DES Action® VOICE

Inside

A Focus On Diethylstilbestrol

SPRING 2016 #148

Cervical Dysplasia Rates Decline as DES Daughters Age

The risk of cervical cancer in women exposed prenatally to DES appears to decrease as women age, suggests the most recent research from the DES Follow-up Study. In the new study, published March 12 in the *American Journal of Obstetrics & Gynecology*, DES lead investigators Rebecca Troisi and Robert Hoover, both at the National Cancer Institute, investigated whether DES Daughters' risk for high-grade cervical and vaginal neoplasia remains high as they age. This neoplasia, also called dysplasia, is not the mild dysplasia often diagnosed by pap smear but the more severe dysplasia that can be pre-cancer if not treated.

Part of the motivation for the new study came from an attempt to determine how DES Daughters should interpret the updated guidelines on cervical cancer screenings. When the American College of Obstetricians and Gynecologists changed their guidelines to extend the interval between screenings, they exempted DES Daughters from the new recommendations. But no one knew whether science backed up that decision because no one had done the research.

In the new study, researchers compared rates of high-grade cervical dysplasia in 4,062 DES Daughters and 1,837 non-DES exposed women. The women had been followed for about 30 years (from 1982 through 2013), and over that time, 178 of the women developed neoplasia of grade 2 or higher. About twice as many DES Daughters developed cervical neoplasia than non-DES daughters: 5.3% of DES Daughters compared to 2.6% of unexposed women. The risk of cervical dysplasia was highest for those who had been exposed earlier in gestation to DES. For example, daughters were first exposed past 15 weeks of their mother's pregnancy had no higher risk than unexposed women, and the increased risk for those first exposed past 8 weeks gestation was not statistically significant. Those exposed before 8 weeks gestation, however, had about 2.6 times greater likelihood of grade 2 cervical neoplasia or higher.

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Environmental Contributors to Endometriosis — Beyond DES

Despite affecting an estimated 10% to 15% of fertile women, endometriosis is a complex condition shrouded in mystery. It's difficult to diagnose without invasive, surgical procedures, and scientists don't fully understand what causes it. It does appear, however, that various exposures to a fetus during pregnancy can increase the likelihood that those children will later develop endometriosis. DES exposure is a well-established risk factor for endometriosis, but additional exposures from other compounds may up amplify that risk. A research review published in the journal *Reproductive Sciences* in March described what scientists currently understand about prenatal environmental exposures and the risk of endometriosis.

The endometrium is the tissue that lines the inside of the uterus. Endometriosis occurs when that tissue grows out of control and into the pelvic area outside the uterus. Each month, that tissue thickens and breaks down during menstruation as all endometrial tissue does, but instead of exiting the body through the cervix and vagina, it stays stuck in the pelvic area. There, it irritates other tissue and develops scar tissue and chronic inflammatory lesions. The biggest symptom of endometriosis is pain, particularly around menstruation. Severe endometriosis can also negatively affect fertility.

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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

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MISSION STATEMENT

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

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Published quarterly by:

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ISSN 1522-0389

Environmental Contributors to Endometriosis

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Researchers haven't discovered precisely how or why endometriosis develops, but estrogen likely plays a role. High levels of estrogen, whether natural or synthetically added to medications or products, may encourage the abnormal growth of the endometrial tissue. Prenatal exposure to DES and ethinyl estradiol have therefore been linked to an increased risk of endometriosis. In one study of 33 infertile couples, in which all the women were DES Daughters, endometriosis was responsible for the infertility in one third of the women. Ethinyl estradiol, a common active ingredient in oral birth control pills and in hormone replacement therapy for post-menopausal osteoporosis, is a category X medication for pregnancy—absolutely not to be taken.

Is BPA a Factor?

In addition to these substances, however, prenatal exposure to other environmental contaminants may increase the risk of endometriosis. The first of these, also discussed on page 5, is bisphenol A, or BPA. This endocrine disruptor is used in a wide range of plastics and food containers, including canned foods. In fact, the authors in this study note that "humans are believed to be primarily exposed to BPA through the ingestion of food and beverages that have been contaminated by direct or indirect contact with BPA-derived products."

Most research into BPA has been in rodents, who developed endometriosis as a result of exposure to BPA. It's unclear whether this same effect occurs in women exposed to BPA, but one study of 430 women in 2014 suggested that it could be. That study did not find that BPA concentrations in women's urine increased the risk of ovarian endometriosis, but women between the 25th and 75th percentile of urinary BPA concentrations had three times greater odds of non-ovarian pelvic endometriosis than those with the lowest levels of BPA in their urine.

