Ovarian Tissue Transplantation: Experience From Germany and Worldwide Efficacy

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ABSTRACT: Extraction of ovarian tissue prior to oncologic therapy and subsequent transplantation is being performed increasingly often to preserve fertility in women. The procedure can be performed at any time of the cycle and, therefore, generally does not lead to any delay in oncological therapy. Success rates with transplantation of cryopreserved ovarian tissue have reached promising levels. More than 130 live births have been reported worldwide with the aid of cryopreserved ovarian tissue and the estimated birth rate is currently approximately 30%. In Germany, Austria, and Switzerland, the FertiPROTEKT consortium has successfully achieved 21 pregnancies and 17 deliveries generated after 95 ovarian tissue transplantations by 2015, one of the largest case series worldwide confirming that ovarian tissue cryopreservation and transplantation are successful. Approximately, more than 400 ovarian tissue cryopreservation procedures are performed each year in the FertiPROTEKT consortium, and the request and operations for ovarian tissue transplantation have increased in recent years. Therefore, recommendations for managing transplantation of ovarian tissue to German-speaking reproductive medicine centers were developed. In this overview, these recommendations and our experience in ovarian tissue transplantation are presented and discussed with international procedures.

KEYWORDS: Fertility preservation, FertiPROTEKT, ovarian tissue cryopreservation, ovarian tissue transplantation, pregnancy after chemotherapy, gonadotoxic treatment

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Introduction

Fertility failure is one of the most detrimental consequences of cytotoxic treatment procedures in women who could overcome their cancer disease. Chemotherapy, particularly with alkylating agents such as busulfan, ionizing radiotherapy in the abdomen or pelvic region, and gynecological malignancy surgery can permanently destroy gonads and lead to infertility and premature menopause. Therefore, counseling about concepts to preserve fertility must be an integral part of any patient's oncological treatment and must take into account the patient's personal circumstances, recommended oncological therapy, and individual risk profile.[1] Also, patients with certain benign conditions such as autoimmune and hematologic conditions treated by cytotoxic agents, the presence of bilateral ovarian tumors, severe or recurrent ovarian endometriosis, and recurrent ovarian torsion are candidates for fertility preservation.[2-4]

Ovarian tissue cryopreservation and transplantation have been incorporated into numerous national and international networks and programs as a standard method for fertility preservation.[5] The procedure has the advantage of requiring neither a sperm donor nor ovarian stimulation. It is the only option available for prepubertal girls and patients who cannot delay their cancer treatment for ovarian stimulation, and unlike freezing individual oocytes or embryos, ovarian tissue cryopreservation can preserve hundreds of primordial follicles more effectively at once.

Therefore, in Germany, cryopreservation of ovarian tissue is performed more often than ovarian stimulation and cryopreservation of oocytes.[6,7] Approximately, 400 ovarian tissue cryopreservation procedures are performed each year and the ovarian tissue is mainly stored in 2 central cryobanks (Bonn and Erlangen). Transplantation of cryopreserved/thawed ovarian tissue is also performed in specialized centers. By January 2018, 163 transplantations were performed in 126 women in 16 centers, with most of the transplantations performed at the University Hospital Erlangen.[7-9]

In Germany, Switzerland, and Austria, the FertiPROTEKT network (www.fertiprotekt.com), an association of university and non-university reproductive medicine centers, was established in 2006. This large multicenter network currently consists of 125 centers. To ensure the quality of the cryopreservation and transplantation of ovarian tissue at the individual centers, consistent standard recommendations have been developed over the last years and are constantly underway to adapt to the current state of research.[1,8] In this review, the experience and the recommendations for transplantation of ovarian tissue in Germany are presented and discussed.

