

Decision-making on preimplantation genetic diagnosis and prenatal diagnosis: a challenge for couples with hereditary breast and ovarian cancer

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STUDY QUESTION: How do couples with a *BRCA1/2* mutation decide on preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND) for hereditary breast and ovarian cancer syndrome (HBOC)?

SUMMARY ANSWER: *BRCA* couples primarily classify PGD and/or PND as reproductive options based on the perceived severity of HBOC and moral considerations, and consequently weigh the few important advantages of PGD against numerous smaller disadvantages.

WHAT IS KNOWN ALREADY: Awareness of PGD is generally low among persons at high risk for hereditary cancers. Most persons with HBOC are in favour of offering PGD for *BRCA1/2* mutations, although only a minority would consider this option for themselves. Studies exploring the motivations for using or refraining from PGD among well-informed *BRCA* carriers of reproductive age are lacking. We studied the reproductive decision-making process by interviewing a group of well-informed, reproductive aged couples carrying a *BRCA1/2* mutation, regarding their decisional motives and considerations.

STUDY DESIGN, SIZE, DURATION: This exploratory, qualitative study investigated the motives and considerations taken into account by couples with a *BRCA1/2* mutation and who have received extensive counselling on PGD and PND and have made a well-informed decision regarding this option. Eighteen couples took part in focus group and dyadic interviews between January and September 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Semi-structured focus groups were conducted containing two to four couples, assembled based on the reproductive method the couple had chosen: PGD ($n = 6$ couples) or conception without testing ($n = 8$ couples). Couples who had chosen PND for *BRCA* ($n = 4$) were interviewed dyadically. Two of the women, of whom one had chosen PND and the other had chosen no testing, had a history of breast cancer.

MAIN RESULTS AND THE ROLE OF CHANCE: None of the couples who opted for PGD or conception without testing found the use of PND, with possible pregnancy termination, acceptable. PND users chose this method because of decisive, mainly practical reasons (natural conception, high chance of favourable outcome). Motives and considerations regarding PGD largely overlapped between PGD users, PND users and non-users, all mentioning some significant advantages (e.g. protecting the child and family from the mutation) and many smaller disadvantages (e.g.

the necessity of *in vitro* fertilization (IVF), low chance of pregnancy by IVF/PGD). For female carriers, the safety of hormonal stimulation and the time required for PGD before undergoing preventive surgeries were important factors in the decision. Non-users expressed doubts about the moral justness of their decision afterwards and emphasized the impact the decision still had on their lives.

LIMITATIONS, REASON FOR CAUTION: The interviewed couples were at different stages in their chosen trajectory, up to 3 years after completion. This may have led to recall bias of original motives and considerations. Couples who did not actively seek information about PGD were excluded. Therefore the results may not be readily generalizable to all *BRCA* couples.

WIDER IMPLICATIONS OF THE FINDINGS: The perceived severity of HBOC and, for female carriers, the safety of hormonal stimulation and the time frames for PGD planning before preventive surgeries are essential items *BRCA* couples consider in reproductive decision-making. The emotional impact of this decision should not be underestimated; especially non-users may experience feelings of doubt or guilt up to several years afterwards. PGD counselling with tailored information addressing these items and decisional support in order to guarantee well-informed decision-making is needed.

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Introduction

Hereditary breast and ovarian cancer syndrome (HBOC) is an autosomal dominant predisposition caused by a mutation in breast cancer genes, *BRCA1* and *BRCA2*. Female mutation carriers face risks of 57% (*BRCA1*) and 49% (*BRCA2*) for breast cancer and 40% (*BRCA1*) and 18% (*BRCA2*) for ovarian cancer by the age of 70 (Chen and Parmigiani, 2007). In contrast, Dutch women without a *BRCA* mutation have a lifetime risk of 12.7 and 1.3% for breast and ovarian cancer, respectively (Kiemeneij et al., 2008). Among women worldwide, breast cancer is the most common malignancy and primary cause of cancer mortality. Around 5–10% of all breast cancer cases and over 30% of breast cancer diagnoses under the age of 30 are attributable to a *BRCA1/2* mutation (Szabo et al., 2000; Bray et al., 2004). Breast and ovarian cancer related to *BRCA* mutations is associated with a relatively early age of onset. Female carriers are given the option of periodic screening and/or prophylactic surgery of breasts and/or ovaries to decrease morbidity and mortality (Domchek et al., 2010).

Persons with a *BRCA* mutation have a 50% prospect of passing on the susceptibility for HBOC to their offspring. Preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND) are available reproductive options to prevent this. With PND, non-invasive fetal sex determination is performed at 9 weeks of pregnancy and, in case of a female, this is followed by chorionic villus sampling with the intention to terminate the pregnancy if the fetus is affected. With the relatively new technique of PGD, *in vitro* fertilized (IVF) embryos are genetically diagnosed before implantation and only unaffected embryos are transferred to the uterus. However, the use of the aforementioned techniques, especially PND, for HBOC raises ethical concerns given the reduced penetrance of HBOC, its onset at adult age and the availability of preventive and therapeutic options (Wagner and Ahner, 1998; Lodder et al., 2000). These characteristics may explain the generally low acceptability of PND for *BRCA* among persons affected with HBOC (Lodder et al., 2000; Menon et al., 2007). To date, studies exploring the motivations regarding PND uptake among well-informed *BRCA* carriers of reproductive age are lacking.

