Jurnal 'Ulwan
eISSN: 2600-7843
Jilid 8 (Bil.3) 2023: 249-256

POTENTIALS AND ETHICS OF STEM CELL-DERIVED GAMETES: EXPERT VIEWS FROM MALAYSIA

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Article history:
Received : 20 Oktober 2023
Accepted : 13 November 2023
Published : 22 Disember 2023

ABSTRACT

Stem cell-derived gametes (SCDGs) offer a promising solution for addressing infertility and advancing reproductive technologies. Nevertheless, developing this type of gamete in Malaysia necessitates careful consideration of ethical concerns. This study discusses the expert views on the potential of the application and concerns that might arise if this technology were implemented in Malaysia. It also analyzes their perspectives on whether technology can be allowed in Islam. Library research and interviews with experts in stem cell research and Islamic studies were conducted. This study found that the experts are positive about developing stem cell-derived gametes as this application holds great potential for addressing reproductive issues in the country. It could be allowed in Islam. However, it is necessary to establish strict rules to address ethical concerns and ensure responsible development and use. Continued research and collaboration among scientists, religious scholars, and policymakers are necessary to ensure its safe and ethical implementation.

Keywords: Stem Cell-Derived Gametes; In Vitro Gametogenesis; Ethics; Islam; Malaysia

INTRODUCTION

Stem cells are unique cells capable of self-renewal and can differentiate into one or more mature cell types (Denham et al., 2005). Stem cell research has witnessed remarkable progress recently, particularly in reproductive biology. Among exciting developments is the development of stem cell-derived gametes (SCDGs) through in vitro gametogenesis (IVG). IVG is the reconstitution of germ cell development in vitro from stem cells (Nagamatsu & Hayashi, 2017). Studies in mice showed that

induced pluripotent stem cells (iPSC) could differentiate into primordial germ cell–like cells (PGCLCs) in vitro. The PGCLCs can form fully functional sperm and eggs upon transplantation into reproductive organs and later generate viable offspring. In 2016, the first functional mouse germ cells were successfully grown in vitro, from skin cells to iPSC and oocytes. The cells were fertilized using in vitro fertilization and live pups were born (Vogel, 2016). Recently in March 2023 a research team from Japan successfully turned a stem cell from an adult male mouse into an egg cell. They discarded the Y chromosome and duplicated the X chromosome. The altered stem cell was later put in a synthetic ovary developed from stem cells. The cell eventually developed into an egg and fertilized with sperm from a male. 7 out of 630 embryos from such egg cells in this study resulted in live pups that grew normally (Bartels, 2023). There are several compelling reasons to produce human SCDGs. First, it provides an opportunity to delve deeper into the intricate study of human germ cells and gamete development, which has historically been challenging. Secondly, it holds the promise of restoring fertility, especially for individuals who have undergone treatments like cancer radiotherapy or chemotherapy. Thirdly, this approach offers a consistent source of gametes, especially oocytes. This not only facilitates studies on early embryos but also reduces the reliance on gamete donors. Lastly, it could potentially pave the way for heritable human genome editing (Lovell-Badge et al., 2021).

The International Society for Stem Cell Research (ISSCR) has categorized IVG for human reproductive purposes as a category 3A prohibited research activity, due to unresolved safety and ethical concerns (Lovell-Badge et al. 2021). Despite the speculation that IVG might one day account for a large proportion of human pregnancies, researchers have not yet attempted to produce human egg or sperm cells from stem cells, a process that has been smoother in mice (Bartels 2023). Even though IVG is currently viewed more as a model system to enhance understanding of gametogenesis and fertility (Nagamatsu & Hayashi 2017), its potential applications in human reproductive medicine and the associated ethical conflicts demand urgent discourse. Even though significant research is still required to navigate safety and efficacy challenges, and human trials have not been initiated, the ethical ramifications of stem cell-derived gametes should be discussed now (Ishii & Saitou, 2017; Bredenood & Hyun, 2017; Bartels 2023; Horer et al., 2023).

Little is known about religious and socio-cultural perspectives on the ethics of SCDGs. In a survey of the Japanese public, only half of them would accept using embryos from SCDGs for research purposes and only a quarter of them would accept childbirth from the gametes (Sawai et al., 2021). In Belgium, the public is positive towards SCDGs except for application in postmenopausal women (Mertes et al., 2022).

Given that the research on stem cell-derived gametes is still at the basic and pre-clinical stage, it has not been much discussed from an Islamic perspective. A study by Serour et al. (2023) concluded that developing SCDGs could be permissible by strictly adhering to Islamic ethical principles related to marriage, biological/genetic relatedness, sexual intercourse, and the moral status of the embryo/fetus versus that of the gamete. To add more discussion to that, this study explores the view of Malaysian experts on the potentials and concerns that might

arise if SCDGs were used in Malaysia. It also discusses their perspectives on whether technology can be allowed in Islam.