Surgical Technique and Transplantation Site

The technique for ovarian tissue transplantation varies in international reports. There is no current standard for the transplantation of ovarian tissue, despite the increasing use of ovarian tissue cryopreservation. In general, the procedure is classified as orthotopic or heterotopic according to the site of transplantation and the possibility of natural conception. In orthotopic implantation, the tissue is transplanted to its place

of origin or to the pelvic cavity, whereas in the case of heterotopic transplantation, the ovarian tissue is transplanted to a different site or to an extraovarian region.[10]

Orthotopic sites

In clinical routine, the ovarian tissue is primarily transplanted orthotopically.[11] In this type of transplantation, the tissue is transplanted to its original physiological surroundings. The development of transplanted tissue is very effective, as temperature, pressure, paracrine factors, and blood supply are like those observed in a physiological situation. The main advantage of orthotopic transplantation of ovarian tissue is that natural conception could occur without the intervention of assisted reproductive techniques; nevertheless, ovum pickup and in vitro fertilization (IVF) can be performed.

Internationally, various orthotopic transplantation techniques have been described. The variations in the orthotopic techniques included grafting of ovarian cortical pieces to the pelvic sidewall,[12] subcortical tunnels,[13] denuded medulla,[14] and subcortical pockets of the residual ovary.[15] The ovarian tissue is fixed by means of stitches, Interceed, and/or fibrin glue.[16] To enhance revascularization at the site of grafting, some groups have performed the transplantation in 2 steps.[17-19] Moreover, the utility of a human extracellular matrix scaffold with robot-assisted transplant to bivalve contralateral menopausal ovary was reported in 2 patients, with both resulting in a live birth.[20]

All these methods and transplantation sites have reached practicable results in restoration of ovarian endocrine function and pregnancy rates. However, it is still unclear which of the techniques and which locations are superior or whether there are differences in the clinical outcomes at all.[16]

Orthotopic ovarian tissue transplantation in Germany

At the beginning of the ovarian tissue transplantations in Germany, ovarian tissue was transplanted to different orthotopic sites including the ovary, a peritoneal pouch, or a combination of both.[21] In fact, in the FertiPROTEKT network, there is a consensus for mainly transplanting ovarian tissue to a peritoneal pocket of the fossa ovarica.[8] Reasons for transplantation under the pelvic peritoneum as compared with the situation in the generally atrophied ovary are the better circulation in the pelvic wall and the easier surgical feasibility with thereby associated low surgical risk for the patient. The standard access route is laparoscopy. The parietal peritoneum of the ovarian fossa is incised over a length of approximately 0.5 to 1 cm. By blunt dissection without bleeding, a subperitoneal pocket is created and the tissue pieces are implanted into the pocket. The tissue pieces should preferably lie side by side and not on top of each other to allow revascularization. In case of the ovarian tissue being taken once again after live birth, the tissue is marked with titanium clips. Besides ovarian tissue transplantation, a fertility assessment (tubal, uterine, and extrauterine factors) and correction, if necessary, is performed; the patency of the fallopian tubes is checked by means of "chromo"-perturbation and a hysteroscopy to rule out polyps, myomas, adhesions, or chronic endometritis. The transplantation is performed on the side on which the tube is patent and where the anatomical conditions are the most favorable. The average time for the procedure is 15 to 30 minutes. The patient is discharged on the same day or on the first postoperative day[8] (Figure 1).

Heterotopic sites

Heterotopic autotransplantation of ovarian tissue included subcutaneous areas in the forearm[22] or abdomen,[23] rectus muscle,[24] and retroperitoneal space under the abdominal wall.[25] Like orthotopic sites, it aims to resume both endocrine and reproductive ovarian functions. The advantages of heterotopic transplantation are that both the transplant surgery and excision, in the event of recurrent malignancy, of the transplant tissue are easier to perform, allow easy monitoring of the grafted ovarian tissue, and can be used in cases where factors make orthotopic transplantation difficult, for example, by severe pelvic adhesions or poor pelvic vasculature. However, heterotopic transplantation usually does not allow spontaneous pregnancy and therefore requires subsequent ovum pickup and IVF. To date, heterotopically transplanted ovarian tissue to the anterior abdominal wall has resulted in the delivery of twins.[25] Furthermore, recurrent live births from spontaneous conception following subcutaneous ovarian transplants in patients with primary ovarian insufficiency (POI) have been reported and therefore the question assumed was whether the grafted tissue can augment the function of in situ menopausal ovary.[26] Heterologous ovarian tissue transplantation to the subcutaneous adipose tissue of the lower arm was performed in 1 patient in Germany, but no pregnancy occurred.[21] The main problem by heterotopic site is that it may not provide an optimal environment for follicle and oocyte development, possibly because of differences in temperature, pressure, paracrine factors, and blood supply.[27]