For PGD, a physically demanding *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment is necessary regardless of the

couple's fertility. Moreover, the chance of conception with IVF/ICSI is limited even among normally fertile couples given the pregnancy rate of 28.7% per aspiration in Europe (Ferraretti et al., 2012). This rate decreases even further when PGD is added due to the reduction of eligible embryos for transfer when excluding those with the genetic condition.

In the Netherlands, PGD was introduced in 1995 and, after nationwide political and ethical discussions, approved for late onset inherited cancer predisposition syndromes in 2008. Nowadays, HBOC is one of the most frequent indications for PGD in the Maastricht University Medical Centre+ (MUMC+), the only licensed PGD centre in the Netherlands. PND for HBOC is available on a case-by-case base in several University Medical Centres. In the Netherlands, PGD and PND treatments are covered by the health insurance system. The female exclusion criteria for a PGD treatment are specified as following: age >40, BMI >30 and FSH level >15 mIU/ml. Both PGD and PND are available for *BRCA* in many European countries as well as in the USA (Wagner and Ahner, 1998; Quinn et al., 2009; Sagi et al., 2009; Julian-Reynier et al., 2012; Ormondroyd et al., 2012).

In 2003, the European Society of Human Reproduction and Embryology (ESHRE) ethics taskforce argued that PGD was acceptable for adult onset and multifactorial diseases such as HBOC and other cancer predispositions, despite uncertainties about prospective improvements in preventive and therapeutic options (Shenfield et al., 2003).

Opinion surveys among persons affected by HBOC show that the majority, after being informed about PGD, is in favour of offering PGD for *BRCA1/2* mutations, although only a minority would consider this option for themselves (Menon et al., 2007; Staton et al., 2008; Quinn et al., 2009, 2010a,b, 2012; Hurley et al., 2012; Julian-Reynier et al., 2012; Ormondroyd et al., 2012; Dekeuwer and Bateman, 2013). However, the aforementioned studies were not designed to explore the process from hypothetical acceptability or PGD intention to actual PGD use, since they frequently lacked a focus on *BRCA* carriers of reproductive age and included persons with diverse levels of knowledge regarding PGD. The few studies available on attitudes and motives regarding PGD among couples who were well informed (i.e. who had had an informative PGD consultation) or who had experience with PGD have been carried out in the general PGD population (Lavery et al., 2002; Roberts

and Franklin, 2004; Kalfoglou *et al.*, 2005). Nevertheless, motives may be dependent on the genetic condition PGD is considered for. In-depth studies regarding the motives and considerations taken into account by couples carrying a BRCA mutation are needed, in order to gain insight into the aspects influencing reproductive decision-making in this population. This knowledge can be valuable for the optimization of patient decision support for a growing group of couples facing this quandary.

This study therefore aims to provide an integral qualitative account of the decision-making process among couples, carrying a BRCA1/2 mutation, who seriously considered PGD as a reproductive option. Motives and considerations for opting for or against PGD, as well as the reproductive alternatives (PND and conception without testing), were addressed. Furthermore, PGD users, PND users and non-users were asked to reflect on the reproductive option chosen.

Materials and Methods

Recruitment of couples

Couples carrying a BRCA1/2 mutation were eligible for participation if they had received standardized counselling on their reproductive options by an expert in reproductive genetics between 2008 and 2012 at the PGD centre of Maastricht UMC+, and had made a final decision whether or not to use PGD or PND. During counselling, verbal and written information was provided about the PGD procedure (including IVF/ICSI, embryo biopsy, chance of pregnancy, risk of misdiagnosis and health of children born after PGD). In addition, PND was discussed, consisting of non-invasive fetal sex determination, followed by chorionic villus sampling in case of a female fetus and termination of pregnancy (TOP) in case of an affected female fetus. Inclusion criteria for the study were at least 18 years of age and a full understanding of the Dutch language. Exclusion criteria were presence of one or more medical reasons to reject the couple from PGD, severe physical or psychological illness, presence of more than one indication for PGD, divorce and foreign place of residency.

Out of a total of 69 potential couples, 47 couples were selected and invited to participate by letter. Purposive sampling (Pope *et al.*, 2002) was conducted in order to include at least four couples from each reproductive choice (PGD, PND and natural pregnancy without testing) with variable demographic factors (i.e. sex of the carrier, BRCA1 and BRCA2 mutations, asymptomatic carriers and breast cancer survivors). Based on an expected participation rate of 25%, 47 out of 69 eligible couples were selected. After informed consent, couples were contacted by telephone to schedule the interviews. Reasons for non-participation were collected (Table I).

