The futility of fertility research? Barriers to embryo research in New Zealand

Lucy Goodman, Lynsey Cree, Gareth Jones, Michael Legge, Andrew Shelling, Cindy Farquhar

ABSTRACT

AIMS: Successive New Zealand Health Ministers have failed to approve guidelines for research using viable human embryos, which effectively places a blanket ban on all research that “uses” viable human embryos in this country. This includes research that aims to improve currently available reproductive technologies, illustrated by a failed application to ministerial ethics committees for a clinical research project investigating the efficacy of in vitro fertilisation procedures. However, no data currently exists describing the degree to which these restrictions are inhibiting reproductive research in this country.

METHODS: We have conducted a qualitative survey of New Zealand researchers from 20 major academic, clinical and governmental institutes to qualify the impact these restrictions are having on New Zealand’s research outputs.

RESULTS: The results suggest dissatisfaction with the current guidelines, and the lack of guidance from the Ministry of Health and associated ethics committees regarding what constitutes embryo research and therefore what research can be performed.

CONCLUSIONS: The lack of current guidelines regarding the use of embryos for research is restricting improvements to established reproductive technologies, and any future research. We suggest that the Minister of Health instructs ministerial advisory and ethics committees to review the current guidelines and to define the term “use of embryos”.

As many as 20 percent of New Zealanders will experience infertility at some point in their lives and many couples will seek fertility treatment in the form of assisted reproduction.\(^1,2\) Since the first successful in vitro fertilisation (IVF) procedure in 1978, the range of available treatments has expanded to include intracytoplasmic sperm injection (ICSI)\(^3\) and preimplantation genetic testing (PGT),\(^4\) to name a few. However, the success of assisted reproduction is by no means guaranteed, with only 18.1% of all ART treatments initiated in Australia and New Zealand during 2015 resulting in a live birth.\(^5\) Regardless, many thousands of infertile couples go on to enjoy the benefits of these technologies annually, thanks to many years of extensive research and development programmes conducted using animal and human embryos in research and clinical laboratories. Currently, this human embryo research is performed overseas and not in New Zealand.

In New Zealand, the use of human embryos for assisted reproduction or for human reproductive research is governed by the HART Act 2004.\(^6\) This policy framework was developed to secure the benefits of assisted reproduction for individuals and society while maintaining the health and wellbeing of children born as a result of this technology. While ART treatment facilities are widely available, and treatments are performed routinely throughout New Zealand, the stance on the use of embryos for research purposes is restrictive. While the HART Act itself is permissive for research using human embryos (section 19), research
applications must be referred to the ministerial ethics committee known as the Ethics Committee on Assisted Reproductive Technology (ECART). As the current guidelines developed in 2005 only allow for non-viable human embryos to be used in research, ECART is unable to grant ethics approval for research that uses viable human embryos. This includes research projects using identical procedures to those already approved by ACART for clinical use, as the following case study illustrates.

In September 2013 one of the authors [CF] made a preliminary enquiry to ECART about a clinical research project titled “The Day of Embryo Transfer (DOT) Study”, which aimed to improve pregnancy rates for women undergoing IVF. During an IVF procedure, the embryo is transferred into the woman’s uterus either during the cleavage stage (three days after fertilisation), or the blastocyst stage (when the culture time is extended and the embryo has reached five to six days after fertilisation). Both cleavage stage and blastocyst embryo transfer procedures have been approved by ACART as established procedures, and are performed routinely in fertility clinics throughout New Zealand. The fertility clinics’ decision on whether to perform a Day 3 or Day 5 transfer on each individual woman is usually governed by the number of viable embryos present on Day 3 (among other things), and does not require ACART approval.

Blastocyst culture is thought to improve pregnancy rates above cleavage stage transfer by better synchronising the embryo with the receptive state of the endometrium at the time of transfer. However, extending the culture from Day 3 to Day 5 can reduce the number of embryos available for transfer (or cryopreservation). Statistically, this may improve pregnancy rates (when measured as a proportion of transferred embryos), without individual women themselves necessarily experiencing a benefit. To examine whether blastocyst transfer can achieve superior pregnancy rates without the confounding influence of embryo availability, the DOT study proposed to randomise couples with four or more embryos to either transfer day, without altering any aspect of these routine, ACART-approved procedures. The trial also aimed to include neonatal outcome data as there have been concerns about the epigenetic changes in embryos with prolonged culture.

