

Original Article

Childbirth and fertility preservation in childhood and adolescent cancer patients: a second national survey of Japanese pediatric endocrinologists

Yoko Miyoshi^{1, 2}, Tohru Yorifuji^{2, 3}, Reiko Horikawa^{2, 4}, Ikuko Takahashi^{2, 5}, Keisuke Nagasaki^{2, 6}, Hiroyuki Ishiguro^{2, 7}, Ikuma Fujiwara^{2, 8}, Junko Ito^{2, 9}, Mari Oba¹⁰, Hiroyuki Fujisaki¹¹, Masashi Kato¹², Chikako Shimizu¹³, Tomoyasu Kato¹⁴, Kimikazu Matsumoto¹⁵, Haruhiko Sago¹⁶, Tetsuya Takimoto¹⁷, Hiroshi Okada¹⁸, Nao Suzuki¹⁹, Susumu Yokoya²⁰, Tsutomu Ogata²¹, and Keiichi Ozono¹

¹*Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan*

²*Childhood Cancer Survivor Committee of the Japanese Society for Pediatric Endocrinology*

³*Division of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka, Japan*

⁴*Division of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo, Japan*

⁵*Department of Pediatrics, Akita University Graduate School of Medicine, Akita, Japan*

⁶*Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*

⁷*Department of Pediatrics, Isehara Kyodo Hospital, Kanagawa, Japan*

⁸*Department of Pediatrics, Tohoku University Hospital, Sendai, Japan*

⁹*Department of Pediatrics, Toranomon Hospital, Tokyo, Japan*

¹⁰*Department of Medical Statistics, Faculty of Medicine, Toho University, Tokyo, Japan*

¹¹*Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan*

¹²*Consultation, Counseling and Support Service Center, National Cancer Center Hospital, Tokyo, Japan*

¹³*Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*

¹⁴*Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan*

¹⁵*Department of Pediatric Hematology and Oncology Research, National Center for Child Health and Development, Tokyo, Japan*

¹⁶*Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan*

¹⁷*Center for Clinical Research and Development, National Center for Child Health and Development, Tokyo, Japan*

¹⁸*Department of Urology, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan*

¹⁹*Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, Kanagawa, Japan*

²⁰*Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan*

²¹*Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan*

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Corresponding author: Yoko Miyoshi, MD, PhD, Department of Pediatrics, Osaka University Graduate School of Medicine, Yamadaoka 2-2, Suita, Osaka 565-0871, Japan E-mail: miyoshi@ped.med.osaka-u.ac.jp

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Abstract. Although existing guidelines recommend long-term follow-up of childhood cancer survivors (CCSs), their fertility has not been fully investigated in Japan. To address this issue, we organized a working panel consisting of medical specialists in foundation hospitals. We conducted questionnaire surveys targeting pediatric endocrinologists regarding reproduction in pediatric and adolescent cancer patients in collaboration with the CCS committee of the Japanese Society for Pediatric Endocrinology (JSPE). The first questionnaire was sent to 178 directors or councilors of the JSPE, and the second was sent to those who had provided answers on their experience with childbirth or fertility preservation. A total of 151 responses (84.8%) were obtained in the first survey. In the second survey, the response rate was 100% (39 respondents). There were 27 answers describing experiences with childbirth (16 from partners of male CCSs, 22 from female CCSs). A few cases of premature birth and low birth weight were reported. There were 25 answers describing experiences with fertility preservation; 21 were from male and 17 from female CCSs. It was mainly physicians who recommended fertility preservation. This nationwide questionnaire survey revealed that a limited number of Japanese pediatric endocrinologists had experience with childbirth and fertility preservation in CCSs. A further long-term follow-up study of their fertility is needed.

Key words: childhood cancer survivor, pediatric endocrinologist, questionnaire survey, childbirth, fertility preservation

