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Chapter 9

Adults with congenital heart disease: patients’ knowledge and concerns about inheritance

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Abstract

With recent advances in medical and surgical management, most patients with congenital heart disease (CHD) survive to reproductive age. Current guidelines recommend counseling about inheritance and transmission of CHD to offspring. We evaluated whether adult CHD patients recalled having received information about the inheritance of their CHD, patients' knowledge about inheritance and their concerns in this regard. A questionnaire was sent to 486 non-syndromic CHD patients aged 20 to 45 years. We received 332 useful questionnaires (response rate 68%). One-third (33%) of patients recalled receiving information about inheritance of CHD from their cardiologist, and 13% had consulted a clinical geneticist. Eight percent of patients who were considering having children estimated the recurrence risk for their own offspring to be 1% or lower, whereas one fourth (25%) estimated it to be higher than 10%. According to our classification, 44% estimated the recurrence risk in a correct range of magnitude. Additional information about inheritance of CHD was desired by 41% of patients. Forty-two percent of patients considering having children reported concerns about transmitting CHD to offspring. We conclude that a substantial proportion of adult CHD patients lacks knowledge and desires more information about inheritance, indicating a need for better patient education. Current guidelines and/or their implementation do not seem to meet the needs of these patients. A dedicated program of counseling for adults with CHD has to be developed to optimize knowledge and satisfaction with information provision and to reduce or manage concerns regarding inheritance of CHD.
Introduction

Congenital heart disease (CHD) affects approximately 6 to 8 per 1,000 live-births.\(^1\) With medical and surgical advances, most children survive to adulthood, significantly increasing the number of adult patients with CHD.\(^2,3\) Reproduction and inheritance, including transmission of CHD to offspring, are important issues in this population. Current guidelines for care for adults with CHD recommend counseling about these topics.\(^4-7\)

The recurrence risk for CHD in offspring largely depends on the etiology of the CHD in the parent. CHD mostly occurs as an isolated anomaly, but may also be part of a large number of specific syndromes or chromosomal abnormalities, or as a consequence of teratogenic exposure.\(^8,9\) Many syndromes with CHD are monogenic, including Noonan syndrome, Alagille syndrome and Holt-Oram syndrome, or caused by a chromosomal abnormality or contiguous gene microdeletion, such as 22q11 deletion syndrome. The recurrence risk for offspring in an individual with syndromic CHD depends on the specific syndrome and can be up to 50%. Although single gene defects and copy number variations have also been described in non-syndromic CHD,\(^10,11\) the majority of non-syndromic CHD is historically believed to be multifactorial in origin, with multiple genetic and environmental factors interacting to produce CHD.\(^6,12\) Offspring of patients with non-syndromic CHD have an increased risk of CHD, for which empirical estimations are available. Overall, the recurrence risk for children of males with non-syndromic CHD is estimated to be around 2-3%, whereas the risk for children of females with non-syndromic CHD is estimated to be about 5-6.5%.\(^9,13,14\) In the presence of a positive family history of CHD the recurrence risk may be higher and occasionally, non-syndromic CHD can be inherited as a simple Mendelian trait.\(^14\)

Little is known about CHD patients’ knowledge about inheritance, the concerns they have about transmission of CHD to offspring and the consequences thereof for reproductive choices and use of prenatal screening. Only a few studies have briefly addressed inheritance issues, generally concluding that patients lack significant knowledge about inheritance of their CHD.\(^15-18\)

To evaluate the current guidelines and optimize care for adult CHD patients regarding inheritance issues, we feel that an assessment of knowledge, concerns and desire for information of adult patients with CHD is needed. The aims of our study were to assess 1) whether adult patients with non-syndromic CHD recall receiving information about the inheritance of their CHD, 2) the patients’ level of knowledge and concerns regarding transmission of CHD to offspring, 3) their desire for more information, and 4) if level of knowledge, concerns and desire for more information can be predicted from clinical and demographic factors.

