and discussed. They are formally presented in a decision tree, taking into account the presence or absence of a fully penetrant allele (FPA), a reduced penetrant allele (RPA) or an intermediate allele (IA). A table compares invasive and non-invasive PD and PGD. From a psychological perspective, the complex process of counselling and decision-making regarding reproductive options is discussed. Special attention is paid to the decision to avoid the transmission of the mutation and to the confrontation and coping of a mutation-free child growing up with a parent developing disease symptoms. From an ethical point of view, reflections on both PD and PGD are brought forward taking into account the difference between FPA, RPA and IA, direct testing or exclusion testing and taking into account the welfare of the child in the context of medically assisted reproduction.

CONCLUSION: Recommendations and suggestions for good clinical practice in the reproductive care for HD families are formulated.

Key words: reproduction / Huntington's disease / prenatal diagnosis / preimplantation genetic diagnosis

Introduction

Huntington's disease (HD) is a hereditary late onset neurodegenerative condition characterized by involuntary movements, cognitive deterioration, mood and behavioural problems and changes in personality (Roos, 2010). In most populations, between 5 and 7 individuals per 100 000 are affected (Walker, 2007). For the majority of patients, onset of the disease is between 30 and 50 years of age, but first symptoms may sometimes appear early in infancy or late in the elderly (Tabrizi et al., 2012). So far, no treatment is available (Imarisio et al., 2008; Novak and Tabrizi, 2011). Life expectancy with progressive deterioration after the disorder has become manifest, is ~15–20 years (Pfister and Zamore, 2009; Roos, 2010). The disease is caused by an unstable CAG trinucleotide repeat expansion in exon 1 of the ITI5 gene (The Huntington's Disease Collaborative Research Group, 1993). The CAG expansion leads to an expanded polyglutamine tract in the Huntington's protein causing a toxic gain of function (Walker, 2007; Imarisio et al., 2008).

In general, the size of the CAG expansion is inversely correlated with the age of onset: the longer the repeat the earlier the onset. However, there is still a large variation in the clinical expression with a given CAG repeat size (Imarisio et al., 2008). Therefore, individual predictions of the age of onset based on the repeat size are almost impossible, although prediction models do exist (Langbehn et al., 2004, 2010). About 50–70% of the variability in the age of onset is thought to be due to the CAG repeat length, with the remainder probably due to modifying genes, the environment and somatic mosaicism (Langbehn et al., 2004; Tabrizi et al., 2012).

Currently, four broad categories of repeat sizes have been identified (Sequeiros et al., 2010).

(i)   40 CAG repeats or more are full penetrance alleles (FPAs) and will cause symptoms.
(ii) Thirty-six to 39 repeats are incomplete or reduced penetrance alleles (RPAs) and may cause symptoms, usually later in the adult life. A maximum risk of 60% that a person with an RPA will be symptomatic at the age of 65 years, and a 70% risk of being symptomatic at the age of 75 years were reported (Quarrell et al., 2007).
(iii) Twenty-seven to 35 repeats represent the category of intermediate alleles (IA), sometimes called large normal alleles, which are not associated with symptomatic disease, but may be unstable on transmission.
(iv) Twenty-six or less repeats are not associated with HD.

It has been observed that the repeat is unstable upon transmission to the next generation (MacDonald et al., 1993; Aziz et al., 2011). The age at onset may decrease in successive generations, especially when transmitted through males, and this is associated with expansion of the CAG repeat, the larger the expansion the higher the risk for further expansion (Walker, 2007; Imarisio et al., 2008; Aziz et al., 2011). This phenomenon is called anticipation. CAG repeats may also contract, although mostly only slightly and mainly when transmitted by females (Semaka et al., 2010; Aziz et al., 2011).

'New' cases of HD mostly result from an RPA in a (yet) asymptomatic parent. It has been shown that RPAs are unstable upon transmission, mainly through the male germline (Goldberg et al., 1993; Brocklebank et al., 2009; Sequeiros et al., 2010). RPAs show instability in at least one of three parent–offspring pairs (Sequeiros et al., 2010; Aziz et al., 2011). Brocklebank et al. (2009) reported that 14% of alleles transmitted from the reduced penetrance (RP) range expanded into the fully penetrant (FP) range in a large Venezuelan kindred.

There are conflicting reports about the extent of the instability of IAs (Sequeiros et al., 2010). Out of the 69 transmitted alleles in this range, one expansion from 33 to 35 CAGs was found, but none expanded into the RP or FP range (Brocklebank et al., 2009). However, it has been demonstrated by analysing the CAG repeat size in single spermatozoa that IAs can expand to RPAs (Chong et al., 1997). Semaka et al. (2010) examined the intergenerational stability of IAs. Overall 30% of the alleles were unstable upon transmission with more expansions than contractions. The mean change in the CAG size was 1.39. Expansions were present in 24% of the transmissions from the 31 to 35 CAG range and in 14% of the transmissions from the 27 to 30 CAG range (Semaka et al., 2010). Overall, there clearly is a need for CAG-size-specific risk estimates for IA expansion for use in clinical practice.

Clinical experience with genetic counselling for HD has learned that couples with one partner at increased risk worry about the prospects of their (future) children. This paper provides an overview of reproductive options for prospective parents confronted with a late onset neurodegenerative disorder in their family, hereby using HD as a paradigm. The main goal is not to provide a systematic review of the literature but to share a personal view on reproductive options and their complexity, based on a long experience with predictive testing for HD and counselling of families, in order to contribute to good clinical practice and assist families in restoring their reproductive confidence.

Materials and Methods

Selected and relevant literature was combined with personal views and experience from clinical geneticists, psychologists and an ethicist to discuss (i) the reproductive options for mutation carriers and at risk persons with the construction of a decision tree and a comparative table, (ii) the complex process of decision-making and counselling with emphasis on unplanned pregnancies, prenatal diagnosis (PD) with exclusion testing, PD for IA carriers, reproduction by a symptomatic parent and growing up in an HD family and (iii) ethical aspects of PD and preimplantation genetic diagnosis (PGD).

