

LATE BREAKING news

from the **National Wilms Tumor Study**



Pregnancy After Treatment for Wilms Tumor

by Claire Carlson, RN, BSN and Wendy Hobbie, MSN, CRNP

For many women, becoming pregnant and having a child can be one of life's greatest joys. For female survivors of childhood malignancies, approaching this life milestone can sometimes create a certain degree of uncertainty and anxiety. Questions regarding fertility and the ability to successfully carry a baby to term are of paramount concern. Will the treatment that I received make it difficult for me to become pregnant? If I do get pregnant, am I at risk for certain complications and what can I do to make sure that I have a healthy pregnancy? These are some of the questions that resonate with many female survivors now entering their childbearing years. Proportionally speaking, only a small number of Wilms Tumor survivors will experience difficulty becoming pregnant or maintaining a pregnancy. The most important factor is to understand those treatment exposures that may place you at the highest risk for complications. And, while some Wilms tumor survivors may have

a greater risk of complications, these risks should not discourage you from trying to become pregnant when you are ready. Identifying your risk factors and taking proactive steps to care for yourself before, during and after pregnancy is the key.

TREATMENT FACTORS and YOUR RISK

To better understand your potential risks during pregnancy, each survivor must know the therapy they received and the risks associated with that treatment. The treatment for Wilms tumor typically involves surgery, chemotherapy and in some cases radiation. Depending on the extent of disease at the time of diagnosis, a combination of these different modalities is used to offer the best chance for long-term survival. Survivors who were treated with a nephrectomy (removal of the kidney) in combination with limited chemotherapy (usually

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drugs like actinomycin D and vincristine) are not likely to have difficulty conceiving or carrying a child. Survivors treated with additional types of chemotherapy or radiation may be at increased risk for having problems with fertility or pregnancy.

RADIATION

Radiation can cause damage to the healthy cells of the ovaries, sometimes impairing a woman's ability to become pregnant. Radiation can also affect the elasticity and blood flow of the uterus. This can make it more difficult for the uterus to expand and stretch during pregnancy. Studies have shown that Wilms tumor survivors who received radiation to the flank (the side of the body between the upper abdomen and the back with doses between 10-20 Gy) can still achieve a successful pregnancy. Those who received radiation to the whole abdomen, including the pelvis, are at higher risk for infertility. Pregnancy for these women is likely to be more difficult to achieve but is not necessarily impossible.¹ Reports from the National Wilms Tumor Study indicate that women who have received radiation to the flank or upper parts of their abdomen may not have problems becoming pregnant but are at risk for premature labor, low birth weight, premature birth (<36 weeks), and malposition of the fetus.² Thankfully, current therapies for Wilms tumor have been modified in an attempt to minimize long-term effects on the female reproductive organs. Flank or upper abdominal radiation is only used for more advanced disease and total doses of radiation to this region have been reduced to minimize toxicity while maintaining cure. Hopefully, future generations of Wilms tumor survivors will benefit from these therapeutic adjustments as they move into their reproductive years.

EXPOSURE to ANTHRACYCLINES on TREATMENT

In more advanced cases of Wilms tumor, drugs known as anthracyclines (drugs like Adriamycin and Doxorubicin) are sometimes utilized. Not everyone treated for Wilms tumor receives this class of drug as part of their therapy. Anthracyclines can cause weakening of the heart muscle later in life. This is especially true for those who received larger doses of the drug, at younger ages (less than 5 years) or in combination with radiation in the area of the chest or to the left side of the abdomen (this radiation may have reached the lower chambers of the heart). Effects on the heart, if any, may not be seen for many years after treatment. While many Wilms tumor survivors do not develop problems with their heart, the added stress of pregnancy on the body requires those who received this class of drug to be vigilant about a heart healthy pregnancy. Close monitoring of the heart's function, especially during the later stages of pregnancy and during labor and delivery, is strongly recommended. Suggested monitoring includes an echocardiogram (an ultrasound of the heart)

before and periodically during pregnancy, especially during the third trimester, and cardiac monitoring during labor and delivery.³ Your doctor can decide what the best monitoring schedule is for you. Involvement of a doctor who specializes in the function of the heart (cardiologist) may also be advised.