Procedure

A semi-structured topic guide was developed to direct both the focus group and the dyadic interviews, focussing on perception of the (dis)advantages of PGD and PND and the most decisive reasons for making the final reproductive decision. The topic guide was pretested in a personal interview, which was included in the analyses since no adjustments were made following. Focus groups were conducted containing two to four couples ($n =$ four to eight persons), assembled based on the reproductive method the couple had chosen and subsequently used after counselling (PGD or conception without testing) in order to avoid disconcerting discussions within groups. All participants who were assembled in a focus group were offered a dyadic interview if they preferred this but none made use of this alternative. Focus group interviews are an effective qualitative research method to explore and clarify individuals' experiences, perceptions and beliefs concerning a certain topic (Morgan and Krueger, 1998). Couples who had chosen PND for HBOC were scheduled in dyadic interviews (i.e. an interview

including both partners). This was done because of the delicate character of the subject and to avoid participants being confronted with couples who had experienced different pregnancy outcomes after PND. Focus groups were held at geographically convenient and neutral locations throughout the Netherlands, whereas dyadic interviews were held at the couples' homes. During the focus groups, the moderator, trained by an expert on (group) interviewing techniques, was accompanied by an assistant who took observational notes. Interviews were conducted between January and September 2012 and lasted between 80 and 100 min. Before initiation of the interviews, participants completed a questionnaire on demographic parameters, personal reproductive and oncologic history, and family history (Table II).

Table I Reasons for non-participation.

Reason	n (couples)
Not interested	7
No response to the invitation	5
Unwillingness to participate in an interview	5
Unwillingness to look back at the decision made to conceive without testing (with or without unsuccessful PGD attempt in the past)	5
Divorce	2
Lack of time	1

Table II Couples' characteristics.

	Reproductive choice (initial use)		
	PGD (n = 6)	PND (n = 4)	No testing (n = 8 ^a)
Partner at risk (M/F)	3/3	1/3	2/6
History of breast cancer ^b (M/F)	0/1	0/0	0/1
Gene mutation			
BRCA1 (M/F)	1/1	0/3	2/4
BRCA2 (M/F)	2/2	1/0	0/2
Mean age (years) at time of the interview (SD)			
Male	33.5 (3.3)	33.5 (4.5)	32.9 (5.6)
Female	31.8 (2.2)	32.3 (1.9)	31.6 (2.3)
Education			
Education middle (M/F)	2/0	1/1	3/1
Education high (M/F)	4/6	3/3	4/7
Religious (Christianity) (M/F)	1/3	0/0	1/2
Not religious (M/F)	5/3	4/4	6/6
Time interval (months) between counselling and interview (SD)	22 (18.6)	33 (18.4)	31 (9.8)

PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis; n number of couples.

^aFor one of these couples, only the female partner participated in the interview.

^bBoth women were treated for breast cancer before PGD counselling.

Data preparation and analysis

All interviews were audio-taped and transcribed verbatim. Data analysis was performed using the software program Nvivo 9.0. Grounded theory approach was used allowing codes, concepts and categories to emerge from the data (Glaser and Strauss, 2009). Open coding of the data was followed by axial coding, organizing the data into segments based on keywords and concepts to form categories and identify major themes. For reliability reasons, data were coded by two independent researchers with consultation of a third independent researcher in case of discordance. Since no new major themes emerged in the final interviews, saturation of themes was suggested.

Ethical approval

The procedures were approved by the local medical ethics committee of Maastricht UMC+.

Results

Couples' characteristics

Of the 47 invited couples, 22 were willing to participate. The overall response rate was 46.8%: 39.1% for PGD, 66.7% for PND and 50.0% for non-users. Four willing couples were not interviewed because saturation of themes had been achieved. Thus, 18 couples participated in the interviews (17 males and 18 females). One female partner of a male carrier participated alone since her partner found the topic too difficult to discuss. This personal interview acted as a pre-test, but did not substantially deviate from the dyadic interviews. Other reasons for non-participation are summarized in Table I.

Four focus groups were conducted, two among couples who decided to use PGD (three and two couples, respectively) and two among couples who decided not to use PGD nor PND (three and four couples, respectively). Furthermore, five dyadic and one personal interviews were conducted; four dyadic interviews were among couples who opted for PND for HBOC (of whom one couple had initially chosen PGD but converted to PND after an unexpected natural conception, and one couple who converted their choice to PGD after a TOP), one was with a PGD couple (dyadic interview because of logistic reasons) and there was the aforementioned pre-test (personal interview) with the female partner of a couple who chose no testing (Fig. 1). Counselling took place between 6 months and 4 years prior to the interviews and although all couples had made a reproductive decision, participants were in different stages of enactment of their reproductive decision at the time of the interview (Fig. 1). The couples' characteristics are summarized in Tables II and III.

General results

All participants but one indicated that they wanted a child biologically related to both partners. Reproductive decisions such as remaining childless, adoption or use of donor gametes were only considered briefly, if at all. Most couples saw PGD and conception without testing as the only reproductive options. A minority of couples considered PND as a third option; all these couples ultimately decided to use PND. Before PGD counselling, the majority of couples, including those refraining from PGD, indicated that they intended to opt for PGD.

