Oocyte donation in women cured of cancer with bone marrow transplantation including total body irradiation in adolescence

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Female survivors of cancer in childhood and adolescence who have been treated with bone marrow transplantation including total body irradiation (TBI) are at high risk of developing ovarian follicular depletion and infertility. The lack of oocytes may be compensated for by oocyte donation but these patients also seem to have a uterine factor. Even though oestrogen replacement therapy is given, the growth of the uterus during adolescence is impaired. To our knowledge there have been no earlier reports of live births after oocyte donation in such patients. We report three cases of oocyte donation in women who, at a young age, were cured of haematological malignancies with bone marrow transplantation including TBI. In adolescence they developed ovarian failure and uterine volumes were assessed by ultrasonography. One woman with a uterus of almost normal size delivered a healthy child in the 37th week of gestation. Another woman with severely diminished uterine volume miscarried in the 17th week of gestation. The third woman has not yet conceived. Pregnancy achieved by oocyte donation is possible despite TBI in adolescence. However, the uterine factor is a concern and complications during pregnancy and preterm birth may be expected in these patients.

Key words: bone marrow transplantation/childhood cancer/oocyte donation/total body irradiation/uterine factor

Introduction
The overall survival rate of childhood cancer—defined as a malignant neoplasm diagnosed before the age of 15 years—has improved during the last three decades and is now close to 70% (Meadows and Hobbie, 1986; Stiller, 1994). Consequently, the frequency and severity of late effects after treatment for childhood cancer have increasingly gained importance, and future prognosis for gonadal function and fertility is of major concern for these patients.

Allogeneic bone marrow transplantation (BMT) has commonly been recommended in the treatment of children with relapsed or very high risk leukaemia and lymphoma, and today the 10 year survival rate after BMT in our centre is close to 50% regardless of diagnosis. BMT is preceded by high-dose chemotherapy alone or in combination with total body irradiation (TBI). In cancer treatment TBI is only used as a conditioning regime prior to BMT. Although the total doses are low (8.5–10 Gy), the fraction doses are high and so cause substantially more damage than would be anticipated from the total dose. The whole body is irradiated in contrast to, for example, inverted Y and abdominal irradiation where the radiation fields are carefully planned in order to minimize complications.

BMT with TBI has severe late side-effects, including gonadal dysfunction and infertility (Levy and Stillmann, 1991; Lewitt, 1998). In childhood and adolescence this treatment causes follicular depletion, and the ovarian damage becomes more severe the older the girl (Sarafoglou et al., 1997; Thibaud et al., 1998). Therefore IVF with donated oocytes is a possibility for pregnancy and delivery in the female survivors. However, a recent study from our group demonstrated that BMT with TBI in childhood not only depleted the ovarian follicles but also caused severe impairment of uterine growth. Despite oestrogen replacement therapy the average uterine volume in adult age was reduced to about 40% of the normal adult volume (Holm et al., 1999).

To our knowledge there have been three reports on successful pregnancy and delivery with oocyte donation after BMT (Gulati and Poznak, 1998) but in two cases (Rio et al., 1994; Lee et al., 1995) the women were more than 30 years old when treated for cancer. In a third case (Bierman et al., 1993) the age is unknown.

We report three case histories of oocyte donation in women who had cancer diagnosed in childhood and as adolescents were cured for haematological malignancies with BMT including TBI. Approximately 3 years prior to the infertility treatment they participated in the previously mentioned study where they had uterine size assessed by ultrasonography.

Case reports
The malignant diagnosis, anti-neoplastic treatment, and conditioning regimes prior to BMT are listed in Table I.