WHAT YOU CAN DO

Successful pregnancy is possible for most survivors of Wilms Tumor. For many survivors, there is no reason to expect that your treatment will prevent you from having a baby when you are ready. For survivors who may have received radiation and/or anthracyclines as part of their treatment, there are certain key points to remember if you are pregnant or are considering having a baby.

1. Know your treatment history including the total dose of any anthracyclines received as well as total dose and location of radiation. Your treating oncologist can provide this information to you.
2. Share information on your treatment exposures with your obstetrician as soon as you know you are pregnant.
3. Be proactive. Seek specialized care and careful monitoring throughout your pregnancy, even if you feel fine and are not having any problems. This may include care by an obstetrician with skills in high-risk pregnancy as well as regular visits to a cardiologist both during and after your pregnancy.

1. Kalapurakal, JA, Peterson, S, Peabody, EM, Thomas, PRM, Green, DM, D'Angio, GJ, Breslow, NE (2004). *Pregnancy outcomes after abdominal irradiation that included or excluded the pelvis in childhood Wilms tumor survivors: a report from the National Wilms Tumor Study.* *Int. J. Radiation Oncology Biol. Phys.* 58(5):1364-1368.

2. Green, DM, Peabody, EM, Nan, B, Peterson, S, Kalapurakal, JA, Breslow, NE (2002). *Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group.* *J Clin Oncol* 20:2506-2513.

3. *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, Version 1.2-March 2004.*

ABOUT THIS ISSUE

Several articles in this volume address issues concerning pregnancy and participants' children. We would like to thank all of you who have shared information with us about your or your partner's pregnancies and the birth of your children. We also thank those of you who have let us know you are unable to have children. For many of you this was painful to remember and report, and we cannot possibly thank you enough for having the courage to do so. All reports of pregnancy and fertility are valuable to answer questions about the effects of treatment for Wilms tumor on men's and women's fertility and their children. We are happy to share with you this series of articles that reflect everyone's contributions.

Eva Eaton's Path to Parenthood

Today Eva Eaton is a happily married mother of two girls. In the early 1960s no one would have believed this would be her future. In 1962, two year old Eva Sennewald was living with her parents and younger sister in Mexico City where she was diagnosed with Wilms tumor in both kidneys. Her alarmed father, a physician, flew her to Boston for surgery and treatment.

Eva's left kidney was removed, and she was treated with high dose radiotherapy and the chemotherapy drug vincristine. Three years later the tumor recurred in her right kidney. Eva was once again treated in Boston where one quarter of her right kidney was removed and she was retreated with radiotherapy and vincristine. Eva was never aware of the possible consequences of her treatment until an annual visit with a doctor who told 13 year old Eva that she probably would never be able to have children. "It was a terrible shock. It never crossed my mind that I would not be able to lead a normal life," says Eva. "It was such a bombshell. Why had no one told me this any sooner? It could have been handled better."

Despite this life-altering news Eva moved on. She graduated from the University of Victoria in British Columbia, BC and took a job with the Canadian government working in employment counseling and immigration. After a promotion she found herself in Port Hardy, BC, an isolated logging and mining town. There at age 29 she met Tim Eaton, a geotechnical engineer. They married in 1990, and Eva then joined Tim in Papua New Guinea, where he was working at a large copper and gold mine.

"I think I understand now what my parents must have gone through."

Eva and Tim returned to Canada two years later hoping to start a family despite everyone's negative expectations. Although she received infertility treatment, her specialist did not hold much hope. Even if Eva became pregnant he was concerned about her kidney function and whether she could sustain a pregnancy. Eva's largely uncomplicated pregnancy had to be ended suddenly with the onset of toxemia. Eva's and Tim's daughter, Elizabeth, was born in 1994 via caesarian section. Encouraged by the birth of Elizabeth, Eva again approached her fertility specialist. He was skeptical but she says, "He agreed to treat me, largely to humor me, I think." After four treatments Eva was again pregnant, and Sarah was born 37 weeks later via caesarian section following the onset of toxemia.

