



Original Article

Attitudes of patients with IVF/ICSI toward human embryo in vitro culture beyond 14 days

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ABSTRACT

When the International Society for Stem Cell Research revised its 2021 guidelines, it reversed its ban on the *in vitro* culture of human embryos beyond 14 days. However, despite widespread recognition of the importance of public debate on embryo research, it remains unclear how patients who have undergone *in vitro* fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) perceive this change in the guidelines. Three focus group interviews were conducted with IVF/ICSI patients to understand their opinions on extending the *in vitro* culture of human embryos beyond 14 days. Thematic analysis revealed a primarily favorable attitude toward the extension of *in vitro* embryo culture, identifying six reasons for this positive perspective. However, two reasons for negative attitudes were identified, along with some concerns that need to be addressed. To facilitate an open discussion, the following suggestions were made to the government and scientific community. The government and scientific community should provide sufficient knowledge to IVF/ICSI patients about research before discussions. It's important to consider diverse views on embryo models, including distrust and resistance. Ensuring IVF/ICSI patients' psychological safety is essential. "Public conversations" with citizens, including IVF/ICSI patients, should be promoted, and their opinions should be considered as part of a broader public spectrum.

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1. Introduction

Since the 1980s, global stem cell research has followed the 14-day rule, which prohibits the *in vitro* culture of human fertilized embryos beyond 14 days or after the emergence of a primitive streak. Recent studies indicate that the *in vitro* culture of human embryos is becoming possible beyond 14 days [1,2]. The specific duration of an extension beyond 14 days is a matter of some debate: some advocate extending the period to 28 days [3,4], while others support retaining the 14-day rule [5,6].

Abbreviations: FGI, Focus group interview; IVF, In vitro fertilization; ICSI, Intracytoplasmic sperm injection; ISSCR, International Society for Stem Cell Research.

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The International Society for Stem Cell Research (ISSCR) has expressed concern that maintaining a blanket ban on the culture of human embryos beyond 14 days could impede necessary research. In May 2021, the ISSCR revised its guidelines, calling for "national academies of science, academic societies, funders and regulators to lead public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research" [7].

Many researchers advocate incorporating public opinion into discussions on extending the 14-day rule [3,8–10]. However, the ISSCR 2021 guidelines lack specific directives on communicating with embryo or gamete donors. A better understanding is therefore needed of how people who have undergone *in vitro* fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) (hereinafter "patients with IVF/ICSI"), the most important stakeholders for research on human embryos, evaluate the extension of the 14-day rule. When the 14-day rule was first introduced in the United Kingdom in 1984, potential embryo and gamete donors did

not participate in the discussion. However, when discussing the 14-day rule, recent studies have increasingly included participants in the discussion who have had fertility treatment [11]. According to the ISSCR 2021 guidelines, future patients undergoing IVF or ICSI are potential beneficiaries of embryo research, which provides advances in infertility treatment, pregnancy loss prevention, and fetal disorder management [7]. To understand how IVF patients view the *in vitro* culture of human embryos beyond 14 days, it is necessary to engage them in public discussions through “deliberative democracy, where groups of the public are given information in as unbiased a manner as possible and then they can provide their views” [4]. From these perspectives, it is worthwhile to focus on patients undergoing IVF/ICSI who are potential donors of human embryos and beneficiaries of embryo research.

Studies on patients with IVF/ICSI indicate that some prefer discarding surplus embryos over contributing to research [12]. According to one study, 58.8% of Chinese couples preferred to dispose of surplus embryos rather than donate them for research, citing a lack of information and distrust in science as significant reasons for their decision [13]. Although one study has examined public views on extending the 14-day rule [14], perspectives from patients with IVF/ICSI have not yet been explored. This is important because some individuals who have undergone IVF regard their fertilized eggs as “children” or “potential children” [15] and manifest attachment to their embryos [16,17].

