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Original Article

Attitudes towards human fetal tissue research: Survey of researchers and the public in Japan



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A R T I C L E I N F O

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ABSTRACT

Introduction: The rules for human fetal tissue (HFT) research in Japan are unclear. *Methods:* In this paper, we conducted a web survey to examine the attitudes of Japanese researchers (n=535) and the public (n=3,000) toward HFT research. *Results:* The results demonstrated that 5.8% of researchers and 18.8% of the public explicitly opposed HFT research, and 71.8% of the researchers thought that the rules for HFT research need to be clarified. Even among researchers who intended to consider conducting HFT research, 74.2% responded that the rules should be clarified. Although different from attitudes to make decisions regarding HFT donation, being non-religious and in their reproductive age among women in the public group were factors for accepting

attitudes toward HFT research. *Conclusion:* To establish the rules, it is necessary to develop a system that can adequately protect vulnerable women who are asked to provide HFT.

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1. Introduction

Human fetal tissue (HFT) obtained from elective abortions has been regarded as an important research tool [1]. However, research using HFT has been controversial due to the ethical issues of using the fetus as it is developing into a human being, especially in the US in conjunction with the abortion dispute [2]. The Trump administration, which had a significant pro-life support base, drastically

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restricted federal funding for research involving HFT obtained from elective abortions. In 2019, intramural National Institute of Health (NIH) researchers were forbidden from conducting such research, while extramural researchers were required to provide scientific justification for HFT use and descriptions of processes for HFT collection and informed consent (IC) processes, which were reviewed by the Ethics Advisory Board of the NIH appointed by the Department of Health and Human Services (HHS) secretary. In the first and last board meeting held on July 31, 2020, the board recommended the HHS secretary to withhold funding from 13 of the 14 applications reviewed [3]. Following the board's decision, the International Society for Stem Cell Research (ISSCR) sent the board a letter signed by 90 scientific, medical, and patient organizations that explained the importance of HFT research [4]. After the establishment of the Biden administration, intramural NIH researchers were allowed to conduct HFT research, and the Ethics Advisory Board system was abolished. However, researchers are still required to provide detailed scientific justification for HFT use and descriptions of processes for HFT collection and disposal [5].

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Abbreviations: AMED, Japan Agency for Medical Research and Development; HFT, human fetal tissue; HHS, Department of Health and Human Services; IC, informed consent; iPSCs, induced pluripotent stem cells; ISSCR, International Society for Stem Cell Research; JSRM, Japanese Society for Regenerative Medicine; NECTAR, Network of European CNS Transplantation and Restoration; NIH, National Institute of Health; OR, odds ratio; 95% CI, 95% Confidence Intervals.

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HFT research has been conducted for a considerable period, and regulatory frameworks were established early on. The first set of guidelines was the Peel Code, which was issued by the UK government in 1972 [6]. Subsequently, as research on human tissue transplantation progressed, the UK government issued the Polkinghorne Report in 1989, which detailed the conditions for conducting HFT research, including obtaining consent from women for HFT donation [7]. Although the Polkinghorne Report lack legal authority, researchers are advised to adhere to it [8]. The Polkinghorne Report has influenced various organizations' guidelines [9], such as the Network of European CNS Transplantation and Restoration (NECTAR) guidelines of 1994. The NECTAR guidelines stipulate that fetuses must have died due to legal abortion and should not be kept alive artifically to obtain useable material. The decision to terminate a pregnancy should not be influenced by HFT research, and the need for HFT should not influence the timing or method of abortion. Additionally, obtaining consent from women involved in HFT donation is necessary. All hospital or research staff involved in any procedure must be fully informed. Procuring HFT must not involve profit or remuneration; other related stipulations also apply [10]. In its 2021 guidelines, the ISSCR recommends that researchers refer to the NECTAR guidelines when conducting HFT research to ensure that the potential for HFT donation does not affect abortion decisions. The guidelines also state that "informed consent for fetal tissue procurement and research should be obtained from the woman only after her decision to legally terminate her pregnancy but before the abortion procedure, or after a spontaneous abortion. Medical procedures must not put the woman at any increased risk solely to facilitate the research use of donated fetal tissues. Clinicians obtaining informed consent and clinics at which informed consent is sought may not profit from the procurement of fetal tissues for research [11]." When conducting HFT research, various issues identified in these guidelines must be considered.