Methods

Patients and study design

In this cross-sectional survey study we randomly derived 486 patients from one university hospital from the CONCOR registry, the Dutch national registry for adult patients with CHD, described in detail previously.\(^19\) The inclusion criterion was age between 20 and 45 years on September 1, 2009,
assuming reproduction issues to be most relevant for individuals this age. Exclusion criteria were 1) any kind of known syndrome or developmental disability, and 2) residence outside The Netherlands. After receipt of the questionnaire, patients stating to have an additional cardiac disorder with a specific genetic cause (e.g. hypertrophic cardiomyopathy) were excluded. Cardiac diagnoses of remaining patients were divided into 13 categories of main diagnoses and into three groups of complexity level.2

All patients were sent a questionnaire. After four weeks, we sent a reminder to non-responders to encourage participation. After another four weeks, we phoned the non-responders to establish receipt of the questionnaire and once again request participation.

The Medical Ethics Committee (MEC) of the Academic Medical Center stated that formal approval for this study was not required, as the study does not fall within the range of the Dutch Medical Research Involving Human Subjects Act.

**Questionnaire**

We designed a questionnaire covering seven domains including 1) basic demographic (age, gender, level of education, etc) and clinical characteristics (comorbidities, family history of CHD etc), 2) information about inheritance patients recalled receiving from health care providers, 3) knowledge about recurrence risks of CHD for own offspring, 4) general knowledge about inheritance of CHD, 5) concerns regarding transmission of CHD to offspring, 6) satisfaction with knowledge and counseling needs, and 7) pregnancy-related actions including prenatal screening.

Information received from health care providers was assessed using multiple choice questions and statements (response options: very much, some, none, do not remember) (see Table 2). Patients’ notions about the recurrence risk of CHD for their own children were evaluated by having patients estimate the risk on a scale from 0% to 100%. As a rough screening tool for evaluation of the estimations we broadly classified the estimations into four groups including 1) correct range of magnitude, 2) too low, 3) slightly too high, 4) far too high. To classify each individual we used empirical literature data; in females: an estimation of 4-8% was considered a correct range of magnitude; 0-3% too low; 9-13% slightly too high; >13% far too high. In males: 1-5% correct range of magnitude; 0% too low; 6-10% slightly too high; >10% far too high. We accounted for the reported family history of CHD and roughly estimated the recurrence risk, adjusting the accuracy of the answer accordingly. The type of CHD was not taken into account. General knowledge about the inheritance of CHD was evaluated using 10 questions. There were four multiple choice questions regarding the magnitude of the risk of CHD for offspring in different situations (e.g. risk of CHD for offspring of a healthy couple, risk of CHD in offspring of a male with CHD), and six statements related to factors potentially influencing the magnitude of the recurrence risk (e.g. gender of parent with CHD, family history of CHD, number of surgical procedures in the parent with CHD). We assigned one point for each correct answer and zero points if the answer was false or no answer was given, resulting in an individual knowledge score ranging from 0 to 10 points.

Concerns about transmission of CHD to offspring were assessed with six statements (response
options: totally agree, somewhat agree, do not agree/do not disagree, somewhat do not agree, totally do not agree). Counseling needs were evaluated with yes/no questions. Pregnancy-related actions were evaluated by yes/no questions and multiple choice questions. The face validity of the questionnaire was evaluated by three genetic counselors and one clinical psychologist. We did a pilot involving 10 patients visiting the cardiology outpatient clinic and adapted the questionnaire according to their remarks.
Data analysis
For statistical analyses, SPSS (version 17.0) for Windows was used. Statistical significance was set at P < 0.05. Descriptive data are presented as mean with standard deviation as they were normally distributed. For comparison of discrete variables between two groups (e.g. those informed and those not informed by health care providers) we used the Chi-square or Fisher’s exact test and for comparing continuous variables we used the unpaired Student’s T-tests (data were normally distributed). To identify clinical and demographic predictors for estimation of recurrence risk in the correct range of magnitude, having concerns about transmission of CHD and desire for more information we used multivariate logistic regression (dichotomous outcome variables), while for identification of predictors for a higher knowledge score we used multivariate linear regression (continuous outcome variable). Predictor variables were gender, age, having children, considering having children, education level, complexity of CHD, comorbidities, family history of CHD, reporting to have received information from the cardiologist, reporting to have consulted a clinical geneticist and general knowledge score. We included variables in the multivariate regression analyses if univariate analysis showed P-value < 0.1.