In contrast, many fertility clinics around the globe are challenged by “abandoned surplus embryos” [18], while the demand for assisted reproductive treatment with donated embryos has increased [19,20]. An interview study of Parkinson’s patients awaiting embryonic stem cell-based therapy reported that some thought it was important that the donating female or couple voluntarily donated the embryos, while others considered their consent unnecessary if it was clear that the couple did not wish to keep the embryos [21].

The ISSCR 2021 guidelines further state that “research using embryos is also crucial to validate integrated stem cell-based embryo models, which in the future may provide a more practical alternative to understanding some aspects of early human development” [7]. In recent years, research on integrated stem cell-based embryo models has shown steady progress [22,23]. However, this area of study also faces several challenges. For example, public and stakeholder engagement and transparency are needed, as is consensus on the naming and definition of embryo models [24]. Additionally, Yui et al. (2024) point out that Japanese researchers believe that the regulations for research on embryo models need clarification [25].

It has been suggested that attitudes and expectations toward stem cell research and regenerative medicine vary from country to country [26]. How patients who have undergone IVF/ICSI would rate the extension of the 14-day rule and the use of embryo models for research needs to be investigated in each country.

Therefore, the purpose of this study was to provide insights for “public conversations” among Japanese patients who had undergone IVF and/or ICSI by clarifying their evaluation of the extension of the 14-day rule and the use of embryo models for research. We employed a deliberative democratic approach and conducted online group interviews with 22 participants across Japan to explore how to foster discussions about the *in vitro* culture of human embryos beyond 14 days. Additionally, the evaluation of embryo models in patients undergone IVF/ICSI treatment was investigated. The survey details are in [Supplementary information S1](#) and [S2](#). The questions used in the focus groups, including questionnaires and works translated into English, are in [Supplementary information S3](#).

2. Methods

FGIs with 22 IVF-experienced individuals were held on October 9, 16, and 28, 2022. This research protocol was approved by the institutional review board at the Institute of Medical Sciences, University of Tokyo (approval number: 2021-67-1222, approval date: July 21, 2022).

Participants were recruited with the cooperation of the largest nonprofit organization of people affected by infertility in Japan, FINE [27]. A preliminary questionnaire was used to confirm the participants’ gender, age, treatment experience and status, and availability on the date of the scheduled interview. The following recruitment criteria were stated in the request: Participants must be at least 20 years old and under 55 years old, have previous experience with IVF or ICSI, and be currently stopping or terminating infertility treatment. They must be able to participate in online (Zoom) group interviews on Sunday, October 9, 2022, from 10:00 a.m. to 12:00 p.m. (for women) and Sunday, October 16, 2022, from 10:00 a.m. to 12:00 p.m. (for men). Participants are required to speak while showing their face, though participation using a pseudonym is possible. Participants were selected by Fine board members based on these criteria. One of the reasons for the age requirement is to target those who have recently experienced infertility treatment. Twenty-three members were selected in total, and one member (E–2) was absent. The participant selection did not account for parenthood status or religious beliefs, reflecting Japan’s largely nonreligious populace [28].

We adopted an online group interview method, which also included the exchange of opinions via a chat function, to conduct an evaluation before and after the participants interacted and to observe how the participants’ ideas and thoughts transformed. Zoom was utilized as an online communication tool for conducting interviews. This method was chosen because we could include participants from all over the country who could help each other develop discussions on scientific topics that are not thought about every day, and communication using chat can boost group dynamics.

The interview method used was devised by the Institute for Science Communication, based on Fishkin’s deliberative poll [29]. The intention is to construct dialogue by asking about the public’s mental images around an issue rather than their preferred solutions. While the solutions are highly contingent on factors such as information sharing, the way the dialogue is conducted, and the participants’ attributes, we believe that issues expressed by the general public as consumers are more truthful and more valuable to refer to.

The online group interviews were led by a trained facilitator from the Institute for Science Communication, with the authors making nonverbal observations. The participants’ questions were answered as appropriate. Before the participants were given a detailed explanation, they were asked via the chat function whether they had positive or negative feelings about the extension of the 14-day rule. They were asked the same question again during the latter part of the opinion exchange.