Eva was diagnosed and treated before the National Wilms Tumor Study (NWTS) was founded, but she has close ties to the study. At Boston Children's Hospital two of her physicians were Dr. Giulio D'Angio and Dr. Audrey Evans. She has remained in close contact with both of these physicians. In 1969 Drs. Evans and D'Angio founded the NWTS, and they remain active to this date. Shortly before Eva's wedding they visited her in Port Hardy as they were unable to attend the wedding ceremony. It was a very special reunion. In 1994 after the birth of Elizabeth they approached her about becoming a member of the NWTS Data and Safety Monitoring Committee (DSMC) which oversees the conduct of the NWTS clinical trial protocols. They thought she would bring a personal touch to the committee.

Eva remained an active member of the DSMC until the last clinical trial ended in 2002. When asked to recall her impression of being on the committee and attending annual NWTS meetings, she stated that it was "incredible to meet these world-class physicians and researchers and see what great efforts were being made on behalf of children with Wilms tumor."

Today Eva lives with her husband and daughters in Calgary. She says that being a mother has given her an insight about what it must have been like for her parents when she was being treated. "I think I understand now what my parents must have gone through. When I think of what it would be like for one of my daughters to undergo surgery, it gives me added insight about my parents."

Eva would like her experience to be of help to others. Dr. D'Angio once put her in contact with another young woman who had Wilms tumor. After they discussed their experiences and Eva shared her road to parenthood, the young woman finally decided to adopt children. "We all take our experiences and decide the best thing to do for ourselves," Eva reflects. For Eva her experiences have led her to a happy life in Calgary filled with joy and pride for her daughters and husband.



What Causes a Wilms Tumor? Why Does It Affect Children and Not Adults?

by *Giulio J. D'Angio, MD*

First, there are no known causes of Wilms tumor (WT). Some cancers in adults are associated with specific environmental factors or with life-style habits; for example, smoking and lung cancer. There are no such direct causative links in the case of a child with WT. Nothing the parent or the child did led to the appearance of a WT. Also, the vast majority of WTs are not inherited. There are very rare families in which WT occurs in more than one member of the family. This is usually a close relative such as a grand-parent, aunt or uncle, parent or sibling.

Nothing the parent or child did led to the appearance of a Wilms tumor

Then, why does a WT appear in an otherwise healthy little girl or boy? It may be helpful at this point to liken a rose bush in the spring to one of the known pathways to WT. The rose bush may have many buds some of which will remain as such and never progress beyond the bud stage. Other buds may wither and die, but the much greater number will develop into lovely flowers. Only a rare bud without obvious cause will produce a misshapen, malformed blossom.

The developing kidney in the embryo can be envisioned in that way. The “buds” are the building blocks of the kidney called nephrons. Some of them, like the rose buds, remain dormant without maturing further. These are called “nephrogenic rests” abbreviated as NRs. Others wither away and die, but most develop normally to form the kidney. Rarely, one or more of the NRs for reasons that are largely unknown grows into a misshapen, malformed “blossom;” in this case, a Wilms tumor.

Microscopic NRs are fairly frequent in babies. Dr. Bruce Beckwith found them in the kidneys of approximately one percent of 1000 children under 3 months of age that he examined. So, if NRs always gave rise to Wilms tumors—which is not the case—then one would expect to find 1000 WTs among 100,000 children. The actual incidence of WTs in the pediatric age group is about ten per 100,000. This means that the NRs either faded away or remained dormant in at least 99% of those children who had kidneys that were so affected as infants. Most Wilms tumors do not arise from NRs.



This story of the rose bush may help to picture how seldom the embryonic kidney units become confused along the normal developmental pathways, and how very rarely the confusion results in a WT. Also, WTs tend to occur in rare children with certain body abnormalities that follow a pattern. These abnormal patterns are called syndromes that appear to be linked to specific gene defects. The two most common of these patterns are the Beckwith-Wiedemann Syndrome, and the WAGR Syndrome. The former most notably is associated with overgrowth of body parts; for example, one leg is larger than the other, but there are other important elements to the syndrome as well. The letters WAGR stand for the abnormalities found in these patients; Wilms tumor, Aniridia (absence of the iris of the eye), Genito urinary (pathology affecting the sex and urinary tract organs), and mental Retardation. Patients with signs of either of the two syndromes (and some others that are rarer still) need careful frequent examination to check for the presence of a developing WT.

