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FERTILITY PRESERVATION

Treatment history and outcome of 24 deliveries worldwide after autotransplantation of cryopreserved ovarian tissue, including two new Danish deliveries years after autotransplantation

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Abstract
Purpose To report another two successful pregnancies and deliveries resulting from autotransplanted cryopreserved ovarian tissue several years after the autotransplantation procedure took place. Further, to review the literature on the treatment history, number of live births and their outcome so far reported worldwide.
Methods Two women underwent fertility preservation with cryopreservation of their ovarian tissue prior to a potentially sterilizing treatment with bone marrow transplantation. One woman suffered from paroxystic nocturnal hemoglobinuria and one woman from relapse of Hodgkin′s lymphoma. Both suffered from premature ovarian insufficiency after treatment. Because of a pregnancy wish they later had pieces of thawed cortical tissue transplanted to the remaining ovary and the anterior abdominal wall. PubMed was searched for reports of deliveries resulting from cryopreserved ovarian tissue in peer-reviewed papers.
Results Five years after the autotransplantation the first patient became spontaneously pregnant and delivered a healthy baby boy at term. The second patient became pregnant after undergoing one cycle of in vitro fertilisation five years after the autotransplantation. She delivered a healthy baby boy at gestational week 36. Twenty healthy singletons and two sets of twins have been born according to peer-reviewed publications.
Conclusion Contrary to most of the published deliveries our latest two cases occurred several years after the autotransplantation procedure took place. This proves that ovarian grafts are capable of functioning for several years after the autotransplantation has occurred. Today, a total of 26 healthy children have been born as a result of cryopreservation of ovarian tissue.

Keywords cryopreservation · deliveries · fertility preservation · ovary · ovarian tissue

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Introduction

To date cryopreservation of ovarian tissue as a means of fertility preservation is still considered experimental, although more and more encouraging reports about the efficacy of this method emerge. [1, 2]. Cancer patients receiving antineoplastic treatment, which as a side effect can cause irreversible loss of ovarian function, are the primary group of patients who may benefit from this new treatment [3]. The success of autotransplantation of cryopreserved ovarian tissue has been proven by case reports of births worldwide. One concern, however, is the duration of the fertility potential of the graft. It is unknown how many patients have undergone fertility preservation with autotransplantation, but it is documented that the ovarian reserve in patients transplanted with frozen/thawed ovarian tissue is low and that levels of AMH often are very modest or even immeasurable [4]. It has also been documented that most of the pregnancies are conceived within the first 12 months after the autotransplantation, and that the grafts have a limited duration of function [2]. In general, the

lifespan of ovarian grafts is expected to be approximately 4–5 years if follicular density is well preserved, although a longer duration of the grafts has been reported both from orthotopic [5] and heterotopic [6] transplantation sites.

The purpose of this paper is to describe two pregnancies and deliveries both occurring in women several years after autotransplantation of the cryopreserved ovarian tissue. In addition, we want to document all the deliveries resulting from autotransplantation of ovarian tissue on a worldwide basis that have been published in peer-reviewed journals.

Materials and methods

PubMed was searched for deliveries resulting from autotransplanted cryopreserved ovarian tissue from 2004 to May 2014. Terms referring to 'cryopreservation of ovarian tissue', 'autotransplantation of ovarian tissue', and 'live births' were used. We also searched reference lists of identified articles manually for additional references.

Patient 1

In year 2004 at the age of 18 the patient was diagnosed with paroxystic nocturnal heamoglobinuria. As the severity of the disease progressed bone marrow transplantation was planned in year 2005 with the patient′s sister as a donor. Prior to this, the patient was referred for fertility preservation. A vaginal ultrasound revealed two normal ovaries with the expected number of antral follicles. The planned preconditioning protocol of Busulfan and Cyclophosphamide implied a high risk of premature ovarian insufficiency (POI) and a unilateral laparoscopic oophorectomy was performed for fertility preservation. The ovarian tissue was cryopreserved according to the clinic′s standard procedure [7]. After treatment the patient became amenorrhoic. Two years later in 2007 she was referred to the clinic with the aim of autotransplantation of her cryopreserved ovarian tissue as she wished to become pregnant. She had been taking hormonal replacement therapy (HRT) previously but in order to assess her ovarian function correctly she was asked to discontinue the HRT for three months prior to her visit to the clinic. A vaginal ultrasound revealed a small atrophic remaining ovary devoid of antral follicles. Follicle stimulating hormone (FSH) was 96 IU/l and the oestradiol immeasurable (<0.04 nmol/l), consistent with POI. The physician responsible for treating the patient′s haematological disease was contacted and had no objections to the autotransplantation procedure. In April 2008 during a laparoscopically assisted mini-laparotomy seven pieces of cortical tissue were transplanted to the remaining ovary and five pieces to the anterior abdominal wall in a small pocket created underneath the peritoneum. The transplanted tissue comprised of one third of the removed ovary.

