ORIGINAL RESEARCH ARTICLE

Endometriosis in women undergoing ovarian tissue transplantation due to premature menopause after gonadotoxic treatment or spontaneous premature ovarian failure

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Abstract

Introduction: Cryopreservation of ovarian tissue with subsequent transplantation is an efficient option for restoring fertility in women at risk of premature ovarian failure. The association between infertility and endometriosis is well recognized. Although endometriosis usually ends with the onset of natural or iatrogen menopause due to declining estrogen levels, endometriosis can in rare cases occur after menopause. This study aims to investigate women with premature menopause who were diagnosed with endometriosis during laparoscopy for ovarian tissue transplantation, and to address the questions of how endometriotic lesions after cytotoxic treatment and premature menopause might be explained, whether endometriosis affects pregnancy rates, and whether there is an association between endometriosis and the original cancer.

Material and Methods: Seventeen patients who had undergone ovarian tissue transplantation to restore their fertility and who were diagnosed with endometriosis during transplantation were included in this retrospective study. The endometriosis foci were completely removed and ovarian tissue was transplanted into the pelvic peritoneum. Preexisting conditions, use of hormonal preparations, endometriosis stage pain assessment, as well as pregnancy and live birth rate were evaluated.

Results: The mean age of the patients was 29.5 ± 6.3 years (range 14–39) at the time of ovarian tissue harvest and 34.6 ± 4.3 years (range 28–40) at transplantation. Prior to transplantation, four patients had taken hormone replacement therapy, four women oral contraceptives and two patients’ tamoxifen. Twelve women had stage I endometriosis and five stage II endometrioses according to the rASRM classification. Four patients reported dysmenorrhea. None of the women complained of general pelvic

Abbreviations: AMH, anti- Müllerian hormone; FSH, follicle stimulating hormone; HRT, hormone replacement therapy; IVF/ICSI, in vitro fertilization/intracytoplasmic sperm injection; rASRM, revised American Society for Reproductive Medicine.

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INTRODUCTION

Endometriosis is a condition that affects an estimated 6%–10% of women of reproductive age. It is defined as the presence of endometrial-like tissue at extrauterine sites and is an estrogen-dependent chronic inflammatory condition that is associated with dysmenorrhea, lower abdominal pain, dyspareunia, dysuria and infertility. Due to the lack of reliable diagnostic tools and the non-specific nature of the symptoms, diagnosis is often delayed by 8–10 years.\(^1\)

The pathophysiology of endometriosis is complex and not fully understood. Various concepts have been developed to describe the possible causes for the development and maintenance of the disease (eg implantation theory, celomic metaplasia theory, archimetrica theory), without a final satisfactory explanation being found. Estrogen dependence, progesterone resistance, inflammation and genetic predisposition are, among others, considered pathophysiological features of endometriosis, with estrogen-dependent growth being the central feature of this disease. Molecular studies have shown that endometriotic lesions pathologically overexpress the estrogen receptor beta (ER\(\beta\)), which leads, among other things, to locally elevated levels of the biologically active form of estrogen (estradiol).\(^2\) Furthermore, clinical observations and studies have shown that disease remission and symptom relief occur when women reach a hypo-estrogenic state through iatrogenic or natural menopause.\(^3\)

Although endometriosis usually ends with the onset of natural or iatrogen menopause due to declining estrogen levels, endometriosis can occur or reactivate after menopause in some women.\(^3\) There are few reports on this topic in the literature, with the prevalence of postmenopausal endometriosis estimated at 2%–5%.\(^3,4\) However, the real incidence of endometriosis is limited and not consistent.\(^5,6\) Also, the underlying mechanism of endometriosis in the peri- or postmenopausal period is not well known. Estrogen production could be caused by hormonal replacement therapy, which can induce endometriosis and create new implants. Another estrogen production during menopause could also be caused by extraovarian organs—adrenal gland, endometrial stroma, adipose tissue and skin.\(^7\)

Cryopreservation of ovarian tissue is currently used worldwide to preserve fertility in girls and women who are at high risk of losing ovarian function and thus premature menopause. Ovarian tissue cryopreservation has several advantages over embryonic or oocyte cryopreservation and is the only fertility maintenance option for children, adolescents and young adult cancer patients who require immediate chemotherapy and do not have enough time for ovulation induction. The procedure is independent of a menstrual cycle. A large number of oocytes and primordial follicles can be preserved. The hormonal function of the ovary can be restored, and the technique does not require ovarian stimulation or a sperm donor.\(^8-10\) It is also a fertility-reactivation technique in women with premature ovarian failure that has not been caused by an cytotoxic therapy because of an oncological disease.\(^11\)

Numerous research successes have been achieved in the field of ovarian tissue cryopreservation and transplantation, so that the procedure has become established in many countries as an option for fertility preservation. The number of young women who undergo transplantation of their previously frozen ovarian tissue to fulfill their desire to have children is increasing every year. These women usually have an early menopause and, in many cases, have received hormone replacement therapy over a long period of time to prevent osteoporosis.

