Live birth after orthotopic grafting of autologous cryopreserved ovarian tissue and spontaneous conception in Italy

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Objective: To describe a live birth obtained in Italy after autologous orthotopic transplantation of cryopreserved ovarian cortical tissue.
Design: Case report.
Setting: University department of gynecology and obstetrics, reproductive medicine and IVF unit.
Patient(s): A 29-year-old patient affected by β-thalassemia (intermedia phenotype) who underwent chemotherapy and bone marrow transplantation at age 21 years, resulting in a complete precocious ovarian failure.
Intervention(s): Before being treated with chemotherapy (busulfan, cyclophosphamide, and cyclosporine) for bone marrow transplantation, the patient underwent laparoscopic sampling of ovarian cortical tissue that was frozen and cryopreserved in liquid nitrogen. Eight years later, the ovarian tissue was thawed and grafted during laparoscopy at an orthotopic site.
Main Outcome Measure(s): Ultrasound and endocrine monitoring of the postgrafting restoration of ovarian function; conception, pregnancy, and live birth.
Result(s): Three months after grafting, the decrease of circulating FSH levels and the parallel increase of E_2 levels demonstrated ovarian function restoration, which was confirmed by bidimensional ultrasound and color Doppler examinations. After some ovulatory cycles, the patient spontaneously conceived 16 months after transplantation. After 39 weeks of uneventful gestation, a healthy girl weighing 3,970 g was born.
Conclusion(s): Autologous grafting of cryopreserved ovarian cortex at an orthotopic site may allow ovarian function restoration, spontaneous conception, and birth of a healthy baby. (Fertil Steril® 2013;99:227–30. ©2013 by American Society for Reproductive Medicine.)
Key Words: Ovarian tissue transplantation, fertility preservation, ovarian tissue cryopreservation, live birth, β-thalassemia

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The effectiveness of the therapy of some life-threatening diseases affecting prepubertal girls or young women in the fertile age has markedly improved in recent years, increasing the number of long-term survivors who aim at living a normal life and at having their own family. Among such therapies, bone marrow transplantation (BMT) represents the elective option for the treatment of a wide range of disorders. Bone marrow transplantation needs to be preceded by chemotherapy and immuno-depressive drug administration, whose undesired side effects include the induction of precocious ovarian failure (POF) due to the iatrogenic disruption of almost all ovarian follicles (1). As a consequence, precocious menopause and irreversible ovarian infertility occur in approximately 80%–100% of women submitted to chemotherapy and BMT (1).

Fertility preservation using cryobiology techniques represents an important issue to keep the chance of becoming a mother after remission of

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the disease, despite the long-term ablative effect of gonadotoxic treatments (2). Some options are available for female fertility cryopreservation: the storage of frozen embryos, mature oocytes, immature oocytes, or ovarian cortical tissue. Among these, the last can also be used for prepubertal girls and for women who must urgently begin oncostatic treatment and do not have enough time to undergo ovarian stimulation and oocyte retrieval. Although still experimental, ovarian cortex cryopreservation coupled with autologous transplantation has been thoroughly studied, and the possibility of obtaining a pregnancy has been repeatedly documented. Donnez et al. (3) reported the first live birth after autologous transplantation of frozen/thawed ovarian tissue, and since then several other similar reports have been published (4–17).

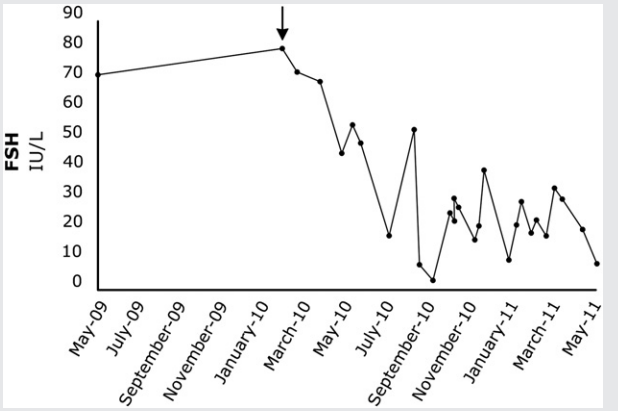
Herein we describe a live birth obtained after autologous orthotopic transplantation of ovarian cortical tissue in a young woman affected by a severe form of β-thalassemia (intermedia phenotype) that forced her to undergo high-dose chemotherapy and BMT. It is the first baby born to date in Italy after autologous orthotopic transplantation of ovarian cortical tissue.

