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Abstract

Abstract STUDY QUESTION How can the decision process for fertility preservation (FP) in adolescents and prepubertal boys be improved based on patient and parent feelings about FP counseling? SUMMARY ANSWER The content of information given to patients and parents and hope for future parenthood appeared to positively impact on the decision to preserve fertility in the pediatric population and, therefore, deserves special attention to improve FP care. WHAT IS KNOWN ALREADY A vast body of literature on adult cancer patients shows that reproductive capacity is a major quality-of-life issue. Patients also have a strong desire to be informed of available FP options with a view to future parenthood of their own genetic child, considering that <10% chose to adopt or used donated gametes. Furthermore, the quality of fertility counseling provided at the time of cancer diagnosis has been identified as a crucial factor in the decision-making process. By contrast, in the pediatric population, whil...

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Fertility preservation in the male pediatric population: factors influencing the decision of parents and children

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STUDY QUESTION: How can the decision process for fertility preservation (FP) in adolescents and prepubertal boys be improved based on patient and parent feelings about FP counseling?

SUMMARY ANSWER: The content of information given to patients and parents and hope for future parenthood appeared to positively impact on the decision to preserve fertility in the pediatric population and, therefore, deserves special attention to improve FP care.

WHAT IS KNOWN ALREADY: A vast body of literature on adult cancer patients shows that reproductive capacity is a major quality-of-life issue. Patients also have a strong desire to be informed of available FP options with a view to future parenthood of their own genetic child, considering that < 10% chose to adopt or used donated gametes. Furthermore, the quality of fertility counseling provided at the time of cancer diagnosis has been identified as a crucial factor in the decision-making process. By contrast, in the pediatric population, while it was shown that parents were able to make an informed and voluntary decision for their prepubertal sons despite the heavy emotional burden at the time of diagnosis, there is so far very limited information on patient expectations regarding FP. A lack of awareness often equates to suboptimal care by oncologists and FP specialists, and poor access to FP, therefore improving knowledge and identifying the expectations of pediatric patients and their parents are crucial for optimizing multidisciplinary collaborative care pathways (MCCPs), including counseling and access to FP methods, in the youngest population.

STUDY DESIGN, SIZE, DURATION: A questionnaire survey was posted to an eligible population between May 2005 and May 2013.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A total of 348 prepubertal boys and adolescents aged 0–18 years, diagnosed with cancer in a university hospital setting, were eligible. Three different questionnaires for two age groups of children (< 12 and 12–18 years) and parents were established based on information from focus groups. Questions were subsequently reviewed by the institutional ethics board before being sent.

MAIN RESULTS AND THE ROLE OF CHANCE: Of the 348 eligible patients, 44 died and 14 were lost to follow-up. Thus, 290 patients (77 aged 12–18 years and 213 aged < 12 years) were sent a questionnaire. In total, 120 questionnaires were recovered, 45.5% ($n = 35/77$) from adolescents and 39.9% ($n = 85/213$) from children. FP acceptance rates were, respectively, 74 and 78.6% for boys aged < 12 and 12–18 years. The content of information provided to patients and parents appeared to positively impact on the decision to preserve fertility ($P = 0.04$). While the majority of boys aged > 12 years considered the information to be clear (72%), complete (80%) and understandable (90.9%), only 33.3% of boys aged < 12 years were able to comprehend the information. Pressure from doctors to reduce the delay between diagnosis and cancer treatment increased the number of refusals ($P < 0.01$), while hope for future parenthood favored acceptance ($P < 0.01$). Family support was considered important for 75% of adolescents and 58% of children, and medical support for 50% of adolescents and 42% of children.

LIMITATIONS, REASON FOR CAUTION: This single-center survey does not allow extrapolation of the information to other settings. Recall bias and lack of full external validation of the questionnaires are further limitations. Modification of the current MCCP should be further evaluated according to our results.

WIDER IMPLICATIONS OF THE FINDINGS: Acknowledging the issues faced and familiarizing oneself with the care of patients undergoing fertility-threatening therapies supply primary care providers with the appropriate quality management tools in the field of FP in centers for reproductive medicine. Expectations reported in the survey allow appropriate support to be included within the MCCP design.

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Introduction

Improvements in cancer therapy and extension of gonadotoxic therapy to benign conditions mean that there is now a steadily growing population of young people affected by reproductive issues after successful fertility-threatening therapies. Cryopreservation of mature sperm collected by masturbation with or without assisted ejaculation techniques or by epididymal or testicular tissue sampling (Wyens, 2013) is increasingly being proposed to adolescents, having been routinely applied in adults for many years now (Lass et al., 1999).