In this study, we therefore wanted to investigate cases of women who have undergone ovarian tissue transplantation due to premature menopause and who were diagnosed with endometriosis...
during this procedure. To date, no study has addressed the issue of endometriosis in menopausal women undergoing ovarian tissue transplantation.

Key questions to be investigated and discussed with the help of this study are: How could the endometriotic lesions after cytotoxic treatment and premature menopause be explained, does the endometriosis affect the pregnancy rate and is there an association between endometriosis and the original cancer disease?

2  |  MATERIAL AND METHODS

2.1  |  Patients

This retrospective study included all patients who underwent ovarian tissue transplantation to restore fertility in the Department of Obstetrics and Gynecology at the University Hospital in Erlangen between May 2007 and December 2019 and were diagnosed with endometriosis during this operation. The database of the University Hospital Erlangen was used for the examined patient group. Data, which included age, preexisting conditions, pre-surgery (especially for endometriosis), taking medication, symptoms, previous pregnancies or fertility treatments, were recorded. Information on the histologic type of cancer and gynecologic conditions was obtained from pathological records.

2.1.1  |  Removal of ovarian tissue for cryopreservation

In all study patients, the removal of ovarian tissue for cryopreservation was performed by laparoscopy. During the laparoscopy, intra-abdominal examinations were routinely performed for abnormalities such as malignancy, but also for endometriosis. If endometriosis was found, the stage of endometriosis was classified according to the revised American Society for Reproductive Medicine (rASRM).12

2.1.2  |  Measurement of hormone levels

Before ovarian tissue transplantation, serum anti-Müllerian hormone (AMH) levels and follicle stimulating hormone (FSH) levels were measured by Access Assay (UniCel DxI 600, Beckman Coulter) or by Cobas (Roche) in accordance with the manufacturer’s instructions to confirm postmenopausal hormone status.

2.1.3  |  Surgery for ovarian tissue transplantation and excision of endometriosis

In all cases, surgery was performed by laparoscopy. During the laparoscopy, endometriosis and other fertility-restricting causes (such as abnormalities of the fallopian tubes) were systematically examined. The stage of endometriosis was scored according to the revised Classification of the American Fertility Society.12 The endometriosis foci discovered during the operations were completely removed by dissection and the removed foci were examined histologically to confirm the diagnosis of endometriosis.

In all patients, ovarian tissue had been frozen in advance for fertility preservation using slow freezing procedures. On the day of the operation, the frozen tissue was thawed and transplanted into a peritoneal pocket of the pelvic peritoneum in the ovarian fossa. Details of the cryopreservation and thawing protocols for ovarian cortex tissue were described previously.13,14

2.1.4  |  Pain assessment and follow-up

Detailed information on pain symptoms was obtained during a postoperative interview with the patients. The women were asked whether they had ever experienced pain during their periods (dysmenorrhea), non-cyclical/general pelvic pain and dyspareunia in their lives either before or after ovarian tissue transplantation. The severity of dysmenorrhea, general pelvic pain and dyspareunia was assessed using the visual analog scale, a 10-point numerical pain rating scale with 0 = no pain and 10 = worst pain imaginable. In addition, information on the frequency of dysmenorrhea, general pelvic pain and dyspareunia was collected. In addition, it was recorded whether regular menstrual bleeding occurred after the transplantation of ovarian tissue, whether there were signs of recurrence of endometriosis (e.g., endometriomas in transvaginal ultrasound) and whether pregnancy and birth occurred, as well as whether in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment had taken place for this purpose.

2.2  |  Statistical analyses

For the analysis, the collected data were entered into the Microsoft EXCEL program. Descriptive statistics were generated to describe demographic data, indications for ovarian tissue cryopreservation, fertility (before and after cryopreservation), laboratory values, staging of endometriosis, and pain assessment. Differences between pregnancy outcomes of patients with and without endometriosis undergoing ovarian tissue transplantation were tested nonparametrically (Chi-square test or Student’s t-test) with a significance level of 5%.