Above it was said that the reasons for transformation of a benign, non-malignant NR into a malignant WT are unknown. Even more puzzling is the fact that most WTs do not grow from NRs or in patients with the known alerting syndromes. Thus, in most children with WT, there is even less understanding as to why the cancer appeared. It is believed that there are other, as-yet-to-be-identified in-born errors in normal kidney formation that lead to the growth of WTs.

One thing seems clear, however, and that is that the abnormalities that can eventually produce a WT develop during embryonic life. This is because WTs have occasionally been found in newborns, although most are clustered in the one to four year old age group, suggesting a similar “lag time” for the majority. Exceptions are the rare adults who develop typical WTs. These tumors are identical to those found in children both microscopically and in their clinical behavior. The same in-born triggering mechanism of childhood therefore is likely to be responsible in the case of adults. Why there is such a long delay in the malignant transformation in these older individuals remains to be explained.

Why the NWTs Is Now Following Your Children

A major purpose of the NWTs Late Effects Study is to answer the question asked by NWTs participants who are now parents: Will my children be at a higher risk of having health conditions present at birth or developing them later?

We now must try to answer this question: Has the chemotherapy and radiation therapy used in modern treatment caused changes in the eggs and sperm which might lead to an increased chance of developing Wilms tumor or serious birth defects in their children? Scientists already believe that about 10% of Wilms tumors are caused by certain genetic mutations. Mutations occur naturally in all dividing cells. The complicated genetic changes resulting in the passing down of any mutation to yet another generation is even rarer. Accurately counting how often these rare events happen in the children of those who have been successfully treated for Wilms tumor is very important.

So far, we have not collected nearly enough information to answer these questions, but recently we began to systematically collect information about these births and to regularly ask about the growing children in order to monitor their health. Sixty years ago children with Wilms tumor did not often survive to grow up and have their own children. Since then radiation therapy helped more children survive, but at first left many of them unable to have children themselves. Now, with modern treatment, including lower doses of radiotherapy, most children survive Wilms tumor and are able to become parents.

From October, 1969 through May, 2002, we completed five clinical trials for the treatment of newly diagnosed Wilms tumor—each trial building on the results of the one before to improve treatment outcome. Each trial tried to identify which patients needed more treatment to survive and which could survive with less treatment and consequently with fewer late effects. There is no “one best treatment” for Wilms tumor because treatment depends on many factors including extent of disease, cell type, age at diagnosis, and the size of the tumor. With each new trial, effective treatment for most patients included lower doses of radiotherapy and chemotherapy over shorter periods of time. The goal has always been to improve treatment so that more children would live and grow up with as few late effects as possible. Today 90% of children diagnosed with Wilms tumor survive, and we are continuing to collect information to see if we have eliminated many of the late effects that had previously been observed and to detect any effect treatment might have in the next generation.

Solitary Kidney and Sports Participation

by Michael Ritchey, MD

Many physicians advise physical restrictions on children who have only one kidney whether it is a condition the child is born with or acquired after surgical removal of a kidney. The American Academy of Pediatrics (AAP) has published recommendations regarding sports participation for children with medical conditions.¹

They state that children with a single kidney need individual assessment for contact, collision, and limited-contact sports. They do not recommend participation in boxing and suggest only a limited amount of body checking for hockey players 15 years and younger. Sports with high contact/collision potential include football, martial arts, rugby, rodeo, basketball and wrestling.

A review of 49,651 patients reported to the National Pediatric Trauma Registry from 1996-2001 identified 813 renal injuries of which only 85 were due to sports.² (None of these injuries occurred in a patient with a solitary kidney, but this is likely due to the rarity of this condition.) The most common sports injuries were due to football, followed by sledding, snowboarding, skiing and skateboarding. Of interest, renal trauma due to bicycle injuries was more common than sports related injuries. Bicycling is considered a limited contact sport. The most common cause of renal injury in both children and adults is a motor vehicle accident. Although the risk of renal injury from sports is low, children with a solitary kidney who participate in contact sports should consider protective equipment. A number of products are now commercially available, e.g. TKO kidney protector, and WIS Wikmax kidney protection shirts.

