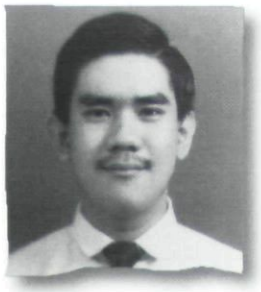
Ethics, social, legal, counselling

International egg-sharing to provide donor oocytes for clinical assisted reproduction and derivation of nuclear transfer stem cells



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Abstract

Recent advances in nuclear transfer technology for derivation of patient-specific stem cells have opened up new avenues of therapy for various human diseases. However, a major bottleneck is the severe shortage of human donor oocytes. Egg-sharing in return for subsidized fertility treatment has been suggested as an ethically justifiable and practical solution to ease the shortage of donor oocytes both for derivation of nuclear transfer stem cells and assisted reproduction. However, it is envisioned that many patients would be more comfortable with their supernumerary oocytes going into derivation of nuclear transfer stem cells, rather than having another potential anonymous offspring in assisted reproduction. Nevertheless in more economically developed countries, fertility treatment is easily affordable to a large segment of the population, which reduces the pool of available egg-sharers. In less affluent countries, fertility treatment is often beyond the financial resources of most sub-fertile couples. Hence, a possible solution may be to allow egg-sharing across international borders. Potential egg-sharers would come from less economically-developed countries that are more in need of financial subsidies for sub-fertile couples seeking clinically assisted conception. This is ethically justifiable because it makes fertility treatment affordable to childless couples from poorer countries, while at the same time easing the shortage of donor oocytes in more affluent countries.

Keywords: *assisted reproduction, egg-sharing, ethics, nuclear transfer, oocyte, stem cells*

The recent advances in the derivation of nuclear transfer stem cells by Hwang and colleagues (Hwang *et al.*, 2004, 2005), have generated worldwide interest and have opened up new avenues of therapy for various human diseases. However, the major bottleneck of this new technology is the severe shortage of human donor oocytes, as well as the need to use them fresh immediately upon retrieval (Hwang *et al.*, 2005; Stojkovic *et al.*, 2005).

Egg-sharing in return for subsidized fertility treatment has been suggested as an ethically justifiable and practical solution to ease the shortage of donor oocytes for both derivation of nuclear transfer stem cells (Heng, 2005) and assisted reproduction (Ahuja *et al.*, 2000). Compared with the rampant commercialization that is associated with the direct sale and purchase of donor oocytes (Sauer, 1999), egg-sharing appears to be more morally palatable. On the one hand, the financial burden for a childless couple is greatly eased, while on the other hand, either new hope of conception is given to a barren woman (Ahuja *et al.*, 2000), or a new lease of life given to a terminally sick patient (Heng, 2005). Because the therapeutic value of nuclear transfer stem cells has not yet been proven in human clinical trials, shared oocytes should preferably be allocated to assisted reproduction rather than therapeutic cloning. However, it is envisioned that patients would be more comfortable with their supernumerary oocytes going into derivation of nuclear transfer stem cells, rather than having another potential anonymous offspring in an unknown family. The question of donor and recipient anonymity in egg sharing is discussed in greater depth in the excellent review of Craft *et al.* (2005).

More importantly, egg sharing minimizes medical risk by reducing the need to recruit oocyte donors from healthy women not seeking assisted conception (Rimington *et al.*, 2003).

Furthermore, it must be noted that most couples that need oocyte donation are usually 10–15 years older than those who need either IVF or intracytoplasmic sperm injection (ICSI). It is often the case that oocyte recipients are highly educated dual-income professional couples who married late in life, due to pursuit of their educational or career goals in their younger days. Hence, the extra years of dual income give recipients a financial advantage that can be shared with younger couples.

Moreover, recent evidence would suggest that egg sharing does not significantly compromise the success of fertility treatment (Thum *et al.*, 2003), if judiciously managed. For example, potential egg-sharers may be narrowed down to indications for male partner sub-fertility or to younger women with tubal blockage, who are likely to produce excess supernumerary oocytes in response to gonadotrophin stimulation. In any case, all prospective egg-sharers must receive mandatory counselling and obtain enough informative consent material before any decision is made. Additionally, the patients, clinicians and scientists involved should strictly follow regulations and keep clear documentation of all clinical and scientific procedures being performed.

Nevertheless, in more economically developed countries with higher median incomes, fertility treatment is easily affordable to a large segment of the population, except for those in the lower income groups. Consequently, this reduces the pool of available egg sharers, which in turn translates to a severe shortage of donor oocytes for infertile women in developed countries (Pennings, 2001). At the same time in less affluent countries, fertility treatment is often beyond the financial resources of most sub-fertile couples (Serour *et al.*, 1991; Inhorn, 2003).