2.3  |  Ethical approval

Approval was obtained from Erlangen University local ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg on 12 June 2018 (application number: 192_18 B).
3 | RESULTS

3.1 | Patient characteristics at the time of ovarian tissue removal and time of transplantation

A total of 82 women had undergone ovarian tissue transplantation in the period studied. Endometriosis was diagnosed in 17 (20.7%) of them during the ovarian tissue transplant surgery. The mean age of these 17 patients at the time of ovarian tissue removal was 29.5 ± 6.3 (range 14–39) years. Fourteen (82.4%) of the patients underwent the procedure for conditions involving malignancy. Seven had Hodgkin’s lymphoma, five breast cancer, one cervical cancer and one borderline tumor of the ovary. Three patients had spontaneous premature ovarian failure without a demonstrable triggering cause (genetic and autoimmune factors were excluded).

At the time of the transplantation, the patients’ mean age was 34.6 ± 4.3 (range 28–40) years.

Characteristics of the 17 study patients are summarized in Table 1.

3.2 | Hormone levels before transplantation, menstruation and medication intake

Eight patients had taken hormone therapy for several years prior to ovarian tissue transplantation due to premature ovarian failure. Four patients had taken hormone replacement therapy and four others had taken combined oral contraceptives. In addition, two patients with post-breast cancer condition had taken tamoxifen for 5 years prior to transplantation.

Of the remaining seven patients, three reported amenorrhea and four reported irregular menstrual cycles with oligomenorrhea.

All patients showed elevated FSH levels (mean: 53.8 ± 35.5 IU/L, range 15–135) and decreased AMH levels (mean: 0.08 ± 0.14 pmol/L, range 0.01–0.54) in the preoperative hormone determination, corresponding to a depleted ovarian reserve.

3.3 | Endometriosis stage and pain assessment

In two patients, endometriosis was already known at the time of removal of the ovarian tissue for cryopreservation. Both patients (ID 8 and 10; see Table 1) had stage I according to rASRM at this time. In the patient (ID 8) with POI, the endometriosis had been completely removed when the ovarian tissue was harvested. At the time of ovarian transplantation, she was diagnosed with stage II rASRM. In the other patient (ID 10) with breast cancer, the endometriosis was left in place because of the upcoming chemotherapy and only a biopsy was taken for histologic examination. During ovarian tissue transplantation, the patient was still diagnosed with stage I rASRM.

In the remaining 15 women, no endometriosis was diagnosed, and no endometriosis lesions were found during the laparoscopy for removal and freezing of the ovarian tissue. In the laparoscopy for ovarian tissue transplantation, 11 of these women had endometriosis stage I and four stage II according to rASRM classification. No case of advanced stage endometriosis (rASRM III and IV) was detected in any women.

Four patients reported dysmenorrhea (4–9/10) prior to ovarian tissue transplantation. Two of these women had oligomenorrhea, one was taking cyclical hormone replacement therapy and one was taking a cyclic combined oral contraceptive pill. The hormonal values and endometriosis staging of these patients are provided in Table 1 (ID 1, 7, 12 and 16). None of the women complained about general pelvic pain or dyspareunia. After ovarian tissue transplantation, regular menstrual bleeding was restored in 14 of the 17 patients. In the three patients with POI, menstrual bleeding did not occur. Only one patient (ID 7) with previous dysmenorrhea reported a recurrence of dysmenorrhea about 9 months after transplantation. The other women did not complain about endometriosis symptoms after resumption of their cycles. No signs of endometriosis, such as endometriomas, could be detected in any of the women by pelvic ultrasound after ovarian tissue transplantation.

3.4 | Pregnancy and live birth rates

Before ovarian tissue transplantation, none of the patients had given birth to a child. After ovarian tissue transplantation, seven women (41.2%) became pregnant. One woman even became pregnant twice. The pregnancies occurred in three women after spontaneous conception (42.8%) and in four women (57.2%) after natural cycle IVF/ICSI. The mean time to pregnancy was 58.1 ± 114.9 days. In total, six women gave birth to seven healthy children, resulting in a live birth rate of 35.3%. There was no significant difference in the age at time of cryopreservation or the AMH values of women who conceived and who did not (P = 0.28 and 0.22). One patient who had her ovarian tissue removed and transplanted due to POI fulfilled her desire to have a child by donating eggs, due to ovarian tissue transplant failure.