In Japan, artificial abortion is prohibited by the Criminal Code in principle; however, under the Maternal Protection Law, if certain requirements are met, artificial abortions are allowed [12]. These requirements include cases in which the continuation of pregnancy and delivery would be detrimental to the health of the women for physical or economic reasons, or in the case of pregnancy resulting from rape. In addition to these requirements, spousal consent is required in principle. Although the restrictions on abortion appear to be strict, as there is no requirement to submit a medical certificate or to declare income, women can undergo abortion procedures on demand if they are less than 22 weeks pregnant. In 2020, the number of artificial abortions was 141,433 [13] compared to 840,835 births [14]. Thus, Japan has a permissive attitude for artificial abortion, and many artificial abortions are performed. Although there were abortion disputes in the 1970s and 1980s [15], they were far more moderate than those in the US. The use of HFT for research is allowed to a certain extent by the Postmortem Examination and Corpse Preservation Act in 1949 if the fetus is 12 weeks or longer in gestation, but the act does not specify any procedures for conducting such research including how to obtain IC. Subsequently, there is no clear law defining whether HFT can be used in research if the fetus is less than 12 weeks gestation.

Under such circumstances, human fetuses have been used in medical research. In the aftermath of the thalidomide drug incident, a project was initiated in 1961 to collect human embryos and fetuses, accumulating over 40,000 cases, known as the Kyoto Collection of Human Embryos [16]. In 1987, the Japan Society of Obstetrics and Gynecology published "A View on the Pros and Cons of Using Organs of Dead Fetuses and Newborn Babies for Research," the only Japanese guidelines on HFT research [6]. However, they are too simplistic and do not detail specific procedures for obtaining informed consent. In 2002, the Japanese government established the Special Committee for the Establishment of Guidelines for Clinical Research Using Human Stem Cells. The committee discussed the research on transplanting HFT into patients. During the discussion, the committee chair shared the results of his survey in which 15 of the 606 sites indicated that they had conducted basic regenerative medicine research using HFT, and seven sites indicated that they would soon be conducting a study in which HFT would be implanted in patients [17]. However, the committee could not reach a consensus, and a provision was added to exclude HFT from the guidelines established in 2006, thereby imposing a moratorium on it [6,17]. In 2014, the guidelines were repealed, and the Act on the Safety of Regenerative Medicine was enacted [18]. However, the act does not mention HFT (but does not place a provision excluding HFT from the law); therefore, it is unclear whether the moratorium is still in place.

Meanwhile, laboratory-based HFT research can and has been conducted in accordance with general guidelines for medical research involving human subjects (the current Ethical Guidelines for Medical and Biological Research Involving Human Subjects) [19]. However, the guideline does not mention HFT and does not specify the conditions for conducting HFT research, including IC procedures for HFT collection. Therefore, the possibility of conducting HFT research is left to the decision of the ethics review committee based on these guidelines. Due in part to the ambiguity of the rules, HFT research has not been active in Japan. However, the ambiguity of the rules means that there is no system to adequately protect the vulnerable women who need to have artificial abortions when they participate in research. Furthermore, the lack of standards to refer to in conducting research activities also confuses researchers.

In clarifying the rules, we must understand what people think of HFT research. Several attitude surveys were conducted in Western countries in the 1990s. For example, a survey of 434 Canadian physicians suggested that there was general approval for the transplantation of HFT [20]. In a UK survey of 108 women about to have a therapeutic abortion, 167 women who had had a pregnancy terminated in the past, and 419 women who had never had an artificial abortion, most of the women (94%) were in favor of HFT research regardless of their past experiences [21]. In a survey of 266 Canadian women living in an urban area, 12.0% of them responded that they would be more likely to have an artificial abortion if they could donate HFT for transplantation, 66.9% reported that they would not be more likely to do so, and 21.1% were uncertain [22]. In recent years, a UK study that interviewed 23 women who had had artificial abortions found that most participants wanted the opportunity to access information about disposal of HFT but did not favor being asked to make decisions about disposal [23]. A US study that interviewed 79 pregnant and recently pregnant women found that the majority generally supported HFT research [24]. According to a study with 25 women living in Hawai'i who reported undergoing an artificial abortion in the previous six months, 18 women were open to donating HFT from their abortion for research, and altruism was a common motivator [25]. In previous studies in the Western countries mentioned above, women generally gave positive evaluations of HFT transplants or HFT research. However, a UK study that involved focus group interviews with 31 women who had had abortions and 10 women who had not had abortions found that the initial enthusiasm for donating HFT decreased as participants gained more information and began to consider the potential implications of their decision [8].

In Japan, a general public survey (n=217) demonstrated that while many were positive about using HFT for regenerative medicine, 30% thought that aborted fetuses should not be used for any research or treatment [26]. However, this survey was conducted in 2006 on the premise of transplanting HFT to patients, and public awareness may have changed with the development of medical research since then. In addition, if there is a significant gap between the attitudes of researchers who may conduct HFT research and those of the public, communication between the two will be necessary when clarifying the rules for HFT research. Therefore, it is necessary to understand the attitudes of regenerative medicine and stem cell researchers, although no such previous studies have been conducted. Subsequently, in this study, we surveyed the attitudes of Japanese researchers engaged in stem cell-related research activities and of the public. For a detailed analysis, when collecting data for the female group in the public who had (or could have had) the possibility to be asked to provide HFT, we conducted the analysis separately for male and female participants in the public group. The analysis also examined the relationship with religion, a factor that has influenced abortion and HFT research disputes, particularly in the US.