1 American Academy of Pediatrics Committee on Sports Medicine and Fitness. Medical Conditions Affecting Sports Participation. *Pediatrics* 2001; 107:1205-1209.

2 Johnson B, Christensen C, Dirusso S, et al.; A need for reevaluation of sports participation recommendations for children with a solitary kidney. *J Urol* 2005; 174:686-9



BREASTFEEDING SURVEY

Female participants who have had the joyous experience of welcoming a baby into their lives will soon be receiving a questionnaire asking about their experience with breastfeeding. We believe it is important to know if treatment for Wilms tumor has any effect on breastfeeding, but we have been unable to find any research on this topic. For those of you who receive this questionnaire, we would greatly appreciate your taking the time to complete and return it at your earliest convenience. Thank you in advance for your cooperation with this aspect of the study.



Déjà Vu All Over Again — or “Why Am I Asked A Question More Than One Time?”

Sometimes you probably feel like the form that you just received in the mail from the National Wilms Tumor Study asks the same questions that you just answered on an earlier form. In some ways that may be true. Our goal is to obtain answers from as many participants as possible so the data will be as statistically accurate as possible in order to provide you with the most reliable information.

As we mentioned in an earlier newsletter, it is very important for us to hear from all participants, both men and women, young and old, people who have conditions to report and those who have none. Questionnaires and forms are designed to be straightforward and as quick as possible for you to complete.

One of the main reasons we ask repetitive questions is that reporting by mail is not 100% effective. Sometimes you receive a mailing and it gets buried on your desk and is never returned or is inadvertently thrown away. Sometimes after you have completed and mailed it, it gets lost in the mail. And sometimes we make a mistake and the information that you report to us is not correctly recorded. If we did not repeat our inquiry, we might miss your report of a very important event. We hope the follow-up mailing reaches you at a convenient time to complete it and put it in the return mail. New information will then be recorded and repeat information is double checked to verify if we recorded it accurately.

We do not want gaps in the information you report about yourself. We'd much rather have you tell us something twice than not at all. For example, periodically we send a Pregnancy Survey requesting you to complete a comprehensive list of all of your or your partner's pregnancies to make sure we have not missed any reports due to a lapse in contact with you.

Also, sometimes participants are in and out of contact with us. During college or at times of illness or when you bring a new baby home, your life might be too hectic for you to correspond with us. So it is important that we ask our question a second or third time to try to capture complete information.

Many of you have questions or concerns about pregnancy or fertility, and some of you have already informed us that you have been unable to become pregnant. Yet we continue to ask you about this each year. We do not intend this to be a painful reminder of something that has already been reported. Unfortunately, our resources are limited and as a result, we are unable to personalize questions on each form more than they already are. The same forms are sent to annual respondents as are sent to those who have resumed participation after a significant gap in time. We must ask questions that bring us up-to-date since we last heard from each one.

We highly regard your time and try not to waste it. We appreciate the time you take to complete and return our forms. It is important to us to be as thorough as possible so we can reliably answer your questions with scientifically accurate results.

Patience, Persistence and Humor: Longtime DSC Colleagues' History Goes Back 27 Years

This year we introduce to you two people who have a long history with the National Wilms Tumor Study Data and Statistical Center (DSC). Pat Norkool and Janice Takashima have devoted years and expertise to the study.

Pat and Janice have come a long way since they first started working at the DSC in the mid-seventies. They both started as technical assistants who provided support to Dr. Norman Breslow, the study's Principal Investigator and statistician. Acting as the backbone of the DSC, Pat and Janice are credited for all that they have done. Over the years their knowledge and resourcefulness have been valued by colleagues, participants and physicians.

Looking back, at first their work consisted of doing everything by hand. There were no personal computers. Pat and Janice did everything from opening mail, coding patient data onto paper forms and then hand delivering these data to the University of Washington where it would be entered into a gigantic computer using punch cards. They drew graphs by hand and typed analysis tables for statistical reports. Susan Peterson, the study's Database Manager, says, "While it is often entertaining to hear stories of the old days, one thing that both Pat and Janice have retained from the beginning is their dedication to the well being of the study participants. They are always ready and willing to answer questions and seek appropriate referrals whenever necessary."