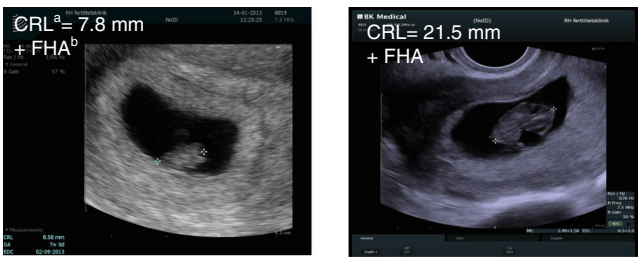
Patient 2

In 2001 at the age of 25 the patient was diagnosed with Hodgkin′s lymphoma stage II B for which she received chemotherapy (adriamycin, bleomycin, vincristine and dacarbazine (ABVD) × 6 and mitoguazone, ifosfamid, metothrexate and etoposide (MIME) × 2 and localized radiotherapy. Two years later the patient relapsed and a protocol of dexamethasone, cytarabine and cisplatin (DHAP) followed by a bone marrow transplantation was planned. Prior to this the patient had her left ovary cryopreserved for fertility preservation [7]. After treatment the patient became amenorrhoic. In 2005, due to a pregnancy wish, the patient was again referred to the clinic with the aim of autotransplantation of her cryopreserved ovarian tissue. At the time of referral she complained of hot flushes and other symptoms associated with POI. Her FSH was 42 and her estradiol immeasurable (<0.04 nmol/l). During a laparoscopically assisted mini-laparotomy ten pieces of cortical tissue were transferred to the remaining right ovary just below the cortex. She then underwent seven IVF cycles without becoming pregnant, and in order to increase her chances of a pregnancy the patient requested a second transplantation, which was performed in June 2006. Two longitudinal inscisions were created along the surface of the ovary thus creating two subcortical pockets into which 12 small pieces of cortical tissue were aligned, six in each pocket, making sure the tissue did not overlap. The size of the ovary was big enough to accommodate these pieces. The collective amount of tissue transplanted to this patient comprised 69 % of the removed ovary.

Results

Patient 1

Four months after the autotransplantation in August 2008 the patient had her first menstrual bleeding after the transplantation and her FSH had dropped to 7.5 IU/l. From September 2008 to January 2009 the patient underwent one cycle of



[a]CRL= crown rump lenght
[b]FHA= fetal heart action

Fig. 1 Ultrasonography in *patient 1* at gestational week 7 and 9 respectively

Table 1 Live births after transplantation of frozen-thawed ovarian tissue published in peer-reviewed papers / : symbolizes the number of autotransplantations or births