Surgical Complications of Ovarian Tissue Transplantation

Removal and transplantation of ovarian tissue are considered to be safe. Complications occurring directly as a result of the surgical procedures appear to be rare, and severe complications are estimated to occur in $<1\%$ of cases.[21,28]

In the FertiPROTEKT network among women in whom ovarian tissue was removed for cryopreservation, the complication rate was 0.2%.[21] In 1302 women, only 2 postoperative complications (1 abdominal wall hematoma requiring revision and 1 postoperative urinary tract infection) have been reported and no severe complications occurred up to now. For ovarian tissue transplantation, only 1 intraoperative complication not related to the surgery technique occurred. In 1 patient out of

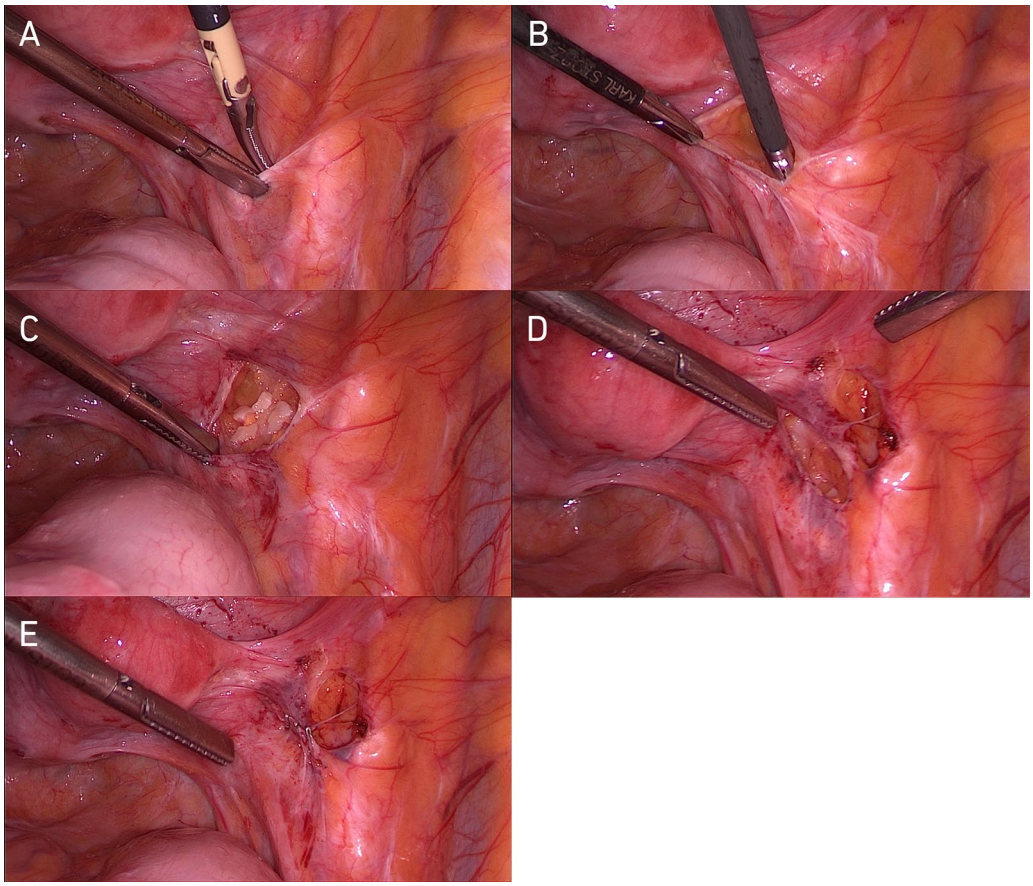

Figure 1. Orthotopic transplantation of ovarian tissue to a peritoneal pocket of the pelvic peritoneum of the ovarian fossa and marking the transplantation site with titanium clips. (A and B) Incision of the peritoneum of the fossa ovarica. (C and D) Insertion of ovarian tissue into the created subperitoneal pocket. (E) markation of the transplantation site with titanium clips.
Source: Photo adapted from Department of Obstetrics and Gynecology, Erlangen.

