OPINION

Embryonic stem-cell gametes: the new frontier in human reproduction
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As infertility increases and gamete donations decline, an alternate source of sex cells may prove valuable for research and infertility treatment. This article examines the social and scientific value of gametes derived from the differentiation of established human embryonic stem (ES)-cell lines (ES-cell-derived gametes) and customized gametes created using nuclear transfer technologies to contain a haploid set of genes creating children genetically related to parent(s). ES-cell-derived gametes may be valuable as a resource for biomedical research, instruction and training in assisted reproductive technologies and perhaps for creating children. The creation of children by ES-cell-derived and customized gametes may not result in psychological harm to children but customized gametes may lead to physical harm to children or an accumulation of gene mutations in a population. Although the creation of new types of children using ES-cell gametes provides more reproductive choices to both fertile and infertile individuals, the risk or physical harm to children from customized gametes may be so severe that the scope of reproductive liberty must be limited. Further scientific and ethical analysis of the creation of children by ES-cell gametes is required.

Key words: assisted human reproduction/embryonic stem cells/nuclear transfer/reproductive liberty/scientific and social value

Introduction

Human gametes (oocytes and sperm) are a valuable resource for research, infertility training and treatment by assisted human reproduction. Ova from female donors have become increasingly valuable, given the decline in fertility rates in the USA since the 1960s due to many women choosing to have children at later ages (Mathews and Hamilton, 2002) and to the increase in the causes of infertility such as chlamydia infection in women (National Center for Health Statistics, 2004). Currently, the rate of gamete donations is low and may decline due to social policy no longer permitting anonymity in some nations (Human Fertilisation and Embryology Authority, 2005). Owing to these various social and environmental factors, the demand for gamete donation, primarily ova, is at an all-time high.

In the last few years, several reports have shown that mouse embryonic stem (ES)-cells can differentiate into sperm (Toyooka et al., 2003; Geijsen et al., 2004) and ova (Hubner et al., 2003) and that human ES cells can also differentiate into germ cells in culture (Clark et al., 2004; Lacham-Kaplan et al., 2005). Gametes may be created through the differentiation of currently established human ES-cell lines and are herein referred to as ES-cell-derived gametes. It may theoretically be possible to create ‘customized gametes’ by using nuclear transfer technology to derive ES cells cloned from an embryo. These cloned ES cells may differentiate into either sperm or ova which contains a haploid set of genes from the individual. This article analyses the social and scientific value of ES-cell-derived and customized gametes by examining the harms and benefits of their potential applications. Amongst several ethical concerns raised in the use of ES-cell gametes in human reproduction (Testa and Harris, 2005), this article focuses on the reproductive liberty offered to individuals who use ES-cell gametes and the potential physical and psychological harm to children born from them. I argue that ES-cell-derived gametes may be tremendously valuable for biomedical research and infertility training and possibly even to create children. It is doubtful that the use of either ES-cell-derived or customized gametes will affect the psychological development of children. However, the molecular technologies used to create customized gametes may result in gene mutations in gametes or may accumulate in a population over time. Although the use of ES-cell-derived and customized gametes to create children offers greater reproductive choices to individuals, this reproductive liberty must be weighed relative to the potential risk of physical harm to the child. Further research on the medical, ethical, legal and social implications of using ES-cell gametes to create children should be performed in order to adequately understand the harm and benefits of these technologies in human reproduction.

The science of creating ES-cell-derived and customized gametes

Several cell and molecular techniques were used to demonstrate the in vitro differentiation of mouse ES cells into sperm
or ova (Hubner et al., 2003; Toyooka et al., 2003; Geijsen et al., 2004; Lacham-Kaplan et al., 2005). ES cells can spontaneously differentiate into ova which could undergo meiosis (Hubner et al., 2003; Lacham-Kaplan et al., 2005) or differentiate into male germ cells which display proper erasure of methylated genes (Geijsen et al., 2004). Interestingly, ova may be created from the differentiation of male ES-cell lines (Hubner et al., 2003), which suggests that ES cells containing X and Y chromosomes may be genetically sufficient to create both male and female gametes. These studies demonstrate that ES-cell-derived gametes display similar biological characteristics to gametes derived from germ cell precursors.

