Mortality in inherited cardiac diseases: directing care in affected families

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Chapter 7

Prenatal diagnosis and preimplantation genetic diagnosis for inherited cardiac diseases: a 15 year overview


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Submitted
ABSTRACT

Background
Inherited cardiac diseases, like cardiomyopathies and channelopathies, are associated with an increased risk of sudden cardiac death (SCD). A common hallmark is the variable disease expression and incomplete penetrance. Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD) provide carriers of a mutation that causes an inherited cardiac disease the possibility of having a child without the familial gene mutation and reduce the disease burden and risk of SCD in their offspring.

Methods and Results
We retrospectively evaluated the number of prenatal diagnoses and referrals for PGD for inherited cardiac diseases in the Netherlands in the last 15 years. PND was performed 8 times for 3 different inherited cardiac diseases: hypertrophic cardiomyopathy (HCM) (n=3), dilated cardiomyopathy (DCM) (n=4), and long QT syndrome (LQTS) (n=1). Twenty nine couples came for PGD intake; HCM (n=10), DCM (n=8), noncompaction cardiomyopathy (n=1), arrhythmogenic (right ventricular) cardiomyopathy (n=3), Brugada syndrome (n=2), idiopathic VF (n=3) and LQTS (n=2). After intensive counseling and advisory of the National Board for PGD Indications, two couples (DCM, idiopathic VF) continued the PGD procedure. All other couples decided to fulfill their child wish by other means.

Conclusion
Although inherited cardiac diseases can exhibit a severe phenotype or a severe family history of SCD, the number of patients opting for or continuing with PND and PGD is small.
INTRODUCTION

Inherited cardiac diseases, i.e. cardiomyopathies and cardiac channelopathies, are associated with an increased risk of arrhythmias and sudden cardiac death (SCD).1 Cardio-myo-pathies include hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), dilated cardiomyopathy (DCM), noncompaction cardiomyopathy (NCCM) and arrhythmogenic (right ventricular) cardiomyopathy (A(RV)C). Cardiomyopathies can present in all age groups; from infancy to (late) adulthood. Many patients follow a benign course, but a significant number may experience life-threatening ventricular arrhythmias or progressive symptoms, caused by a decline of mainly left ventricular function. Indeed, some patients die suddenly at young age from arrhythmias, while others die from complications of progressive heart failure or thromboembolism.2 Genetic cardiomyopathies cannot be cured, but therapeutic options are available for treatment of the symptoms such as lifestyle advice, antiarrhythmic drugs, heart failure medication and ultimately heart transplant and devices to cover the risk for life-threatening arrhythmias. Most cardiomyopathies have an autosomal dominant mode of inheritance with incomplete penetrance and variable expression.3-5

The main subtypes of the channelopathies - also referred to as primary electrical disorders or inherited arrhythmia syndromes - are long QT syndrome type 1, 2, and 3 (LQTS1-3), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and in the Netherlands idiopathic ventricular fibrillation caused by a specific risk haplotype on chromosome 7q36 harbouring the DPP6 gene.6 All channelopathies are characterized by increased morbidity and an increased risk of SCD, especially when untreated. Events can occur already at a young age. Preventive treatment options - such as lifestyle advice, betablockers, and ICDs - are available for most channelopathies and have proven to reduce the risk of SCD.7 In all described channelopathies, the mode of inheritance is autosomal dominant with incomplete penetrance and variable expression.

The discovery of genes known to be associated with cardiomyopathies and channelopathies, has made genetic testing possible in many patients with one of these diseases.1 When a disease causing mutation is identified, predictive genetic testing of (asymptomatic) relatives can be performed to identify other individuals at risk, which then allows for timely treatment.8 For several inherited cardiomyopathies, the effect of treatment in a presymptomatic disease stage is still debated.1,9

Not only after birth, but also before birth predictive genetic testing (prenatal diagnosis; PND) is available. PND for inherited cardiac diseases can be performed by a chorionic villus- or amniotic fluid sampling in hospitals throughout the country. The sample is then analyzed in one of the five DNA diagnostic laboratories for inherited cardiac
diseases in the Netherlands. Preimplantation genetic diagnosis (PGD) is a reproductive option for mutation carriers of inherited diseases wishing to avoid transmission of the predisposition to their offspring. Embryos obtained by in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI) are tested for the presence of the mutation. Only mutation-negative embryos are transferred into the uterus. PGD has been successfully applied since 1990 for an expanding list of monogenic disorders and chromosomal abnormalities. In 2003, the Ethics Taskforce of the European Society of Human Reproduction and Embryology stated that it is acceptable to perform PGD for late onset and multifactorial diseases. The appliance of both prenatal diagnosis as well as PGD for mutation carriers of inherited cardiac diseases is controversial, considering the reduced penetrance of the condition and the availability of prophylactic and therapeutic options. In the Netherlands, the Maastricht University Medical Center is the only licensed PGD center since 1995. The costs for PGD and PND are reimbursed by the health care system. All indications for PGD are judged by the local PGD workgroup and all new indications have to be judged by the National Board for PGD Indications. In this study, we present an overview of PND and PGD performed for inherited cardiac diseases in the Netherlands in the last 15 years.

