ORIGINAL ARTICLE: FERTILITY PRESERVATION

Xenotransplantation of cryopreserved human ovarian tissue—a systematic review of MII oocyte maturation and discussion of it as a realistic option for restoring fertility after cancer treatment

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Objective: To systematically review the reporting of MII (MII) oocyte development after xenotransplantation of human ovarian tissue.
Design: Systematic review in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).
Setting: Not applicable.
Patient(s): Not applicable.
Intervention(s): Formation of MII oocytes after xenotransplantation of human ovarian tissue.
Main Outcome Measure(s): Any outcome reported in Pubmed.
Result(s): Six publications were identified that report on formation of MII oocytes after xenotransplantation of human ovarian tissue.
Conclusion(s): Xenografting of human ovarian tissue has proved to be a useful model for examining ovarian function and follicle development in vivo. With human follicles that have matured through xenografting, the possibility of cancer transmission and relapse can also be eliminated, because cancer cells are not able to penetrate the zona pellucida. The reported studies have demonstrated that xenografted ovarian tissue from a range of species, including humans, can produce antral follicles that contain mature (MII) oocytes, and it has been shown that mice oocytes have the potential to give rise to live young. Although some ethical questions remain unresolved, xenotransplantation may be a promising method for restoring fertility. This review furthermore describes the value of xenotransplantation as a tool in reproductive biology and discusses the ethical and potential safety issues regarding ovarian tissue xenotransplantation as a means of recovering fertility. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, ovarian tissue xenotransplantation, ovarian tissue cryopreservation

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Survival rates for cancer patients have substantially increased as a result of the tremendous advances that have been made in early diagnosis and more effective treatment schemes for malignant diseases. However, chemotherapy and/or radiotherapy very often lead to partial or complete impairment of the ovaries,

severely reducing or eliminating a woman's fertility. Approaches aimed at preserving fertility and providing patients with the relevant advice on the issue must therefore form an integral component of oncologic treatment in prepubertal girls and patients of reproductive age (1, 2).

Several options are currently available for preserving fertility, including transposition of the ovaries before radiation, embryo and oocyte cryopreservation, and treatment with GnRH analogues (3). A promising alternative is the cryopreservation of ovarian tissue before oncologic treatment. This makes it possible to store a large number of primordial and primary follicles; it can be performed rapidly at any time during the menstrual cycle without delaying the oncologic treatment; and it is a unique option for preserving fertility in prepubertal or premenarchal female patients (4). To date, more than 30 live births have been achieved after transplantation of cryopreserved ovarian tissue, and it is expected that in the near future, more and more cancer patients who have been cured of their disease are likely to request reimplantation of cryopreserved ovarian tissue (5–7).

Cryopreservation of ovarian tissue from women with cancer, however, involves a risk that malignant cell clones may be cryopreserved at the same time, potentially inducing a relapse following retransplantation. The extent of the risk of reintroducing malignancy in specific situations is not currently known, although it has been hypothesized that it may be influenced by the cancer type and stage, the quantity of malignant cells transferred, and the time of ovarian tissue harvesting relative to the oncologic treatment (8–10).

To prevent reimplantation of tumor cells in patients who are at high risk—e.g., those with neoplasia with systemic metastases, or with ovarian tumors and ovarian metastases—several attempts have been made to obtain mature oocytes that can be used for in vitro fertilization procedures without transplantation into the patient (11). These methods include in vitro culture of ovarian tissue (12, 13), the use of artificial ovaries (14, 15), and xenotransplantation (16–20) (Fig. 1). The goal of reproducibly obtaining mature oocytes has so far only been achieved with xenotransplantation. Xenotransplantation of ovarian tissue might therefore be an option for these cancer survivors, and the following discussion focuses on these patients in particular, because currently there are no options other than xenotransplantation for them to have their own children. Transplantation of frozen-thawed ovarian tissue into an animal host, with subsequent maturation and collection of oocytes, can offer considerable advantages. With this technique, the possibility of cancer transmission and relapse can be eliminated, because cancer cells are unable to penetrate the zona pellucida (21); and some technical difficulties with in vitro growth and maturation of primordial follicles can be bypassed. Complete oocyte development in vitro from the primordial stage has been achieved in mice, but the larger size and longer growth period of human follicles has made the interspecies translation of these techniques difficult (11). In addition, xenotransplantation of ovarian tissue can be used in patients who are at high risk for hyperstimulation syndrome (e.g., those with polycystic ovary syndrome) and patients in whom hormone replacement therapy is contraindicated, such as those with hormone receptor–positive breast cancer.

Numerous studies have shown that xenografted ovarian tissue from a range of species can produce antral follicles that contain oocytes (16, 22–25). It has been shown in animals that oocytes derived from such xenografted ovarian tissue have the potential to give rise to live young (22). For ethical reasons, however, fertilization and embryo development of human oocytes that have developed in animal hosts have not so far been investigated.

The present paper describes the value of xenotransplantation as a tool in reproductive biology and discusses the ethical and potential safety issues associated with ovarian tissue xenotransplantation as a means of restoring fertility.

MATERIALS AND METHODS

Search Strategy, Data Extraction, and Eligibility Criteria

A systematic literature search in Pubmed for relevant publications was conducted in October 2014. The following terms were used: xenotransplantation, ovarian tissue, human, MII. Bibliographies of the retrieved articles were also scanned and searched manually for relevant articles. We included only articles that described the formation of metaphase II (MII) oocytes from human ovarian tissue xenotransplantation. All the abstracts retrieved from the search were assessed, and the full manuscripts of citations that met eligibility criteria were obtained. The articles were evaluated and the data extracted. Institutional Review Board approval was not obtained for this systematic review. It was determined that none was necessary, because all data were taken from previously published papers.

RESULTS

The search terms generated six references in Pubmed. No references were excluded. All of the references reported on the formation of human mature MII oocytes (Table 1).

DISCUSSION

Overview of Xenotransplantation in the Fields of Transplantation and Reproductive Biology

Xenografting means the transplantation of cells, tissues, or whole organs across a species barrier, that is, from one species to another. The method was primarily developed to cope with the shortage of human organs for transplantation. The idea of performing xenotransplantation is more than 100 years old, and there are historically recorded incidences of xenotransplantation occurring in ancient China with the transfer of animal penile tissue to humans, and of transfusions of sheep blood to humans in 1667 (26). In 1963, a kidney from a rhesus monkey was transplanted into a 43-year-old man; he died of pneumonia 63 days after the procedure. In the same year, a chimpanzee kidney was transplanted into a human, who survived for 9 months after transplantation (27). That is the longest documented xenograft survival in a human. The most widely publicized