As the numbers of study participants have grown over the years so indeed have their responsibilities. As Project Coordinator, Pat oversees all DSC activities and a staff that has grown to 11. She talks with other data managers, participants and medical investigators across the country. She is skilled at writing thoughtful responses to the many inquiries she receives on a daily basis from data managers and families who are seeking guidance and information. Besides her critical role in working with grant renewals and regulatory issues she strives to help staff by providing insight to situations that require clarification and attention.

In her 29th year with the study, Janice has always been an extremely valuable contributor to the DSC. "Problem solving is one of the things I like best about my work," she says. "And in this work you do a lot of it. If I don't know the answer already, I can usually find it." With her depth of knowledge, Janice too, has a certain knack for answering questions which often involve understanding the history of previous clinical trials and providing important clinical and study information for her colleagues.

You may wonder what has kept them strong for so long? "Janice and I have worked together for 27 years, which is longer than many people have stayed married," Pat says. Besides believing that this is a very important study, "I think the most important trait we share is the ability to find humor in stressful or demanding situations."

And demanding it can be when much of the study relies on the day-to-day attention to detail to carefully capture and abstract data, and correspond with data managers across the country. At the same time, they oversee special short-term study projects and provide families and participants with timely responses to their questions and concerns. Dr. Breslow in reflecting the years of work that he, Pat and Janice have shared, said "I think the continuity of staff support provided by Pat and Janice's long term service has been one of the principal reasons for the success of the DSC. Their detailed, intimate knowledge of the collected data has been of great benefit to the clinical researchers who have worked with them. These researchers have appropriately included Pat and Janice as co-authors on manuscripts resulting from such interactions."

When Janice and Pat first met at the DSC they learned that they had both lived and taught English in Japan. That shared experience has been a touchstone for their working relationship and friendship. Janice said, "We both have learned to survive experiences by finding the humor in the situation. We were using that stress-relieving technique long before it became an acceptable survival skill and were even criticized early on for our "excess of levity." Lately we both have discovered the value in blessing our burdens rather than cursing them. That works too, and is a little quieter for our neighbors." They also share a love for animals—especially cats, bunnies and pigs. Pat has a fabulous collection of pig figurines that the entire office enjoys contributing to.



Although the last clinical trial ended in 2002, the Late Effects Study continues. Early this year we will be requesting continued funding to support the study for five more years. Janice and Pat will be very involved in preparing this application as they are committed to continuing the study in order to support participants and their families. Pat reflects "When Janice and I first started working here we never talked with families. Our interaction was strictly with institutions. Now we hear directly from participants on a daily basis. This has personalized our work for us, and we value these conversations. We also receive photographs of participants and their children. These decorate a whole wall in our office and serve as a daily reminder of why we do this job."

Frequently Asked Questions

I am a long-term survivor of Wilms tumor. Is it all right for me to be an organ donor?

Except for corneal transplantation, the answer unfortunately is "No." This is for several reasons. The curative treatments you received may have damaged the organ to be donated. There might be nothing suspicious detected either on physical or imaging examinations, or on laboratory tests, but invisible, healed scarring of greater or lesser degree could nonetheless be present. The extent of the injury depends largely on the doses of the treatment used and the side effects of that treatment. Those invisible scars could lead to early failure of the transplanted organ. This is beside the fact that it needs to be able to withstand the shocks and stresses associated with the transplant process itself. Examples are the hidden damage to the liver and heart caused by dactinomycin (Actinomycin D) and doxorubicin (Adriamycin) respectively. The same can be said of the radiation therapy (RT) that injures every irradiated structure. The amount of RT damage depends on the dose delivered, as with the chemotherapy. Moreover RT can cause second cancers to develop in irradiated parts, usually after the passage of many years. Another point concerning delayed problems: late relapses in the lungs have been recorded in rare patients who appear to have been disease-free for as long as ten or more years. Transplanted lungs from individuals treated years ago for Wilms tumor could contain such unsuspected metastases. These could grow in the donated lungs with obviously very unfortunate consequences for the recipients.

Please go to our website www.nwtsg.org for more Frequently Asked Questions.



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