Results

Reproductive options

Individuals carrying or being at risk of carrying an expanded CAG repeat and who wish not to pass on the CAG expansion to their offspring have several options to have unaffected offspring. The emphasis will be on PD and PGD. Gametes, being sperm or oocytes, from donors can also be used to avoid disease transmission. In this situation, one parent still transmits his or her own genes (Lansac and Royere, 2001; Klein and Sauer, 2002). Also the use of donated embryos may be considered; this procedure is in fact prenatal adoption (Sauer and Kavic, 2006). Gamete or embryo donation is only rarely used in practice by fertile at-risk couples. Most couples prefer to have a genetically related child. Therefore, they will not be discussed further.

Procedures and molecular methods

PD includes DNA testing of chorionic villi, obtained by transcervical or transabdominal biopsy in the 10–13th week of pregnancy or of cultured amniotic fluid cells, obtained by amniocentesis from the 15th week of pregnancy on (Maat-Kievit *et al.*, 1999).

Since 2003, non-invasive PD (NIPD) of HD by examination of cell-free fetal DNA in maternal blood has been investigated (González-González *et al.*, 2003a, b). Between 6 and 12 weeks of pregnancy, NIPD can be performed by direct and indirect analysis. At present, NIPD for HD is limited to at-risk pregnancies due to an affected male partner and is rarely available (Bustamante-Aragones *et al.*, 2008; González-González *et al.*, 2008).

PGD is generally performed on cleavage stage embryos on the third day after IVF with ICSI. Only embryos with two normal alleles and/or normal haplotypes are transferred to the uterus (Sermon *et al.*, 1998, 2002; Moutou *et al.*, 2004; van Rij *et al.*, 2012). The mean delivery rate per oocyte retrieval is 17–20% (Geraedts and de Wert, 2009; Verpoest *et al.*, 2009; Harper *et al.*, 2010; van Rij *et al.*, 2012). PGD via polar body biopsy of the fertilized oocyte, if the female partner is the carrier of an HD expansion, is feasible (Harton *et al.*, 2011; Kuliev and Rechitsky, 2011). PGD via trophectoderm biopsy of the blastocyst has been performed for monogenic conditions (McArthur *et al.*, 2008; Harton *et al.*, 2011).

Testing of the fetal/embryonic material is possible by means of direct testing of the expanded repeat and/or testing with markers closely linked to the HD locus, usually by PCR-based methods (Maat-Kievit *et al.*, 1999; Simpson *et al.*, 2002). Optimal reliability in PD as well as in PGD requires the establishment of the origin of the repeats or haplotypes of both parents in the fetus or embryo. This policy implies that in the context of direct testing, the healthy partner's CAG repeat lengths in the HD gene are also tested.

In PGD, the expanded repeat may be difficult to visualize or may be absent due to technical problems, such as allelic drop out (Sermon *et al.*, 1998; Harton *et al.*, 2011). Hence, the decision that an embryo is diagnosed as free of the HD mutation is mainly based on the presence of normal alleles of both parents. Combined direct and linked marker analysis is necessary in PGD if the couple is non-informative for the CAG repeat length, that is if the normal allele of the affected parent corresponds with one or both alleles of the normal parent.

Linked marker analysis without direct testing of the repeat is used in exclusion testing, which can be applied for at-risk persons who do not want to know their carrier status. The principle of exclusion testing is that the transmission of the HD region of chromosome 4 from the affected grandparent is followed. If the analysis indicates that the HD haplotype, which has been passed to the fetus/embryo, originates from the affected grandparent, the fetus or embryo has the same increased risk of being an HD carrier as the parent at risk (Quarrell *et al.*, 1987; Sermon *et al.*, 2002; Decruyenaere *et al.*, 2007). In the case of PD, a termination of pregnancy (TOP) will most probably follow while in PGD, the at-risk embryos will not be transferred.

Decision tree

At-risk members from an HD family, who wish to know their own carrier status or not, and thus choose for predictive testing or not,

may want to have children and make use of the possible reproductive options to avoid the transmission of the mutation. We describe these options for FPA, RPA and IA carriers (Figure 1).

A carrier (of an FPA) has the options to refrain from offspring (A), or to have a natural conception without (B) or with PD (C).

C.1: with 50% chance that the fetus is not carrying the mutation.

C.2: with 50% risk that the fetus will carry the mutation. The pregnancy will in most cases be terminated (C.2.a). Exceptionally, the pregnancy is continued and the carrier status of the child is known (C.2.b).

If the at-risk person carries an RPA, the situations A, B and the outcome in C.1 and C.2 (Figure 1) is not different from that for an FPA carrier.

C.3: if the fetus carries an RPA, the length may be similar to that of the parent or be somewhat smaller or larger. Occasionally contraction of an FPA in the parent may lead to an RPA in the fetus. The option to terminate the pregnancy (C.3.a) or not (C.3.b) is discussed further.

For carriers of an IA, options A, B, and the outcome in C.1, C.2 (very seldom) or C.3 is in fact not different from that for parents who are carriers of an FPA or an RPA.

C.4: if the fetus carries an IA it seems controversial to terminate the pregnancy (C.4.a).

IVF and PGD with transfer of one or two embryos without the mutation into the uterus is also possible (D):

D.1: the result may be a pregnancy followed by the birth of offspring not carrying the mutation. If more transferable embryos are available, they will be cryopreserved.

D.2: if no pregnancy will be established, cryopreserved embryos can then be thawed and transferred or a new IVF/PGD treatment can be initiated.

Couples who are at 50% prior risk and who do not wish to know their own status may opt for

E: a natural conception without PD. The child has 25% prior risk (half of the parent's risk) and the carrier status of the parent will not be known.

