



# CHAPTER

# REPRODUCTIVE DECISION-MAKING: A QUALITATIVE STUDY AMONG COUPLES AT INCREASED RISK OF HAVING A CHILD WITH RETINOBLASTOMA



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## ABSTRACT

Little is known about the reproductive decision-making process of couples with an increased risk of having a child with retinoblastoma (Rb). A qualitative study was conducted to explore the impact of prospective risk on reproductive decisions, factors influencing these decisions, and the needs of couples with regard to reproductive counselling.

Fourteen couples of childbearing age who received genetic counselling between 2002 and 2006 participated in semi-structured interviews in 2008. The risk of having a child with Rb ranged from less than 1% to 50%. In most cases, the diagnosis of Rb influenced subsequent family planning. Prenatal diagnosis was used by two couples, while others refrained from having more children.

Reproductive decisions were influenced by the burden of the disease for the patient and family members, the impact of ophthalmological screening under anaesthesia, and couples' perceived risk, which did not always relate to their actual risk. Reproductive choices with regard to the number of children wanted changed over time.

Our findings indicate topics to be discussed during genetic counselling of couples at increased risk for a child with Rb. We suggest continued access to genetic counselling also after the initial diagnosis and treatment.

## INTRODUCTION

Retinoblastoma (Rb) is the most common primary intraocular malignancy in children and originates from developing cells of the retina. The estimated incidence is between 1 in 15,000 and 20,000 live births.<sup>1</sup> The initiating event in Rb is inactivation of both alleles of the retinoblastoma(*RB1*)-gene.<sup>2</sup> About 60% of patients have Rb in only one eye (unilateral Rb), the other 40% have both eyes affected (bilateral Rb). All bilateral and familial cases of Rb and around 15% of non-familial unilateral cases are heterozygous for a germline *RB1* mutation, followed by a second somatic mutation in the tumour. Hereditary Rb is an autosomal dominant disorder, with a penetrance of 90%. Current molecular screening techniques detect around 90% of *RB1* mutations in bilateral and/or familial cases.<sup>3</sup> Treatment options may include enucleation (removal of the eye), radiotherapy, chemotherapy, and photocoagulation (laser therapy). Early diagnosis and treatment can reduce morbidity, therefore children at increased risk for Rb, including healthy children, are offered regular ophthalmological screening under anaesthesia during the first four years of life.<sup>4</sup>

Parents who have had Rb themselves and healthy parents who have a child with Rb, have an increased risk of having a child with Rb. This increased risk varies between less than 1% and 50%, and depends on the results of DNA testing and family history. Reproductive options for all couples at increased risk are: becoming pregnant with acceptance of the increased risk (i.e. doing nothing), refraining from having (more) children, or choosing to adopt children. If the causative *RB1* mutation is known, couples can also opt for prenatal diagnosis (PND), through chorion villi sampling, with an option to terminate the pregnancy should the child be affected. Since 1999 pre-implantation genetic diagnosis (PGD) is a possibility for couples with a 50% risk and a known *RB1* mutation. Currently, reproductive genetic counselling is offered to all couples in the Netherlands with an increased risk of a child with Rb. Few studies have addressed reproductive decision-making of affected individuals with Rb or parents with a child affected with Rb. One study from the USA described the long-term effects of a genetic testing service for families with a proband with unilateral, non-familial Rb.<sup>5</sup> It was found that *RB1* testing of these children influenced parents' decision to have more children in 20% (10/49) of the families. However, no further details were given on how experience of living with Rb influenced decisions. Byrne et al. (1995) interviewed 56 Rb survivors (15 with heritable Rb) to assess long-term consequences of Rb.<sup>6</sup> One of their findings was that fewer married survivors than controls reported a pregnancy and of the female survivors who married and became pregnant, 42% had only one pregnancy compared to 16% of female controls. They concluded that these differences reflected lifestyle choices more than impaired fertility, possibly in response to advice about the heritable nature of cancer. Van Dijk et al. recently interviewed 156 Dutch Rb survivors<sup>7</sup>

and found that 68% of the 38 adult hereditary Rb survivors and 32% of the 54 non-hereditary Rb survivors indicated that Rb had an impact on their desire to have children. Overall, 12% of all Rb survivors in their study decided not to have children due to the increased risk of having a child with Rb. Neither the study of Van Dijk et al. nor the study of Byrne et al. mentioned factors that might have influenced reproductive choices.<sup>6,7</sup>

