CASE REPORT

Malignancy may adversely influence the quality and behaviour of oocytes

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A case series of eight cycles of in-vitro fertilization (IVF) in five women diagnosed with malignant disorders is presented. These patients chose to defer definitive treatment for a chance for preservation of potential fertility. The response of these patients to ovarian stimulation, and the outcome, was compared with 17 IVF cycles in 12 age-matched patients with isolated tubal infertility. An apparent adverse influence of malignant disease on the quality and behaviour of oocytes was observed. Despite a comparable total number of oocytes per cycle in the two groups, a significantly reduced percentage of mature oocytes was retrieved per cycle from patients with malignant diseases. The oocytes from patients with malignant disorders were of a poorer quality and exhibited a significantly impaired fertilization rate compared to the controls. We propose that neoplastic processes, irrespective of the site or cell of origin, may have a detrimental impact on the biology of oocytes, an effect akin to that seen on spermatozoa in men with certain malignancies.

Key words: fertilization/IVF/malignancy/oocyte/quality

Introduction

Women in the reproductive age group may be diagnosed with a malignant process, the treatment of which will render them subfertile. Prior to undergoing the definitive treatment, which may involve total hysterectomy, chemotherapy or pelvic radiotherapy, in-vitro fertilization (IVF) and subsequent embryo cryopreservation is a feasible option for parenting a biological child. Embryo transfer could then be deferred, or the patient may decide to utilize a gestational carrier. The stage and course of the malignancy must be carefully weighed and individualized before considering postponement of definitive treatment while the patient undergoes one or more cycles of IVF. Oocyte cryopreservation is still experimental (Baka et al., 1996; Saunders et al., 1996), despite documented pregnancies resulting from the use of cryopreserved oocytes (Chen, 1986). The adverse impact of malignancy on sperm parameters has been well established (Chapman et al., 1981; Thachil et al., 1981; Berthelsen and Skakkebaek, 1983; Botchan et al., 1997), but little is known about the influence of malignant disorders on ovarian function. With refinements in embryo cryopreservation techniques, more patients with recently diagnosed malignant disease are utilizing the option of undergoing IVF for preservation of potential fertility. This provides an opportunity for analysis of the impact of neoplastic disease on oocyte physiology.

The IVF programme at the Massachusetts General Hospital has treated several couples with diagnosed malignancy in either partner, who desired to undergo IVF prior to undergoing definitive therapy for their disease. We now report on a series of eight cycles of IVF in five women with non-hormone producing neoplasms of varying nature. Our preliminary impression in this small group of young women with no prior history of infertility is that the neoplastic process, irrespective of site of origin, may have a detrimental impact on the quality and behaviour of oocytes.

Case report

Design

Retrospective analysis, by review of records of all female patients presenting for IVF with a diagnosis of malignancy at the Vincent Memorial IVF unit at the Massachusetts General Hospital (MGH), between July 1995 and July 1997. A total of 245 patient records was reviewed for this period. A total of six patients was identified in whom the female partner was diagnosed with a malignant process and underwent IVF in an attempt to conserve potential for future fertility. Of these, one patient had undergone a unilateral oophorectomy for borderline ovarian cancer and her husband’s semen parameters were bordering on male factor infertility. This patient was therefore not included in the study. The remaining five patients was identified in whom the female partner was diagnosed with a malignant process and underwent IVF in an attempt to conserve potential for future fertility. Of these, one patient had undergone a unilateral oophorectomy for borderline ovarian cancer and her husband’s semen parameters were bordering on male factor infertility. This patient was therefore included in the study. The remaining five patients underwent a total of eight cycles of IVF and the data are presented below. Of note, only one of these patients underwent four successive cycles of IVF (case 3 below), whereas the remaining four patients each underwent only one cycle of IVF.

Patients

Case 1

A 31 year old woman, gravida 0, diagnosed with adenocarcinoma of the descending colon. Status: post-partial colectomy
with colorectal anastomosis. The patient anticipated undergoing radiotherapy and chemotherapy in the near future. She was referred to MGH for consideration of an IVF cycle with embryo cryopreservation. The partner’s semen analysis was within normal limits. Cycle day 3 hormone profile [follicle stimulating hormone (FSH) and oestradiol] was not obtained in view of the urgency of management. The patient underwent one IVF cycle. A total of 14 oocytes was retrieved. Three embryos were cryopreserved at the two-pronuclei (2PN) stage.

Case 2
A 31 year old woman, gravida 0, was diagnosed with stage 3 adenocarcinoma of the left lung with mediastinal metastases. Involvement of the left recurrent laryngeal nerve and cachexia were present at the time of diagnosis. After discussion with the oncologist, the couple decided to proceed with IVF and embryo cryopreservation prior to initiation of chemotherapy and radiotherapy. Basal day 3 FSH and oestradiol were not obtained in view of the urgency of management. The patient underwent one cycle of IVF; a total of 24 oocytes was retrieved and nine embryos were cryopreserved at 2 PN stage.

