DES Action® VOICE

Inside

A Focus On Diethylstilbestrol

WINTER 2016 #147

Your Health: Navigating Colposcopy and Biopsy Procedures With a DES Exposure History

By Virginia Pelley

Although abnormal Pap results tend to taper off for DES daughters after age 40, regular gynecological care is still important in the decades that follow; as you read in our lead story this issue, rare DES-related health complications could reappear later in life.

After an abnormal Pap smear or positive test result for human papilloma virus (HPV), your physician might order a colposcopy, a procedure that uses an instrument with a magnifying lens and a light, called a colposcope, to examine the cervix (opening to the uterus) and vagina for abnormalities, according to the Johns Hopkins Medicine Health Library. The presence of bleeding, polyps (growths), genital warts and DES exposure itself might also prompt a doctor to order one.

"Women with DES exposure have higher rates of abnormalities of the lower genital tract, including an increased risk of clear cell adenocarcinoma and a higher risk of high grade dysplasia [abnormal growth or development of cells],"

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Welcome to Our New Editor

Selection of noted medical and science journalist reflects nonprofit's commitment to serve future generations of DES-exposed

Tara Haelle

This issue of the VOICE was produced by our new editor, Tara Haelle. I met Tara at a health journalism conference and I was struck by her passion for deep diving into topics. When she expressed interest in being the editor of and writing the articles for VOICE, I knew she'd have the commitment and medical health knowledge that we need. Tara dove into the existing and ongoing research on DES with the intensity I expected. She reached out to DES Action's long-time research head, Kari Christianson, but also to medical professionals leading in DES research.

Tara's previous reporting has been published widely in top-tier media outlets such as National Public Radio, Scientific American, Medscape, MedShadow, Washington Post, NOVA Next, Forbes and Parents. She also serves in a leadership role as a core topic leader of medical studies for the Association of Health Care Journalists. Please think of Tara as the professional research expert for all of us DES-exposed. Even though Tara is not a DES Daughter herself, she an extremely knowledgeable and empathetic member of our team.

Tara's role will focus on ensuring that VOICE will continue being a reliable source of research news and helpful information to take to your health care professionals in seeking care. She will also share informative articles on the DES Action Facebook and Twitter accounts. Tara will not be participating in any advocacy roles to maintain her status as an independent journalist.

"I find the history of DES fascinating, and the consequences of pushing a drug into the marketplace too quickly hold lessons for all areas of medicine," Haelle said. "I look forward to helping identify and report on evidence-based science as I do in my other work to provide all exposed to DES with valuable information."

Send your questions and—even better—send ideas for articles you want to info@DESAction.org.

—Suzanne B. Robotti

JOIN THE CONVERSATION

New Member Benefits!

Part of our upgrade to the DES Action USA website includes a new members-only area. As a member, you'll be able to log in to the Members Area for access to:

- **Rate Your Doc**—we've always offered lists of doctors that were recommended by other DES-exposed members. Now you can share your knowledge, and maybe spare some fellow members some pain, about the doctors in your area. Rate your doctor by entering his or her name, location and specialty, then add your comments: Is he or she knowledgeable about DES? Open to discussing options or fears? Tell your fellow members.
- **VOICE Newsletter**—current and historical. The VOICE is the most popular member benefit of DES Action. Now access all 36 years of newsletters and search for any topics or articles you need. The VOICE documents the history, the science and the personal stories of DES and all of us who were exposed.
- **Attorney List**—If you're interested in getting involved in possible future DES-related litigation, we offer a list of knowledgeable attorneys DES Action members have shared with us who might be able to help.
- **Exclusive Content**—an expanding collection of articles and videos accessible only to current DES members.

And more! Update your mailing address, pay your membership dues or make a donation online.

DES Action USA on Facebook

Like DES Action USA on Facebook and follow us on Twitter to stay up-to-date on medical and environmental health news that affects you, your loved ones and the planet. Share your thoughts with an engaged and active community. There's a ton of information swirling online 24/7 that affects the DES population—don't let it pass you by!