Several studies have examined reproductive choices of couples at risk for having a child with another hereditary disease. For example, a Dutch study among parents of a child with cystic fibrosis (CF) revealed that most parents decided against further pregnancies or used other reproductive options to avoid having another affected child. Another study did a follow-up of 164 couples who had visited a Clinical Genetics Department for a variety of disorders concerning childbearing.<sup>8</sup> Forty-three percent of the couples experienced the decision-making process as difficult, had doubts about the decision that was made, or were unable to make a decision. Several factors were shown to be associated with difficulty in reproductive decision-making, including the anticipation of a high reproductive risk, a decision against having children, and the presence of an affected child. A recent study showed that parents of children with a genetic condition or impairment may not pursue further childbearing or decline the use of prenatal diagnostics, in order to avoid making a difficult decision<sup>9</sup>, i.e. parents chose not to choose. As was already shown in 1979 in the study by Lippman-Hand: parents tend to make a “non-decision” if they are not able to process the “facts” to provide a sense of coping.<sup>10</sup>

In order to get more insight in the potential needs with regard to reproductive counselling of couples at increased risk of a child with Rb, we conducted a qualitative interview study. We aimed to explore the impact of prospective risk on reproductive decisions, identify factors influencing these decisions and investigate the needs of couples with regard to reproductive counselling.

## **MATERIALS AND METHODS**

### **Participants in the interview study**

Since 1992, the VU University Medical Center in Amsterdam has been the national treatment centre for Rb in the Netherlands. All Rb patients in a reproductive age are invited to the Department of Clinical Genetics for genetic counselling via the ophthalmologist, as are all healthy parents with a child with Rb. Between 1990 and September 2008, 230 counselees visited the Department of Clinical Genetics at the VU University Medical Center for genetic counselling regarding Rb. From this group we selected couples who had had a counselling session in the context of reproduction and Rb between 2002 and 2006. The restricted time period was chosen because these couples were most likely to have recently dealt with

reproductive decisions. Couples had to be fluent in Dutch and therefore capable of expressing themselves well in an interview.

Eligible couples were divided into four groups, characterized by the different risk categories of Rb (see also **Table 1**):

- 1) Healthy parents and a child with unilateral Rb, without a detectable *RB1* mutation (recurrence risk (RR) <1%)
- 2) Unilateral Rb in one of the partners, without a detectable *RB1* mutation (RR 0.5-1%)
- 3) Healthy parents and hereditary Rb in a child (RR 2-3%)
- 4) Hereditary Rb in one of the partners (RR 50%).

Thirty-three couples were invited from the four different risk groups via purposive sampling. Seven couples did not want to participate (six of whom had been affected with Rb themselves, three of these were at 50% risk) and 11 couples did not respond, even after a reminder had been sent. Fifteen couples agreed to be interviewed. One couple reported their family to be complete before unilateral Rb was diagnosed in their eldest child, so this interview has not been included in the analysis. Only one couple from the lowest risk category (healthy parents with a child with unilateral Rb and no *RB1* mutation detected) was included. This category has become less relevant. In 2007 tumour DNA testing became available in the Netherlands, making it possible to exclude an increased risk for most parents in this situation.

**Table 1.** Characteristics of the study group

<i>Rb1</i> in family	Recurrence Risk (RR)	Number of couples interviewed	Couple identification number (C)
UL <sup>2</sup> Rb in child, <i>RB1</i> <sup>3</sup> -negative	<1%	1	C1
UL Rb in parent, <i>RB1</i> -negative	0.5 – 1%	4	C2, C3, C4, C5
Child <i>RB1</i> -mutation carrier	2-3%	5	C6, C7, C8, C9, C10
Parent <i>RB1</i> -mutation carrier	50%	4	C11, C12, C13 <sup>4</sup> , C14

<sup>1</sup>Rb = retinoblastoma

<sup>2</sup>UL = unilateral

<sup>3</sup>*RB1*-negative = no mutation detected with current screening techniques

<sup>4</sup>One of the partners of couple C13 was affected with bilateral Rb, but the *RB1* mutation could not be detected at the time they were considering children. New screening techniques did detect a mutation several years later.

