Does the Use of Stem Cells to Create Gametes Hold a Viable and Ethical Option for Infertility Treatment in the Future?

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ABSTRACT
Phenomenal advancements in stem cell research, has potentially discovered a new era for infertility treatment after successful trials in mice produced gametes from adult stem cells. 1 in 7 couples have difficulty conceiving, hence approximately 3.5 million people in the UK[^1] attempt to time menstrual cycles, increase their sperm quality and undergo IVF treatment, yet in spite of this 15% of couples remain unsuccessful[^2]. Alongside this, there are individuals who are infertile due to transgender surgery, chemotherapy and early menopause, which can cause much grief as IVF treatment isn’t always possible. The prospect of using stem cells to produce gametes has aroused much discussion as its ethics are highly questionable. Thus I propose the debate for the viability of such a ground-breaking medical discovery, morally and scientifically. On balance, the abundance of benefits this treatment could provide for many medical conditions, coupled with a renovated society from eradicating infertility in the future, outweighs all downsides, on the basis that current complications can be resolved.

INTRODUCTION
The known battle against infertility is captioned by the popularity of IVF treatment, of which celebrates 25 years of success since the first *in vitro* conception of Louise Brown, at a clinic based in Cambridge. Worldwide more than a million ‘test-tube’ babies have been born and Professor Alan Trounson, from the Monash Institute of Reproduction and Development in Victoria, Australia, further elucidates that IVF treatment has excelled so significantly that in fact ¾ of all infertile couples can be helped via this method[^3]. This does not however hide the reality that some remain impossible to treat, especially those who are unable to produce egg and sperm cells. This has resulted in an increase in the number of people opting for donated gametes (figure 1) as data collected from the Human Fertilisation and Embryology Authority (2012-2013) affirms that in 2013, 10% of all IVF cycles used donated gametes and 4,611 DI cycles (broad term regarding fertility treatment using donor sperm) were also recorded[^4]. Thus this displays a great popularity and it has been increasing over the last decade. Although this option is available, it is preferred by most couples to have their own biological children.
In light of this, researchers have turned to the use of stem cells derived from the skin, to restore egg and sperm cells. Stem cells are defined as ‘an unspecialised cell characterized by the ability to self-renew by mitosis while in undifferentiated state and the capacity to give rise to various differentiated cell types by cell differentiation’.[5] There are two types of stem cells, adult stem cells, found in adults and have limited differentiation potential hence are termed multipotent, and embryonic stem cells, which are early stage stem cells that can form any tissue in the body and are pluripotent. In order to create germ cells genetically similar to the parent, adult stem cells are extracted from the parent and are reprogrammed to behave like embryonic stem cells. This is achieved by altering the adult stem cells to express high level of genes that control self-renewal and pluripotency, creating induced pluripotent stem cells (iPSC). In 2012, Mitinori Saitou, a stem-cell biologist stationed in Kyoto University in Japan, alongside his collaborators, used iPSCs derived from skin cells to create the first set of artificial gametes genetically similar to its parents, known as primordial germ cells (PGCs). He discovered that placing the PGCs into the testes of mice allowed them to mature to sperm and when placed into the ovaries, they matured into egg cells.[6] Instead of using adult stem cells, embryonic stem cells can be used, by extracting cells from a blastocyst conceived by a couple who are fertile, however the ethics of embryonic stem cells research hinder this option and couples wishing to have biological children cannot do so since the child’s genetics will carry part of the initial blastocyst.[7]
Based upon this awe-inspiring discovery, a research team led by Azim Surani of the University of Cambridge and Jacob Hanna of the Weizmann Institute of Science, are attempting to develop this method for use in humans instead of mice. Together they used male and female iPSCs to create gamete precursor cells (cells that have not yet specialised) with an efficiency of 25-40% \[8\]. Later they transpired that the PGCs found in humans are different to those in mice, due to a protein known as SOX17 which influences this mechanism in humans where as in mice a different protein known as SOX2 influences the mechanism \[9\]. Hence much research is still required before its application in humans is viable and it in turn opens the gates to ethical views also.

Undeniably, the possible implications for this new treatment are vast, for instance sex reassignment, chemotherapy induced infertility, postponing menopause and gender reassignment surgeries. However since this phenomena is presently in its early stages, there are great doubts of whether this treatment, practiced in mice, will work in humans since sometimes the mice born are abnormal. Moreover, if it is possible complications should be kept to a minimum, thus opens the question of ethics, for instance what are the potential complications of using this treatment on older women? Furthermore if human trials are to take place, considerations such as consent, confidentiality and human rights are greatly important.