71, a switch had to be made from laparoscopy to laparotomy due to extensive adhesions. This represents a complication rate of 1.4% with ovarian tissue transplantation.[21]

These data are in agreement with reports from other centers, which have reported ovarian tissue cryopreservation and transplantation to be a safe activity in female programs for fertility preservation. Dolmans et al[29] evaluated the safety of cryopreservation of ovarian tissue in a large cohort of 476 patients and did not report any severe adverse events during laparoscopy. Jadoul et al[2] reported, among 140 patients, 5 minor complications, raised temperature, labial hematoma, urinary infection, bowel irritation, and psychological distress, and 1 severe complication, a second laparoscopy for intra-abdominal hemorrhage due to ovarian biopsy. Additional surgery to manage complications after ovarian tissue cryopreservation was also necessary in 3% of a patient collective presented by Rosendahl et al.[30] In the literature, 1 death due to fatal acute respiratory distress syndrome by the surgery of ovarian tissue removal due to systemic lupus erythematosus was associated with the procedure.[31]

For operative gynecological laparoscopy, the known rate of intraoperative and postoperative major complications is less than 1%, and the mortality rate is between 4 and 8 deaths per 100 000 cases.[32] Therefore, the risks and complications of laparoscopic removal and transplantation of ovarian tissue are similar to those of standard laparoscopy. Nevertheless, it is essential to conduct a thorough preoperative evaluation to exclude women with high risk from surgery and in case of ovarian tissue removal to remain mindful that the patients are already weakened by their oncological condition.[31]

Risk of Reintroducing Malignant Cells

A further risk of ovarian tissue transplantation might be the potential spread of tumor cells as a result of transplantation. Safety issues related to the transplantation of ovarian tissue from patients with cancer have been the subject of debate for many years now, and several studies have analyzed the risk of reintroducing malignant cells that may be present in frozen-thawed ovarian tissue that could induce recurrence of the primary tumor.[33]

The highest level of risk is associated with hematological malignancies, particularly leukemia, and transplantation has been considered to be best avoided in these cases. Experimental studies have shown the presence of leukemic cells in the cryopreserved

ovarian tissue of patients with leukemia by polymerase chain reaction (PCR) and flow cytometry techniques[34-36] and the possibility of disease transmission through the graft in xenotransplantation models.[27] However, data have also demonstrated that the risk is likely to be very low if the ovarian cryopreservation procedure is performed in women in complete remission.[34] Recently, live births have been achieved after transplantation of cryopreserved ovarian tissue that had been harvested after inducing the remission of leukemia, following sufficient assessment for minimal residual disease, and there has been no recurrence in any cases up to now.[37-39]

The same safety issues have also been raised in ovarian tissue transplantation in ovarian malignancies such as borderline ovarian tumors (BOTs) or early stage of patients with ovarian cancer, as they are also candidates for fertility preservation.[40,41] Masciangelo et al[40] analyzed frozen-thawed and xenografted ovarian tissue from 11 patients with BOT. Borderline ovarian tumor cells were found in 1 patient. In patients with ovarian cancer, 2 pregnancies after transplantation of frozen-thawed ovarian tissue, one from our department, have been reported.[42,43] In both cases, the grafted ovarian tissue was removed soon after delivery for safety reasons. However, although this approach does not reduce the risk of reintroducing tissue susceptible to malignancy development, preimplantation analysis is an absolute prerequisite.