## Interview guide and procedure

An interview guide was developed by the research team consisting of a clinical geneticist, a researcher, a psychologist, two ophthalmologists and a health scientist. Questions were designed based on literature study and upon the following key topics: the impact of Rb on reproductive decisions, factors influencing the reproductive decision-making process and attitudes towards reproductive options (PND and PGD). In addition, satisfaction with the genetic counselling provided was explored.

Two investigators conducted the interviews (CJD and MRH). Interviews lasted between 30 and 70 minutes. Partners were interviewed together at their home, except for one couple (C14), where only the affected partner was available for the interview.

The Medical Ethical Committee of the VU University Medical Center approved the study protocol and every participant signed an informed consent form before participation.

## Data preparation and analysis

All interviews were audio-taped, transcribed verbatim and anonymised. All interviews were read and discussed by three researchers. Segments of the interviews were coded based on the different key topics of the study. The codes were then grouped together into different themes and coding was discussed by the members of the research team to ensure uniform coding. To assess reliability of coding, 6 interviews were independently coded by two members of the research team (CJD and MRH). Differences in coding were minimal. All coding was discussed with another member of the research team (LH).

In the results section, quotations are used to illustrate the meanings that couples attach to a theme. The couples' identification number (C) and recurrence risk (RR) of a child with Rb for that particular couple is given in brackets. Interview statements were translated from Dutch.

# RESULTS

## Impact of Rb on reproductive decisions

Several couples stated that Rb had influenced their reproductive decisions. Two couples had used PND to test whether their child would be a carrier of the *RB1* mutation. One of these couples had a 50% risk and the other was a healthy couple with a child with hereditary Rb (2-3% RR), suffering from both Rb and pineoblastoma (pineal tumour, histologically identical to retinoblastoma). The latter couple became pregnant very shortly after their first child started intensive treatment. While they were fighting for the life of their child, they could not face another child with Rb, nor any other disease.

*"We were barely thinking about the pregnancy, only in a way like: checking, checking, checking. We were 180% busy with X [child with Rb] and I kept thinking: what if X's treatment is not finished and we will have to go to the hospital with the new baby? We will get a problem who to give our attention to. So to get more certainty, we did PND."* [C10, RR 2-3%]

A couple with a 50% risk, but with an undetectable *RB1* mutation, had been struggling with the decision whether to have children or not:

*"I wanted someone to say: 'Do it!' At least someone to say: 'Do become pregnant.' But that didn't happen."* [C13, RR 50%]

Other couples also mentioned that they had difficulty deciding whether to have (more) children. One other couple with a 50% risk decided not to have any children at all:

*"I think Rb is a very serious disease and looking at it that way, you know, that decides I don't want to try it. I know for sure I don't want a child with Rb."* [C14, RR 50%]

Several couples reported having changed their plans about the number of children they intended to have, after the diagnosis of Rb in one of their children:

*"That second pregnancy was emotionally heavy. It was a hell in a way. [...] I really wanted three children, but now I am hesitating. I mean, I have two healthy children [one with bilateral Rb], all is going well. I don't want to tempt fate. I feel Rb should not rule your life, but basically it does."* [C7, RR 2-3%]

*"We would have considered another child. But now we decided against it. [...] We didn't want to go through this another time. The agony! They say it's not hereditary, but still..."* [C1, RR <1%]

In five couples, the diagnosis of Rb did not influence their decision to have children. This included all four interviewed couples with a unilaterally affected partner and no known *RB1* mutation (0.5-1% risk of having a child with Rb). The fifth couple, who felt that Rb did not impact their desire to have children, had a 50% risk. They had already had two affected children before they found out that the unilaterally affected mother was a carrier of a germline *RB1* mutation. This couple did not feel that the diagnosis of hereditary retinoblastoma influenced their decision and they did not consider PND or PGD for their next pregnancy because the procedure did not feel right for them:

*"It feels for me like going to the market and buying yourself a baby. [...] You don't take a child, you get one and you get it like it is. Actually, that is how it's meant to be. [...] You know life after Rb is a good and complete life, it's what you make of it."* [C12, RR 50%]

### **Changing their minds with time**

For some couples, opinions regarding the number of children wanted changed over time and this seemed to relate to the treatment of their child with Rb. After finding out their child had Rb, two couples stated they were sure that they did not want any more children. They described the period of diagnosis and treatment of the disease in their child as traumatic. After Rb in their child was successfully treated, their desire to have more children recurred.