Results from the follow-up study, which also included a staging according to Marshall and Tanner (1969), are listed in Table II. Uterine volumes were assessed by transabdominal ultrasound scans using ALOKA SSD 680 (Aloka Co., Tokyo, Japan) with a curved linear 3.5 MHz transducer. Ultrasound examinations were performed when the participants had a full bladder. Uterine volume was calculated by measuring length, width, and depth of the organ and by assuming the
Table I. Malignant diagnosis, age at diagnosis, initial treatment, age at bone marrow transplant (BMT) and conditioning regime in the three cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Case B</th>
<th>Case C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant diagnosis</td>
<td>Acute lymphoblastic leukaemia</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>12.8</td>
<td>12.0</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>15.0</td>
<td>-</td>
</tr>
<tr>
<td>Treatment</td>
<td>Asparaginase, Methotrexate, Puri-nethol, Vincristine, Prednisolone, Radiation to the right eye</td>
<td>Adriamycin, Vinristin, Prednisone, Intraspinal Methotrexate, Cranial radiation</td>
</tr>
<tr>
<td>Age at BMT (years)</td>
<td>17.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Cyclophosphamide (g/m²) (total dose)</td>
<td>4.3</td>
<td>7.9</td>
</tr>
<tr>
<td>TBI (Gy fractions)</td>
<td>11.4 (3)</td>
<td>10 (1)</td>
</tr>
</tbody>
</table>

TBI = total body irradiation.

Table II. Results from the follow-up study; ultrasound examination and Tanner staginga

<table>
<thead>
<tr>
<th>Case A</th>
<th>Case B</th>
<th>Case C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner staging (breast and pubic hair, respectively)</td>
<td>V, V</td>
<td>IV, IV</td>
</tr>
<tr>
<td>Uterine volumeb (SDS)</td>
<td>-1.8</td>
<td>-6.3</td>
</tr>
<tr>
<td>Uterine volumec (md)</td>
<td>41.8</td>
<td>9.4</td>
</tr>
<tr>
<td>HRT at follow-up</td>
<td>E, N</td>
<td>E, N</td>
</tr>
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</table>

bThe sizes of the uteri were related to a study of internal genitalia in 166 healthy Danish females aged 6.4–25.4 years (Holm et al., 1995). Age-specific standard deviation scores (SDS), were calculated for uterine volumes using the formula: (observed value – predicted value)/SD.
cUterine volume calculated using the formula based on an ellipsoid: \(d_1 \times d_2 \times d_3/2\), where \(d_1\), \(d_2\), and \(d_3\) are the three maximal longitudinal, anteroposterior, and transverse diameters.

agent chemotherapy for 3 years (Table I). At the age of 17 years she had a relapse, and was treated with chemotherapy and irradiation to the right eye. Half a year later in her second remission, allogeneic BMT including TBI was performed with her human leukocyte antigen (HLA) identical brother as a donor. A mild graft versus host disease (GVHD) was treated with cyclosporine for 6 months post transplant. Since BMT there have been no symptoms or clinical signs of relapse.

Menarche was at age 15 years and her menses were regular pre-transplant. After BMT she developed ovarian failure requiring oestrogen–gestagen sequential therapy. This induced regular withdrawal bleedings and she progressed through an apparently normal puberty.

In March 1996, at her second attempt, she conceived after transplantation of two embryos (Table III). An ultrasound examination showed a singleton pregnancy. Oral oestradiol and vaginal progesterone was taken until the 12th week of gestation. Pregnancy was uneventful until the 29th week of gestation. At that time she was admitted with premature contractions and glucocorticoids were given to mature the lungs of the fetus. The contractions ceased spontaneously. Four weeks later gestational diabetes was diagnosed. Blood sugar was regulated sufficiently on diet prescription. In the 37th week of gestation, a subacute Caesarean section was done because of premature contractions and mild pre-eclampsia. A healthy girl, birth weight 2870 g, length 47 cm, and Apgar scores 10 after 1 and 5 min, was delivered in October 1996. When last seen in August 1998, nearly 2 years after the delivery, both mother and child were healthy.