3. Results

FGIs were conducted with 22 participants, both male and female, aged 20–54 years, who had undergone IVF and/or ICSI and had either stopped or completed treatment. The participants were divided into three groups by gender (two groups of females and one group of males). The participant demographics are delineated in [Table 1](#).

The schedule of each FGI, which lasted two and a half hours, was as follows:

1. Provision for social and scientific information on the 14-day rule and a question-and-answer session.

2. First survey: Four-step evaluation of the in vitro culture of human embryos beyond 14 days.
3. Discussion of good points, bad points, and questions.
4. Second survey: Four-step evaluation of the in vitro culture of human embryos beyond 14 days.
5. Additional survey: Four-step evaluation of embryo models.

3.1. Evaluation results

In the first survey, 21 of 22 participants (95.5%) viewed extending the 14-day rule positively (Supplemental Table S1). After 1 h of discussion, a second survey showed that 19 out of 22 (86.4%) maintained positive attitudes (Supplemental Table S2). These results, indicating that a majority favored longer in vitro human embryo culture, were the same in all three groups. Thematic analysis was used to investigate positive and negative permissive attitudes among the participants toward extending the 14-day rule [30]. The identified themes are delineated in Table 2.

3.2. Reasons for positive evaluation

Six themes were identified that explained permissive attitudes among the participants toward extending the 14-day rule.

Theme 1. Expectations for the progress of fertility treatment and medical research

Most participants referenced medical research, advancements in medical technology, and the anticipation of developing new treatments as the basis for their evaluations:

If the times were different, we might not have been able to have children, but thanks to modern medicine, we could have children. On the basis of this experience, I hope that further research will be conducted by changing the rules, if it will lead to the development of reproductive medicine. (E–1, Questionnaire 2, somewhat positive, female).

If the change is used for fertility treatment, infertility treatment, and various other medical developments, I think it will be effective for the future development of medicine, and

I think it is commendable. (C–4, Questionnaire 2, positive, female).

The participants tolerated extending human embryo culture beyond 14 days for research, seeing benefits for advancing fertility treatments and medical research in general. However, their ideas for medical research or cures were related to infertility, and despite having received prior explanations of the potential for regenerative medicine, they did not mention ES cell-derived therapies for other diseases.

Theme 2. Passive acceptance of the research use of embryos, with mixed feelings

Some participants noted that if human embryos were slated for disposal, it was preferable to use them for extended in vitro culture beyond 14 days to avoid wastage:

If fertilized eggs are scheduled to be discarded, I would like them used for research. However, in reality, I believe that some people, like myself, have feelings about fertilized eggs. Of course, I would sign a consent form for research use, but I may have mixed feelings about it. (E–4, Questionnaire 2, somewhat positive, female).

This participant had mixed feelings about the use of fertilized eggs in research; however, after weighing the disposal of fertilized eggs against their potential use in research, the participant passively accepted their use as a trade-off to disposal.

Theme 3. Assessing the social value of science

Throughout the discussions, some participants maintained a positive stance toward extending the in vitro culture period of human embryos beyond 14 days, prioritizing the advancement of research over the absence of progress. Despite recognizing the complexities involved in extending the culture period of human embryos beyond 14 days, the participants appreciated the potential long-term value of this research. Their acceptance was influenced by the anticipated advantages of facilitating research endeavors.

Table 1
Participant characteristics (n = 22).

