Ovary transplantation: to activate or not to activate

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Transplantation of human organs, either in their entirety (kidney, heart, lung and uterus) or in part (liver and pancreas), has been successful. In contrast, the ovary consists of hundreds and thousands of follicles as functional units, allowing grafting of ovarian fragments containing varying numbers of follicles. Ovary transplantation is also different from stem cell transplantation (e.g. bone marrow) and more comparable with the transplantation of hair follicles, if one considers skin as an organ.

Ovarian transplantation has been investigated for more than a century (Gosden, 2008). In this issue of *Human Reproduction*, Meirow et al. (Meirow et al., 2015) discuss the decade-old ovarian tissue cryopreservation and transplantation procedure (OTCP) in fertility preservation patients (Donnez and Dolmans, 2013; Donnez et al., 2013) together with the recently reported in vitro activation (IVA) and grafting approach (Kawamura et al., 2013; Suzuki et al., 2015) in patients with primary ovarian insufficiency (POI). In addition to documenting differences in procedures and patient criteria, the authors compared these two methods in terms of four key measurements: safety, graft lifespan, endocrine function and fertility outcomes.

As discussed by Meirow et al., conventional OTCP deals with cryopreserved large ovarian strips obtained from cancer patients prior to germ cell-damaging chemo- or radiation therapies whereas the IVA-grafting method deals with transplantation of fragmented ovarian cubes in patients with POI (Fig. 1). Because fertility preservation using conventional OTCP requires ovarian tissue cryopreservation, which is optional during IVA-grafting, we will use OTCP to denote the well-established conventional ovarian transplantation approach for cancer survivors.

There are major differences in the goals of the two approaches: OTCP is for fertility preservation and restoration of ovarian functions whereas IVA is for infertility treatment. To avoid follicle loss due to cryopreservation, the tissue vitrification step is sometimes omitted during IVA when it is feasible to perform grafting 2 days after ovary removal and tissue exposure to IVA drugs. Furthermore, the in vitro drug treatment could also be skipped for immediate grafting if patients still have residual secondary or early antral follicles. As discussed below, both cryopreservation-free and drug- and cryopreservation-free IVA procedures have recently been practiced with initial success.

Several issues were raised by Meirow et al. We shall discuss them below.

Safety

Cancer survivors after OTCP have increased risk for minimum residual disease if malignant cells were re-introduced during grafting of large ovarian strips (Donnez and Dolmans, 2013). In contrast, IVA allows grafting of smaller ovarian cubes if fertility is the goal for cancer survivors and could decrease risks for disease recurrence when the amount of transplanted tissue is reduced. Of course, types and metastatic potential of cancers are major factors to consider before either grafting procedure. For cancers with high residual disease risks, development of more advanced cancer cell detection methods to allow grafting of disease-free follicles and in vitro follicle culture systems (Skory et al., 2015) to avoid grafting are needed. Considering the prolonged duration (minimal of 4 months) of human folliculogenesis in vivo and difficulties involved in maintaining intact follicle structures in vitro, further research is warranted.

It has to be pointed out that most patients undergoing fertility preservation will have their tissue cryopreserved before chemotherapy. The other clinical situation when IVA could be applied to fertility preservation patients is when they are cured and pregnancy is allowed, usually at 2–5 years after chemotherapy. Therefore, data suggesting a detrimental effect of chemotherapy on miscarriage and fetal malformations based on animals becoming pregnant during chemotherapy (Meirow et al., 2001) do not replicate the clinical scenario. Indeed, data from large population studies suggest that pregnancy after cancer treatment does not imply higher risks of fetal malformations (Magelssen et al., 2008).