Hence, a possible solution may be to allow egg-sharing across international borders to ease the shortage of donor oocytes for assisted reproduction and the derivation of nuclear transfer stem cells. Potential egg-sharers would come from less economically developed countries that are more in need of financial subsidies for sub-fertile couples seeking clinically assisted conception. This is ethically justifiable because it makes fertility treatment affordable to childless couples from poorer countries, while at the same time easing the shortage of donor oocytes in more affluent countries where the technology of nuclear transfer for the derivation of patient-specific stem cells is currently being developed.

Because the prospective recipients of an international egg-sharing scheme are usually financially better off than the prospective donors, they should be the ones taking the initiative to travel to a less affluent country. Alternatively, they could instead sponsor the travel and accommodation expenses of the prospective egg-sharer and her partner. The ready availability of better medical facilities in more economically developed countries could be an additional boon to sub-fertile couples from poorer countries, where treatment facilities are often sub-standard (Rojanasakul *et al.*, 1994).

Certainly, it can be argued that such as system is akin to 'neo-colonialism' and would be exploitative of childless couples from poorer countries. However, it must be remembered that it would be an even greater tragedy for such couples to remain childless for life simply because they do not have enough money to seek fertility treatment. Hence, egg sharing across international borders is therefore likely to bring much hope to many desperate couples from poorer countries.

To minimize phenotypic differences, international egg-sharing may be carried out between countries which share the same racial stock. For example, the richer countries of Western Europe can look to the less affluent countries of Eastern Europe and Russia for potential egg sharers; while in Asia, more affluent countries like Japan, South Korea, Singapore, Hong Kong and Taiwan can look towards mainland China, or even Vietnam. Certainly, egg sharing across international borders would be beneficial to both parties involved. However, it must be noted that because of cultural and religious differences between different countries, there are varying ethical standards and legislation that must first be addressed before such a scheme can be successfully implemented.

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Organization of biological clocks

Many clocks regulate biological systems (Gillette and Sejnowski, 2005). Diurnal rhythms, sleep patterns, cellular and molecular systems are all tightly regulated. They form a small proportion of the total number of active timers. Instead of being studied in isolation, as now, chronobiology has emerged as a novel scientific subject and covers interactions among various clocks. Mitosis is regulated by genetic, cellular and molecular clocks (Johnson *et al.*, 2002). Cells pass various amounts of time in the successive stages of the cell cycle and key proteins, known as the cyclins, control cycle progression by means of phosphorylation, proteolysis and spatial targeting. Such decisions are made at specific check-points which determine whether to proceed along specific pathways. This timing system may be influenced by other time keepers. Metabolic and mitotic systems are present in high-density cultures of human cells, and the interface of these systems may be a general feature of clock-controlled systems. The cycle of cell division is basically a relaxation oscillator of embedded negative feed-back loops involving the cyclins.

The circadian clock has been studied in relation to cycles of cell division and metabolism. It involves an innate timekeeping system governing a cycle of rhythmic activity. It has a control point, like the cell cycle, located in the suprachiasmatic nucleus, which is where decisions are made about proceeding or abandoning the cycle. Its regulatory genes include *BMAL*, *PERIOD*, *CRYPTOCHROME* and *CLOCK*, which also regulate their own transcription. Feedback loops generating circadian time are based on the transcriptional–translational and post-translational regulation of clock genes. Mice lacking some of these genes, e.g. *per2*, suffer from altered levels of cyclic regulators, e.g. c-*myc*. The mammalian cell cycle is also regulated by such clocks, and information on them is emerging from the use of microarrays at different stages of timing. Links between the circadian cycle and the metabolic cycle involve a cluster of genes encoding rate-limiting enzymes of intermediary metabolism. The sleep–wake cycle involves two processes, the drive to sleep and wakefulness in relation to night and day. It is also related to energy stores in the brain where the sleep–wake cycle controls a cascade of oscillatory electrical activity.

Biological systems also adapt to long time scales, while seasonal rhythms regulate long-term behavioural and developmental changes. They may have evolved from earlier cyclic processes, e.g. opposing metabolic states imposed by the availability of solar energy and light-induced stress. External light and dark cycles could have interfaced with the circadian clock and with metabolic cycles, and physiological systems may then have been organized around these and other cycles as organisms became increasingly complex. Computer models have been designed to investigate these possibilities. They are needed to analyse the interelationships between numerous cyclic processes in relation to temporal and spatial scales.

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