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Public attitudes in Japan toward the creation and use of gametes derived from human-induced pluripotent stem cells

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Aim: To ascertain to what extent the Japanese general public accept the creation and use of in vitro derived (IVD)-gametes derived from human-induced pluripotent stem cells. Materials & methods: We conducted an online survey and obtained answers from 3096 respondents. Results: 78.6% of the respondents answered that they would accept the creation and use of IVD-gametes for research purposes, 51.7% answered that they would accept the creation and use of embryos with IVD-gametes for research purposes, and 25.9% answered that they would accept childbirth using embryos with IVD-gametes. Discussion: The results that approximately half of the respondents answered that they would accept the creation of embryos with IVD-gametes, which has not been allowed in the current Japanese research guidelines, is astonishing.

Lay abstract: This paper reports the results of an online public survey about the creation and use of in vitro derived (IVD)-gametes, conducted in Japan with 3096 respondents selected from the monitor members of a survey company. While IVD-gametes generate interest for research purposes as well as reproductive use, ethical issues have been discussed in relation to such usage. It is of value to understand the extent to which the creation and use of IVD-gametes are considered acceptable by the general public and the expectations and concerns they may have, which will inform future discussions on regulations of this technology.

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Keywords: assisted reproductive technologies • concerns • degree of acceptance • ethics • expectations • human-induced pluripotent stem cells • in vitro derived-gametes • in vitro gametogenesis • public survey

In recent years, research progress has been made in creating in vitro derived (IVD)-gametes from human pluripotent stem cells, including human-induced pluripotent stem cells (hiPSCs) and human embryonic stem cells (hESCs). In mice, Hayashi et al. have reported the generation of offspring from sperm and ova derived from mouse pluripotent stem cells (PSCs) [1,2]. Furthermore, although the creation of IVD-gametes has not been achieved in humans at present, Irie et al. created primordial germ cell-like cells from human pluripotent stem cells in 2015 [3], and Sasaki et al. successfully created primordial germ cell-like cells from hiPSCs through more efficient procedures in 2015 [4]. Furthermore, in September 2018, Yamashiro et al. reported the successful generation of oogonia, which finally differentiate into ova, from primordial germ cell-like cells derived from hiPSCs [5].

The creation of IVD-gametes and their use for research would help acquire biological insights into human development, to elucidate the etiologies of infertility and genetic diseases, and to establish therapeutic modalities for these conditions [6]. The creation of IVD-gametes would also enable the procurement of unfertilized/fertilized ova, which has so far been difficult, for research purposes [7]. Furthermore, the use of IVD-gametes for reproductive purposes would pave the way for those who cannot have children with the current assisted reproductive technology (ART), including couples suffering from infertility, persons who are congenitally infertile for conditions such as...
congenital disturbance of spermatogenesis, and individuals who lose their fertility owing to cancer treatment and other noncongenital reasons, to have genetically related children [8]. Thus, in vitro gametogenesis (IVG) technology is expected to bring many benefits to both research and reproduction.

However, ethical issues have also been raised from the beginning with regard to the creation and use of IVD-gametes [8,9]. For instance, it is theoretically possible to produce as many embryos as needed from embryos with IVD-gametes; however, unlike in the case of using the embryos that were created for infertility treatment but were finally not used (‘surplus embryos’) and then donated for research, the theoretical possibility of creating embryos with IVD-gametes poses the following question: “Is it acceptable to produce and use embryos solely for research purposes (‘research embryos’) in the first place?” [7]. In addition, the use of IVD-gametes for reproductive purposes poses the problem of safety risk for the children to be born and the future generations [10], and the question of to whom and for what purposes the use of IVG technology should be permitted [7,11–14].

For IVG technology, which is thus controversial, in May 2010, the Japanese government established research guidelines that allow the creation of IVD-gametes [15]. Later, in 2015, the Expert Panel on Bioethics of the Cabinet Office resumed the discussion on whether to allow the creation of embryos with IVD-gametes; however, deregulation was postponed on the grounds that it was inappropriate to judge the necessity of creating embryos with IVD-gametes at the stage where the creation of IVD-gametes had not yet been achieved [15–17]. In contrast, the Japanese government has allowed the limited use of research embryos created without using IVD-gametes, only in research expected to contribute to the advancement of ART [18].

In other countries, no special regulations have been established for research using IVD-gametes and embryos with IVD-gametes [19], and such research is likely to be subject to the general regulations for research using human embryos. For instance, the US NIH guidelines prohibit federal funding of research that might result in the destruction or risk of damage to human embryos with the exception of utilizing surplus embryos to create hESCs [20], but the statutes enacted in California allow the creation of embryos for research purposes. Many European countries, except the UK, Denmark, Sweden and Belgium, ban the creation of embryos for research purposes.

The creation and use of IVD-gametes can affect not only individuals but also the whole society and even future generations. Once IVG technology is established, the issue of discussion will be ‘how should IVD-gametes be used ethically in research and clinical settings’ rather than ‘whether the creation and use of IVD-gametes should be permitted’. Therefore, it is necessary to discuss with potential stakeholders who are likely to be affected by the creation and use of IVD-gametes to what extent they should be permitted before the creation of IVD-gametes is achieved [21,22]. The aim of this study was to elucidate using a questionnaire survey what expectations and creation and use of IVD-gametes to what extent they should be permitted before the creation of IVD-gametes permitted’. Therefore, it is necessary to discuss with potential stakeholders who are likely to be affected by the creation and use of IVD-gametes.

Materials & methods
Selection of respondents
The study was conducted in an online-only format because we considered this to be a suitable method to survey the opinions of a group of people representative of the Japanese population (in terms of age and gender) simultaneously. In this survey, we prepared a questionnaire and then outsourced the data collection to a survey company (a confidentiality agreement is in place with the survey company prohibiting the disclosure of the company name and details). To recruit the participants of the online survey, the survey company sent an e-mail on 17 May 2017, to all the monitor members who were between 20 and 80 years of age. The survey company asks monitor members to update their personal information once a year, such as addresses, annual incomes, and other sociodemographic attributes. Our study specified that the recruiting conditions included only those individuals living in Japan; thus, we can reasonably assume that all the respondents were residents of Japan at the time of the survey.

The e-mail contained the URL of the webpage for informed consent of the survey. The webpage specified the aim of the survey, the estimated time required for answering (10–15 min in total), remuneration for participation (i.e., redeemable points issued by the company; for confidentiality reasons, the incentives cannot be explained in greater detail), that personal information would be handled according to the company's policy, that the answers would be anonymized, and the information regarding the executive agency of this survey. The ‘Next’ and ‘Cancel’ buttons were placed at the bottom of the webpage. Clicking the ‘Next’ buttons was considered as giving consent: volunteer opt-in panels [23]. On 18 May 2017, the number of participants reached the necessary sample size.
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Research Article

Increasing the ease of obtaining fertilized eggs for research

Creating sperm/ova from hiPSCs

Elucidate human embryonic development and genetic mechanisms

Elucidate causes of infertility attributable to sperm or ovum

Creating fertilized eggs (embryos) from the sperm/ova

Develop therapies for infertility attributable to sperm/ova

Increase the ease of obtaining fertilized eggs for research

Implanting the embryos into a woman’s uterus

Have a genetically-related children

Figure 1. Process of creating and using human-induced pluripotent stem cells-derived sperm/ova.

hiPSCs: Human-induced pluripotent stem cells.

