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Transplantation of Frozen Thawed Ovarian Tissue – State of the Art

K. T. Schmidt¹, E. Ernst², T. Greve³, C. Y. Andersen³

Worldwide, an increasing number of cancer patients have some of their ovarian tissue cryopreserved for fertility preservation purposes prior to treatment of a malignant disease. The purpose of this review is to summarize the results from ovarian tissue transplantation and the different techniques that can be applied when autotransplanting the tissue. To date, a total of 18 babies have been born as a result of cryopreserved/thawed autotransplanted ovarian cortical tissue and an even larger number of premenopausal women have regained their ovarian function and menstrual cyclicity as a result of autotransplantation. Orthotopic or heterotopic sites can be chosen for the cortical grafts, but so far all babies born have been from orthotopic graft sites. Follow-up studies after transplantation have shown encouraging results regarding the longevity of the grafts with up to 8 years of graft viability. Reassuringly, no cases of introduction of the original disease have so far been reported in cancer survivors grafted with frozen/thawed ovarian tissue.

Key words: cancer, cortex, cryopreservation, fertility preservation, ovary

Introduction

The 5-year survival rate after many cancers has improved significantly over the past decades, especially regarding childhood cancers and cancers in the young adults [1]. As a consequence, one in 593 adults will be a survivor of a childhood cancer [2] and this can be attributed to the more aggressive chemotherapy regimens and the targeted radiotherapy treatment that are used today. A paradox exists, however, between the wanted destruction of the malignant cells and the unwanted side effects that may arise due to destruction of benign cells. For younger women in their fertile years a most unwanted and serious side effect to cancer treatment is the loss of ovarian function that occurs if all the ovarian follicles are destroyed. This is a known side effect to both chemotherapy, especially if the protocol includes an alkylating agent, and to abdominal radiation therapy [3, 4]. For many young women who have not yet attempted to conceive before they are diagnosed with cancer, this risk of infertility is very serious and alarming and for this reason, several options of fertility preservation have been developed and are offered to more and more young women before the initiation of their cancer treatment. Cryopreservation of ovarian tissue is one method of fertility preservation, which has been developed and refined primarily over the last decade [5]. An entire ovary, a semi-ovary or ovarian cortical biopsies are collected and cryopreserved for later use. If the woman as a consequence of her treatment experiences premature ovarian insufficiency (POI) she can request the frozen ovarian tissue thawed and transplanted. This has been performed on many cancer survivors worldwide and the majority of these have regained their ovarian function after transplantation [6, 7] and so far a total of 18 children have been born as a result from transplantation [8–20].

Effect of Chemo- and Radiation Therapy on the Ovary

Different chemotherapeutic agents exert different mechanisms of action on the cells and on the follicles in the ovary. The alkylating agents act on both resting and dividing cells and the quiescent, meiotically inactive oocytes in the primordial follicles are more susceptible to the damaging effects of alkylating agents than other chemotherapeutic agents. This has been found in a study by Meirow, who compared the risk of POI in young cancer patients according to which drugs they received. Administration of alkylating agents had an OR of 4.0 for POI, which was a significantly higher risk than when platinum agents (OR = 1.8), plant alkaloids (OR = 1.2), or antimetabolites (OR < 1) were used [21]. Oocytes are very susceptible to the damage caused by radiotherapy [4] and the majority of patients receiving a dose > 20 Gy will become sterile as a consequence [22]. Treatment with bone marrow transplantation (BMT), which is often used in leukaemia patients or patients with non-malignant haematological conditions such as Thalassaemia or aplastic anaemia, causes loss of ovarian function in most patients [23] as a consequence of the pre-conditioning protocols consisting of high-dose chemotherapy and total body irradiation.

Cryopreservation of Ovarian Tissue

By laparoscopy, ovarian tissue can be excised on a short notice, usually without any significant delay of a potentially gonadotoxic treatment. Cryopreservation of ovarian tissue involves removal of an entire ovary or parts of an ovary prior to treatment. The ovarian cortex, which harbours the primordial follicles, is isolated in a thickness of approximately 1 mm. After appropriate equilibration in a cryoprotectant medium the tissue is frozen and stored in liquid nitrogen and can potentially be kept frozen for many years [24]. When the woman has been cured she can have some of the pieces of tissue thawed and transplanted, if she has become menopausal as a consequence of her treatment. Some of the primordial follicles within the pieces of cortical tissue will survive the freezing and transplantation procedure and have the capacity to be reactivated and start to grow and thus re-establish a cyclic endo-
Orthotopic transplantation

Orthotopic transplantation means transplanting tissue into its normal place in the body, which, in the case of ovarian tissue, means grafting it into the remaining ovary or at the site of the removed ovary. So far, all the children that have been born as a result of ovarian tissue transplantation originate from orthotopically grafted tissue. Table 1 gives an overview of the 18 children that have so far been born following autotransplantation of cryopreserved/thawed ovarian tissue. The first report came from Donnez’ group in Belgium in 2004 [8]. They transplanted strips and small cubes of cryopreserved/thawed ovarian cortical tissue to a small peritoneal window, which was created by laparoscopy 7 days earlier, beneath the right ovarian hilus. This was repeated after 4 months. After 10 months the patient conceived spontaneously and later gave birth to a healthy baby girl. Later, other groups followed reporting successful pregnancies in cancer patients after orthotopically transplanted tissue into the remaining ovaries as either cortical strips or fragments [9–12, 14–16] or tiny ovarian fragments imersed in oocyte wash buffer [9], although in the latter method ovarian function never resumed. Other orthotopic grafts sites have been introduced such as the broad ligament or a peritoneal pocket close to the broad ligament [18, 19] or a peritoneal pocket between the iliac vessels [13]. In theory, when grafting to an orthotopic site, the patient should be able to conceive naturally and so far, the majority of the babies born following this procedure have resulted from spontaneous conceptions. But some women will need in vitro fertilization, IVF, in order to become pregnant, either because they already had a history of sub-fertility before their cancer diagnosis or for other reasons such as a partner with a low sperm count.