Other Possible Culprits

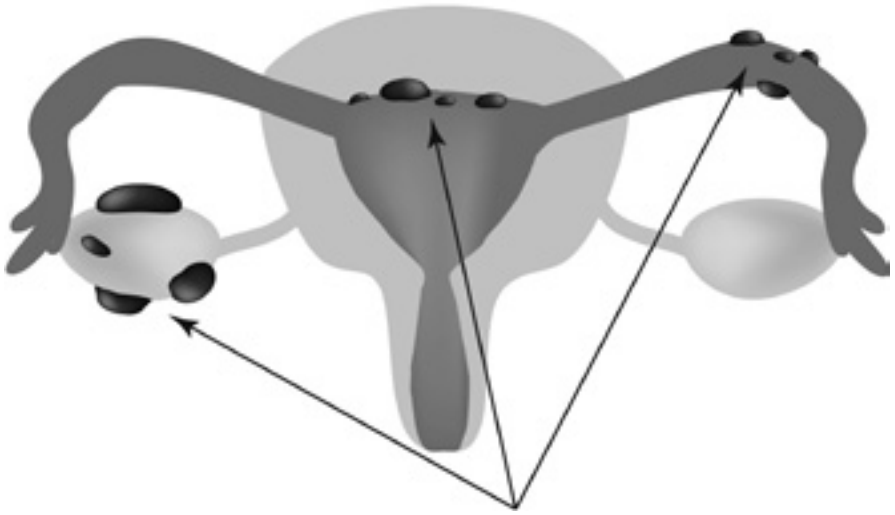
Polychlorinated biphenyls, or PCBs may also contribute to endometriosis. PCBs are synthetic organic chemicals not naturally found in the environment, but they were used as coolants and lubricants in electrical equipment up until 1977 in the U.S. and have remained in the environment since. Older fluorescent lighting, appliances or electrical devices may still contain PCBs. Exposure to these chemicals by breathing them or by their contamination of water and agriculture can increase odds of endometriosis by three to five times, depending on the PCB.

Finally, a chemical called TCCD (2,3,7,8-Tetrachlorodibenzo-p-dioxin) has caused endometriosis in rodents, but there's too little evidence to know if it does the same in humans. TCCD is an industrial waste product that resulted from past manufacturing herbicides and from pulp and paper bleaching, but its presence in the environment dropped by more than 80% between 1987 and 2000 due to regulations and voluntary changes in manufacturing. People's exposure to TCDD peaked in the early 1970s but has dropped to nearly zero since the early 2000s. Although those born between 1960 and 1980 likely had greater exposure to TCCD, research has shown these concentrations have dropped by 50 to 70% since the 1980s.

It's difficult to know how much these chemicals, beyond DES, increase risk of endometriosis, but knowing about the possibility may help explain why some DES Daughters had more problems with endometriosis than others. DES VOICE

In one study of 33 infertile couples, in which all the women were DES Daughters, endometriosis was responsible for the infertility in one third of the women.

Endometriosis



Locations of endometriosis

Q&A with a DES Action Member: How Does DES Action Help You?

Individuals join DES Action for different reasons, and sometimes a member whose membership has lapsed returns to the organization because of what it offers. We asked Teresa, one such member, about her journey with DES.

Q: Can you describe finding out about your DES exposure?

A: When I became sexually active at age 19, I bled every time I had sex. I went to my college infirmary, and they sent me to the only OB/GYN in our small college town who had the equipment to do a colposcopy. He took one look and asked if my mother had taken DES when she was pregnant with me. When I asked her, she remembered only that she had taken a pill that was supposed to prevent miscarriage. (Her first daughter died of a heart defect before she was a year old; her second pregnancy ended in miscarriage.) She innocently contacted her doctor, told him about my bleeding and asked for her records. He claimed (from his high-rise office) that the records had been destroyed in a flood.

For the first couple of years, I was getting vaginal or cervical biopsies every month, which was really scary. I also felt isolated in those pre-internet days because I didn't know anyone else dealing with this and didn't feel that I had many people I could confide in.

Q: How did you find out about DES Action and how has it helped you?