Results
Sample
Three hundred thirty-six (69%) of 486 patients returned the questionnaire. We excluded four patients after receipt of the questionnaires because two patients had not completed most of the items, and two patients reported additional genetic cardiac disorders (1 patient with hypertrophic cardiomyopathy and 1 patient with arrhythmogenic right ventricular cardiomyopathy). We analyzed total of 332 (68%) useful questionnaires. There were no statistically significant differences in gender, age and complexity of CHD between responders and non-responders. Characteristics of the included patients (mean age 31.9 ± 7.3 years, 52% male) are shown in Table 1. Of the 119 patients with children (total of 233 children), five patients reported having a child with CHD (2% of all children). Comorbidities were reported by 23% of patients. Ten (3%) patients reported additional malformations that suggested an underlying syndrome.

Information provision
One-third (33%) of the patients reported receiving information about inheritance from their cardiologist or specialized nurse, while 14% did not remember if they received any information. Statements about the received information and patients’ answers are shown in Table 2. Patients who reported receiving information were significantly older (P = 0.001), more often had children (P = 0.011) and less often considered having (additional) children (P = 0.007). The information was stated to be provided before a first pregnancy by 80%, during the first pregnancy by 12% and after having the first child by 8% of patients. Two thirds (67%) of patients reported having asked for information, while in 33% the information was said to be provided on the cardiologist’ or nurse’s initiative.
A minority (13%) of patients reported having consulted a clinical geneticist. Table 2 shows statements and patients’ answers about the information received from the geneticist. Patients who stated having consulted a geneticist were older (P = 0.049), more often reported a positive family history of CHD (P = 0.023) or additional congenital malformations suggestive of an underlying syndrome (P = 0.028), a low level of education (P = 0.002) and more often had children (P = 0.009). Over half (54%) of the patients said that the cardiologist had taken the initiative for the referral, while 46% of patients reported having requested referral themselves. Most patients (72%) stated having consulted the geneticist before the first pregnancy, 14% during the first pregnancy and 14% after having the first child.

Three percent of patients reported receiving information about inheritance of CHD from someone other than the cardiologist or geneticist, such as a general practitioner, and 22% said they searched for information using the internet or through patient organizations.

Knowledge

Knowledge about recurrence risk for offspring.

Among the patients who were considering having (additional) children (n = 211), 67% estimated the recurrence risk to be 2-10%. One fourth (25%) estimated the recurrence risk higher than 10%, of which 8% higher than 50%. The remaining 8% of patients thought that the recurrence risk would be 0%.
According to our classification, which included reported family history, 44% estimated the recurrence risk of CHD for offspring in the correct range of magnitude, 15% too low, 18% a little too high and 23% far too high. Multivariate regression analysis showed that male gender (P = 0.002) and higher general knowledge score (P = 0.013) were independent predictors for estimating the recurrence risk in the correct range of magnitude (Table 3).

**General knowledge.**
The risk of having a child with CHD for a healthy couple was answered correctly by 53%, for a man with CHD by 30%, for a woman with CHD by 35% and for a healthy couple with a previous child with CHD by 24%. The majority of patients knew that the recurrence risk is higher if more than one relative has CHD (69%), and that the number of surgical interventions in the parent does not influence the recurrence risk (70%). About half of the patients answered correctly that the cause of the CHD in the parent might influence the recurrence risk, and that the severity of a particular type of CHD in the parent does not (46% and 44% respectively). Twelve percent knew that the recurrence risk for children of women with CHD is generally higher than the recurrence risk for children of men with CHD and 40% knew that diseases in the mother other than CHD may contribute to CHD. The mean knowledge score was 4.2 (±1.9; range 0-9). A high education level was the only independent predictor for a higher knowledge score, explaining 14% of the variance (P < 0.001, Table 4).