Introduction

The incidence of childhood cancer is estimated as 2,000 to 2,500 cases per year in Japan. Because of improvements in the treatment and prognosis of cancer, the number of childhood and adolescent cancer survivors has increased (1). A significant proportion of survivors experience chronic health problems that result from cancer, its treatment, or both (2–4). The Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, issued by the Children's Oncology Group, are recognized resources for healthcare professionals who provide ongoing care to survivors of pediatric malignancies (5). Endocrine disorders are major problems that can occur after the cancer treatment is over (6, 7). Thus, the Japanese Society for Pediatric Endocrinology (JSPE) issued a follow-up guide in 2011, with a minor revision in 2016, regarding childhood cancer survivor (CCS) care with the aim of ensuring all physicians involved in clinical

practice undertake medical examinations for endocrine disorders (8). Chemotherapy, radiation therapy, and surgery may damage gonadal function in patients with malignant and non-malignant diseases (9–12). In 2013, the American Society of Clinical Oncology (ASCO) revised its guidelines for healthcare providers regarding fertility preservation in adults and children with cancer (13). Even though gonadal dysfunction, subfertility, and premature ovarian insufficiency (POI) have been recognized as important late effects in CCSs (14), few surveys on this topic have been conducted in Japan (15–18). Most CCSs in Japan do not receive outpatient follow-up care as adults, resulting in no data on their long-term prognosis. Therefore, we conducted a survey to reveal the current clinical practice among pediatric endocrinologists in order to investigate issues and unmet needs associated with gonadal function or fertility in CCSs (19). We subsequently conducted a second questionnaire survey to elucidate issues regarding childbirth and fertility preservation in CCSs; this survey

was based on the practical experience of Japanese pediatric endocrinologists.

Subjects and Methods

The first questionnaire was sent to 178 directors or councilors who are members of the JSPE (19). The questionnaire consisted of 36 closed-ended questions regarding the professional background of the respondents, their experience with the follow-up of pediatric cancer patients, their opinions regarding gonadal function or fertility in these patients, the current status of their clinical practice, and a free-entry field to describe what measures they believe should be taken in the future to maintain gonadal function or preserve fertility in pediatric cancer patients.

The second survey was sent to 39 directors or councilors of the JSPE who had experience with childbirth in CCSs or fertility preservation, based on their answers to the previous survey. The questionnaire consisted of 2 main questions. Question 1 targeted respondents who had indicated experience with childbirth in CCSs (or their partners if male). Information regarding the number of such births, the associated hospitals, the health issues in the offspring of CCSs (for men), and the health issues in offspring, as well as the course of pregnancy/childbirth (for women) was collected. Question 2 was used for respondents who indicated experience with fertility preservation in childhood and adolescent cancer patients. The respondents were asked to provide data on the number of each preservation treatment method experienced, the associated hospitals, and the persons who suggested the treatment. Finally, respondents were given an opportunity to write free-response comments about issues or impressions. These self-reporting questionnaires were sent by mail along with an addressed return envelope. The survey period lasted from October 2015 to December 2015.

This study was approved by the ethical review board at Osaka University Hospital (approval No. 15203). The work was conducted

as a joint study by the Working Panel Tasked with Compiling Evidence Regarding the Fertility of Long-Term Survivors of Cancer during Childhood or Adolescence and with Developing a Reproductive Medicine Network (organizer: Yoko Miyoshi) and the CCS Committee of the JSPE. This project was supported by a Health and Labour Sciences Research Grant (Research for Promotion of Cancer Control Program: H26-Ippan-016).

Results

Questionnaire responses

The first questionnaire was sent to 178 (139 male and 39 female) directors or councilors of the JSPE. A total of 151 valid responses were obtained, giving a response rate of 84.8%. The second questionnaire was sent to 39 respondents who had indicated experience of childbirth or fertility preservation in CCSs in the first survey. We received 35 responses received from the 39 subjects who were sent the second survey. However, in some cases, several or all respondents from the same hospital submitted their answers collectively. Thus, the response rate was 100%. Therefore, the statistics below are given not as the number of respondents or the number of hospitals, but as the number of answers.

Childbirth in CCSs

Sixteen of the 35 (45.7%) answers indicated experience of childbirth in partners of male CCSs (Table 1). The numbers of births experienced up to now were 1 ($n = 8$), 2 ($n = 5$), 3 ($n = 1$), 18 ($n = 1$), and unknown ($n = 1$). The experience was acquired at the respondent's current hospital ($n = 8$), at another hospital ($n = 7$), or both ($n = 1$).

Twenty-two of the 35 (62.9%) answers indicated experience of childbirth in female CCSs (Table 2). The numbers of births experienced so far were 1 ($n = 6$), 2 ($n = 6$), 3 ($n = 3$), 4 ($n = 3$), 5 ($n = 2$), 8 ($n = 1$), and 21 ($n = 1$). The experience was gained at the respondent's current hospital

Table 1. Childbirth in partners of male CCSs

No. of childbirths experienced	No. of answers (n = 16)
1	8
2	5
3	1
18	1
Unknown	1

CCS, childhood cancer survivor.

