

## New Study Confirms Link Between DES and Endometriosis

**R**esearchers have long known that DES Daughters are at higher risk for endometriosis, a painful condition in which the endometrial tissue that lines the uterus begins growing outside the uterus, often even in ovaries, Fallopian tubes and in the pelvic area.

However, an important part of the scientific process is regularly revisiting scientific questions to gather more evidence on them. The more evidence that exists, the stronger an association is, and strong evidence of a condition's link with DES means physicians have to take the concerns of DES-exposed people more seriously.

Now a new meta-analysis looks at all the evidence on endometriosis and DES exposure combined to see what the overall consensus is from the results. In the study, published May 14 online in the journal *Reproductive Biomedicine Online*, a group of Italian OBGYN researchers examined the data on a variety of factors in women's early lives and their risk of endometriosis. (DOI: 10.1016/j.rbmo.2020.04.005).

The authors combed through three major research databases for all English-language studies published up through February 2019. They looked at how strong the links were between endometriosis and several different characteristics. They identified six studies that involved 4,170 women, 2,360 of whom had endometriosis.

When the studies' results were combined and analyzed together, the authors found that DES Daughters had a 65% increased relative risk of developing endometriosis. That means for every 100 non-DES-exposed women with endometriosis, there are 165 DES Daughters with endometriosis.

Interestingly, however, only two of the six studies actually looked at DES exposure. The other factors linked to endometriosis risk included premature birth, a low birthweight, and being fed formula as an infant. Low birthweight is de-

fined as less than 5 lbs, 8 oz (2,500 grams), regardless of what week of pregnancy the baby was born.

These results do not mean that being born prematurely or small, or being formula-fed, caused endometriosis to develop later on. There are probably other underlying factors that increase endometriosis risk and also are related to premature birth, low birthweight and formula feeding. The researchers also noted their data on formula feeding was incomplete. They had no information on when infants began formula, how

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## Does DES Cause Adenomyosis? Probably, but we can't be certain.

The most common and serious effects of prenatal DES exposure in women occur in their reproductive systems, such as a T-shaped uterus, endometriosis and an abnormally shaped cervix. It's reasonable to wonder which problems related to the uterus or surrounding organs and tissue might have been affected by DES beyond the most commonly known. Recently, multiple DES Daughters have asked us whether adenomyosis might be related to DES.

Adenomyosis is a condition where the tissue lining the uterus, called endometrial tissue, pushes

into the uterus's muscular wall. There, it continues to thicken, break down and bleed during menstrual cycles, so it can make periods especially painful and extra heavy.

Doctors and researchers do not know what causes adenomyosis. Women with past surgery on their uterus might be at higher risk. Some studies have also suggested that female sex hormones, such as estrogen, progesterone, prolactin and follicle stimulating hormone, might be involved with the condition, but a lot remains unknown.

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# We've Refreshed Our Website — See What's New

Have you visited our website lately? You will find some important changes to the website, including updates to research, and additions to our Timeline, plus an entire new section on DES and Sex, Sexuality and Gender. We have more research findings on DES Sons, updated research information on DES Grandchildren, reconfirmed study findings on DES links to breast cancer and heart disease, and reconfirmed advice from Dr. Herbst that clear cell adenocarcinoma of the vagina/cervix continues to be a risk for DES Daughters as they age, necessitating annual Paps and DES pelvic exams.

One major change is where you will find members-only content behind our login wall. When you login successfully, you will see the **Members-Only Content** link on

the left side navigation bar (instead of on the tab across the top where it used to be located). When you click on **Members-Only Content** you will see an index of member content: interview videos, VOICE archives, doctor and lawyer lists, and much more. This Members-Only area will only appear when you are logged in.

Our Timeline has been completely updated to 2020 to highlight everything of significance that occurred with DES Action USA; DES research, DES Symposia, and DES Action Archives.

We have added a LGBTQ+ tab to a page that reports on the February 2020 study article completed by the NIH/NCI researchers done with the DES cohorts entitled "Gender Identity and Sexual Orientation Identity in Women and Men Prenatally Exposed to

Diethylstilbestrol." There is also the DES Action-funded sociological gender study conducted by Jacquelyne Luce, PhD, Principal Investigator, and her student research assistants entitled: "Embodying Transgenerational Exposure: Gender/sex/sexuality and Experiences of Being DES-Exposed," plus another sociological qualitative study by Scott Kerlin, PhD, entitled: "Prenatal Exposure to Diethylstilbestrol (DES) in Males and Gender-Related Disorders: Results from a 5-Year Study."