	ID	Age group	Occupation	Timing of infertility treatment initiation	Timing of infertility treatment interruption or termination
Female patients with IVF/ICSI Group A (2022/10/9)	C-1	30s	Healthcare worker	2016	2021
	C-2	20s	Healthcare worker	2018	2022
	C-3	40s	Nutritionist	2009	2019
	C-4	40s	Healthcare worker	2004	2014
	C-5	50s	Yoga instructor	2008	2018
	C-6	50s	Telephone operator	2008	2018
	C-7	30s	Engineer	2020	2022
	C-8	30s	IT-related worker	2020	2021
Female patients with IVF/ICSI Group B (2022/10/28) (E–2 was absent from this interview)	E-1	30s	Unemployed	2018	2018
	E-3	40s	Office worker	2012	2014
	E-4	40s	Career consultant	2013	2020
	E-5	40s	Office worker	Missing data	2022
	E-6	40s	Service worker	2018	2020
	E-7	40s	Acupuncturist	2015	2021
	E-8	30s	Office worker	2021	2021
	Male patients with IVF/ICSI Group C (2022/10/16)	D-1	50s	Company employee	2000
D-2		30s	Sales consultant	2018	2021
D-3		30s	Manager	2016	2018
D-4		40s	Researcher	2009	2016
D-5		40s	Manager	2018	2022
D-6		30s	Educator	2018	2020
D-7		50s	Office worker	2003	2012

Table 2
Positive and negative themes.

Positive Themes	<p>Theme 1: Expectations for the progress of fertility treatment and medical research</p> <p>Theme 2: Passive acceptance of the research use of embryos, with mixed feelings</p> <p>Theme 3: Assessing the social value of science</p> <p>Theme 4: Ambiguity in drawing the line at 14 days</p> <p>Theme 5: Entrusting the evaluation of the 14-day rule's value</p> <p>Theme 6: Need for flexibility in rules</p>
Negative Themes	<p>Theme 7: Difficulty understanding the context</p> <p>Theme 8: Experience of embryos not developing with IVF and/or ICSI</p>

I have come to understand that there are many issues that need to be addressed, as I have heard many stories this time. However, I really hope that this research will continue. I think that any research has challenges and needs discussions and I don't want the research to take so long that it cannot proceed, so I would like to think positively about proceeding with the research. (C-3, Questionnaire 2, positive, female).

Theme 4. Ambiguity in drawing the line at 14 days

Demarcation of the 14-day limit was perceived by some participants as ambiguous and unconvincing, leading some to endorse the in vitro culture of human embryos beyond this timeframe.

I felt that the reason for the 14 days was not clear; therefore, I thought that an extension could be considered. (C-2, Questionnaire 1, somewhat positive, female).

In the survey, some participants agreed with the logic of the 14-day rule, while others were skeptical, viewing the boundary as a compromise. However, the latter group lacked a strong rationale for this limit and thus evaluated it positively.

Theme 5. Entrusting the evaluation of the 14-day rule's value

Some participants gave positive evaluations because as laypersons they could not judge the research and felt that they had to trust the researchers:

Above all, researchers in this field are sending out messages that they will change this rule; therefore, I think there is a solid possibility [for medical research] there. I think that amateurs like us, people who do not know, people who are waiting, have no choice but to believe in them. I really evaluate it and wish the researchers the very best. (D-5, Questionnaire 2, positive, male).

The participants took a positive view of the possibilities presented by scientists, and they believed in them. Therefore, they favored the in vitro culture of human embryos beyond 14 days, if required by scientists.

Theme 6. Need for flexibility in rules

One participant positively evaluated the in vitro culture of human embryos beyond 14 days because of the need for a little leeway in the rule:

If we don't make some rules, we definitely need rules because I think that researchers are people, and we all have our own ethics. I think this discussion has come to a boil because researchers have become more intellectually demanding and more knowledgeable based on the rules that have been in place until now. Hence, if we don't give a little leeway before the

balloon bursts, there is a possibility, for lack of a better word, of some research getting out of control ... (E-7, Questionnaire 1, somewhat positive, female).

Here, balloon is used as a metaphor for the rule. The participant feared that the balloon would pop. Rules are necessary, but the concern was that if the rules were rigid, some researchers would run amok. This participant felt that flexibility would be needed in regulations to prevent researchers from engaging in unethical or uncontrolled behavior.

3.3. Reasons for negative evaluation

In the first survey on extending human embryo culture, 1 out of 22 participants (4.5%) was "somewhat negative" (Table S1). The second survey showed that 3 out of 22 (13.63%) had this view (Table S2). The inability to evaluate was analyzed, yielding two themes.