METHODS

From all five University Medical Centers in the Netherlands with a DNA diagnostic laboratory for inherited cardiac diseases, data were collected by performing a search in the databases of the these laboratories on PNDs performed for inherited cardiac diseases (disease) from 1998 until 2013. Furthermore, information about the gene involved, the mutation, and outcome of the pregnancy were obtained from the patients’ chart at the departments of clinical genetics. Additionally and for internal control of our data, all PNDs performed for inherited cardiac diseases were extracted from the yearly reports of the working party prenatal diagnosis and fetal therapy in the Netherlands (available from 1998-2010). In this report, we also extracted the total annual number of prenatal diagnoses that were performed with DNA diagnostics. We collected data on the number of couples consulting for PGD for inherited cardiac diseases, the gene, and mutation involved, and the decision of the National Board for PGD Indications for the disease. Furthermore, we collected the number of patients proceeding with PGD, the number of cycles, embryos, pregnancies, and births from the Maastricht University Medical Center from 1995 until 2013. To protect confidentiality of the patients, specific information on the mutations and
detailed information about the family histories were omitted. From the annual reports of the Dutch society of Clinical Genetics (available from 1998-2011), we extracted data of the yearly total number of genetic consultations for heart diseases (www.vkgn.org).

For comparison purposes, we collected data of the number of PNDs and PGDs performed for Marfan syndrome and hereditary breast and ovarian cancer in the annual reports of the working party prenatal diagnosis and fetal therapy in the Netherlands and in the PGD database of the Maastricht University Medical Center.

RESULTS

Prenatal diagnosis (PND)

In the Netherlands, yearly between 241 and 287 (from 2001 to 2010) PNDs were performed with DNA diagnostics. Yearly, between 618 and 4688 (from 2001 to 2011) genetic consultations for heart diseases at the departments of clinical genetics were registered (Table 1). During the past 15 years, PND has been performed 8 times for different channelopathies and cardiomyopathies (Table 1); 3 couples for HCM, 2 couples for DCM and 1 for LQTS. This is approximately 0.3-0.7% of the total number of PNDs performed yearly and a fraction of the total number of patients counseled with an heart disease at the departments of clinical genetics (0.02-0.2%).

Three couples performed prenatal diagnosis for HCM (Table 1), caused by pathogenic mutations in the $MYH7$, $TNNT2$, and $MYBPC3$-gene. In one family, the patient was diagnosed with HCM at a very young age. Family members underwent an heart transplantation around age 40 years. In another family, the HCM patient who choose for PND carried an ICD, because of severe arrhythmias. There was a severe family history of SCD; four persons died suddenly under the age 40. In another family, both parents were carrier of a pathogenic HCM causing mutation, resulting in a severe phenotype in a previously born child. This child, that was carrier of two pathogenic mutations, died weeks after birth, due to HCM. PND was performed once for LQTS type 1 (pathogenic $KCNQ1$ gene mutation). In this family, a child died at the age of 5 years during exercise. PND was performed for DCM, caused by pathogenic mutations in the $TNNT2$- and $LMNA$ gene. One patient had a low ejection fraction and was previously resuscitated from ventricular fibrillation after which he received an ICD. In the other DCM patient, there was a severe family history of sudden cardiac death at a young age (under the age of 50 years).

carriership of the familial pathogenic mutation four times, and these pregnancies were terminated. The other four times the fetus was not a carrier, and these pregnancies were continued.

**Preimplantation genetic diagnosis (PGD)**

Before a PGD procedure is started all couples undergo a PGD intake counselling, discussing the motivation and dilemma's, possibilities, and limitations of PGD. A total of 2969 couples were referred for PGD in the Netherlands between 1995-2013. Of these couples, 29 couples (~1%) with an inherited cardiac disease, caused by pathogenic mutations in disease-causing genes, have visited the PGD clinic for intake during this period (Table 2). In 22 referred couples (76%) the indication was a cardiomyopathy. Couples came for PGD intake for HCM (n=10), DCM (n=8), NCCM (n=1) and ARVC (n=3). Seven couples were referred for a channelopathy (24%), i.e. BrS (n=2), idiopathic VF (based on a risk haplotype on chromosome 7) (n=3), and LQTS (n=2) (Figure 1).