DES Action USA continues to be the only comprehensive organization that identifies, educates, empowers and advocates for everything DES related since 1978. Explore our updated website for the most current, accurate information!

## Renew Your Membership

It's easier than ever to renew your membership. Just log into the site using the email you registered with and your password. If you don't remember your password, you can reset it.

If you no longer use the email you signed up with, send your new address to Britt Vickstrom at [britt@desaction.org](mailto:britt@desaction.org). She will set a temporary password for you.

Thank you for supporting DES Action USA with your membership.



## MISSION STATEMENT

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

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# More Evidence Supports Multigenerational Effects from DES

Researchers are discovering more evidence to suggest that multigenerational effects of DES exposure may contribute to a condition in which a male fetus does not develop typical male genitals, called partial androgen insensitivity syndrome, or PAIS. The latest study appeared in May in the *Journal of Endocrinological Investigation* (DOI: 10.1007/s40618-020-01310-9).

The authors of the new study, based in France, pointed out that past research has shown a higher rate of hypospadias in the sons of DES Daughters. Hypospadias occurs when the urethral opening—the hole for urine and semen—occurs somewhere along the penis shaft besides the tip. The authors then present new findings about a small group of DES Grandsons that further suggest multigenerational effects from DES on sexual development.

Partial androgen insensitivity syndrome occurs when someone has XY chromosomes—typically associated with male sex—and normal testosterone levels, but their genital development does not respond normally to male sex hormones, called androgens.

Androgens are made in the testes, so a developing fetus with XX (female) chromosomes, who lacks testes, will go on to develop female genitals. But in someone with XY chromosomes, the body does not respond to the androgen in the testes and may not develop nor-

mal male genitals. The genitals may be ambiguous or appear similar to female genitals.

Someone with PAIS may appear to have mostly female genitalia, or underdeveloped female-appearing genitalia, despite having XY chromosomes. Or, the person could have underdeveloped male genitalia, such as a micropenis, undescended testicles or hypospadias.

Complete androgen insensitivity syndrome occurs when the body does not respond at all to androgens and develops female external genitals despite XY chromosomes and no internal female sex organs. This condition involves a known genetic mutation about 90% of the time and therefore is not caused by DES exposure. But only about 15% to 20% of PAIS cases result from that gene mutation. The other cases occur on their own for unknown reasons.

Those unknown reasons are what led the researchers to take a closer look at 11 DES Grandsons out of nearly 2,000 people they have studied who have PAIS characteristics. The 11 boys were all sons of DES Daughters and had a micropenis, hypospadias and/or undescended testicles, but they also had normal testosterone levels.

None of the boys had the gene mutation that is known to cause partial or complete androgen insensitivity syndrome. Further, none of their parents lived in areas or held jobs that

would expose them to high levels of endocrine disruptors.

Although it's not possible to say for certain that generational effects of DES are responsible for the boys' condition, lab experiments with DES exposure in mice have shown changes in the DNA that continue through multiple generations. The changes have to do with a process called methylation, where additional molecules of a chemical called methyl attach to the DNA molecule and can change how the DNA acts even if the DNA sequence does not change.

The authors cite several past studies in DES Grandchildren whose findings, when considered together, “strengthen the suspicion of the multigenerational effects of environmental endocrine disruptors,” they wrote. They add that it's important for physicians and researchers to pay attention to concerns that drugs containing any endocrine disruptors could have long-term, multigenerational risks if given to pregnant women.

“Indeed, pregnancy drugs may contribute to the ‘missing heritability’ of many pathologies, and this highlights the need for intensified research to ascertain the generational impacts of DES,” the authors wrote. In other words, prenatal DES exposure may be a contributor to this condition and others that can explain how it occurred when it was not inherited from parents.





*Britt Vickstrom*

of my three cats are okay with that.

**Q: Tell us about how you learned of your family's DES exposure and what it meant to you.**

**A:** I think I was in high school, in the early 1990s, and my mother had recently found out from her own mother. My mom told me that her mother (my nana) had a miscarriage in the mid-1940s, so her doctor gave her DES to prevent another one. My mom was born in 1947, and I was born in 1974.