Online Support Group for DES Daughters

Here is a safe place for discussing very personal issues that arise for DES Daughters. We live in the farthest reaches of the country but have developed a sense of community together, via our email listserv.

What we talk about is private—just between us—so we can feel free to raise questions on topics we aren't comfortable bringing up with others. What is amazing is the depth of knowledge in the responses.

It's a terrific resource for information and support from DES Daughters who wrestle with the effects of menopause, family relationships and medical diagnosis issues specific to DES exposure. To join the support group, send an email to: DESactionDaughters-subscribe@yahoogroups.com.

How to Log In

To log into the members area, go to http://members.desaction.org and click on Members in the navigation bar. Enter the email address we have on file and the default password: desUSA2015. Once you are logged in, you can go to Your Account and change your password and update other information.

If you have any problems, email us at members@desaction.org or call us at 800-337-9288.

Find us on Facebook

twitter

MISSION STATEMENT

The mission of DES Action USA is to identify, educate, empower and advocate for DES-exposed individuals.

Contacts

Sister Organizations

Australia

DES Action Australia, Inc.
PO Box 282
Camberwell 3124 Vic. Australia
info@desaction.org.au
www.desaction.org.au

DES Action NSW
14 Edmundson Close
Thornleigh NSW, 2120, Australia
C_devine@bigpond.net.au
www.desnsw.blogspot.com

France

Reseau DES France
1052 rue de la Ferme de Carboue
40000 Mont de Marsan, France
reseaudesfrance@wanadoo.fr
www.des-france.org/accueil/index.php

The Netherlands

DES Centrum
Wilhilminapark 25
Postbox 1173
3860 BD Nijkerk
voorlichting@descentrum.nl
www.descentrum.nl

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DES Action USA
178 Columbus Avenue #237182
New York, NY 10023

(800) DES-9288
(800) 337-9288
Email: info@desaction.org

Editorial Director and Social Media Manager..... Tara Haelle
Membership and Operations Manager..... Kimberly Bliss
Communications Director..... Julie Livingston
Financial Manager..... Aundra Goodrum

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MedShadow Foundation, Inc.
President..... Suzanne B. Robotti
Digital Director..... Deirdre Wyeth

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DES Action USA Meets with NIEHS Director

DES Daughter Kari Christianson represented DES Action USA at an annual meeting last December with director and staff of the National Institute of Environmental Health Sciences. DES Action USA is among 30 other health and education advocacy organizations that make up the NIEHS Partners, whose members focus on concerns about disease, disability, and the environment.

Kari Christianson

"This meeting allows the director to hear directly from the public about the kind of research questions being asked by our members," Christianson said. "Additionally, the groups were and are able to suggest ways NIEHS can communicate with the public about research topics."

What is the Partners program?

As the NIEHS describes the Partners, they "provide a grassroots perspective on the NIEHS research agenda and serve as a key contributor to the translation of research findings for the public, policymakers, and private foundations."

Linda S. Birnbaum, Ph.D., Director, NIEHS & NTP

The Partners program began in the late 1990s, and DES Action USA was among the first organizations invited with other groups to the annual in-person meetings, held for the past 15 years. At this year's meeting, the Partners representatives met with Dr. Linda Birnbaum, the current director of NIEHS and the National Toxicology Program.

"Beyond sharing and asking questions about our particular research area at the NIEHS, the Partners are dedicated to learning about new aspects of NIEHS research and sharing the environmental health message and mission of the NIEHS," Christianson explained. "Dr. Birnbaum is outstanding in the depth of her knowledge about current and past research at the Institute. To say these are lively and informative conversations is certainly an understatement."

Operating in many environmental areas

The Partners heard not only from Dr. Birnbaum—who emphasized the importance of focusing research on early exposure to environmental origins of disease—but also from three members of the NIEHS staff based in Bethesda, Maryland. These staffers provided an overview of their roles on different governmental committees related to toxicology, disaster response research and the heath impacts of climate change.

Among the topics discussed at this year's December meeting was the DES Sister Study run by the NIEHS, which is tracking the health of more than 50,000 sisters of women who developed breast cancer, Christianson said.

