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Paternal exposure to chemotherapy

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How many environmental agents with mutagenic properties have been found to increase the rate of genetic disorders in humans (Brent, 2005)? The answer: None. Infertility is the only established outcome following certain paternal exposures. For example, clinicians were never able to document an increase of genetic disease in the offspring of male atomic bomb survivors. Unfortunately, the topic of male-mediated teratogenesis has not been thoroughly studied and the available research is inadequate to rule out any increased risk for adverse pregnancy outcome. Because an increase in genetic disease would be at a much lower magnitude than an increase in congenital anomalies following a maternal teratogen exposure, further studies with very large populations are still needed.

The maturation of sperm takes approximately 3 months. Mutations are more likely to occur in the actively reproducing cells like spermatogonia and are less likely to occur in female oocytes (Davis et al., 1992). Therefore, preconception exposures are a greater theoretical concern for males. There are several mechanisms by which paternal exposure could theoretically result in reduced fertility or exert teratogenic effects on the fetus:

- Medicines could exert a direct effect on sperm causing anatomic abnormalities with reduced sperm motility or function or even induce chromosomal anomalies or new gene mutations
- Medicines could interfere with the pituitary-hypothalamic function (decrease testosterone or libido) and subsequently reduce fertility
- Medicines could lead to direct exposure of the developing fetus through contaminated seminal fluid via unprotected intercourse

This newsletter will focus on studies addressing the first mechanism. Since ionizing radiation and antineoplastic drugs are biologically plausible agents for inducing mutations in sperm, possible paternal teratogenicity with various cancer treatments will be discussed.

Survivors of childhood cancer

There is concern for long lasting effects in the sperm of male survivors since cancer therapies are targeted to induce cell damage. These concerns are further prompted by the presence of higher rates of chromosomal abnormalities in sperm of some successfully treated patients (Martin et al., 1999; Frias et al., 2003).

However, while male infertility has been documented with germ cell loss due to radiation or antineoplastic drug treatment, an increased frequency of adverse pregnancy outcomes has not been documented in the offspring of survivors of childhood cancer.

For example, the National Cancer Institute collaborated with three hospital-based cancer registries and two population based registries to evaluate childhood cancer (diagnosis < age 20 years) survivors' pregnancy outcomes. There were no differences in the rates of cytogenetic diseases, single gene defects,

or simple malformations in the offspring when compared with sibling controls (Byrne et al., 1998). Genetic disease occurred in 3.4% of 2,198 offspring of survivors, compared with 3.1% of 4,544 offspring of controls ($P = 0.3$; not significant).

Several other large population studies report the same findings. This includes the Childhood Cancer Survivor Study, a multi-institutional retrospective cohort study started in 1994. This database was used to review 4,214 livebirths from childhood cancer survivors. Again there were no significant differences between the two study groups. The total rate of cytogenetic abnormalities, single gene defects, and malformations was 3.7% in the survivor offspring and 4.1% in the siblings (Boice et al., 2003). Additionally, when cancers with a known single gene inheritance were excluded, no increase in offspring childhood cancer was seen.

A study conducted using the Danish Cancer Registry of childhood cancer survivors compared the pregnancy outcomes to their unaffected siblings (Winther et al., 2004). The cancer survivor group had 2,630 live births from 4,676 childhood cancer survivors. There was no difference in the rate of chromosomal abnormalities between the groups.

It should be noted that a limitation of these studies is that the individual treatment regimens have not been evaluated separately. There may be subtle long-term differences between treatment types that are not detectable by grouping all survivors together (Wyrobek et al., 2005).

Testicular Cancer

Testicular cancer and Hodgkin's disease represent two of the most common cancers in young males.

Several researchers have noted oligospermia in patients with testicular cancer even prior to treatment (Gandini et al., 2003). Bahadur et al. (2005) analyzed semen quality in 314 males before and after gonadotoxic therapy over a 26 year period. The testicular cancer group ($N=102$) had the lowest level of sperm concentration of all disease categories before treatment. Following cytotoxic treatment, this group had the lowest level of azoospermia (12%) but the highest level of oligospermia (38%). The rates of normal sperm counts after treatment (50%), however, were also the highest of all the cancer types evaluated.

Testicular cancer is commonly treated with the polychemotherapy regimen bleomycin, etoposide and cisplatin (BEP). Recovery of sperm function following treatment has not been predictable. While azoospermia following BEP occurred initially in all patients in the Bahadur et al. study, 50-80% of men recovered some level of motile sperm 2-5 years following treatment.