However, for prepubertal boys, the only option for fertility preservation (FP) is cryopreservation of immature testicular tissue (ITT) (Keros et al., 2007; Wyens et al., 2008; Curaba et al., 2011; Poels et al., 2013) with a view to future autografting or *in vitro* maturation of spermatogonial stem cells (for review, see Wyens et al., 2010). While human ITT cryopreservation is still at an experimental stage, research related to fertility restoration strategies using cryopreserved ITT is actively ongoing, showing promising results with respect to clinical application (Hermann et al., 2012). This raises specific issues of practice, information provision to patients, their parents and professionals, and specific ethical issues of consent. More precisely, such ethical issues concern the ability of children to consent to both treatment and preventive measures, such as gamete storage, where understanding, the key to this process, may not be such that they are legally competent. Even more complex is the scenario where children and parents' autonomy clash, the child refusing what the medical team and parents feel is both the most beneficial and the least harmful approach in the proposed care (Miller et al., 2004).

Providing patients with the most effective treatments means that infertility issues often take second place for most oncologists (Bradlyn et al., 2004). Consequently, when they begin therapy, most young patients are not informed of the risk of fertility impairment or loss (Schover et al., 2002a; Zebrack et al., 2004). While rates at which adult patients are informed of potential infertility steadily improve with increasing oncologists' awareness of the importance of FP issues (Quinn et al., 2009; Adams et al., 2013; Buske et al., 2015), there is still a long way to go in the pediatric population. Indeed, it was shown that only 46% of pediatric oncologists refer their male pubertal cancer patients to a fertility specialist (Köhler et al., 2011). Furthermore, the emergency context and lack of time in the case of cancer, insufficient knowledge of care providers regarding FP options and patient and parent expectations, apprehension about patients' receptiveness to discussing FP, and the availability of FP resources constitute other barriers to talking about fertility issues (Goodwin et al., 2007; Vadapampil et al., 2008). Moreover, the patient's health before treatment and the disease prognosis may influence care providers not to push FP at such a sensitive time

(Achille et al., 2006; Gilbert et al., 2011) or consider delaying treatment because of the aggressiveness of the disease (Reebals et al., 2006).

As a result, sperm banking rates are disappointingly low, reported to be only 18–28% of affected adolescents (Klosky et al., 2009; Nagel et al., 2009), although defining appropriate clinical pathways for FP has improved referrals (Anderson et al., 2008). For prepubertal boys, however, because ITT cryopreservation is new and not yet widespread, corresponding figures are not available. Reported clinical experience is also scarce (Wyens et al., 2011) or limited to small pilot studies (Ginsberg et al., 2010), even if spermatogonial stem cell cryopreservation by testicular sampling appears to be just as acceptable 'to parents' as freezing of a semen sample collected by masturbation or assisted ejaculation (Van den Berg et al., 2007).

Besides the strong desire of patients to be informed of available FP options, reproductive capacity has emerged as a major quality-of-life issue among survivors, and even a slight chance of infertility is considered a major burden. Indeed, it was found that loss of fertility is often perceived as loss of masculinity (Schover et al., 1999; Eiser et al., 2011). In addition, for the majority of cancer survivors, their illness increases the value they place on parenthood and family (Schover, 2005), and < 10% chose to adopt or used donated gametes (Schover et al., 1999; Schover et al., 2002a).

FP measures must, therefore, be given greater priority. This is even more challenging in the pediatric population, where children are asked to consider parenthood when they do not generally contemplate this matter and to project themselves to some distant point in the future, and where joint decisions between parents and children need to be reached during the acute phase of the disease.

The quality of fertility counseling provided at the time of cancer diagnosis has been identified as a crucial factor in the decision-making process (Schover et al., 2002a; Achille et al., 2006). However, very few papers discuss decisions on FP in the pediatric population. Three pilot studies assessed parental acceptance of FP strategies in adolescents (Sadri-Ardekani et al., 2013) and prepubertal boys (Van den Berg et al., 2007; Ginsberg et al., 2010; Sadri-Ardekani et al., 2013), but two (Van den Berg et al., 2007; Sadri-Ardekani et al., 2013) used retrospective scenarios with hypothetical access to the technique in the future because of its unavailability at the time. One more recent preliminary study of interest evaluated the decisional process of parents of 48 prepubertal boys undergoing ITT cryopreservation, within the context of a research protocol investigating a specific population at high risk of infertility (Ginsberg et al., 2014). While this study analysed parent decision-making influences and perceived levels of personal decision-making control and mood states, neither the child's attitudes or emotional states related to FP acceptance and implementation nor the importance placed on

medical staff and family support during the decisional process was addressed. Moreover, children who could benefit from ITT cryopreservation were considered to be too young to be surveyed (Ruutiainen et al., 2013). Our experience with ITT cryopreservation since its implementation in our department has allowed us to gather information about children's feelings toward this FP method.