2. Method

2.1. Research participants and data collection

We conducted web-based attitude surveys of researchers and members of the public. The survey questionnaires differed between the two groups.

2.1.1. Researchers

A link to the survey screen was sent to all members of the Japanese Society for Regenerative Medicine (JSRM) via email and mail. As of 2022, the number of members in the JSRM is 6,052. In addition, the same link was emailed to researchers conducting stem cell-related research, supported by Project for Regenerative/ Cellular Medicine and Gene Therapies in Japan Agency for Medical Research and Development (AMED), which is a government fund. The number of researchers supported by AMED, to whom emails were sent, was 345. The survey period was from March 2 to 31, 2022.

2.1.2. The public

For the public group, the criteria of participants were those aged between 20 and 69. The target number of respondents was 3,000. Participants were recruited from those who had voluntarily registered with a panel of the Nippon Research Center for web-based surveys in response to online affiliate advertising. This private company conducts research and studies on markets, public opinion, and other related topics on a contract basis. We commissioned the Nippon Research Center to undertake the data collection, which was conducted from January 5 to 13, 2022, until the number of participants reached 3,000, with age and sex consistent with the distribution of the Japanese population.

2.2. Ethical statements

The surveys were conducted with the approval of the Ethics Review Committee of the University of Yamanashi (approval number: CS0005). As they were web-based surveys, IC was obtained from all participants by requesting them to click on a checkbox on the online platform.

2.3. Survey items

Our surveys asked for opinions on several stem cell or embryorelated research activities, including creating an embryo by gamete generated from induced pluripotent stem cells (iPSCs), using these embryos for pregnancy, creating an embryo model from iPSCs, creating a human-pig chimera, using the organ of these chimera animals for organ plantations in a patient, using an embryo undergoing mitochondrial replacement for pregnancy, human embryo culture beyond 14 days, and HFT research. In this paper, we focus on the questions about HFT research.

Our research team developed the questionnaires, which included members who have conducted similar attitude surveys and is stem cell research scientist. The designs were such that each time a respondent answered a question, the screen would change, and the respondent could not return to the previous screen. The web-based survey platform was the Nippon Research Center's system for researchers and the public. Background information on these research activities, including the status of domestic regulations, was also presented. In our public survey, we used an original video explaining the questions (video available from: https://figshare.com/articles/media/Explanation_by_video/19977308).

2.3.1. Questions for the researchers

Questions for the researchers regarding HFT research were as follows. First, we asked about their plan to conduct HFT research: "Would you consider conducting research activity involving HFT obtained from artificial abortions in the future, or if you are currently conducting such research, would you consider continuing to do so? Please answer on the assumption that the tissue would not be transplanted into the patient." The answer choices were "Would consider conducting," "Don't know," and "No plan to conduct."

For those who answered "No plan to conduct," we then asked about their acceptability of HFT research, "Do you think Japanese rules should be changed to prohibit such research?" The answer choices were "No change, should remain allowed," "Change, should be prohibited," and "Cannot judge."

We then asked their opinion about the Japanese rules, "Do you think that the rules for the collection and use of HFT should be clarified in Japan?" The answer choices were "Clarification of the rules is necessary," "Clarification of the rules is not necessary," and "Cannot judge." In addition, we asked demographic questions about their sex and age. See Supplemental Material 1 for a partial English translation of the questionnaire, including the background explanations of the questions.

2.3.2. Questions for the public

For the public, we asked about their acceptability of HFT research, "Do you think these types of experiments (experiments involving tissues from artificially aborted fetuses) should be allowed in Japan?" The answer choices were "Should be allowed," "Should be prohibited," and "Cannot judge."

In addition, we asked questions about their sex, age, religion, and education level. See Supplemental Material 2 for a partial English translation of the questionnaire, including the background explanations of the questions.

2.4. Data analysis

First, we presented the characteristics of the respondents. Second, a simple tabulation of the researchers' plans to conduct HFT research and a simple tabulation of their acceptability of HFT research were presented. Third, we presented a simple tabulation of the public acceptability of HFT research, and then compared the percentage of those who explicitly opposed HFT research between researchers and the public for whom a simple comparison could be made with different configurations of the questions. A chi-square test was used for the comparison. For researchers, we considered

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	archers (II=535).	
	n	%
Age		
20-29	21	3.9
30-39	104	19.4
40-49	172	32.1
50-59	161	30.1
60-69	66	12.3
70-	11	2.1
Sex		
Male	413	77.2
Female	122	22.8

those who answered "Change, should be prohibited" as those who explicitly opposed HFT research. For the general public, we considered those who responded "Should be prohibited" as those who explicitly opposed it.

