The Risk for Cancer among Children of Women Who Underwent In Vitro Fertilization

Liat Lerner-Geva, M.D.[1]
Amos Toren, M.D.[2]
Angela Chetrit, M.Sc.[1]
Baruch Modan, M.D., Dr.P.H.[1]
Mathilda Mandel, M.D.[2]
Gideon Rechavi, M.D., Ph.D.[2]
Jehoshuah Dor, M.D.[3]

[1] Department of Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, Israel.

[2] Department of Pediatric Hemato/Oncology, Chaim Sheba Medical Center, Tel Hashomer, Israel.

[3] In-Vitro Fertilization Unit, Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Israel.

Supported in part by Grant Number 960570 of The Eisen Foundation Center-Biology Research Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Address for reprints: Liat Lerner-Geva, M.D., Department of Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, 52621, Israel.

Received November 19, 1999; revision received February 15, 2000; accepted March 3, 2000.

BACKGROUND. The possible association between ovarian carcinoma and ovulation-inducing drugs has led to renewed interest in the potential carcinogenic risks of these drugs. In vitro fertilization (IVF) has been linked to multiple pregnancies and possibly congenital malformations. However, to the authors' knowledge the association between IVF and pediatric cancer has been described only in sporadic case reports. The aim of this study was to assess the incidence rate of pediatric cancer among a cohort of children born after IVF.

METHODS. A historic prospective study based on a cohort of 332 children from 1254 women who underwent IVF treatment between 1981–1994 was performed. Medical files were reviewed and names were linked to the National Population and Cancer Registries. Pediatric cancer incidence rates were compared with the expected age-adjusted rates of the general population during the respective time period.

RESULTS. No cancer cases were observed among the study cohort with respect to 1.7 cases that were expected.

CONCLUSIONS. Because the small cohort analysis in the current study lacked the necessary power to reach definite conclusions, larger prospective studies are needed to assess the potential carcinogenic effect on children born after ovulation induction and IVF. ***Cancer*** **2000;88:2845–7.** © *2000 American Cancer Society.*

KEYWORDS: in vitro fertilization, infertility, pediatric cancer, neuroblastoma.

Over the last 30 years, only a few follow-up studies and multiple case reports have evaluated the safety of ovulation induction drugs and the risks associated with their use.[1-3] These included multiple pregnancies,[3] a slightly higher than expected rate of congenital malformations,[4-6] and potential carcinogenic effects to the women treated.[7-10]

To our knowledge, pediatric tumors among children who were born after ovulation induction treatment and/or in vitro fertilization (IVF) have been described only as sporadic case reports.[11-17] The aim of the current study was to assess the incidence rate of pediatric cancer among a cohort of children born after IVF.

MATERIALS AND METHODS

The proposed study is a historic prospective cohort analysis. The study cohort included all children born after IVF treatment at the IVF unit of the Chaim Sheba Medical Center between 1981 and 1994. This unit is the first IVF unit to be established in Israel. The Chaim Sheba Medical Center is one of the largest tertiary hospitals in the country.

The medical records of all 1254 women who attended the IVF unit since its foundation were reviewed to determine the number of pregnancies and live births. In addition, information regarding the number of IVF cycles, type of medication, and type of procedure also were

TABLE 1
Selected Characteristics of Women Who Underwent IVF Treatment and Their Children

No. of women	1254
Last day of follow-up	12/31/94
Women-years of follow-up	5343
Mean years of follow-up	4.3 ± 2.8
Mean age at first IVF treatment (yrs)	33.4 ± 5.0
Mean age at the end of follow-up (yrs)	37.2 ± 5.4
No. of children	332
Mean age of children at the end of follow-up (yrs)	5.2 ± 2.8
Gender	
Male	165 (49.7%)
Female	167 (50.3%)

IVF: in vitro fertilization.

abstracted using a constructed questionnaire. The identification number of each child then was verified with the aid of the National Population Registry.

To evaluate the cancer incidence rate among the children, the study cohort file was linked to The Israeli Cancer Registry, which was updated to December 1994. The Cancer Registry was established in 1960 and maintains data regarding all malignancies (excluding nonmelanoma skin cancer) and some benign tumors (primarily those of the central nervous system) in Israel.

The expected number of cancer cases were computed by applying patient age, patient gender, and year of diagnosis to year specific national cancer incidence rates between 1981–1994.

The study was approved by the Institutional Review Board of the Chaim Sheba Medical Center.

RESULTS

Table 1 presents the characteristics of all women who attended the IVF unit since its foundation. During the study period 332 children were born after IVF (Table 1), thus contributing 710 person-years of follow-up. Linkage with the Israeli Cancer Registry revealed no cancer cases among these children compared with the 1.7 cancer cases that were expected on the basis of patient age, patient gender, and year of diagnosis.