LITERATURE REVIEW

Potentials And Concerns Of SCDGs

Based on our review, it can be understood that research on SCDGs garners considerable interest and holds promise for the future. Notably, Matthews et al. (2009) observed that when scientists present on the subject of SCDGs during conferences and meetings, the majority of attendees perceive it as a technology brimming with potential scientific values. The application not only allows scientists to understand more about gametogenesis and fertility (Nagamatsu & Hayashi 2017) but also brings hope to infertile couples to have offspring that are genetically related. There are many factors that can cause infertility, including the inability to produce functional gametes due to cancer, genetic abnormalities and age-related factors (Bredenood & Hyun 2017; Horer et al. 2023).

Sawai et al. (2021) emphasized that the impact of introducing SCDGs would extend beyond the individual level, affecting society as a whole and potentially influencing future generations. Therefore, it becomes paramount to carefully consider societal viewpoints before incorporating any new technology, as it is ultimately the end-users who will interact with and utilize it. Galea (2021) argued that the use of IVG or SCDGs can evoke feelings of disgust and fear. This reaction stems from the fact that the process deviates from what is considered natural as ordained by a higher power or deity. Understandably, this non-natural aspect is bound to pose challenges within the public sphere, as societal values often place great importance on embracing the inherent naturalness and preserving the sanctity of nature. Sawai et al. (2021) further asserted that despite the potential benefits that this technology can bring, concerns and antipathy from the public are likely to arise due to the underlying issue of naturalness associated with SCDGs.

Furthermore, this technology also raises profound questions regarding family formation. A significant proportion of these inquiries arise from religious perspectives, centering around the formation and procreation of families. These concerns encompass the dignity of the family, the identity of its members, and the origins from which they spring (Dutney 2007).

Last but certainly not least, the issue surrounding same-gender couples is perhaps the most prevalent concern when discussing using SCDGs. Numerous apprehensions have been documented in this regard. Douglas et al. (2012) stated that if IVG were employed by same-sex couples, the well-being of the resulting children would be comparatively lower when compared to those born through conventional IVG practices involving different-sex partners.

Islamic Perspectives On Assisted Reproductive Technology And Stem Cell Research

Several assisted reproductive technologies (ART) including in vitro fertilization (IVF) are considered lawful in Islam (see for example fatwa on IVF in JAKIM 2015). This is because seeking medical assistance for infertility falls within the scope of preserving one's lineage, and family, and fulfilling the desire for children within the bounds of Islamic teachings. However, there are certain conditions and limitations that Islamic scholars emphasize when it comes to assisted reproductive technologies. One crucial aspect is that the procedures should not involve any prohibited acts, particularly those that contradict the principles of Islam (Ahmad Murad et al. 2014).

One of the main principles is the preservation of human lineage, which is among the five principles of *maqasid al-shariah* (objectives of shariah). According to this principle, procreation is only allowed between married couples. This ensures that the child born will have a legitimate father, who is linked to his grandfather, his great-grandfather, and so on. Such a clear lineage is important to preserve the child's dignity and well-being (Clarke 2009). It determines who will be the child's custody and responsibility, who he/she can marry, and whether he/she will inherit properties (Buruqʿah 2007).

Reproductive human cloning is not allowed in Islam. One of the main reasons, according to the Malaysian fatwa, is that it does not involve the fertilization of an egg by a sperm, which is clearly against human nature (JAKIM 2015; Zawawi 2001). The production of stem cells using somatic cell nuclear transfer (SCNT), the same method that could be used to produce human clones, is also prohibited based on the legal principle of *sadd al-zara'i*. This is the opinion of the Fatwa Committee of the National Council for Islamic Affairs of Malaysia. The use of other sources of stem cells such as adult or child stem cells, placenta and umbilical cord surplus embryos from IVF is allowed under the condition that informed consent is given by the individuals (adult stem cells) or parents (cells from child, placenta or umbilical cord or aborted fetus and surplus embryos) (JAKIM 2015). So far there have been no fatwa issued on research and use IVG or SCDGs.

METHODS

This qualitative study conducted semi-structured interviews to explore the views of experts in Malaysia regarding the potential and ethics of the SCDGs. Initially, we planned to interview six experts but unfortunately, two of them were not available due to their busy schedules. We managed to interview four experts, two of them were university researchers in stem cells (coded as S1 & S2) and the other were experts in Islamic bioethics (coded as A1 & A2). All the interviews were transcribed verbatim and analyzed using thematic analysis.