Although the creation of ES-cell-derived gametes may be a relatively simple process of *in vitro* spontaneous differentiation, the creation of customized gametes would theoretically be much more labour intensive involving multiple steps. The creation of customized gametes involves somatic cell nuclear transfer (SCNT) technology that creates a cloned embryo (Figure 1). SCNT involves injection of a diploid nucleus into an enucleated oocyte and the initiation of embryonic development by parthenogenesis. Cloned ES cells can be derived from the embryo and differentiated into either sperm or ova *in vitro* (Figure 1). Customized gametes of the opposite sex may also theoretically be created. For example, SCNT of a male nucleus and the derivation of male ES cells can differentiate into ova. Although ova have been shown to form from X- and Y-chromosome-containing ES cells, a nucleus from a woman may not be able to differentiate into sperm, given that women do not carry Y-chromosome-specific genes. The transient or stable expression of human DAZ genes (Vogt and Fernandes, 2003) that function in male gamete formation may induce ES cells to differentiate into sperm. Clearly, there are several additional technological barriers impeding the actual creation of customized gametes of the opposite sex for women.

The creation of customized gametes in general is theoretically possible because human ES cells have been cloned from individuals (Hwang et al., 2004) and human ES cells have been shown to differentiate into germ cells (Clark et al., 2004). However, what has not been demonstrated is the differentiation of sperm or eggs from cloned ES cells in order to derive customized gametes. The efficiency of creating cloned ES cells after autologous transfer of a somatic cell nucleus from a woman into her own oocyte is between 3 and 5% (Hwang et al., 2004). The creation of customized gametes would be a less efficient process because additional factors, such as the age of a woman or heterologous nuclear transfer, may interfere with normal embryonic development. The creation of customized gametes may therefore require further research and development to become an efficient process, and rapid advances in molecular technologies and ES-cell biology may soon be able to create customized gametes.

**The benefits of ES-cell-derived gametes**

There are two major benefits for ES-cell-derived gametes. ES-cell-derived gametes may be used in the near future as a resource for both basic and applied scientific research (Dennis, 2003; Vogel, 2003c; Westphal, 2003; Surani, 2004; Testa and

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**Figure 1.** The creation of customized gametes. Customized gametes could theoretically be created using somatic cell nuclear transfer technology. A nucleus from a skin cell from Parent 1 can be transferred into an enucleated oocyte and begin embryonic development by parthenogenesis. Parthenogenic activation of an oocyte could be provided by an electrical impulse or by chemical induction. Between day three to five of embryonic development, cells from the inner cell mass (ICM) of the resulting blastocyst are harvested to derive ES cells. Diploid ES cells could then differentiate into haploid oocytes (shown here) or sperm (not shown). The oocyte from Parent 1 could be fertilized with the sperm from Parent 2 through standard IVF procedures. Those embryos that are selected as best suitable for further embryonic development will be transferred to surrogates who will carry the child to term. Images are not drawn to scale. N, the sets of chromosomes, 1N, haploid; 2N, diploid; ICM, inner cell mass; ESC, embryonic stem cell; ET, embryo selection and transfer. The oocyte, embryo and blastocyst images were adapted from the Colour Atlas of Clinical Embryology (Moore et al., 2000).
Harris, 2004; Newson and Smajdor, 2005) and for instruction and training in assisted human reproduction. It is unlikely that customized gametes will be used as a resource for basic research because their creation involves additional technical steps that would cost more and serve as additional variables to control for in experiments.