*"We always wanted to have two children. But after we had X [child with retinoblastoma] we never wanted to go through this process ever again. [...] But after you get out of the hospital, you forget what you have been through. And your child is playing again and everything is all right and you start to think: Well, it doesn't have to happen..."* [C6, RR 2-3%]

### **Factors influencing reproductive decisions**

Three factors seemed to influence couples' reproductive decisions: 1) burden of the disease, 2) the need for ophthalmological screening under anaesthesia for children at risk, and 3) the perceived risk of Rb for a (subsequent) child as opposed to the actual risk.

#### **1. Burden of the disease**

The burden of the disease seemed to have an impact on reproductive decisions and could be divided into four categories: impact of treatment on the affected child, impact of treatment of the affected child on the family, impact of sequelae of Rb on social life and, lastly, uncertainty as to the extent to which the future child will suffer from retinoblastoma and second primary cancer.

#### **Impact of treatment on the affected child**

Several parents commented that the distress of the treatment for the affected child had an effect on their reproductive decisions. For example this couple:

*"You can't explain to your child what's happening. He is suffering but doesn't know what's happening at all. [...] Due to the chemotherapy his skin was ruined and changing diapers became very painful. So with a second child you risk having to go through this again. No, we couldn't face it."* [C9, RR 2-3%]

### Impact of treatment of the affected child on the family

The treatment of the affected child was identified as putting a strain on the parents themselves and the rest of the family:

*“Our eldest [healthy] son is very sensitive. I can never do this to him again. Being away all the time and having all the emotional distress. I wasn’t able to be there for him when he needed me. [...] I was thinking: Just because I really want to have another child, my whole family might have to suffer again.” [C8, RR 2-3%]*

### Impact of sequelae of Rb on social life

Almost all individuals affected by Rb themselves reported negative experiences with the sequelae of treatment for Rb (e.g. visual impairment and cosmetic deformities caused by the treatment) regarding their social lives. For some, this affected their decisions toward childbearing. Like this couple, who chose PND:

*“Yes, my childhood has been unpleasant. I was bullied for being different, until halfway through high school, day in and day out: they beat me up, they ruined my glasses, they nicked my stuff. [...] I don’t want this for my child, such a life.” [C11, RR 50%]*

Nevertheless, negative experiences of affected parents in childhood were not always mentioned as having had an impact on the decision to have children. Affected individuals interviewed still considered their life with Rb worth living. Moreover, since children carrying the mutation would be screened from birth, some felt that consequences of the disease, if treated in time, might be less severe.

*“I don’t experience my life in a negative way, so if I wouldn’t have children for that reason, it would mean I would have a negative perception of my own life. And, you know, nowadays retinoblastoma can be detected at an early stage, which means the consequences will be relatively small.” [C12, RR 50%]*

### Uncertainty as to the extent to which the future child will suffer from retinoblastoma and second primary cancer

Several couples reported the uncertainty as to the severity of the impact of disease upon their future child as a factor of influence on their reproductive decisions:

*“We decided that we would terminate the pregnancy if the child turned out to be a carrier. [...] They can’t predict the severity of the disease. We were afraid it [the child] would be blind at birth or that it would not survive cancer. I know*

someone who has lost a child to retinoblastoma. I absolutely would not want to live through that.” [C11, RR 50%]

## 2. Ophthalmological screening under anaesthesia

An important factor mentioned influencing reproductive decision-making was the ophthalmological screening. Children at increased risk for Rb are advised to undergo frequent ophthalmological screening under anaesthesia during the first 4 years of their life. Although most parents felt that the screening programme was needed, because it leads to detection and treatment at an early stage, at the same time they described it as a burden:

*“We understood that our next child would have to be screened. X [affected child] hated going to the hospital, she had to be held down before going under anaesthesia and when she woke up, she was always sick, so I really felt: No, never again.”* [C1, RR <1%]

## 3. Perceived risk of having a child with Rb

The magnitude of the recurrence risk was not always interpreted in the same way. For some couples the perceived risk did not relate to the actual risk. All couples with the hereditary form of Rb experienced their 50% risk of passing the mutation on to their children as high. Although some accepted the risk as it was:

*“It was hard to realize the fact that there is such a high risk and that your child might get retinoblastoma. But we had a strong desire to have children [...] and in the end you just accept this risk...there’s nothing else you can do.”* [C13, RR 50%]

Another couple with a 50% risk decided to refrain from having children, because of their increased risk:

*“I would have to choose prenatal diagnosis. There is of course a chance of 50% of a healthy child. But because of the burden of a negative outcome, it’s better to think: I don’t want a child, than having to make the difficult decision of terminating a pregnancy.”* [C14, RR 50%]

Furthermore, four of the five couples perceived their recurrence risk of 2-3% as high:

*“Yes, the risk is very small, but for X [child with Rb] the risk had also been very small, so very small is of no value for me. [...] During my second pregnancy, that two percent really started to feel as something much bigger.”* [C7, RR 2-3%]

The other couple interpreted the 2-3% risk as low:

*"We did all the genetic tests. [...] If we had had the mutation in our blood, it would have been a 50% chance, and then the decision would have been difficult for us. But it turned out to be negligible really. So we went ahead and got pregnant again."* [C6, RR 2-3%]

All interviewed couples with one unilaterally affected parent and a (presumed) non-hereditary form of Rb felt the risk to be acceptable and decided to have children:

*"The chance was so small, we felt relieved. So then we said: let's go for it!"* [C4, RR 0.5-1%]

### **Needs with regard to reproductive genetic counselling**

In general, couples reported being satisfied with the genetic counselling they had received, although they did not always remember all the information received. They stated that the counselling had helped them to better understand the cause and consequences of Rb. One couple, however, reported dissatisfaction with regard to the timing of the genetic counselling session. Part of their counselling took place just weeks after the diagnosis of Rb in their child.

*"Maybe it's better not to talk to the geneticist during the treatment of your affected child, but later on. Because you are so busy getting your child healthy again. If you get the genetic counselling later, you might be able to understand and remember more of it."* [C9, RR 2-3%]

Despite differences in opinion concerning future pregnancies between partners, most interviewed couples reported they were able to come to a decision by themselves without needing the help of others. When asked whether they had needed more support during their decisional process, one couple said:

*"Look, at some point you need to decide just the two of you. You can hear things which you interpret both in different ways. You gather all information and talk it over together to get on the same track again. [...] It takes some time, but you make the decision together."* [C8, RR 2-3%]

Several couples reported that getting in contact with other couples in a similar situation was felt to be supportive and helped them in making decisions about family planning.

## DISCUSSION

This qualitative study focuses on reproductive decisions of couples at increased risk of having a child with Rb, and identifies factors of influence on these decisions. We found that for most couples, the diagnosis of Rb in a partner or in a child significantly influenced future reproductive decisions. Some of the couples in our study decided to refrain from having (more) children or made use of PND. Others reported being anxious throughout a pregnancy or were undecided about having (more) children. We showed that several factors influenced decision-making. First of all the burden of the disease itself: the impact of treatment for Rb on the child and the family, sequelae of treatment and concern regarding the extent to which a future child will suffer from Rb. Other factors mentioned by the couples were the need for ophthalmological screening for children at risk and the perceived risk of having a child with Rb.

This is the first study to explore the factors that influence reproductive choices of couples at increased risk for a child with Rb. Earlier studies have shown that Rb seems to influence reproductive choices for some Rb survivors<sup>6,7</sup>, but did not investigate what aspects of the disease were of influence, as was explored in the present study.