**Concerns**
Of the patients who were considering having children, 42% had concerns about future children having CHD. Eighty percent found it important that their future children would be screened for CHD during pregnancy and 93% after delivery. One out of five patients (21%) assumed feelings of guilt if their child would have CHD. Of the five patients who did have a child with CHD, two felt guilty to some extent, three did not. Of all women, 21% had concerns about having a miscarriage due to their CHD. Multivariate regression analysis showed that having children (P = 0.031) and having estimated the recurrence risk too high according to our classification (P = 0.041) were independent predictors for concerns about transmitting the CHD to future offspring (Table 5).

**Satisfaction with knowledge and counseling needs**
Personal knowledge about inheritance aspects of their CHD was considered insufficient by 68% of patients, and 41% desired more information. In the multivariate analysis, considering having children (P = 0.001) was an independent predictor for desire for information, while patients who reported receiving information from their cardiologist or a clinical geneticist less often desired more information (P = 0.03 and P = 0.04, respectively) (Table 6). Of patients who said not to have consulted a clinical geneticist, 38% would like to do so.
Table 3. Multivariate logistic regression results for variables determining estimation of recurrence risk in correct range of magnitude (n = 211)*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>2.63</td>
<td>1.43 - 4.76</td>
<td>0.002</td>
</tr>
<tr>
<td>Severe complexity of CHD</td>
<td>0.60</td>
<td>0.34 - 1.09</td>
<td>0.095</td>
</tr>
<tr>
<td>Knowledge score</td>
<td>1.20</td>
<td>1.04 - 1.39</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* Only patients considering having (additional) children are included.

Table 4. Multivariate linear regression results for variables determining knowledge score (n = 332)

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having children</td>
<td>0.38</td>
<td>-0.02 - 0.77</td>
<td>0.060</td>
</tr>
<tr>
<td>High education level</td>
<td>1.29</td>
<td>0.91 - 1.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Reportedly having received information from cardiologist</td>
<td>0.30</td>
<td>-0.11 - 0.70</td>
<td>0.147</td>
</tr>
</tbody>
</table>

Table 5. Multivariate logistic regression results for variables determining having concerns about transmitting CHD to offspring (n = 211)*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having children</td>
<td>2.55</td>
<td>1.09 - 5.96</td>
<td>0.031</td>
</tr>
<tr>
<td>Reportedly having consulted clinical geneticist</td>
<td>1.92</td>
<td>0.74 - 4.96</td>
<td>0.177</td>
</tr>
<tr>
<td>Too high estimation of recurrence risk</td>
<td>1.90</td>
<td>1.03 - 3.54</td>
<td>0.041</td>
</tr>
</tbody>
</table>

* Only patients considering having (additional) children are included.

Table 6. Multivariate logistic regression results for variables determining desire for more information about inheritance of CHD (n = 332)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.96 - 1.05</td>
<td>0.926</td>
</tr>
<tr>
<td>Having children</td>
<td>0.84</td>
<td>0.44 - 1.58</td>
<td>0.577</td>
</tr>
<tr>
<td>Considering having children</td>
<td>3.32</td>
<td>1.61 - 6.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Reportedly having received information from cardiologist</td>
<td>0.56</td>
<td>0.33 - 0.96</td>
<td>0.034</td>
</tr>
<tr>
<td>Reportedly having consulted clinical geneticist</td>
<td>0.52</td>
<td>0.19 - 0.95</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Pregnancy-related actions

Past events

Of the patients who had children (n = 119), 78% had used folic acid related to their pregnancy (in case of male patients; their female partner). Ten percent of patients did not know folic acid is advantageous. During pregnancy, 80% of patients underwent prenatal screening: nuchal translucency measurement in 28%, combination test (nuchal translucency measurement in combination with maternal serum markers) in 20%, ‘regular’ ultrasound screening in 33% and advanced ultrasound screening in 79% of patients.