In the absence of clear information about such patients' expectations, clinicians are often left to make decisions based on assumptions about their patients' or parents' wishes regarding future fertility and FP, and on their own moral codes.

The aim of this article is, therefore, to critically analyse the multidisciplinary collaborative care pathway (MCCP) in the pediatric population, focusing on factors influencing the decision, and to elucidate and characterize the feelings of patients and their parents, with a view to better fulfilling their expectations. To our knowledge, this is the largest study evaluating FP in prepubertal boys in whom testicular biopsy for spermatogonial stem cell preservation was a real option. Ethical considerations related to FP in the pediatric population have also been addressed.

Materials and Methods

Patient recruitment and questionnaires

A total of 348 prepubertal boys and adolescents aged 0–18 years diagnosed with cancer between May 2005 and May 2013 were eligible for this study. Three different questionnaires, for children (<12 and 12–18 years) and parents, were prepared based on information gathered from focus group discussions with patients and parents, and the scientific literature. Interviews with families conducted by a nurse from the pediatric hematology–oncology department also aimed at controlling for use of unfamiliar terminology and appropriateness of questions, as well as uncovering issues that the medical team would not have considered. Survey questionnaires used mainly closed-ended questions followed by response options to minimize random errors in the data collection process and allow quantitative interpretation. The proposed answers were defined based on the experience of the survey developers and the study hypothesis set by them, which could be seen as 'leading' questions/answers. Nevertheless, we left the possibility to add spontaneous answers in free text boxes allowing further communication of patient and parent feelings or thoughts on the situation. Items and related questions were subsequently reviewed by the oncologic, reproductive and liaison psychiatry medical teams for content validity, before being analysed and approved by the institutional ethics board, and sent by regular mail to the parents. Two reminders were also sent with the right to decline to participate during the survey period from June 2013 to October 2013. Consistency of response was evaluated on a population sample at a randomly scheduled follow-up consultation.

The questionnaires comprised two parts. Part 1 included sociocultural population characteristics, type of disease and questions about information received by patients and parents. Part 2 focused on communication (information content, time of information transfer, information provider), emotional state and perceptions during discussion of FP, reasons for refusal, parental views on the involvement of their children in the decisional process, as well as the importance of medical/paramedical and family supports.

The difference between parent and patient questionnaires was the wording, which was simplified to facilitate understanding for children. For adolescents, an additional question about the method of sperm collection for FP was included.

For children who were too young to answer the survey themselves, parental help was sought, and for those who were too young to participate in the

survey (below the age of 5 years at diagnosis), only answers from parents were obtained.

The study was performed at Cliniques Universitaires Saint Luc, a Belgian university setting, and approved by the institutional review board of the Catholic University of Louvain. Hence, from 2005 on, all children subjected to fertility-threatening therapies could undergo ITT cryopreservation if their parents (and child if applicable) were informed about the experimental nature of the method and lack of currently available fertility restoration techniques (see next paragraph for consent issues), according to the Belgian law on human experimentation (Moniteur Belge, *Loi relative aux expérimentations sur la personne humaine*, 7th May 2004), which sets out the consent process, need for ethics committee approval and specific issues related to the protection of minors. Because no children have yet been born as a result of the ITT technique and, hence, its efficacy cannot be established, it is not covered by national insurance and was not paid for by the patient.