Heterotopic Transplantation

So far, no children have been born following transplantation to a heterotopic transplantation site. In our group, we have had 2 biochemical pregnancies arising from oocytes aspirated from a graft site in the anterior abdominal wall, but unfortunately these pregnancies never developed further [7]. But the fact that IVF led to the aspiration of mature metaphase II oocytes that were fertilized and able to implant, although only briefly, means that oocytes deriving from cryopreserved/thawed ovarian tissue are able to undergo a normal maturation process and there is no reason to believe that the pregnancies reported after transplantation have not arised from the grafted tissue. Oktay and co-workers used a heterotopic graft site for their first autotransplantation. Two women with cervical cancer and recurrent benign ovarian cysts, respectively, had some of their ovarian tissue transplanted subcutaneously to the forearm [25]. After 10 weeks and 6 months, respectively, a follicle appeared at the graft site and levels of FSH normalized. Percutaneous oocyte aspirations yielded a mature oocyte. The same author later transplanted cryopreserved/thawed ovarian tissue below the skin of the abdomen but several IVF attempts only yielded three metaphase II oocytes from a total of 20 follicles [26]. Kim transplanted ovarian tissue into the space between the rectus sheath and the rectus muscle in five cancer survivors, who all regained their ovarian function between 12–20 weeks after transplantation [27]. We have transplanted fragments of cortical tissue into a peritoneal pocket corresponding to the abdominal wall between the umbilicus and the pubic bone. After IVF this graft

<table>
<thead>
<tr>
<th>Age at Cryopreservation (Years)</th>
<th>Disease</th>
<th>Gestation (Weeks)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Neuroectodermic Tumor</td>
<td>38</td>
<td>M</td>
<td>2.830</td>
<td>Donnez, 2011 [17]</td>
</tr>
<tr>
<td>28</td>
<td>Non Hodgkin’s Lymphoma</td>
<td>38</td>
<td>F</td>
<td>3.000</td>
<td>Meirw, 2006 [9]</td>
</tr>
<tr>
<td>20</td>
<td>Hodgkin’s Lymphoma</td>
<td>38</td>
<td>M</td>
<td>3.089</td>
<td>Silber, 2008 [12]</td>
</tr>
<tr>
<td>27</td>
<td>Microscopic polyangiitis</td>
<td>37</td>
<td>M</td>
<td>2.030</td>
<td>Donnez, 2011 [17]</td>
</tr>
<tr>
<td>19</td>
<td>Thalassemia</td>
<td>39</td>
<td>M</td>
<td>3.026</td>
<td>Revel, 2011 [18]</td>
</tr>
<tr>
<td>n. s.</td>
<td>Hodgkin’s Lymphoma</td>
<td>n. s.</td>
<td>n. s.</td>
<td>n. s.</td>
<td>Silber, 2012 [20]</td>
</tr>
<tr>
<td>n. s.</td>
<td>Premature Ovarian Failure</td>
<td>n. s.</td>
<td>n. s.</td>
<td>n. s.</td>
<td>Silber, 2012 [20]</td>
</tr>
</tbody>
</table>

n. s.: not stated, M: male, F: female
Transport of Ovarian Tissue
Risk of Reintroduction of the Original Disease after Transplantation

Our Experience
The duration of the transplants in our series has varied. In general, the age of the patient at the time of cryopreservation is a determining factor on the longevity of the graft; i.e. the younger the patient at the time of cryopreservation the longer the graft will last. Other determining factors are the amount of tissue that is transplanted and whether or not the patient has received any chemotherapy prior to collection of the tissue. Most patients in our series have experienced at least 2–4 years of activity with the tissue still functional. One patient had her first transplant in 2004 and a second transplant in 2008 while the first graft was still functioning and still has functional tissue 8 years after the first transplant. Additionally, most of the patients in our series still have tissue in the freezer for 1 or 2 more transplants after their first grafts stop functioning. 

Fertility After Cryopreservation of an Ovary and Cancer Treatment

We have recently conducted a questionnaire study looking at the ovarian function and fertility after treatment of a malignant disease in women with one ovary due to cryopreservation of the other. Fortunately, not all women experienced POI after their potentially gonadotoxic treatment. In fact, we found that only 21% of 143 responders stated that they had become menopausal after treatment. In the remaining women with an intact ovarian function those with a pregnancy wish succeeded in becoming pregnant and giving birth to healthy children in the majority of the cases [37].

Conclusion

Although still considered experimental, cryopreservation of ovarian tissue has proved to be a viable way of restoring ovarian function after cancer treatment and with 20 babies born worldwide, the results are promising. For many women facing a potential gonadotoxic treatment and a risk of POI, cryopreservation of ovarian tissue offers a hope of keeping her fertility in the future and her own endogenous hormone production and for many cancer patients this is a relief during an otherwise difficult period of their lives. It is very likely that in the future, fertility preservation will be an integrated part of the cancer treatment addressed to young cancer patients thus improving their quality of life and reducing one of the potential side effects of cancer treatment: infertility.

Conflict of Interest

No potential conflict of interest to this article was reported.

References:

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