Pregnancy and live birth rates were higher in patients diagnosed with endometriosis and removed during transplantation than in the other 65 patients without endometriosis who underwent ovarian tissue transplantation in our department (41.2% and 35.3% with endometriosis vs 29.2% and 23.1% without endometriosis; χ²(1) = 11.2 (n = 82), P = 0.28 and χ²(1) = 1.1 (n = 82), respectively, P = 0.30). There were no significant differences between patients with and without endometriosis regarding age at the time of cryopreservation (29.5 ± 6.3 vs 30.6 ± 4.5; P = 0.47) and transplantation (34.6 ± 4.3 vs 34.9 ± 4.8; P = 0.84) and the type of conception (spontaneous conception: 42.8% vs 48.2% and IVF/ICSI: 57.2% vs 51.8%).

4 | DISCUSSION

Endometriosis in peri- and postmenopausal women is a rare occurrence in the literature, with an estimated prevalence of 2%–5%. In
**TABLE 1** Characteristics of patients in whom endometriosis was detected and removed during ovarian tissue transplantation

| ID | Age at cryopreservation | Age at transplantation | Reason for POI | AMH pmol/L | FSH IU/L | E2 pmol/L | Oocyte transfer (ICSI) | Pregnancy | Live birth | Endometriosis stage | Hormone therapy |
|----|-------------------------|------------------------|----------------|------------|----------|-----------|------------------------|------------|------------|---------------------|-----------------|
| 1  | 33                      | 37                     | HD             | 0.01       | 19.04    | 79        | Yes                    | Yes (2x)   | Yes (2x)   | rASRM I ENZIAN 0    | HRT             |
| 2  | 35                      | 35                     | POI            | 0.14       | 135      | 70        | No                     | No         | No         | rASRM I ENZIAN 0    | No              |
| 3  | 39                      | 40                     | Breast cancer  | 0.01       | 56       | 14        | Yes                    | No         | No         | rASRM I ENZIAN 0    | No              |
| 4  | 30                      | 32                     | HD             | 0.01       | 48       | 42        | No                     | Yes        | Yes        | rASRM I ENZIAN 0    | HRT             |
| 5  | 30                      | 30                     | POI            | 0.01       | 41       | 104       | No                     | No         | No         | rASRM I ENZIAN 0    | HRT             |
| 6  | 28                      | 28                     | BOT            | 0.01       | 47       | 46        | Yes                    | No         | No         | rASRM I ENZIAN 0    | OCP             |
| 7  | 34                      | 39                     | Cervical cancer| 0.02       | 25       | 192       | Yes                    | No         | No         | rASRM I ENZIAN 0    | No              |
| 8  | 27                      | 29                     | POI            | 0.01       | 63       | 31        | No                     | No         | No         | rASRM II ENZIAN 0   | HRT             |
| 9  | 26                      | 33                     | HD             | 0.28       | 102      | 41        | No                     | Yes        | Yes        | rASRM I ENZIAN A0 B1 C0 | No             |
| 10 | 33                      | 37                     | Breast cancer  | 0.01       | 88       | 110       | Yes                    | Yes        | No         | rASRM I ENZIAN A0 B2 C0 | No             |
| 11 | 33                      | 39                     | Breast cancer  | 0.01       | 15       | 124       | Yes                    | Yes        | Yes        | rASRM II ENZIAN A0 B1 C0 | Tamoxifen       |
| 12 | 17                      | 31                     | HD             | 0.02       | 23       | 48        | No                     | No         | No         | rASRM I ENZIAN 0    | OCP             |
| 13 | 33                      | 38                     | Breast cancer  | 0.09       | 110      | 23        | Yes                    | Yes        | Yes        | rASRM II ENZIAN 0    | No              |
| 14 | 33                      | 40                     | HD             | 0.54       | 22       | 242       | No                     | Yes        | Yes        | rASRM II ENZIAN 0    | No              |
| 15 | 26                      | 32                     | HD             | 0.19       | 59       | 96        | No                     | No         | No         | rASRM I ENZIAN A0 B2 C0 | OCP            |
| 16 | 14                      | 29                     | HD             | 0.05       | 29       | 189       | No                     | No         | No         | rASRM II ENZIAN A0 B2 FA | No             |
| 17 | 31                      | 39                     | Breast cancer  | 0.03       | 32.6     | 22        | No                     | No         | No         | rASRM I ENZIAN A0 B0 C0 | Tamoxifen       |