MCCP for patients at risk of infertility

Information on FP was initially given to parents and patients by pediatricians and oncologists, who referred the case to one of two reproductive medicine specialists. All patients/parents could have access to a method of FP before initiation of cancer therapy. Rapid and flexible access to medical consultation with a reproductive medicine specialist, and to facilities for sperm or tissue sampling that could accommodate acutely ill young patients before they undergo gonadotoxic therapies, was provided. From the age of 5 years and provided his health permitted, the child's presence was strongly encouraged during this consultation. The fertility specialist then assessed the potential testicular content based on physical examination and previous history, and investigated the possibility of obtaining an ejaculate by masturbation or penile vibratory stimulation (for boys close to 12 years or older). Appropriate case-by-case information on sexual maturation, including pubertal events, testicular maturation with potential content linked to age, sperm emission, reproduction, as well as semen or testicular tissue cryopreservation and storage, was given. The language was adapted to the child's age. In the course of the consultation, boys and their parents were encouraged to ask questions freely. From the age of 12 years, the patient was invited to discuss FP without his parents being present. For peripubertal boys who were candidates for semen sampling, a trained nurse or laboratory technician from the unit of reproductive medicine also explained the procedure of sperm collection and assisted the patient in the absence of his parents at the laboratory facilities. For prepubertal boys, information on tissue sampling was provided as previously reported (Wyns et al., 2011), and potential fertility restoration approaches from testicular biopsies were explained to each individual child and his parents, making sure they understood that there is no guarantee of success with stored ITT as yet and that it therefore must be considered experimental. In all cases, parents or legal guardians gave their consent for cryobanking in writing, and the child's assent was sought if he was mature enough to understand the implications of the procedure. Parents of minors were advised to have a consultation at their majority to confirm earlier decisions and to receive information on the evolution of fertility restoration techniques.

Because of the high volume of information exchanged during such a consultation, adolescent patients were invited at least 1 year after the end of cancer treatment for fertility monitoring and discussion about the subsequent disposition of stored samples. Prepubertal patients were asked to return any time after completing cancer therapy, but in any case at the age of 18 years to discuss scientific progress on ITT banking and sample disposition.

Statistics

Proportions were compared using the chi-square test or Fisher's exact test. NCSS statistical system 2007 (Kaysville, Utah 84037) was used. Bilateral testing was applied. A *P* value of <0.05 was considered statistically significant.

Results

Population characteristics and response rate

Of the 348 eligible patients, 44 patients died and 14 were lost to follow-up. Thus, 290 patients (77 aged 12–18 years and 213 aged <12 years) and their parents were sent questionnaires. Among them, 96 (33.1%) responded to the first mailing and 8 declined to participate in the survey. After three reminders, a total of 120 questionnaires were recovered from parents (with or without the corresponding questionnaire from their child), yielding an overall response rate of 41.4%, including 45.5% from adolescents ($n = 35/77$) and 39.9% from children ($n = 85/213$). For these 120 questionnaires and a further 51 recovered from children out of a total population of 290 parents and 290 children, we obtained a margin of error of 7 and 12% for parents and patients, respectively, (confidence level = 95%). Response rates by the type of pathology are presented in Table I.

Median age at diagnosis was 6.05 ± 3.74 years (range 0.1–143 months) and 14.41 ± 1.5 years (range 144–212 months) for boys aged <12 and 12–18 years, respectively. Mean (\pm SD) follow-up from diagnosis to the time of the survey was 3.4 ± 2.3 years.

Since 42 patients (35%) did not receive information on FP issues, only 78 questionnaires included responses to Part 2. Among these 42 patients who did not have exposure to a FP discussion, we recorded patients who did not require chemotherapy (16), very young patients [<2 years of age (11)], patients who received previous chemotherapy (1), very high emergency for starting chemotherapy (2), trisomy 21 (1 patient) and unknown reason (1). Patient perceptions of FP could be recorded from the age of 9 years (at diagnosis). Indeed, 39.3% of children aged <12 years did not answer these questions compared with only 8% of boys aged 12–18 years.

Table I Pathology and response rate in a male pediatric population.

Cancer type	N	N deceased	Response rate
Acute lymphoblastic leukemia	67	7	55% (33/60)
Acute myeloid leukemia	15	2	15.4% (2/13)
Non-Hodgkin's lymphoma	34	6	46.4% (13/28)
Hodgkin's lymphoma	15		40% (6/15)
Medulloblastoma	15	3	25% (3/12)
Nephroblastoma	15		26.7% (4/15)
Neuroblastoma	30	6	37.5% (9/24)
Osteosarcoma	34	6	32.1% (9/28)
Retinoblastoma	46		15.2% (7/46)
Ewing's sarcoma	10	2	75% (6/8)
Rhabdomyosarcoma	13	2	54.5% (6/11)
Hepatoblastoma	10	2	50% (4/8)
Brain tumor	24	6	38.9% (7/18)
Astrocytosis	5		40% (2/5)
Ependymoma	3		33% (1/3)
Benign pathologies	12	2	70% (7/10)
TOTAL	348	44	39.1% (119/304)

Response by patients, parents or both

No questionnaires were received from children without the completed questionnaire from their parents. In addition to the 120 answers from parents who did not decline to participate, 28 patients under 12 years of age and 23 aged 12–18 years answered the questionnaire with or without parental help, the youngest patient being just 5 years old at the time of diagnosis.