For IVA, undesired actions of residual IVA drugs in grafts represent a concern. However, ovarian cubes exposed to IVA drugs are routinely

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rinsed extensively before grafting. For all POI patients treated with IVA, no apparent abnormal growth in graft sites was found under ultrasound during follicle monitoring. Eleven patients received a second ovarian graft via laparoscopic surgery; initial grafts were adsorbed and no abnormality in Fallopian tubes could be detected (unpublished data). For two babies delivered following IVA, no abnormality in Apgar score, body weight, placental weight, as well as physical and mental development was found (Kawamura et al., 2013; Suzuki et al., 2015). In addition, safety of IVA-grafting has been investigated extensively in mice (Adhikari et al., 2012). Long-term monitoring of animals up to the second generation of progeny showed that animals were reproductively active and free from any overt signs or symptoms of chronic illnesses. Liu and co-workers concluded ‘the use of PTEN inhibitors could be a safe and effective way of generating mature human oocytes for use in novel IVF techniques’ (Adhikari et al., 2012).

**Graft lifespan and endocrine function**

Although OTCP restores ovarian endocrine functions by producing sex steroids and inhibins for 4–5 years in patients, additional OTCP procedures are still needed if endocrine function restoration up to the normal menopausal age is desired (Table I). The goal of IVA-grafting for patients

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### Figure 1

Comparison between ovarian tissue cryopreservation and transplantation procedure (OTCP) for cancer survivors and in vitro activation (IVA)-grafting for POI patients. OTCP involves cryopreservation of ovarian strips for transplantation followed by spontaneous pregnancy. In contrast, IVA involves in vitro activation of follicles followed by fragmentation into smaller ovarian cubes and incubation with drugs before grafting. Although the cryopreservation step is optional, IVA involves additional steps of oocyte retrieval followed by IVF and embryo transfer before pregnancy.

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### Table I Types of patients for ovarian transplantation and possible outcomes.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Cancer survivors</th>
<th>PR/DOR</th>
<th>POI</th>
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<tbody>
<tr>
<td></td>
<td>Fertility</td>
<td>Endocrine</td>
<td>Fertility</td>
</tr>
<tr>
<td>OTCP</td>
<td>+</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>IVA-grafting</td>
<td>(+ + +)</td>
<td>–</td>
<td>(+ +)</td>
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</tbody>
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+: success; (+): anticipated success; –: low success.

PR, poor responder; DOR, diminished ovarian reserve; POI, primary ovarian insufficiency; OTCP, ovarian tissue cryopreservation and transplantation; IVA, in vitro activation.
with POI is to obtain as many mature oocytes as possible for subsequent IVF; therefore, graft lifespan is by nature short following activation of most follicles. In general, approximately one-third of an ovary removed from patients with POI is used for grafting and the remaining strips are cryopreserved; therefore, up to two additional grafting procedures could be performed if no pregnancy occurred after initial grafting. Because estrogen replacement therapy is widely used to minimize osteoporosis and cardiovascular diseases, oral or transdermal steroid replacement is considered a better approach than additional grafting surgeries for cancer survivors. For patients with POI already exhibiting decreased ovarian endocrine functions, hormonal replacement is routinely used even before IVA.

**Fertility outcomes**

OTCP has been practiced for more than a decade in multiple centers with more than 36 babies delivered worldwide (Macklon et al., 2014). IVA-grafting is a new procedure and has achieved initial success as an infertility therapy for patients with POI. Further improvements of IVA are needed to become a potential therapy for poor success as an infertility therapy for patients with POI. Further improvements of IVA are needed to become a potential therapy for poor success as an infertility therapy for patients with POI.

In conclusion, we postulate that the widely accepted hormonal replacement therapy is adequate to meet most endocrine needs provided by the ovary. We view IVA as a modified and more advanced version of OTCP that is applicable to a wider infertility patient population to improve fertility outcomes in cases of extremely low ovarian reserve. Although OTCP usually involves grafting to the medulla of residual ovaries, IVA consists of grafting into artificial pouches near the Fallopian tubes, both approaches suffer from follicle loss during grafting. Future studies to minimize grafting-induced loss of follicles and to identify optimal graft sites could improve success of ovarian transplantation.

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**Conflict of interest**

The authors declare no actual or potential competing financial interests.

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