Company closed the URL and terminated the recruitment of participants and the collection of answers on the same day. Therefore, this procedure does not yield valid response rates.

While the data collection procedure was based on the non-probability sampling strategy, the sample sizes were designed based on the probability sampling [23]. In general, the minimum sample size for a public opinion poll is estimated to be 384 (confidence level: 95%; margin of error: 5%; and response rate: 0.5%). To grasp the attitudes of the Japanese general public, we classified the Japanese general public aged 20–79 years into six age groups set at a constant interval (20–29, 30–39, 40–49, 50–59, 60–69 and 70–79 years old). We assigned 384 people to the 20–29 age group as the least populated group based on the latest available demographic statistics [24], and estimated the number of respondents in each group as 384, 481, 543, 463, 546 and 415, respectively (2832 in total). Minors younger than 20 years and elderly people aged 80 years or older were excluded from the survey. Complete responses were obtained from 3096 respondents, which exceeded the required sample size due to its web platform specifications. The distribution of age groups and sex was consistent with demographic data.

Content & questionnaire preparation procedures

This questionnaire is part of a survey project investigating the opinions of the Japanese general public (i.e., Japanese nationals in an inclusive sense – people who are members of the Japanese population [please see ‘Selection of respondents’ in the ‘Materials & methods’ section for more information]) on a wide range of ethical issues regarding the creation of IVD-gametes and their use for research and reproduction. This study aimed to elucidate the extent to which the creation and use of IVD-gametes are considered acceptable by the general public and the expectations and concerns they may have. While some parts of the survey results were showed elsewhere [25], the content reported in this paper comprises the following six parts (see the Supplementary Box 1 for 1–3):

- Fact-based explanation of ‘iPSCs’ and questions regarding the respondents’ degree of awareness and interest
- Fact-based explanation of research for creating sperm/ova from hiPSCs and a question regarding the respondents’ degree of awareness
- Explanation of ‘the creation and use of hiPSC-derived sperm/ova’, Figure 1, and a question regarding the respondents’ degree of understanding
- Questions about the respondents’ expectations and concerns regarding ‘the creation and use of hiPSC-derived sperm/ova’
- Questions regarding the respondents’ degree of acceptance of ‘the creation and use of hiPSC-derived sperm/ova’
- Questions regarding respondents’ demographic characteristics.
The distinctive feature of this survey was that the respondents received detailed explanations with a figure on IVG research (Figure 1), and were then asked about their expectations, concerns and degree of acceptance regarding the creation and use of hiPSC-derived sperm/ova. This was because, to meet the purpose of this survey, which was to grasp the interests of the general public, we considered it important to have the respondents express their attitudes based on accurate information regarding IVG-gametes, a topic with which the respondents were unfamiliar.

The items for the expectations and concerns associated with the creation and use of IVG-gametes were set based on a review of the scientific aspects of IVG technology compiled by the Expert Panel on Bioethics in the Cabinet Office [16] as well as literature in bioethics research. We listed the following 12 items as expectations: elucidate human development and genetic mechanisms (hereafter, elucidation of the mechanism of embryonic development), elucidate causes of infertility attributable to sperm and eggs (hereafter, elucidation of the etiology of infertility), develop therapies or drugs for infertility attributable to sperm or eggs (hereafter, development of therapeutic modalities and drugs for infertility), elucidate the cause of congenital diseases (hereafter, elucidation of the etiology of congenital diseases), develop therapies or drugs for congenital diseases (hereafter, development of therapeutic modalities and drugs for congenital diseases), increase the ease of obtaining sperm and eggs for research (hereafter, availability of gametes for research), increase the ease of obtaining fertilized eggs (embryos) for research (hereafter, availability of embryos for research), enable anyone who desires a child to have a genetically related child (hereafter, birth of genetically related children), increase the ease of obtaining sperm and eggs to be used for reproductive medicine (hereafter, availability of gametes for reproduction), increase the ease of obtaining fertilized eggs (embryos) to be used for reproductive medicine (hereafter, availability of embryos for reproduction), enable curtailment of genetic diseases in society through intensive use of sperm and ova with specific characteristics (hereafter, reduction in genetic diseases), and enable parents to choose the characteristics they desire in their babies (such babies are referred to as designer babies in this paper). For the item of ‘reduction in genetic diseases’, we added the following explanatory note: “Huntington’s disease and some types of hemophilia are caused by genetic abnormalities, and when the parents possess the gene responsible, it is inherited by their children at a certain probability. This item assumes such genetic diseases caused by the abnormalities of specific genes.” We asked the respondents to provide an answer for each item using a 4-point Likert scale (1. Not expected at all; 2. Not expected; 3. Expected; 4. Strongly expected).

Next, we listed the following 16 items as concerns: it is an unnatural process (hereafter, unnaturalness), it impinges on God’s territory (hereafter, playing God), it infringes on human dignity (hereafter, infringement of human dignity), the traditional values of family and reproduction will be lost (hereafter, loss of values), it will generate confusion owing to an undeveloped social system, including family registration and inheritance (hereafter, social turmoil), it will spur the commercialization of reproductive medicine by commodifying sperm and eggs (hereafter, commercialization of reproductive medicine), genetic diversity will be lost owing to intensive use of sperm and eggs with specific characteristics only (hereafter, loss of genetic diversity), the precise physical risks and disadvantages associated with children born through this process are unknown (hereafter, unknown risk to children), the children born through this process will be concerned about their origin and identity (hereafter, infringement of identity), the risks associated with use of these gametes and their effects on the next generation and environment are unknown (hereafter, unknown risk to future generations), it will encourage the tendency to use sperm and eggs as tools (simply as parts of the process) (hereafter, use of gametes as tools), it will also fortify the tendency to use fertilized eggs (embryos) as tools (simply as part of the process) (hereafter, use of embryos as tools), it will promote the destruction of fertilized eggs (embryos) (hereafter, promotion of embryo destruction), it will increase the pressure to have children who are genetically related (hereafter, pressure on parents), it will only be available to limited people, such as wealthy or heterosexual couples (hereafter, limited access to reproduction), and it will lead to the birth of designer babies (children with characteristics desired by the parents [hereafter, designer babies]). Our study presupposes that iPSCs are produced under very strict quality-controlled conditions. We asked the respondents to provide an answer for each item using a 4-point Likert scale (1. Not concerned at all; 2. Not concerned; 3. Concerned; 4. Strongly concerned).

In addition, we framed the following questions to grasp the respondents’ degree of acceptance over a series of processes involving research using IVG-gametes to the clinical use of IVG-gametes:

Regarding ‘the creation and use of sperm/ova derived from hiPSCs’, up to which stage do you feel that you can personally accept it? Please choose the answer that is closest to your opinion.

- Up to the first stage: the creation of sperm/ova from hiPSCs
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- Up to the second stage: the creation of fertilized eggs (embryos) from the sperm/ova (derived from hiPSCs)
- Up to the third stage: the birth of children derived from fertilized eggs (embryos) created from sperm/ova (derived from hiPSCs)
- I cannot accept it at all

Owing to the structure of the question, the following possibilities of choice were excluded: the option of allowing the first and third stages (but not allowing the second stage); the option of allowing the second and third stages (but not allowing the first stage); the option of allowing only the second stage (but not allowing the first stage); and the option of allowing only the third stage (and not allowing the first and/or second stage).

