Commentary

Freezing the Biological Clock: A Viable Fertility Preservation Option for Young Singaporean Women?

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Abstract

In March 2012, an article in The Straits Times entitled 'Freezing eggs could reverse falling birth rate' suggested that employing the latest oocyte cryopreservation techniques could both foster individual women's reproductive autonomy and impact Singapore's fertility rate, which in recent years has consistently been among the world's lowest. The article cited both local and international fertility specialists' approval of elective oocyte cryopreservation for young women wishing to protect their reproductive potential against ageing and as a potential antidote to the contemporary 'delay and defer' model of family-building. Later in 2012, the Ministry of Health announced a review of oocyte cryopreservation policy taking into account related medical, scientific and ethical issues, while the Singapore College of Obstetricians and Gynaecologists endorsed oocyte cryopreservation as an "important, safe and efficient technology". This paper outlines and analyses the arguments and empirical evidence used both to support and oppose offering elective oocyte cryopreservation as a routine fertility service, before concluding that this remains unjustifiable on the basis of insufficient evidence of its clinical efficacy and safety as regards either pregnancy rates or birth outcomes. If it is to be made available at all for these reasons in Singapore, it should be subjected to rigorous clinic-specific evaluation in accordance with accepted clinical and ethical norms.

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Introduction

For almost 4 decades, Singapore has experienced total fertility rates (TFR) below population replacement levels and which have stubbornly defied a raft of pro-family policies initiated by the government since the mid-1980s, that have sought to encourage marriage and childbearing, provide support for childcare and facilitate the balancing of work and family responsibilities.[1] Although Singapore is far from alone in this demographic predicament, since most of Europe and other East Asian nations are similarly afflicted, the virtually remorseless downward slide has, in recent years, consistently placed it at the foot of the global fertility "league table".[2-4] Assisted reproductive technologies (ARTs) have evolved since the mid 1970s into a suite of medical interventions that have resulted in the birth of more than 5 million children worldwide.[5] Among these, the ability to store gametes and embryos for future reproductive use has been a major technological advancement. While effective techniques of semen and embryo cryopreservation have been developed for some time—more than 60 years in the case of semen cryopreservation,[6] the unique characteristics of the human oocyte have rendered the perfection of preservation techniques more problematic, most notably because of its high water content and the subsequent iatrogenic consequences of the formation of ice crystals as part of the freezing process. The first live human birth from cryopreserved-thawed oocytes was reported in

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1986,[7] although the challenges associated with successful oocyte freezing, thawing, fertilisation, implantation and pregnancy have resulted in relatively few subsequent live births compared to those resulting from both cryopreserved-thawed embryos and cryopreserved-thawed semen.

Initial procedures used for oocyte cryopreservation involved slow freezing. Efforts to refine these concentrated on trying to extract water from the oocyte during the freezing process to minimise damage caused by ice crystal formation. A more promising method of oocyte cryopreservation involving vitrification has been developed more recently. It eliminates the formation of ice crystals by combining high cooling and warming rates with a high concentration of cryoprotectants.[8] However, the risk of contamination is elevated because the procedure involves direct contact between the oocytes and liquid nitrogen and use of relatively high concentrations of cryoprotectan.[9] In efforts to reduce this risk, ultraviolet liquid nitrogen sterilisation[10] and high security closed vitrification devices,[11] have recently been reported.

As an assisted reproductive procedure, oocyte cryopreservation has potential clinical application in the following circumstances[12-14] for:

1. women facing surgery, chemotherapy or radiotherapy that is likely to compromise their fertility, and who are not in a position to freeze embryos;
2. women at risk of familial premature menopause because of a genetic condition such as Turner's syndrome or galactosaemia;
3. women at risk of premature pathogenic or iatrogenic fertility loss;
4. couples who have ethical and/or religious objections to embryo cryopreservation;
5. salvaging a cycle where partner sperm is not available at the time of oocyte retrieval.

