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REVIEW

Oocyte vitrification in the 21st century and post-warming fertility outcomes: a systematic review and meta-analysis

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Abstract Oocyte cryopreservation is a rapidly developing technology, which is increasingly being used for various medical, legal and social reasons. There are inconsistencies in information regarding survival rate and fertility outcomes. This systematic review and meta-analysis provides evidence-based information about oocyte survival and fertility outcomes post warming to help women to make informed choices. All randomized and non-randomized, controlled and prospective cohort studies using oocyte vitrification were included. The primary outcome measure was ongoing pregnancy rate/warmed oocyte. Sensitivity analysis for donor and non-donor oocyte studies was performed. Proportional meta-analysis of 17 studies, using a random-effects model, showed pooled ongoing pregnancy and clinical pregnancy rates per warmed oocyte of 7%. Oocyte survival, fertilization, cleavage, clinical pregnancy and ongoing pregnancy rates per warmed oocyte were higher in donor versus non-donor studies. Comparing vitrified with fresh oocytes, no statistically significant difference was observed in fertilization, cleavage and clinical pregnancy rates, but ongoing pregnancy rate was reduced in the vitrified group (odds ratio 0.74), with heterogeneity between studies. Considering the age of women and the reason for cryopreservation, reasonable information can be given to help women to make informed choices. Future studies with outcomes from oocytes cryopreserved for gonadotoxic treatment may provide more insight.

KEYWORDS: ICSI, IVF outcomes, oocyte cryopreservation, slow freezing, vitrification

Introduction

Globally, various medical, legal and social reasons have emerged for oocyte cryopreservation. Traditionally, cryopreservation of oocytes has been considered for fertility preservation in women undergoing gonadotoxic treatment; other reasons are cryopreservation for oocyte donation programmes, and, in certain countries where the law

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prohibits embryo cryopreservation and gamete donation, excess oocytes have been cryopreserved for future use. Furthermore, with changing social cultures and role of women in the 21st century, social egg cryopreservation is gaining prevalence as a method of preserving reproductive potential.

Since oocyte cryopreservation is a rapidly developing technology, there are inconsistencies in information provided to women with regard to survival rate and fertility outcome. Until recently, oocyte cryopreservation has been considered experimental; therefore clinicians and service providers have not been sure themselves of the actual success rate for oocyte cryopreservation. Many centres have cryopreserved oocytes for years, especially for oncology patients, before fertilization and transfer into women's uteri. Many other oocytes have never been used because patients either regained their natural fertility or deceased.

The first human birth from a cryopreserved oocyte was reported in 1986 (Chen, 1986). The primary challenge with oocyte cryopreservation has been maintaining survival of the mature metaphase-II oocyte post warming, which is indirectly related to oocyte plasma membrane stability and permeability to water and cryoprotectants (Agca et al., 1998; Ford et al., 2000). In addition, the oocyte meiotic spindle, which is required for chromosomal segregation, is noted to be extremely sensitive to temperature changes and the dehydration–rehydration process (Baka et al., 1995; Bianchi et al., 2005; Chen et al., 2004; Cobo et al., 2008a; Larman et al., 2007). However, it has been demonstrated that the spindle disintegrates during the freeze–thaw process and that it reassembles again in most oocytes (Gook et al., 1994; Rienzi et al., 2004). Moreover, studies have shown that oocyte cryopreservation does not increase the frequency of developmental abnormalities and pregnancy complications (Chian et al., 2008; Forman et al., 2012; Noyes et al., 2009).

The initial technique of oocyte cryopreservation began as slow freezing, followed by modifications to improve oocyte survival (Bianchi et al., 2012; Boldt et al., 2006; Fabbri et al., 2001; Parmegiani et al., 2008; Trad et al., 1999). In the last decade, vitrification techniques have been developed and modified to enhance survival and implantation rates for the oocytes and embryos, respectively (Alpha Scientists in Reproductive Medicine, 2012; Borini et al., 2004; Cobo et al., 2010; Fabbri et al., 2001; Kuwayama et al., 2005; Smith et al., 2010; Vajta and Nagy, 2006). Previously, live birth rate per thawed–warmed oocyte was reported as 1.9% for slow freezing and 2.0% for vitrification (Oktay et al., 2006). Studies have compared fertility outcomes using slow-frozen versus vitrified oocytes and fresh versus vitrified oocytes (Cobo et al., 2008b; Rienzi et al., 2010; Ubaldi et al., 2010). The systematic review and meta-analysis by Oktay et al. (2006) compared outcomes of slow-frozen with fresh oocytes and concluded that fertilization, implantation and live birth rates were significantly better with fresh oocytes. Subsequently, Cobo and Diaz (2011) presented a meta-analysis for clinical application of oocyte vitrification and concluded that oocyte survival, fertilization and embryo cleavage rates per warmed oocyte were higher with vitrification compared with slow freezing. Since then, seven additional prospective studies have been conducted (Cai et al., 2012; Chang et al., 2013; Forman et al., 2012; Garcia et al., 2011; Parmegiani et al., 2011; Rienzi et al., 2012; Trokoudes et al., 2011) providing further evidence regarding outcomes using vitrified oocytes.

To help women to make informed choices, this systematic review and meta-analysis was performed to compare fertility outcomes using vitrified oocytes with fresh oocytes and to provide evidence-based information about oocyte survival and fertility outcomes post warming (including ongoing pregnancy and clinical pregnancy rates per warmed oocyte).

Materials and methods

Literature search

Online searches of databases were performed in MEDLINE (1980–June 2013), EMBASE (1980–June 2013) and the Cochrane Library. The searches also included Conference Proceedings Citation Index and databases for registered and ongoing trials. A combination of Medical Subject Headings and words were used to generate a subset of citations for oocyte cryopreservation ('oocyte', 'slow cooling', 'slow freeze', 'vitrification' and 'cryopreserv*'); for citations including outcomes after IVF and intracytoplasmic sperm injection (ICSI) ('outcome', 'IVF', 'in-vitro fertilization', 'intracytoplasmic sperm injection', 'ICSI' and 'assisted reproduct*'). These subsets were combined using 'AND' to generate final citations addressing the research question. The reference lists of all published articles including review articles were examined to identify articles not noted by the electronic search of the databases. No language restrictions were placed on the searches so that relevant non-English studies were included. Authors were contacted to obtain further information, as appropriate.

Study eligibility criteria

This study included randomized controlled trials (RCT), prospective non-randomized controlled trials (NRCT) and prospective cohort studies that used vitrified oocytes for ICSI. The inclusion criteria were study population of women undergoing IVF treatment with exclusion of poor responders and intervention of vitrification and/or comparison with fresh or slow-frozen oocytes in the matched control group. In all studies, ICSI was performed because removal of cumulus has the potential to reduce fertilization and because there can be hardening of the zona pellucida post thawing/warming (Gook et al., 1994; Porcu et al., 1997).

Observational studies were vigorously reviewed and prospective trials that met all other predefined criteria were included. These studies were included since their exclusion would have led to the omission of vital data and available evidence. The primary reasons for excluding studies were retrospective design or case series, no outcome measure reported and use of different intervention.

Study selection and data extraction were performed by two authors (NP and TAG) independently. All articles, including abstracts from the electronic searches, were assessed and citations that met the predefined selection criteria were obtained. After quality assessment of full manuscripts, final inclusion decisions were made. Any disagreement between the two reviewers was resolved by consultation with the third author (LNG).