F: a natural conception with PD by direct testing of the fetus (despite the fact that originally the at-risk person did not want to know his/her status).

F.1: the fetus does not carry the mutation and the parent at risk will not know his/her status.

F.2: the fetus does carry the mutation, and the parent's carrier status is revealed at the same time.

G: a natural conception with PD by exclusion testing (ePD).

G.1: the fetus has the 'not-at-risk haplotype' and the risk status of the parent will remain unknown.

G.2: the fetus has the 'at-risk haplotype'.

G.2.a: usually the pregnancy will be terminated. In half of the cases, the aborted fetus will in fact not carry the CAG expansion, but this information is not available. The risk status of the parent remains unknown.
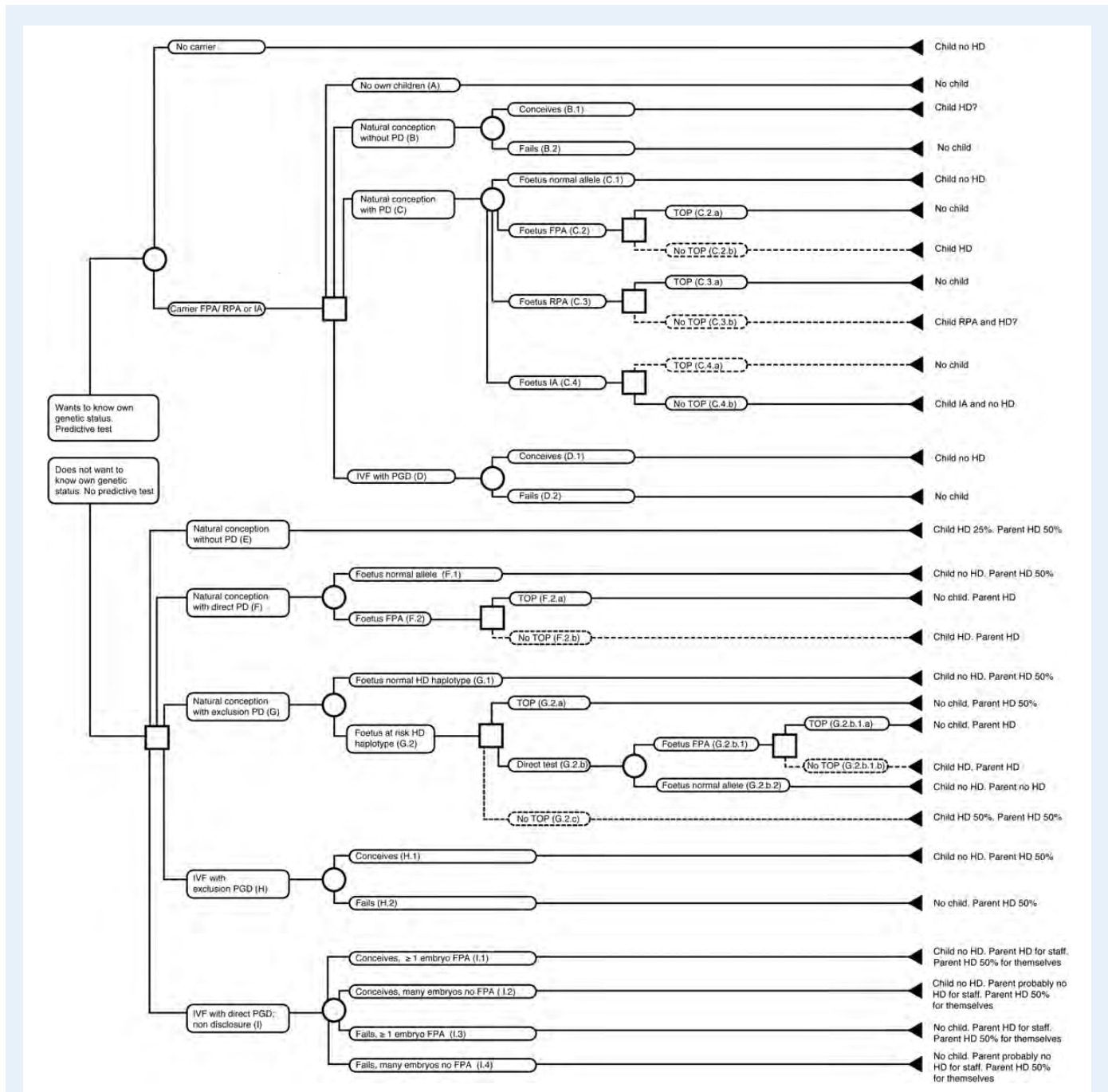
Figure I Overview of reproductive options and outcomes for prospective parents at risk of transmitting HD to offspring. In PGD only embryos with normal alleles and/or normal haplotype are transferred. FPA, fully penetrant allele; RPA, reduced penetrant allele; IA, intermediate allele; PD, prenatal diagnosis; PGD, preimplantation genetic diagnosis; TOP, termination of pregnancy. Gamete and embryo donation is not discussed. Dashed lines represent common practice and dotted lines debated or unusual.

G.2.b: a 'rescue' direct test could still be performed to detect whether the fetus has the mutation.

G.2.b.1: if the mutation is present in the fetus, the parent is also a mutation carrier.

G.2.b.2: if the direct test shows the absence of the mutation in the fetus, the parent is also not a mutation carrier (as the parent and fetus share the same haplotype).

G.2.c: the pregnancy with the 'at-risk haplotype' continues, the child as well as the parent stays at risk.

The couple may also opt for IVF and PGD.

H: with exclusion testing (ePGD) and transfer of the embryos with the 'non-at-risk' haplotype. In fact, in half of the couples, none of the embryos with an 'at-risk haplotype' will have the CAG expansion.

H.1: the child to be born will not develop HD and the status of the parent will stay unknown

H.2: no pregnancy occurs.