Reference	Chemotherapy before cryopreservation[a]	Surgical method	Disease	Chemo./BMT[b] after cryopreservation	Sign of menopause before transplantation[c]	Age at cryopre-servation	Age at trans-plantation	Graft site
[8]	No	1	Hodgkin′s lymphoma	MOPP/ABV	Am, FSH 91, LH 85, E2 17	25	31	PW
[9]	VACOP-B+MINE-ESHAP	1	Non-Hodgkin′s lymphoma	BEAM/BMT	Am, FSH and LH 40–104, AMH+ inhibin-B immeasurable	28	30	O
[10, 11]	1xABVD	2	Hodgkin′s lymphoma	5xABVD/3xEVA/CBV BMT	Am, FSH 87, Inhibin B <15	24	29/31	0+A/ 0+A
[12, case 2]	6xABVD/ 2xMIME	2	Relapse of Hodgkin′s lymphoma	3xDHAP/BMT	Am, FSH 42, E2 immeasurable	25	28/29	O/O
[12–14]	No	3	Ewing′s Sarcoma	6xVIDE/3xVAI	Am, FSH 80	27	28	O
[15]	No	2	Sickle cell anemia	Busulfan+Cyclophosphamide/BMT	ultrasound: no follicles FSH 98 LH 32	20	23	O+PW
[16, 17]	No	4	POI[d]	No	Am, FSH 82, LH 34	25	28/30	O/O
[17]	No	2	Hodgkin′s lymphoma	ABVD/Cisplastin+Gemcitabine/BMT	Am, FSH 63, LH 34	20	31	O
[18]	No	1	Breast cancer	3xFEC/3xdocetaxel	Am FSH 36 AMH 1	36	38	O
[19]	No	5	Neuroecto-dermic tumor	BMT	FSH 75 E2<10	17	25	O
[20, 21]	No	1	Thalassemia	Fludarabine+Busulfan+ Antithymocyticglobulin/ PBSCT	Am, FSH>30	19	23/nd/nd	O+BL/O+ BL/ BL
[22]	No	6	PID[f]	No	Am	18	26	BL
[23]	6 × ABVD	5	Hodgkin′s lymphoma	BCNU+Etopside+Cytarabine+ Melphalan/ BMT	Am, AMH<0.1 FSH+LH high E2 low	27	32	BL
[24]	No	6	POI	No	Am (FSH >40)	29	-	PW
[25]	No	1	Thalassemia	Busulfan+Cyclophosphamide+ Cyclosporine/ BMT	FSH 72 LH 32 E2<12	21	29	O
[26[e]]	No	7	Granulosa cell tumor	No	FSH >120 E2<10	25	32/34	PW+A/ A
[27]	No	6	Bilateral Dermoid cysts	No	Am FSH >30	20	30	BL
[21]	2.55 g cyclophos-phamide	2	Microscopic polyangiitis	7.65 g Cyclophosphamide+58 g orally	FSH 235 LH 98	27	35/35	O+PW/ O+PW
(case 1)	No	2	Paroxystic noctural haemoglobinuria	Busulfan+Cyclophosphamide	Am FSH 96 E2 immeasurable	18	21	O+A

[a] All samples are cryopreserved with the slow freezing technique except in reference 20

[b] bone marrow transplantation

[c] FSH and LH IU/l; AMH ng/ml; Inhibin B pg/ml.; E2 pg/ml

[d] Premature ovarian insufficiency

[e] After personal communication with CJ Stern it has been confirmed that the pregnancy resulted in a delivery of twin girls

[f] pelvic inflammatory disease

Surgical method

1=Unilateral ovarian biopsy/ Partial left oophorectomy

2=Unilateral oophorectomy/ Unilateral salpingo-ooforectomy

3=Unilateral ovarian biopsi. The patient previously had a left oophorectomy because of a dermoid cyst

4=NA. The patient suffered from idopathic benign POI for many years. She therefore had no surgical procedure prior to transplantation of ovarian tissue from twin sibling

5=Bilateral ovarian biopsy

6=Bilateral oophorectomy

7=Unilateral Oophorectomy. Four years earlier the patient had a left oophorectomy

Chemotherapy

ABVD: doxorubicin, bleomycin , vinblastin, dacarbazine

ALLTO: lapatinib, trastuzumab

BEP: bleomycin, etopside, cisplatin

BCNU: high-dose cyclophosphamide, carmustine

BEAM: carmustine, etopside, cytarabine, melphalan

CBV: cyclophosphamide, carmustine, etopside

EVA: etopside, vinblastine, doxorubicin

FEC: fluorouracil, epirubicin, cyclophosphamide

MIME: Methyl-GAG, ifosfamide, methotrexate, etopside

MINE-ESHAP: mesna, ifosfamide, mitoxantrone, etopside, cytarabine, cisplatin and corticosteroids

MOPP/ABV: mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine

PBSCT: Peripheral blood stem cell transplantation

VACOP-B: etopside, doxorubicin, cyclophosphamide, vincristine, bleomycin and corticosteroids