Abbreviations: AMH, anti-Müllerian hormone; BOT, borderline ovarian tumor; E2, estradiol; FSH, follicle stimulating hormone; HD, Hodgkin’s disease; HRT, hormone replacement therapy; OCP, oral contraceptive pill; POI, premature ovarian failure; rASRM, revised American Society for Reproductive Medicine.
this study, 17 of 82 women were found to have endometriosis at the time of ovarian tissue transplantation, so the prevalence we found is significantly higher in the study population (at 20.7%).

The reason for this high prevalence as well as the underlying pathomechanism by which endometriosis can be explained in relation to menopausal hormone levels is widely unclear. It is thought that endometriosis lesions develop as a side effect of therapy with administered hormones or due to the presence of endogenous hormones.

Hormone replacement therapy (HRT) may be able to reactivate endometriosis. Gemmell et al. reviewed the evidence for the treatment of menopause in the presence of endometriosis. They found only 32 case reports/series with 42 patients. Recurrence of endometriosis was reported in 17 case reports, of which 12 patients with previous hysterectomy received estrogen therapy alone. Most patients had extensive endometriotic disease prior to hormone use. Due to a lack of sufficiently large and high-quality studies, the risks of HRT in women with a history of endometriosis is uncertain and remains contradictory. In particular, no specific data are available for the group of young women entering premature or early menopause either after gonadotoxic treatment or due to primary ovarian insufficiency. For this group of women, several medical societies recommend HRT to treat climacteric symptoms and prevent bone loss, at least until the natural age of menopause. In the present study, four women were taking combined hormone replacement therapy over several years and one of them had a history of endometriosis.

Furthermore, two patients with breast cancer had taken tamoxifen for 5.5 and 7 years before ovarian tissue transplantation. Both women had amenorrhea while taking tamoxifen and after stopping it. During surgery for ovarian tissue transplantation, one of them was diagnosed with stage rASRM I endometriosis, the other with rASRM II. Neither of them had a history of endometriosis or endometriosis-like symptoms. There are a growing number of cases in the literature which suggest that tamoxifen is an antagonist of the estrogen receptor in breast tissue but behaves as an agonist in the endometrium and is associated with the development of endometriosis in postmenopausal women with breast cancer.

Recurrence of endometriosis is also possible without HRT. There are case reports of endometriosis in postmenopausal women who have not received HRT. In these women, other risk factors such as hyperestrogenemia and obesity may play a role in the pathogenesis. Estrogen production during menopause may originate from other extraovarian sources in addition to adipose tissue, such as the adrenal gland, endometrial stroma and skin. De Almeida Ascencio et al. reported seven cases of their own and 29 cases in the literature in which women developed clinically progressive endometriosis after menopause without ingesting estrogen or having excessive systemic endogenous production. They suspected that a genetic and/or epigenetic incident caused estrogen-independent progression, increased sensitivity to estrogens or increased local production of estrogens. However, it remains to be clarified whether a genetic predisposition, together with environmental factors, medication or fat distribution, increases the risk of endometriosis after menopause.

The association between endometriosis and infertility is well recognized. In a large cohort study of women of reproductive age, the risk of infertility was twice as high in women <35 years of age with endometriosis compared with women without endometriosis. However, the causal relation between endometriosis and infertility is not yet fully understood. It has been postulated that a combination of impaired pelvic anatomy, altered peritoneal function, alteration of the immunological milieu in the peritoneal cavity, decreased ovarian reserve, impaired oocyte competence and altered endometrial receptivity may be the cause of infertility.

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 one of three to four women attempting ovarian tissue transplantation being able have at least one child. In the present study, the clinical pregnancy rate was 41.2% and the live birth rate 35.3%. In the present study, the clinical pregnancy rate was 41.2% and the live birth rate was 35.3% in patients with endometriosis. A non-significantly higher pregnancy rate was found compared with women who were not diagnosed with endometriosis during ovarian tissue transplantation in our clinic. The reason for the tendency of higher pregnancy rates is unclear and can only be speculated. One reason could be that the endometriosis was completely removed in all cases. Prospective studies have shown that the removal of endometriosis increases the conception rate compared with just diagnostic laparoscopy. On the other hand, it may be that the patients received more intensive follow-up care due to the endometriosis and were transferred to assisted reproductive measures at an early stage. Finally, the present study is a retrospective evaluation and bias cannot be excluded due to the small study size. Nevertheless, it seems that the success rates after ovarian tissue transplantation in women with removed endometriosis did not differ significantly from the success rates that can be achieved internationally with ovarian tissue transplantation. However, prospective studies with larger patient collectives and a matched control group are needed to make a generally reliable statement in this regard.