I: The last option is IVF and PGD with non-disclosure of the direct test results (Schulman *et al*., 1996; Braude *et al*., 1998).

I.1./I.3: if the result of the embryo testing is a mixture of embryos without the mutation and embryos with the mutation, embryos without the mutation can be transferred. It will be known to the staff that the parent at risk is in fact a mutation carrier but this information will not be 'disclosed' to the couple.

I.2./I.4: if the result of the embryo testing is many embryos without the mutation and none with a mutation, any embryo can be transferred. The staff will know that the parent at risk is most probably not a mutation carrier but cannot disclose this to the couple. If no pregnancy occurs (I.4.), repeated IVF/PGD treatments are offered although most are probably not necessary.

Comparison of the different reproductive options

A comparison of the different reproductive options is given in Table I. Although the decision process and the expected or experienced emotional burden can be very different for couples and can also differ between the spouses, some remarks can be made. PD has the main advantage of a natural conception, however, with the threat of a TOP in case of an unfavourable result. NIPD is not yet widely available but this may change in due time and may be a more attractive option than invasive PD, although it still involves a TOP, but without the risk of procedure-related miscarriage (de Jong *et al*., 2010). PGD has the advantage over PD that couples are not faced with the difficult decision of (repeated) pregnancy termination(s) and the possible mourning process (Braude *et al*., 1998; Decruyenaere *et al*., 2007). Also for couples with an increased genetic risk combined with infertility, PGD may be the best option. The main disadvantages of PGD are the relatively low pregnancy rate and the risk and burden of the IVF treatment for the woman (van Rij *et al*., 2012).

The complex process of decision-making and counselling about prenatal diagnosis and PGD

Feelings of responsibility when planning a family underlie one of the most cited reasons to have a predictive DNA test, and play a major

Table I Comparison of prenatal and PGD, assuming that the diagnosis of HD is confirmed in the proband or relative.

	Chorionic villus biopsy	Amniocentesis	Non-invasive prenatal diagnosis	IVF with PGD
Conception	Natural	Natural	Natural	Artificial
Availability	Widely	Widely	Very limited	Limited
Suitable for infertile couples	No	No	No	Yes
DNA test technically possible	Always	Always	Only if male is at risk	When the couple is informative for the repeat and/or linked markers
Failure of diagnostic procedure or technical problem	1–3%	Very seldom	Few data	Possible, few data
Timepoint in pregnancy	10–13 weeks	15–17 weeks	6–12 weeks	Before pregnancy
Procedure time	10–15 min	5–10 min	5 min	3–5 weeks
Procedure-related risk of miscarriage	1–2%	0.5%	None	n.a.
Waiting time for results	1–3 weeks	2–5 weeks	3–7 days	24–48 h
Risk of misdiagnosis	Minimal	Minimal	Probably low	<1%
Procedure-related physical burden for women	Some	Some	None (only blood sampling)	Variable
Psychological burden (very personal)	Burden of TOP if child is at risk	Burden of late TOP if child is at risk	Burden of TOP if child is at risk	Burden of IVF treatment and disappointment if no pregnancy
Eventual pregnancy termination	Yes	Yes	Yes	n.a.
Chance of success (birth of a healthy child)	≈50%	≈50%	≈50%	20% per oocyte retrieval
Pretest examination necessary	Yes, if exclusion	Yes, if exclusion	No	Always
Time to start procedure	Few weeks, if exclusion	Few weeks, if exclusion	None	1–6 months
Cooperation family members necessary	Yes, if exclusion	Yes, if exclusion	No	Always
Ethical/moral objection	Related to TOP for late onset disorder	Related to TOP later in pregnancy for late onset disorder	Related to TOP for late onset disorder	Related to selection of embryos for late onset disorder
Number of attempts	Unlimited theoretically	Unlimited theoretically	Unlimited theoretically	Limited by law in some countries

role in decision-making about PD or PGD for HD (Duisterhof *et al.*, 2001; Evers-Kiebooms *et al.*, 2002; Downing, 2005; Decruyenaere *et al.*, 2007; Tibben, 2007). Reproductive decision-making is a complex psychological process, subject to cognitive, emotional, moral and unconscious elements, especially for couples at risk of HD and for whom a strong child wish may contradict with the compelling need to prevent a child from getting HD. The updated international guidelines have stressed the importance of preconception counselling which allows couples to consider their thoughts, feelings and moral values at an early stage when more options are still available, in particular PGD, and gives them time for informed decision-making (MacLeod *et al.*, 2012).

The desire to have a child and even more a child who will be free of HD, may be an expression of the need to have a life which is as normal as possible. Extensive in-depth counselling to eventually minimize the degree of ambivalence, to enhance personal control and to promote free informed decision-making is of the utmost importance. Partner discordance regarding the reproductive option to be chosen, traumatic personal experiences with HD (Demyttenaere *et al.*, 1992; Downing, 2005), lack of support from relatives (Craufurd, 2002; Codori *et al.*, 2004), rejecting attitudes in professional caregivers (Elger and Harding, 2006), the technological imperative of PD/PGD (Adam *et al.*, 1993; Decruyenaere *et al.*, 2007) and having non-at-risk or at-risk children growing up within an HD family are all important factors to recognize in counselling.

Growing up in an HD-family

It is likely that a mutation-free child will be at some point confronted with a parent who insidiously develops symptoms (Brouwer-Dudok de Wit *et al.*, 2002). This issue is, according to clinical experience, less explicitly considered by professionals offering and couples requesting PD or PGD and may raise mixed feelings in the couple when brought up for consideration by the counsellor. Hence, an important question is how parents can reconcile their wish to not transmit HD to their future offspring and the substantial probability that their children will face a parent who becomes less accessible for the support of the child, gradually more impaired and less able to take parental tasks and responsibilities. However, a promising and supportive perspective is provided by the studies on attachment which may help couples to offer their children secure relationships and a safe childhood, despite the burden of the parent's disease (Van der Meer *et al.*, 2006; Forrest Keenan *et al.*, 2007). Some couples may start a family as soon as possible to prevent potential traumatic experiences in early childhood and to increase the chance of a secure attachment. For some this implies opting for PD, as PGD takes more time.