ES-cell-derived gametes may be used for both basic and applied scientific research as a new resource, and as a new bioassay system to study stem-cell development (West and Daley, 2004). Further experiments need to be performed with ES-cell-derived gametes to ensure that they are morphologically and functionally similar to gametes derived through germ-cell differentiation. ES-cell-derived gametes may be used in several areas of basic scientific research to study ES differentiation, gametogenesis, X-chromosome inactivation, fertilization, early embryonic development, germ-cell tumours and imprinting (Surani, 2004; West and Daley, 2004; Lippman et al., 2005; Newson and Smajdor, 2005). One of the most likely applications of ES-cell-derived ova may be to further develop SCNT technology to advance patient-specific therapies and create cell lines for studying the biology of degenerative disorders and diseases (Vogel, 2003c; Surani, 2004; Testa and Harris, 2004; Hwang et al., 2005; Newson and Smajdor, 2005; Pickering et al., 2005). Moreover, ES-cell-derived gametes may also be used for applied research in understanding the causes of infertility or for creating new, or for improving existing, assisted reproductive technologies (ARTs) or methods of contraception (Westphal, 2003; Surani, 2004; Testa and Harris, 2004; Newson and Smajdor, 2005). ES-cell-derived gametes are of tremendous potential scientific value as a new resource and assay system for society.

An additional source of human sperm and ova may have immediate social benefit as a resource to train individuals in human reproduction and for the practice of ARTs. Currently, in most cases, animal semen and ova are used for practical purposes, but in some instances it will be unavoidable to use human sperm and ova. For example, ova could be used to train technicians performing various ARTs that involve a degree of technical mastery. Intracytoplasmic sperm injection (ICSI) is a technically challenging ART used to treat male infertility, which involves holding the oocyte steadily in suspension while injecting a needle into the rigid oocyte membrane to allow a single sperm cell to enter. Furthermore, a new source of sperm and oocytes from ES cells may be used to train infertility specialists to recognize proper morphological development of human embryos to select the ones best suited for transfer. Thus, ES-cell-derived gametes provide an excellent training tool for infertility technicians, researchers and obstetricians and gynaecologists and are also a valuable resource for scientific and medical research.

Physical harm to children created by customized gametes

Many pregnancies achieved through the use of ARTs have been known to result in multiple gestations, with infants being born with low birth weights (Yu, 1998; Bonduelle et al., 2002; Olivennes et al., 2002) as well as other birth defects such as retinoblastoma (Cruysberg et al., 2002; Moll et al., 2003), the imprinting diseases Beckwith–Wiedemann syndrome and Angelman syndrome (Cox et al., 2002; DeBaun et al., 2003; Gicquel et al., 2003; Maher et al., 2003; Maher, 2005), chromosomal abnormalities (Bonduelle et al., 1998; Meschede et al., 1998; Bonduelle et al., 2002; Kurinczuk, 2003) and various other congenital defects including cerebral palsy (Sutcliffe et al., 1995; Ferraris et al., 1999; Antebi et al., 2001; Roesch et al., 2001; Hansen et al., 2002; Stromberg et al., 2002). These outcomes demonstrate that children born using various ARTs may be physically harmed because the technology bypasses natural mechanisms of selecting out embryos containing genetic abnormalities (Engel et al., 1996; Baschat et al., 1996; Johnson, 1998; Kim et al., 1998). However, it has been suggested that some reproductive technologies such as ICSI may also cause de novo gene mutations due to the extensive micromanipulation involved (Bonduelle et al., 1998; Bonduelle et al., 2002; Kurinczuk, 2003).

The micromanipulation of cells during SCNT has also been shown to adversely affect spindle formation (Simerly et al., 2003; Simerly et al., 2004), telomere length (Lanza et al., 2000; Tian et al., 2000; Nakayama et al., 2000; Betts et al., 2001; Miyashita et al., 2002), X-chromosome inactivation (Eggan et al., 2000; Wrenzyci et al., 2002), imprinting and other epigenetic changes (Dean et al., 2001; Humphreys et al., 2001; Kang et al., 2001; Humphreys et al., 2002; Kang et al., 2002) and also fails to activate key embryonic genes (Boiani et al., 2002; Bortvin et al., 2003). The cause(s) of these genetic and epigenetic changes is thought to explain the low success of viable embryos after nuclear transfer and why many animals born using SCNT technology display physical defects that result in their death by multiorgan failure (Rideout et al., 2001; Cibelli et al., 2002; Ogonuki et al., 2002; Wilmot, 2002; Edwards et al., 2003; Hochelinger and Jaenisch, 2003; Vogel, 2003a). It is possible that these genetic and epigenetic changes alter genome integrity such that a high number of attempts may be required for the successful birth of a single cloned offspring. Since the creation of customized gametes involves SCNT, it is possible that the mutations resulting from the use of this technology to create cloned embryos may occur in the creation of customized gametes. The use of customized gametes in combination with other ARTs may result in an accumulation of genetic mutations in a population. At present, it remains unknown to what extent micromanipulation of cells causes aberrant de novo genetic or epigenetic changes using various technologies. Based on evidence of the physical problems of offspring born either from ARTs or from SCNT, the risk of creating de novo genetic and epigenetic mutations from creating customized gametes should be evaluated.