For 22 patients under 12 years of age and 3 aged 12–18 years, only answers from parents were obtained. Parents considered their child capable of understanding and participating in the decisional process in 91.4% of adolescents (versus 26.2% of children aged <12 years).

FP acceptance rates were 74 and 78.6% for boys aged <12 and 12–18 years, respectively. Acceptance by disease is shown in Table II.

No discrepancy between patient and parent decisions was noted, indicating that decisions were essentially made jointly.

Six adolescents and 13 children under the age of 12 years refused to undergo FP procedures, corresponding to, respectively, 7.7 and 16.7% of the total population of responders. Reasons for refusal were the urgency of cancer treatment, diminished general health, the FP procedure not being a priority or the experimental status of FP before puberty. Wishing to avoid an additional procedure was not an issue for FP acceptance.

Population sociocultural characteristics

Population sociocultural characteristics were analysed and correlated with FP acceptance (Table III). The age of patients was not found to be a relevant factor in the acceptance of FP ($P = 0.79$), and the same was true for nationality, religion and parental employment.

Table II FP acceptance by disease in a male pediatric population.

Pathology	Sample stored, n	Sample not stored, n
ALL	21	12
AML	0	2
Osteosarcoma	7	2
Brain tumor	3	4
Non-Hodgkin's lymphoma	6	7
Hodgkin's lymphoma	5	1
Neuroblastoma	3	6
Rhabdomyosarcoma	5	1
Nephroblastoma	0	4
Hepatoblastoma	2	2
Medulloblastoma	1	2
Retinoblastoma	0	7
Testicular cancer	1	0
Sarcoma	5	1
Astrocytoma	0	2
Ependymoma	0	1
Benign pathology	0	7

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Table III Population characteristics and acceptance of FP.

	FP refused, n (%)	FP accepted, n (%)	P-value
Age of male patients			
< 12 years	13 (26%)	37	0.79
12–18 years	6 (27.3%)	22	
Nationality			
Belgian*	14 (73.7%)	52 (88.1%)	0.15*
European (non-Belgian)*	5	6	
Other	0	1	
Religion			
Catholic*	13 (72.2%)	37 (62.7%)	0.35*
Muslim	2	2	
Protestant	0	2	
Jewish	0	1	
Atheist	0	5	
Other	2	10	
No answer	1	2	
Employment of parents			
Employee*	14 (73.7%)	50 (84.7%)	0.31*
Manual worker	3	4	
Civil servant	0	1	
Retired	0	1	
Without employment	1	2	
No answer	1	1	

Data are from $n = 78$ questionnaires.

A comparison was made between accepted or refused FP. The chi-square test was applied for comparisons between Belgian and European*, Catholic and non-Catholic*, and employee and non-employee*.

Communication issues

Only 78 questionnaires included responses to Part 2. Information content, timing and provider are described in Table IV. The completeness of information provided to patients and parents appeared to positively impact on the decision to preserve fertility ($P = 0.04$).

For boys over 12 years of age, 91.4% of parents considered their child capable of participating in the decision process (versus 26.2% for those under 12 years, with the youngest being 7 years old). For the rest, not only immaturity of the child (5.7%) but also poor general health (2.9%) explained their inability to do so.

Emotional state of parents and children during FP explanations

For the parents, this is summarized in Table V. Pressure from doctors to reduce the delay before cancer treatment increased the number of refusals ($P < 0.01$), while hope for future parenthood favored acceptance ($P < 0.01$).

With regard to the patients, 52% of adolescents felt anxious at the time of discussion versus 23.5% of children. The main reason was their concern about future fertility, rather than the method of FP.

Table IV Communication of FP information.

	FP refused (n)	FP accepted (n)	P-value
Information content (completeness)			
Satisfactory	12	51	0.04
Not satisfactory	7	8	
Timing of FP information			
At diagnosis*	6	15	0.77*
A few days after diagnosis	4	17	
When explaining cancer treatment	7	23	
At first chemotherapy session	2	4	
Information provider			
GP or pediatrician	2	5	ND
Oncologist	15	49	
Specialist	2	3	
Nurse	0	2	

Data are from $n = 78$ questionnaires.