Unplanned pregnancies

It is not uncommon that couples apply for the first time for counselling when faced with an unplanned pregnancy. Nevertheless, they wish to avoid passing the HD risk on to their children (Decruyenaere *et al.*, 2007). They may or may not have considered prenatal testing before, but decision-making under stress and time pressure is extremely burdensome for both the couple and the professionals involved (Hardman, 2009). Such an event may be considered as an existential crisis, and may be an expression of fear, ambivalence and the inability to take responsibility for any decision regarding reproductive options. Therefore, they need ample support and help.

An unplanned pregnancy, where one of the partners is at 50% risk of having a mutation, might happen in a period that a couple already has 'vaguely' considered predictive testing. In this situation, a first approach is to test the parent at risk. There is hardly time for sound pre-test counselling of all consequences of unfavourable test outcomes, let alone coming to terms with the result. Soon after the disclosure of an unfavourable predictive test result, the focus has to be directed to testing the pregnancy. After an unfavourable prenatal test result, this second bad news is usually followed by a TOP, a third negative event in such a short period of time. A second possible preferable approach is to directly test the fetus at 25% risk to have a mutation. When the fetus has the HD mutation, this simultaneously identifies the parent as mutation carrier. Either way, both approaches of testing imply the risk of a 'double loss'. Either scenario requires the utmost care and follow-up. A third approach in case of an unplanned pregnancy of a parent with a 50% prior risk is prenatal exclusion testing.

Prenatal exclusion testing

Prenatal exclusion testing allows a couple to have a child who is free of HD without learning their own genetic status. However, the drawback is the couple's awareness that they may end up terminating an unaffected pregnancy. This may be even more problematic if, afterwards, the at-risk parent finds out that he/she is not a mutation carrier. Moreover, the couple may find it difficult to continue with prenatal exclusion testing after one or more unfavourable outcomes and decide to have either predictive testing, opting for PGD or refraining from any further reproductive assistance. These complexities of prenatal exclusion testing should be brought to the attention of the couple to enable informed decision-making and to anticipate future dilemmas (De Die-Smulders *et al.*, 2002; Jacopini *et al.*, 2002; van Rij *et al.*, 2013). Professional support ought to be available to address anticipatory grief reactions.

Prenatal diagnosis in carriers of an intermediate allele

Usually, the intention of the prenatal test for couples with a parental mutation in the IA range is to exclude the small risk of an expansion of the CAG-repeats into the RPA (or very seldom FPA) range. But what if the PD shows an IA in the fetus? The unborn child will almost certainly not develop HD but may pass the mutation on to his or her future children with a small risk of expansion in future generations. Parents may wish to prevent any future HD-related decisional problems in their (grand)children and ask for a TOP. The future parents' illness perception and their burdensome experience with being at risk may underlie such attitude and/or request. Not withstanding the fact that reproductive decision-making is not merely a rational process but an emotionally loaded one, it is very important to check the prospective parents' understanding of the instability of CAG repeats as well as their awareness of the small risk of expansion of an IA into an RPA and the almost zero chance of expansion of an IA into an FPA.

Symptomatic parent and assisted reproduction

If one member of a couple already presents and is aware of the first signs of the disease, the issue of the impact of the approaching disorder on all involved, deserves, when discussing the reproductive options, even more attention and a more prudential approach than for couples with a still asymptomatic or at-risk member. If there is no awareness or negation of obvious disease onset, it is even more

difficult. Moreover, impaired judgment may complicate free informed decision-making. In case of a successful PD, the mutation-free child will from the start be confronted with an insidiously deteriorating parent in early childhood with subsequent higher risks for impaired quality of life and insecure attachment relationships (Van der Meer et al., 2006). The non-HD partner is challenged to take over a steadily increasing number of roles and responsibilities. Couples may need additional support to anticipate the complexities and impact of the disease on their lives.

The situation is even more complex when a couple, with one of the parents presenting early signs, opts for PGD, which requires the involvement of a team of professionals helping to conceive. Given the potential psychosocial burden for future children, should PGD be available for them? If yes, the children will not get the disease but will be confronted with a symptomatic parent. In the guidelines, it is commented that being symptomatic is not *a priori* an exclusion criterion for PGD. However, special attention should be given to the effects of the symptoms of HD upon the future child's welfare (MacLeod et al., 2012). The counsellor and gynaecologist involved in PGD may require the couple's willingness to face and discuss the far-reaching consequences of exposing a child right from the start to a parent with HD. This requirement is even more pronounced in case of impaired judgment due to psychiatric problems, which is, at the same time, an obstacle for a balanced discussion with the patient and the partner.

Ethical reflection

The reproductive options and related counselling for HD raise moral questions for prospective parents, professionals and for society, which need further ethical reflection. Some countries prohibit particular reproductive options. Therefore, we want to stress the importance of the recent Good Practice Guide of the European Society of Human Reproduction and Embryology (ESHRE) for cross-border reproductive care for centres and practitioners treating foreign patients (Shenfield et al., 2010).

Prenatal diagnosis

There is a strong consensus that PD, possibly followed by a TOP, is morally justified in case of a high risk of transmitting a serious disorder, such as HD. PD for late-onset disorders, like HD, raises specific moral questions and concerns. Critics argue that PD for late-onset disorders is ethically unjustified as a future child with the mutation would be asymptomatic for a long period (Post, 1991). This view, however, is widely considered to be unconvincing. It disregards the fact that the prospect of developing a late onset disorder often entail(s) severe burdens for the carriers and their families, especially if the condition is untreatable. Furthermore, a dichotomy between early- and late-onset disorders seems simplistic, as HD has a juvenile onset in some cases. Whereas there seem to be no convincing *a priori* objections to PD for HD, some further comments are necessary in view of the diversity of tests and situations.

