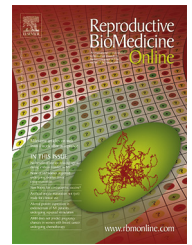




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## ARTICLE

# Ovarian tissue cryopreservation and retransplantation – what do patients think about it?




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Ralf Dittrich completed his dissertation on the influence of gonadotropins in the development of malignant germ cell tumours in 1989 at the University Hospital Erlangen, Germany. Since 1994, he has been director of the reproductive biology and gynaecological endocrinology laboratories at the same hospital. In 2006 he obtained his habilitation (adjunct professor) and in 2009 the professorship in Experimental Reproductive Medicine, both at the University of Erlangen-Nuremberg. His main research topic is cryopreservation of ovarian tissue and gametes (others being gynaecological endocrinology, the function of the uterus in mammalian reproduction and antioxidative properties of steroids and food compounds).

**Abstract** Cryopreservation of ovarian tissue has been successfully applied clinically, with over 60 live births to date. The aim of the present study was to perform a survey of patients who have had ovarian tissue cryopreserved in the Department of Obstetrics and Gynecology, Erlangen University Hospital, in order to obtain information about: why patients opt for fertility preservation; their current fertility; pregnancy attempts and outcomes; and their intended plans for the cryopreserved ovarian tissue. In total, 147 women took part in the survey (average age  $25.0 \pm 7.0$  years; response rate 48%; mean follow-up period 6 years). Sixty-six reported regular menstrual cycles; 48 were amenorrhoeic. Sixty-two women had tried to conceive; 33 reported pregnancies. Twenty-five had delivered healthy children after conceiving naturally; eight had conceived with assisted reproduction. Five patients had had their ovarian tissue retransplanted. Although many patients continued to have ovarian function, none of them regretted choosing cryopreservation of ovarian tissue. Cryopreservation of ovarian tissue is an effective option and is very important for women diagnosed with cancer. Analyses of the clinical outcomes in these patients are essential in order to identify those patients capable of benefiting most from the procedure and in order to improve the technique. 

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**KEYWORDS:** cancer, cryobank, fertility preservation, ovarian tissue cryopreservation, ovarian tissue transplantation, survey

## Introduction

Increasing survival rates among cancer patients and increasing awareness of the importance of quality of life after chemotherapy and radiotherapy have focused attention on the preservation of fertility after cancer treatment. Due to the considerable advances that have been made in reproductive medicine, patients can now be offered measures that make it possible for women who have been affected by cancer to have children after recovering from the disease (Anderson et al., 2015).

A number of strategies for fertility preservation have been developed in recent years. Fertility-preserving measures have to be customized to match the patient's individual clinical situation. Aspects that need to be taken into account include the time available before the start of oncological therapy, the patient's age, her relationship status, potential ovarian involvement in the cancer and the gonadotoxic measures that are planned (De Vos et al., 2014).

Research on the cryopreservation of ovarian tissue as a method of fertility preservation has now been continuing for more than a decade, and considerable successes have recently been achieved (Gamzatova et al., 2014). The removal of ovarian tissue is a simple procedure. Ovarian tissue can be obtained using minimally invasive techniques during laparoscopy, with unilateral ovariectomy or partial ovariectomy. Ovarian tissue can be cryopreserved independently of the menstrual phase and the procedure therefore does not lead to any delays in oncological therapy. In centres that offer cryopreservation of ovarian tissue, the procedure can be performed 1 day after the patient's first visit. After the tissue has been removed, it can be processed immediately or transferred in special transportation containers to a centre specializing in the cryopreservation of ovarian tissue, with an associated cryobank (Dittrich et al., 2012).

Donnez et al. reported the first live birth after autotransplantation of human ovarian tissue in 2004 (Donnez et al., 2004). In Germany, the first live birth after retransplantation of cryopreserved ovarian tissue was reported in 2012 (Müller et al., 2012). To date, 60 live births have been reported worldwide following transplantation of cryopreserved ovarian tissue (Dittrich et al., 2015; Donnez and Dolmans, 2015; Donnez et al., 2013; Macklon et al., 2014b). In the near future, it is expected that more and more patients who have been cured of cancer will be wishing to undergo reimplantation of ovarian tissue.

Due to a lack of follow-up data, little information is available regarding the benefits of ovarian tissue cryopreservation in relation to reproductive outcomes. The aim of the present study was therefore to conduct a survey of patients who have undergone ovarian tissue cryopreservation in the Department of Obstetrics and Gynecology at Erlangen University Hospital, in order to obtain information about why they opted for fertility preservation, about their current fertility, pregnancy attempts and outcomes and about their intended plans for the cryopreserved ovarian tissue. Analyses of the clinical outcomes in these patients are essential for identifying those patients most capable of benefiting from the procedure and for improving the technique and its efficacy.

## Materials and methods

### Study population and ovarian tissue freezing

The database of Erlangen University Hospital was used for the group of patients examined. It includes all patients since 1998 for whom ovarian tissue was harvested and frozen for purposes of fertility preservation. The collection and cryobanking of ovarian tissue were performed in accordance with the standard procedure used at the centre. For each patient, one strip of cortex was used to analyse the tissue histology and follicular density and to assess for the presence of malignant cells.

Ovarian tissue removal was carried out in an external hospital in 57 patients (17 in Dresden University Hospital, 11 in Regensburg University Hospital, 11 in Amberg Hospital, seven in Nuremberg Hospital, six in Darmstadt Hospital, three in Karlsruhe Hospital, one in Ansbach Hospital and one in Hamburg University Hospital). Cryopreservation and storage of the ovarian tissue took place at Erlangen University Hospital in all cases. All patients ( $n = 306$ ) for whom ovarian tissue was cryopreserved in the department in Erlangen and who had completed at least 1 year of follow-up were asked to participate in the survey.

### Data collection and survey

Medical data on the indications for cryopreservation of ovarian tissue were obtained from the patients' medical files. A questionnaire was developed to enquire in particular into the patients' personal situation, both before the removal of ovarian tissue and at the time of the survey. Selected questions were aimed at obtaining information about why the patients opted for fertility preservation, about their current fertility status and family planning, and about their current wishes in relation to their cryopreserved ovarian tissue. Finally, the questionnaire also covered the following topics: the medical diagnosis established and fertility-threatening treatment received, menstrual cycle changes and use of contraception, attempts to conceive and intended plan for cryopreserved ovarian tissue. All of the questions had multiple-choice answers available, but a free-text option for adding explanatory notes was provided for each. Up-to-date postal addresses for the entire group were retrieved from the central hospital registry.

### Ethical approval

Approval was obtained from the local university ethics committee on 19 March 2013 (reference no. 48\_13 B). The study was conducted with informed consent from the patients, or if they were under the age of 18 with consent from their parents or legal guardians.

### Patients' characteristics at the time of ovarian tissue removal

Of a total of 306 patients, 147 women (48%) agreed to take part in the survey and 26 (8%) declined to participate; 34 (11%)

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