Table 3. Fertility preservation in male CCSs

No. of patients given fertility preservation	No. of answers (n = 21)
1	4
2	6
3	2
5	1
6	2
Multiple	4
Unknown	2

(n = 13), at another hospital (n = 6), or both (n = 3). We eliminated any overlapping answers and consolidated them. Experience was gained in 21 hospitals, of which 6 were major pediatric cancer hospitals and 1 was a core pediatric cancer hospital.

Health issues in pregnancy and childbirth in CCSs

Of the 16 answers indicating experience with childbirth in partners of male CCSs, 10 reported no health issues, none reported health issues, and 6 indicated that the responders did not know. Of the 22 answers indicating experience of childbirth in female CCSs, 14 reported no health issues, 3 reported health issues in the child alone, 1 reported health issues in the mother alone (significant hemorrhage due to postpartum placental retention), 1 reported health issues in both the mother and child (threatened premature labor, low birth weight, and respiratory distress

Table 2. Childbirth in female CCSs

No. of childbirths experienced	No. of answers (n = 22)
1	6
2	6
3	3
4	3
5	2
8	1
21	1

Table 4. Fertility preservation in female CCSs

No. of patients given fertility preservation	No. of answers (n = 17)
1	3
2	3
3	1
4	1
5	1
8	1
10–15	1
26	1
Multiple	3
Unknown	2

syndrome), and 3 indicated that they did not know if there were any health issues. Specific health issues were described in the free-style comments for 8 answers. Six premature births were reported, and these occurred in mothers who had received stem cell transplantation (n = 4) and/or abdominal radiation (n = 4). There was 1 neonatal death, 1 spontaneous abortion, and 1 child with a cleft palate; however, there was no major fetal malformation.

Fertility preservation in male CCSs

Twenty-one of 35 (60.0%) answers indicated experience of fertility preservation in male CCSs. The numbers of patients experiencing fertility preservation based on these positive answers are detailed in Table 3. Sixteen answers indicated experience with sperm cryopreservation, and the numbers of patients detailed in these positive

answers were 1 (n = 7), 2 (n = 4), 3 (n = 2), 5 (n = 1), and 'unknown' (n = 2). Two answers also indicated experience with testicular tissue cryopreservation, but these answers referred to the same patient. Ten answers indicated experience with gonadal (testicular) shielding before radiotherapy, and the numbers of patients described in these positive answers were 1 (n = 2), 2 (n = 1), 5 (n = 2), multiple (n = 3), and unknown (n = 2). There were no answers indicating other forms of male CCS fertility preservation.

Fertility preservation in female CCS

Seventeen of 35 (48.6%) answers indicated experience with fertility preservation in female CCSs. The patient numbers experiencing fertility preservation according to these positive answers are detailed in Table 4. Three answers indicated experience with oocyte cryopreservation, and the numbers of patients given in these positive answers were 1 (n = 2) and 2 (n = 1). Four answers indicated experience with ovarian cryopreservation, and the numbers of patients detailed these positive answers were 1 (n = 2), 3 (n = 1), and 10–15 (n = 1). Nine answers indicated experience with gonadal (ovarian) shielding before radiotherapy, and the numbers of patients described in these positive answers were 1 (n = 2), 2 (n = 1), 4 (n = 1), 6 (n = 1), multiple (n = 2), and unknown (n = 2). Four answers indicated experience with ovarian transposition before radiotherapy, and the numbers of patients seen for undergoing this procedure were 1 (n = 1), 2 (n = 2), and multiple (n = 1). Seven answers indicated experience with gonadal suppression with a luteinizing hormone releasing hormone analog, and the numbers of patients detailed in these positive answers were 1 (n = 3), 2 (n = 2), 20 (n = 1), and multiple (n = 1). There were no answers indicating other forms of female CCS fertility preservation.

Person who proposed fertility preservation

Of the 25 answers indicating experience with fertility preservation in male and/or female

CCSs, fertility preservation was proposed by the medical care provider (n = 21), the patient (n = 1), the patient's guardian (n = 1), or was unknown (n = 4) [multiple answers were accepted].

Details of childbirth and issues regarding fertility preservation

Twenty-seven (77.1%) answers included information detailed as free-response comments. Because of the retrospective nature of this study, it is difficult to be sure of the cause; however, health issues were reported both in the mother (at birth) and in her children. Both premature birth and low birth weight were speculated to be caused by the radiation to the uterus in childhood. Various difficulties and problems with fertility preservation were reported. Although rare, unexpected childbirths were reported at 6 hospitals as a result of natural conception in women receiving estrogen replacement therapy (Kauffman therapy) for POI caused by cancer treatment.