There are also reports of ovarian involvement in Hodgkin lymphoma, non-Hodgkin lymphoma, pulmonary carcinoma, gastric carcinoma, and colon carcinoma.[44,45] But, on the other side, results from studies in patients with breast cancer and bone and soft tissue sarcoma are reassuring.[46-48] More importantly, no disease relapses due to tumor cell spread after transplantation have been identified either in the literature reviewed or among our own patients. In none of the women diagnosed with relapse, the recurrence was considered to be related to the transplantation.[28]

Finally, the risk of ovarian metastasis cannot be excluded for any type of tumor and the bias of sampling error can with the currently available preimplantation analysis, due to destroying the analyzed tissue itself, not completely eliminated.[49] Any transplantation of frozen-thawed ovarian cortex to a patient with a previous malignancy should always be preceded by extensive information to the patient, examination of a representative biopsy by histology, immunohistochemistry, and, if possible, molecular biology or xenotransplantation. Following this procedure and taking into account the type and stage of malignancy, transplantation of ovarian tissue can be performed safely for most malignancy indications, although there is no sufficient evidence. Furthermore, we believe that even patients with high risk of introducing malignant cells should not be denied the opportunity of having their ovarian cortex cryopreserved, in light of potential future developments in the technology, such as in vitro maturation and the development of an artificial ovary.[50-54]

Clinical Characteristics of Patients for Ovarian Tissue Transplantation

Most ovarian tissue transplantations were performed in women with a history of malignancies and, to a minor degree, with benign conditions. Breast cancer (~30%) and Hodgkin disease (~32%) are the common indications for transplantation besides sarcoma and gynecological cancer in Germany[7,9] as it is worldwide.[28]

Normally, transplantation of ovarian tissue takes place after successful oncological therapy in female patients with a manifest desire for a child and in the case of failure of ovarian function for the resumption of folliculogenesis and to lead to a pregnancy.[8] If a transplantation is to be recommended at the earliest following oncological treatment, this should be determined depending on the underlying oncological disease and individually together with the attending oncologists, taking the age of the patient and the oncological prognosis into account.

Ovarian tissue transplantation can also be considered for patients who still have a menstrual cycle but limited ovarian reserve. Worldwide, there have been successful reports helping women to get pregnant in such constitution. In the FertiPROTEKT network, transplantation has been performed in 9 patients without failure of ovarian function. The patients had tried to conceive without success for a considerable period of time and transplantation was performed to augment the ovarian pool and the fertility potential. Three of them each delivered a healthy child.[7]

Age limits for reimplantation of ovarian tissue have been considered by some groups, and some agree to the fact that the tissue should not be transplanted to postpone the natural menopausal age.[5] In the FertiPROTEKT network, there is a consensus that the age of 45 years should not be exceeded. Moreover, transplantation to restore long-standing ovarian function which would, where applicable, replace necessary hormone replacement therapy is also possible, but, in our view, it should not be primarily recommended due to the limited or unknown activity of the transplanted tissue at the moment.[55]

Follow-up Care of Patients Who Have Undergone Transplantation

Following transplantation, the resumption of the follicular development in ovarian tissue and the recovery of ovarian tissue function typically take 4 to 5 months and is closely related to the folliculogenesis process. Regarding the given literature, the ovarian function can be restored in 63% to 95% of cases through transplantations of ovarian tissue.[28,56] The mean length of ovarian function after transplantation is about 2 to 5 years on average[28,57]; however, this depends on the number of follicles in the ovarian tissue and the age of the woman at the time of cryopreservation and therefore there is a large variation of the duration of endocrine activity. Most of the pregnancies have been conceived within the first 3 years after transplantation,[58] but also reports of live births exist where the conception

occurred 5 and 6 years after autotransplantation also sustaining long-term fertility.[59]

In case of orthotopic transplantation, a spontaneous pregnancy can be attempted if the tubes are patent and there are no other relevant infertility factors. It is noticeable that a considerable proportion of the live births have been conceived naturally after transplantation without requiring further medical intervention. According to Donnez et al,[60] orthotopic transplantation allowed more than half of the women to conceive naturally. In Denmark, most women are allowed a 1-year period after transplantation to achieve a natural conception before IVF or other assisted reproductive technology (ART) techniques are considered.[28] In Germany, most of the reported pregnancies developed spontaneously. To increase the likelihood of conception, the patient is offered cycle monitoring with induction of ovulation through human chorionic gonadotropin (hCG) within the framework of intercourse at the optimal time. Moreover, there are also reports of women who delivered 2 or 3 babies each, demonstrating the possibility of natural conception several times after one procedure.[61]