**Finding out has been slow going. The hospital only accesses records every 30 days and only keeps records for 10 years. Having worked in an archive as a student, I understand that space can be at a premium, but since DES exposure can take years to present, this is disturbing.**

At the time I found out, there wasn't a lot of information about DES grandchildren — and there isn't that much more today — but I remember storing away that knowledge.

Then, a few years ago, Karen Calechman wrote a letter to the editor of the Mount Holyoke Alumnae Quarterly about DES exposure and I remembered our family his-

tory. I reached out to Karen and we kept in contact.

**Q: In what ways have you been affected by your family's DES exposure?**

**A:** I have a tipped cervix. I remember a doctor years ago saying that it wasn't bad, but it was unusual. I can't remember if I'd told her I was a DES grandchild. I've recently been trying to find my birth records to see if I might also be a DES daughter (most likely not, but I was born in a rural area of Iowa in 1974).

Finding out has been slow going. The hospital only accesses records every 30 days and only keeps records for 10 years. Having worked in an archive as a student, I understand that space can be at a premium, but since DES exposure can take years to present, this is disturbing.

I've also struggled with depression, but that's also present on the other side of my family.

I also have Raynaud's syndrome, which, for me, primarily means poor circulation in my hands and feet. There is primary Raynaud's, but secondary Raynaud's is a result of rheumatoid arthritis.

I've tested negative several times for rheumatoid arthritis, but I do wonder whether it might also be linked to being a DES Granddaughter.

**Q: What interested you about becoming the DES Action Community Manager?**

**A:** A lot of the position's responsibilities are the same as what I've

been doing for the last 20 years working with nonprofits, plus it gave me the chance to learn more about DES and, hopefully, my own health. Working in this position also gives me the opportunity to support DES-exposed people, help keep us connected, and advocate for us.

**Q: What has surprised you or what have the early days with DES Action been like?**

**A:** Due to the pandemic and the position being remote-friendly, this is the first time I've started a job without meeting coworkers in person. I'm grateful for video calls to put faces to names and voices. I've been impressed with the dedication of everyone to the DES-exposed community and their commitment to educating others. There are still so many people who don't know what DES did, and continues to do, to people.

**Q: Tell us how you learned about DES Action and came to be involved with the organization.**

**A:** I learned about it from Karen Calechman in the Mount Holyoke Alumnae Quarterly. It's hard to pick one thing that I have found most valuable. I'm thankful for information that I can share with my mom and items specific to my generation of exposure. I'm also thankful for the communities that have formed where people can share their stories and support each other.

**Q: What is your hope for the future based on your experience as a DES Grandchild?**

**A:** I hope that more information will become available for what DES grandchildren might experience, what we should be aware of, and that we can continue to support each other. And I really hope that great-grandchildren won't have to worry about the effects of exposure.





long and what types of formula they ate.

The authors suggest that the link to endometriosis could, for example, be related to the estrogen found in soy formulas. DES exposure was a bigger risk factor than premature birth and low birth-weight. Women born prematurely had a 21% increased risk of endometriosis. A low birthweight was linked to a 35% increased risk of endometriosis. The risk from being formula-fed was the same as the

risk from prenatal DES exposure.

“The possible relationship between DES exposure and endometriosis may result from a combined effect of increased retrograde menstruation, immune dysfunction and increased estrogen concentrations,” the authors wrote. During retrograde menstruation, the blood and tissue released during a period goes back up into a woman’s body, often carrying with it the endometrial waste tissue that the body is attempting to discard.

“Assessing how intrauterine environment influences health

outcomes in the offspring is a challenging task,” the authors wrote in their paper. They noted that several past studies have looked at the link between DES exposure and endometriosis, but those studies did not report findings with a numerical risk that the authors could calculate into their analysis in this study.

Several of these studies were also less reliable and rigorous because they included a small number of women, they did not confirm medical diagnoses, or because the samples of people studied were not random.