A: I think I first heard of DES Action at my doctor's office. I wanted more information about DES exposure and about how other people were dealing with it. Because of DES Action, I was informed enough to ask for high-risk pregnancy care. My doctor checked my cervix every week after about 16 weeks of pregnancy. It started thinning out and she was worried I'd give birth prematurely, so she did a cerclage (stitched my cervix shut). I carried the pregnancy to term and was blessed to have a healthy baby.

Now that I am post-menopause, I like the information on how often we need checkups and what the checkups should include. I'm very grateful that DES Action exists, and I appreciate the people who created and maintain it.

Q: At one point your membership lapsed for a short time. Why did it lapse, and why did you eventually renew?

A: In my mid-20s, my adenosis improved. I continued getting annual colposcopies and thought that was all I needed to do at that point. Then, the first time I got pregnant, at age 32, I miscarried. My doctor recommended a hysterosalpingogram—an x-ray of the uterus and Fallopian tubes—which revealed that I had the classic DES T-shaped uterus as well as a blocked Fallopian tube. She said I would have a hard time getting pregnant again and a hard time carrying a baby to full term if I did get pregnant. I renewed my DES Action membership to see how other people were dealing with this and to keep up to date on high risk pregnancy care. (I was not interested in fertility treatment because I was unwilling to take any drugs or hormones.)

Q: What has been most valuable about DES Action for you?

A: Education and community. Talking about sexual issues, even to close friends, can be uncomfortable. The DES listserv includes people who know what I'm dealing with, have sometimes had the same issues and often offer useful advice from their experiences. It is also helpful to know what tests I should be getting regularly and to be able to provide information to my doctor. I have also used the list of recommended doctors.

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

A: I hope to see the United States get single-payer universal health care. Currently, U.S. health care is not about health—it is about profit. Pharmaceutical companies are too powerful and need some form of oversight/limits. I'd like to see further research on endocrine disruptors in general and how pollutants, drugs and chemicals in the environment affect everyone's health. I think our country does not pay enough attention to environmental issues. DES Daughters and Sons (and grandchildren) are the canaries in the coal mine, but ultimately, these issues affect everyone.

Next Steps in DES Research Focus on DNA Methylation

Now that the DES Follow-up Study has published new findings DES exposure and cervical dysplasia (see page 1), National Cancer Institute researchers Rebecca Troisi and Robert Hoover will be turning their attention to a new pilot study on genetics. The new study focuses on understanding the possible epigenetic effects of DES exposure by comparing DNA methylation patterns in those who have and haven't been exposed prenatally to DES.

DNA methylation refers literally to a methyl (CH3) group joining a DNA strand. In practical terms, though, it's a mechanism that can switch genes off and on. Abnormal methylation can play a role in different diseases. Switching off a gene that suppresses tumors, for example, may lead to cancer developing. DNA methylation happens in all mammals and is essential to healthy growth and development, but scientists still have a lot to learn about how it works. Troisi and Hooper hope to find out if methylation plays a role in the intergenerational effects of DES exposure.

They're currently conducting a study to see whether they can bring together 60 DES-exposed and unexposed women, draw blood samples, extract DNA from the blood and then compare the samples to look for differences in DNA methylation patterns. If successful, a larger study could follow, but they're facing a number of scientific challenges. "There's a lot of 'ifs' here," Troisi said. For example, DNA methylation patterns can change throughout a person's lifetime, so it's not clear whether any differences would even show up in women who were exposed many decades ago. The pilot study is the first step to finding answers. DES VOICE

Zebrafish Experiments Reveal Concerns about BPA and BPS

One of the endocrine disruptors best known to the general population today is bisphenol A, or BPA, a compound used in manufacturing everything from plastic containers and canned foods to paints and paper products. When concerns about possible health effects from BPA came to light, many companies began phasing it out (though it's still widely used), and the FDA banned its use in baby bottles and children's drinking cups. But bisphenol S, or BPS, replaced BPA in many products, and a study published February in the journal Endocrinology suggests BPS may carry similar health risks as BPA, including potentially affecting human reproductive functioning and interfering with normal hormone activity.

Researchers at Shanghai University in China and at the University of California at Los Angeles conducted a series of experiments to see how BPA and BPS each affected the reproductive neuroendocrine system in zebrafish. Zebrafish are commonly used in research because they share a great deal of biology and genetics with mammals, but they're transparent, so scientists can observe what's happening in them without having to cut them open. The researchers in this study "tagged" the zebrafish neurons they wanted to watch with fluorescent green to make it easier to observe how the neurons were affected in the fish exposed to BPA or BPS and those not exposed.