Theme 7. Difficulty understanding the context

One participant (E-3, female) did not immediately understand the survey content and chose "somewhat negative" in the chat box and entered "because I do not have the answer in my mind" as the reason for her choice. Even in her verbal explanation, this participant said, "It's a little difficult for me, too, and I still don't understand it 100%."

Theme 8. Experience of embryos not developing with IVF and/or ICSI

One participant (C-5, female) opted for "somewhat negative," owing to her experience with fertilized eggs failing to develop. The participant's preference was for researching human embryos within the initial 14-day period, rather than extending their in vitro culture.

3.4. Thoughts on fertilized embryos

Apart from the themes raised by the participants, we asked them, "What kind of entity is an autologous fertilized or frozen embryo?" Thirteen out of 15 women and two out of seven men described their fertilized and frozen embryos as "children" or "near life." It was noted that the patients with IVF/ICSI, while perceiving these embryos in such terms, generally agreed with the justifications for conducting research, albeit with ambivalent sentiments:

In a word, they're like your own children It's like a life in my mind. (E-5, Questions from researchers, female).

I also think they are near life, but ... as a result, when the child was successfully born, the frozen eggs, of which there were several, were discarded, so there are no more left now. However, when it came to discarding them, there was still a dilemma. (C-4, Questions from researchers, female).

3.5. Attitudes toward integrated stem cell-based embryo models

As an additional topic, the participants were briefed on integrated stem cell-based embryo models and asked to evaluate their use in research in a four-step evaluation. One participant (E-3) withheld an evaluation, while the other 21 participants rated it either positively or negatively. Sixteen of 22 (72.7%) expressed "positive" or "somewhat positive" views on using embryo models (Supplemental Table S3), noting advances in medical research and reduced ethical concerns versus human embryos. Nonetheless, even those with a positive outlook harbored concern:

This one [embryo models] is somewhat more ethically resistant. I think there is some resistance to artificial creation itself, so I chose ... “somewhat positive.” (E-6, somewhat positive, female).

I can't shake the feeling of distrust or uneasiness about whether the research using this [embryo models] can really be called a correct result or not. (C-6, somewhat positive, female).

The first participant quoted above showed an instinctual resistance to research with embryo models compared with research using human embryos, while the second participant quoted above mentioned distrust and anxiety about research results when embryo models are used. These findings indicate that the prevalent positive sentiment toward embryo models did not negate the existence of underlying concerns.

4. Discussion

We analyzed the significant and less significant reasons for extending the *in vitro* culture of human embryos beyond 14 days. Most participants were in favor of extending this practice. Our analysis identified six themes underpinning this positive evaluation. Themes 1 and 3 suggest that patients undergoing IVF/ICSI positively viewed the extension of the 14-day rule, given the potential scientific benefits. However, Theme 2 indicates that the participants had mixed feelings due to their emotional connection to their embryos. For patients with IVF/ICSI, a fertilized egg is perceived as “children” or “near life.” Despite the prospect of destroying embryos at a more mature stage, the participants did not refer to the dilemma of destroying more mature embryos but to the classic dilemma they faced when donating their embryos for research. Themes 4–6 reflect the participants' understanding of the difficulties in establishing and applying reasonable rules.

Conversely, Themes 7 and 8, which were associated with negative evaluations, do not directly conflict with the positive evaluations. Overall, the participants were largely unfamiliar with discussions on regenerative medicine and stem cell research, which they found difficult to comprehend. For instance, the challenges in evaluating the extension stemmed from the absence of a specific research protocol and concerns about credible governance. As Melamed et al. (2009) and Hug et al. (2008) demonstrated, ambiguity surrounding the goals of extending the 14-day rule might discourage individuals from donating their fertilized or frozen embryos [12,31]. Fuscaldò et al. (2007) also highlighted the importance of clear communication about research objectives, methodologies, and potential applications for encouraging donations [32]. Although discussions based on research ethics documents can be challenging, dialogue with researchers in human and animal embryo studies may uncover future research directions and aid in making informed decisions on extending embryo culture. Thus, the possibility remains that more opportunities for dialogue could shift opinions toward a more favorable evaluation.

