Review / Derleme

DOI: 10.4274/tjod.galenos.2022.59827

Turk J Obstet Gynecol 2023;20:59-63

Oocyte vitrification for oncological and social reasons

Onkolojik ve sosyal nedenlerle oosit vitrifikasyonu

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Abstract

The aim of this review is to present information related to oocyte cryopreservation, and particularly oocyte vitrification, performed to preserve fertility in oncologic and social indications. The success rates of oocyte cryopreservation have increased with the widespread use of the vitrification technique and are currently similar to those of in vitro fertilization performed with fresh oocytes. Vitrification is the most successful technique for oocyte cryopreservation. The most important factors that influence the success rate are the patient's age at the time of vitrification and the number of mature oocytes frozen. Thus, live birth rates differ for each age depending on the number of oocytes thawed and the freezing method. The American Society of Reproductive Medicine and the American Society of Clinical Oncology recommend presenting the option of oocyte cryopreservation for fertility preservation in cancer patients. Besides cancer patients, use of oocyte vitrification is increasing in women who wish to postpone pregnancy age and to have reproductive freedom with the development of the cryopreservation technique and the achievement of pregnancy rates similar to the use of fresh oocytes. Patients are provided consultancy service in terms of indication, the success rates by age, and the total number of oocytes frozen. It should be emphasized that this procedure is not a type of insurance policy for fertility, especially in elective oocyte cryopreservation.

Keywords: Oocyte vitrification, fertility preservation, oocyte cryopreservation

Öz

Bu derlemenin amacı onkolojik ve sosyal endikasyonlarla fertilitenin korunması amacıyla oosit kriyoprezervasyonu özellikle de oosit vitrifikasyonu ile ilgili güncel bilgileri sunmaktır. Oosit kriyoprezervasyon başarı oranları, vitrifikasyon tekniğinin yaygınlaşması ile birlikte artmış ve günümüzde taze oositlerle yapılan in vitro fertilizasyon gebelik oranlarına benzerdir. Vitrifikasyon oosit kriyoprezervasyonunda en başarılı tekniktir. Başarı oranını etkileyen en önemli faktör vitrifikasyon sırasında hastanın kaç yaşında olduğu ve kaç olgun yumurtasının dondurulduğudur. Dolayısıyla, çözülen yumurta sayısı ve dondurma yöntemine göre de her yaş için canlı doğum oranları farklıdır. Amerikan Üreme Sağlığı Birliği ve Amerikan Klinik Onkoloji Birliği, kanser hastalarında fertilite prezervasyonu için oosit kriyoprezervasyon seçeneğinin sunulmasını önermektedir. Kanser olguları dışında dondurma tekniğinin gelişmesi ve taze oositlerle benzer gebelik oranlarının elde edilmesiyle, gebelik yaşını ertelemek isteyen ve üreme özgürlüğünü kaybetmek istemeyen kadınlarda oosit vitrifikasyonunun kullanımı artmaktadır. Hastalara endikasyon, yaş ve toplam dondurulan oosit sayısına göre başarı oranları ile ilgili danışmanlık verilmelidir. Özellikle, elektif oosit kriyoprezervasyonunda bu işlemin fertilite için bir tür sigorta poliçesi olmadığı gerçeği vurgulanmalıdır.

Anahtar Kelimeler: Oosit vitrifikasyonu, fertilite prezervasyonu, oosit kriyoprezervasyonu

Introduction

A wide range of advancements have occurred in the area of assisted reproductive technology (ART) since the birth of Louise Brown in 1978[1]. In this area, maximum improvement has been observed in fertility preservation. Fertility preservation is a method of giving individuals the right to have their own genetic offspring by preserving the germ cells (oocytes, sperms) and the gonadal tissues (testicles, ovaries). Each condition that can create a risk of reduction in reproductive capacity in women and men is an indication for fertility preservation. The most common reasons for patients presenting for fertility preservation are as follows: will to have a surgical operation or receive chemotherapy because of cancer; they have medical conditions that could lead to premature menopause; or they wish to postpone pregnancy because of social reasons[2].

Oocyte and embryo cryopreservation has been one of the most important advancements in ART in the last 20 years. Although vitrification is entitled a novel technology, it was successfully used to freeze mouse embryos 35 years ago[3]. However, the use

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Received/Geliş Tarihi: 14.10.2022 **Accepted/Kabul Tarihi:** 14.12.2022

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Turkish Journal of Obstetrics and Gynecology published by Galenos Publishing House.

of vitrification in human oocytes and embryos did not become widespread until the end of the 1990s. Oocyte cryopreservation, which was previously considered experimental, was accepted as a method that should be routinely presented to patients who had indications for fertility preservation and was no longer considered an experimental method after a journal published in 2013 by the American Society of Reproductive Medicine (ASRM)[4].

