

A reproductive dilemma?

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Valorization

Introduction

Breast cancer is the most frequently diagnosed type of cancer in women in the Netherlands and the number of diagnoses continues to rise to an estimated 20.000 in 2020. One in seven women will develop breast cancer during lifetime.¹ Aside from the individual burden, the societal and economic burden are high.²

Five to ten percent of breast cancer cases are caused by a hereditary predisposition.^{3,4} Various gene mutations can increase the risk of breast cancer, of which a mutation in the *BRCA1* or *BRCA2* gene is most common. A mutation in one of these two genes increases the risk of developing several types of cancer, most significantly breast and ovarian cancer in female carriers. A *BRCA1/2* mutation increases the risk of breast cancer from 14% to 72% in women⁵ and from less than 1% to 6.9% in men.⁶⁻⁸ The risk of developing ovarian cancer is increased from less than 1% to 44% for women with a *BRCA1/2* mutation.^{5,9} With regards to risk management, women with hereditary breast and ovarian cancer (HBOC) can opt for preventive surgeries (i.e. removal of breast and tuba or ovaries before a certain age) or intensive screening. Preventive measures are however rigorous and have a substantial impact on physical, emotional and psychological wellbeing, while intensive screening is associated with high levels of stress and cannot prevent cancer.

Since HBOC is an autosomal dominant predisposition, both male and female carriers have a 50% risk of passing the *BRCA1/2* mutation on to their children. Until 2008, prenatal diagnosis (PND) was the only reproductive option in the Netherlands to prevent transmission of a *BRCA1/2* mutation to a genetically related child. PND is a technique used to detect the *BRCA* mutation in the foetus at around 11 weeks of pregnancy with the intention to terminate the pregnancy in case the foetus is a female *BRCA* carrier. Terminating a pregnancy because of a late onset condition with incomplete penetrance such as HBOC is often regarded as emotionally demanding and morally (too) drastic. The low uptake of PND for HBOC suggested a need for an alternative method to prevent hereditary transmission of the *BRCA1/2* mutation. In 2008, preimplantation genetic diagnosis (PGD) became available for couples with HBOC in the Netherlands. This enabled selection of embryo's without the *BRCA* mutation before pregnancy through IVF, thereby establishing a pregnancy of a child without the *BRCA* mutation. PGD has been practiced in the Netherlands since 1995 for serious genetic conditions with an early age of onset. In its early years, PGD was not made available for late onset conditions such as HBOC because a slippery slope was feared. After an intense political and public debate, PGD for late onset hereditary cancer syndromes was approved trusting the responsibility of patients and professionals.

Relevance of scientific results for clinical practice and society

Although HBOC is nowadays the most frequently requested indication for PGD, a majority of couples with HBOC still opt for a natural pregnancy. The availability of PGD has in a way complicated reproductive decision-making for these couples. On the one hand, a less invasive method than PND to prevent transmission of the *BRCA* mutation is now being offered. On the other hand PGD can be a burdensome treatment with many physical, psychological, moral, social and practical aspects to consider. A female *BRCA* carrier additionally has to consider the integration of a lengthy PGD treatment into the timeline of possible preventive surgeries and may worry about the effect of the IVF hormones on her cancer risk. A common moral concern is that HBOC differs from most PGD indications in terms of its gender specific cancer risk. Currently all embryos with a *BRCA* mutation are discarded even though male embryo's with a mutation only have a slightly increased cancer risk.

At the Maastricht UMC+ PGD outpatient clinic it was noticed that many couples with hereditary breast and ovarian cancer struggle with making a reproductive choice and it is not uncommon that they alter their decision even while they are already in the process of fulfilling their child wish. Our qualitative assessment of the perceived (dis)advantages of PGD for HBOC shows that couples with HBOC who consider PGD are at risk for decisional conflict, possibly resulting in feelings of guilt and regret which may have a long-lasting impact on their lives (**chapter 4**).

Understanding the reproductive decision-making process and the support needs and wishes of these couples is imperative to provide proper support and prevent decisional conflict and its potential subsequent psychological burden. Besides their relevance for couples with HBOC and health care providers, the results of this dissertation show relevance at a political and economic level. The findings provide insight into the motives and considerations of couples who consider PGD for a late onset condition with an incomplete penetrance for which a slippery slope was feared by policy makers. Results show that couples extensively consider their reproductive options and thoroughly take into account the perceived seriousness of the condition. This indicates that the public shows responsibility in utilizing this reproductive option and that the legalization of PGD for late onset cancer syndromes was justified. Hence, the fear of a slippery slope which was the most profound argument against legalizing PGD for HBOC appears to be unfounded.

Economically, these studies can stimulate awareness of preventive measures regarding cancer among both end-users and professionals, possibly increasing their uptake and therefore decreasing the costs involved in the care and cure of one of the most expensive diseases in our society; cancer. The cost effectiveness of PGD has been investigated in the USA for Cystic Fibrosis (CF) and in Australia using retinoblastoma as an example.^{10,11} Both studies concluded that PGD was cost-effective. The USA study demonstrated that the cost savings to the health care system of providing free IVF/PGD to all CF carrier couples compared to the lifetime costs of medical treatment for patients

affected by this disease, run to dozens of billions of dollars.^{10,13} The results also provide tools to prevent and decrease the societal costs of long lasting adverse psychological effects that can be caused by undeliberate or uninformed reproductive decision-making. In addition, they provide a starting point for (inter)national guidelines for referral, counselling and decision support regarding PGD for HBOC. Possibly this may serve as a blueprint for other PGD indications. With these insights, counsellors can focus on subgroups that are more vulnerable for decisional conflict (couples who are young, religious, who experienced a severe medical intervention due to HBOC and those who are inclined to refrain from PGD) and we can start building a framework to introduce personalized decision support in reproductive counselling in order to enable the genetic counsellor to efficiently use her time and resources.

A direct effect of the findings generated by our qualitative assessment of the perceived (dis)advantages of PGD (**chapter 4**) and couples' support needs in reproductive decision-making (**chapter 6**) pertains to the development of the digital decision aid concerning reproductive decision-making for couples with hereditary cancer, developed by Reumkens et al., 2018.¹³ This decision aid has proven to reduce decisional conflict, increase levels of knowledge and improve realistic expectations. Moreover, it improved levels of deliberation and decision self-efficacy for individuals with low baseline levels. Outcomes of this dissertation have been and will be published in scientific medical journals and presented at national and international congresses and expert meetings. Where appropriate, outcomes will also be presented at patient organization meetings. Conclusions will be incorporated in an updated and extended version of the current digital decision aid regarding reproductive decision-making.

Remaining questions and future plans

Based on these results, counselling at our local PGD outpatient clinic has been improved. However a need for (inter)national standard of care guidelines remains. Current results are an important step but not sufficient to facilitate the development of such a guideline and additional research is needed. More specifically, investigation of appropriate decision support in reproductive decision-making that incorporates various PGD indications and international contextual differences such as the reimbursement of PGD, is required. Our results can serve as a starting point for more in depth and larger studies. When focussing on a specific genetic predisposition such as HBOC, achieving large sample sizes is challenging as the population of interest is limited. Therefore, we aim to expand our research to the entire PGD population while appreciating the conditions' variety in characteristics. Ultimately, we strive to develop a standard of care guideline for PGD referral, counselling and decision support in general.

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