There was a large overlap in motives and considerations to opt for or refrain from PGD mentioned by the participants who decided in favour of PGD and those who opted for PND or conception without testing. All three categories of couples mentioned a small number of important

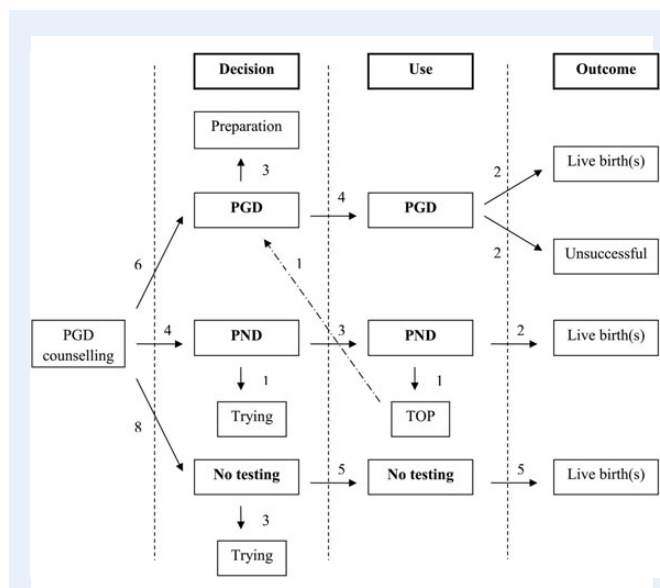


Figure 1 Couples' decisional process from PGD counselling until the interview. Dotted arrow, change of reproductive choice; n, couples; PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis; TOP, termination of pregnancy.

advantages and a larger number of less important disadvantages of PGD. Motives and considerations in the reproductive choices could be classified as physical, psychological, social, ethical/moral and practical (Table IV). In the results, we distinguish moral from ethical considerations, by defining moral considerations as individual internal principles regarding a person's ideals and right or wrong conduct, and by defining ethical considerations as social or external rules of conduct in respect to human actions (Barnett, 2001).

Motives and considerations to opt for PGD

The most frequently mentioned motive in considering PGD was, in all categories of couples, protecting the future child from the *BRCA* mutation. In this context, the majority of couples primarily indicated they wanted to protect their child from the physical and psychological impact of the *BRCA* mutation, i.e. the risk of cancer and the quandary of whether or not to opt for genetic testing, preventive surgeries and/or reproductive options. One father said: 'For me that was the most important thing. I don't want to burden my child with a little time-delayed bomb.' (C6, conception without testing). Often, female participants illustrated their comments with personal experiences: 'My mother died because of cancer, I am a mutation carrier myself. My breasts are removed... Therefore, I don't want my child to experience the same things that I did.' (C17, PND). Some women specifically pointed out that radical surgery should not be classified as a good preventive measure for breast and/or ovarian cancer and that they felt a strong need to protect a potential daughter from this choice between two evils: 'They say that nowadays there are good preventive measures. Well, if you classify this as a good preventive measure... when you, as a 27 or 28 year old woman, have to let them amputate your breasts... This I think, you cannot classify as a good measure, that's just nonsense.' (C12, PGD). The two female breast cancer survivors emphasized the physical and emotional severity of their disease, e.g. 'What I have been

Table III Couples' reproductive history at the time of interview.

Reproductive history	Couples (n = 18)	Couple codes	Time interval (months) counselling – interview
<i>Before reproductive counselling:</i>			
Infertility (IVF/ICSI indication)	3	3-7-14	3-38-38
≥ 1 child(ren) without testing	3	1-5-8	8-41-30
≥ 1 miscarriage(s)	1	1	8
<i>After reproductive counselling:</i>			
Preparation phase PGD:	3	1-2-3	8-6-3
Experience PGD:	4	11-12-16-17 ^a	27-42-44-26
1 PGD attempt, 0 live births	1	17	26
2 PGD attempts, 1 live birth	1	12	42
2 PGD attempts, 1 live birth, 1 ongoing pregnancy	1	16	44
3 PGD attempts, 0 live births	1	11	27
Preparation phase PND:			
Trying to conceive	1	13	20
Experience PND:			
1 PND attempt, 1 live birth of unaffected female	1	14	38
1 PND attempt, 1 TOP of affected female	1	17	26
2 PND attempts, 2 live births of males	1	15	39
Preparation phase no testing:			
Trying to get pregnant	3	4-7-10	16-38-18
Experience no testing:			
≥ 1 child(ren) without testing	5	5-6-8-9-18	41-36-30-28-41

PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis; TOP, termination of pregnancy.

^aCouple converted their choice from PND to PGD (after TOP).

through, that's just really horrible, yes horrible, you know. I mean my surgeries and all. . . and the moment you have to undergo the chemotherapy, well, that is something you wish no one ever has to go through.' (C8, conception without testing). A majority of couples expressed the desire to not only protect their own children, but to completely wipe out the BRCA mutation in the family line. For instance: 'I strongly feel that I want to stop it with me.' (C17, PND).