VIDE: vincristine, iphosphamide, etopside, doxorubicin

Sign of menopause before autotransplantation

Am: amenorrhoeic

Age at transplantation

Nd: not described

Graft site

A: Abdominal wall, O: Ovary, PW: peritoneal window, BL: Broad ligament

Table 2 Transplantation to pregnancy and pregnancy outcome

Ref.	Amount transplanted Graft size ($cm^{2)}$	Recovery of ovarian function[a] (in months) E2; FSH[b]	Pregnancy	Time from transplanta- tion to pregnancy (months)	Live births No.	Sex	Gestational age (weeks)	Birth weight (gram)	Pregnancy complications	Delivery mode
[8]	4,2/1,4	5	SC	11	1	Girl	39	3,720	nd	nd
[9]	2,3+ tiny fragments	8	IVF	9	1	Girl	38	3,000	None	CS
[10, 11]	4,5/ 1	3	SC/SC	5/33	2	Girl/Girl	41/39	3,130/2,870	None/nd	nd/nd
[12, case 2]	1,25/3	5/5	IVF/IVF	19/85	2	Boy/Boy	37/36	2,600/2,600	Mild preeclampsia+ Hypothyroidism+ cervical insufficiency	CS/CS
[12–14]	1,5	4	IVF/SC/SC	5/24/59	3	Girl/Girl/Boy	38/41/40	3,204/3,828/ 4,015	None/ None/ None	CS/ VD/ VD
[15]	nd	4	SC	6	1	Girl	38	3,700	nd	CS
[16, 17]	nd/nd	4/nd	nd/nd	5/nd	2	nd/nd	nd/nd	nd/nd	nd/nd	nd/nd
[17]	nd	4	SC	8	1	Boy	38	3,089	nd	nd
[18]	nd	2	IVF	10–11	2 (twins)	Boy+Boy	33	1,650+1,830	None	CS
[19]	nd	4 E2>110 FSH+LH <10	SC	9	1	Boy	38	2,830	none	nd
[20, 21]	nd/nd/nd	nd/nd/nd	IVF	10	1	Boy	-	3,026	Cholecysto-lithiasis	nd
[22]	1,8	5 E2 19 FSH 26	IVF	13	1	Boy	38	2,370	nd	CS
[23]	nd	3 E2 114 FSH 11 LH 4	SC	8	1	Boy	38	3,360	None	CS
[24]	nd	nd	IVF	-	1	Boy	37	3,254	nd	nd
[25]	4,3	3 E2 79 FSH 46	SC	16	1	Girl	39	3,970	None	CS
[26]	4,8/ 2,4	4.5	IVF	7	2 (twins)	Girl+Girl	37	3,320 3,262	nd	CS
[27]	nd	5 E2 25 FSH >10	IVF	5	1	Boy	39	3,500	nd	CS
[21]	0,64/ nd	6 FSH 10	IVF	14	1	Girl	37	2,030	HELLP syndrome	VD
(case 1)	3	4 FSH 7,5	SC	57	1	Boy	40	3,351	None	VD

/: symbolizes the number of autotransplantations or births

[a] as defined by resumption of spontaneous menstruation

[b] FSH and LH in IU/l; E2 in pg/ml

[c] After personal communication with CJ Stern it has been confirmed that the pregnancy resulted in a delivery of twin girls

Pregnancy

S: spontaneously conceived

IVF: after in vitro fertilization

ND: Not described

Delivery mode

CS: ceasarean section

VD: vaginal delivery

13 births worldwide from non peer-reviewed papers

ovulation induction, two cycles of intrauterine insemination (IUI) with partner's sperm and three cycles of in vitro fertilization (IVF) without becoming pregnant. She then split up with her partner and moved to another part of Denmark. All follow-up visits for her haematological condition were normal revealing no signs of recurrence of the disease. In January 2013 five years after the autotransplantation the patient called the clinic to tell that she had become spontaneously pregnant with a new partner. This pregnancy occurred within the first month of trying. She continued having regular menstrual bleedings from August 2008 and until she got pregnant. At no time did she use any hormonal contraception or intrauterine device (IUD).. Ultrasonography revealed a viable intrauterine pregnancy with a crown-rump length (CRL) of 7.8 mm corresponding to gestational age 7+0 weeks and again 14 days later 21.5 mm corresponding to gestational age 9+0 (Fig. 1). After an uneventful pregnancy the patient delivered a healthy baby boy vaginally at gestational age 40+2 weeks weighing 3351g.

Patient 2

Five months after the first autotransplantation procedure the patient had a menstrual bleeding.

After the second autotransplantation her FSH level was 16.5 IU/l and her estradiol 200 pg/ml. She was diagnosed with uterine adenomyosis and was operated using the transverse H incision technique. She then had one more cycle of IVF and conceived after transfer of a 4-cell embryo and delivered a healthy baby boy weighing 2,600 g in gestational week 37 by caesarean section (12). After a lactation period of three months the patient had an IUD inserted. She was followed for her cancer with regular visits every 6 months at the haematological department with no signs of recurrence of the disease. Five years later in 2012 the patient returned to the clinic, as she wanted a second child. She still experienced regular menstrual cycles. Her FSH was 6.1 IU/l and her estradiol 0.09 nmol/l on cycle day 3. It was decided to offer IVF again. In the first antagonist cycle the patient was stimulated with rFSH with a starting dose of 200 IU/l increasing to 300 IU/l. After 11 days of stimulation 4 oocytes were aspirated from 4 follicles, ICSI was performed and two embryos were transferred on day 2 but the patient did not become pregnant. In her second antagonist cycle the starting dose of rFSH was 300 IU/L and the patient developed 4 follicles from which 2 oocytes were retrieved, ICSI was performed and both cleaved. The patient conceived after transfer of two embryos (one 4-cell and one 2-cell). The patient developed hypothyroidism during the pregnancy and it was further complicated by a shortening of the cervix causing hospitalization from gestational week 26 and until an elective caesarean section was performed in week 36+3. A healthy baby boy weighing 2,600 g was delivered.