Fourth, the researchers' opinions on whether the Japanese rules on HFT research should be clarified or not were presented in a cross-tabulation, with those who explicitly opposed HFT research, those who intended to consider conducting HFT research, and others. Fifth, the general public was divided into male and female groups to present the level of acceptability of HFT research. To compare the responses of these two groups, a chi-square test was performed and p-values were adjusted using the Bonferroni correction. Sixth, we divided the general public by sex and performed a multinomial logistic regression analysis, adjusted for age and education, to examine whether religion affects the acceptability of HFT research. Responses to religion were reorganized into "Non-religious" and "Religious belief." Those who answered "I don't want to answer" were excluded from the analysis. Age was divided into two groups based on female reproductive age (20-49 age group and 50-69 age group). Education level was dichotomized between "With a university/college degree" and "Without a university/college degree."

The significance level was set to 0.05 (5%) in each analysis. Data were analyzed using IBM-Statistical Package for the Social Sciences (version 27).

Table 2

Tuble 2				
Characteristics	of the	public	by sex	(n=3,000).

3. Results

3.1. Characteristics of research participants

Table 1 illustrates the characteristics of researchers, and Table 2 illustrates the characteristics of the public by sex. In the researcher group, there were 588 respondents, of whom 542 were members of the ISRM. Journalists and other categories are also members of the society; 53 respondents who answered that they were not engaged in research activities were excluded, leaving 535 respondents for the analysis. As several members of the JSRM were conducting research with support from AMED, it was impossible to ascertain whether those who did not respond to the survey link from AMED were members of the JSRM. Thus, the exact response rate was unclear. However, of the JSRM members, 8.96% responded to our survey.

In the public group, there were 3,000 respondents as of the research design. Thus, the age and sex ratios of the public were consistent with the population distribution in Japan.

Researchers were mostly in their 40s-50s, fewer were in their 20s, and more were male. Religion, asked only of the general public, was most frequently non-religious, followed by Buddhism. Although it appears that many respondents to our survey were non-religious (64.2% in males, 69% in females), another survey conducted in Japan also found that 61% of respondents were nonreligious in 2008, and this was 62% in 2018 [27].

3.2. Researchers' plan to conduct HFT research and acceptability

Table 3 illustrates researchers' plans to conduct HFT research and their acceptability. In total, 128 (23.9%) researchers responded, "Would consider conducting," 114 (21.3%) responded, "Don't know," and 293 (54.8%) responded, "No plans to conduct."

Then we asked about the acceptability of HFT research to those who responded, "No plan to conduct," and 173 (59.0% of 293, 32.3% of 535) researchers responded, "No change, should remain allowed," 89 (30.4% of 293, 16.6% of 535) researchers responded "Cannot judge," and 31 (10.6% of 293,5.8% of 535) researchers responded, "Change, should be prohibited."

		Male (n=1,517)		Female (n=1,483)	
		n	%	n	%
Age					
20-29	Female reproductive age	244	16.1	231	15.6
30–39		279	18.4	267	18.0
40-49		364	24	351	23.7
50-59	Not female reproductive age	331	21.8	324	21.8
60-69		299	19.7	310	20.9
Religion					
Non-religious		974	64.2	1024	69.0
Buddhism	Religious belief	371	24.5	303	20.4
Christianity		16	1.1	33	2.2
Shinto		52	3.4	22	1.5
Islam		1	0.1	2	0.1
Other		4	0.3	4	0.3
I don't want to answer		99	6.5	95	6.4
Education level					
Graduate school	With a university/college degree	100	6.6	46	3.1
University/college		806	53.1	517	34.9
(Two years) junior college	Without a university/college degree	25	1.6	267	18.0
Vocational school/technical school		157	10.3	200	13.5
High school		391	25.8	424	28.6
Junior high school		38	2.5	29	2.0

Table 3

Researchers' plan to conduct HFT research and their acceptability.

Plan to conduct HFT research Degree of acceptance of HFT research						
	n	% of 535		n	% of 293	% of 535
Would consider conducting	128	23.9				
Don't know	114	21.3				
No plan to conduct	293	54.8	No change, should remain allowed	173	59.0	32.3
			Cannot judge	89	30.4	16.6
			Change, should be prohibited	31	10.6	5.8

Table 4

Public acceptability of HFT research.

Should be allowed Cannot judge		Should be prohibited			
n	%	n	%	n	%
1363	45.4	1074	35.8	563	18.8

Table 5

Researcher's acceptability of HFT research and their opinion about clarification of the Japanese rules.