Case B

In 1982, when the patient was 12.0 years old, a non-Hodgkin malignant lymphoma was diagnosed. Complete remission was obtained with combination chemotherapy (Table I). In January 1983, a relapse in the central nervous system was diagnosed and chemotherapy was intensified and combined with cranial irradiation. In May 1983, in her second remission, an allogeneic
Oocyte donation in women cured of cancer

Table III. Results from the egg-donation programme

<table>
<thead>
<tr>
<th></th>
<th>Case A</th>
<th>Case B</th>
<th>Case C</th>
</tr>
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<tbody>
<tr>
<td>Age at oocyte donation (years)</td>
<td>28.7</td>
<td>26.3</td>
<td>26.4</td>
</tr>
<tr>
<td>Oestrogen dose at oocyte donation (mg)</td>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Endometrial thickness at oocyte donation (mm)</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>No. of embryos transferred on day 3 (quality):*</td>
<td>2 (6-cells, score 2.1)</td>
<td>2 (one 7-cell, one 6-cell, both score 2.1)</td>
<td>2 (one 5-cell, one 6-cell, both score 2.1)</td>
</tr>
<tr>
<td>Serum HCG (IU/l)</td>
<td>154 (positive)</td>
<td>324 (positive)</td>
<td>&lt;2 (negative)</td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td>Healthy girl</td>
<td>Mid-trimester abortion</td>
<td>Not pregnant</td>
</tr>
</tbody>
</table>

*Quality scoring system applied from Ziebe et al. (1997).
HCG = human chorionic gonadotrophin.

BMT including TBI was performed using her HLA identical sister as a donor. A severe skin GVHD was treated with steroids and cyclosporine. Since BMT there have been no symptoms or clinical signs of relapse.

She developed normally and entered puberty but she did not have menarche. An endocrinological examination at the age of 15 years revealed primary ovarian failure and oestrogen–progesterone replacement therapy was started. One month later she had her first withdrawal bleeding.

In October 1996 she conceived at the first attempt of oocyte donation where two embryos were transferred (Table III). Oral oestriadiol and vaginal progesterone was taken as in case A. In the 10th week of gestation vaginal bleeding occurred but an ultrasonography showed a normal intrauterine singleton pregnancy. Two weeks later when bleeding and pain had stopped ultrasonography showed a normal intrauterine pregnancy with a fetal crown rump length of 49 mm. However, she miscarried in the 17th week of gestation. In January 1999, a second but unsuccessful oocyte donation was performed.

**Case C**

In 1984, a few days before her 15th birthday, this patient was treated for acute myeloid leukaemia (Table I). In her first remission an allogeneic BMT including TBI was performed with her HLA identical brother as a donor.

Menarche was at age 14 years. After BMT she developed ovarian failure requiring sex steroid hormone replacement therapy (HRT) as in cases A and B. Withdrawal bleedings were regular. In 1995 she was treated with oocyte donation with a negative result. Two embryos were transferred (Table III).

In 1996, when 27 years of age, a malignant tumour was diagnosed in her thyroid gland. After a total thyroidectomy, radioactive iodine was given in two series. Regular visits to the oncological department have shown no signs of relapse. When last seen in February 1999 the patient was in good health. No further attempts of oocyte donation have been performed.

**Discussion**

To our knowledge this is the first report where a woman, cured with BMT including TBI for a malignancy treated in childhood and adolescence, has conceived and delivered following IVF of donated oocytes.

In other reports (Rio et al., 1994; Lee et al., 1995) the women were adults, 30 and 33 years respectively, when a haematological malignancy was diagnosed and only one woman (Rio et al., 1994) received TBI. In another case (Bierman et al., 1993), there is no exact information on age, but apparently the woman was <25 years old at BMT, and she did not receive TBI.

Pubertal maturation of the internal genitalia was studied (Holm et al., 1995) in 166 healthy girls assessed by ultrasonography. During normal puberty the greatest increase in uterine size occurred between Tanner stages 3 and 4 (Marshall and Tanner, 1969). When uterine growth normally ceased at the age of 20 years, the uterine volume was about 60 ml. Multiple regression analysis suggested that uterine growth post-menarche was related to number of years after menarche and not to height, weight or age.