## Does DES Cause Adenomyosis

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### Early Research in Adenomyosis

Nearly all of the research into adenomyosis and DES is in animal studies. In the earliest study, in 1982 (DOI:10.1016/0002-9378(82)90189-2), researchers exposed mice fetus’s genital tracts to DES. One mouse developed a lesion in the genital tract that resembled adenomyosis in human females. A study a year later similarly exposed female mice to DES prenatally and found that adenomyosis was common in them (J Natl Cancer Inst. 1983 Mar;70(3):477-84).

However, studies in 1984 (DOI:10.1093/jnci/73.1.133) and 1985 (DOI:10.1093/jnci/74.1.121) did not find adenomyosis in DES-exposed mice. A 1987 study found adenomyosis in DES-exposed mice only after their ovaries were removed in adulthood (DOI:10.1016/0304-3835(87)90001-2)

The next study, in 2000, involved researchers giving DES to mice that had BRCA1, BRCA2 or another mutation that increases the likelihood of developing breast cancer.

Receiving DES caused adenomyosis—along with other uterine, vaginal and epithelial problems—in the mice. (They were not prenatally exposed, so they were akin to DES Mothers.) The problems varied according to the different mutations,

but the mice had no offspring, so the study doesn’t offer data about prenatal DES exposure.

### Hox Genes: The Missing Link

We could not find other studies specifically examining DES and adenomyosis, but a 2016 analysis by OBGYNs at Yale does shed more light on how DES and adenomyosis might be linked. The paper was a summary and explanation of research related to a group of genes called Hox genes (DOI: 10.1101/cshperspect.a023002). This group of genes carries instructions on where body parts are “placed” on developing organisms—basically which parts are supposed to develop in which places when these genes are expressed.

Think of Hox genes as similar to someone putting together a puzzle. Each piece has a place it’s supposed to go, and it’s the Hox genes that put it there. But if something interferes with the puzzle solver—their attention is diverted or someone knocks their hand—they might place a piece where it doesn’t fit. Even if the rest of the puzzle is done correctly, that piece won’t work in the overall puzzle as it should. The 2016 paper cites past research finding that DES can interfere with Hox gene expression in a mouse’s reproductive tract. In other words, DES causes Hox genes to give the wrong instructions, lead-

ing to developmental abnormalities in reproductive organs.

The earlier research had shown that DES decreases Hoxa10 and Hoxa11 gene expression in mice. Those decreases then caused a T-shaped uterus in the mice, just as DES causes in humans.

This evidence suggests that prenatal DES may interfere with Hox-genes to cause a T-shaped uterus in DES Daughters, though that hasn’t been confirmed.

The authors also note that changes in Hoxa10 and Hoxa11 gene expression have previously been linked to lower rates of embryo implantation related to various conditions, including endometriosis, polycystic ovarian syndrome and adenomyosis.

What does all that mean? It means we do not have direct evidence showing that prenatal DES exposure definitely causes adenomyosis in humans. However, enough evidence exists to show how DES could cause genetic changes that affect the female reproductive tract—including changes that increase risk of adenomyosis. Some limited evidence also shows development of symptoms similar to adenomyosis in mice exposed prenatally to DES. There is enough evidence to say it’s possible, and probably likely, that adenomyosis in DES Daughters could be related to their prenatal DES exposure.



# Denise Scott:

## A DES Daughter, Her Doctor and Their Story

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*Denise Scott, a retired Floridian, was born in 1955, at the height of DES prescribing before more research revealed that it did not reduce the risk of miscarriage. It wasn't until she was a teenager that she learned her mother had been given the medication, a discovery that ultimately led her to the office of Dr. Farhad Talebian, an OBGYN in Garden City, New York.*

*Dr. Talebian would soon become an integral part of Denise's life. He never stopped caring for her health or about her as a person, no matter how angry or up-*

*set she got about the problems she suffered as a DES Daughter.*

*Denise's story is not a happy one. It's a familiar story of frustration, anger, pain, loss, sorrow, and more anger that many in the DES community can relate to. But if there's a single positive note in her tale, it's that a lifelong patient-doctor relationship with the right physician can make all the difference in pushing through the hardest times and ensuring that you always have an advocate in your corner.*

When Denise was 16 years old, her mother read an article in Long Island's newspaper *Newsday* about the link between in utero DES exposure and a gynecological cancer being discovered in young girls. "My mother knew she took something and it sounded similar," Denise said. Fortunately, her mother had the same OBGYN for all those years. She called him in tears and told him what she read, but he didn't seem too concerned.