	All: n (%)	Explicitly opposed HFT research: n (%)	Intended to consider conducting HFT research: n (%)	Other: n (%)
Clarification of the rules is necessary Clarification of the rules is not necessary	384 (71.8) 64 (12)	29 (93.5) 1 (3.2)	95 (74.2) 24 (18.8)	260 (69.1) 39 (10.4)
Cannot judge	87 (16.5)	1 (3.2)	9 (7.0)	77 (20.5)

3.3. Public acceptability of HFT research and comparison to researchers

Table 4 illustrates the public acceptability of HFT research and illustrates that 1363 (45.4%) respondents answered "Should be allowed," 1074 (35.8%) respondents answered "Cannot judge," and 563 (18.8%) respondents answered "Should be prohibited."

A comparison of the percentage of those who explicitly opposed HFT research between researchers and the public had a significant difference; 5.8% for researchers and 18.8% for the general public (p<0.01).

3.4. Researchers' opinion about clarification of Japanese rules

Table 5 illustrates the researcher's opinions about whether or not the Japanese rules on HFT research should be clarified. Also demonstrated here is a tally of the group crosses that explicitly opposed HFT research, intended to consider conducting HFT research, and others. It found that 71.8% of all respondents, 93.5% of those who explicitly opposed HFT research, 74.2% of those who intended to consider conducting HFT research, and 69.1% of other thought the rules needed clarification. At least 93.5% of those who explicitly opposed HFT research would like to see the rules prohibiting HFT research. In addition, at least 74.2% of those who intended to consider conducting HFT research would like to see the rules allowing HFT research.

3.5. Public acceptability of HFT research by sex

Table 6 illustrates the public acceptability of HFT research by sex. For both groups, the percentages were "Should be allowed,"

Table 6

Public acceptability of HFT research by sex.

	Should be allowed		Should prohibi	be ted*	Cannot judge*		
Male	n 699	% 46.1	n 310	% 20.4	n 508	% 33.5	
Female	664	44.8	253	17.1	566	38.2	

Notes: *p<0.05; A chi-square test was performed and the p-values were adjusted for the Bonferroni correction.

"Cannot judge," and "Should be prohibited," in that order. Compared to male and female respondents, the percentages of "Should be allowed" and "Should be prohibited" were higher for males, while the percentage of "Cannot judge" was higher for females. Significant differences were found between males and females for "Should be prohibited" and "Cannot judge" (p<0.05).

3.6. Factors influencing public acceptability of HFT research

Table 7 presents the results of an analysis of the association between the public acceptance of HFT research and religion by sex, adjusted for age and education. Significant differences among females were found in age (OR:1.43, 95% CI: 1.13-1.82) for the comparison between "Should be allowed" and "Cannot judge," and in religion (OR: 1.49, 95% CI: 1.05-2.09) for the comparison between "Should be prohibited" and "Cannot judge." Thus, those aged 20-49 tended to answer "Should be allowed" rather than "Cannot judge" more often than those aged 50-69. Those in the religious belief group tended to answer "Should be prohibited" rather than "Cannot judge" more often than those who were non-religious. The only significant difference for males was in education (OR:1.42, 95% CI: 1.11–1.81) for the comparison between "Should be allowed" and "Cannot judge." Thus, those with a university/college degree tended to answer "Should be allowed" rather than "Cannot judge" more often than those without a university/college degree.

4. Discussion

The percentage of those who explicitly opposed HFT research was higher among the public than among researchers. Therefore, the research community needs to engage in a dialogue with the public in developing the rules that define the conditions for HFT research. Positive attitudes toward research activities were more prevalent among researchers than among the public, consistent with the results of surveys of attitudes toward chimeric research conducted in Japan [28,29]. In previous Japanese study conducted in 2006, 30% of 217 respondents thought that aborted fetuses should not be used for any research or treatment [26]. In our survey, respondents who explicitly opposed to HFT research in the public

Table 7

Factors influencing public acceptability of HFT research.