Half of the couples believed it was their moral duty to protect their future child(ren) from suffering, given the fact that they are aware of the risk and the reproductive options to avoid it: 'I couldn't feel at ease with consciously burdening my child with this.' (C13, PND). Avoidance of feelings of guilt towards future child(ren), accompanied by a fear of immense future regret when choosing the 'easier way', was frequently mentioned by couples of all three categories as a motive in favour of PGD or PND: 'What I was afraid of myself, or still am actually, are those feelings of guilt. They might not be so relevant now, but in about twenty or thirty years when my child would go for a DNA test. . . Imagine it will be positive, then I would have to relive this all over again. And then, I would tell myself: it's your own fault and you could have prevented this. . . ' (C6, conception without testing). Another woman expressed her concern that her son might go through the same reproductive dilemma as she did in case he turns out to be a BRCA carrier: 'Sometimes I look at my son and think: "Will you end up in the same sticky situation with your partner as we did, just because we may have chosen the easy way out?"' (C18, conception without testing).

Motives and considerations to refrain from PGD

Couples in all three categories mentioned many motives to refrain from PGD, which could be subdivided into general motives, BRCA-related motives and motives that are only of relevance to female carriers.

General motives concerned the physical and psychological burden of an IVF treatment, especially for fertile couples: 'To me it felt very serious, needing an IVF treatment while we are normally fertile.' (C14, PND). The necessity to convert conception into a medical process and losing the sense of romance and control as a couple were a major drawback. Male carriers expressed feelings of guilt towards their partner: 'I would especially regret that I am the source of the evil in this case and you (i.e. the female partner) would have to go through all this hormone misery. . . ' (C5, conception without testing). Couples who already had children before PGD for HBOC became available felt a moral drawback when considering PGD for a next child. Additionally, many couples feared the dilemma of what to do in case PGD would turn out to be unsuccessful. For some couples, especially those who had a desire for a large(r) family, this was a decisive reason to refrain from PGD: 'Preferably, we would like to have two children. But what are the chances that we eventually would get two children through PGD?' (C15, PND). Moreover, almost half of the couples said that ethical motives regarding selection in general had influenced their decision-making process, as well as the disposal of (male) affected embryos. As one participant expressed: 'We talked about it a lot, and then I slowly

Table IV Motives considered regarding PGD, PND and no testing for HBOC.

Preimplantation genetic diagnosis – Prenatal diagnosis – No testing		
	Motives to choose (n)	Motives to refrain (n)
Physical	Protecting the child from mutation (13) Protecting potential daughter from radical preventive surgeries (7) Additional medical check-ups woman (3)	Potential influence of ovarian stimulation on cancer risks (10) Potential effects on child's health due to biopsy in embryonic stage (9) Physical strain of IVF treatment (5)
Psychological	Avoidance of feelings of guilt towards child (15) <i>Avoidance of TOP (7)</i> Reassurance from beginning of pregnancy (6) Preventing mutation in both males and females (3) <i>Avoidance of stress and tension associated with PND (1)</i> Participation in a remarkable process (1) Reassuring feeling of simulating nature by selecting the highest quality embryo (1) Preservation of romance and control regarding pregnancy (14) <i>Faith in future medical developments regarding HBOC (10)</i>	Loss of romance and control regarding pregnancy (14) Psychological strain emerging from success-related uncertainties during trajectory (11) Dilemma in case of unsuccessfulness (8) Tired of medical procedures regarding BRCA (6) Inevitability of involving direct environment (6) Despite complex procedure, no guarantee for a healthy child (5) Emotional influence of hormone injections (4) Necessity of IVF when normally fertile (4) Fear of disappointment (3) Potential impact on relationship (3) Male carrier's feelings of guilt towards partner undergoing procedure (3) Daily reminder of the seriousness of the predisposition during treatment (1)
Social	Wiping out mutation in family line (12) Protecting child from reproductive dilemma (8) Pioneering for (younger) family members (1) <i>Confidence in capability to guide/support child with mutation through personal experiences (4)</i>	Fear of negative reactions from environment (5)
Moral/ethical	Moral duty to protect the child (9) <i>Nature of condition (i.e. late onset, incomplete penetrance, preventive possibilities) (9)</i>	Nature of condition (i.e. late onset, incomplete penetrance, preventive possibilities) (9) Disposal of affected (male) embryos (7) Interference in a natural process/playing for God (4) Treatment was or could not be considered for previous child(ren) (8)
Practical	PGD only minor addition in case of IVF or ICSI indication (4) Good accessibility and reimbursement of treatment (3) Relatively high chance of success (8)	Relatively low chance of successful pregnancy (14) Frequent hospital appointments (13) Relatively long duration of trajectory (8) Difficult integration in timely planning of preventive surgeries (5) Desire for (large) family less achievable (3) Necessity to collect blood from near family members (2)

n, number of couples that considered this motive (non-correlated to decisiveness); HBOC, hereditary breast and ovarian cancer; PGD, preimplantation genetic diagnosis; TOP, termination of pregnancy; PND, prenatal diagnosis.

began to realize that there would also be embryos which will be, well, discarded. And although they are affected, they are still embryos and therefore children, if you look at it that way. I've never been able to shake that off...' (C18, conception without testing). Additionally, practical issues like the relatively low chance of pregnancy, the frequent hospital appointments, the need to involve family members for the genetic preparation and the long duration of the PGD trajectory played a role.