DISCUSSION

Applications:

Infertility in Men:
Considering the variety people suffering from infertility, stem cell research holds great significance and a clear demand. Statistics and data of male infertility further supports this claim. It is evident that due to our modern lifestyle, problems and potential risk factors will accompany it, some of which may correlate to an overall decrease in fertility. As displayed by a study from Professor Niels Skakkebaek, at the University of Copenhagen, who recorded data of sperm count in semen for over 50 years and deduced that the count had
fallen by 50% as well as recording that in the 1940s the normal sperm count per millilitre was above 100 million, however it has fallen to approximately 60 million. If infertility is to continue to drop at this rate, IVF treatment will become increasingly more difficult therefore the appeal for stem cell use will swell. It is said that infertility in males is caused by the mother’s condition whilst pregnant, for instance by obesity or smoking. Smoking whilst pregnant permanently reduces the child’s sperm count by up to 40%, whereas a male adult smoking, temporarily reduces the count by 15% only. Since it is very unlikely that our society will deviate greatly from these problems, to create any significant change in these statistics or that future generations will regain high fertility, as the reduced sperm count can be passed down genetically, this treatment has the potential to become very popular. Unfortunately, further studies infer that adult men exposed to low concentrations of chemicals with small oestrogenic properties such as pesticides, traffic fumes, plastics and supposedly soya beans, can experience reduced fertility [9]. Hence suggests that the demand for this treatment may be focused more towards men as they are more susceptible to infertility decline in their lifetime as well as from birth.

Since 1 in 100 men suffer from Azoospermia, the worst case of infertility in men [10] and around 15 to 20% of all young males have the abnormal sperm count of less than 20 million per millilitre of semen [9], the astounding developments by Renee Reijo Pera, a former director of Stanford’s Center for Human Embryonic Stem Cell Research and Education, provides a promising solution. They conducted some research with 3 healthy men, and though one man carried a mutation of his Y chromosome that prevented his body from producing sperm, the other two men were fertile. The iPSCs, converted from the skin cells given by these men, formed germ cells and were placed into the testis of mice but stopped differentiating before they could mature into sperm cells [10]. This is due to an evolutionary block which prevents the human germ cells to undergo spermatogenesis when placed into the testis of another species, unless the germ cells were place into a the testis of a very similar species [11]. Yet the mere idea that the infertile man’s cells could produce germ cells is fascinating and most importantly can be seen in use in the near future. Therefore Pera’s research gives hope for the many men currently infertile and those men in the future who will be part of the inevitable, as well as ever increasing, decline in fertility.

**Infertility in women:**
A prospectus to ‘cure’ infertility in women also seems encouraging due to successful trials in mice where 8 cubs were born via the use of stem cells. This method is rather unique, as the germ cells derived from iPSCs, were allowed to grow with a sliver of ovary cells from the mother and later transferred to the mother’s ovaries themselves to mature. The matured eggs were then removed via the normal IVF treatment method and fertilised *in vitro* [12].
This option has great potential, especially for incidences of early menopause - a topic not spoken about often, despite affecting more than 1 in 20 women in which 6% of all women do not know the cause of it. Early menopause increases the relative risk of heart attacks, strokes and bone disease but above all it is very distressing for a young person to accept due to its spontaneous nature, hence may give no chance to for them to freeze their eggs beforehand. Similar to the infertility in males, early menopause has become more prevalent over the years, as illustrated by data from 1980s where only 1% of women experienced it \cite{13}. From this it can be inferred that the viability of this treatment is very high and since researchers plan to use the skin adult stem cells over the embryonic they used in mice, makes this option very socially acceptable and far less controversial. The main downside is that this treatment will not be available for another decade, since much safety testing and precaution is required with humans over mice during research of this method.

**Transgender:**
In its application for transgender individuals, who don’t have the appropriate gametes for their identified sex, there is tremendous benefit using this treatment as they will be able to connect with their gender completely. Research has already taken off to use this
technique to support transgender individuals as displayed by a team led by Jonathan Tilly, a biologist, from the Massachusetts General Hospital, who are trying to develop a method to create egg cells from human ovarian stem cells and were successful in mice trials. Now in human trials, the team used reproductive ovarian tissue donated by transgender women undergoing sex reassignment at the Saitama Medical Centre in Japan. They were then able to isolate the reproductive cells and produce immature egg cells, before injecting them into the mice to create follicles, hence producing mature eggs [14]. This is a necessary step for transsexuality, as there are 853 men between 2000 to 2010, who have undergone sex reassignment surgery [15] as well as approximately 1,300 to 2,000 people transitioning from male to female and between 250 to 400 transitioning from female to male in the UK alone, as stated in The Home Office’s ‘Report of the interdepartmental working group on transsexual people’ [16]. Thusly worldwide stem cells could provide so many the joys and fulfilment of having their own biological children and will hopefully create a world open to a flourishing Trans community.