Can children be psychologically harmed?

Claims have been made that children created from ES-cell-derived gametes have either ES-cell lines as parents (Vogel, 2003b; Newson and Smajdor, 2005) or no parents (Weiss, 2003), suggesting that children may be psychologically harmed from the knowledge that they were created in an artificial manner (Newson and Smajdor, 2005). Similar claims have also been made that genetically related children created from same-sex couples may face psychological harm or alter their childhood experience.
(Newson and Smajdor, 2005). Others on the other hand have claimed that overcoming biological barriers to create children from two same-sex individuals using customized gametes may be a way to further democratize human reproduction in society (Testa and Harris, 2005). I will argue that the claims that children born from ES-cell gametes may have altered childhood experiences or suffer psychological harm are not true and that such claims may be problematic as they precipitate notions that non-traditional families may be harmful to the child’s psychological development or that ES-cell-derived ‘artificial’ gametes themselves may be harmful because they are created by different biological means than gametes collected from adults.

Parents who use ES-cell gametes may contribute to the genetic make-up of the child, socially by rearing the child, or in some cases surrogate women may carry the child during pregnancy to term. It is unlikely that children created with one ES-cell-derived gamete and raised by a single social parent, such as a single mother, will exhibit any greater childhood psychological problems than a child raised socially by a single heterosexual mother. For example, children in fatherless families experience a closer relationship with their social mother and are more dependent on them than children from father-present families (MacCallum and Golombok, 2004). Although children in fatherless families seem not to be affected negatively from the absence of a social father, mothers raising children without a father reported had increased severity in disputes with their children than mothers in father-present families (MacCallum and Golombok, 2004). However, the psychological development and personality characteristics of children in families headed by a single mother would depend heavily on economic factors (Golombok, 2005). Children created using ES-cell-derived sperm and raised by a single mother may not display behavioural differences when compared to children raised in heterosexual two-parent families. Empirical research on the gender identification and development of school children raised by single lesbian social mothers found no differences compared with children raised by a heterosexual single social mother (Golombok et al., 1983). Similarly, the emotional and gender development of children raised by two lesbian social mothers, where the child was created through donor insemination did not differ in their psychological development when compared with children raised in heterosexual families who naturally conceived a child (Brewaeys et al., 1997). These studies show that the psychological development of a child is dependent on socio-economic factors and how the parent(s) raise their children than on whether a single social mother or a same-sex couple are the social parent(s). It is unlikely that creating genetically related children from two men or two women. Both ES-cell-derived and customized gametes offer new ways of procreation to both fertile and infertile individuals, creating different genetic relationships with their children. The desire to have a child that is genetically related to the parent because of religious practices or social or cultural norms is a deeply cherished value for many (Buchanan et al., 2000). The scope of reproductive liberty should allow for the use of ES-cell-derived gametes for all types of reproduction and should not be limited to individuals with infertility as the moral right to reproduce and to have genetically related children applies equally to both fertile and infertile individuals.