"Some of these women were prenatally exposed to DES, and adverse reproductive tract problems have been reported in several published articles from the Sister Study," she said. Christianson was especially happy to hear Dr. Birnbaum discuss the importance of prevention.

"Understanding adverse health outcomes is not enough unless we all work to prevent future health and reproductive problems caused by environmental exposures," Christianson said. "DES Action always has recognized that prevention of toxic exposures throughout our lives, but especially prenatal and generational exposures, is our goal, too."

NIEHS celebrates its 50th Anniversary

In addition, because this year is NIEHS's 50th anniversary, DES Action had the opportunity to recommend speakers for various anniversary events planned throughout the year. These speakers included ones who can discuss the diethylstilbestrol research that has been a part of NIEHS since the early 1970s, starting with animal models, Christianson said.

"NIEHS continues to include DES in its research portfolio," Christianson said. "Additionally, as new research methods are being developed by NIEHS-funded projects, there may be opportunities to add to DES knowledge, particularly about the questions of any adverse health in future generations." DES VOICE

> "Understanding adverse health outcomes is not enough unless we all work to prevent future health and reproductive problems caused by environmental exposures."

DES Action Joins Others in Call to Action to FDA

If you've ever tried to read the information about side effects on a medication's packaging, you understand how frustrating it can be to understand precisely what the risks are and how common or rare they are. It's even more frustrating to try to make sense out of how that medication might interact with other drugs you're taking. Obviously, this is the kind of information women who took DES in the 1930s through 1960s had a right to know and did not have.

Today, millions of women taking hormonal contraceptives lack adequate information about the potential side effects of these drugs or the ways they might interact with other medications. Many doctors may require women to take hormonal birth control while taking medications known to cause birth defects, such as Accutane for dermatology conditions. Yet often, research has not even been done to find out how that contraception might interact with the drug that causes birth defects or with other drugs a woman might also be taking. That leaves women and their healthcare providers without the information they need to make important clinical decisions.

DES Action USA teamed up with several other health advocacy organizations to address these concerns in a letter to the U.S. Food and Drug Administration. The letter describes the shortcomings of research as it relates to hormonal contraception and makes three specific recommendations to the FDA. Below, we have reprinted the letter to the FDA in full.

Comments of members of the Patient, Consumer, and Public Health Coalition on "Drug Interactions with Hormonal Contraceptives: Public Health and Drug Development Implications"

[Docket No. FDA-2015-N-3156-0001]

As members of the Patient, Consumer, and Public Health Coalition, we support FDA's effort to better characterize drug interactions with hormonal contraceptives since reliable and accurate information is necessary to ensure women's health. In particular, we recommend clinical evaluation of drug interactions for all drugs that are likely to be used in women of reproductive age and that have the potential to cause birth defects, in addition to improving the quality and usefulness of information in FDA-approved labeling.

There are currently 61 million women of childbearing age in the United States and 62% of them use a contraceptive. In addition, 12% of women ages 18-44 take three or more prescriptions, which means that millions of women may be affected by drug interactions with their hormonal contraceptives. Despite the large public health impact, women and their providers do not have access to adequate information that helps provide a recommended course of action, especially for women who are on medication for chronic disease at the same time they are using hormonal birth control.

There are numerous gaps in currently available drug interaction information. For example, many hormonal contraceptives were developed before the availability of modern methods for studying drug interactions; as a result, drug interaction information is lacking on these contraceptives. Unfortunately, many new drugs still do not examine effects on hormonal contraceptives before they are used in large numbers of women. In fact, a recent FDA review of new drugs with the potential to cause birth defects found that drug interaction studies were not routinely conducted. When information is lacking, information from one contraceptive is often extrapolated to others, even though the specific type of hormone or route of administration may be different (e.g. pills versus IUD). Information is also limited for other patient-specific factors (e.g. obesity, age) that may affect drug interactions with hormonal contraceptives.

We offer the following recommendations:

1. Prior to phase 3 studies, FDA should require clinical evaluation of drug interactions for all drugs that are likely to be used in women of reproductive age and that have the potential to cause birth defects.