Petersen et al. (1994) found a dose-dependent effect of cisplatin and impaired spermatogenesis by analyzing sperm samples in 33 patients treated with a conventional dose of BEP and 21 patients treated with high dose BEP. The conventionally treated group had a higher sperm count (19% azoospermic) than the high dose group (47% azoospermic) following treatment.

Chromosomal abnormalities in sperm were found to be increased up to one year post treatment for testicular cancer (Martin et al., 1999) but not increased 2-13 years after BEP chemotherapy (Martin, 1998). Bahadur et al. (2005) reported that waiting 1.5-2 years may allow for a sufficient turn over of cells to expel any mutagenic effect but then recommended waiting a more practical 6-12 months prior to attempting conception.

There is limited information on the pregnancy outcomes of fathers treated specifically for testicular cancer. The majority of research has focused on issues of fertility and sperm quality.

Hartmann et al. (1999) distributed a questionnaire on fertility and sexual function to patients treated for testicular cancer. Twenty-one out of the 40 couples (53%) that wanted children were able to achieve pregnancy at a median time of 54 months (3-108 months) after treatment ended. Although the authors

reported no major birth defects, one child reportedly had cryptorchidism and one had hip dysplasia. Normal development in all children was reported up to a median age of 62 months (1-180 months). In another study, 15 patients treated for testicular cancer by polychemotherapy fathered 20 children with no congenital malformations (van der Kolk, et al., 1990). The mean time from the end of treatment to conception was 39 months (9-82 months). Development of the children was reportedly normal in the children age 3 months-6 years old.

Hodgkin's Disease

Akin to testicular cancer, several researchers have noted that 30-65% of men have oligospermia or other alterations of semen quality pre-treatment with Hodgkin's disease (Gandini et al., 2003).

Sperm from men treated for Hodgkin's disease with Novantrone, Oncovin, Vinblastine and Prednisone (NOVP) chemotherapy was examined for frequency of chromosomal abnormalities. Sperm was collected before treatment, shortly after treatment, and 1-2 years after treatment. Researchers examined the chromosomes that are involved in the most common aneuploid syndromes, chromosomes 18, 21, X, and Y. They found a 2-14 fold elevation in abnormal chromosome number in the sample collected shortly after treatment but did not find an increase 1-2 years post treatment (Frias et al., 2003). A similar study found that sperm aneuploid levels were transient and returned to pre-treatment levels approximately 100 days after the completion of NOVP chemotherapy (Robbins et al., 1997).

Swerdlow et al. (1996) found no excess of stillbirths, low birthweight, chromosome abnormalities, or congenital malformations, and no cancers in 49 offspring of women and men previously treated for Hodgkin's disease. Sixteen of the children were conceived after chemotherapy, 25 after radiotherapy, and 8 after a combined modality therapy. Sixteen of the children had been conceived less than 5 years after treatment. Additionally, there were no major or minor birth defects among 26 offspring of male patients treated for Hodgkin's disease (Aisner et al., 1993). The median treatment free interval at the birth of the child was 8 years (1.25-16).

The previous studies with testicular cancer and Hodgkin's disease illustrate that men should not be counseled that infertility is a definite result of treatment. Cryopreservation of semen prior to treatment is also recommended. Depending on the post thaw semen quality, patients can be advised whether additional fertility assistance procedures should be utilized. A follow-up study on 29 patients did not find a difference in successful pregnancy based on the malignancy type which led to the sperm cryopreservation (Agarwal et al., 2004). If cryopreservation is not performed and normal fertility does not resume, in-vitro fertilization with single sperm (ICSI) could be attempted post treatment.

Methotrexate

Methotrexate interferes with DNA synthesis and cellular replication. In this way it is effective against malignant cells and cellular proliferation in cancerous tissues. Methotrexate is becoming increasingly prescribed for rheumatoid arthritis and psoriasis. The exposure of fetuses to methotrexate when ingesting directly by women increases the chance for birth defects when taken during the first trimester (and particularly between 8-10 weeks gestation) when the limbs and skull are still forming.

Oligospermia has been seen in individuals taking methotrexate as part of cancer treatment. Whether low dose monotherapy methotrexate taken for rheumatoid arthritis or psoriasis reduces male fertility is still not clear. Reversible sexual dysfunction was reported in three men with rheumatoid arthritis who were treated with weekly doses of 12.5 mg methotrexate. However, two case series published in the 1970s found no change in sperm concentration, motility or quality in 22 men treated with methotrexate for psoriasis (French and Koren, 2003).