Exercising reproductive liberty and the creation of children using ES-cell gametes

The freedom to control one's own reproductive capability to have or avoid having children by coital or non-coital reproduction can be defined as reproductive liberty (Robertson, 1994). One of the major benefits offered by ES-cell-derived and customized gametes is to provide more reproductive choices to individuals, allowing them to create genetically related children. For example, ES-cell-derived gametes may be used by fertile single parents who desire to create a child with a gamete from a non-living person. Customized gametes can be used to create children genetically related from two men or two women. Both ES-cell-derived and customized gametes offer new ways of procreation to both fertile and infertile individuals, creating different genetic relationships with their children. The desire to have a child that is genetically related to the parent because of religious practices or social or cultural norms is a deeply cherished value for many (Buchanan et al., 2000). The scope of reproductive liberty should allow for the use of ES-cell-derived and customized gametes for all types of reproduction and should not be limited to individuals with infertility as the moral right to reproduce and to have genetically related children applies equally to both fertile and infertile individuals.

Although ES-cell gametes in general provide more reproductive choices to individuals to have children, if their use in assisted human reproduction proves harmful to children, then the scope of reproductive liberty should be limited and used only when proven safe. The potential physical harm caused by ES-cell gametes must be placed in context since as a society, we do
accept some risks to children created using ARTs, or by natural conception (Testa and Harris, 2005), for the benefit of existence to the child and the reproductive autonomy granted to parents. If ES-cell-derived or customized gametes were unsafe to children, as a society how much risk are we willing to accept in order to create children and exercise parental reproductive autonomy? A decision to accept the risks of physical harm to children using ES-cell gametes will depend on the frequency and magnitude of harm to the child, the extent of correctable intervention(s) needed and the liberty provided to parents to take extensive risks in having children (Robertson, 2004). Increasing parental freedom at the expense of posing severe risk of physical harm to children may be unfair to the child and violates a principle of parental responsibility (Steinbock and McClamrock, 1994). The risk of physical harm in using customized gametes may resort to ‘devastating’ harm where the harm to children renders life beyond a minimal standard of decency (Steinbock and McClamrock, 1994; Cohen, 2000; Pence, 2004). Several forms of physical harm that require major surgery for correction with risk of death or permanent disability may be considered devastating. The assessment of physical harms to offspring from customized gametes will require thorough scientific investigation using appropriate non-human primate models (Hewitson, 2004) prior to the use of customized gametes for the creation of human children. Along with scientific investigation of the physical harm to offspring, the meaning of reproductive liberty provided from creating and using ES-cell-derived and customized gametes for individuals and society requires further ethical discourse.

Summary and conclusions

Gametes derived from the spontaneous differentiation of ES-cell lines could be created and cultured in large quantities using bio-reactors in the near future (Dang et al., 2004; Gerecht-Nir et al., 2004; Bauwens et al., 2005). ES-cell gametes should be made relatively inexpensive and may be scientifically and socially valuable for biomedical research and for training infertility specialists. Both ES-cell-derived and customized gametes may prove socially valuable as they offer new reproductive choices to individuals who desire to have children. However, the freedom to exercise the reproductive choice to use ES-cell-derived and customized gametes will depend on several medical and ethical concerns; one extremely important issue is the potential physical or psychological harm to children born from them. It is doubtful that psychological harm to children born from ES-cell gametes will occur due to feelings of being born in an artificial manner or from being created by two same-sex parents because children born from other ‘artificial’ ARTs or who have same-sex social parents do not display any psychological differences. Although it remains to be tested, the potential physical harm to children created from ES-cell gametes may also be minimal since other ARTs such as in vitro maturation uses similar procedures for maturing gametes in culture as would ES-cell-derived gametes. However, the creation of customized gametes using extensive microsurgical procedures such as SCNT may create de novo genetic mutations or epigenetic changes. These gene mutations may manifest as physical harm to children or accumulate in a given population over time, having unknown effects in the future. Other important moral concerns not discussed explicitly in this article also deserve attention when creating customized gametes. For example, the creation of customized gametes treats human embryos only as a means to derive ES cells and not as an end in itself (Master, 2005). This moral conflict is inherent in therapeutic cloning and ES-cell research, and many nations have social policies which prohibit the practice of therapeutic cloning and the use of embryos for research or other purposes (Pattinson and Caulfield, 2004). Physical harm to the mother, the technocratic control of human reproduction and the medical and ethical implications in using customized gametes to bypass biological boundaries of sexual reproduction by ES-cell gametes require further discussion and debate.

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