After gaining legal advice from the Crown Law Office, ECART refused the application due to its use of viable embryos. While the HART Act does not specifically prohibit embryo research using viable embryos, ECART is unable to give approval for this research unless the activity is consistent with relevant guidelines or advice issued by the ACART. However, because the current guidelines by ACART will only permit the use of non-viable human embryos for reproductive research, ECART advised that it cannot currently approve the DOT study. The Ministry of Health’s two legal opinions that supported their decision were made publicly available only after [CF] made a complaint to the Office of the Ombudsman that this information was in the public’s best interest. However, no progress has been made by ACART and the Ministry of Health to define the term “use of embryos” for human reproductive research.

As this case illustrates, New Zealand’s ‘restrictive by default’ stance on the “use” of embryos for reproductive research effectively allows fertility clinics to provide reproductive treatments, while preventing all potential research projects that could improve these existing treatments. While seeking to respect human embryos, these restrictive policies militate against best practice in healthcare with possible negative repercussions for women and their offspring.

Against this background, we have conducted a qualitative survey to understand the extent to which the HART Act, as interpreted by the Ministry of Health and respective Ministers of Health since 2005, is inhibiting reproductive research in New Zealand. Our aim was to understand the types of embryo research currently being conducted in this country, the major barriers to such research faced by reproductive researchers, and the potential research opportunities restricted by existing policies and attitudes.
Methods
A survey was administered by Survey Monkey and distributed to 20 major academic, clinical and governmental institutes in New Zealand, via email between August and December 2017. The survey consisted of 22 closed or open-ended questions regarding respondents’ research experience, field of expertise and experiences obtaining ethical approval from New Zealand ethics committees. Responses were transcribed and qualitatively described. Frequencies are described as a percentage of total survey participants. The project was approved by The University of Auckland Human Ethics Committee (reference number 019608).

Results
Research demographics
Invitations were sent to 88 email addresses from 20 institutions. Twenty-eight researchers (35%) responded. Of these, 10 were experienced researchers with more than 20 years’ research experience, six cited 10–20 years, eight had 5–9 years, with four having had less than five years’ research experience (Table 1). Participants were employed in universities (14), clinics or hospitals (4) or non-university research institutes (1), with an additional nine participants being employed across multiple institutions.

Table 1: Research demographics of survey participants.

<table>
<thead>
<tr>
<th>Research experience</th>
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<tbody>
<tr>
<td>Less than 5 years</td>
<td>4</td>
</tr>
<tr>
<td>5–9 years</td>
<td>8</td>
</tr>
<tr>
<td>10–20 years</td>
<td>6</td>
</tr>
<tr>
<td>More than 20 years</td>
<td>10</td>
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<tr>
<td>Place/s of work</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>14</td>
</tr>
<tr>
<td>Clinic or hospital</td>
<td>4</td>
</tr>
<tr>
<td>University and clinic or hospital</td>
<td>5</td>
</tr>
<tr>
<td>Multiple clinics or universities</td>
<td>4</td>
</tr>
<tr>
<td>Research institute (non-university)</td>
<td>1</td>
</tr>
<tr>
<td>Total respondents</td>
<td>28</td>
</tr>
</tbody>
</table>

Current or previous embryo research in New Zealand
Fifteen researchers had previously and/or were currently conducting research involving embryos in some way. The majority of respondents classified their research as ‘basic science research’ (12), ‘embryology’ (6) and/or clinical research (4), with six respondents conducting research projects across multiple disciplines (Figure 1).

Figure 1: Types of embryo research currently or previously conducted in New Zealand.

A subset of seven respondents provided further details describing their previous or current embryo research. In brief, the four research projects with direct use of human embryos referred to the use of non-viable embryos (2), analysis of embryo culture media (2), embryo development in vitro (1) and/or human embryo research conducted overseas (1). Other research projects not directly working with human embryos described the use of animal embryos (3) or research into the psychology and perceptions of reproduction (1).