"Margie, they don't really know," he told Denise's mother. But through the phone, she could hear him flipping through her medical files. He confirmed that he had given her DES. He seemed to blow off the risk but offered to examine Denise anyway. Denise's mother wasn't ready to tell her daughter why she needed to see a gynecologist when she was 16 and still a virgin. She lied and said all females must see the gynecologist after turning 16.

The appointment did not go well. The doctor made Denise feel awful, and she refused to see him again. When he unexpectedly died at a medical conference two years later, his staff called while going through his estate. Did Denise's mother want her medical files? Denise didn't hesitate: "Get the

file," she told her mom. Denise didn't have any medical problems—yet—but her gut told her the records were important.

### Finding the Right Doctor

Soon after the doctor's death, Denise's mother learned about DES Action, which was still in its early days with just a few DES Mothers running the phones. She called the organization to ask for a doctor recommendation for Denise. They said Dr. Talebian had an

expected. He was kind and gentle. He explained things in a way that made sense. From that day forward, Dr. Talebian was the only doctor Denise would ever really trust.

That doesn't mean their appointments were easygoing. Especially as she began developing DES-related problems, Denise hated going to his office, hated seeing happy, carefree pregnant women in the office who didn't have to deal with her issues. She hated sitting for what felt like hours in the waiting room so much

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**The Air Force doctor's notes made it clear he was going to order procedures Denise didn't need. She was little more than an experiment to him.**

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excellent bedside manner. Denise still refused to go at first—the first experience had been too awful. But then she got engaged and she had been hearing more about miscarriage and ectopic pregnancies in DES Daughters.

"I thought, if I'm going to get married, my future husband and I need to know if I'm going to be able to have kids," Denise said.

The visit with Dr. Talebian was the opposite of everything she ex-

pected. He was kind and gentle. He explained things in a way that made sense. From that day forward, Dr. Talebian was the only doctor Denise would ever really trust. That doesn't mean their appointments were easygoing. Especially as she began developing DES-related problems, Denise hated going to his office, hated seeing happy, carefree pregnant women in the office who didn't have to deal with her issues. She hated sitting for what felt like hours in the waiting room so much

Several months after her wedding, Denise had what she suspected was a miscarriage. Her husband was in the

Air Force, so she saw a doctor at the base, but he couldn't tell if she'd had a miscarriage. He ordered a D&C, which wasn't clinically necessary, and afterward told her she had cancer—and one year to live.

"My husband fell apart. It was very difficult," she said. "We were newly married, and I didn't have my family or friends close by for support."

So she got a copy of her medical records, headed home, and took her file to Dr. Talebian. The news wasn't good, but it wasn't cancer either.

"You're a classic DES Daughter—a cervical hood, a vaginal hood, a cervix not in the right place—and he was going to use you as a guinea pig," Dr. Talebian said. The Air Force doctor's notes made it clear he was going to order procedures Denise didn't need. She was little more than an experiment to him.

Ultimately, though, Denise would need surgeries. The first was a cold knife conization for early stage cervical cancer. She hemorrhaged a week and a half later, and her mother frantically called Dr. Talebian's office. They told her to bring Denise in immediately but that Dr. Talebian wouldn't be in for a few days.

"Can I bleed like this and live until Thursday when Dr. Talebian comes back?" Denise asked. Other doctors called from the practice and hospital, begging her to come in. She finally did.

The cancer came back after the conization, and Denise had four more procedures over the next two years, including cryosurgery, two laser surgeries and another cold knife conization. "Whatever we were doing wasn't working," she recalled. "Whenever I had surgery, the cancer got worse."

During this time, Denise's mother regularly called Dr. Talebian, begging him to give Denise a hysterectomy. "She's going to die, she's going to die, she's going to die," Denise recalls overhearing her mother say in every call. "I'm not

going to give her a hysterectomy," Dr. Talebian said.

Denise was dead set against losing her uterus. But she was also in pain all the time. During a trip to Europe, her mother told her that she'd been holding herself in her sleep, with her hands over where her ovaries would be. "She thought I was going to die," Denise said.

After the fifth surgery, Dr. Talebian realized he had no choice: A hysterectomy really was the only

with Dr. Talebian, going over her records, he told Denise, "You need a hysterectomy."