Current FDA drug interaction guidance states that a drug with the potential to cause birth defects "needs to be studied in vivo for effects on contraceptive steroids if

the drug is intended for use in fertile women, regardless of in vitro induction study results." In other words, studies in people are still required even if non-human studies are negative for drugs with the potential to cause birth defects. However, an FDA review of new drugs with the potential to cause birth defects found that only 4 of 18 drugs had clinical (in vivo) drug interaction information available in time for phase 3 studies. Drug interaction studies for an additional 4 drugs were completed after phase 3 studies. Therefore, many women may have been exposed to drugs with the potential to cause birth defects without accurate information regarding appropriate contraception.

This is clearly unacceptable since drugs with the potential to cause birth defects require the use of contraception in women of reproductive age. Women and their providers need information about potential interactions and, in order to determine the risks to individual patients, the potential interactions should be known prior to phase 3 studies.

2. Improve the clinical usefulness of drug interaction information in FDA-approved labeling for hormonal contraceptives.

Providers and pharmacists need specific and useful information in drug labeling so they can accurately instruct women on the appropriate course of action. The same FDA review mentioned previously found significant variability with regard to contraception recommendations in drug labeling, with some recommending use of hormonal contraceptives without studying drug interactions and others not including any information about contraception. For example, the study found that 50% of the drugs with the potential to cause birth defects included only general contraception instructions in their labeling and 17% had no contraceptive information at all. Consistent recommendations regarding reliable contraceptive methods are needed to adequately protect women who are taking drugs with the potential to cause birth defects.

3. In addition to being available, information about drug interactions should also provide guidance on the recommended course of action.

A label that states only that drug levels may be increased or decreased does not give enough information for providers to know what to do. For example, the label for Yaz (drospirenone/ethinyl estradiol) states, "Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors." In this situation, it is unclear to what extent the effectiveness of hormonal contraception is affected. Providers need evidence-based, specific, and concise information to guide their decisions.

Additionally, the clinical usefulness, or even applicability, of drug interaction labeling for non-oral hormonal contraceptives (e.g. IUD, vaginal ring) is unclear since they are labelled with the same information as the oral contraceptives but potentially have a different level of interaction. Labeling should address this difference.

Lastly, obese women have a higher risk of both venous thromboembolism AND contraceptive failure due to inadequate hormone levels with hormonal contraceptives but information on the recommended course of action is sparse. More labeling guidance for these women and their providers and pharmacists is needed.

Conclusion

In summary, women and their providers need accurate information about drug interactions with hormonal contraceptives that provides clear guidance on the recommended course of action. We strongly urge the FDA to require clinical evaluation of drug interactions for all drugs that are likely to be used in women of reproductive age and that have the potential to cause birth defects. We also strongly urge the FDA to improve the quality of information about drug interactions in FDA-approved labeling, ensuring that it is more clinically useful.

Sincerely,

National Center for Health Research

TMJ Association

Woody Matters

MedShadow

DES Action

The Medication-Induced Suicide Prevention and Education Foundation in Memory of Stewart Dolin (MISSD)

MRSA Survivors Network

National Consumers League

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explains Kimberly Levinson, MD, assistant professor of gynecologic oncology at Johns Hopkins Hospital and Greater Baltimore Medical Center. "Therefore, it is more likely that these women require additional evaluation by colposcopy to rule out any additional lesions and to catch lesions at the earliest stage possible."

A colposcopy takes about 10 minutes. Many women don't find it painful or uncomfortable but some do. An acetic acid solution is often used to swab the cervix because it dehydrates cells so they appear white, making them easier to see. "This helps us better identify areas of dysplasia," Levinson says.

Lugol solution is an iodine solution that helps doctors see dysplastic areas as well.

Neither solution should hurt or sting, says Levinson.

"One thing about DES Daughters and the DES screening exams we've found over the decades is that there are plenty of individual differences in how women experience the exam," says Kari Christianson, MedShadow Foundation board member and former co-director of DES Action USA. "Some have lots of discomfort, some have none and some have anywhere in between."