Whereas half of the couples indicated that the (very) high perceived severity of HBOC was an important reason to opt for PGD or PND, the other half stated that they had taken the nature of the condition into consideration and decided not to interfere in the reproductive process. One female non-carrier said: 'We went thinking... what if? It's fifty-fifty... Maybe it's a boy, that would be positive. If it's a girl, she only has a 50% chance of being a carrier. Well, in case she inherits the mutation, there is a chance she won't fall ill at all. And if she does, there may be good therapeutic options. That was our consideration, and we keep reminding ourselves of that.' (C18, conception without

testing). While half of the couples felt moral drawbacks from selection in general, a substantial portion of the remaining couples had difficulties with accepting methods such as PGD and PND for HBOC because of the reduced penetrance and late onset character of the condition and the preventive and therapeutic options available. Not all female carriers experienced their genetic predisposition as a burden to the extent that they wanted to prevent transmission of their mutation by means of PGD or PND: 'It's not like it makes you unhappy or something like that.' (C6, conception without testing), and 'The amputation of my breasts you know, it all sounds very intense but I am not really that upset about it.' (C10, conception without testing). Other mentioned BRCA-related motives to refrain from PGD were the fact that using PGD would not guarantee a child free of breast and ovarian cancer due to the non-genetic background risk, confidence in being able to guide and support a child in case he/she inherits the mutation and faith in future medical developments. As one father said: 'It makes you start thinking... imagine you would have a girl, yet another thirty years along the road medical science will look completely different.

Who knows if they don't have a vaccine for breast cancer by then?' (C7, conception without testing).

For female carriers uncertainty regarding a potential influence of ovarian stimulation on the cancer risk was a very important aspect: 'That's actually your biggest concern, right? That you bring a child into this world and then you fall ill yourself, due to the hormones. . . ' (C2, female breast cancer survivor, PGD). In addition to this, most female carriers were very aware of the fact that their time window was limited due to the need for preventive surgeries: 'If afterwards you still need preventive breast surgery and subsequently your ovaries have to be removed. . . and you don't want to do all that on the same day. . . So then you start to calculate and eventually we became aware of the fact that maybe we should already be initiating the PGD trajectory while we were not even that occupied with the matter of having children yet.' (C12, PGD). Moreover, the necessity of medical interference once more, next to all procedures female carriers had gone through already, was mentioned as a disadvantage of PGD.

PGD versus PND

A minority of seven couples stated they would not opt for PND because of religious and/or ethical objections against TOP in general. Eleven couples, however, had made a personal reflection on the acceptability of TOP for HBOC. All six couples who opted for PGD clearly indicated perceiving a moral difference between embryo selection and TOP specifying that termination is a too drastic measure to avoid HBOC: 'It depends on the consideration of selection which I think is still okay. But when taking my own life as an example, terminating a pregnancy is simply not justified.' (C12, PGD).

The four couples who found PND for HBOC acceptable in fact chose this method. All four couples indicated that for them PGD was the most ideal option from a moral point of view as well. However, the relatively low chance of pregnancy by PGD, mostly in combination with the duration of the trajectory, directed their choice to PND. Furthermore, they appreciated the possibility of conceiving naturally without medical intervention: 'Getting pregnant this way is a natural process like it is for other couples. You know, I have had my breast surgery and one day I will have to remove my ovaries. . . Sometimes you just want to be normal'. (C17, PND, TOP affected girl). The PND couples all judged the 75% chance of a good outcome as fairly high. When explicitly discussing the possibility of conceiving an affected girl and the necessity of TOP, the couples said they felt prepared and had confidence in standing by their choice. One couple said: 'Termination of pregnancy in case of an affected girl would obviously be a massive burden for us. However, I would prefer that instead of having to tell my daughter she might be a carrier.' (C13, planning to use PND after conception). However, the only PND couple who experienced TOP because of HBOC converted to PGD for their second attempt to fulfil their child wish, indicating that in spite of having no regrets about this first endeavour, they could not emotionally cope with another TOP. They additionally specified that after this experience, the disadvantages of PGD had diminished in their perception.

Other advantages of PND compared with PGD mentioned by the PND couples were the absence of the need to inform others about their attempts to conceive, which for PGD is necessary given the genetic preparations involving family members, and the possibility to control their own planning. The couples who already experienced PND perceived the two consecutive diagnostic steps as beneficial, like

they had two chances to receive a good result: 'The possibility of the sex determination in blood was a kind of a trigger for us. . . That could prevent us from the necessity of chorionic villus sampling, at only eight or nine weeks of pregnancy. At that point we would already know what sex we would be dealing with.' (C15, PND, two sons). Another couple said: 'It just became really burdensome when we found out it was a girl. We did not expect that at all. (. .) That tough decision suddenly became much more imminent and I was really concerned by that. But well, we still had a 50% chance. . . ' (C14, PND, one unaffected girl).