Australia: Burmeister L, Kovacs GT and Osianlis T have published a case report of 1 ongoing pregnancy (Burmeister L, Kovacs GT, Osianlis T. First Australian pregnancy after ovarian tissue cryopreservation and subsequent autotransplantation. The Medical journal of Australia. 2,013;198(3):158–9.)
Through the media it is well known that the woman from this case report gave birth to a healthy baby girl in 2013, GA38+
Sweden: 1 birth of a baby girl, mentioned in a newspaper, see attached link: http://www.dn.se/nyheter/vetenskap/historisk-bebis-ger-hopp/
South Africa: 1 birth of a baby boy, mentioned in a newspaper, see attached link: http://www.iol.co.za/capetimes/medical-method-bears-miracle-baby-1.1570087#.Us1MAZHDN8B
Germany: 3 undocumented births (confirmed from Fertiprotekt)
Israel: 5 undocumented births
Brussels: 2 undocumented births

Table 3 Gestational age (*GA*) and birth weight of 26 children, 22 singletons and 2 sets of twins published in peer-reviewed journals

	GA Median (weeks)	GA (weeks) Mean±SEM (Range)	Birth weight (grams) Median	Birth weight (grams) Mean±SEM (Range)	Boys N	Girls N
Singletons	38	38,5±0,3 (36–41)	3,167	3,172±116 (2,030–4,015)	11	9
Twins	35	35±1 (33–37)	2,546	2,516±447 (1,650–3,320)	2	2

Table 1 and 2 gives detailed information on all the deliveries so far published in peer-reviewed journals. Information on the patient′s history before the autotransplantation procedure is given as well as information on the autotransplantation procedure, the results and information on the pregnancies and deliveries.

Table 3 gives information on the babies (gestional age, birthweight and gender).

Discussion

Here we report two new successful Danish pregnancies and deliveries occurring five and six years, respectively, after the autotransplantation procedure. Most of the deliveries described in the literature from autotransplanted ovarian tissue have occurred within the first one to two years after transplantation (Table 1 and 2). However, in the two cases described here the grafts were capable of functioning and providing a normal, intra-ovarian milieu for the oocytes to mature and later fertilize years after grafting: This gives hope to other women with autotransplanted ovarian tissue, who may not become pregnant immediately after autotransplantation. Both of the patients in this study were young, 18 and 24 years of age, when they had their ovarian tissue cryopreserved and thus the grafts were expected to contain many primordial follicles enabling them to function for several years after the autotransplantation. Indeed, apart from two women who were in their mid-thirties when they had their ovarian tissue cryopreserved, all deliveries reported so far have occurred in women who were in their twenties at the time of cryopreservation (Table 1 and 2) supporting the theory that a substantial number of primordial follicles augment the fertility potential of these grafts.

With a mean gestational age at delivery of 38.5 weeks in the singleton pregnancies and a mean birthweight of 3,167 g the uteri of these cancer survivors with autotransplanted ovarian tissue seem to be able to function in a normal way and to provide a healthy milieu to support the growth and development of the fetus (Table 3). What can also be seen from Table 1 and 2 is that despite of the lack of pregnancy complications being described the majority of the deliveries (11/15) were by Caesarean section, probably reflecting that these pregnancies are considered very precious. Another interesting observation is that 11 of the 21 pregnancies in which the history of how the pregnancy was achieved was reported, were naturally conceived and 11 occurred after IVF. This knowledge is very important when counselling the patients before autotransplantation that they may not need IVF in order to conceive and that naturally occurring pregnancies are as likely to happen.

With 24 babies born worldwide we now report two more deliveries thus reaching 26 babies on a worldwide basis and a total of six babies in Denmark. The two latest pregnancies occurred years after the autotransplantation and serve as proof that cryopreservation of ovarian tissue is becoming a method of fertility preservation that may give the patient a chance of motherhood for several years following the autotransplantation procedure.

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