More often than not, a cervical, vaginal or vulvar biopsy is necessary at the time of colposcopy, in order to confirm whether dysplasia is present and if so, how severe it is. This is the part that may cause some pain or discomfort, Levinson continues.

A biopsy is performed by scraping cells with small brush or small metal loop called a curette. Another method is to take a tissue sample with an instrument similar to paper punch, which is known as a punch biopsy. Some say it feels like a sharp pinch or bad menstrual cramps, but not everyone finds it bothersome.

Because a dull biopsy curette might pull on the cervix and cause pain rather than quickly remove the tissue, the instruments doctors use are generally very sharp, Levinson says. Certainly most providers try to utilize the smallest size needed when taking any biopsy, but it would be fine for a patient to ask for a small instrument, she adds.

"HPV testing has drastically changed cervical cancer screening over the past several years," Levinson says, which is likely leading to a greater number of women being referred for colposcopies. "HPV testing is a more sensitive test than Pap smear screening, meaning we're better able to determine who's at risk for severe dysplasia."

"HPV testing is a more sensitive test than Pap smear screening, meaning we're better able to determine who's at risk for severe dysplasia."

Advancements in screening options will help doctors better determine health risks earlier and decrease the number of colposcopies ordered, Levinson says: "There are several different molecular and cytologic tests being investigated to help determine which patients need colposcopy (and are most at risk for severe dysplasia) and which patients are at lower risk." DES VOICE

Call To Action

Help Us Update the Doctors List

When we launched the members-only area of the DES Action website, we created a star rating system for members to share opinion doctors.

Our doctors list was based on an existing list that is a few years old. We'd like to update this list with current doctors with your help.

First, we'd like you to log in and see if you doctor is listed with us. Go to: http://members.desaction.org and log in using your email and password. (If you are a member and haven't logged in before, use the default password: desUSA2015.) Click on Doctor's List in the main navigation. You can sort the list by last name, city, state or zip. If your doctor is there, please leave a rating.

If you don't see your doctor and would like to add your physician to our list, email the name and full address to: doctors@desaction.org

Finally, if you see a doctor in our list who has retired, please email: doctors@desaction.org and let us know.

A Request from a DES Daughter

"I am a DES-exposed baby 61'. I am searching to find, other, non-cancer 3rd generation impacts, and to specifically learn if anyone's child or grandchild has a mitochondria disorder, dysautonomia, cyclic vomiting syndrome, auto-immune disease, or other non-cancer related issues. If so, please contact me at mitro@desaction.org. I am digging and have found some reason to believe in a casual link, but there is little available information in the research community, and I have a long way to go. The first step is to find others like me. If you can share this information with me, I promise to keep your information confidential." DES VOICE

Research the Risks of Breast Implants After Mastectomy

If going through breast cancer were not enough, the dizzying array of options for breast reconstruction after a mastectomy can be overwhelming. The two broad categories of options are implants and flap surgery, but many options exist within these categories. Although the benefits include a woman's ability to have breasts after their surgical removal, the risks for each of these procedures are substantial enough to warrant serious consideration.

DES Daughter Joanna Katzen found this out herself firsthand. Her bilateral mastectomy 20 years ago was followed with immediate reconstruction involving silicone breast implants. Over time, she developed symptoms such as headaches, joint pain and extreme fatigue. She soon found out one of her implants had silently ruptured and led the silicone gel to leak. She has since found a large community of women who have experienced similar difficulties, and she began to learn more about the risks her original doctors didn't tell her about.

"A lot of women have emotional trouble accepting their body after mastectomy; it's a physical reminder that you had cancer, and they want to go on with their lives and enjoy their lives," Katzen said. "But I think it's immensely important for anybody who has any kind of silicone put into their body, that if they start to have unexplained fatigue or joint pains, they should look to their implants and see what's going on at the very least." Related problems have occurred with saline implants as well. Although rare, medical studies have identified several cases of mold or other fungi growing in saline breast implants. Researchers are still trying to determine risk factors for these cases.