Regarding the demographic characteristics, we used the registration data obtained from the survey company for age, sex, marital status and personal income. For other characteristics including educational background, presence or absence of children, religious affiliation and experience of infertility treatment, we set separate questions.

While preparing the questionnaire, we consulted with science communicators who hold PhDs and currently work at a stem cell research institute, regarding the content and readability of the questionnaire. In addition, we asked scientists involved in IVG research to offer advice from a scientific viewpoint regarding the explanations and figures for the creation and use of IVD-gametes as well as the content of the questions.

**Data analysis**

To grasp the relationships between the degree of acceptance and the demographic characteristics, expectations, and concerns, simple and multiple regression analyses were performed using the degree of acceptance as an objective variable and each item of the demographic characteristics, expectations and concerns as explanatory variables. In the single regression analysis, the coefficient of determination ($R^2$) was regarded as the effect size, and when $R^2$ exceeded 0.02, 0.13 or 0.26, it indicates a small effect, middle effect, or large effect, respectively [26]. To avoid multicollinearity in the multiple regression, we estimated the variance inflation factor of each explanation [27,28].

In addition, to identify the characteristics of the respondents who answered ‘I cannot accept it at all’ to the question on the degree of acceptance, binomial logistic regression analysis was performed. In the analysis, the degree of acceptance was used as the objective variable, and respondents were grouped into two groups, those who answered ‘I cannot accept it at all’ and those who answered otherwise.

For the statistical analyses reported herein, we used IBM SPSS Regression 24.0 (IBM Corp., NY, USA) and Microsoft Office Professional Plus 2016 Excel (Microsoft Corp., WA, USA). The significance level was set at $p < 0.01$, and the effect size was calculated.

**Results**

**Demographic characteristics of the respondents**

We conducted a survey using the described method and obtained complete answers from 3096 respondents. The respondents’ demographic characteristics are shown in Table 1.

The question on the degree of awareness regarding IVG research, 49.5% of respondents answered that they had known about it. 72.0% of the respondents answered that they had understood the explanation regarding the creation and use of IVD-gametes.

**Expectations**

For each item of expectation, we calculated the sum of the number of respondents who answered ‘Expected’ and the number of those who answered ‘Strongly expected’, and arranged the items in descending order of that sum (Figure 2). The expectations of the respondents were as follows (in descending order): ‘elucidation of etiology of congenital diseases’ (89.7%), ‘development of therapeutic modalities and drugs for congenital diseases’ (89.7%), ‘development of therapeutic modalities and drugs for infertility’ (85.8%), ‘elucidation of etiology of infertility’ (85.6%), ‘elucidation of the mechanism of embryonic development’ (81.9%), ‘reduction in genetic diseases’ (70.2%), ‘birth of genetically related children’ (68.7%), ‘availability of gametes for reproduction’ (63.3%), ‘availability of embryos for reproduction’ (63.0%), ‘availability of embryos for research’ (62.8%), ‘availability of gametes for research’ (62.6%) and ‘designer babies’ (27.6%).
| Table 1. The demographic characteristics of the respondents (n = 3096). |
|---------------------------------------------------------------|
| **n** | **%** |
| **Sex** |  |
| Male | 1533 | 49.5 |
| Female | 1563 | 50.5 |
| **Age (years)** |  |
| 20–29 | 419 | 13.5 |
| 30–39 | 525 | 17.0 |
| 40–49 | 593 | 19.2 |
| 50–59 | 507 | 16.4 |
| 60–69 | 597 | 19.3 |
| 70–79 | 455 | 14.7 |
| **Marital status** |  |
| Yes, I am married | 2066 | 66.7 |
| No, I am not married | 1030 | 33.3 |
| **Presence or absence of children** |  |
| Yes, I have children | 1871 | 60.4 |
| No, I do not have children | 1225 | 39.6 |
| **Experience of infertility treatment** |  |
| No | 2772 | 89.5 |
| Yes | 261 | 8.4 |
| I do not want to answer | 63 | 2.0 |
| **Educational background** |  |
| Elementary school | 4 | 0.1 |
| Junior high school | 75 | 2.4 |
| High school | 1041 | 33.6 |
| Technical college | 351 | 11.3 |
| Two-year college | 327 | 10.6 |
| Four-year college | 1159 | 37.4 |
| Postgraduate studies (master's degree) | 105 | 3.4 |
| Postgraduate studies (doctorate) | 23 | 0.7 |
| Other | 11 | 0.4 |
| **Personal income (yen/year)** |  |
| Less than two million | 1175 | 38 |
| Two to four million | 698 | 22.5 |
| Four to six million | 410 | 13.2 |
| Six to eight million | 185 | 6.0 |
| Eight to ten million | 66 | 2.1 |
| Ten to twelve million | 33 | 1.1 |
| Twelve to fifty million | 7 | 0.2 |
| Fifty to twenty million | 6 | 0.2 |
| Over twenty million | 7 | 0.2 |
| I do not know | 195 | 6.3 |
| I do not want to answer | 314 | 10.1 |
| **Religious affiliation** |  |
| No, I do not have a religious affiliation | 2646 | 85.5 |
| Yes, I have a religious affiliation | 313 | 10.1 |
| I do not want to answer | 137 | 4.4 |
| **How much did you know about iPSCs?** |  |
| I knew enough about them to be able to provide an explanation to a certain extent | 607 | 19.6 |
| I had only heard a bit about them | 2267 | 73.2 |
| I was not aware of them | 222 | 7.2 |

hiPSC: Human-induced pluripotent stem cell; iPSC: Induced pluripotent stem cell.
Table 1. The demographic characteristics of the respondents (n = 3096) (cont.).

| Are you interested in iPSCs?              | n  | %   |
|------------------------------------------|----|-----|
| Yes, I am interested                     | 2220 | 71.7 |
| No, I am not interested                   | 876  | 28.3 |

| How much did you know about the ‘research for creating sperm/ova from hiPSCs’? |
|-------------------------------------------------------------------------------|
| I knew enough about it to be able to provide an explanation to a certain extent | 212  | 6.8  |
| I had only heard a bit about it                                                  | 1322 | 42.7 |
| I was not aware of it                                                           | 1562 | 50.5 |

| How much did you understand the explanation on ‘the creation and use of hiPSC-derived sperm/ova’? |
|-----------------------------------------------------------------------------------------------|
| I fully understood it                                                                       | 128  | 4.1  |
| I mostly understood it                                                                      | 2101 | 67.9 |
| I could not understand it very well                                                         | 743  | 24.0 |
| I could not understand it at all                                                            | 124  | 4.0  |

hiPSC: Human-induced pluripotent stem cell; iPSC: Induced pluripotent stem cell.