		Crude			Adjusted		
		OR*	95% CI**	р	OR	95% CI	р
Should be	allowed (Ref. Cannot judge)						
Female	Religion ¹ : Religious belief (Ref. Non-religious)	1.19	0.91-1.55	0.22	1.26	0.95 - 1.64	0.12
	Age: 20–49 (Ref. 50–69)	1.44	1.14 - 1.82	< 0.01	1.43	1.13-1.82	< 0.01
	Education: With university/college degree (Ref. Without university/college degree)	1.25	0.98 - 1.59	0.07	1.19	0.93-1.52	0.17
Male	Religion ² : Religious belief (Ref. Non-religious)	0.88	0.69 - 1.14	0.35	0.89	0.69-1.15	0.38
	Age: 20–49 (Ref. 50–69)	1.10	0.87-1.39	0.42	1.18	0.93-1.51	0.18
	Education: With university/college degree (Ref. Without university/college degree)	1.41	1.12 - 1.79	< 0.01	1.42	1.11-1.81	< 0.01
Should be	prohibited (Ref. Cannot judge)						
Female	Religion ¹ : Religious belief] (Ref. Non-religious)	1.48	1.05 - 2.07	0.03	1.49	1.05 - 2.09	0.02
	Age: 20–49 (Ref. 50–69)	1.01	0.74 - 1.37	0.97	1.01	0.74-1.38	0.94
	Education: With university/college degree (Ref. Without university/college degree)	1.27	0.93 - 1.74	0.14	1.28	0.93-1.76	0.13
Male	Religion ² : Religious belief (Ref. Non-religious)	1.01	0.73-1.38	0.98	0.97	0.70-1.33	0.82
	Age: 20–49 (Ref. 50–69)	0.78	0.59 - 1.04	0.09	0.80	0.60 - 1.08	0.15
	Education: With university/college degree (Ref. Without university/college degree)	1.26	0.94-1.68	0.12	1.19	0.88-1.61	0.25

Notes: ¹95 respondents who answered "I don't want to answer" to the religion were excluded from the analysis; ²99 respondents who answered "I don't want to answer" to the religion were excluded from the analysis; *OR=Odds Ratio; **95% CI: 95% Confidential Interval.

was 18.8%. It is unclear whether the Japanese public acceptance of HFT research has increased over the past 15 years. However, about 80% of the respondents in the previous study were 50 years of age or older. Among the female respondents to our survey, the 20–49 years old group indicated a tendency to be more accepting of HFT studies. Thus, one of the major reasons for this gap may be due to the different age distribution of respondents.

In total, 23.9% of the researchers in our survey indicated that they would consider conducting HFT research. Even among researchers who intended to consider conducting HFT research, our survey demonstrated that many were seeking clarification of the rules. In other words, the lack of clarity in the rules has been confusing to many researchers. However, some researchers thought the clarification was not necessary, as 18.8% of those who intended to consider conducting HFT research responded that clarification was unnecessary. These researchers may fear the possibility of complex procedures for conducting HFT studies. Therefore, while building a system to protect vulnerable women, it is also important not to require from researchers overly complex procedures to the extent that it has nothing to do with the protection of these women.

Among women in the public group, those who held religious beliefs tended to answer "Should be prohibited" rather than "Cannot judge." However, the leaders of Buddhism, which constitutes the majority of religious beliefs in Japan, have not taken a particularly clear position on artificial abortion, unlike the leaders of Catholicism. Women aged 20–49 were more likely to answer "Should be allowed" than "Cannot judge" compared to women aged 50–69. Therefore, within the scope of our survey results, nonreligious women in their reproductive ages tend to have a more accepting attitude toward HFT research. However, this finding is not immediately applicable to HFT donations. This is because the religion of the woman is not asked in the donation process and because not all non-religious people are positive about HFT research. In addition, the acceptability of HFT research differs from the question of whether one agrees to donate HFT.

Among the general public, 35.8% responded, "Cannot judge," which is not a small percentage. This is not limited to HFT research but is characteristic of the Japanese attitude toward science and technology. For example, in an international comparison of public attitudes toward whether regenerative medicine research should be promoted (Japan, South Korea, the US, the UK, Germany, and France), Japan had the highest percentage (16%) of respondents who answered "I don't know [30]." In a Japanese survey on attitudes toward reproductive medicine that used options similar to those used in our survey ("Should be approved," "Should be

prohibited," and "Indecisive"), 37.3% of respondents answered "Indecisive" for gamete donation and embryo donation, and 37.3% answered "Indecisive" for gestational surrogacy [31]. The result was at the same level as the "Cannot judge" in this study.

Less than half of the general public responded "Should be allowed." In comparison with the fact that many of the women surveyed in the UK [21] and the US [24] favored HFT research, fewer Japanese women may favor HFT research. A key reason why fewer Japanese people supported HFT research compared to the respondents in the UK and US surveys may be that many people in Japan prefer to avoid making value judgments about science and technology. As a circumstance specific to HFT research, it is necessary to consider the culture that accepts aborted fetuses as objects of mourning, as seen in the Japanese practice of "mizuko kuyo"-memorial services for aborted, miscarried, or stillborn fetuses that began in the 1970s [32]. In Japanese culture, artificial abortion is considered a woman's sin or a sign of incompetent motherhood [33]. Such a culture may have influenced the unclear attitude toward HFT research. Moreover, the issue of HFT in Japan is seldom discussed in the context of women's rights. In the US, pro-choice activists see the donation of HFT as a woman's right to make proactive choices concerning the issue of abortion [34]. In Japan, the feminist perspective regards artificial abortion as a woman's right, and the prohibition of artificial abortion under the Criminal Code is criticized (as the Maternal Protection Law precludes illegality, Japanese women can receive abortion services on demand) [33]. However, the topic of HFT donations is rarely discussed in this context. Furthermore, as part of a government committee in the 2000s to develop the Guidelines for Clinical Research Using Human Stem Cells, a member who had been involved in the women's movement and advocated for abortion rights criticized clinical research involving HFT transplants, unlike pro-life activists in the US [17]. However, the committee's discussion did not attract significant public attention at the time, and HFT research has rarely appeared in subsequent Japanese policy discussions. In other words, there has been limited discussion on HFT research in Japan.