It should also be noted that all women in this study had ASRM stage I/II endometriosis and all visible endometriosis lesions could be removed during laparoscopy for ovarian tissue transplantation. In patients with ASRM stage III/IV, it can only be speculated that endometriosis causes a negative impact on success rates in terms of pregnancy and birth rate after ovarian tissue transplantation. There appears to be a relation between the extent of disease and the degree of reduced spontaneous fertility in endometriosis, although the strength of this relation varies. In women with minimal/mild endometriosis, about 50% can conceive without treatment, whereas in women with moderate disease only 25% conceive spontaneously, and in severe disease few spontaneous conceptions occur. Indeed, the rate of spontaneous pregnancies is comparable in women with minimal/mild endometriosis and women with unexplained infertility, suggesting that minimal/mild endometriosis may have little impact on fertility. Nevertheless,
superficial peritoneal lesions are more strongly associated with infertility than are endometriomas and deep infiltrating endometriosis.26

Furthermore, women with endometriosis are more likely to need in vitro fertilization (IVF) to improve the chances of pregnancy.25 In our patient population, the proportion of women who had undergone Nature-ICSI treatment to achieve pregnancy was relatively high, but did not differ from women who had undergone ovarian transplantation without endometriosis. Seven of the examined women (41.2%) underwent IVF/ICSI treatment to achieve pregnancy after ovarian tissue transplantation and four of them became pregnant, three women delivering a healthy child. The severity of endometriosis has been shown to have a direct influence on the results of IVF/ICSI treatment. In a meta-analysis, women with ASRM stage I/II endometriosis who underwent IVF/ICSI treatment had a slight reduction in fertilization rates. Women with severe pelvic endometriosis and stage III/IV disease had significantly lower implantation rates and clinical pregnancy rates.27

Recent studies have found a link between endometriosis and certain types of malignancies, particularly ovarian cancer, breast cancer, skin melanoma and non-Hodgkin's lymphoma.28 The molecular mechanisms underlying these associations are still largely unexplored.29 The increased risk of various forms of malignancy and the lower average age at diagnosis of malignancy compared with the general population suggest an underlying dysregulation of tumor growth in these women and strengthen the hypothesis of a disturbed immune system.28 However, there are no studies to date on women with a history of cancer and subsequent endometriosis diagnosis. Further studies are needed to determine the association between endometriosis and the development or comorbidity of malignancy.

Despite the small number of cases, it is surprising that so many women had newly diagnosed endometriosis at the time of ovarian tissue transplantation. Whether this is due to overdagnosis by laparoscopy or other causes such as taking hormone replacement therapy, tamoxifen or chemotherapy, as well as whether endometriosis exerts an influence on the subsequent pregnancy rate, can only be answered using higher patient numbers. However, it is striking that the patients did not have a diagnosis of endometriosis during the laparoscopy to remove the ovarian tissue. Therefore, surgeons should carefully examine these patients for endometriosis during transplantation.

5 | CONCLUSION

This study highlights an important and under-researched area of gynecology—the association between endometriosis in women entering premature or early menopause either after gonadotoxic treatment or due to primary ovarian insufficiency. As more and more patients want to have their cryopreserved ovarian tissue transplanted to fulfill their desire to have children, specialists will inevitably encounter women with this condition. Our results show with a pregnancy rate of 41% that transplantation of ovarian tissue has a pregnancy rate that is comparable to published data, indicating that the appearance of endometriosis does not reduce the success after transplantation of ovarian tissue. However, whether and especially to what extent advanced endometriosis in transplanted women has an influence on the success rate regarding pregnancy and birth rate, as well as recurrence rate and development of gynecological second malignancies remain subjects for further investigations.

AUTHOR CONTRIBUTIONS

LL and RD designed the study and wrote the manuscript. LL, AD and IH analyzed the data. RD, AM, and MWB supervised the study. LL and SB revised the manuscript. All the authors read and approved the final manuscript and revision.

CONFLICT OF INTEREST

None.

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