The aim of this review is to present information related to oocyte cryopreservation, and particularly oocyte vitrification, performed for fertility preservation in oncologic and social indications.

Oocyte Vitrification

The first birth following the use of cryopreserved oocytes occurred at the end of the 1980s[5]. In all the studies after that, researchers have attempted to establish an ideal oocyte cryopreservation protocol. However, the expected advancements in this area could not be achieved due to technical issues and low success rates[6]. This was associated with difficulties related to the use of the slow-freezing technique. It is considerably difficult to freeze oocytes because of their large size and low surface area-to-volume ratio[7]. In oocyte cryopreservation, the large amount of water in oocytes leads to intracellular ice formation, chilling injury, and osmotic injury. Additionally, studies have shown that cryopreservation has negative effects on microtubule and microfilament stability, which are essential for normal chromosome segregation in mammalian oocytes[8,9]. Other difficulties related to cryopreservation include the hardening of the zona pellucida and the low fertilization rates related to this[10]. In later studies, it was shown that human oocytes regained morphology and chromosomal integrity following cryopreservation[11,12]. The number of studies related to oocyte cryopreservation has increased, especially in countries where embryo cryopreservation is illegal[13]. The use of the vitrification technique instead of slow freezing enabled both the reduction of injury in the internal structures of oocytes and higher pregnancy rates[14,15]. Oocyte cryopreservation, which was previously considered experimental, was accepted as a method that should be routinely presented to patients who had indications for fertility preservation, and it was no longer considered an experimental method with the journal published in 2013 by the ASRM[4]. Fertilization and pregnancy rates for in vitro fertilization (IVF) performed using vitrified/warmed oocytes have been reported to be similar to those using fresh oocytes[4].

Cryopreservation is the complete stopping of biological reactions by storing cells and tissues at temperatures below zero degrees Celsius for long periods. Cryoprotectant additives (CPA) are used to prevent ice formation and cryoinjury. They are classified as permeating or non-permeating CPAs depending on their ability to permeate the cellular membrane[16]. Various combinations of permeating and non-permeating CPAs can be used. Two techniques are used in the cryopreservation of human oocytes: Slow-freezing and ultrarapid cooling with vitrification.

In the slow-freezing technique, oocytes are exposed to low concentrations of CPAs and the temperature is reduced slowly. Cooling to -5 to -7 °C, at which point balance and seeding occurs, is conducted primarily. Subsequently, cooling at a slow rate (0.3-0.5 degrees/min) continues until a temperature of (-30)-(-60) °C is achieved. Afterwards, liquid nitrogen is added for storing[17]. Studies comparing slow-frozen and fresh oocytes have shown that the results are worse with frozen/thawed oocytes[18,19].

Higher concentrations of CPA are used in vitrification and this reduces the risk for crystallization and ice nucleation. Additionally, the cooling rate is 100s-10.000 °C/minute[17]. In the early days of vitrification, high concentrations of CPA were used for longer periods, and this used led to osmotic stress. In later studies, the use of CPA mixtures was initiated to reduce this osmotic stress. A combination of ethylene glycol-dimethyl sulfoxide (1:1) is considerably efficient[20]. A high number of studies have shown that vitrification is superior to slow-freeze protocols. Although a low number of pregnancies were obtained with cryopreserved oocytes in this period, a meta-analysis emphasized that better pregnancy rates were achieved with oocytes frozen by way of the vitrification method[21]. When the IVF results obtained with slow-frozen and vitrified oocytes were compared, better survival, fertilization, and pregnancy rates were shown with vitrification[15,22]. There is accumulated evidence showing that the results of IVF performed with vitrified oocytes are similar to the results of IVF performed with fresh oocytes[23]. Clinical pregnancy rates range between 35.5% and 65.2% per transfer[24,25]. A meta-analysis found that the fertilization, embryo cleavage, high-quality embryo, and continuing pregnancy rates with the vitrification method were similar to the rates obtained with the use of fresh oocytes[2]. These studies concluded that the appropriate technique for oocyte cryopreservation was vitrification and the 2013 National Institute for Health and Care Excellence guideline reported that the vitrification technique should be used instead of controlled-rate freezing in oocyte and embryo cryopreservation if the required equipment is available[26]. In a retrospective cohort study, which compared 96 frozen embryos obtained from frozen oocytes with 4.394 frozen embryos obtained from fresh oocytes, no significant difference was found between embryo viability rates following thawing and live birth rates per cycle (97.2% vs. 95.7%, $p<0.005$, survival rate; 33.8% vs. 30.9%, $p<0.005$, live birth rates)[27].

Two classifications are related to the vitrification technique: open and closed vitrification. In open vitrification, there is direct contact between oocytes and liquid nitrogen, and low-volume devices, including capillary glass, cooper devices, pulled straws, and loops, are used[28]. In closed vitrification, there is indirect contact between oocytes and liquid nitrogen because tubing systems are used[28].