In the case of occluded tubes or other infertility factors, assisted reproductive medicine techniques (IVF, intracytoplasmic sperm injection) must be used. If there is a high follicle density (antral follicle counts and anti-Müllerian hormone), gonadotropin stimulation can be considered, depending on the patient's age and the underlying oncological disease, to accelerate conception, if applicable. Alternatively, egg cells obtained in several spontaneous cycles or stimulated cycles can also be vitrified so that an egg cell pool is created for later use in an assisted reproductive medicine technique.

If there are no signs of activity visible after approximately 0.5 year after transplantation, another transplantation of cryopreserved ovarian tissue could be considered.

Pregnancy Outcomes From Cryopreserved and Transplanted Ovarian Tissue

Pregnancy rate

After a long history of animal experiments, the first successful human transplantation of thawed cryopreserved ovarian tissue was reported by Oktay and his colleagues in 2000.[62] Ovarian tissue was grafted beneath the left pelvic peritoneum, and approximately 4 months after transplantation, the grafted ovarian tissue developed a follicle and produced estradiol. In 2004, the first live birth after transplantation of cryopreserved ovarian cortex was reported in Belgium,[63] representing a groundbreaking event in reproductive technology.

Since then, many other case reports of live births have subsequently followed. More than 130 live births worldwide have been reported with the aid of transplantation of cryopreserved ovarian tissue (not included unreported cases and ongoing pregnancies).[64] The presentation of case studies of significant size from Belgium, Denmark, United States, and Spain gives some indication of the likely success rate of this approach.

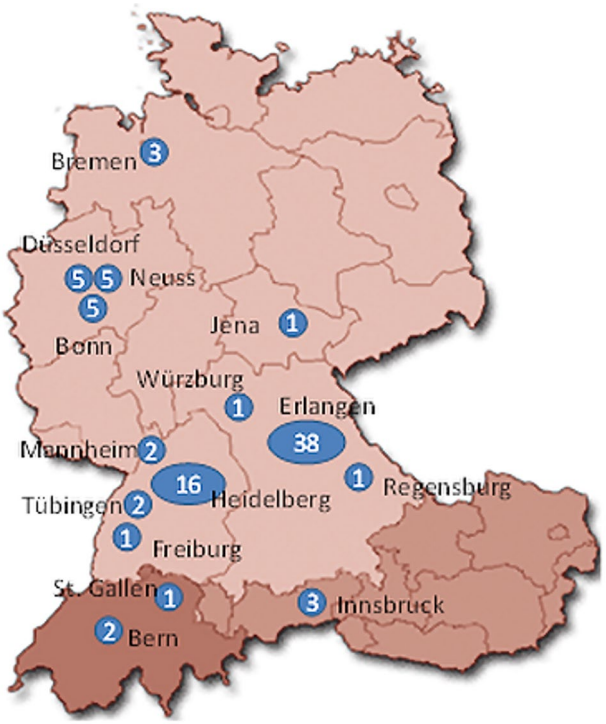

Figure 2. FertiPROTEKT centers in which ovarian tissue was transplanted up to September 2015, with numbers of procedures shown.[20]

Based on the currently available publications worldwide, the birth rate per ovarian tissue transplantation varies between 20% and 40%. According to a recent meta-analysis, the cumulative live and ongoing pregnancy rate was nearly 38%, with approximately 1 of 3 to 4 women attempting ovarian tissue transplantation being able have at least 1 child.[56]

In Germany, the first transplantation of ovarian tissue was performed in 2007 and the first live birth was achieved in 2011 in a 25-year-old cancer survivor with previous Hodgkin disease and relapse.[65] The special thing about this case was that the ovarian tissue was transported overnight prior to freezing.[66] In the FertiPROTEKT network, up to 2015, 95 orthotopic transplantations in 74 patients were performed (Figure 2). The pregnancy and delivery rates were 33% and 25%, respectively. In a subgroup analysis of this group, Liebenthron et al[67] recently reported pregnancy and delivery rates of 46.7% and 43.3% after transplantation of ovarian tissue, transported overnight prior to freezing, in 30 women. Ovarian tissue transplantation procedures have been successful at several centers in Germany, with the greatest experience of transplantation of frozen and thawed ovarian tissue at the University Hospital Erlangen. In addition, there were currently 1 live birth and 2 ongoing pregnancies at Erlangen at the time of preparing this report.

