**Childhood Cancer Survivor Study**
**Analysis Concept Proposal (#10-07)—updated May 23, 2010; updated June 13, 2010**

**1. Study Title:** Outcomes of Pregnancies Exposed to Cancer Therapy: A Report from the Childhood Cancer Survivor Study

**2. Working Group and Investigators:**
This proposed publication will be within the Chronic Disease Working Group.


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**3. Background and Rationale:**

According to the 2000 US census, approximately 62 million females of childbearing age reside in the United States (US Department of Commerce, 2002). Among these women, cancer is the leading medical cause of death for those aged between 15 and 34 and the leading cause of death for those between 35 and 45 years (Anderson & Smith, 2003). For women between 15 and 44 years of age, the National Cancer Institute estimates that more than 1 in 1,000 women are likely to be diagnosed with cancer each year (National Cancer Institute, 2004). Based on these estimates, approximately 62,000 women of child-bearing age can be expected to be diagnosed with cancer in any given year if the events are independent, which they obviously are not. Given the prevalence of cancer during the reproductive years, the association of cancer and pregnancy is inevitable.

Though relatively uncommon, the co-incidence of pregnancy and cancer can pose a significant clinical dilemma (Orr & Shingleton, 1983; Wallace, Wiegrand & Warren, 1997). Initially, the process of diagnosing and treating cancer may be so focused that a pregnancy is overlooked. Consequently, symptoms indicative of pregnancy onset can be misattributed either to the disease state or its subsequent treatment, possibly delaying the identification of a pregnancy. But, the converse is possible: cancer will be diagnosed during pregnancy as a consequence of the overall increase of medical attention directed toward maintaining a healthy pregnancy.

Once simultaneous pregnancy and cancer is recognized, difficult choices follow. While neither condition significantly impacts the other (Merkel, 1996), the *treatment* of cancer can have side effects (Orr & Shingleton, 1983), including the potential for therapy to adversely affect pregnancy outcome. By design, most cancer treatments are targeted to interfere with the synthesis of DNA in rapidly dividing tissues, such as cancers, embryos and fetuses. Ionizing radiation and most cancer drugs are known or suspected to produce teratogenic effects in offspring (Bitran & Roth, 1976; Doll, Ringenberg & Yarbro, 1988; Shepard & Lemire, 2004; Sorosky, Sood & Buekers, 1997). Because of these potential risks, chemotherapeutic drugs have been rated by the US Food and Drug Administration as Pregnancy Category X, which states:

> *Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.*

Therefore, the standard recommendation for management has been elective termination of the pregnancy. This option is unambiguous and simple, however, it is also unacceptable to many women for a variety of reasons. Another possible solution is to postpone cancer treatment until after delivery. Given the profound and life-threatening consequences associated with untreated cancer, physicians and patients are often reluctant to delay treatment. The difficulty of choosing the most appropriate treatment regimen would be significantly eased if authoritative information on the use of specific chemotherapeutic agents at clearly defined stages of pregnancy were readily available.

However, the traditional avenues of cancer research have not well addressed this issue. Basic research using animal models, while indispensable to the identification and assessment of cancer and innovative treatments for them, cannot overcome the criticism that embryonic and fetal effects may differ among species. Classic analytical epidemiology, such as case-control studies or cohorts, is likewise impossible. While the most accurate pharmacologic data usually come from large, double-blind, placebo-controlled, randomized clinical trials, these types of studies are not appropriate for this rare patient population, due to ethical concerns. To date, most published research findings have either been individual case studies or small case series (Bergstrom & Altman, 1998; Grendys & Barnes, 1995). While clinically noteworthy, these studies do not lend themselves well to broad-based clinical application. The most useful data for physicians, counselors, and other health professionals are likely to come from comprehensive research efforts aimed at collecting and summarizing outcome data on as many individuals diagnosed and treated for cancer while pregnant as possible, with no bias by prior knowledge of outcome.

This work was begun in 1984 at the National Cancer Institute. Dr. John Mulvihill developed the *Registry of Pregnancies Exposed to Chemotherapeutic Agents* in an effort to document, collate, and summarize data presented in published case studies, reports submitted by physicians and counselors, and direct correspondence with current and remitted cancer patients, concerning the effects of chemotherapy on the developing fetus (Hamm, Sandefer, Hassed & Mulvihill, 2009; Hassed, Mumm, Reed, Kohl, & Mulvihill, 2003; Mulvihill & Stewart, 1986). Preliminary findings based on analysis done on this dataset are presented in **Tables 1** and **2** below. Currently, this Access dataset is maintained at the University of Oklahoma Health Sciences Center and data collection is ongoing. A University of Oklahoma IRB approval is in place.