(Un)conditional access for carriers? According to the dominant moral framework, PD should be available for women with a medical indication irrespective of their intention to opt for TOP in the case of an unfavourable outcome. Prospective parents may have various legitimate reasons for requesting information about the condition of the

fetus, e.g. reassurance or preparing for the birth of an affected child. However, such 'unconditional access' to PD raises a specific moral problem in the context of HD: should the fetus prove to be a carrier of HD and should the pregnancy be carried to term, then in effect a child has been presymptomatically tested (Duncan et al., 2006). Such testing is at odds with international ethical guidelines and is widely considered to be a violation of the child's right not to know, i.e. the right of the child to decide for himself later, when competent, about predictive testing, and may harm the child by generating burdensome information (De Wert, 1999; Borry et al., 2009). Providing 'conditional access' to PD for HD, namely only to prospective parents who are willing to terminate pregnancy in the case of an unfavourable test result, is therefore morally justified (De Wert, 2002; Evers-Kiebooms et al., 2006). Obviously, in view of the emotional context and the complexities involved, it cannot be excluded that couples change their minds. As they are entitled to do so, they should not be pressurized afterwards, let alone be forced, to terminate the pregnancy.

Direct testing of the fetus of a person at 50% risk. Persons at 50% risk of being a carrier, who prefer not to know their own genetic status, may ask for direct prenatal testing of the fetus. Critics may point to possible psychological harms resulting from a 'double unfavourable' test result (for the fetus and the parent at risk), resulting in 'double loss'. However, it is important to also take into account the burden and (immaterial) costs of alternative options: no testing, just terminating the pregnancy, 'sequential' testing, i.e. predictive testing of the at-risk person, followed by direct testing the fetus if indicated or prenatal exclusion testing. Because these alternatives carry their own psychological risks and ethical problems, and because direct testing of the fetus has a lower risk of generating unfavourable information about the applicants' own genetic status in comparison with predictive testing of themselves (25% instead of 50%), we conclude that direct testing of the fetus of a person at 50% risk may be justified in individual cases (Maat-Kievit et al., 1999; De Wert, 2002; MacLeod et al., 2012). It is of paramount importance however that people who really do not want to know their carrier status realize that this option does not suit them.

Prenatal exclusion testing. Prenatal exclusion testing is considered by some people to be especially controversial. Critics wonder as to whether aborting a fetus at 50% risk instead of trying to preserve the non-carrier fetus (by performing mutation analysis) is not too high a price for protecting people's right not to know. Secondly, they fear that women will suffer from regret reactions if they abort a fetus at 50% risk and eventually find out that it did not carry the HD mutation. Still, we think that (offering) prenatal exclusion testing is justified. Accepting the dominant view that the moral value of the fetus is not absolute, we argue that the at-risk person's right not to know overrules the moral status of the fetus.

Prenatal diagnosis for carriers of reduced penetrance or intermediate allele. When PD is requested by carriers of an RPA, the test may indicate that the fetus carries an RPA. TOP because of an RPA in the fetus is debatable, as one-third of the future RPA carriers will not be symptomatic at the age of 75 years. Prospective parents will be concerned first and foremost about the substantial risk that the future child carrying an RPA develops HD in (late) adulthood. But, secondly, they

regularly want to avoid the 'transgenerational' risk, that is the reproductive dilemma of future RPA carriers confronted with the risk that their own children will carry an FPA. In view of these risks, we argue that carriers of an RPA may justifiably opt for TOP of a fetus carrying an RPA. A dilemma may arise if a carrier of an RPA requests PD, and intends to terminate pregnancy only in case of an FPA in the fetus, not if the fetus would prove to carry an RPA. Should PD be withheld then, to protect the future child's right not to know? Or would this be a too extensive interpretation of this right, as unsolicited knowledge about carrying an RPA may well be less harmful than unsolicited knowledge about carrying an FPA?

PD for carriers of an IA is (so far) requested only rarely. These requests should be carefully counselled; the risks and burdens of PD should be balanced against the presumed advantage of PD for IA carriers. It is crucial that possible concerns and misunderstandings regarding a presumed (highly theoretical) direct expansion to an FPA in the fetus are clarified. At the same time, taking into account the possible risk of an IA to expanding to an RPA, the risk of a future child carrying an RPA developing HD in (late) adulthood and, finally, the reproductive dilemma of future carriers of an RPA (see before), carriers of an IA may justifiably opt for PD. TOP in the case of an IA in the fetus is, however, problematic in view of the quasi-zero risk of HD in the future child.

Preimplantation genetic diagnosis

There is a strong consensus that PGD is morally justified in case of a high risk of transmitting a (serious) disorder (De Wert, 1999, 2009; Shenfield et al., 2003). Notwithstanding the relatively low 'take-home baby rate', many people, including the members of HD families, perceive PGD as a good alternative for PD, as it avoids the emotional and/or moral problems regarding TOP (Decruyenaere et al., 2007; van Rij et al., 2012). With regard to PGD for HD, the ethical discussion usually concentrates on the issue of embryo selection per se: are late-onset disorders such as HD 'serious enough' to discard embryos that carry the mutation? A preliminary issue, however, is whether it would be justified for medical doctors to provide medically assisted reproduction for these couples.

A preliminary issue: access to medically assisted reproduction and the welfare of the child.

Doctors involved in IVF have a professional responsibility to take into account the interests of the future child who will be conceived as a consequence of their professional assistance. Access to IVF may be contraindicated in view of possible risks for the welfare of the future child. There is substantial support, internationally, for the so-called 'reasonable welfare principle' or the 'high risk of serious harm standard' (De Wert, 1998; Pennings, 1999; Pennings et al., 2007). According to this principle, it is wrong to expose future children to high risks of serious suffering. How does this apply in the current context?