MATERIALS AND METHODS

The patient, a young woman affected by a severe form of the intermedia phenotype of β-thalassemia, required repeated blood transfusions and iron chelation therapy since early infancy. At the age of 7 years she underwent splenectomy. When she was aged 21 years, BMT was scheduled as the only option after the onset of progressive resistance to the previously administered treatments. Before BMT, the patient was treated with high-dose chemotherapy including alkylating drugs (busulfan 3.5 mg/kg/d/4 days alternating with cyclophosphamide 50 mg/kg/d/4 days) and cyclosporine (3 mg/kg/d) plus methylprednisolone (0.5 mg/kg/d). After such preliminary treatment, the patient underwent BMT from a human leukocyte antigen–identical donor (her sister). In the following weeks, circulating gonadotropins increased to postmenopausal levels (FSH 71 IU/L, LH 30 IU/L), E_2 fell to very low levels (<10 pg/mL), and clinical symptoms of POF (e.g., hot flashes, insomnia, vaginal dryness) appeared. The patient was given hormone replacement therapy to control symptoms and prevent the unfavorable effects of precocious menopause on the vascular system, the bone, and the brain.

Before chemotherapy and BMT we proposed to the patient to cryostore mature oocytes for fertility preservation, but she judged the 2 weeks' time needed for ovarian stimulation and egg retrieval too long, wishing to start preparation for BMT as soon as possible. Alternatively, she agreed to undergo cryostorage of ovarian cortical tissue, which could be organized in a couple of days. Institutional review board approval was obtained by the local ethics committee. A laparoscopy was performed, during which slices of ovarian cortex were cut (20 × 15 mm), immediately rinsed in IVF-buffered medium (Origio), and transported to the laboratory for further processing. The slices of ovarian cortex were carefully handled, manually dissecting the cortical tissue from the medullary tissue; then the cortical tissue was cut into smaller strips (5 × 5 × 1 mm) as previously described (2) and stored in liquid nitrogen.

FIGURE 1



Circulating levels of FSH before and after transplantation (indicated by the *black arrow*).

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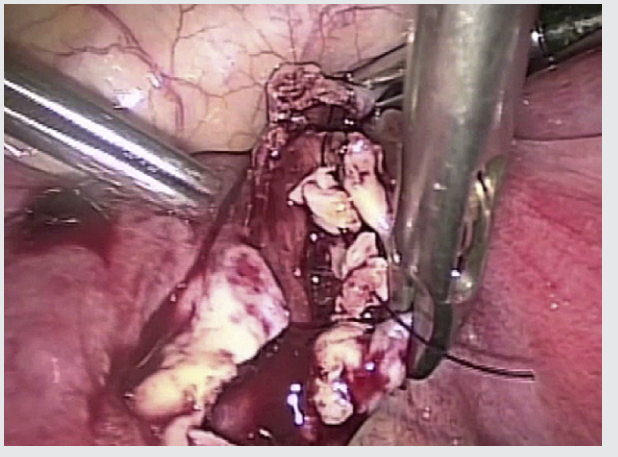
Two fragments of a strip were analysed to calculate the mean follicular density, which was high (28 follicles/mm^2), as expected in a young patient.

Eight years after ovarian tissue collection and storage, the patient was judged completely remitted from her disease and in health condition, good enough to undergo a pregnancy. Thus, she asked to have her ovarian tissue back to try to conceive; she stopped hormone replacement therapy, and a quick rise of circulating gonadotropin levels (FSH 72.3 IU/L, LH 32.1 IU/L) with a drop of E_2 levels (12 pg/mL) occurred (Fig. 1), with the reappearance of menopausal symptoms.

In March 2010 the autologous grafting of ovarian cortex was scheduled. Beforehand a small piece of frozen tissue was thawed, and histologic analysis detected morphologically normal primordial follicles at a mean density of 30 follicles/mm^2.

According to the technique described by Donnez et al. (18), a first laparoscopic surgery was performed to decorticate atrophic ovaries, create ovarian pouches, and promote

FIGURE 2



Grafting site, with some grafted fragments of ovarian tissue.

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