Concerns

For each item of concern, we calculated the sum of the number of respondents who answered ‘Concerned’ and the number of those who answered ‘Strongly concerned’, and arranged the items in descending order of that sum (Figure 3). The concerns of the respondents were as follows (in descending order): ‘unknown risk to children’ (80.3%), ‘designer babies’ (77.6%), ‘use of gametes as tools’ (76.1%), ‘use of embryos as tools’ (76.0%), ‘unknown risk to future generations’ (75.7%), ‘loss of genetic diversity’ (74.9%), ‘commercialization of reproductive medicine’ (74.8%), ‘unnaturalness’ (71.6%), ‘infringement of identity’ (71.2%), ‘limited access to reproduction’ (68.4%), ‘promotion of embryo destruction’ (64.6%), ‘social turmoil’ (62.0%), ‘loss of values’ (58.6%), ‘infringement of human dignity’ (56.2%), ‘pressure on parents’ (55.7%) and ‘playing God’ (53.9%). It should be noted that our main objective here was to arrange the items in the order of the degree of concern; therefore, we decided that a nonparametric test was unnecessary.

Degree of acceptance

Regarding the degree of acceptance of the creation and use of IVD-gametes, 21.4% of the respondents answered that they could not accept it at all, 26.8% answered that they would accept it to the first stage (creation and use...
of IVD-gametes for research purposes), 25.8% answered that they would accept it to the second stage (creation of and use of embryos with IVD-gametes for research purposes), and 25.9% answered that they would accept it to the third stage (childbirth using embryos with IVD-gametes) (Figure 4). These results indicate that 78.6% of the respondents accepted the creation of IVD-gametes because approving the second or third stage entails approving the first stage. Similarly, these results indicate that 51.7% of the respondents accepted the creation of embryos with IVD-gametes because approving the third stage entails approving the second stage.

Regarding the relationship between the degree of acceptance and demographic characteristics, variables such as age, interest in iPSCs, and degree of understanding of the explanation for the creation and use of IVD-gametes...
showed statistical significance in multiple regression analysis and a small effect size in a simple regression analysis (p < 0.01; R² > 0.02) (Table 2). These results revealed that the respondents with a younger age, a higher degree of interest in iPSCs, and a higher degree of understanding of the explanation for the creation and use of IVD-gametes had a higher degree of acceptance over the series of processes involved in the creation and use of IVD-gametes. It was also revealed that the experience of infertility treatment did not affect attitudes toward the use of IVD-gametes for reproductive purposes (n.s., R² = 0.001).

Regarding the relationship between the degree of acceptance and the expectations, variables such as ‘birth of genetically related children’, ‘reduction in genetic diseases’ and ‘designer babies’ showed statistical significance in multiple regression analysis and a small effect size in a simple regression analysis (p < 0.01; R² > 0.02) (Table 3). These results revealed that the respondents with those expectations had a higher degree of acceptance over the series of processes involved in the creation and use of IVD-gametes. Similarly, regarding the relationship between the degree of acceptance and the concerns, the variables such as ‘unnaturalness’, ‘playing God’, ‘infringement of human dignity’, ‘loss of values’, ‘unknown risk to children’, ‘promotion of embryo destruction’ and ‘pressure on parents’ showed statistical significance in multiple regression analysis and a small effect size in a simple regression analysis (p < 0.01; R² > 0.02) (Table 4). These results revealed that the respondents with those concerns had a lower degree of acceptance of a series over processes involved in the creation and use of IVD-gametes.

In addition, to identify the demographic characteristics of the respondents who answered ‘I cannot accept it at all’ to the question on the degree of acceptance, binomial logistic regression analysis was performed. Regarding the relationship with the demographic characteristics, ‘interest in iPSCs’ and ‘degree of understanding of the explanation for the creation and use of IVD-gametes’ showed statistical significance in multivariate logistic regression analysis and a small effect size in univariate logistic regression analysis (p < 0.01; R² > 0.02) (Table 5). These results indicate that the respondents with a lower degree of interest in iPSCs and a lower degree of understanding of the explanation for the creation and use of IVD-gametes tended to answer that they could not accept the creation and use of IVD-gametes at all. In addition, the expectations such as ‘development of therapeutic modalities and drugs for congenital diseases’ and ‘birth of genetically related children’ showed statistical significance in multivariate analysis and a small effect size in univariate analysis (p < 0.01; R² > 0.02) (Table 6). These results indicate that the respondents with expectations such as ‘development of therapeutic modalities and drugs for congenital diseases’ and ‘birth of genetically related children’ tend to accept the creation and use of IVD-gametes at a certain stage.

| Table 2. Relationship between the iterative acceptance and demographic characteristics of the respondents. |
|---------------------------------------------------------------|

| Demographic characteristics | Simple regression analysis† | Multiple regression analysis‡, † | |
|----------------------------|-----------------------------|---------------------------------|---|
|                             | β  | 95% CI | t   | p-value | R² | β  | 95% CI | t   | p-value | VIF§ |
|-----------------------------|----|--------|-----|---------|----|----|--------|-----|---------|------|
| Sex                         | 0.056 | 0.045 - 0.199 | 3.112 | 0.002 | 0.003 | 0.066 | 0.059 - 0.228 | 3.335 | 0.001 | 1.1 |
| Age                         | -0.155 | -0.013 - 0.008 | -8.744 | 0.000 | 0.024 | -0.164 | -0.014 - 0.008 | -7.649 | 0.000 | 1.3 |
| Marital status              | -0.077 | -0.260 - 0.097 | -4.300 | 0.000 | 0.006 | -0.041 | -0.204 - 0.014 | -1.716 | 0.086 | 1.6 |
| Personal income             | 0.038 | 0.000 - 0.066 | 1.944 | 0.052 | 0.001 | 0.028 | -0.008 - 0.056 | 1.475 | 0.140 | 1.0 |
| Awareness of iPSCs          | 0.135 | 0.217 - 0.369 | 7.565 | 0.000 | 0.018 | 0.002 | -0.093 - 0.101 | 0.090 | 0.929 | 1.4 |
| Interest in iPSCs           | 0.190 | 0.377 - 0.545 | 10.780 | 0.000 | 0.036 | 0.139 | 0.236 - 0.442 | 6.457 | 0.000 | 1.3 |
| Awareness of AG research    | 0.079 | 0.078 - 0.202 | 4.424 | 0.000 | 0.006 | -0.029 | -0.127 - 0.022 | -1.382 | 0.167 | 1.3 |
| Understanding of the        | 0.270 | 0.428 - 0.551 | 15.623 | 0.000 | 0.073 | 0.231 | 0.341 - 0.500 | 10.384 | 0.000 | 1.4 |
| explanation                |     |         |      |         |     |     |         |      |         |      |
| Educational background      | 0.040 | 0.004 - 0.057 | 2.250 | 0.025 | 0.002 | -0.029 | -0.051 - 0.007 | -1.464 | 0.143 | 1.1 |
| Religious affiliation       | 0.023 | -0.044 - 0.210 | 1.278 | 0.201 | 0.001 | 0.029 | -0.031 - 0.243 | 1.522 | 0.128 | 1.0 |
| Children                    | -0.085 | -0.269 - 0.112 | -4.772 | 0.000 | 0.007 | -0.019 | -0.150 - 0.063 | -0.799 | 0.425 | 1.6 |
| Experience of infertility   | 0.027 | -0.032 - 0.245 | 1.512 | 0.131 | 0.001 | 0.006 | -0.129 - 0.173 | 0.292 | 0.770 | 1.0 |
| treatment                  |     |         |      |         |     |     |         |      |         |      |

† Respondents who chose ‘I do not want to answer’ for their religious affiliation and their experience of infertility treatment and those who chose ‘I do not know’ or ‘N/A’ for their annual income were excluded from the analyses of the respective demographic characteristics.
‡ The adjusted coefficient of determination, R²adj = 0.119.
§ For multiple regression analysis, all explanatory variables were entered using the forced entry method.