In view of the fact that a carrier (of an FPA) will inevitably develop HD, competence as a parent will be lost steadily with increasing burdens on the other parent (Braude et al., 1998; De Wert, 2002). Future symptoms of HD, and, eventually, the (untimely) death of the affected parent, may have adverse effects for the flourishing of the child. Do these psychological risks constitute an overriding argument to not provide IVF/PGD? Or are these risks acceptable in view of the 'high risk of serious harm' standard? We consider a 'black-and-white' approach to be inadequate. It is important to make a double distinction,

firstly between carriers of an FPA, an RPA and an IA, and secondly between asymptomatic carriers and symptomatic people, as both may have implications for the harm-probability ratio.

Request of a full penetrance-, reduced penetrance- or intermediate allele carrier. Obviously, the request of a carrier of an IA is the simple case, as the prospective parent will not develop symptoms of HD. If the applicant carries an RPA or an FPA, the situation becomes more difficult or more of a threat, but even then, some differentiation is necessary. Although, the development of HD symptoms in a parent is always burdensome for children, it is well known that many children of HD families are able to cope reasonably well with the situation (Forrest Keenan et al., 2007). Relevant variables include the coping skills of the parent not affected by HD, communication among family members about the disorder, the quality of the network of the family, the availability of social support, and, last but not least, the age of the child when confronted with HD in the parent. In many cases the child will be an adolescent or even an adult when the parent at-risk becomes symptomatic, especially when (s)he carries an RPA. In practice, it has been suggested that it may make a difference as to whether the woman or the man is at risk; in view of the fact that mothers are often more involved in the daily care for the child(-ren), her carriership will regularly entail a larger risk for the welfare of the child.

Request of a symptomatic carrier. Obviously, if the prospective father or mother is already symptomatic, the psychosocial risks for the future child will be much greater, as the child would be confronted with the agony of the progressive disorder in one of the parents 'right from the start'. The provision of medically assisted reproduction is, in these cases, problematic, especially if the affected parent will be the primary care-giver for the future child(-ren). Most importantly, all applicants of PGD for HD should receive expert counselling (see above). Further discussion is needed to see how the above variables would allow decisions to be made 'case by case'.

Issues related to PGD for HD per se.
If medically assisted reproduction for HD carriers is not *a priori* unsound indeed, what, then, about PGD for HD?

PGD for carriers of a FPA: mutation analysis.
Although PGD for HD is somewhat more controversial than PGD for early-onset disorders, there is a strong consensus that PGD for HD is (like PD for HD) morally justified. People who accept the dominant view that the early embryo has a lower moral status than a fetus may even ethically prefer PGD above PD. Internationally, HD is among the major indications for PGD (Harper et al., 2012; Van Rij et al., 2012).

Embryo transfer: the locus of decision-making. In the context of PD, the principle of respect for (reproductive) autonomy is a central guiding principle (though it needs qualification in the context of PD for HD). This means that doctors should not pressure prospective parents to opt for prenatal testing or to terminate pregnancy in case of an unfavourable test result, but the doctor should support them. When applied to PGD, this principle would imply, first, that doctors should never put pressure on prospective parents to opt for PGD,

and, second, that prospective parents should be free to have embryos with an inconclusive test result or even carrier embryos transferred. But is this, indeed, good IVF/PGD practice?

Infertile couples who also are at high genetic risk of having an affected child will regularly welcome the option of PGD. But a number of these couples who face late onset disorders like HD, may not be very concerned about transmitting the mutation, but may anticipate the timely availability of (gene) therapy in the future (Schover *et al.*, 1998). In view of the professional responsibility of doctors involved in medically assisted reproduction to avoid a high risk of serious harm to the future child, a (partial) shift with regard to the 'locus of decision-making' is then inevitable (De Wert, 1999, 2002). In view of the severe nature of HD, the present lack of preventive and therapeutic interventions, and the complete penetrance of the mutation, offering PGD for HD as a condition for access to IVF is morally justified. A similar view has recently been accepted by ESHRE's Taskforce Ethics and Law (De Wert *et al.*, 2011). Critics of such 'coercive offers' appear not to take professional responsibility sufficiently serious (Meschede, 1995).

Similarly, when the result of the PGD analysis is inconclusive, an infertile couple might ask to transfer the embryo(s) at risk, especially in those cases where there are no 'healthy' embryos available and another IVF/PGD cycle would not be feasible for medical, psychological and/or financial reasons. In theory, a similar request may even arise when confronted with a carrier embryo.

It is sometimes argued that the choice, whether to have the embryo transferred or not, must lie with the potential mother (Dunstan, 1993). A transfer of either an embryo with an inconclusive PGD/HD result or (a fortiori) an embryo carrying HD would, however, be at odds with professional responsibility (Thornhill *et al.*, 2005). Obviously, the transfer policy of IVF/PGD clinics should be discussed with the couple in advance of IVF/PGD as part of the informed consent procedure. However, the criteria to be used for overruling the reproductive autonomy of the applicants need further ethical debate and fine-tuning.