Women asked to consent to HFT donations have already decided on artificial abortion, and there are many circumstances leading up to this decision. In other words, these women are very vulnerable, and being presented with the option of HFT donations by researchers can be violent. Therefore, it is important to clarify the rules and standards to be followed by researchers and issues such as who obtains the IC for donations and from whom, how, and when should be packed so that vulnerable women are protected. In addition, to gain support from society, it is necessary to have arrangements to prevent the abuse of fetal tissue, such as sufficient scientific rationale and a minimum amount of collection necessary. According to a study conducted in the UK, women become less optimistic about HFT donations as they become more informed through focus group interviews [8]. This finding may help strike a balance between HFT research and the protection of women in vulnerable situations. If information about HFT donation for research is widely available and women can access such information before becoming pregnant, this may prompt contemplation before they find themselves in a vulnerable situation and help them to make informed decisions when asked to donate HFT.

There are some limitations in this study. One of these was the low response rate of the researcher. Moreover, we asked about the acceptability of HFT research only for those who answered "No plan to conduct" to the question about the plan to conduct HFT research. Therefore, although 5.8% of researchers are explicitly opposed to HFT research, some respondents who answered "Don't know" to the question about their plan might be opposed to HTF research. In addition, respondents' attitudes could have differed if the explanations and relevant information provided in the videos and questions were changed.

It is important to note that even among those researchers who intended to consider conducting HFT research, as indicated in this study, a large number believed that clarification of the rules was necessary. Along with the development of scientific research, further investigation is needed to determine what is needed to create a system that can adequately protect women in vulnerable situations and what form of the rules is preferable, whether it is a law, a guideline by the government, or a guideline by an academic society. In particular, it is important to investigate the opinions of women who have experienced artificial abortion through interviews, as done in previous studies in the UK or the US [8,23,25].

5. Conclusion

Respondents who explicitly opposed HFT research were more likely to be in the public group than researchers. A large number of researchers sought clarification of the rules for conducting HFT research. While developing scientific research, it is necessary to establish the rules that can adequately protect vulnerable women who are asked to consent to donate HFT. In addition, the research community needs to engage in a dialogue with the public in developing the rules for HFT research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2023.05.007.

References

- [1] Voices. The importance of fetal tissue research. Cell Stem Cell 2019;24(3): 357–9.
- Wadman M. The truth about fetal tissue research. Nature 2015;528(7581): 178–81.
- [3] National Institutes of Health. Report of the human fetal tissue research ethics advisory board- FY2020. 2020.
- [4] ISSCR. ISSCR reportStatement on NIH human fetal tissue ethics advisory board Report 2020 [Available from: https://www.isscr.org/isscr-news/isscr-statement-on-nih-human-fetal-tissue-ethics-advisory-board-report.