While specific studies have not been performed, there are no reports of genetic disease following paternal methotrexate exposure. Therefore, the concern remains theoretical. 6-Mercaptopurine (6-MP)

Azathioprine (Imuran) is metabolized to 6-mercaptopurine (6-MP). Both 6-MP and azathioprine appear to work by inhibition of nucleic acid synthesis. 6-MP has been used as a chemotherapeutic agent and in some transplant recipients. These agents are now commonly prescribed to treat inflammatory bowel disease (IBD). Long-term 6-MP treatment in male mice did not impair sperm production or sperm morphology or increase congenital anomalies in offspring (Ligumsky et al., 2005). However, a significantly high rate of embryonic resorption was observed, which the authors postulated could indicate occult sperm damage.

Semen was collected from 23 patients with IBD that had been on azathioprine treatment for at least 3 months. This small study showed no negative association between azathioprine therapy and semen quality (Dejaco et al., 2001). Human paternal studies have yielded conflicting findings in regards to adverse pregnancy outcomes. Studies that have suggested an increased risk for congenital anomalies have been criticized for their small sample size, methodology, and timing contradictions.

Congenital anomalies were seen in 3.3% of 273 pregnancies and 4.8% of 42 pregnancies in male renal or cardiac transplant recipients taking azathioprine (Polifka et al., 2004). These rates are similar to the baseline risk of congenital malformation in the general population. 6-MP use was analyzed in relation to birth outcomes in fathers with IBD. Thirteen pregnancies that had been conceived within 3 months of 6-MP use were compared to a control group consisted of 37 pregnancies that had been conceived at least 3 months after 6-MP use. There were two birth defects and two miscarriages in the infants whose fathers were using 6-MP at the time of conception, and no birth defects and one miscarriage in the group with more remote use.

Based on the better outcomes with the remote use, the authors suggested that males should stop this medicine and wait three months before attempting to conceive. (Rajapakse et al., 2000). However, the rate of birth defects and miscarriage in the control group were lower than expected. Due to the small sample, the results may reflect chance.

A second study in 2003 found no increased risk of birth defects. The authors identified 37 pregnancies in which men were exposed to 25-175 mg 6-MP at the time of conception, 44 pregnancies in which men stopped taking 6-MP at various times prior to conception, and 73 pregnancies in which there was no exposure to 6-MP (Francella et al., 2003). There was one birth defect in the group with exposure at conception, three birth defects in the group with exposure prior to conception (10 months earlier, 3 years earlier, and 4 years earlier), and two birth defects in the group with no exposure. These authors concluded that there is no need for males to discontinue the medicine.

A third study suggested an increased risk for congenital anomalies. Norgard et al. (2004) used a Denmark population database to identify 54 children fathered by men who had filled a prescription for either 6-MP or azathioprine at any point before conception. Four of the 54 children (7.4%) had congenital abnormalities, compared with 2,334 of the 57,195 children (4.1%) fathered by men who had not filled such a prescription. The congenital abnormalities in the exposed group included polysyndactyly; esophageal atresia; hydronephrosis with megaloureter; and a ventricular septal defect. There was no known underlying single gene or chromosomal abnormality.

Additionally, the odds ratio was not statistically significant between the exposed and control group outcomes. Also, the timing of the last prescription for the drugs and conception among the 4 cases with abnormalities ranged from 9 months to 38 months, also casting doubt on the causative effect of the medications upon subsequent birth defects (Cohen, 2004). In fact, none of the 19 pregnancies for which prescriptions for either drug were filled within 3 months of conception resulted in congenital abnormalities.

The question of an increased risk of congenital abnormalities in pregnancies fathered by men on azathioprine or 6-MP based on the available studies should be viewed with skepticism and the benefit

to male health kept in mind (Cohen, 2004). Additional studies on larger populations are still needed.

Summary

All men requiring chemotherapy should be offered cryopreservation of sperm before cancer treatment. Individuals receiving cancer treatment that can affect male fertility and sperm quality should be counseled about appropriate contraception for the duration of treatment since infertility cannot be assumed. It is advisable that couples wait at least 3 months (the time period of one complete spermatogenesis cycle) to one year before attempting conception. Banked sperm may reduce the risk of genetic abnormalities that theoretically could be induced in the stem germ/spermatogonia cells and thus never be eliminated from the mature sperm cells. However, couples should be counseled that there is no evidence of an increased risk for genetic disease in the offspring and that a waiting period is based only on theoretical concerns.

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