This proposal seeks to broaden the existing data collection strategies by including relevant data captured by the Childhood Cancer Survivors Study. A preliminary search of this dataset by statistician John A. Whitton indicates that some potentially useful data are available. See **Table 3** below for details; this analysis will be rerun to assure cases exposed to radiotherapy are also included. Inclusion of the CCSS cohort represents a rare opportunity to assemble a case series that is not based entirely on cases whose outcome is known, whether normal or not. Subject accrual through this database will help to minimize the impact of ascertainment bias that so often plagues case reports and small case series.

**Table 1:** Results Based on review of 720 Pregnancies

- 667 abstracted from literature
- 47 physician referrals
- 4 clinical records

- 633 cases with cancer (48% leukemia, 25% lymphoma, 13% breast cancer, 14% other)
- 87 cases with another diagnosis (transplant, auto-immune disorders, attempted abortion)

- 482 were multiple agent exposures
- 234 exposed to a single agent

**Table 2:** Relationship of Exposure Timing and Congenital Malformations

| | 1st Trimester | 2nd and 3rd Trimester | Total |
|---|---|---|---|
| Number exposed | 314 | 392 | 706 |
| No. affected cases | 60 | 23 | 83 |
| Percent affected | 19.1 | 5.8 | 11.5 |
| Expected population freq. (5%) | 15 | 19 | 36 |

**p**<.001

**Table 3:** Pregnancies Exposed to Chemotherapy in the CCSS registry

| | Freq. | Pct. |
|---|---|---|
| Number of women receiving chemotherapy ***before*** pregnancy | 2828 | 51 |
| Number of women receiving chemotherapy ***during*** pregnancy | 43 | 1 |
| Number of women receiving chemotherapy ***after*** pregnancy | 75 | 1 |
| No Chemotherapy | 1383 | 25 |
| Chemotherapy status unknown | 663 | 12 |
| Chemotherapy status OR Pregnancy Date unknown | 559 | 10 |

## 4. Specific Aims/Objectives:

1. To summarize the CCSS cohort experience with various cancer treatments during pregnancy,
2. To demonstrate the range of possible pregnancy outcomes after exposure to various agents during specific times in pregnancy; and,
3. To compare outcomes in exposed pregnancies in the CCSS registry with 708 outcomes derived mostly from the case report literature.

**5. Analysis Framework:**

**Null Hypothesis**: There are no differences in the outcome of pregnancies of 43 cancer survivors in CCSS who were treated for cancer during pregnancy *versus* those identified from a 25 year survey of the literature. We would expect the case series to show adverse outcomes that vary with amount and timing of exposure. For example, first trimester exposures should have more structural anomalies than second and third trimester exposures.

The methods will be to obtain PDF versions of all relevant CCSS questionnaires from the 43 survivors who received cancer treatment during. Similar information is already available from the nearly complete analysis of adverse pregnancy outcomes in the entire cohort in the draft manuscript given to D. Green on June 9, 2010, "Genetic diseases in offpring of survivors of childhood and adolescent cancer: The Childhood Cancer Survivor Study." The datasheet form used in the existing registry study (Appendix I) will be completed in detail and will be summarized for publication in the format of **Table 4**, next page.

After entry and verification in the existing Access database, appropriate summary tables will be prepared and simple frequency statistics applied to the data. The CCSS case series will be interpreted based on the larger, but biased, world literature survey of now 707 cases (which will be updated this summer, as well.) Hence, the major comparison will be with the aggregated data of the entire registry and with the summary tables of outcomes of all pregnancies.

**Table 4:** Date Entry Form

| ID # | Maternal Diagnosis | Diagnosis During Preg Year? | Maternal Age at Conception | Chemo Agents: Total Dose | Radiation Treatment: Total Dose (cGY) | Birth Outcome | Sex | Gest Age | Weight (g) | Centile of Average Weight | Anomalies | Additional Pregnancy Exposure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
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# Appendix I

Cancer Chemotherapy Data Entry Form

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Case ID_____

# Registry of Pregnancies Exposed to Chemotherapeutic Agents

**1)** *Source Information*

a. Type of Source

____ Literature
____Clinical Record
____Physician referral
____Self-referral
____Other (specify)_____

b. Publication References

Title of Journal_____
Author (first initial and last name)_____
Volume_____ Number_____
Date__-__-____ First page_____ Last page_____