Chemotherapy:
The battle against cancer is one that no one can truly relate to or understand how challenging and painful it is to endure, apart from those experiencing it. The diverse number of cancer patients who show perseverance and optimism, during the lowest point of their life, and survive, are people who I respect. Grievously, a side effect of chemotherapy is infertility. This has created a lot of problems, for example between 1999 and 2011, a French study recorded that 34% of chemotherapy treatment cases had been delayed before women were given gonadotoxic agents (drugs affecting the gameteproducing gland used in chemotherapy) so that their embryos could be frozen [17]. Therefore though the option to remove gametes and freeze embryos for IVF treatment later is available, there may be detrimental effects if your chemotherapy is urgent and realistically shouldn’t be delayed – stem cells could be the answer to this dilemma.

Furthermore, a survey from the California Cancer Registry asked women about their infertility from chemotherapy and gives results from 1,021 women between the ages of 18 to 40, with 620 reporting that they were treated with only chemotherapy. The data presents a great correlation between age of diagnosis and likelihood of becoming infertile, for example at the age of 20, 18% were infertile with Hodgkin’s disease, whereas 57% were infertile aged only 35. Moreover, the proportions of women reporting acute ovarian failure were 8% for Hodgkin’s disease, 10% for non-Hodgkin’s disease, 9% for breast cancer and 5% for gastrointestinal cancers [18]. These percentages are relatively high and as only 5 main types of cancer were surveyed we can expect significantly more people using stem cells from other cancer therapies and diseases also.

IVF demand:
Due to great demands and successes in IVF treatment, stem cell reproductive treatment has the potential to follow on this trend, as demonstrated by its many applications listed above. In a survey conducted by myself, 117 senior school students between the ages of 14 to 18 answered questions on IVF treatment and infertility. 44% claimed that they knew
1 or more women who have either undergone or are currently undergoing IVF treatment (figure 4).

Figure 4: survey question - Do you know anyone who is undergoing / undergone IVF treatment?

Additionally, 55% reported to know at least 1 or more people born due to successful IVF treatment (figure 5).
Figure 5: survey question - Do you know of anyone born due to successful IVF treatment?

However there are some limitations, for example some students may know the same people who are IVF babies in the school and the survey was not on a great scale, therefore the results are not completely reliable. Despite this, considering the small community of people asked, there are a substantial number of people part of IVF treatment and this will be sure to expand after the introduction of stem cells. 2.2% of all babies born in the UK in 2012 were due to successful IVF treatment and overall 221,555 babies from 1991 to 2012 in the UK were IVF babies [19]. Therefore stem cell reproductive treatment is worth investing in researching.

Ethics:
Applications for older women:
Adult skin stem cells, unlike embryonic, will always be available to remove in a person’s lifetime, therefore should older women, or women past menopause, be offered this treatment? It is not unknown that more pregnancy complications arise the older the mother however this doesn’t stop many from continuing to try for a child. This is likely to continue and in fact studies in the ages of women applying for IVF since the treatment first started in 1991, has slowly been increasing. Figure 6 shows that IVF treatment has increased by approximately 1 and ½ years of age and DI treatment has increased by 3 years, before the average becomes steady from 2006 onwards. We can deduce from this that the age may increase further after the introduction of stem cells for treatment, since many women post menopause can now have a new artificial supply of eggs.
Likewise, the greatest number of cycles performed per age has slowly increased over time and now peaks at the age of approximately 40 as well as the peak becoming more pronounced, as displayed by figure 5 \cite{19}.

Figure 6: Average age of women undergoing IVF and DI treatment using fresh eggs
Henceforth, as older women are currently able to undergo IVF treatment, it may not be too difficult to provide stem cell treatment also, however if the age continues to steadily increase there will be less chance of a successful treatment. The gametes created from stem cells are very short lived and have a high fatality rate therefore if this is to accompany current data on IVF success at different ages, for example 32% of women under 35 years of age successfully have an IVF child whilst only 5% aged 43 to 44 do and 1.9% aged 45 above are successful, then it will be even less likely that an older women can realistically benefit from the stem cells [20].