Oocyte Cryopreservation Results

In studies evaluating long-term obstetric and perinatal outcomes related to vitrification, negative obstetric and perinatal outcomes related to vitrification have not been reported[29]. The mean birth weight and frequency of congenital anomalies in infants produced by oocyte vitrification are not different from those of spontaneous pregnancies or IVF[29]. In another study, the frequency of congenital anomalies (1.3%) was found to be the same in pregnancies obtained by cryopreservation performed with slow-freezing and vitrification[30]. In conclusion, more than 5.000 live births have occurred with oocyte freezing up to the present, and the rate of congenital anomalies reported for these births is not different from the rate reported for ART and the normal population. However, no data related to long-term follow-up with these children have been published yet.

Fertility Preservation in Cancer Patients

Approximately 10% of women diagnosed with cancer are 45 years old or younger[31]. Requests for fertility preservation are increasing with an increase in the survival rates of cancer[30]. Gonadal failure and related infertility are among the long-term negative effects of radiotherapy and chemotherapy.

In 2006, the ASRM presented an opinion that oncologists should also discuss potential infertility problems and fertility-preserving approaches when informing and counseling patients who are at the reproductive age before cancer treatment and refer to these patients to reproductive health specialists if needed[32]. Although awareness is greatly increased, fertility-preservation approaches are not being applied at an adequate level. Strengthening multidisciplinary cooperation and the widespread use of fertility-preservation services will increase the number of patients.

In oncologic patients, embryo, ovarian tissue, and oocyte cryopreservation are the available options for fertility preservation[31]. Although embryo cryopreservation is the best option, the need for a partner and separations that could be experienced during treatment processes are the disadvantages[33]. The most appropriate option for single women to have a chance of getting pregnant with their own gametes is oocyte cryopreservation. With the advances in the oocyte cryopreservation technique, oocyte cryopreservation is being routinely recommended in fertility preservation. The most important disadvantage in oocyte cryopreservation in these patients is the need for controlled ovarian stimulation to collect oocytes. This leads to a delay in cancer treatment for weeks and poses a risk related to high levels of estrogen in hormone-receptive cancers[34]. However, these problems have been solved, particularly with the use of protocols that are independent of the menstrual cycle, shortening the delay period in initiating treatment, and the use of anti-oestrogens in stimulation in women with breast cancer[35,36].

Social Oocyte Cryopreservation

Worldwide, women are postponing pregnancy to later ages. Currently, oocyte cryopreservation is considered an acceptable method for age-related fertility reduction[37,38]. The popularity of social egg freezing is gradually increasing.

It is a well-known phenomenon that fertility rapidly decreases in women after the age of 35 years[37]. With oocyte freezing, women attain reproductive freedom later in life, like men. The two most important factors that determine the possibility of live birth with cryopreserved oocytes are the total number of mature oocytes and the age of the woman at the time of oocyte collection. Although the primary studies showed that collecting at least eight oocytes increased the rates of live birth at all ages from 22% to 46%, later studies found that this effect was lower in older women[39]. At the age of 35 years and below, the rates of live birth per patient are approximately two-fold higher compared to 36 years and above, and it was concluded that oocyte cryopreservation should be recommended to women aged 36 years and below for maximum success rates[40]. The possibility of live birth per thawed oocyte, which is known as oocyte efficiency rate, was 6.5%. As expected, the oocyte efficiency rate decreases with age, and this decrease is more prominent after the age of 37 years (7.4% for <30 years, 7% for <35 years, 6.5% for 35-37 years and 5.2% for 38-40 years)[41]. In conclusion, women should be informed accurately about the oocyte cryopreservation technique and success rates, and the fact that this procedure is a medical procedure rather than being an insurance policy should be emphasized. Another concern is the high cost of oocyte cryopreservation. Physiologically, the most appropriate age range for oocyte cryopreservation is the early- and middle-thirties. However, the most cost-effective strategy is still unclear[42]. Nevertheless, it was shown that the age range between 35 and 37 was the most appropriate period in terms of cost-effectiveness, and cryopreservation could be performed up to the age of 40 years[42].

Conclusion

The oocyte vitrification technique is efficient and safe for oocyte cryopreservation. The fertilization, embryo development, and pregnancy rates are similar compared to fresh oocytes. In oncologic patients, oocyte cryopreservation is the only chance for fertility preservation for these patients. Women who wish for elective oocyte cryopreservation should be informed about success rates by age and the number of mature oocytes, and it should also be emphasized that long-term outcomes of babies obtained by way of cryopreserved oocytes are not known.

Ethics

Peer-review: Internally and internally peer-reviewed.

Authorship Contributions

Concept: N.K., Design: N.K., Analysis or Interpretation: N.K., T.A., Literature Search: N.K., T.A., Writing: N.K., T.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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