A predictive factor for success rate seems to be the patient's age at the time of cryopreservation. In several countries that offer ovarian tissue cryopreservation to patients, one of the inclusion criteria is that the women should be no more than 30 to 35 years old, as most pregnant women were below the age of

30.[61,68] The higher the ovarian reserve is, that is, the follicular density in the cryopreserved and transplanted ovarian tissue, the chances for a later pregnancy are greater. In Germany, the pregnancy rates following transplantation of ovarian tissue were 33% in women who were below the age of 35 at the time of cryopreservation, in comparison with 18% in women who were above the age of 35 at the time of cryopreservation. In women above 40 years of age, pregnancy could not be achieved.[7] Therefore, we recommend not performing cryopreservation of ovarian tissue in women above 40 years of age, having in mind the individual ovarian reserve.

The prepubertal girls are the main group of patients who could benefit from ovarian tissue cryopreservation and transplantation as ovarian stimulation is not feasible in this population. Successful natural conception following the storage of tissue in early puberty[69] and subsequently successful pregnancy after IVF where tissue was stored in childhood have been reported.[70] However, to assess the efficacy of ovarian tissue cryopreservation for prepubertal girls, more cases need to be reported. In Germany, no transplantation of prepubertal ovarian tissue has been performed so far.

Regarding the pregnancy rates for ovarian tissue transplantation, we must bear in mind the actual unavailability of clear data on success rates. The number of transplantations performed worldwide is not known,[56] as many centers may not have yet reported their results due to a lack of an international register; in most studies or case series, the total number of transplantation attempts has not been specified and there may be an underreporting of failed cases. Due to the size and heterogeneity of the groups of patients and affected surgical techniques, reliable and practical information on success rates is difficult to obtain.

Furthermore, it should also be noted that the utilization rate of the cryopreserved ovarian tissue is still relatively low. In one of our studies, the return rate for ovarian tissue transplantation was 5 out of 306.[3] According to Jadoul et al,[2] merely 3% to 4% of the frozen ovarian tissue have undergone transplantation, with less than 1% ultimately generated pregnancies and deliveries. In Germany, the number of applications for ovarian tissue transplantation has increased noticeably in recent years and most of the live births worldwide occurred after 2010, compared with the prior period, indicating an accelerated progress of the procedure.[56] The further optimization of cryopreservation and surgical techniques is expected to increase the pregnancy rate in the near future.

Pregnancy complications and perinatal outcome

Pregnancy complications after transplantation of ovarian tissue have rarely been reported. Jensen et al[58] described in a review about 32 women, who had given birth to 40 children worldwide, that 4 women developed complications, which potentially would affect the pregnancy. Of the 4 women, 2 had cervical insufficiency, where 1 of the 2 also developed preeclampsia, the third woman developed preeclampsia, and the fourth woman developed HELLP syndrome. In Germany, so far, no pregnancy complications have been reported.[58] The pregnancies after transplantation of ovarian tissue in our institution and in the FertiPROTEKT network were known to be uncomplicated. The pregnancies were carried to term and the children born had a normal birth weight and were healthy.[7]

Data regarding the perinatal outcome of children born after transplantation of ovarian tissue have shown that the gestational age and birth weight were within internationally recognized normal standards.[56] There was only 1 case of a baby born with arthrogryposis, but the patient had a family history of other limb malformations.[71] According to Pacheco and Oktay,[56] this yields an anomaly rate of 1.2% among the babies born and reported after ovarian tissue transplantation worldwide and is not different from the 1% to 2% major malformation rate seen in the general population. Although it is obvious that there need to be a larger number of births to have a reliable assessment for this issue, it is unlikely that there will be a higher risk of genomic damage with the procedure compared with oocyte cryopreservation.