A comparison was made between accepted or refused FP. The chi-square test was applied for information content (satisfactory or not). Fisher's exact test was applied for the timing of FP information (*at diagnosis or at any other time).

Nevertheless, 46% of boys aged 12–18 years considered the FP method challenging because of poor general health, lack of experience with masturbation and its taboo or embarrassing nature.

Seventy-six percent of children considered their health to be more important than the ability to have a family (compared with 48% of adolescents).

Finally, family was considered important for 75% of adolescents and 58% of children, and medical support was considered important for 50% of adolescents and 42% of children. Nursing support was relevant for 16.6% of adolescents.

Information understanding

While the majority of boys aged > 12 years considered the information to be clear (72%), complete (80%) and understandable (90.9%), only 33.3% of boys aged < 12 years were able to comprehend the information, the youngest being 11 years old (although, respectively, 71.4 and 57.9% of subjects found it to be complete and clear).

Discussion

While survival studies document the struggles of having children after cancer treatment, concerns of children and their parents about future fertility at the time of diagnosis and factors influencing the FP decision-making process are not well documented, especially in the pediatric population. It was reported that families of children affected by cancer do indeed have concerns about fertility-related side effects of their treatment (Oosterhuis et al., 2008) and want to be presented with options (Van den Berg et al., 2007), but the literature also shows a gap between the medical team's awareness of the need to address FP issues and taking action when the opportunity arises. Indeed, while

Table V Emotional state of parents during discussion of FP.

	FP refused	FP accepted	P-value
General			
Satisfactory	11	42	0.40
Too much information at once	3	13	
Overwhelmed by child's diagnosis	3	3	
Not a priority: child's health comes first	2	1	
Anxiety			
Present	13	27	0.12
Absent	6	32	
Self-reported feelings			
Pressure from doctor to reduce delay before cancer treatment	9	1	<0.01
Hope for future parenthood	4	50	<0.01
Other (avoiding additional procedures, child's health first, etc.)	6	8	0.09

Data are from $n = 78$ questionnaires.

A comparison was made between accepted or refused FP. The chi-square test was applied to compare emotional state (anxiety present or not). Fisher's exact test was applied for emotional state (satisfactory or not) and for each self-reported feeling.

91% of practitioners felt that sperm banking should be mentioned to patients whose treatment could impair fertility, 48% never mentioned it or informed less than a quarter of their patients (Schover *et al.*, 2002b). Paucity of training for clinicians and lack of information for patients were also identified as contributing factors (Gilbert *et al.*, 2011). This has been recently reflected in survey data, which showed that patients had poor knowledge of FP options (22% of pediatric patients), with only 15% adequately informed before the start of therapy (Sadri-Ardekani *et al.*, 2013). In our study, despite a well-established multidisciplinary collaborative approach between oncologists and reproductive physicians, one-third of the patients were still lacking information about FP options when seen by the oncologist. Insufficient or inappropriate knowledge and training of cancer care providers most probably play a key role in such poor figures. Although defining a FP pathway represents an important step in the management of patients facing fertility-threatening therapies, further optimization is required.

The decision-making process is highly complex in the pediatric population. On the one hand, children may lack the capacity to understand the implications of FP. On the other hand, parents are forced to consider their child's potential wish to have children in the future, while faced with the life-threatening nature of the disease, which may reduce their competence in decision-making (Grundt *et al.*, 2001) at an already stressful time. This is even more critical when FP requires an additional surgical procedure that may be regarded experimental on account of its unknown potential for fertility restoration.

Because of the highly emotional state of those affected by such a serious diagnosis, awareness of feelings and expectations of patients and parents and knowledge of factors influencing FP acceptance are of utmost importance.

Acceptance of FP in the pediatric population appears to be linked to the way the subject is introduced, with acceptance rates in prepubertal boys ranging between 54 and 76% (Van den Berg *et al.*, 2007; Ginsberg *et al.*, 2010; Sadri-Ardekani *et al.*, 2013). The highest rate was obtained with face-to-face consultation at the time of cancer diagnosis in a small pilot study that included 21 patients for whom ITT sampling was a real option (Ginsberg *et al.*, 2010), which is in accordance with our larger series (74 and 78.6% for boys aged < 12 and 12–18 years, respectively).