While the use of oocyte cryopreservation under circumstances such as these has become virtual common practice, on the grounds of there being no alternative,[15,16] the use of oocyte cryopreservation by ostensibly fertile young women wishing to preserve their reproductive potential against the threat posed by ageing has generated considerable controversy.[17] In Singapore, use of cryopreserved oocytes for family building is currently restricted to women whose fertility might be impaired following necessary medical treatment, although several (unidentified) local fertility practitioners are said to support the availability of elective oocyte preservation, also claiming that "it might even reverse the Republic's birth rate"[18] (p.C1) and an unspecified number of Singaporean women are reported to have used overseas elective oocyte cryopreservation services.[19] In November 2012, the Ministry of Health announced a review of government policy regarding oocyte cryopreservation that would take account of related medical, scientific and ethical issues, while the Singapore College of Obstetricians and Gynaecologists was reported to have described oocyte cryopreservation an "important, safe and efficient technology".[19]

Promotion of the (more) ready availability of elective oocyte cryopreservation portrays it as enhancing the autonomy of women faced with the conflicting demands of contemporary motherhood[20-23] resulting from the interaction of women's increased participation in education and the labour market, the pressures of multitasking and increasing opportunity costs of childrearing, while the female "biological clock" continues to dictate a rapid decline in female fertility from the age of about 35 years. Underscoring pragmatic reasoning, some advocates of elective oocyte cryopreservation have argued that women who are able to freeze their own oocytes when they are still at the peak of their fecundity are less likely to require donor oocytes later on, thus reserving this pool of scarce resources for other women who were never able to produce oocytes of sufficient quality in the first place.[24] Goold and Savulescu[20] suggest 3 additional advantages of elective oocyte cryopreservation: the use of young oocytes could reduce the incidence of chromosomal abnormalities in infants, and elective oocyte cryopreservation used in combination with preimplantation diagnosis could potentially eliminate many genetic abnormalities; children born to older parents may be advantaged because older parents are likely to be more stable financially than if they had started to build their family earlier; and a possible increase in the donor oocyte pool because women who have stored their oocytes but who subsequently conceive without recourse to them may be willing to donate them to other women.

Current Discourses on Elective Oocyte Cryopreservation

Enterprising entrepreneurs have readily promoted the "benefits" of elective oocyte cryopreservation:

> "Egg freezing *effectively* suspends the ever-present ticking of the reproductive biological clock, *giving women more choices than ever before*"[25] (emphasis added).

> "Freezing eggs offers women planning to have children after the age of 35 the opportunity to *effectively* slow down their biological clocks. *Egg freezing gives women the unprecedented chance* to store their eggs during their reproductive prime for use when they wish to start or expand their families."[26] (emphasis added).

> "*Young women now can preserve their fertility* by storing their healthy unfertilized eggs or oocytes

> until a time in the future when they are ready to begin their family without feeling the pressures of the "biologic clock"……. *The physical properties that make an egg fertile during youth, can now be preserved* by freezing a woman's eggs until such a time *when she is ready to initiate her family on terms that are suitable for her*"[27] (emphasis added).

Such commercially-inspired claims have received at least implicit support from reassurances about the safety and efficacy of oocyte preservation provided by some academic[20] and clinical commentators.[6,21] Somewhat self-contradictorily, the European Society of Human Reproduction and Embryology (ESHRE) Task Force on Law and Ethics[28] acknowledged that "data about long-term safety is [*sic*] still lacking" (p. 1231) and "there is [*sic*] no data available on the long-term child follow-up" (p. 1232), but nevertheless concludes that "arguments against allowing [elective oocyte cryopreservation] are not convincing" (p. 1231). In contrast, The American Society for Reproductive Medicine's (ASRM's) approach towards oocyte cryopreservation has been more cautionary. Although ASRM concluded in September 2012 that "dramatic" improvements in success rates and "reassuring" preliminary safety data, merited oocyte cryopreservation's declassification as an "experimental procedure",[17] it nevertheless concluded that current data regarding safety, efficacy, cost-effectiveness, and emotional risks did not justify recommending that elective oocyte cryopreservation should become a universal service. ASRM specifically warned of deceptive marketing of elective oocyte cryopreservation, thus reinforcing concerns expressed elsewhere that the procedure may be perceived as a form of "fertility insurance", which could perversely contribute to female infertility by generating a false sense of security among potential customers that conception may be safely postponed.[19,29]