This study also suggests that patients with IVF/ICSI intuitively oppose embryo models, associating them with ethical concerns. Notably, these patients showed psychological resistance and discomfort toward embryo models, even though such models might help them avoid the difficult decision of consenting to the research use of their embryos. This underscores the need for comprehensive explanations and active dialogue with patients with IVF/ICSI when using embryo models in research.

Our results indicate that it is feasible to involve IVF/ICSI patients in “public conversations.” Even in online group interviews, the

participants demonstrated their ability to learn about human embryo research and the 14-day rule, as reflected in the narratives under Theme 3. Dialogue conducted with patients with IVF/ICSI could be one method to involve them. However, one limitation of this online method is its exclusion of those without online access, highlighting the value of traditional face-to-face dialogue. Nevertheless, it has facilitated broader and more geographically diverse participant engagement. We believe that the online interview method we employed is valuable for enhancing the psychological safety of patients with IVF/ICSI and for establishing a method to listen to voices that might not be heard at consensus meetings, which often attract only groups with a high interest in stem cell research.

We offer suggestions to ensure the inclusion and consultation of patients with IVF/ICSI in “public conversations” about extending the 14-day rule and using embryo models in research. First, the government and the scientific community should provide sufficient opportunities for patients with IVF/ICSI to become familiar with the research process before inviting them to discussions. Our findings show that patients with IVF/ICSI tend to assume that research involving human embryos or embryo models primarily aims to address infertility, IVF, pregnancy loss, and fetal developmental disorders occurring or originating soon after implantation. Simultaneously, they view research favorably in anticipation of general advances in infertility treatment. It is necessary to clearly communicate the significance of using human embryos or embryo models in basic research to elucidate and treat diseases unrelated to infertility. Second, it is important to listen to diverse views on embryo models, as some participants expressed distrust and anxiety about the outcomes of such research, while others resisted the research itself. Efforts should be made to understand the perspective of IVF/ICSI patients who did not participate in our interviews and who are in favor of the embryo models. Third, ensuring the psychological safety of patients with IVF/ICSI is essential. Efforts should be made to avoid situations in which they feel pressured to discard or donate their embryos or gametes. Finally, it is crucial not to rush the extension of the 14-day rule based solely on positive views from IVF/ICSI patients, as they are only one group of stakeholders. The key is to foster “public conversations” that include IVF/ICSI patients and consider their views as part of a broader public opinion spectrum.

The primary strength of this study lies in revealing that many patients with IVF/ICSI view the extension of the 14-day rule positively. Another strength is its demonstration of the diverse reasons behind these positive evaluations, which do not fit into a single category. Furthermore, this study highlights that individuals who lack an understanding of regenerative medicine and stem cell research, or who have experienced unsuccessful fertilized egg development, may negatively evaluate an extension of the 14-day rule. Thus, this study is unique in its detailed discussion of the reasons behind both positive and negative evaluations of extending the *in vitro* culture of human embryos beyond 14 days.

5. Study limitations

This research obtained valuable data by asking potential cell donors directly about their views on culturing embryos for more than 14 days. However, it has certain limitations: it was a qualitative interview study, and we cannot generalize the results. We need to review this study by combining the survey with an expanded-scale questionnaire survey and interviews with experts. This aspect warrants investigation in future research. Future considerations should also include the differences between patients with IVF/ICSI and other citizens.

Author contributions

Conceptualization, Y.K., S.W., and K.M.; Data curation, Y.K. and S.W.; Investigation, Y.K., S.W., K.H., H.Y., Y.Y., and K.M.; Methodology, Y.K., S.W., and K.M.; Writing – Original Draft, Y.K.; Writing – Review & Editing, Y.K., S.W., K.H., H.Y., Y.Y., and K.M.; Project administration, K.M.; Funding acquisition, Y.Y. and K.M.; Supervision, K.M.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Chat GPT and Claude in order to improve the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare no competing interests.

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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.2024.09.005>.

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