Anticipated actions in the event of increased risk of CHD.

Of patients considering having children, 74% would consider advanced ultrasound screening during pregnancy in case of a 5% risk of a child having CHD, and slightly more patients (76%) in case of a 50% risk. Fifteen percent would consider giving up having children if the risk of CHD would be strongly increased (50%), as opposed to 4% in case of a slightly (5%) increased risk.

Discussion

In this study addressing inheritance issues in adult patients with CHD, we found the majority of patients having no recollection of being informed about inheritance. The patients’ general knowledge about inheritance of CHD is limited, and more importantly, many seem to have imperfect knowledge about the recurrence risk for their offspring. Almost half of patients desire more information about inheritance of CHD.

Current guidelines for care for adult CHD patients recommend counseling about genetics and recurrence risks of CHD in offspring, some more explicitly and extensively than others. In our study, only one third of patients stated to have received information about inheritance of their CHD from their cardiologist or nurse practitioner, a minority finding the information very clear and sufficient. Although some patients may not recall having received information, this nevertheless suggests that most patients either did not receive any information or information provision was insufficient to be remembered. Patients who reported not receiving information were younger and childless, suggesting that cardiologists may not have considered inheritance issues as relevant for these patients yet. A clinical geneticist had been consulted by only 13% of all patients. Although patients with a family history of CHD or additional congenital malformations suggestive of an underlying syndrome were more likely to have consulted a geneticist, most of these had not seen a geneticist. This is recommended as an underlying syndrome may have clinical consequences for the patient and may significantly increase recurrence risks (e.g., in certain syndromes, as high as 50%), and offspring may not only being at risk for CHD but also for the non-cardiac features of the syndrome. Additionally, a family history of CHD may imply a specific underlying genetic cause and/or a higher recurrence risk.

The patients’ lack of knowledge about inheritance in our study is consistent with other studies,
showing gaps in knowledge about inheritance as well as other topics regarding CHD, including complications, endocarditis prophylaxis, pregnancy risks and contraception. While the topics we addressed to evaluate the overall knowledge about inheritance of CHD were general and not necessarily relevant for all patients, adequate knowledge of recurrence risk is relevant to patients. In our study, eight percent of patients estimated the recurrence risk to be 0%, which is similar to or lower than the frequency in the general population, while one fourth estimated the risk higher than 10%. According to our broad classification, only 44% of patients estimated the recurrence risk in the correct range of magnitude, the risk often estimated too high. We want to stress though that an individual’s recurrence risk can only be estimated accurately after an in-depth work up has been performed, including review of medical history, physical examination, extensive family history, cardiac evaluation of family members and possibly genetic analyses. As we did not perform such work-up, the recurrence risks and classification as used by us represent only a rough estimate. We also did not take into account type of CHD, though some types of CHD have been reported to have higher recurrence rates than others (e.g. left sided obstructive heart defects were reported to have relatively high heritability). We chose this strategy as we did not want to stress current knowledge about specific recurrence risks of different CHD types, but this may also have led to a non-optimal classification of recurrence risk by us.