Case 3
A 29 year old woman, gravida 1 para 0, was diagnosed with adenocarcinoma of the cervix on cone biopsy following an abnormal Papanicolaou (PAP) smear. The surgical margins were involved on histology. Subsequent surveillance, including repeat PAP smears and endocervical curettage, colposcopic examination and random biopsies, did not show any residual malignancy. The patient was advised to undergo total hysterectomy as the definitive treatment. The couple was referred for discussion regarding options for potential preservation of fertility. In view of the negative surveillance, the couple decided to proceed with IVF and fresh embryo transfer and cryopreservation of supernumerary embryos. A tentative plan was made for the patient to undergo a total hysterectomy after delivery. The day 3 serum FSH was 11.4 IU/l and oestradiol was 52 pg/ml. The patient underwent an IVF cycle and a total of eight oocytes was retrieved. Five embryos were cryopreserved at the 2 PN stage. The patient subsequently underwent a total abdominal hysterectomy.

Case 4
A 28 year old woman, gravida 1 para 0, was diagnosed with squamous cell cervical carcinoma, stage 1B, grade II. The patient decided to defer the definitive treatment of radical hysterectomy and underwent a cycle of IVF aiming to cryopreserve the embryos. The couple anticipated utilizing a gestational carrier at a later date. There was no history of infertility, and her partner’s semen parameters were within normal limits. The day 3 serum FSH was 14.5 IU/l and oestradiol was 52 pg/ml. The patient underwent an IVF cycle and a total of eight oocytes was retrieved. Five embryos were cryopreserved at the 2 PN stage. The patient subsequently underwent a total abdominal hysterectomy.

In-vitro fertilization
IVF cycles employed a standard protocol using pituitary–ovarian suppression with gonadotrophin releasing hormone agonist [leuproline acetate, (LA); Tap Pharmaceuticals, Deerfield, IL, USA] initiated in the late luteal phase. Ovarian stimulation was achieved using human menopausal gonadotrophins. The ovarian response was monitored by serial ultrasound and serum oestradiol concentrations. Oocyte maturation was induced with 10 000 IU of human chorionic gonadotrophin (HCG) administered i.m., when at least three of the leading

### Table I. Comparison of IVF cycle parameters between patients with malignant disorders and cases of tubal infertility

<table>
<thead>
<tr>
<th>Parameters assessed</th>
<th>Malignancy cases (n = 5)</th>
<th>Tubal cases (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31 ± 2</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>Basal FSH IU/l</td>
<td>11 ± 2</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Basal oestradiol pg/ml</td>
<td>50 ± 2</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>Ampoules/cycle</td>
<td>30 ± 3 &lt;p&gt;</td>
<td>35 ± 3 &lt;p&gt;</td>
</tr>
<tr>
<td>Max. oestradiol pg/ml</td>
<td>1491 ± 300 &lt;p&gt;</td>
<td>2101 ± 154</td>
</tr>
<tr>
<td>Total oocytes/cycle %</td>
<td>13 ± 3</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Mature oocytes/cycle %</td>
<td>67</td>
<td>81*</td>
</tr>
<tr>
<td>Immature oocytes/cycle %</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Postmature oocytes/cycle %</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Quality I/II oocytes/cycle %</td>
<td>36</td>
<td>68*</td>
</tr>
<tr>
<td>Quality III oocytes/cycle %</td>
<td>64</td>
<td>32*</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>51 ± 0</td>
<td>82 ± 0*</td>
</tr>
<tr>
<td>Abnormal fertilization rate (%)</td>
<td>20 ± 0</td>
<td>18 ± 0</td>
</tr>
</tbody>
</table>

FSH = follicle stimulating hormone.
*Total of eight cycles, b total of 17 cycles.

Values are expressed as mean ± SEM and/or percentage as appropriate.
P* value < 0.05.
Malignancy and oocyte quality

follicles attained diameters of ≥16 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 35 h after the HCG injection. The oocytes were graded in terms of maturity according to published criteria based on the configuration of the cumulus–corona complex (Veeck et al., 1983). The quality of the oocytes was assessed using ×200 magnification under light microscope using an institutional grading system (Dr L. Leykin, personal communication, Massachusetts General Hospital). The following criteria were scrutinized: outline and regularity of the zona pellucida, size of the perivitelline space, darkness and/or granularity of the cytoplasm, presence of intracytoplasmic vacuoles and or inclusions. Three categories of oocyte quality were recognized; quality 1 oocytes had regular oolemma and zona pellucida and distinct cytoplasm; quality 2 oocytes showed some intracytoplasmic fragments defects or discoloration; quality 3 oocytes exhibited dark cytoplasmic defects, an irregular outline with membrane interruptions and signs of degeneration. The earliest signs of fertilization were assessed at 16–18 h post-insemination. Any number of pronuclei other than two was regarded as evidence of abnormal fertilization. Cryopreservation of embryos was undertaken at 2PN stage of development.