The scientists found that exposure to low levels of BPA and, separately, to BPS—similar to what would be found in the environment—increased the number of a particular neuron in the hypothalamus and affected the expression of a half dozen genes related to reproduction. Zebrafish exposed to BPA or BPS had shorter length pregnancies without apparent damage to the newborn zebrafish. It's not clear exactly how all this might translate to humans, but it's possible that effects of BPA or BPS could relate to the timing of puberty, for example, or otherwise affect human reproductive systems. The researchers' findings also suggested the effects of these endocrine disruptors depends on an organism's stage of development and how long it's exposed to the chemical.

"This study demonstrates that alternatives to BPA used in the manufacture of BPA-free products are not necessarily safer," the researchers wrote. "Using zebrafish as a model for investigating the impact of endocrine disrupting chemicals on vertebrate embryonic development, we show that ecologically relevant levels of BPA and BPS alter many aspects of the reproductive neuroendocrine system." DES VOICE

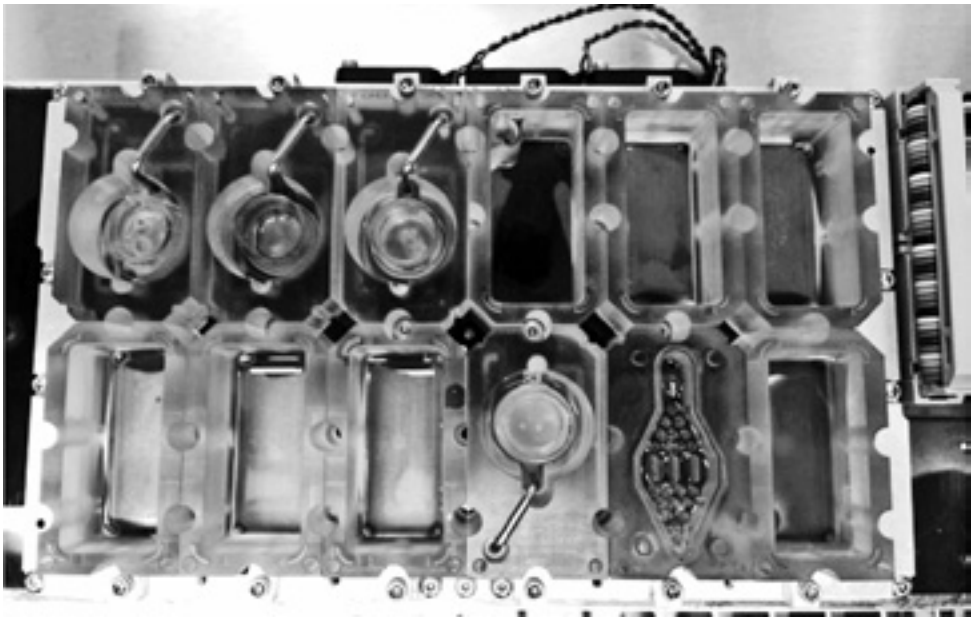
'Organ on a Chip' Allows Testing Chemicals in Female Reproductive Tract

Imagine having a model of the female reproductive tract not much bigger than what a Barbie doll's reproductive organs would be—but made of real human tissue that operates just as the human body's tissue operates. That sounds like science fiction, but it's basically what the Evatar project is, a research initiative at the National Institute of Health that has created an "organ on a chip."

But it's not just one organ: It's a miniature three-dimensional model of the ovaries, Fallopian tubes, uterus, cervix and vagina all contained on a tiny platform that fits in the palm of your hand. Think of it as a living robot—without a brain—that scientists can use for testing chemical exposures. Each of these organ tissues is interconnected, along with liver tissue, in a self-contained system that mimics a woman's 28-day reproductive cycle.

The top layer of the chip has the cells for each organ, and the bottom two layers contain the miniaturized pumps and tubes to carry liquids and hormones throughout the tissues. The entire chip mimics the environment of the female body, and the reproductive organs can be added or removed as needed. The liver was included in Evatar because it plays an important role in metabolizing reproductive hormones. The liver also regulates the effects of reproductive hormones, endocrine disruptors and therapeutic drugs such as chemotherapy agents.