**2)***Patient Information*

a. Patient's age at conception of index pregnancy _____

b. Patient's diagnosis (please specify)

- Neoplastic Disease_____
- Transplant_____
- Non-neoplastic Disease_____

c. ICD-9 code of diagnosis: _ _ _ _ _ _ _ _ _

d. Patient's age at diagnosis _____

e. Did diagnosis occur in pregnancy year?
(Pregnancy year = 3 months before index conception to delivery or termination)

_____Yes
_____No
_____Not stated

e. Gestational age (weeks) at diagnosis _____

f. Total number of pregnancies that the

f. Please list any observed abnormalities in previous pregnancies

_____
_____
_____

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**3)** *Index Pregnancy Year* (3 months before conception to delivery or termination)

a. Index disease clinically evident in pregnancy year?
   _____Yes
   _____No
   _____Not stated

b. Cigarette smoking? (anytime in pregnancy)
   _____Yes _____1st Trimester
   _____No _____2nd Trimester
   _____Not stated _____3rd Trimester

c. Alcohol consumption? (anytime in pregnancy)
   _____Yes _____1st Trimester
   _____No _____2nd Trimester
   _____Not stated _____3rd Trimester

d. Diabetes mellitus?
   _____None
   _____Yes, onset before conception
   _____Yes, onset after conception
   _____Yes, onset time unspecified
   _____Not stated

e. Pre-eclampsia?
   _____Yes
   _____No
   _____Not stated

f. Eclampsia?
   _____Yes
   _____No
   _____Not stated

g. Radiotherapy administered during pregnancy year?

_____Yes Total radiation dose in pregnancy year_____
_____No
_____Not stated

h. Chemotherapy during pregnancy year

Table 3.1 Chemotherapeutic Agents Used During Index Pregnancy Year

| Drug Name | Number of Cycles | Total Dosage (mgs) |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
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| | | |

**4)** *Index Pregnancy*

a. Outcome of pregnancy
_____Live birth
_____Stillbirth (>28 weeks)
_____Spontaneous abortion (<28 weeks)
_____Elective abortion
_____Ectopic pregnancy
_____Hydatidiform Mole
_____Other (Specify)

b. Index Pregnancy Outcome

Table 4.1

| Gestational Age | Number of Infants | Weight (g) | Sex | Number of Anomalies |
|---|---|---|---|---|
| | | | | |

Congenital anomalies observed: _____
_____
_____
_____
_____

If the index pregnancy included more than one infant, use Tables 4.2 and 4.3

Table 4.2 – Second Infant

| **Gestational Age** | | **Weight (g)** | **Sex** | **Number of Anomalies** |
|---|---|---|---|---|
| | Infant #2 | | | |

Congenital anomalies observed: _____
_____
_____
_____
_____

Table 4.3 – Third Infant

| **Gestational Age** | | **Weight (g)** | **Sex** | **Number of Anomalies** |
|---|---|---|---|---|
| | Infant #3 | | | |

Congenital anomalies observed: _____
_____
_____
_____
_____

**5)** *Index Pregnancy Worksheet*
Please fill out this worksheet as a timeline of the index pregnancy. Use the category codes listed below.

Categories:

1. Chemotherapy: drug name, dose, times per day, route, day(s) of administration, gestational weeks of administration
2. Other drugs: drug name, dose x per day, route, day(s) of administration, gestational weeks of administration
3. Radiation: site, dosage per x-ray, total weekly dosage and gestational week(s) of administration

4. Index disease: code week of diagnosis and weeks in which it is clinically evident, and week(s) remission is diagnosed
5. Other disease: disease name, time of diagnosis, week(s) it is clinically evident
6. Surgery/other procedures: surgery site, procedure name, gestational week it occurred

7. Pregnancy: conception, diagnosis, termination, or delivery

Table 5.1 Index Pregnancy Calendar

| **Week of Pregnancy** | **Category** | **Description** |
|---|---|---|
| Preconception (~ 14 days) | | |
| Preconception (~ 7 days) | | |
| 1 | | |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |
| 6 | | |
| 7 | | |
| 8 | | |
| 9 | | |
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| 37 | | |
| 38 | | |
| 39 | | |

| | | |
|---|---|---|
| 40 | | |

If you have any other comments regarding the index pregnancy, please list them here. Thank you for your time and contribution to the Registry of Pregnancies Exposed to Chemotherapeutic Agents.

_____
_____
_____
_____
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_____