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**Table 1. Couples performing prenatal diagnosis for inherited cardiac diseases.**

<table>
<thead>
<tr>
<th>Couple</th>
<th>Disease</th>
<th>Gene</th>
<th>Material</th>
<th>Total number of PNDs performed with DNA in the year the patient performed PND</th>
<th>Total number of genetic consultations for heart diseases at the departments of Clinical Genetics in the Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCM</td>
<td>MYH7</td>
<td>Chorionic villi</td>
<td>241</td>
<td>618</td>
</tr>
<tr>
<td>2</td>
<td>HCM</td>
<td>TNNT2</td>
<td>Chorionic villi</td>
<td>287</td>
<td>1266</td>
</tr>
<tr>
<td>3</td>
<td>HCM</td>
<td>MYBPC3</td>
<td>Amniotic fluid</td>
<td>287</td>
<td>1266</td>
</tr>
<tr>
<td>4</td>
<td>LQTS</td>
<td>KCNQ1</td>
<td>Chorionic villi</td>
<td>255</td>
<td>2068</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>TNNT2</td>
<td>Chorionic villi</td>
<td>270</td>
<td>4049</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>LMNA</td>
<td>Chorionic villi</td>
<td>Data not available</td>
<td>Data not available</td>
</tr>
</tbody>
</table>

Abbreviations: HCM= Hypertrophic cardiomyopathy, LQTS= Long QT syndrome, DCM=Dilated cardiomyopathy, PND=Prenatal diagnosis
Nomenclature according to hgvs using the following reference sequences: MYH7: NM_000257.2; TNNT2: NM_000364.3; MYBPC3: NM_000256.3; KCNQ1: NM_000218.2; LMNA: NM_170707.3
† Annual Report 2001-2010 Vereniging Klinische Genetica Nederland
### Table 2. Couples referred for preimplantation genetic diagnosis for inherited cardiac diseases.

<table>
<thead>
<tr>
<th>Couple</th>
<th>Disease</th>
<th>Gene</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCM</td>
<td>MYH7</td>
<td>2001</td>
</tr>
<tr>
<td>2</td>
<td>HCM</td>
<td>MYH7</td>
<td>2001</td>
</tr>
<tr>
<td>3</td>
<td>HCM</td>
<td>TNN2</td>
<td>2005</td>
</tr>
<tr>
<td>4</td>
<td>HCM</td>
<td>MYBPC3</td>
<td>2009</td>
</tr>
<tr>
<td>5</td>
<td>HCM</td>
<td>MYBPC3</td>
<td>2010</td>
</tr>
<tr>
<td>6</td>
<td>HCM</td>
<td>MYBPC3</td>
<td>2010</td>
</tr>
<tr>
<td>7</td>
<td>HCM</td>
<td>MYBPC3</td>
<td>2010</td>
</tr>
<tr>
<td>8</td>
<td>HCM</td>
<td>TPM1</td>
<td>2011</td>
</tr>
<tr>
<td>9</td>
<td>HCM</td>
<td>MYH7</td>
<td>2011</td>
</tr>
<tr>
<td>10</td>
<td>HCM</td>
<td>MYBPC3</td>
<td>2011</td>
</tr>
<tr>
<td>11</td>
<td>DCM</td>
<td>TNN2</td>
<td>2009</td>
</tr>
<tr>
<td>12</td>
<td>DCM</td>
<td>LMNA</td>
<td>2011</td>
</tr>
<tr>
<td>13</td>
<td>DCM</td>
<td>LMNA</td>
<td>2011</td>
</tr>
<tr>
<td>14</td>
<td>DCM</td>
<td>LMNA</td>
<td>2012</td>
</tr>
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<td>15</td>
<td>DCM</td>
<td>MYL2</td>
<td>2013</td>
</tr>
<tr>
<td>16</td>
<td>DCM</td>
<td>DES</td>
<td>2013</td>
</tr>
<tr>
<td>17</td>
<td>DCM</td>
<td>LMNA</td>
<td>2013</td>
</tr>
<tr>
<td>18</td>
<td>DCM</td>
<td>MYH7</td>
<td>2013</td>
</tr>
<tr>
<td>19</td>
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<td>MYH7</td>
<td>2013</td>
</tr>
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<td>20</td>
<td>ARVC</td>
<td>PKP2</td>
<td>2007</td>
</tr>
<tr>
<td>21</td>
<td>ARVC</td>
<td>PKP2</td>
<td>2011</td>
</tr>
<tr>
<td>22</td>
<td>ARVC</td>
<td>PKP2, DSG2</td>
<td>2013</td>
</tr>
<tr>
<td>23</td>
<td>BrS</td>
<td>SCN5A</td>
<td>2012</td>
</tr>
<tr>
<td>24</td>
<td>BrS</td>
<td>SCN5A</td>
<td>2012</td>
</tr>
<tr>
<td>25</td>
<td>Idiopathic VF</td>
<td>DPP6</td>
<td>2011</td>
</tr>
<tr>
<td>26</td>
<td>Idiopathic VF</td>
<td>DPP6</td>
<td>2012</td>
</tr>
<tr>
<td>27</td>
<td>Idiopathic VF</td>
<td>DPP6</td>
<td>2011</td>
</tr>
<tr>
<td>28</td>
<td>LQTS</td>
<td>KCNH2</td>
<td>2011</td>
</tr>
<tr>
<td>29</td>
<td>LQTS</td>
<td>KCNH2</td>
<td>2013</td>
</tr>
</tbody>
</table>