Discussion

This questionnaire survey revealed that a limited number of Japanese pediatric endocrinologists have experience with childbirth and fertility preservation in childhood and adolescent cancer patients. The second questionnaire was sent to the respondents of the previous survey who had indicated experience with childbirth (or childbirth in partners for men) or fertility preservation. Although the sample size for the secondary survey was small (n = 39), its reliability is strengthened by the high rate of responses (151 out of 178: 84.8%) from the previous nationwide study supported by the JSPE (19). There were 35 responses to the secondary survey, which equates to a 100% response rate when taking into account respondents from the same institution collating their responses. This excellent response rate indicates a high awareness of the importance of these issues among Japanese pediatric endocrinologists. In

addition, it is noteworthy that many responses were obtained from collaborations between pediatric endocrinologists and pediatric oncologists working at the same hospitals.

Twenty-seven of the 35 (77.1%) answers indicated experience with childbirth in CCSs. One physician working at the cancer center reported experience including young adult patients; therefore, the number of births was much larger than that reported by others. A smaller number of answers were obtained about childbirth in partners of male CCSs than in female CCSs. It is unlikely that this is because of a lower rate of childbirth among the partners of male CCSs; rather, it indicates that less information was obtained about childbirth among the partners of male CCSs, or that there were a greater number of male CCSs who were lost to follow-up prior to the birth of their child. For example, 6 out of 16 answers (37.5%) about health issues in children born to male CCSs were unknown. One free-response comment was, "I do not think there are any health issues, but I have not specifically asked on them". In contrast, more information was collected about childbirth among female CCSs because the patient herself experiences pregnancy and birth. The number of unknown responses among female CCSs ($n = 3$, 13.6%) was lower than that of male CCSs. It is unclear whether these CCSs were adequately followed-up during pregnancy. A few cases of premature birth and low birth weight were reported. It has been reported that CCSs do not have an increased risk of congenital anomalies (20, 21), although female CCSs have a higher risk of premature birth and a low birth weight after radiation exposure to the uterus (22–25). It is not known how many of the pregnancies described in this survey were facilitated by assisted reproductive technology; further research is required to elucidate the degree of infertility in CCSs.

Notably, multiple responses described pregnancy in CCSs undergoing estrogen replacement therapy. Pediatric endocrinologists usually explain to these patients that POI makes

conceiving almost impossible; however, these results demonstrate that this may not be the case. Further surveys on this issue may improve medical care for female cancer survivors.

The most common form of fertility preservation described was sperm cryopreservation. This is a relatively simple, long-established, and non-invasive procedure in which adult men provide semen samples for cryopreservation. However, as described in a free-response comment, collecting sperm from young patients is problematic and may involve significant embarrassment and other forms of psychological impact. Even if sperm collection was possible, cryopreservation expenses may have become a burden for a prolonged period until patients desired children. The young age of patients is a key factor affecting these issues for both sexes, and healthcare providers must be aware of the potential physical, psychological, and economic burdens. Many other issues are also highlighted in the surveys. In terms of the healthcare system, the quality varies among hospitals and can be affected by a lack of specialists in the same hospital, medical expenses, doctors' transfer, movement of young people from rural to urban areas, and the difficulty of collecting historical information. In terms of the treatment itself, issues include different treatment regimens, differences in diseases, a lack of information provided to the patients, and cessation or completion of follow-up.

In almost all cases, it was a doctor who proposed fertility preservation. Faced with imminent cancer treatment, both children and their guardians are hard-pressed to consider fertility preservation treatment. Compared with Western countries, discussion of fertility issues is insufficient in Japan (26). To increase such opportunities for patients, the ASCO guidelines revised in 2013 and oncofertility, an important collaboration between reproductive medicine and oncology, should be widely understood (13, 27). To this end, we are aiming to perform various

trials and research, construct medical networks, offer information using booklets and the internet, open consulting services for oncofertility, and educate both healthcare providers and cancer patients (26, 28, 29).

There are some limitations in this questionnaire survey. The sample size is small, and we could not gather information from institutions that did not have a pediatric endocrinologist. Similar long-term follow-up studies on a larger scale should be performed from the viewpoints of specialized pediatric oncologists, gynecologists, and urologists. A prospective nationwide collaborative study is anticipated in Japan.

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