Since the woman in the case studied by Rio et al. (1994) was adult at TBI, the uterus presumably had a normal size at oocyte donation. In the cases reported in the present paper only case A had a uterus of approximately normal size, whereas cases B and C had abnormal uterine volumes. This may explain why case A brought pregnancy nearly to term before subacute Caesarean section in the 37th week of gestation. In case C the uterus was extremely small, even when compared to cases A and C. Case B had not experienced menarche when BMT with TBI was performed whereas case A had had regular menses for a period of 2.6 years before the transplantation and case C for 1.6 years. Thus, pubertal status at TBI may play a part in final uterine volume. Age at TBI may also be an important factor. The woman in case A was 12.8 years old at diagnosis. However, she was 17.6 years old at TBI, that is 4.7 and 2.0 years older than the women in cases B and C respectively. This observation is in accordance with a recent study (Bath et al., 1999) where five female long-term survivors of childhood cancer treated with TBI (14.4 Gy) were available for detailed investigation of uterine and ovarian function. Four women had ovarian failure and one had preserved ovarian function. Bath et al. (1999) found that uterine volume was correlated with age at irradiation: the younger the age, the smaller the uterus.

Sanders et al. (1996) reported an increased risk of spontan-
euous abortions in women treated with BMT including TBI (Sanders et al., 1996). Furthermore, pregnancies among women who received a BMT were more likely to be accompanied by preterm labour and low birth weight infants. In case B the pregnancy had an adverse outcome, i.e. a mid-trimester abortion. It is possible that the reduced uterine volume was the main reason, but also radiation-induced damage, as previously suggested (Wallace et al., 1989), may be of importance. In that study, women treated with abdominal irradiation in childhood due to a Wilms' tumour were followed prospectively. None of the reported six pregnancies were carried beyond the second trimester, and Wallace et al. (1989) suggested that uterine distensibility affected through the presence of fibrosis or an action on elastic tissue could explain the adverse outcome.

Pregnancies after oocyte donation are high. Most centres report success rates of 25–50% per embryo transfer (Söderström-Antilla, 1998). In one study (Pados et al., 1992) the highest pregnancy rate was observed among women with primary ovarian failure (26.4%; 14/53) while the lowest was among women who had received chemotherapy and/or radiotherapy (9%; 1/11). It has been suggested (Critchley, 1999) that the modalities employed to treat childhood cancer, especially irradiation, may result in damage to the uterine musculature and vasculature with potential impairment of normal uterine function and increased risk of subsequent defective implantation. Thus it seems that women treated for a childhood cancer, besides the problem with uterine size, also have to overcome endometrial structural and functional damage.

It is important that pubertal girls without ovarian function get sufficient doses of oestrogen in order to achieve an appropriate final height and to permit sexual development. In Denmark young women without ovarian function get 2–4 mg oestrogen orally administered per day. This dose seems not to be sufficient to facilitate uterine growth in adolescent women treated with TBI in childhood. In the study mentioned above (Bath et al., 1999) the four women without ovarian function had uterine characteristics investigated before and after 3 months of physiological sex steroid replacement therapy (transdermal oestradiol patches 100 µg/24 h week 1, 150 µg/24 h week 2, 3, and 4 in all three cycles). At the baseline ultrasound scan, where they had discontinued HRT for 4 weeks, they all had small uteri [6.5 ml (1.7–12.7)] [median (range)] and absent endometrium. After 3 months of physiological sex steroid replacement therapy there were no significant differences in endometrial thickness when compared to the control groups. Uterine volume increased [16.3 ml (7.0–25.9)] but still remained significantly lower than in the control groups [41.5 ml (28.1–57.9)]. Therefore, further studies are needed in order to determine both the optimal delivery route and the most appropriate dose of oestrogen.

The population of long-term survivors of childhood and adolescent malignancy is growing. It has been estimated that in year 2000, one in 1000 adults between 20 and 29 years of age will be a survivor of a childhood cancer (Meadows and Hobbie, 1986). As a consequence, an increasing number of adolescent girls are facing a future with no ovarian function and their only possibility for motherhood is adoption or oocyte donation. Although it is now possible to cryopreserve ovarian tissue, it is still not possible to culture the primordial follicles or to replace the ovarian tissue after treatment for cancer. These problems will probably be overcome in the future and perhaps these women will eventually be able to give birth to their own genetic children. Nevertheless, the problem regarding the uterine volume factor has still to be solved and a sceptical attitude is needed regarding the possibility of bringing pregnancy to term.

References


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