All four PND couples took the fact that PND did not prevent HBOC in males into consideration in their decision-making. One couple initially had difficulties with the impossibility to avoid male carriers by PND: 'At first we struggled with the fact that in case of a boy no additional diagnostics would be carried out. We preferred a child without BRCA mutation, to put an end to this. . . But since termination of pregnancy is such a drastic measure we felt at ease to do it this way.' (C17, PND, TOP affected girl). Besides the risk of TOP, the weeks of uncertainty when waiting for the PND results were mentioned as a major disadvantage of PND. One male said: 'You only know after several weeks, it takes so long. . . For me that is the most prominent disadvantage.' (C13, PND, trying to conceive). The same couple regretted the fact that their chance of having a girl was no longer 50/50 but dropped to 1/3, since both boys and girls have a 50% risk of carrying the BRCA mutation but only a girl with the mutation will be medically aborted in the Netherlands.

Emotional impact of reproductive decision-making

None of the couples regretted the choice they made. However, several couples said that becoming parents had changed their perspectives on pregnancy and parenthood. One woman who underwent PND said: 'Only since I was pregnant myself I can really estimate the value of a pregnancy. Before that time I could not have imagined. I simply thought "if it's not okay we'll terminate and try again."' (C14, unaffected girl after PND). At the time of the interview, this couple had the intention to re-use PND for a second child. However, a few months later the couple was pregnant and informed the researcher that they had decided to continue this pregnancy of a second daughter, without invasive diagnostics of HBOC. They did not feel capable of terminating the pregnancy in case of an unfavourable result and were confident in being able to guide and support a daughter with HBOC.

The couples who chose for PGD did not regret that choice, but indicated that although they had prepared themselves for the physical burden and the practical impact of the treatment, they had been unable to anticipate on the psychological strains: 'The waiting during the actual treatment. . . during those two weeks of hormonal stimulation, if you are even able to manage that, until the moment of embryo transfer and the pregnancy test two weeks later. The tension. . . I never could have prepared myself for that.' (C12). In addition, in some cases, the IVF/PGD treatment had had more impact on their spousal relationship than previously imagined. A male said: 'There were many moments when you (i.e. the partner) were troubled and you couldn't really express yourself or I didn't really understand and then I could clearly feel the tension between us.' (C11). During the treatment, the dilemma of how to proceed in case PGD would not succeed eventually arose. Since many couples perceived PGD as the most ideal option, they feared that the

choice between remaining childless and choosing another option which might not (completely) protect the child from HBOC would cause an emotional load: 'It's a real drawback that once you have completed the trajectory it might not have been successful. What are you going to do then? Are you still going for the natural way? Well, that will obviously cause an emotional burden.' (C11). Couples agreed that using PGD to conceive a first child made it ethically difficult to make a different choice for a second child. However, when PGD was not successful for any child, the conversion to conception without testing seemed to be much easier to make: 'Our desire to become parents has only increased since our PGD experience. In case PGD remains unsuccessful, we will try to conceive the natural way. Ultimately, we have done whatever was possible. That was very important for us.' (C11).

The PND couples felt at ease with the decisions made. Two out of three couples experiencing PND said they had been unsure about the extent to which they should involve their social network in the procedure; they needed support, but feared disturbing advice and social judgements: 'At that point, you don't want to hear any arguments in favour of a different decision. You only want to hear that your decision is the only right one to make.' (C17). Some couples experienced difficulties in explaining their choice to their social surrounding: 'It is much easier to explain your choice for PGD to your social network than your choice to terminate the pregnancy in case of an unfavourable outcome. (...) It felt like we were among the very few who make a decision like this.' (C15).

Half of the couples who had chosen for conception without testing expressed their doubts about the moral justness of their decision, even when the decision was made a few years ago and the couple had completed their family in the meantime: 'And now you do hope that she doesn't have it. That is something you start to think about... We did make the right choice, didn't we?' (C9) and 'But still, if it turns out that my second daughter would have it, while I did have this choice for her... I think I would go to pieces at that moment. I would always keep thinking; what if I had... I wish I had, maybe...' (C8). Several couples emphasized that the reproductive decision-making process they went through still had a major impact on their lives: 'It is so hard not to know whether we have made the right choice, I really can't say... But I still dwell on that on a daily basis.' (C18). Many of these couples said they felt uncomfortable when confronted with the decision made. This is confirmed by the fact that unwillingness to look back at the decision made was one of the main reasons not to participate in the study among non-users.

Discussion

This study provides a qualitative assessment of the motives and considerations that well-informed couples carrying a *BRCA1/2* mutation take into account when deciding on PGD and PND. Perceived (dis)advantages and reasons to opt for or refrain from these reproductive methods were explored and satisfaction with the choice made was assessed during semi-structured (focus group) interviews.

The most important factor taken into account was the perceived severity of HBOC, which was generally based on personal and familial experience with cancer and sacrifices to be made for preventive measures. Half of the couples perceived that living with HBOC was serious enough to outweigh disadvantages of PGD and/or PND; the others did not. All couples who opted for PGD clearly indicated perceiving a moral difference between embryo selection and the termination of a

pregnancy, specifying that they considered PND as a too drastic measure to avoid HBOC. In contrast, all couples who found PND for HBOC acceptable actually chose this option, despite the fact that all these couples had a preference for PGD from a moral point of view. Some significant practical and psychological aspects directed their final choice towards PND, showing that the possibility of avoiding the risk of TOP by choosing PGD could not outweigh the negative aspects. This corresponds with findings from previous studies (Snowdon and Green, 1997; Chamayou et al., 1998). Several previous studies indicated that experience with TOP for a genetic disorder influences the acceptance of PGD, in particular for women (Chamayou et al., 1998; van Rij et al., 2011). This was also the case for the interviewed couple that experienced TOP after PND and subsequently opted for PGD, indicating that they did not want to terminate another pregnancy.

