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The possible association between *in vitro* fertilization treatments and cancer development

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The objective of this paper is to assess whether ovarian hyperstimulation and *in vitro* fertilization (IVF) are associated with increased risk of cancer development, using an historical cohort analysis of infertile women who attended the IVF unit, Lis Maternity Hospital Tel Aviv Medical Center, Tel Aviv, Israel. One thousand and 82 women participated in the IVF treatment program between 1984 and 1992. Cancer incidence rates were determined through the National Cancer Registry and were compared to the expected rates with respect to appropriate age and continent of birth. Twenty-one cases of cancer were observed as compared to 11 that were expected (SIR 1.91; 95% CI 1.18–2.91). When cancer cases that were diagnosed within one year of the IVF treatment were excluded from the analysis (SIR = 1.46; 95% CI 0.83–2.36), no significant excess risk of cancer was noted. We conclude that in this cohort of infertile women, the higher than expected cancer rate could not be attributed to IVF treatments. Special attention should be made to women who may be diagnosed with cancer during or shortly after IVF treatment.

KEYWORDS: cancer, infertility, *in vitro* fertilization, ovulation induction.

Over the last three decades a few follow-up studies and multiple case reports have discussed the safety of ovulation-inducing drugs and the risks associated with their use[1–6]. Some complications of ovulation-inducing therapies and their incidence are well established, such as ovarian hyperstimulation syndrome[7] and multiple pregnancies[8]. Ovulation-inducing drugs are widely used for ovarian follicular stimulation during *in vitro* fertilization (IVF) cycles. IVF treatment programs were initially designed for infertile women with mechanical infertility and no evidence of ovulation disturbances. Now, however, IVF treatment programs are used for treatment of all types of infertility.

A series of articles that suggested an association between the use of ovulation-inducing drugs and ovarian cancer led to renewed interest in the potential carcinogenic risks of these drugs[9–13]. Although the authors of those articles have been appropriately cautious in interpreting their results, the public perception of ovarian cancer and the risk associated with ovulation-inducing drugs caused widespread apprehension.

Only few cases of individual ovarian cancer have been described in women that participated in IVF programs[14–17]. In most of these cases the tumor was diagnosed shortly after the IVF treatment and developed very rapidly[18,19]. Even though these individual

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reports do not prove a relationship between IVF treatment and the development of ovarian cancer, they raise the possibility that ovarian stimulation or other factors like oocyte aspiration accelerate the growth of an existent tumor. In the only studies that assessed the incidence of cancer in cohorts of women that were referred to IVF units, no overall increased risks for ovarian and breast cancer were found[20–22].

Based on these data, the aim of the present study was to evaluate the cancer incidence in a cohort of infertile women treated with IVF, with special attention to women who were diagnosed with cancer within the first year of the IVF treatment.

Patients and methods

Study cohort

The study cohort included women who were treated for infertility between 1984 through 1992 at the IVF unit, Lis Maternity Hospital, Tel Aviv Medical Center, Tel Aviv, Israel. Patients were identified by a meticulous review of the medical records of the unit since it was founded. Included in the study cohort were patients attending the IVF unit who received at least one treatment cycle. We obtained data regarding demographic characteristics (age, continent of birth) in addition to information regarding the type of infertility, diagnosis of infertility, number of treatment cycles and treatment outcome, using a preconstructed questionnaire.

The study was approved by the Institutional Review Board (IRB) – number 5909/845 dated December 1995.

Cancer identification

The study cohort computerized file was linked to the Israel National Cancer Registry to identify cancer cases through December 1996. The Cancer Registry was established in 1960 and maintains data on all malignancies, including borderline and some benign tumors (primarily central nervous system) in Israel. The Registry receives notification of all malignancies from hospital discharge reports, as well as from oncology and pathology departments throughout the country. Depending on the cancer site, cancer ascertainment during internal verifications was found to be 90–95% complete[23].