- [5] MacDuffie KE, Hyun I, Krogen MM, Dempsey JC, Murry CE, Copp AJ, et al. Rescuing human fetal tissue research in the United States: a call for additional regulatory reform. Stem Cell Rep 2021;16(12):2839–43.
- [6] Kawasaki H, Yamada T, Wada T, Kosugi S. Current status and legal/ethical problems in the research use of the tissues of aborted human fetuses in Japan. Congenital Anom 2020;60(6):166–74.
- [7] Keown J. The Polkinghorne Report on Fetal Research: nice recommendations, shame about the reasoning. J Med Ethics 1993;19(2):114.
- [8] Pfeffer N. What British women say matters to them about donating an aborted fetus to stem cell research: a focus group study. Soc Sci Med 2008;66(12): 2544–54.
- [9] Pfeffer N, Kent J. Framing women, framing fetuses: how britain regulates arrangements for the collection and use of aborted fetuses in stem cell research and Therapies. BioSocieties 2007;2(4):429–47.
- [10] Boer GJ. Ethical guidelines for the use of human embryonic or fetal tissue for experimental and clinical neurotransplantation and research. Network of European CNS Transplantation and Restoration (NECTAR). J Neurol 1994;242(1):1–13.
- [11] ISSCR., ISSCR. Guidelines for stem cell research and clinical translation. 2021 [Available from: https://www.isscr.org/docs/default-source/all-isscrguidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4.
- [12] Miyazaki M. The history of abortion-related acts and current issues in Japan. Med Law 2007;26(4):791–9.
- [13] Ministry of Health LaW. reportSummary of health administration Report in 2020 (Japanese only) 2022 [Available from: https://www.mhlw.go.jp/toukei/ saikin/hw/eisei_houkoku/20/dl/gaikyo.pdf.
- [14] Ministry of Health LaW. Summary of vital statistics (Fixed Number) in 2020 (Japanese only) 2022 [Available from: https://www.mhlw.go.jp/toukei/saikin/ hw/jinkou/kakutei20/dl/16_all.pdf.
- [15] Norgren T. Abortion before birth control: the politics of reproduction in postwar Japan. Princeton: Princeton University Press; 2001.
- [16] Kyoto Human Embryo Visualization Project [Available from: http://bird.cac. med.kyoto-u.ac.jp/index_e.html.
- [17] Yui H, Yamagata Z. Human fetal tissue research and research ethics guidelines: an analysis of discussions in the "Expert committee on clinical research using human stem cells" (in Japanese). Journal of Health Care and Society 2022;32(1):95–107.
- [18] Tobita M, Konomi K, Torashima Y, Kimura K, Taoka M, Kaminota M. Japan's challenges of translational regenerative medicine: act on the safety of regenerative medicine. Regen Ther 2016;4:78–81.
- [19] Sperm and egg source created from human iPS cells (in Japanese). Kyoto Shinbun 2017:1. News paper article. Published January 1, 2017.
- [20] Mullen MA, Williams JI, Lowy FH. Transplantation of electively aborted human fetal tissue: physicians' attitudes. CMAJ (Can Med Assoc J) 1994;151(3):325–30.
- [21] Anderson F, Glasier A, Ross J, Baird DT. Attitudes of women to fetal tissue research. J Med Ethics 1994;20(1):36–40.
- [22] Martin DK, Maclean H, Lowy FH, Williams JI, Dunn EV. Fetal tissue transplantation and abortion decisions: a survey of urban women. CMAJ (Can Med Assoc J) 1995;153(5):545–52.
- [23] Myers AJ, Lohr PA, Pfeffer N. Disposal of fetal tissue following elective abortion: what women think. J Fam Plann Reprod Health Care 2015;41(2):84–9.
- [24] Spach NC, Jaffe EF, Sullivan KA, Goldfarb IT, Anderson JR, Coleman J, et al. Pregnant individuals' views on fetal tissue research in the United States. Obstet Gynecol 2021;138(5):755–61.
- [25] Stowers P, Fontanilla T, Elia J, Salcedo J, Tschann M, Kaneshiro B, et al. Fetal tissue donation for research at the time of abortion: a qualitative study of individuals who experienced an abortion in Hawaii in 2018-19. Contraception 2022;113:84–7.
- [26] Enosawa S. Public survey on the perception of the regenerative medicine (in Japanese) 2006 [Available from: http://nrichd.ncchd.go.jp/MONTHREPT/houkoku/opinionaire.pdf.
- [27] Kobayashi T. How have Japanese attitudes and behavior on religion changed?: from the ISSP survey on religion: survey results in Japan (in Japanese). Houso Kenkyu to Chousa 2019;69(4):52–72.
- [28] Inoue Y, Shineha R, Yashiro Y. Current public support for human-animal chimera research in Japan is limited, despite high levels of scientific approval. Cell Stem Cell 2016;19(2):152–3.
- [29] Sawai T, Hatta T, Fujita M. Public attitudes in Japan towards human-animal chimeric embryo research using human induced pluripotent stem cells. Regen Med 2017;12(3):233–48.
- [30] Shineha R, Inoue Y, Yashiro Y. A comparative analysis of attitudes toward stem cell research and regenerative medicine between six countries - a pilot study. Regen Ther 2022;20:187–93.
- [31] Yamamoto N, Hirata T, Izumi G, Nakazawa A, Fukuda S, Neriishi K, et al. A survey of public attitudes towards third-party reproduction in Japan in 2014. PLoS One 2018;13(10):e0198499.
- [32] Harrison EG, Midori I. Women's responses to child loss in Japan: the case of "mizuko kuyo. J Fem Stud Relig 1995;11(2):67–100.
- [33] Tsukahara K. Discrepancies of abortion methods and values between Japan and the world. Journal of Philosophy of Life 2014;4(4):99–120.
- [34] Pennathur K. Fetal tissue research restrictions are part of the anti-choice agenda. Here's why 2020. Available from: https://prochoicemd.medium. com/fetal-tissue-research-restrictions-are-part-of-the-anti-choice-agendaheres-why-7fea331d6e2f. article from the internet.