The same motives and considerations played a role for couples opting for PGD and couples refraining from PGD. The PGD couples mentioned numerous negative aspects of PGD, but indicated that the main advantage, 'preventing transmission of the *BRCA* gene mutation, both for their own child as well as future generations', outweighed the accumulated disadvantages. In the previous literature this advantage is usually separated from the benefit of protecting the child from possible physical and mental suffering (Roberts and Franklin, 2004; Hershberger and Pierce, 2010; Ormondroyd et al., 2012; Werner-Lin et al., 2012; Dekeuwer and Bateman, 2013). The majority of motives to refrain from PGD, such as limited success rates, duration of the trajectory, procedural and human risks and safety, correspond to those reflected in previous studies (Hershberger and Pierce, 2010; Ormondroyd et al., 2012). Moreover, in the specific context of HBOC, we found in concurrence with Dekeuwer and Bateman (2013) that female *BRCA* carriers worry about the unknown influence of hormonal stimulation needed for IVF on their breast cancer risk. Several studies suggest an association, although inconsistent, between IVF medication and an increased breast cancer risk in both the general female population (Klip et al., 2000; Venn et al., 2003; Salhab et al., 2005) and in women with HBOC (Braga et al., 1996; Gauthier et al., 2004; Cullinane et al., 2005; Kotsopoulos et al., 2008).

Women carrying a *BRCA* mutation have to cope with many decisions and life events in a short period of time (i.e. DNA testing, coping with an unfavourable test result, decision-making on possible medical interventions as well as reproductive decision-making). Since female *BRCA* carriers are generally advised to undergo a preventive oophorectomy from their mid-thirties, the timeframe in which they can have offspring is tight. As a result, female carriers may feel forced to cope with complex reproductive issues at a (much) younger age than they might have wanted to (Quinn et al., 2010a,b; Dekeuwer and Bateman, 2013; Donnelly et al., 2013).

Several couples who eventually decided in favour of conception without testing for *BRCA* expressed feelings of doubt or even guilt afterwards, and feared the moment if it turns out that their child(ren) have inherited the *BRCA* mutation. These feelings are not uncommon among parents with a genetic susceptibility (Hallowell et al., 2006; James et al., 2006). The mere possibility of PGD and PND can cause an emotional burden once people become aware and choose to refrain from it, known as the technological imperative. This aspect should not be neglected in reproductive counselling. Couples choosing for a natural pregnancy without testing might be as much in need for emotional support during and even after this trajectory, as PGD or PND users may be. This group must not be forgotten.

Study strengths and limitations

This is the first study on motives and considerations regarding PGD and PND use in well-informed BRCA1/2 couples of reproductive age. A substantial diversity of responses was attained by including PGD users, PND users and non-users, male and female asymptomatic carriers, as well as female breast cancer survivors, and their partners. Interviews were assembled according to the reproductive option chosen, in order to guarantee a safe environment in which one could express and discuss feelings and opinions openly and without judgement. We believe it therefore gives a rich and in-depth overview of reproductive motives.

All couples had made a reproductive decision, but the fact that the couples were at different stages in their chosen reproductive trajectory may have led to a coloured perception of experiences and outcomes, as well as recall-bias of motives and considerations. Our design excluded couples who did not actively seek information about PGD, or a priori decided to refrain from having their own, genetically related, children.

Conclusions and recommendations

Reproductive decision-making regarding PGD and PND has proven to be a very complex and stressful process for couples with HBOC. We found that the process was mainly guided by the couples' perceived seriousness of the predisposition as well as their moral views regarding selection. The safety of IVF and the compatibility of the PGD planning process with preventive surgeries were essential factors for female carriers. For some couples, the emotional impact of the decision was substantial and long-lasting. Non-users could be confronted with feelings of doubt or guilt up to years after the decision has been made.

Reproductive counselling requires highly skilled professionals who are able to guide couples in a challenging process of reconciliation with a wide variety of moral considerations and emotions regarding their reproductive wishes. Knowledge of the condition-specific reproductive motives may motivate the adaptation of current best practice guidelines by means of further tailoring of counselling practices, e.g. by providing additional decision support in the form of a patient decision aid (Thornhill *et al.*, 2005). Such a decision aid should be offered complementary to counselling.

In addition, the emotional burden which is experienced by non-users after they have made their decision to refrain requires more attention. Emotional support, during the decision-making process as well as afterwards, should be actively offered to all couples, including those refraining from PGD and PND. Further research regarding the long-term consequences of the reproductive decision on emotional well-being is required.

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Authors' roles

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Conflict of interest

All authors declare they have no conflict of interest.

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