Topical Challenges and Future Opportunities

Due to the promising results achieved in the past, a significant challenge remains in the optimization of the survival of replaced follicles and thus the function of the transplanted tissue. Approximately two-thirds of follicles are lost following ischemia until revascularization took place after transplantation. Therefore, the optimization of ovary transplantation may require preparing the right thickness of tissue and finding the best site of transplantation. Furthermore, to promote rapid revascularization, the site of transplantation could be prepared by encapsulated vascular endothelial growth factor (VEGF) and stromal cells enriched in CD34 cells as shown in experimental studies or patient treatment with melatonin or ovarian tissue incubation with hyaluronan-rich biological glue, plus VEGF-A, and vitamin E may improve graft survival.[61,72,73] As mentioned above, the issue of contamination of malignant cells and the risk of recurrence after transplantation also remain a significant concern. Therefore, further development of in vitro culture systems for ovarian tissue and artificial ovary constructs is necessary for the clinical applications.[50-54] Furthermore, as Kristensen and Andersen[74] highlighted in a recent review, novel ideas for utilization of ovarian tissue cryopreservation include cell/tissue-based hormone replacement therapy, nonmedical reasons, optimizing culture systems for immature oocytes, and performing a modern ovarian resection for women with polycystic ovaries. These kind of ideas, which are technically possible but not yet proven, will undoubtedly raise controversies in the field and a plethora of questions concerning the ethics, safety, cost-effectiveness, superiority, and implications of the proposed procedures.[74]

Table 1. Summary of recommendations and joint decisions according to the personal opinions of experts in German-speaking reproductive medical centers and centers of the FertiPROTEKT network.[1,8]

Transplantation of ovarian tissue should be performed in women with a manifest desire for a child and failure of ovarian function (amenorrhea/oligomenorrhea), up to the age of 45 y.
A basic clarification of causes of infertility should be performed prior to transplantation.
The patient must be informed before harvesting the tissue about the possible risk of transferring malignant cells by transplanting the harvested ovarian tissue.
The transplantation of ovarian tissue is performed laparoscopically.
In the case of a transplantation, a "chromo"-perturbation (eg, with NaCl) should be performed.
Blunt preparation of a pocket is performed in the pelvic peritoneum for this purpose and the ovarian tissue is implanted into this pocket.
If the ovarian tissue preparation is to be taken again later, it is recommended to mark the transplantation site (eg, titanium clips).
Patients with amenorrhea should be offered a monthly blood test (FSH, estradiol, progesterone) 8-10 wk before the transplantation until signs of activity are detected, and every 2 mo, an ultrasound examination should be offered.
If there are signs of activity of the transplanted ovarian tissue, it is recommended to perform cycle monitoring to increase the chances of pregnancy, after other causes of infertility have been clarified.
In patients with causes of infertility (such as tubal infertility, reduced male fertility), ART measures must be taken.
Patients who still had an active cycle prior to transplantation should be offered monthly cycle monitoring 8-10 wk after the transplantation.

Abbreviations: ART, assisted reproductive technology; FSH, follicle-stimulating hormone.

Conclusions

Ovarian cryopreservation followed by orthotopic ovarian tissue transplantation is the only fertility preservation approach that can restore ovarian endocrine function and natural fertility. At least 25% to 30% of women undergoing transplantation will go on to give birth at the moment. The pregnancies so far have been uncomplicated in most of the cases and no negative effects on the outcome of cancer treatment or live births have been observed. In Germany, the standard technique that has emerged is laparoscopy transplantation to a peritoneal pouch in the pelvic wall. Surgical complications during the laparoscopic removal and transplantation of ovarian tissue are rare and correspond to those seen with standard laparoscopy for indications not involving fertility preservation. Based on our experience and the results in the published literature, the technique of removal and transplantation of ovarian tissue can be regarded as already established (Table 1). Nevertheless, it is important to conduct and report long-term observations and studies with large numbers of patients to optimize the procedure and to answer the question on the full potential of this procedure.

Author Contributions

LL wrote the manuscript. All of the authors read and approved the final manuscript.

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