p: Standardised partial regression coefficient; iPSC: Induced pluripotent stem cell; LL: Lower limit; R²: The coefficient of determination; UL: Upper limit; VIF: Variance inflation factor.
Furthermore, concerns such as 'unnaturalness', 'playing God', 'infringement of human dignity', 'loss of values', 'promotion of embryo destruction' and 'pressure on parents' showed statistical significance in multivariate analysis and a small effect size in univariate analysis ($p < 0.01; R^2 > 0.02$) (Table 7). These results revealed that the
Table 5. Demographics characteristics of the respondents who do not accept the creation and use of artificial gametes at all.

| Demographic characteristics | Univariate binomial logistic regression analysis† | Multivariate binomial logistic regression analysis‡ |
|----------------------------|-----------------------------------------------|-------------------------------------------------|
|                            | B     | SE    | Wald | OR    | 95% CI | df | p-value | B     | SE    | Wald | OR    | 95% CI | df | p-value |
| Sex                        | -0.175| 0.088 | 3.976| 0.707 | 0.997 | 1   | 0.046  | 0.001 | -0.197| 0.114 | 2.998 | 0.821 | 0.657 | 1.026 | 1 | 0.083  |
| Age                        | 0.018 | 0.003 | 4.215| 1.013 | 1.024 | 1   | 0.000  | 0.013 | 0.028 | 0.004 | 50.291| 1.029 | 1.021 | 1.037 | 1 | 0.000  |
| Marital status             | 0.166 | 0.095 | 3.082| 0.981 | 1.421 | 1   | 0.079  | 0.001 | 0.131 | 0.146 | 0.809 | 1.140 | 0.857 | 1.517 | 1 | 0.368  |
| Personal income            | -0.073| 0.040 | 3.736| 0.930 | 1.005 | 1   | 0.066  | 0.001 | -0.068| 0.046 | 2.198 | 0.934 | 0.853 | 1.022 | 1 | 0.138  |
| Awareness of iPSCs         | -0.887| 0.095 | 87.070| 0.342 | 0.496 | 1   | 0.000  | 0.029 | -0.174| 0.135 | 1.664 | 0.840 | 0.645 | 1.094 | 1 | 0.197  |
| Interest in iPSCs          | -1.202| 0.092 | 172.567| 0.251 | 0.360 | 1   | 0.000  | 0.053 | -0.966| 0.128 | 56.643| 0.381 | 0.296 | 0.489 | 1 | 0.000  |
| Awareness of AG research   | -0.305| 0.074 | 28.729| 0.638 | 0.852 | 1   | 0.000  | 0.005 | 0.229 | 0.107 | 4.600 | 1.257 | 1.020 | 1.550 | 1 | 0.032  |
| Understanding of the explanation | -1.259| 0.074 | -0.829| 0.245 | 0.329 | 1   | 0.000  | 0.097 | -1.080| 0.100 | 116.520| 0.340 | 0.279 | 0.413 | 1 | 0.000  |
| Educational background     | -0.150| 0.039 | 24.277| 0.861 | 0.811 | 0.914 | 1 | 0.000  | 0.008 | -0.038| 0.040 | 0.906 | 0.963 | 0.891 | 1.041 | 1 | 0.341  |
| Religious affiliation      | -0.221| 0.156 | 2.016| 0.801 | 0.590 | 1.088 | 1 | 0.156  | 0.001 | -0.291| 0.197 | 2.194 | 0.747 | 0.508 | 1.099 | 1 | 0.139  |
| Children                   | 0.242 | 0.091 | 7.067| 1.274 | 1.066 | 1.524 | 1 | 0.008  | 0.002 | 0.007 | 0.144 | 0.002 | 1.007 | 0.760 | 1.334 | 1 | 0.963  |
| Experience of infertility treatment | -0.414| 0.178 | 5.421| 1.661 | 0.466 | 0.937 | 1 | 0.020  | 0.002 | -0.250| 0.225 | 1.240 | 0.779 | 0.501 | 1.210 | 1 | 0.265  |

† Among the items of demographic characteristics, ‘I do not want to answer’ in religious affiliation and experience of infertility treatment was excluded from analysis. In addition, ‘I do not know’ or ‘I do not want to answer’ were also excluded from analysis.

‡ The coefficients of determination, Cox-Snell $R^2 = 0.142$, Nagelkerke $R^2 = 0.222$.

B: Partial regression coefficient; iPSC: Induced pluripotent stem cell; LL: Lower limit; OR: Odds ratio; R²: The coefficients of determination; UL: Upper limit.
Table 6. Expectations of the respondents who do not accept the creation and use of artificial gametes at all.

| Expectations                                                                 | Univariate binomial logistic regression analysis¹ | Multivariate binomial logistic regression analysis¹/² |
|------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------|
|                                                                              | B      | SE      | Wald  | OR    | 95% CI  | df | p-value | R²       | B      | SE      | Wald  | OR    | 95% CI  | df | p-value |
| Elucidation of the mechanism of embryonic development                      | -0.919 | 0.071   | 168.767 | 0.347 | 0.458 | 1   | 0.000 | 0.055 | 0.111 | 0.096 | 1.324 | 0.895 | 0.741 | 1.081 | 1   | 0.250   |
| Elucidation of the etiology of infertility                                  | -1.133 | 0.073   | 238.223 | 0.322 | 0.279 | 0.372 | 1   | 0.000 | 0.085 | -0.097 | 0.135 | 0.522 | 0.907 | 0.697 | 1.181 | 1   | 0.470   |
| Development of therapeutic modalities and drugs for infertility             | -1.152 | 0.071   | 262.765 | 0.316 | 0.275 | 0.363 | 1   | 0.000 | 0.095 | -0.315 | 0.129 | 5.996 | 0.730 | 0.567 | 0.939 | 1   | 0.014   |
| Elucidation of the etiology of congenital diseases                         | -0.982 | 0.068   | 206.622 | 0.375 | 0.328 | 0.428 | 1   | 0.000 | 0.071 | -0.065 | 0.129 | 0.255 | 0.937 | 0.727 | 1.207 | 1   | 0.614   |
| Development of therapeutic modalities and drugs for congenital diseases     | -0.999 | 0.066   | 230.123 | 0.368 | 0.324 | 0.419 | 1   | 0.000 | 0.080 | -0.335 | 0.123 | 7.429 | 0.716 | 0.562 | 0.910 | 1   | 0.006   |
| Availability of gametes for research                                       | -0.870 | 0.064   | 187.510 | 0.419 | 0.370 | 0.475 | 1   | 0.000 | 0.062 | 0.123 | 0.163 | 0.569 | 1.131 | 0.822 | 1.555 | 1   | 0.451   |
| Availability of embryos for research                                        | -0.912 | 0.064   | 199.882 | 0.402 | 0.354 | 0.456 | 1   | 0.000 | 0.067 | -0.204 | 0.166 | 1.509 | 0.815 | 0.588 | 1.129 | 1   | 0.219   |
| Birth of genetically related children                                       | -0.904 | 0.057   | 249.508 | 0.405 | 0.362 | 0.453 | 1   | 0.000 | 0.085 | -0.243 | 0.088 | 7.649 | 0.784 | 0.660 | 0.932 | 1   | 0.006   |
| Availability of gametes for reproduction                                     | -1.017 | 0.063   | 259.741 | 0.362 | 0.320 | 0.409 | 1   | 0.000 | 0.090 | -0.190 | 0.165 | 1.330 | 0.827 | 0.599 | 1.142 | 1   | 0.249   |
| Availability of embryos for reproduction                                     | -1.019 | 0.063   | 261.056 | 0.361 | 0.319 | 0.408 | 1   | 0.000 | 0.090 | -0.277 | 0.162 | 2.922 | 0.758 | 0.552 | 1.041 | 1   | 0.087   |
| Reduction in genetic diseases                                                | -0.813 | 0.056   | 212.001 | 0.443 | 0.397 | 0.495 | 1   | 0.000 | 0.071 | -0.154 | 0.081 | 3.655 | 0.857 | 0.732 | 1.004 | 1   | 0.056   |
| Designer babies                                                             | -0.314 | 0.052   | 35.796  | 0.731 | 0.659 | 0.810 | 1   | 0.000 | 0.012 | 0.139 | 0.069 | 4.112 | 1.149 | 1.005 | 1.314 | 1   | 0.043   |