The records were linked by computer matching of patients' identification numbers, names, and demographic variables with the Cancer Registry data file.

For all patient matches, the Cancer Registry provided cancer diagnosis, coded according to the International Classification of Diseases, Ninth Revision, along with date and place of diagnosis. Diagnoses were verified by reviewing the original histopathologic report for each case.

Cancer cases that were diagnosed within one year of the initiation of IVF treatment were then excluded from the analyses, to allow a minimal latency period between exposure and cancer development, and are described separately.

Statistical analysis

Standardized incidence ratios (SIR) were computed as a ratio of observed to expected cancers, with estimated 95% confidence intervals (CI)[24]. Person years at risk were calculated from the date of first treatment until date of last follow-up (31 December 1996, the last update of the Cancer Registry at the time) or until date of diagnosis of malignancy.

Expected numbers of cancer were computed based on age, sex, continent of birth, and year-specific national cancer incidence rates.

Results

The study cohort included 1082 women, who contributed 7002 person-years of follow-up (mean years of follow-up 6.5 ± 2.2). The mean age at the first IVF treatment was 32.7 ± 4.8 and the mean age at the end of follow-up (12/31/96) was 38.7 ± 5.2.

When the study cohort was linked to the Israeli Cancer Registry of 1996, we observed 21 cases of cancer as compared to 11 that were expected (SIR 1.91; 95% CI 1.18–2.91) (Table 1). These included five cases of breast cancer, compared to 4.88 that were expected (SIR 1.02; 95% CI 0.33–2.39), three cases of ovarian cancer as compared to 0.60 expected (SIR 5.0; 95% CI 1.02–14.6), and three cases of cervical cancer

Table 1. Observed and expected cancer cases in a cohort of women treated with IVF ($n = 1082$)

	Observed	Expected	SIR[a]	95% CI[b]
All sites	21	11	1.91	1.18–2.91
Breast	5	4.88	1.02	0.33–2.39
Ovary	3	0.60	5.0	1.02–14.6
Cervix	3	0.65	4.61	0.93–13.49
Other[c]	10	4.87	2.05	0.98–3.78

[a]SIR = Standardized Incidence Ratio.
[b]95% CI = 95% Confidence Interval.
[c]Other: melanoma (2), Hodgkin's lymphoma (2), multiple myeloma, angiosarcoma, brain, sarcoma, rectum, vulva.

Table 2. Observed and expected cancer cases in the cohort of infertile women treated with IVF excluding cancer cases that were diagnosed within one year of the IVF treatment

	Observed	Expected	SIR[a]	95% CI[b]
All sites	16	11	1.46	0.83–2.36
Breast	4	4.88	0.82	0.22–2.10
Ovary	1	0.60	1.67	0.02–9.27
Cervix	3	0.65	4.62	0.93–13.49
Other[c]	8	4.87	1.64	0.71–3.24

[a]SIR = Standardized Incidence Ratio.
[b]95% CI = 95% Confidence Interval.
[c]Other: melanoma (2), Hodgkin's lymphoma (2), multiple myeloma, angiosarcoma, brain, sarcoma.

as compared to 0.65 expected (SIR = 4.61; 95% CI 0.93–13.49).

When the cancer cases who were diagnosed within one year of the initiation of the IVF treatment were excluded from the analysis (Table 2), we observed only 16 cancer cases (SIR = 1.46; 95% CI 0.83–2.36). Ovarian cancer risk diminished (SIR = 1.67; 95% CI 0.02–9.27) with the exclusion of diagnosis during the first year, while cervical cancer was still in excess, although not significantly (SIR = 4.62; 95% CI 0.93–13.49). The observed and expected cancer cases according to continent of birth, type of infertility, diagnosis of infertility, number of IVF cycles and the treatment outcome, were compared (Table 3), revealing no significant increased risk for cancer development.