Abbreviations: HCM= Hypertrophic cardiomyopathy, DCM=Dilated cardiomyopathy, NCCM= Non-compaction cardiomyopathy, ARVC= Arrhythmogenic right ventricular cardiomyopathy, BrS= Brugada syndrome, LQTS= Long QT syndrome

Nomenclature according to hgvs using the following reference sequences: MYH7: NM_000257.2; MYBPC3: NM_000256.3; TNN2: NM_000366.5; LMNA: NM_170707.3; MYL2: NM_000432.3; DES: NM_001927.3; PKP2: NM_004572.3; DSG2: NM_001943.3; KCNH2: NM_000238.3
After intensive counselling two couples (DCM and idiopathic VF) continued the PGD procedure. All other couples decided to fulfill their child wish by other means, e.g. natural conception without testing, use of donor gametes or adoption. During the PGD procedure, the idiopathic VF couple withdrew after the customized single cell PGD test had been designed, because of emotional and ethical considerations. The DCM couple is currently at the start of the procedure. Until now, no embryo selection, embryo transfers, or pregnancies have been established with PGD for any inherited cardiac disease in the Netherlands.

The vast majority of the couples who seek counseling at the PGD clinic have a severe phenotype or have experienced a family history of sudden cardiac death; teenagers dying of sudden cardiac death, or the need for an heart transplant or an ICD in young adults are not an exception. During the past years, an increase of PGD consultations is observed (Figure 2).

Since 2009 the National Board for PGD Indications has given their advisory opinion on a number of inherited cardiac diseases. The National Board for PGD Indications considers that PGD for inherited cardiac diseases is only eligible when compelling arguments emerge after careful and extensive counselling of (future) parents. For instance, in families with many cases of SCD at a young age with an increased risk of a severe phenotype.

DISCUSSION

Over the past 15 years, PND has been performed 8 times for 3 different inherited cardiac diseases (HCM, DCM, and LQTS) in the Netherlands. Four of these pregnancies were terminated because of fetal carriership of the mutation(s). Since 1995, 29 patients were referred for PGD for HCM (n=10), DCM (n=8), NCCM (n=1), ARVC (n=3), BrS (n=2), idiopathic VF (n=3), and LQTS (n=2). PGD is currently in preparation for a couple with DCM caused by a LMNA gene mutation. No pregnancies have been established so far.

In the literature, reports of PND and PGD for inherited cardiac diseases are scarce. PND has been described for HCM in a patient with a malignant form of HCM in the family caused by a pathogenic MYH7 gene mutation. In another report from the same group, 22 HCM patients were counselled for prenatal diagnosis yet none of these couples eventually performed PND.

Data on the outcome of assisted reproductive techniques are collected by the European Society for Human Reproduction and Embryology (ESHRE). Between 2007 and 2010, in total 20 PGD cycles have been performed for different inherited cardiac diseases (1 DCM, 9 HCM, 1 ARVC, 1 congenital cardiomyopathy, 2 LQTS, 4 BrS, and 2...
Figure 1. Percentage of couples with an inherited cardiac disease referred for PGD from 1995-2013.

Figure 2. Number of couples with an inherited cardiac disease referred for PGD over the years.
In the literature, PGD data have been described for DCM caused by a \textit{LMNA} mutation, and for HCM caused by \textit{MYBPC3} and \textit{TNNI3} gene mutations. All patients had a severe phenotype or a family history with premature sudden death. Like in our study, the majority of DCM patients carry a \textit{LMNA} mutation and all patients exhibit a severe phenotype themselves or have a family history of premature SCD.