Evaluating the Evidence Base

Currently, available evidence regarding oocyte cryopreservation concerns first, survival, fertilisation and pregnancy rates of cryopreserved oocytes using different cryopreservation protocols, and second, neonatal outcomes of successful conceptions. A meta-analysis of 26 reports of slow freezing methods published between 1997 and 2005,[30] involving 354 patients, 95 clinical pregnancies, 97 children born and 76 live births, showed that success rates of in vitro fertilisation (IVF) using slow-frozen oocytes were significantly lower than IVF using fresh oocytes. A later meta analysis of 5 reports of both slow freezing and vitrification methods published between 2008 and 2010[31] involving 361 slow-frozen oocytes, 4282 vitrified oocytes, and 3524 fresh oocytes indicated similar survival, fertilisation and pregnancy rates of fresh oocytes and oocytes cryopreserved following vitrification, and the superiority of both compared with slow-frozen oocytes. Similar fertilisation and pregnancy rates were observed in an analysis of 4 randomised controlled trials comparing outcomes of intracytoplasmic sperm injection (ICSI/IVF) treatments using vitrified and fresh oocytes,[17] involving 755 patients, 3809 vitrified oocytes and 3524 fresh oocytes.

While the results of vitrification are, indeed, encouraging, the ASRM[17] warns:

> "Given the limited number of randomized controlled trials, it is not clear that these data are generalizable. Indeed, it is likely that only programs with the highest pregnancy rates conduct and publish such studies, limiting the generalizability of their results to other clinical programs. In addition, the majority of these data derives from experience using oocytes obtained from healthy, young oocyte donors under the age of 30 years, which have been vitrified for a limited duration. Therefore, such data cannot be extrapolated to other clinics, different patient populations (particularly older women), and to programs that utilize different cryopreservation protocols". (p. 3)

Survival, fertilisation and pregnancy rates, self-evidently, provide only a partial picture. Since the principal objective of these procedures is the birth of a healthy child, more significant outcomes relate to the implications for the children born as a result of the procedure. Two extensive reviews of extant literature regarding children born as a result of oocyte preservation have been published.[32,33] Noyes et al endeavoured to identify the outcomes for all verified live-born infants conceived following oocyte cryopreservation, 609 live born babies. Their study included a review of 23 case reports and 35 series reports published between 1986 and 2008, of which 43 referred to infants born as a result of slow freezing (308 babies), 12 to infants born as result of vitrification (289 babies) and 3 to infants born using both methods (12 babies). The literature review was supplemented with in-person contact with the authors to verify birth outcomes and provide updates. This resulted in the verification of a further 327 live births. Of the total 936 liveborns (532 from slow freezing, 392 from vitrification and 12 from both methods), 12 (1.3%) were affected by congenital anomalies, a prevalence comparable to that occurring in naturally conceived infants or infants conceived following conventional IVF. The authors caution that not all evaluations of the births reported were subject to the scrutiny of peer reviewed publication, and conclude: "with [the accumulation of] more live born data [….] this procedure may become mainstream as a fertility preservation option" (p. 768). Wennerholm et al[33] undertook a systematic

review of 30 observational studies examining the neonatal health of children born following oocyte cryopreservation that were published between 1998 and 2008. Twenty-three of these were included in the review undertaken by Noyes and colleagues.[32] Of these 22 reported on slow freezing and 8 on vitrification, and provided details of 148 and 221 infants respectively, for whom 'some' information on health status was provided. Wennerholm et al[33] report that most reviewed studies involved small numbers and describe the information regarding neonatal outcome as "scanty" (p. 2162). Thirty-six of the children (9.8%) underwent karyotype examination—and all results were normal. Limited information was provided regarding birthweight, and most reports of outcome data failed to distinguish between babies born as singletons and multiples.

While short-term neonatal data appear reassuring, most studies reported the health status of children simply as 'healthy' and in the absence of long-term data concerning the health of children born from oocyte cryopreservation that would provide compelling evidence of its safety, Wennerholm et al urge the "need for properly controlled follow-up studies of neonatal outcome and a careful assessment of evidence currently available before these techniques are added to daily routines" (p. 2169).

Two points should be made about these reviews. First their authors are themselves practising fertility specialists rather than critics of reproductive medicine outside the ranks of the profession. Second, their caution regarding the premature routine clinical application of elective oocyte cryopreservation is in marked contrast to the unrestrained claims cited earlier in this article.