FINDINGS AND DISCUSSION

Potential benefits of SCDGs in Malaysia

Infertility is a major health concern globally. According to the World Health Organization, it is estimated that one in six adults experience infertility at some point in their life. (Free Malaysia Today 2014). In Malaysia, the Total Fertility Rate (TFR) has declined from 4.9 children per woman in 1970 to 1.7 in 2021 (Free Malaysia Today 2022). One of the factors that cause infertility is the inability to produce functional gametes. All respondents in this study, who are scientists and experts in Islamic studies, are positive that the development of SCDGs can help improve the fertility rate. S1 said: "This technology will help in solving the infertility issues for infertile couples that cannot reproduce their fertile gametes…we need to overcome this problem in order to sustain the population in the future." A1 views that technology might hold potential benefits for cancer patients in terms of fertility preservation and reproductive options. He said: "Stem cell-derived gametes can be an option or an alternative for oncology patients if they want to have children since their gametes will be affected when they undergo chemotherapy."

Apart from solving infertility issues, SCDGs can be used in combination with other applications like gene editing and genetic screening can be used for preventing the transmission of genetic defects from parents to children. S2 argued, "In the future, this technology will help to avoid epigenetics that affect the baby like autism, obesity." He further asserted that this application would need a lot of ethical considerations since the discussions surrounding the use of genetic modification and embryo selection continue. Also, it is crucial for the parents to consult with medical professionals and genetic counselors for a comprehensive understanding of the specific genetic condition, potential risks, and available options.

Potential risks and ethical concerns

Safety and efficacy are always concerns in the early stages of new technology. One of the concerns, according to S1, is the potential risk of cancer. She said:

> *"The processes to create the gametes will lead to a lot of errors if you do not do it correctly and all this at the end of the day may lead to cancer production, the misbehave of cells or misregulation of processes, stem cells need the proper physiological environment so that they can behave and differentiate into whatever cell that you tell them to become, so that's very risky if there's an error in doing so…"*

Respondents also expressed their concerns regarding the ethical implications that may arise with the implementation of stem cell-derived gametes in Malaysia. Among the main concerns is the use of this technology by unmarried or same-sex couples that could bring negative impacts on the child born and society as a whole. A2 asserted that "if this technology is used by homosexual couples, it will ruin the

family institution that is made by parents from different genders." S1 said that "reproduce gametes means you are creating another human being out of it, so when you create another human being, you need to provide that human being with a complete family, you can't simply get someone's somatic cells and reprogram them to become sperm simply because we have a request from an unmarried person that wants a child without being married." Having a complete family that consists of different sex parents will expose the child to diverse perspectives, experiences, and gender roles. Therefore, S1 explained that "it is unfair for the unborn child to have incomplete family that consist of a traditional different gender parent".

A1 also raised concerns about the issue of accessibility to the technology. Given the high cost of generating the gametes from stem cells and other assisted reproductive procedures, it may benefit some groups of people only.

None of the respondents talked about the ethical aspects of the research of SCDGs. Apart from the use, the research could also raise ethical dilemmas involving the creation, use, and destruction of oocytes and embryos, such as whether generating gametes for research is ethical. It is also debatable whether the 14-day rule in embryo research should be lifted for research on SCDGs, as it requires extensive research beyond the 14 days (Bredenood & Hyun 2017).

Islamic perspectives on SCDGs

Islam, according to A1, in general supports and encourages the use of technological advancements to alleviate suffering, enhance human capabilities, and promote overall well-being. Islamic tradition has practiced *ijtihad* (independent reasoning) in deliberating the permissibility of a controversial new technology. As long as it does not contradict the fundamental principles and values of Islam, they are generally seen as permissible and even encouraged. Islam provides a flexible framework that allows for the adaptation and integration of new technologies within the boundaries of ethical guidelines and moral principles. S1 believed that "Islam never inhibited any kind of advancement, provided that the advancement and the application that we are doing is not against the Islamic law because we have to remember as we all believe Islam is the way of life right whatever guidelines that Islam provides is actually meant do men good for us."

All respondents concurred that the development of SCDGs could be allowed under strict conditions like IVF. If using stem cell-derived gametes is seen as a legitimate medical intervention to address infertility or other reproductive health issues, it may be considered permissible as a form of treatment. A2 said "I don't see any problems in implementing the technology in Malaysia because the reason behind it or the aim of the technology is meant to be good for human beings. Islam is never against that, in fact, Islam promotes that, but it has to be properly regulated". According to A1, the development of SCDGs is consistent with Islamic teachings that encourage seeking treatment for any illness.

Their views on the permissibility of SCDGs from Islamic perspectives are similar to those of Serour et al. (2023).

FINAL REMARKS

This study found that experts in Malaysia are positive about developing stem cell-derived gametes. It could bring great potential in resolving infertility issues in the country. Nevertheless, strict guidelines and regulations should be formulated to avoid the misuse of technology. This could be done by fostering dialogues and collaborations between stakeholders including scientists, religious scholars, and ethicists.

While this study provides valuable insights, it is imperative to acknowledge its limitations, primarily the constrained sample size. The time constraint restricted the breadth of inquiries that could be made. Future research is essential to build upon the foundation laid by this study, possibly by delving deeper into the experts and public attitudes in Malaysia as well as into the Islamic perspectives.

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