When Denise next saw Dr. Talebian, she remained steadfast: She would rather die than leave the world with less of herself than she entered it with. But somehow, during a foggy period Denise cannot recall, she consented to the procedure. July 24, 1986 was the last day Denise had a uterus, and she mourns her loss every year.

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**When she was told she couldn't sue because her conditions were pre-existing—since they developed in utero—she traveled to Albany to lobby legislators. She fought relentlessly with busloads of other DES Daughters, despite her pain.**

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way to save Denise's life. But he knew she would never go for it. "It's going to be up to you and me to convince her," Dr. Talebian told Denise's mother.

### **"You Need a Hysterectomy"**

It took three months before he even brought it up at an appointment. After hemming and hawing, he finally told her, "I'm not sleeping at night. You have to have a hysterectomy. I don't know how high up the cancer goes."

Denise had severe stenosis, where the passage through the cervix is very narrow or completely closed from the cancer. It was amazing she was even continuing to menstruate.

"I'm not doing that," Denise told him. "You better come up with another f\*\*\*ing plan." That would become her refrain the next dozen times it came up. But Dr. Talebian wouldn't give up. He finally persuaded her to talk to another doctor. She met with Dr. Burton Krumholz, who led the DES screening program at Long Island Jewish-Hillside Medical Center.

After Krumholz spent a full day

"He knew better than anyone I would never get over this, and I haven't," Denise said. "It's been 34 years and it's still depressing to me."

The pathology report showed all four quadrants of her cervix were "packed" with cancer. Denise still cried every night for four years. "I don't remember making the decision to live at all," she said.

As sick as Denise was all this time, emotionally, mentally and physically, she never stopped fighting to ensure the public knew what drug companies had done. She was always in pain, but when she was asked to speak on TV and on the radio, she did.

When she was told she couldn't sue because her conditions were pre-existing—since they developed in utero—she traveled to Albany to lobby legislators. She fought relentlessly with busloads of other DES Daughters, despite her pain.

It was while Denise was recovering from the hysterectomy that a New York Public Interest Research Group rep called her about the case. They had won. From that day forward, other DES Daughters would be able to sue as well.



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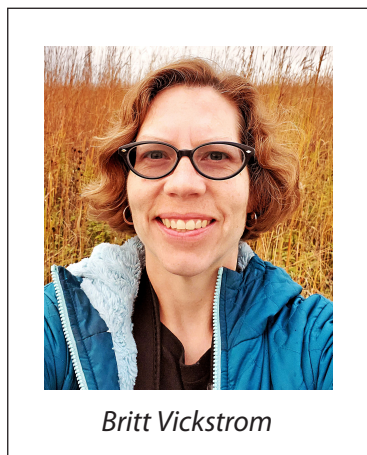
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## Meet Our New Community Manager



Britt Vickstrom

*Britt Vickstrom, a DES Granddaughter, has recently taken over the Community Manager position following Karen Calechman's retirement. We're thrilled to have Britt join the DES Action team. Learn a bit more about her in this Q&A.*

**Q: Tell us a bit about yourself.**

**A:** I'm a 6th generation Iowan, but I've also lived in eight states and two countries. I live in Davenport, Iowa, on the Mississippi River. I went to Mount Holyoke College, in South Hadley, Mass., where I majored in religion and minored in Russian Language and Literature. I spent my junior year abroad at the University of Edinburgh in Scotland, and I later returned there for a master's degree.

I'm an only child. I have learned that my birth was not normal for DES exposure. I was two weeks late, and after inducement, I held on for another 12 hours. I apologize to my mother on a regular basis for this. I've worked for non-profits for 20 years, focusing on teaching, public speaking, member

and volunteer recruitment, fundraising, and public relations. For the past few years, I've worked part-time on a farm that is being restored to native habitats. I enjoy volunteering at a local environmental education center. I am a birder. One of my favorite birds is the roseate spoonbill.

**Q: What are some fun facts about you that people probably wouldn't expect?**

**A:** I used to be a hooker. I played rugby in college and grad school. I played several positions, but the final one was hooker, because that position "hooks" the ball in the scrum. I bought a small accordion a few years ago at a second-hand shop and have been trying to learn to play it. Two out

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