Research on humans:
When researching and applying stem cell techniques in humans, caution is imperative. It is necessary that the human egg cells are made fully functional and that the follicles formed after maturing are also genuine, however there is still no evidence that the egg will fertilise normally or that there are absolutely no abnormalities after fertilisation. Many researchers claim that it is still a long way off before stem cells can be used in this manor, whether it be via a sliver of ovarian tissue or skin stem cells [21]. Embryonic stem cells continue to produce higher quality egg and sperm cells however the germ line cells created from adult stem cells, although they are less controversial, are not reaching the same degree of potency. In addition, part of the maturing process of a germ cell includes gene regulation, thus it is essential that the gametes are in full function so that this process can occur naturally on its own [22]. If not, there may be complications when the baby is born, as displayed by the genetic problems after Dolly the sheep was cloned and
born, such as very short telomeres of her chromosomes resulting in rapid aging of her cells \[23\]. Only around 10% of the germ line cells created by embryonic stem cells actually survive, thus there is a high fatality rate. With this in mind, researchers and the public have a long time to wait before it is safe and medically viable in the future but with that said, its progression to this point in research has happened very rapidly in the past 5 years or so.

On the other hand, this research has hopes to use adult stem cells only, however recent research and future research will continue to use embryonic stem – a far more controvertible topic. Some argue that human life begins at conception therefore using embryonic stem cells is seen as taking an innocent life, others believe that mistakes are very easy when culturing stem cells in the lab which can cause damage or injury to a person. These are valid arguments, however it may also be argued that using stem cell materials that would otherwise be wasted after a miscarriage or IVF treatment failure, is the lesser of two evils. Furthermore the embryonic stem cells are completely undifferentiated hence cannot hold an identity or life on their own \[24\]. Overall, embryonic stem cells are not recommended for reproductive treatment as the couple will prefer to have their own biological children rather than divided between different people’s genetics and their own. Researchers are more focused on using adult stem cells and it is also what makes this treatment very distinctive.

**Consent and confidentiality:**
In there being such a diverse range of views on using stem cells for research, it is necessary that consent from the donors is attained and that they understand how their cells will be used. Especially since people are more emotionally attached and give more moral value to their reproductive cells over other parts of their body. For example, some may be open to research in infertility but object to any research combining animal and human cells to mature germ cells. A method to allow scientists to use donated stem cells without need of consent is by using deidentified biological material which is not associated with a specific donor. For instance, IVF embryos or oocytes that fail to develop in the lab, hence cannot be transferred to the mother, can be deidentified and used. Similarly, frozen embryos that are left over after the couple have completed their treatment and no longer want more children, can either be donated to another couple or deidentified for the researchers. However there are some precautionous measures are needed, such as there should be absolutely no leakage of confidentiality and an assumption needs to be held that the donors would not object to the manner in which their materials were used if they were told \[25\]. In order to see how open people are to stem cell research, I asked in my survey whether the students believed it is ethical to used stem cells for research, 73% believed that it was ethically correct, 1% believed it was not at all and 30% didn’t know (figure 8).
Figure 8: survey question - Do you believe that the use of stem cells for medical research is ethically correct?

With such a ground-breaking research, the donor’s confidentiality mustn’t be violated, thus any breaches by medical staff, computer hackers or theft of computers and records, should be controlled carefully to ensure identities remain hidden. This can be done by investigating the personnel who will have access to files, password protecting computers and isolating them in a closed room which requires a code or card for entry. In all, if the donated stem cells are treated with respect and donors are made fully aware of the research before consenting alongside keeping their confidentiality, this research should be allowed to develop.

CONCLUSION
As elaborated in this paper, the viability of stem cell research to produce artificial gametes in the future holds a special aptitude, as envisioned by its many future uses in medicine. Notably, the millions infertile, whether it be from birth, via sex reassignment, chemotherapy or menopause, there is an unquestionable call for further research fuelled by its demand in patients. We have established that this range of applications is well supported by current research and through the variety of methods, statistics and success in trials, we can prove that this treatment has the potential to prosper. By looking at the exceptional success in IVF treatment we can use this as a concept to predict the popularity of stem cell treatment and hence the number of people who will fulfil their dreams of raising a family.

Drawbacks however are pinpointed towards ethical factors, thus consent and confidentiality of donors must be protected as stem cell experimenting is very controversial. The complications with human trials, from germ cells with a high fatality rate to unregulated genes, makes it unlikely that this treatment will be available soon. Additionally, as these studies are very new, it is difficult to foresee future dilemmas.
entirely, such as complication of older women using artificial gametes. These challenges can only be resolved with time, to allow researchers to develop their methods and further question the treatment’s viability.

Despite all the complications scientists continue to research the future of artificial gametes. Modern science and research could find answers to the obstacles being faced by scientists today, to create a society free of infertility to look forward to.

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