Our survey did not reveal the child's age to be an issue for FP acceptance. However, patients' perceptions were different in the two age groups, with the vast majority of adolescents considering themselves to be fully and clearly informed and able to understand the information, compared with only one-third of boys aged < 12 years. While the reason for this difference seems obvious for the youngest patients, further analysis of the influence of perception on FP acceptance was not possible. Indeed, for minors, even when it was possible to obtain the patient's assent, parents remained the final decision-makers (Bahadur *et al.*, 2000, 2001; Robertson, 2005).

It is interesting to note that parents made joint decisions with their adolescent sons. The way of conducting discussions was also found to play a possible role, but the literature shows conflicting results on patient and parent involvement in the decision-making process. On the one hand, up to almost half of patients preferred to have initial discussions without their parents being present; but on the other hand, they were pleased with their parents' involvement in the decision-making process (Crawshaw and Sloper, 2006). In our setting, patients were seen jointly with their parents, and the discussion was conducted with the aim of securing a joint decision on FP acceptance, respecting the child's best interests (Shenfield *et al.*, 2002). In this regard, it has indeed been suggested that preserving fertility protects patient's choice as adults (Glaser *et al.*, 2004). Setting aside dedicated time for discussion with peri- and postpubertal patients in the absence of their parents could also explain why we did not find the patient's age to be an issue, despite about half of adolescents perceiving the process of FP as difficult, because of feelings of embarrassment talking about masturbation and sexual experience.

From an ethical perspective, the child should be involved in the discussion whenever possible, in order to respect his growing or emerging autonomy. In our clinical experience, this was done from the age of 5 years onward if their state of health allowed it. We found that from the age of 7 years, children were able to understand when the language was adapted and could transcend their fear of undergoing a testicular biopsy. Another reason for the child's involvement is that the parental decision may be complicated by 'the possible imperative character of the offer because of the phenomenon of anticipated decision regret' (ESHRE Task Force on Ethics and Law, 2004), where they fear future regret of a decision taken at a time of crisis. It is also essential to fully inform all decision-makers, whether parents or children, whose legal ability to formally consent to or refuse a treatment varies internationally with jurisdictions, about possible complications or the lack of evidence about future use. Last but not least, public information about the availability of storage will have two ethical benefits: increasing the autonomous choice of affected families, and enhancing justice at societal level to enable fair access to the technique (Tournaye *et al.*, 2014).

While 86.7% of pediatric care providers believe that children of any age should be included in discussions about FP (Goodwin *et al.*, 2007), corresponding figures for parents regarding the involvement of their

children in the decisional process are not yet available. Our survey showed that >90% of parents considered their child above 12 years of age able to participate in the decisional process. However, only a quarter of prepubertal boys aged 7 years or more were considered mature enough to participate when the language was adapted. Interestingly, this proportion is in line with an identical proportion of children who felt anxious, mainly about their future fertility.

The quality of fertility counseling provided at the time of cancer diagnosis has been identified as a determining factor in the decision-making process (Schover et al., 2002a; Achille et al., 2006). This was especially evident in adolescents, who consider their participation in the decisional process as important (Quinn et al., 2011) and who must face the challenge of evaluating their future situation and potential fatherhood (Chapple et al., 2007). Furthermore, information and communication are key elements when it comes to legal consent, requiring the individual to understand the information given, its personal relevance, and then retain and use it to make an informed choice. This may be very difficult in any circumstance, but even more so in a pediatric population.

Our survey highlights a number of decisional factors concerning the quality of communication and content of information provided, which may help care providers to optimize FP clinical pathways. Among them, the completeness of information given to patients and parents appeared to be crucial for FP acceptance. Hence, increasing knowledge of the care team and providing sufficient human resources to adequately accompany the patients must become a priority. Since information tools were shown to reduce decisional conflict in patients (Huyghe et al., 2009), development of educational material adapted to the pediatric population may be of great help in facilitating open communication.

In our study, information was provided in the course of a face-to-face discussion, mainly by physicians and rarely (2.5% of cases) by nurses. Although nurse support was limited in this study, it appeared to be relevant for 16.6% of adolescents. However, because oncology nurses are in a prime contact position (Nagel and Neal, 2008), their cooperation should be sought when trying to optimize FP pathways. Indeed, most specialist nurses perceived such discussion to be well within their scope of practice, and only a minority (6%) felt this was an issue that should only be discussed with physicians (Vadaparampil et al., 2007). However, as knowledge of nurses was somewhat inadequate (Nagel and Neal, 2008), providing them with adapted educational tools is imperative.