Social and Economic Perspectives

The contribution of ARTs to population replenishment, especially in the context of low and declining fertility rates, remains contested, primarily because of inadequate data. In Europe, where systematic collection of ART outcome data was initiated in 1997, ART births comprise up to 4.6% of all births as of 2008 (the most recent year for which data are available).[34] The potential contribution of ART to population replenishment was first explored by RAND Europe[35] that claimed that wider and earlier access to IVF could exert a major impact on birth rates, and compared favourably to other pro-family policy measures.[36] However, Habbema et al[37] considered that the RAND study had inflated the IVF effect and concluded that wider and earlier access to IVF would make a more modest contribution to fertility rates only at the cost of significantly-increased funding for IVF cycles and increasing the multiple birth rate. Other scholars have commented on the increased emotional and social pressures placed on childless women within the context of "generous" publicly-funded ARTs.[38-40]

Since 2008, the Singapore government has subsidised ART for eligible citizens, at least in part, one of the planks of government policy to boost fertility rates.[41] However, since data regarding the outcomes of publicly-funded fertility treatment are not readily available (the authors' request for such information was declined), calculation of these is reliant on incomplete data reported in local media.[42-44] By 2009—the most recent year for which data are available—ART accounted for around 3.64% of all births.[43,45] Since the data compare favourably with European countries where ARTs receive extensive public subsidies, it is unlikely that any expansion of public funding for ARTs in Singapore would significantly impact fertility rates. Within this context, the possibility of even readily available elective oocyte cryopreservation making a positive contribution to Singapore's population appears marginal. At the same time, as ASRM[17] and other observers[38-40] have warned, its availability could exert a negative impact at both a societal and individual level, by generating false expectations of future fertility and by increasing societal and psychological pressures on women in a society in which the root causes of low fertility are well known, but remain unaddressed.[46]

Conclusion

Medically assisted reproduction has earned itself a somewhat dubious reputation for transforming "laboratory breakthroughs into clinical practice without rigorous government-sponsored or supervised clinical trials to ensure safety and efficacy"[47](p.1510). Only comparatively recently, and well after the widespread expansion of services, is longer term evidence of the outcomes of reproductive technology being accumulated.[48,49]

There is a clear risk that much the same could well occur as regards to elective oocyte cryopreservation—indeed, may already have occurred at least in the United States, where the practice is offered by almost two-thirds of ASRM member clinics,[50] despite the efforts of ASRM to reign in both insufficiently-circumspect enthusiasm and rampant commercialisation of offering elective cryopreservation to healthy women as an attractive strategy to delay childbearing.[17] It is evident that elective oocyte cryopreservation is a widely available clinical procedure despite the absence of the necessary evidence to determine its safety, efficacy and cost-effectiveness and with which to inform potential customers to ensure they are fully equipped emotionally to make a truly informed choice.[51]

The social conditions that elective oocyte cryopreservation seek to ameliorate are both real and pressing enough, not least in Singapore. If and when elective oocyte cryopreservation proves to be demonstrably effective and safe, there seems no good reason to withhold it from young women who wish to avail themselves of the service, although the

impact on TFR is likely to be marginal unless elective oocyte cryopreservation enables significant numbers of older women to conceive despite age-related reduction in oocyte quality—an unlikely outcome. In any event, compelling evidence of neither efficacy nor long-term safety currently exists. Available evidence suggests that elective oocyte cryopreservation may be offered under trial conditions, proper counselling to discuss its limitations, risks and benefits, but the time is not yet right for it to be considered as a routine service. By implication this rules out elective oocyte cryopreservation as a "quick fix" either to Singapore's demographic problems or to women wishing to conceive beyond the point of optimum fecundity.

As the spirited debate between Rybak and Lieman[47] and the ASRM[52] indicates, the lessons of the development of reproductive medicine are capable of divergent interpretations, between allowing the clinical application of elective oocyte cryopreservation in the absence of adequate evidence because that is what has characterised previous developments in the field (the case articulated by Rybak and Lieman[47]), or espousing a greater degree of caution now because of previous mistakes and omissions (the position taken by the ASRM[52]).

Self-regulation in the United States has failed to stem the over-hasty availability of commercially driven elective oocyte cryopreservation. This suggests that only the relatively blunt instrument of externally imposed regulation and/or legislation will slow sufficiently the pace of commercial application of the procedure to enable necessary basic research to be undertaken and sufficient clinical evidence to be gathered. The real choice facing Singapore is either to ban elective oocyte preservation entirely and await the outcome of evaluations taking place elsewhere, or to permit comparative and observational trials that conform to the most rigorous evidence-based standards and ensure that potential service users are provided with full information and offered competent professional counselling.

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