Some of the interviewed couples in our study expressed difficulty with reproductive decision-making. Problems with reproductive decision-making of couples at increased risk have been reported in several studies of couples at risk for other genetic disorders.<sup>8,11,12</sup> Various studies of patients at increased risk of a child with hereditary cancer have shown that the diagnosis of cancer in the family had an impact on family planning and many couples in these studies have expressed interest in using PND or PGD.<sup>13-16</sup> In the present study, two couples used prenatal testing for retinoblastoma. Although PGD is discussed with all couples at 50% risk and a known *RB1* mutation, none of the four couples at 50% risk included in our study opted for PGD. At the time of the study, just three couples in the Netherlands had decided to use PGD for Rb.<sup>17,18</sup> Five more had been referred for PGD, but had decided not to go through with the procedure (personal communication C. de Die-Smulders, Dutch PGD working group, Maastricht, the Netherlands). The interviewed couples therefore reflect the decision of the majority of couples at 50% risk for Rb in the Netherlands. In the present study, all four interviewed couples at 50% risk of a child with Rb experienced this risk as high. In the other three risk groups, consisting of healthy parents with an affected child, or a unilaterally affected parent without an identified *RB1* mutation, the risk was also perceived as high in some cases. For these couples perceived risk seemed to influence reproductive decision-making more than the actual risk. This confirms findings of studies on other genetic disorders (see review by Sivell<sup>19</sup>). Sivell et al. concluded that risk is something individuals live with and experience, rather than it being a detached concept. Some parents tend to relate to their risk

as a two-way option: it will or will not happen, rather than a probabilistic figure, provided by genetic counselling.<sup>20,21</sup> In their follow-up study of 164 couples that visited the Clinical Genetics department for different genetic disorders because of wishing to have children, Frets et al. concluded that the magnitude of the genetic risk was of relative importance: 70% of couples with a high risk (>15%) opted for having children.<sup>22</sup> They stated that the desire to have children and the familiarity with the disorder seemed to be more important in reproductive planning than the magnitude of the risk. Burden of disease was also found to be an important factor influencing family planning, as was seen in our study.

A study of the quality of life of adult Rb survivors concluded that bullying in childhood was one of the predictors of a worse quality of life.<sup>23</sup> For some of the interviewed Rb patients in our study these negative experiences were mentioned as influencing reproductive decision-making.

Several couples, who at first decided not to have any more children, changed their mind when retinoblastoma in their child had been successfully treated. A change of opinion over time has been reported in a study on reproductive decisions and CF.<sup>24</sup> This study found that one of the reasons for wanting more children than originally thought was that couples felt more comfortable about the diagnosis of CF. This dynamic aspect shows that parents need ongoing access to genetic counselling, beyond the initial diagnosis and treatment. This seems to count not just for CF, but for RB as well.

Several limitations of our study should be noted. First of all, this is a qualitative study with interviews conducted in a small and heterogeneous study sample. Therefore caution is needed in drawing conclusions from these findings. Secondly, the study group consists of couples that visited the Clinical Genetics Department. It is possible that couples that avoid genetic counselling for Rb make other reproductive choices.

A third drawback might be that quite a few couples declined participation in this study or did not respond to a reminder. Some mentioned lack of time as a reason for not participating. Others stated the subject of Rb and childbearing as too emotionally charged to participate. It is therefore conceivable that couples that participated, reflect a group for which Rb was less emotionally charged. Lastly, we need to be aware of the retrospective character of this study, since the interviews may have taken place some time after the reproductive decisions were actually made.

In conclusion, we have shown that Rb in a child or partner influences reproductive decision-making for many couples and in different ways. We suggest that genetic counsellors, when discussing family planning, draw attention to the burden of treatment of Rb of an affected child, to the perceived burden for the family and to the burden of ophthalmological screening under anaesthesia for children at risk. We also recommend paying attention to the possible negative experiences

with the sequelae of Rb treatment of affected individuals during counselling. We have shown that some couples will consider PND for Rb, not only couples with a 50% risk, but also healthy couples with an affected child with an *RB1* mutation. Since attitudes may change over time, it is important for couples at increased risk to have ongoing access to genetic counselling. Further studies will be helpful to confirm our findings in a larger group of patients.

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