Several factors may contribute to lack of knowledge, including physicians not providing the information, providing inaccurate information, providing information in an inadequate manner and patients not retaining the information. In our study, patients who stated to be informed did not estimate the recurrence risk more often in the correct range of magnitude nor had a higher knowledge score than patients who stated not to be informed, suggesting that patients indeed do not receive or recall the provided information correctly. Lack of continuity of care and coordinated services as well as conflicting information from different health care providers may also contribute to non-optimal knowledge. Men more often estimated the recurrence risk in the correct range of magnitude than women, which might be explained by notable gender based differences in care provision. Generally, women are more likely to receive care from multiple health care disciplines (e.g., cardiology, gynecology) and may be more likely to receive specific information about reproductive issues (e.g., on the adverse effects of pregnancy for themselves, risks of medication use and cardiologic follow-up during pregnancy). These differences might lead to difficulties in recalling the received information, the possibility of receiving conflicting information from different health care providers, or confusion about how the different kinds of information fit together.

Inadequate knowledge about recurrence risk in offspring may falsely reassure or scare patients, and may hamper patients from making informed choices regarding family planning and prenatal screening. As in many patients the actual recurrence risk may be lower than estimated by themselves, counseling about the recurrence risk may therefore prevent or allay concerns in some patients. Concerns were reported by 42% of patients who considered having children, which is comparable to other studies. A gender difference was not present, in contrast to the study of Reid et al, who found women to be more concerned about transmission of CHD.
Most patients were not satisfied with their own knowledge level and almost half of all patients indicated a desire for more information about inheritance, mainly patients who were considering having children. Patients who reported having received information were more satisfied with their level of knowledge and less often desired additional information, suggesting that information provision meets patients' needs. The gaps in patients' knowledge however imply that the current guidelines for the care of adults with CHD and/or the way they are implemented do not meet the goal of having patients knowledgeable about inheritance of CHD. As we learn more about the needs of this population, including the complex and often difficult to disentangle concerns about CHD recurrence and potential burdens of guilt, the value of a coordinated and focused care team becomes increasingly clear. Therefore, a dedicated counseling program for adults with CHD has to be developed to optimize knowledge and satisfaction with information provision and to manage concerns regarding transmission of CHD. This program should include inheritance issues to be discussed at an early age, at least onward from the first meeting with the adult cardiologist after transition from pediatric to adult care, and to be repeatedly addressed. Counseling about inheritance issues by specialized nurses in adult CHD clinics could also be incorporated in the program. Preferably, additional written material should be provided. Moreover, health care providers should take the lead in information provision and not wait for patients to ask questions. Unfortunately, previous studies have shown that many health care providers, including cardiologists, do not have sufficient knowledge about genetics, and this should be optimized for adequate information provision. Close collaboration with clinical geneticists should also be part of the program, as they play a significant role in the clinical and genetic assessment of patients, aiming at an accurate etiologic diagnosis and providing accurate counseling regarding recurrence risk and prenatal diagnosis and screening options. Use of folic acid from 4 weeks before until 8 weeks after conception might reduce the risk of CHD in offspring, which should be explained to patients. The optimal timing and manner to provide the necessary information about inheritance of CHD has to be evaluated in further studies.

Limitations
Although the response rate is satisfactory and no differences in gender, age and complexity of CHD emerged between responders and non-responders, we cannot exclude the possibility that patients who were most motivated or concerned about transmission of CHD did return the questionnaire. Recall bias may have been introduced as some items of the questionnaire referred to events in the distant past. As we did not check medical charts, no data regarding the exact nature of the provided information about inheritance was available. As stated before, recurrence risks were roughly classified as 'correct range of magnitude', 'too low' or 'too high' based on empirical literature data and the provided information by patients, however the actual recurrence risks may be different due to several facts we could not deduce from the questionnaire. Finally, making generalizations about our data may be difficult because they were collected at one tertiary care centre.
Conclusions

The substantial proportion of adult CHD patients lacking knowledge and desiring more information about inheritance of CHD indicates a need for better patient education on these topics. Current guidelines and/or their implementation do not seem to meet the needs of these patients. A dedicated program of counseling for adults with CHD has to be developed to optimize knowledge and satisfaction with information provision and to reduce or manage concerns regarding inheritance of CHD. The optimal timing and manner to provide this education has to be evaluated in future studies.

Acknowledgements
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