¹ Among the items of expectations, ‘Others’ was excluded from analysis.
² The coefficients of determination, Cox-Snell R² = 0.139, R² = 0.140, Nagelkerke R² = 0.214.
B: Partial regression coefficient, LL: Lower limit, OR: Odds ratio, R²: The coefficients of determination; UL: Upper limit.
Table 7. Concerns of the respondents who do not accept the creation and use of artificial gametes at all.

| Concerns                              | Univariate binomial logistic regression analysis† | Multivariate binomial logistic regression analysis‡, ‡ |
|---------------------------------------|--------------------------------------------------|-----------------------------------------------------|
|                                       | B      | SE B   | Wald   | OR    | 95% CI   | df | p-value | B      | SE B   | Wald   | OR    | 95% CI   | df | p-value |
|                                       |        |        |        |       |          |    |         |        |        |        |       |          |    |         |
| Unnaturalness                         | 0.881  | 0.069  | 161.691| 2.414 | 2.107    | 2.765| 1       | 0.000  | 0.057  | 4.72   | 102    | 21.442  | 1.604| 1.313   | 1.959| 0.000   |
| Playing God                           | 0.801  | 0.059  | 185.761| 2.227 | 1.985    | 2.499| 1       | 0.000  | 0.064  | 0.228  | 0.086  | 6.984   | 1.256| 1.061   | 1.488| 0.008   |
| Infringement of human dignity        | 0.896  | 0.063  | 201.337| 2.450 | 2.165    | 2.773| 1       | 0.000  | 0.070  | 0.415  | 0.109  | 14.662  | 1.515| 1.225   | 1.874| 0.000   |
| Loss of values                       | 0.828  | 0.064  | 167.733| 2.288 | 2.018    | 2.593| 1       | 0.000  | 0.058  | 0.341  | 0.105  | 10.604  | 1.407| 1.146   | 1.728| 0.001   |
| Social turmoil                       | 0.527  | 0.060  | 76.375 | 1.693 | 1.505    | 1.906| 1       | 0.000  | 0.025  | -0.025 | 0.090  | 0.076   | 0.975| 0.818   | 1.164| 0.783   |
| Commercialization of reproductive medicine | 0.346  | 0.058  | 35.255 | 1.414 | 1.261    | 1.585| 1       | 0.000  | 0.011  | -0.134 | 0.102  | 1.707   | 0.875| 0.716   | 1.069| 0.191   |
| Loss of genetic diversity            | 0.377  | 0.060  | 40.189 | 1.458 | 1.298    | 1.639| 1       | 0.000  | 0.013  | -0.058 | 0.107  | 0.298   | 0.943| 0.765   | 1.163| 0.585   |
| Unknown risk to children             | 0.247  | 0.061  | 16.349 | 1.280 | 1.136    | 1.442| 1       | 0.000  | 0.005  | -0.300 | 0.104  | 8.256   | 0.741| 0.604   | 0.909| 0.004   |
| Infringement of identity             | 0.436  | 0.061  | 50.660 | 1.547 | 1.372    | 1.744| 1       | 0.000  | 0.016  | -0.018 | 0.105  | 0.029   | 0.982| 0.799   | 1.208| 0.866   |
| Unknown risk to future generations   | 0.424  | 0.062  | 46.427 | 1.529 | 1.353    | 1.727| 1       | 0.000  | 0.015  | 0.054  | 0.112  | 0.234   | 1.056| 0.848   | 1.314| 0.628   |
| Use of gametes as tools               | 0.314  | 0.058  | 29.353 | 1.369 | 1.222    | 1.534| 1       | 0.000  | 0.009  | -0.215 | 0.146  | 2.177   | 0.806| 0.606   | 1.073| 0.140   |
| Use of embryos as tools               | 0.359  | 0.059  | 37.302 | 1.432 | 1.276    | 1.607| 1       | 0.000  | 0.012  | -0.124 | 0.155  | 0.645   | 0.883| 0.652   | 1.196| 0.422   |
| Promotion of embryo destruction      | 0.682  | 0.063  | 118.247| 1.978 | 1.749    | 2.236| 1       | 0.000  | 0.040  | 0.439  | 0.109  | 16.317  | 1.551| 1.254   | 1.919| 0.000   |
| Pressure on parents                  | 0.700  | 0.061  | 133.397| 2.014 | 1.789    | 2.268| 1       | 0.000  | 0.044  | 0.430  | 0.089  | 23.311  | 1.537| 1.291   | 1.830| 0.000   |
| Limited access to reproduction       | 0.275  | 0.055  | 24.523 | 1.316 | 1.181    | 1.467| 1       | 0.000  | 0.008  | -0.056 | 0.081  | 0.466   | 0.946| 0.806   | 1.110| 0.495   |
| Designer babies                      | 0.130  | 0.054  | 5.818  | 1.139 | 1.025    | 1.265| 1       | 0.016  | 0.002  | -0.363 | 0.083  | 19.314  | 0.696| 0.592   | 0.818| 0.000   |

† Among the items of concerns, ‘Others’ was excluded from analysis.
‡ The coefficients of determination, Cox-Snell $R^2 = 0.120$, Nagelkerke $R^2 = 0.123$.

B: Partial regression coefficient; LL: Lower limit; OR: Odds ratio; R2: The coefficients of determination; UL: Upper limit.
The embryo has been discussed actively in the bioethics debate concerning hESC research [32]. Some people argue
that, even in cases where the use of surplus embryos for research purposes is ethically justified, the creation and use of
research embryos is not ethically justified because of the concerns regarding infringement of human dignity and
conversion of embryos into tools [33]. Furthermore, while some argue that the embryo with IVD-gametes is a mere
cell aggregate [10,34], the moral status of the embryo with IVD-gametes is generally considered to be equal to that
of the embryo [8,19,35].

The human embryo is considered to have a special value for various reasons, and conventionally, the moral status of
the embryo has been discussed actively in the bioethics debate concerning hESC research [32]. Some people argue
that, even in cases where the use of surplus embryos for research purposes is ethically justified, the creation and use of
research embryos is not ethically justified because of the concerns regarding infringement of human dignity and
conversion of embryos into tools [33]. Furthermore, while some argue that the embryo with IVD-gametes is a mere
cell aggregate [10,34], the moral status of the embryo with IVD-gametes is generally considered to be equal to that
of the embryo [8,19,35].