The limited data from the literature already suggest that PND and PGD are not often considered in patients with an inherited cardiac disease. Our data are in line with these reports; a fraction of the total number of prenatal diagnoses performed yearly (0.3-0.7\%) and a fraction of the total number of patients counseled with a heart disease (0.02-0.2\%) at the departments of clinical genetics concerns an inherited cardiac disease. Although we know that in some patients and families the phenotype of inherited cardiac diseases can be severe, most patients do not opt for the option of PND. PND involves the abortion of a fetus and therefore emotional, religious, ethical or moral considerations play an important role for many couples. Due to the incomplete penetrance and variable expression it is not sure if their future mutation carrying child will be at increased risk of sudden cardiac death. The possibilities to predict the expression of the mutation in an unborn child are very limited with the current (molecular genetic) techniques and knowledge. Furthermore, the availability of treatment options for some inherited cardiac diseases to reduce the risk of cardiac death, may also contribute to the low request for PND.

Incomplete disease penetrance and variable expression are also a hallmark of hereditary breast and ovarian cancer (HBOC) and Marfan syndrome. In the Netherlands, three PNDs for HBOC were performed until 2010, supporting our presumption that prenatal diagnosis is not commonly requested for diseases with an incomplete penetrance and variable expression. However, for Marfan syndrome, a connective tissue disorder associated with premature SCD due to aortic dilatation/dissection and with a variable expression, prenatal diagnosis was performed 38 times until 2010, suggesting a high (perceived) severity of the disease.

In the past years, requests for PGD for hereditary breast and ovarian cancer have increased, indicating that PGD is considered a more acceptable choice than PND, accounting now for nearly one fifth (17.3\%) of the total number of PGD consultations (yearly reports of PGD Netherlands: www.pgdnederland.nl). Despite the disadvantages of the physically demanding IVF/ICSI procedure, the frequent hospital appointments, the relatively low chance of pregnancy, and the long duration of the PGD trajectory, nearly one fourth of the referred couples started the PGD procedure. At this moment, Marfan syndrome account for 4.6\% of the total number of PGD consultations. As
shown in our study, for inherited cardiac diseases, the number of requests for PGD is much smaller (nearly 1%), although an increase over the years can be observed (Figure 2). Since the disease prevalences of Marfan syndrome (1:5000)\textsuperscript{20} and hereditary breast and ovarian cancer (BRCA1/2 mutation carriers 1:400)\textsuperscript{21} quite resemble the disease prevalences of inherited cardiac diseases (HCM 1:500, LQTS 1:2000, DCM 1:250-1:2500)\textsuperscript{22-24} a lower prevalence seems not a plausible explanation of the differences in consultations for PGD. Despite reports of a decreased quality of life and impaired health status in patients with an inherited cardiac disease,\textsuperscript{25,26} possibly the perceived burden of the disease is less than in the other diseases. Moreover, other disease specific factors like available treatment options or risk reducing options might play a role.

The role of the National Board for PGD Indications can also impede the decision of the couples to continue with the PGD procedure. The relatively large number of patients with an inherited cardiac disease that do not continue with the PGD procedure after the first intake can be in concordance with this.

Finally, the information on PND and PGD to patients can be insufficient. Indeed, for inherited cardiac diseases, until 2013 there were no organized patients associations to inform patients about the possibility of PGD in the Netherlands, contrary to hereditary breast and ovarian cancer and Marfan syndrome. Most patients visit a department of clinical genetics and are under surveillance of the cardiologist. Because pregnancy termination and PGD for diseases with a reduced penetrance and some therapeutic options (like inherited cardiac diseases) is controversial, PND and PGD are not routinely discussed. Furthermore, lack of attention for the reproductive possibilities during the reproductive age of patients and a lack of knowledge about PGD could also contribute to the low numbers of referral for PGD. Attention for and knowledge about the possibilities for PND and PGD for caretakers is important for this category of patients, especially when they have a severe phenotype or a severe phenotype in their family, so patients are capable of making a well informed decision.

In conclusion, although inherited cardiac diseases can exhibit a severe phenotype, the number of patients requesting for and continuing with PND and PGD is small. The incomplete penetrance, variable expression, perceived burden of the disease, available preventive options, lack of knowledge or information about reproductive options might play a role, but remains to be further elucidated in future research.
Chapter 7

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Disclosures
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REFERENCES