PGD with exclusion testing. Preimplantation exclusion testing serves to avoid the transmission of the HD mutation while respecting the applicant's right not to know. The adverse implication is that the procedure is 'unnecessary' in 50% of the cases. Like prenatal exclusion testing, preimplantation exclusion testing raises ethical questions in terms of avoidable burdens for (especially) women, avoidable loss of embryos and avoidable costs. This critique is, however, not convincing/overriding (Asscher and Koops, 2010). First, the psychological burden of preimplantation exclusion testing is highly personal, it is up to the individual couple to weigh the burden of the various reproductive alternatives (van Rij *et al.*, 2013). Secondly, the independent moral status of preimplantation embryos is generally considered to be lower than the moral status of fetuses. The fact that preimplantation exclusion testing may exclude healthy embryos from transfer is therefore not an overriding moral objection, to think otherwise would undermine the (widely accepted) morality of regular IVF. Third, material costs are not decisive; these may be relevant for possible reimbursement, not for the moral acceptability of preimplantation exclusion testing *per se*. Some critics argue that the possible health risks of the biopsy for the health of future children thus conceived is a reason to allow PGD only as a last resort, and to discourage or even prohibit preimplantation exclusion testing. However this argument is weak, as there is no evidence so far that the biopsy has adverse health effects (Desmyttere *et al.*, 2012).

'Non-disclosure' PGD. According to Schulman *et al.* (1996), a promising alternative for couples who do not want to know their genetic status is non-disclosure PGD, reassuring them that they will not have an affected child, without ever being informed of the specific test results. They have high expectations of this strategy as they say: 'Perhaps it is not too early to consider the elimination of Huntington disease and other extremely deleterious dominant traits as a goal for the 21st century'.

What about the ethics of non-disclosure PGD (Braude *et al.*, 1998). First, this eugenic perspective of Schulman *et al.* (1996) seems to be at odds with the (dominant) ethics of clinical genetics which gives priority to the principle of respect for autonomy and informed reproductive decision-making (Evers-Kiebooms *et al.*, 1996). Secondly, the question arises, whether this approach can effectively protect the at-risk parent's preference not to know his/her own genetic status and, if so, at what medical, and psychological and financial costs? Let us suppose, for instance, that in the first PGD cycle a large number of only normal embryos is found: the statistical risk of the parent at risk may then become close to zero. To tell the client this good news would constitute an indirect-and-unintended breach of other at-risk clients' right not to know. After all, they may draw their own conclusions if they do not receive this good news. For this reason, we assume that one would withhold the good news. The problem, then, becomes, whether one should offer a second (and a third, fourth, etc.) IVF/PGD treatment when the genetic risk has become almost nil. Another problem arises, when there are no embryos available for transfer in a given cycle, either because all the embryos are carriers of HD, or for other reasons, such as IVF-failure. The client at risk might, rightly or wrongly, infer that he/she is a carrier. Should one, then, consider a 'sham transfer'? It is not a surprise, therefore, that the large majority of PGD clinics does not consider non-disclosure PGD to be a good alternative.

PGD for carriers of a reduced penetrance and intermediate allele. PGD for carriers of an RPA gene is morally justified, like PD for carriers of an RPA. When there is no other (non-carrier) embryo available, applicants may request the transfer an embryo with an RPA. Even though the 'harm-probability' ratio is not as threatening as in the case of an FPA, transferring an embryo with an RPA is problematic. PGD for carriers of an IA is, no doubt, ethically controversial. After all, the risk of direct expansion from an IA to an FPA seems to be (close to) zero, while the risk of expansion to an RPA is low. In view of this, it is of no surprise that requests for PGD by IA carriers are very rare. Such requests should be counselled, and the risks and burdens of IVF/PGD should be balanced against the presumed advantage of PGD. We consider a reluctant stance towards such requests to be justified. At the same time, like in the context of PD, taking account of the risk of an IA expanding to an RPA, the substantial risk of a future child carrying an RPA to develop HD at (late) the adult age, and the reproductive dilemma of future carriers of an RPA, PGD for carriers of an IA might be justified in individual cases.

Conclusions and recommendations

We conclude the following.

(i) Reproductive decisions for couples at high risk of transmitting HD are rather complex and feelings of ambivalence are omnipresent.

(ii) Reproductive counselling may be seriously impeded if postponed until an existing pregnancy.

(iii) There is no single 'best' reproductive option for couples at risk: weighing the respective pros and cons of the various options is highly personal.

(iv) For the proper moral evaluation of the psychological risk for future children conceived in an HD family, it is important to make a distinction between carriers of an FPA, an RPA and an IA, and also between asymptomatic carriers and symptomatic people, as both may influence the harm-probability ratio. Furthermore, one should take into account the relevant variables such as the coping skills of the partner.

(v) Conditional access to PD for late-onset disorders like HD is morally justified in order to protect the future child's right not to know.

(vi) Prenatal exclusion testing for HD and direct PD for prospective parents at 50% prior risk of HD may well be morally justified.

(vii) Starting from the view that medically assisted reproduction for people at risk of HD should not be categorically dismissed, PGD for proven carriers is justified. Preimplantation exclusion testing, although more controversial, may be justified as well. Non-disclosure PGD is, however, problematic.

(viii) The professional responsibility of medical doctors involved in assisted reproduction to take account of the welfare of the future child makes a (partial) shift in decision-making authority regarding the handling of serious transmissible disorders by means of PGD inevitable.

(ix) PGD for carriers of an RPA is morally justified.

(x) PGD may be, although controversial, justified in individual applicants who carry an IA. It is crucial that possible concerns and misunderstandings regarding a presumed (highly theoretical) direct expansion to an FPA in the fetus are clarified.

Therefore, we want to give the following recommendations.

(i) Genetic and reproductive education of families and caregivers should be improved in order to facilitate well-informed preconception decision-making and to avoid difficult decisions under time pressure and stress in a pregnancy; the availability of expert counselling is crucially important.

(ii) Having children at a younger age (to not postpone procreation) is important, as this would substantially reduce the psychological risks for future children.

(iii) Follow-up studies should be performed to gather more data about the impact of the various reproductive options, especially direct testing the fetus and preimplantation exclusion testing, for parents at 50% risk of being a carrier.

(iv) It is important to do empirical research on the psychosocial risk for children growing up with an affected or at-risk parent. This may help to more adequately answer the question as to whether specific high-risk and protective factors for the welfare of the child can be identified, and may contribute to the development of evidence-based, more differentiated, guidelines.

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