Perceived barriers to embryo research in New Zealand
Fifteen survey respondents identified one or multiple barriers to their own or their institution’s embryo research. The majority (9) perceived the HART legislation (or part thereof) as a barrier to their field of research, followed by ministerial guidance to avoid research that “uses or creates” embryos (8), and the lack of suitable ACART guidelines about the use of human embryos for research purposes (6) (Table 2). The lack of specific funding for research was a perceived barrier for only four researchers, and five researchers specified that they are not facing any current barriers.
Three-quarters (15) of respondents agreed or strongly agreed that the term “use or creation of embryos” as indicated in Section 5 of the HART Act 2004 is a barrier to progressing scientific research in New Zealand (Figure 2). Similarly, 85% of respondents (17) agreed or strongly agreed with the suggestion that New Zealand needs better guidance about the term “use of embryos” for reproductive research as described in the HART act, feel disadvantaged by the lack of specific guidance on this issue and feel that the Minister of Health should direct their ministerial ethics committees to develop guidelines about the use of embryos for research purposes.

Figure 2: Perceived influence of New Zealand legislation on embryo research as reported by researchers in the field (n=20 survey respondents).

Table 2: Barriers to embryo research perceived by embryo researchers in New Zealand.

<table>
<thead>
<tr>
<th>Barriers to embryo research</th>
<th>n</th>
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<tbody>
<tr>
<td>One or more barriers to embryo research identified:</td>
<td>15</td>
</tr>
<tr>
<td>HART legislation (part of)</td>
<td>9</td>
</tr>
<tr>
<td>Ministerial guidance to avoid research that “uses or creates” embryos</td>
<td>8</td>
</tr>
<tr>
<td>No ACART guidelines about the “use” of embryos</td>
<td>6</td>
</tr>
<tr>
<td>Lack of specific funding</td>
<td>4</td>
</tr>
<tr>
<td>Other barriers</td>
<td>3</td>
</tr>
<tr>
<td>No specific barriers to embryo research identified</td>
<td>5</td>
</tr>
<tr>
<td>No response</td>
<td>8</td>
</tr>
<tr>
<td>Total respondents</td>
<td>20</td>
</tr>
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</table>

ARTICLE
Embryo research currently restricted in New Zealand

Eleven respondents had previously applied for ethics approval for human or animal embryo research in New Zealand from one or more ethics committees. Six of these respondents gained approval from ECART, with the remainder gaining ethical approval from University human or animal committees (6), or the Human Fertilisation and Embryology Authority (1). The only research project declined ethics approval by ECART was the “Day of Embryo Transfer” study described in the case study above.

Eleven researchers responded that they have potential research projects that they would consider undertaking in the future but are not permitted under the current ACART regulations. Five respondents described their potential research projects in further detail, namely, they would use surplus embryos in vitro to improve fertility success rates and/or increase understanding of embryo biology (4). The single clinical research study cited above (The “Day of Embryo Transfer” study) would use embryos in patient populations to improve fertility success rates.

Discussion

The early restrictions on embryo research in New Zealand reflected a concern for human life and the rights of an unborn child. The HART Act of 2004 defines human reproductive research as “research that uses or creates a human gamete, a human embryo or a hybrid embryo”, and while research using embryos is not openly restricted, researchers must gain ethical approval from the ministerial ethics committee (ECART), who base their decision on guidelines published by their advisory committee (ACART). In turn, ACART can only issue guidelines for reproductive technologies that have undergone a complete and thorough review process, involving public consultation. Although ACART undertook a public consultation process in 2007 and advised the then Minister of Health that research on human embryos should be allowed (with approval via ECART), this was never enacted, and no guidelines currently exist on the use of viable human embryos for research purposes. Without existing guidelines on which to base their decision, ECART is unable to approve any applications for research using viable human embryos. This effectively places a blanket ban on all such research in this country, including research that is identical in practice to already established ART clinical procedures. For example, while New Zealand fertility clinics offer fertility treatments that routinely transfer embryos and thus “use” embryos, research projects such as the “Day of Embryo Transfer” study, which could improve the efficacy of these procedures has effectively been prevented.