Statistical analysis
This was performed using SAS software package (SAS Institute, Cary, NC, USA). The data are expressed as mean ± SEM. A mixed effect model was utilized for data analysis to account for dependancy secondary to utilization of cycles from the same patient. Statistical significance was defined as P < 0.05.

Results
Table I describes a comparison of IVF cycles in the two groups in terms of response to ovarian stimulation and the outcome. The response of patients in the two groups was comparable in terms of the total number of oocytes retrieved per cycle. The percentage of mature oocytes retrieved per cycle was significantly higher in the control group (81 versus 67%, P = 0.009). The maximal serum oestradiol on the day of HCG administration was higher in the control group (2101 versus 1491 pg/ml, P = 0.09). A significantly higher percentage of quality I/II oocytes were recovered from patients in the control group compared to the study group (68 versus 36%, P = 0.004). The percentage of quality III oocytes retrieved per cycle was significantly higher in the study group compared to the controls (68 versus 36%, P = 0.047). The fertilization rate of oocytes of patients with malignant disorders was significantly poorer compared to the controls (51 versus 82%, P = 0.002). Considering only the mature oocytes, i.e. metaphase 1 and II oocytes, the malignancy group continued to exhibit impaired fertilization rates (69 versus 92%). The rate of abnormal fertilization (both triploidy and parthenogenetic activation) was marginally higher in the oocytes of patients with malignant disorders, compared to the controls (20 versus 18%); interestingly, the rate of 1P parthenogenetic activation of oocytes of patients with malignant disorders was twice that of the controls (6 versus 3%, not significant).

Discussion
Semen cryopreservation has been increasingly utilized as a method of preserving fertility potential for males diagnosed with malignant disorders, prior to their undergoing radiotherapy or chemotherapy. Poor semen quality parameters are seen in the pre-therapy semen in patients with unilateral testicular carcinoma, Hodgkin’s and non-Hodgkin’s lymphoma (Thachil et al., 1981; Thachil et al., 1981; Sanger et al., 1992; Botchan et al., 1997). Oligozoospermia, asthenozoospermia, as well as biopsy proven spermatogenetic arrest and Sertoli cell-only syndrome (Chapman et al., 1981; Thachil et al., 1981; Berthelsen and Skakkebaek, 1983) are recognized sequelae in men affected with neoplasms, despite one or both testes being uninvolved. The impairment in fertility potential appears independent of the extent of the disease (Hendry et al., 1983). Proposed adverse influences associated with the malignant process which could affect gametogenesis include metabolic derangements (Chapman et al., 1981), altered immunological responses (Meyers and Schilsky, 1992; Barr et al., 1993), psychosomatic stress (Chapman et al., 1981), raised scrotal temperature (Berthelsen and Skakkebaek, 1983) and hormone (HCG) elaboration (Berthelsen and Skakkebaek, 1983). A common genetic or environmental factor may be responsible for both altered gametogenesis and the predisposition to development of cancer (Berthelsen and Skakkebaek, 1983). There is no mention in the literature of a similar detrimental effect of neoplastic processes on the quality or behaviour of oocytes. Although there have been reports of successful pregnancies in patients with ovarian malignancy following IVF, no information is available regarding details on the quality or fertilization rate of the gametes (Mantzavinos et al., 1992; Einhorn et al., 1996).

In this small series of cases, we have observed a trend towards deterioration in the quality of oocytes retrieved from patients affected with malignant disorders. The higher percentage of immature oocytes per cycle, and the lower maximal levels of oestradiol in patients with malignancy when compared with tubal cases, appears notable and may suggest a subtle problem in maturation of oocyte cohort and steroidogenesis in cases with malignant processes. The significantly impaired fertilization rate of oocytes from patients suffering from a neoplastic process, using spermatozoa with normal parameters, further corroborates the impression of an adverse impact of the coexisting neoplastic disease on the biology of the oocytes.

Given the known association between the presence of malignancy in men and an adverse impact on semen parameters as discussed earlier, a similar effect on the female gametes is plausible. The negative influences of cancer on continuously dividing spermatozoa manifesting as oligoasthenozoospermia, may translate differently in females where the oocytes remain arrested in the diplotene stage of the first meiotic division until ovulation.

We have identified an adverse association between the existence of a neoplastic process and the quality and behaviour of oocytes. The significant reduction in oocyte quality in young women with no prior history of infertility and an impaired fertilization rate of mature oocytes in the absence of male
factor, appears striking. Although it is premature to establish a conclusion from the small cohort of patients presented, pooling of data from different IVF centres would provide a larger subpopulation for analysis.

References


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