The Japanese government has prescribed the human embryo as ‘a sprout of human life’ and has taken the basic
position of banning the use of embryos for research [36], but has partially permitted the use of surplus embryos
and research embryos for research by making some exceptions. As previously mentioned, it has currently been
considered in Japan that the use of research embryos for research is more ethically problematic than the use of
surplus embryos for research, and the creation and use of research embryos has been permitted only in research
purposes alone (the first stage). Based on these results, their reactions may be explained by the ‘slippery slope
argument’, which is often cited in bioethics discussions [31]. The ‘slippery slope argument’ is a way of thinking
in which, taking IVG technology as an example, the creation and use of IVD-gametes for research is considered
ethically desirable or not morally unjust; however, even the creation and use of IVD-gametes for research should
not be permitted because, once this act is allowed, it may result in some morally unjust consequences such as the
creation and use of embryos with IVD-gametes for research or reproduction. Therefore, among the respondents
who answered that they could not accept the creation and use of IVD-gametes at all, there may be some who do
not necessarily oppose the creation and use of IVD-gametes for basic research, but are concerned about its possible
development into the creation and use of embryos with IVD-gametes for research and clinical practice in the future.

Discussion

Characteristics of the respondents who would not accept the creation & use of IVD-gametes at all

In the conventional bioethics debate, there have been no ethical restrictions on the handling of gametes as long as
due consideration is given, although some people have raised the issue of the moral status of gametes [29]. In this
survey, approximately 80% of the respondents answered that they accepted the creation and use of IVD-gametes
for basic research purposes, which is already permitted by the current Japanese research guidelines, whereas as many
as approximately 20% of the respondents answered that they could not accept it at all. Based on these results, we
examined the characteristics of the respondents who answered that they could not accept the creation and use of
IVD-gametes at all. Our results indicated that such respondents fall into either or both of the following categories.

One is the category of people who have a strong antipathy to life manipulation (artificial intervention in
reproduction). Those who answered that they could not accept the creation and use of IVD-gametes at all tended
to not to express the expectations of ‘development of therapeutic modalities and drugs for congenital diseases’ and
‘birth of genetically related children’ (Table 6).

These results suggest that, even if there is a technology that is likely to bring clinical benefits in the future,
those people would have no expectation of these benefits and show a strong antipathy toward the development of
such technology. They also tended to exhibit the concerns of ‘unnaturalness’, ‘playing God’ and ‘infringement of
human dignity’ (Table 7). In a previously conducted survey involving the Japanese general public on the degree
of acceptance, expectations, and concerns regarding human–animal chimeric embryo research [30], approximately
20% of the respondents answered that they could not accept the research at all and expressed concerns similar
to those observed in the present survey, such as ‘unnaturalness’ and ‘infringement of human dignity’. Those who
expressed these concerns regarding a technology and answer that they cannot accept it at all may display the same
attitude toward other life-manipulating technologies, which should be verified in future research.

Another is the category of people who have concerns regarding the potential ramifications of IVG technology.
Those who answered that they could not accept the creation and use of IVD-gametes at all also tended to express
the concerns of ‘loss of values’, ‘promotion of embryo destruction’, ‘unknown risk to children’ and ‘pressure on
parents.’ These concerns are associated more with the creation and use of embryos with IVD-gametes for research
and reproductive purposes (the second and third stages) than the creation and use of IVD-gametes for research
purposes alone (the first stage). Based on these results, their reactions may be explained by the ‘slippery slope
argument’, which is often cited in bioethics discussions [31]. The ‘slippery slope argument’ is a way of thinking
in which, taking IVG technology as an example, the creation and use of IVD-gametes for research is considered
ethically desirable or not morally unjust; however, even the creation and use of IVD-gametes for research should
not be permitted because, once this act is allowed, it may result in some morally unjust consequences such as the
creation and use of embryos with IVD-gametes for research or reproduction. Therefore, among the respondents
who answered that they could not accept the creation and use of IVD-gametes at all, there may be some who do
not necessarily oppose the creation and use of IVD-gametes for basic research, but are concerned about its possible
development into the creation and use of embryos with IVD-gametes for research and clinical practice in the future.

Characteristics of the respondents who would accept the creation & use of embryos with
IVD-gametes for research purposes

The human embryo is considered to have a special value for various reasons, and conventionally, the moral status of
the embryo has been discussed actively in the bioethics debate concerning hESC research [32]. Some people argue
that, even in cases where the use of surplus embryos for research purposes is ethically justified, the creation and use of
research embryos is not ethically justified because of the concerns regarding infringement of human dignity and
conversion of embryos into tools [33]. Furthermore, while some argue that the embryo with IVD-gametes is a mere
cell aggregate [10,34], the moral status of the embryo with IVD-gametes is generally considered to be equal to that
of the embryo [8,19,35].
expected to contribute to the advancement in ART and research involving the creation and use of hESCs. Within this context, the results of this survey showing that approximately half of the respondents answered that they would accept the creation of embryos with IVD-gametes, which has not been allowed in the current Japanese research guidelines, is astonishing.

Similar results have been reported in previous studies. In 2005, a research group from Johns Hopkins University conducted a survey involving 2212 American general citizens; although the survey did not address the creation of embryos with IVD-gametes. In that survey, they gave a brief explanation to the respondents that there were arguments both for and against the use of research embryos, not surplus embryos, for hESC research, and then asked the respondents about the degree of acceptance. The opinions of the respondents were divided, with approximately 49% approving and 48% opposing the use of research embryos [37].

In our survey questioning the need for the creation of embryos with IVD-gametes as well, the respondents' opinions were divided. However, attention should be paid to interpreting this result. In our survey, slightly less than half of the respondents opposed the creation of embryos with IVD-gametes, but the number of respondents who expressed concerns regarding the use of gametes as tools, use of embryos as tools, unnaturalness, promoting embryo destruction, infringing human dignity and playing God (Figure 3) exceeded the number of those who opposed the creation of embryos with IVD-gametes (Figure 4). These results suggest that the respondents who accepted the creation and use of embryos with IVD-gametes included not only those who approve it unconditionally but also a certain number of people who take cautious attitudes.

Characteristics of the respondents who would accept the birth of children derived from embryos with IVD-gametes

As shown by the results on the degree of acceptance, those who accepted the birth of children derived from embryos with IVD-gametes remained at approximately 20% of the respondents (Figure 4). Furthermore, more than 60% of the respondents had expectations related to the reproductive use of IVD-gametes (reduction in genetic diseases, birth of genetically related children, availability of gametes for reproduction and availability of embryos for reproduction) (Figure 2). Although these results seem inconsistent, findings from a separate survey that we asked the same respondents another question indicated that more than 60% approved the use of IVD-gametes for reproduction by couples suffering from infertility who are unable to achieve pregnancy with existing infertility treatments. This implies that the attitudes toward the use of IVD-gametes for reproduction can change depending on the conditions.