Furthermore, our study showed family support to be more important than that of doctors, by contrast with studies in an adult population where the physician's support was considered most important (Eiser et al., 2011). This underlines different needs to be taken into account when optimizing FP pathways in a pediatric population.

Hope for future parenthood emerged as another positive decisional factor for FP acceptance. Indeed, besides their children's potential future parenthood being an important concern for parents (Van den Berg et al., 2007), the fact of discussing FP served to place the focus firmly on the future and procure a more positive outlook on survival (Achille et al., 2006). It also provided reassurance that the aim of treatment is cure (Wallace and Thomson, 2003; Wallace et al., 2005), thereby improving the quality of life at an already stressful time.

By contrast, pressure from doctors to reduce the time interval before cancer treatment had a negative impact on FP acceptance. Fear that banking may delay life-saving treatment is already known to be a reason to refuse FP in a cancer population (Schover et al., 1999). The

role of oncologists is paramount, since patients appear to follow recommendations on FP in the same way as any other aspects of their cancer treatment (Eiser et al., 2011). An optimal MCCP needs to give oncologists scope to ensure that FP is carried out without delaying the overall treatment plan. Close collaboration between oncologists and fertility specialists is, therefore, essential to protect the needs of cancer patients.

Since the aim of an optimized MCCP is to resolve a huge patient/parent and physician dilemma, potential involvement of a psychiatrist or psychologist familiar with infertility issues may be considered essential. Liaison psychiatry/counseling consultations allowing a more holistic approach to treating pediatric cancer patients and guiding discussions may have a huge impact on their future quality of life.

Limitations

In addition to the fact that this single-center survey from Belgium does not allow extrapolation of gathered information to other settings, a number of other limitations call for caution. One key issue is linked to the time interval between the actual FP procedure and the survey that relates to the so-called recall bias. The non-response error is another potential source of bias that is hard to quantify. The question is indeed whether the people who did not answer are different in any meaningful way from those who did. While the confidence interval or margin of error for the parents' responses was acceptable considering that the study was retrospective on a 10-year basis, it was slightly higher than the traditionally accepted 5–8% margin of error for the children's responses. This could, however, be explained by the fact that the majority (73%) of the patients are prepubertal boys.

Furthermore, because of the unavailability of preexisting validated questionnaires or gold standard adapted to this particular topic, further external validation is required. The obtained data could not be compared with an existing 'gold standard' and hence an extrapolation cannot be made.

Eventually, perceptions of patients and their parents may be altered based on whether the method of FP was successful or not. Due to the unavailability of techniques allowing fertility restoration from ITT cryopreservation and hence their success, we could not exclude this potential bias from our data analysis.

Conclusion

As the technology for effective FP methods in the pediatric population continues to improve at a rapid pace, understanding the factors that may affect their clinical application is vital for practitioners. Acknowledging issues that patients and parents face and familiarizing oneself with the needs of those undergoing fertility-threatening therapies give primary care providers indispensable quality management tools in the field of FP.

Reported expectations and feelings should be considered and used to improve the MCCP design and provide appropriate support for patients and parents.

Thus, discussions about FP should aim to provide full and understandable information and place the emphasis on the future as positive decisional factors. MCCP should accommodate sufficient resources to mitigate time pressure from oncologists and offer appropriate nurse and liaison pedopsychiatry/counseling support to enhance patient and parent quality of life at the time of diagnosis. This also points to the perennial

issue of equity of access for patients to preventive measures, which are not always given the same priority as acute medicine.

Larger multicentric studies are now warranted on the quality of interventions in children and adolescents facing fertility-threatening therapies, in order to provide appropriate information, education and support to patients, parents and care providers alike.

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Authors' roles

C.W. wrote the manuscript, interpreted and critically discussed the results, performed clinical evaluation of patients and was responsible for reproductive counseling during the study period. C.C. ran the focus groups, established the survey questionnaires, and collected and analysed the answers from patients and parents. P.L. performed clinical evaluation of patients and counseled patients and parents during the study period. F.S. reviewed the manuscript, with special input on ethical matters. A.R. performed statistical analysis of the data. L.R. critically reviewed the questionnaires with the local ethics committee, as well as the manuscript, with specific input as liaison psychiatrist for clinical pathways during the study period. B.B. conducted discussions on fertility preservation, reviewed the questionnaires, led critical discussions during result analysis and conducted a critical review of the paper.

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Conflict of interest

None declared.

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