DISCUSSION

To our knowledge the association between pediatric tumors and IVF has not been assessed in great detail. White et al.[11] reported three cases of neuroectodermal tumors (two neuroblastomas and one medulloblastoma) in children who were born after IVF between 1985 and 1987. In addition, two other tumors (one neuroblastoma and one supratentorial primitive neuroectodermal tumor) were found among children conceived during the same period after ovulation induction with clomiphene and artificial insemination. Toren et al.[12] described two children who developed hepatoblastoma and clear cell sarcoma of the kidney after uneventful pregnancies induced by IVF. One additional report described the possible association between maternal use of gonadotropins and the development of hepatoblastoma in offspring.[13]

Kobayashi et al.[14] reviewed the mother's drug history before pregnancy in 6236 cases of childhood malignancies diagnosed between 1985 and 1989. Nine cases (four neuroblastomas, three malignant lymphomas, and two reticuloendothelial tumors) were identified in children born to mothers who underwent ovulation induction.

Maternal use of alcohol or diuretics during pregnancy and exposure to sex hormones up to 3 months prior to or during pregnancy have been reported to elevate the risk for neuroblastoma significantly.[15-17]

Recently, Doyle et al.[18] investigated the cancer incidence rate among 2507 living children born between 1978 and 1991 after the use of assisted reproductive technology. Two tumors were identified compared with the expected number of 3.5 tumors.

Hormonal exposures during pregnancy may cause both morphologic and carcinogenic changes similar to those observed in mutant mice.[19] Because childhood cancer is a rare disease, a sample size of at least 20,000 children would be required to observe doubling of the risk of cancer in the cohort. However, children born after IVF or other assisted reproductive technologies should be followed to establish a large enough cohort that will enable assessment of the long term safety of these procedures.

REFERENCES

1. Ron E, Lunenfeld B, Menczer J, Blumstein Z, Katz L, Oelsner G, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol* 1987;125:780–90.
2. Blankstein J, Shalev J, Saadon T, Kukia EE, Rabinovici J, Pariente C, et al. Ovarian hyperstimulation syndrome: prediction by number and size of preovulatory ovarian follicles. *Fertil Steril* 1987;47:597–602.
3. Hack M, Brish M, Serr DM, Insler V, Lunenfeld B. Outcome of pregnancy after induced ovulation. Follow-up of pregnancies and children born after gonadotropin therapy. *JAMA* 1970;211:791–7.
4. Lancaster PA. Congenital malformations after in vitro fertilization. *Lancet* 1987;2:1392–3.
5. Shoham Z, Zosmer A, Insler V. Early miscarriage and fetal malformations after induction of ovulation, in vitro fertilization, and gamete intrafallopian transfer. *Fertil Steril* 1991; 55:1–11.
6. Czeizel A. Ovulation induction and neural tube defects. *Lancet* 1989;2:167.

7. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 1992;136:1184–203.
8. Harris R, Whittemore AS, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 1992;136:1204–11.
9. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331:771–6.
10. Shushan A, Paltiel O, Ischovich J, Elchalal U, Peretz T, Schenker JG. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil Steril* 1996;65:13–8.
11. White L, Giri N, Vowels MR, Lancaster PA. Neuroectodermal tumours in children born after assisted conception. *Lancet* 1990;336:1577.
12. Toren A, Sharon N, Mandel M, Neumann Y, Kenet G, Kaplinsky C, et al. Two embryonal cancers after in vitro fertilization. *Cancer* 1995;76:2372–4.
13. Melamed I, Bujanover Y, Hammer J, Spirer Z. Hepatoblastoma in an infant born to a mother after hormonal treatment for sterility. *N Engl J Med* 1982;307:820.
14. Kobayashi N, Matsui I, Tanimura M, Nagahara N, Akatsuka J, Hirayama T, et al. Childhood neuroectodermal tumours and malignant lymphoma after maternal ovulation induction. *Lancet* 1991;338:955.
15. Kramer S, Ward E, Meadows AT, Malone KE. Medical and drug risk factors associated with neuroblastoma: a case-control study. *J Natl Cancer Inst* 1987;78:797–804.
16. Michalek AM, Buck GM, Nasca PC, Freedman AN, Baptiste MS, Mahoney MC. Gravid health status, medication use, and risk of neuroblastoma. *Am J Epidemiol* 1996;143:996–1001.
17. Mandel M, Toren A, Rechavi G, Dor J, Ben-Bassat I, Neumann Y. Hormonal treatment in pregnancy: a possible risk factor for neuroblastoma. *Med Pediatr Oncol* 1994;23:133–5.
18. Doyle P, Burach KJ, Beral V, Draper GJ. Cancer incidence in children conceived with assisted reproduction technology. *Lancet* 1998;352:452–3.
19. Miller C, Degenhardt K, Sassoon DA. Fetal exposure to DES results in de-regulation of Wnt7a during uterine morphogenesis. *Nat Genet* 1998;20:228–30.