The purpose of this survey was to highlight the inconsistencies of the current impasse to the newly appointed Minister of Health. We consider that the current policy on human embryo research fails to protect either the rights of the embryo or the couples who seek treatment for infertility. As the ethical and moral implications of New Zealand’s restrictions on embryo research are described in detail elsewhere, here we have sought to quantify the impact these restrictions are having on New Zealand’s research outputs and therefore our contribution to improved healthcare. The surveyed opinions of a proportion of New Zealand’s embryologists, clinicians, biologists and social scientists suggest dissatisfaction with the current indecisive guidelines provided by ACART in 2005, and the lack of guidance from the Ministry of Health and associated ethics committees regarding what constitutes embryo research and therefore what research can be performed. Other than the proposed DOT study, our survey did not identify any other research applications that have been rejected by ECART. However, far from supporting the current procedures, this is probably a reflection that most researchers are aware of the restrictions on embryo research in New Zealand and do not seek ethics approval or even grant funding to conduct research in this area, particularly those working in embryology and basic science research. The DOT study presents a potentially unique case, highlighting that these restrictions extend to all clinical research, a situation that may not be obvious to clinical researchers who routinely conduct these same procedures on patients.
In 2005, ACART published guidelines about the use of gamete and non-viable embryos for research purposes, however the basis for restricting research to non-viable human embryos is unknown. These guidelines are far too restrictive to support research programmes that could benefit women and children in New Zealand. We were able to identify only two researchers using non-viable embryos for research purposes, presumably due to the difficulties in obtaining these tissues and to the inherent limitations of research using non-viable embryos.

While our survey could not detect the full extent of reproductive research that is being inhibited in New Zealand by the current guidelines, more than a third of respondents identified potential research projects using human embryos that are not currently allowed in New Zealand. A small number of researchers described these research projects in more detail, which included basic science, embryology and clinical research almost exclusively aimed at improving the reproductive potential of infertile women. Although we received a relatively small number of survey responses (28), we suggest that this is representative of the small number of New Zealand researchers working in this field and who are likely to hold an opinion on this topic. Strong support for improved guidelines was apparent, despite the fact that many (15) of the respondents did not have any future research ideas that are currently impermissible, and some (5) did not appear to be facing any barriers to their current research. This suggests that researchers are not committing themselves to research projects using human embryos, since they are aware that they will not be able to undertake them in New Zealand's present legislative climate. This in turn suggests that researcher support for improved guidelines on viable embryo research is unlikely to be restricted solely to researchers currently in this field and who responded to our survey.

Looking beyond our survey at research conducted overseas, it is apparent that New Zealand is missing out on opportunities in reproductive science and medicine with this current legislation in place. For example, in addition to clinical research that could improve existing fertility treatments, stem cells from excess embryos have the potential to treat human disease, and recent advances in genome editing may allow scientists to remove genetic diseases from developing embryos. These recent developments are only possible in countries including Australia and the UK, which allow research using donated viable human embryos up to 14 days post-fertilisation. In addition, the HART Act requires that New Zealand fertility clinics discard viable embryos after 10 years if an extension for storage is not requested by the owners of the embryos, thereby wasting a valuable opportunity for reproductive research in this country.

As New Zealand will likely reap the benefits of any future treatment options that arise from embryo research in other countries, the current policies on embryo research pass the burden to researchers overseas by preventing scientists in New Zealand from contributing to our future healthcare. We concede that the ethical and moral issues surrounding the use of embryos for research purposes are polarising and require extensive debate by politicians, researchers and the New Zealand public. In no way are we suggesting that New Zealand opens the door to all possible types of embryo research, but we seek to develop policies to set new boundaries on what is allowed and what should be restricted. We suggest that the Minister instructs ACART to review the current guidelines and to define the term “the use of embryos” and consider allowing research on viable embryos that are being discarded, and where consent for research is received, up to 14 days of gestation.
Competing interests:
CF is the principle investigator for the “Day of Embryo Transfer” study described in the introduction. Authors CF, AS, LC, and ML participated in this survey.

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