Hendriks et al. conducted a survey involving 494 couples with infertility who attended a fertility clinic (couples diagnosed with nonobstructive azoospermia and having opted for testicular sperm extraction with intracytoplasmic sperm injection from 2007 to 2012), and obtained the result that approximately 90% of couples opted for the use of IVD-gametes as the first choice or the final means [38]. In our survey, slightly less than 10% of the respondents had sperm injection from 2007 to 2012), and obtained the result that approximately 90% of couples opted for the use of IVD-gametes with intracytoplasmic sperm injection failed. This may explain why a higher degree of acceptance of the use of IVD-gametes for reproduction was obtained than with our survey, which did not set such limits and included the respondents who had experienced infertility treatment in general (including the rhythm method and the induction of ovulation) in the analysis.

The structure of the question on the degree of acceptance and concerns regarding the use of IVD-gametes for reproduction were also considered as other factors explaining the relatively small number of respondents who accepted the process until childbirth using IVD-gametes in contrast to the high expectations regarding the use of IVD-gametes for reproduction. In that question, accepting the second stage (the creation and use of embryos with IVD-gametes) was a prerequisite for accepting the third stage (childbirth using embryos with IVD-gametes) over the series of processes involved in the creation and use of IVD-gametes. Therefore, those who would not
accept the second stage (creation and use of embryos with IVD-gametes for research purposes) but would accept
the third stage had to choose from ‘I cannot accept it at all’ and ‘up to the first stage’. For example, a respondent
who accepts childbirth using embryos with IVD-gametes but does not accept the creation and use of embryos with
IVD-gametes for research purposes might have exhibited acceptance up to the first stage because this respondent
cannot accept the second stage.

In addition, regarding the use of IVD-gametes for reproduction, a large majority of respondents had concerns
regarding the unknown risk to future generations and the birth of designer babies. These are also the points that
have been highlighted first as ethical problems regarding the use of IVD-gametes for reproduction. These concerns
might have been reflected in the small number of respondents who approved the use of embryos with IVD-gametes
for reproduction.

Limitations & significance of our survey
This is the first survey to reveal the degree of acceptance in the general public toward the creation and use of
IVD-gametes. Certainly, because the respondents of this survey were monitor members of a survey company,
attention should be paid to the fact that the answers do not include the opinions of those who do not usually use
the Internet. However, our sampling method was designed to align age and sex with the vital statistics of Japan in
order to minimize the bias in answers.

Since this survey was carried out in 2017, the publication of the results only taking place now could be considered
a limitation; however, considering that there have been no breakthroughs in IVG technology, nor any policy related
debates thereof in Japan, nor any major events that have stirred public interest (such as the sensational news in
China about the birth of gene-edited babies [39]), we can safely presume that public awareness of IVG technology
has changed very little over the past several years in Japan, and therefore, the time interval between the survey and
this study does not significantly affect the results and discussion.

As often noted in bioethics, we should not deduce any normative argument directly from empirical data. In other
words, we cannot say that the creation of IVD-gametes should be allowed on the grounds that approximately 80%
of respondents approved it, and conversely, we cannot say that the use of IVD-gametes for reproduction should
not be allowed from an ethical viewpoint because almost 30% of respondents disapproved it. However, the results
of this survey, which partly revealed the interests of the general public, would be useful in promoting the public
debate over the ethical/social acceptability of the creation and use of IVD-gametes as well as the ideal way of its
regulation in the future.

Furthermore, this survey successfully revealed the attitudes of the general public toward the fertilization of
IVD-gametes for research purposes, which is considered to become an issue when the creation of IVD-gametes is
achieved in the future. Our results will also be useful in discussing the ideal means of regulating the creation and
use of research embryos, including embryos with IVD-gametes.

We understand that IVG research has progressed and that the possibility of IVG technology further developing
successfully in the future cannot be denied. The ISSCR 2021 conducted a focus session on ‘The Science and Ethics
of Generating Gametes from Stem Cells’ which discussed these issues in detail [40]. Thus, the theme is regarded
as important among the community of stem cell researchers, and it seems to be relevant even today. While it is
understandable that some skepticism exists as to whether IVG technology will be developed into ART, we believe
that it is prudent to consider the ethical and social acceptability of such technology before it is fully developed.
Waiting until the technology is complete before considering this would run the risk of not having enough time
to discuss its implications before the more practical interests of stakeholders overpower ethical considerations and
influence the decision of whether to use it or not. Thus, we believe that the opinions of the general public on IVG
will serve as a valuable source of knowledge from which future debates on the subject may greatly benefit; therefore,
it is the merit of the current study.

Conclusion
Considering the possibility of using IVD-gametes for reproduction in the future, international cooperation will
be necessary for legal regulation. Conducting similar surveys in other countries in anticipation of such a scenario
should reveal the similarities and differences between Japan and other countries in public attitudes toward the
creation and use of IVD-gametes. Such international comparison would be the first step toward the establishment
of an international regulatory framework that considers the interests of different countries.
Summary points

- The creation and use of in vitro derived (IVD)-gametes can affect not only individuals but also the whole society and even future generations. Once in vitro gametogenesis technology is established, the issue of discussion will be ‘how should IVD-gametes be used ethically in research and clinical settings’ rather than ‘whether the creation and use of IVD-gametes should be permitted’.
- While it is necessary to discuss with potential stakeholders who are likely to be affected by the creation and use of IVD-gametes to what extent they should be permitted before the creation of IVD-gametes is achieved, few attitude surveys have been conducted to investigate this, and no such survey has ever been conducted in Japan.
- In this study, an online survey was conducted in May 2017, with the general public as the target population, and 3096 respondents participated.
- In the questions used to grasp the respondents’ degree of acceptance over a series of processes involving research using IVD-gametes to the clinical use of IVD-gametes, 78.6% of the respondents answered that they would accept the creation and use of IVD-gametes for research purposes, 51.7% answered that they would accept the creation and use of embryos with IVD-gametes for research purposes, and 25.9% answered that they would accept childbirth using embryos with IVD-gametes. In contrast, 21.4% of the respondents answered that they could not accept any of the presented conditions.
- The results of this survey showing that approximately half of the respondents answered that they would accept the creation of embryos with IVD-gametes, which has not been allowed in the current Japanese research guidelines is astonishing.
- While more than 60% of the respondents expressed their expectation for reproductive use of IVD-gametes, only about 20% of the respondents answered that they would allow reproductive use. This could be partly because the structure of the questionnaire and the concerns that respondents had about IVD-gametes may have affected the results of their response.
- Considering the possibility of using IVD-gametes for reproduction in the future, international cooperation will be necessary for legal regulation. Conducting similar surveys in other countries in anticipation of such a scenario should reveal the similarities and differences between Japan and other countries in public attitudes toward the creation and use of IVD-gametes.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/suppl/10.2144/fsoa-2021-0066

Author contributions

T Sawai, T Hatta and M Fujita designed the study and collected data. T Hatta analyzed data. T Sawai and K Akatsuka drafted the initial manuscript and made revisions. T Hatta wrote and revised Methods. M Fujita provided feedback on drafts. T Sawai, K Akatsuka and T Hatta prepared the manuscript for submission. M Fujita supervised the whole process. All authors approved the final manuscript as submitted.

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Ethical conduct of research

The survey was conducted with the approval of the Joint Medical Ethics Committee of the Institute for Frontier Life and Medical Sciences and the Center for iPS Cell Research and Application, Kyoto University (date of approval, 11 May 2017; approval no., 81).
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