Most studies evaluating the safety of silicone breast implants were funded by implant manufacturers, plus some by the FDA. The majority of these studies followed women for five to 10 years, possibly not long enough to detect longer-term problems. No studies have specifically investigated breast implants in women exposed to DES. Here is an overview of the risks found in research on implants.

Scarring, Pain and Capsular Contracture

Nearly everyone who undergoes breast reconstruction will experience pain during the procedure and have permanent scars. For some women, pain or discomfort may continue even after healing. Exercise, stretching, massage, anti-inflammatories, yoga, physical therapy and other treatments may help.

Another possible complication is capsular contracture, where scar tissue growing around the implant becomes a hard tissue capsule, causing possible pain and breast shape distortion. An FDA-funded study found about 15 to 20 percent of women experienced capsular contracture 6 years after surgery. At 10 years, a follow-up found 25 percent had capsular contracture and 13 percent had a rupture.

Rupture and Leaking

Both silicone and saline implants eventually need to be replaced, but their lifetime and risk of rupture varies by type and brand. FDA-funded studies found a rupture rate of 3.5 percent at 6 years with one silicone implant and 13 percent at 10 years with another. Another study found a third of women with silicone implants needed another operation 6 years later, and 10 percent needed a full replacement.

Saline implants immediately deflate from rupture, but silicone ruptures may go unnoticed longer because the gel leaks more slowly. Research on the effects of silicone leakage over time are mixed.

A European safety committee declared in 2000 that no studies had "demonstrated any association between silicone-gel filled breast implants and traditional auto-immune or connective tissue diseases, cancer nor any other malignant disease." But this statement was based on just under two dozen studies before 1999. Studies since then have shown the silicone can migrate to the lymph nodes with unknown effects. Several studies have found that women with silicone implant leakage reported higher rates of fibromyalgia, muscle pain, joint pain, fatigue, and other symptoms. Long-term studies since 2000 are sparse.

Tissue Breakdown

If pressure from the implant prevents breast tissue from healing properly, it can lead to necrosis, where the tissue dies, requiring removal. Symptoms include pain, bleeding, dark blue or black skin, fever, nausea, numbness and a bad-smelling discharge.

The FDA also identified a possible link between an extremely rare lymphoma and both silicone and saline implants. The cancer, called anaplastic large-cell lymphoma, formed in the tissue around the implants of 34 women, but it's unclear if it's related to the implants.

For women affected by implant complications, Katzen recommends the Facebook group Breast Implant Illness and Healing. DES VOICE

DES Action® VOICE

DES Action USA
178 Columbus Avenue #237182
New York, NY 10023

www.desaction.org

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Predicting Drug Effects and Interactions Safely

A new initiative at the National Institutes of Health may soon help researchers learn about the effects of various exposures on the female reproductive system—without using animal models or human trials. Though still in the development phase, the "computerized uterus" is a mathematical model that can predict a substance's interaction with estrogen receptors based on the activity of that substance during 16 tests performed in a robotic system.

The computer project is led by Warren Casey, Ph.D., director of the U.S. National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods at the National Institutes of Environmental Health Sciences. His team has used data from running 16 different assays—analytic tests—on about 1,800 chemicals to build a mathematical model for determining if something will have an estrogenic effect. They've also validated this model by comparing it to lab results from animal models—and it was accurate. But it will take more development and testing before it might be able to predict a substance's toxicity.

"The model only tells if you a particular chemical is going to be active. That's not necessarily the same thing as saying it will be toxic or have adverse effects," Casey explained. "We've taken the first step in predicting if they would interact with the estrogen receptor." Next they will try to quantify the effect, and then eventually mix different chemicals together to model how they might interact.

"A + B doesn't always equal C," Casey said. "Sometimes they mix together in ways that we can't predict and aren't intuitive."

DES is complicated because of how its toxicity shows up in later generations, he said, but this model might help scientists understand its mechanisms better. One long-term goal is for the model to predict effects based on a compound's chemical structure, "so they could design chemicals that are safer and not have to test them in cells and in animals," Casey said. DES VOICE