Two of three ovarian cancer cases were diagnosed within the first year of treatment with IVF: a 24-year-old patient and a 40-year-old patient both presented with primary infertility and diagnosed with borderline ovarian malignancy during the first IVF treatment. Both patients were treated conservatively for the borderline tumor and subsequently delivered a healthy child following additional IVF treatments.

Discussion

During IVF treatment multiple folliculogenesis is achieved using intensive ovulation induction treatment. Oocytes are then retrieved through puncture of the ovarian follicles. Both interventions, ovulation induction and ovarian puncture, were associated, in some studies, with ovarian cancer development[11,12,15,18], but not in others[25–27]. In addition, infertility itself has been regarded as a risk factor for both ovarian and breast cancer[28]. In the only studies that assessed cancer risk among patients attending IVF programs[20–22], it was found that for breast and ovarian cancer, the incidence was no greater than expected.

IVF treatment programs were primarily designed for infertile women suffering from tubal infertility. Tubal infertility may be caused by pelvic adhesions or lack of tubal patency as a result of previous pelvic infection. Cervical cancer may share the same

Table 3. Observed and expected all-site cancer by continent of birth, type of infertility, diagnosis of infertility, number of IVF cycles and treatment outcome excluding cancer diagnosis during the first year of follow-up

Characteristic	No. of women	Observed	Expected	SIR[a]	95% CI[b]
Continent of birth					
Israel	789	10	7.90	1.27	0.61–2.33
Asia-Africa	155	3	1.44	2.08	0.42–6.09
Europe-America	138	3	1.68	1.79	0.36–5.22
Type of infertility					
Primary	433	7	3.90	1.80	0.72–3.70
Secondary	649	9	7.10	1.27	0.58–2.41
Diagnosis of infertility					
Mechanical	456	8	5.25	1.52	0.66–3.00
Hormonal	262	3	2.17	1.38	0.28–4.04
Male	326	4	3.30	1.21	0.33–3.10
Unexplained	38	1	0.29	3.45	0.05–19.19
Number of IVF cycles					
1–2	650	10	6.05	1.65	0.79–3.04
3–5	323	6	3.61	1.66	0.61–3.62
6+	109	0	1.35	0	0–1.1
Treatment outcome:					
Pregnancy	265	5	2.80	1.79	0.58–4.17
No pregnancy	817	11	8.22	1.34	0.67–2.39

[a]SIR = Standardized Incidence Ratio.
[b]95% CI = 95% Confidence Interval.

infectious etiology[29]. We observed a higher than expected rate of cervical cancer although without statistical significance in the analysis of all cancer cases and in the analysis excluding cancer cases that were diagnosed during the first year of IVF treatment.

Numerous cancer cases were diagnosed within the first year of IVF treatment. This finding is in accordance with other studies[21,22] that showed a higher than expected incidence of cancer within 12 months of exposure to fertility drugs with IVF. Cancer development, and as a consequence cancer existence, might not be caused by the ovulation-induction treatment, but rather provoked by the hormonal changes enhanced by it. In addition, a cohort of IVF-treated patients is unique, since each and every patient is closely followed before, during, and after each cycle. Close medical surveillance including routine ultrasonographic tests and pap smears may contribute to the early detection of gynecological malignancies, especially ovarian and cervical cancer.

We observed two cases of women who were diagnosed with borderline ovarian tumors during their first IVF treatments. Conservative treatment for borderline tumors is well accepted, yielding excellent prognosis[30–32]. One of the concerns regarding diagnosis of ovarian malignancy during infertility treatments is the safety to continue these treatments following conservative surgery. Beiner *et al*.[33] followed women after conservative management of borderline ovarian tumors and concluded that ovulation induction may be safely considered for these patients. Recurrence of the tumor in two of seven patients remained histologically borderline.

In conclusion, the higher than expected cancer rate in women undergoing IVF treatments was diminished with the exclusion of cancer cases that were diagnosed during or shortly after these treatments. Careful follow-up of women attending IVF may allow better and earlier diagnosis of already existing malignancies, especially of the ovary.

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