"Early in the study of basic reproductive toxicology, people only focused on one tissue, such as ovarian tissue or uterine cancer, but in our system, we can connect all these reproductive organs together and study the whole reproductive



tract and the interaction among these tissues," explained Shuo Xiao, PhD, a postdoctoral fellow at Northwestern University's Feinberg School of Medicine, who is working on the project in the Dr. Teresa K. Woodruff Lab. "This has great potential for studying DES or other chemicals with female reproductive toxicity."

The platform will enable scientists to study cancers and to determine, cost-effectively and quickly, how safe or toxic various drugs or other biologic agents would be, using the miniature liver to process the substances. According to the NIH, "this advance solved a major technical challenge in the field: enabling organ models to communicate with each other via secreted factors, including hormones, to more closely resemble how they work together in the body."

A Need for Better Research About Women

Throughout most of medical research, women have been excluded from preclinical research, making it next to impossible to determine how certain drugs or other chemicals would interact in a woman's body, whether she is pregnant or not. These exclusions have meant too little information about the impact of substances—including DES—on women's bodies.

"Because women have menstrual cycles and hormone cycles and pregnancy, people have tried to avoid using females so they could avoid pregnancy and the hormone changes," Xiao said. "Researchers think using women will affect their results, so they only want to include males, but that is not fair for women who are under potential risk to be exposed to those chemicals."

So far, the scientists have been focused on ensuring that all the tissue cultures are staying alive and working as they should. The researchers connected all the organs in the system last summer, and the researchers have been doing preliminary tests with compounds

whose effects are already well known to make sure the effects are replicated in the model, Xiao said.

"I tried some endocrine disruptors, and they confirmed their toxicity in the female reproductive tract," Xiao said. He tested DES and bisphenol A, or BPA, the compound used in manufacturing many plastics and both showed the expected estrogenic effects. In a similar organ-on-a-chip project of a female breast cancer model, adding DES encouraged breast cell proliferation, and Xiao plans to add DES to the ovarian system in Evatar to test its effects on ovarian follicles.

And after that? "The next step is to apply the system to clinical drugs and to also environmental chemicals," Xiao said. "Now that we have established this system, the final goal is to provide a system for drug screening, so we are going to attach multiple drugs and other chemicals."

Chip Offers Many Opportunities for Research

"The platform also could help scientists understand the various cancers, sexually transmitted infections and benign tumors that can affect female reproductive organs," the NIH stated in their description of the project. "In addition, researchers will be able to use Evatar to predict whether a candidate drug, vaccine or biologic agent is safe or toxic in humans in a faster and more cost-effective way than is possible with current methods." Since each element can be customized for different experiments, Evatar also allows for testing effects on the system at different hormone levels since women's levels can differ and fluctuate across their lifetimes.

Use of the model won't be limited to scientists at the NIH. Xiao expects Evatar will be used at other hospitals and research centers even by those who have little background on female reproductive biology. "We want to make it simple and easy to use," he said.

The project is funded jointly by the National Institute of Environmental Sciences, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the NIH Office of Research on Women's Health and the NIH Common Fund.

"This work is a remarkable advance for understanding female biology, and it will fill an important gap," said Janine A. Clayton, MD, director of the Office of Research on Women's Health, in a story featured by the NIH on Evatar. "It's a perfect example of how considering sex as a biological variable can help us develop individualized treatment and learn more about how females may metabolize drugs differently from males."

> "Researchers think using women will affect their results, so they only want to include males, but that is not fair for women who are under potential risk to be exposed to those chemicals."

The ultimate goal will be to design an entirely integrated human-body-on-a-chip for research and testing, Xiao said. Currently, scientists are also working on the female breasts, the brain, testes and the kidney. "One day in the near future we can connect all this tissue on this chip," he said. DES VOICE

Cervical Dysplasia Rates

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After accounting for which women got regular screenings and other differences, the risk of cervical dysplasia over those three decades was about twice as high overall for DES Daughters, but the risk did not stay constant at all ages. In fact, the higher risk only occurred up until DES Daughters were 44 years old. From age 45 on, DES Daughters and unexposed women had about the same likelihood of developing cervical dysplasia.

"The findings reflect that the risk decreases a lot in older women," Troisi said. However, the findings could also reflect the fact that fewer people in general are getting cervical cancer and so it may be harder to detect large differences between exposed and unexposed women. For that reason, she does not necessarily suggest that women should follow the new ACOG guidelines that stretch out the time between each screening for women without a DES history.

"I would hesitate to say they should feel reassured about not being screened," Troisi said. "Hopefully they have a physician who is familiar with the problems associated with DES, and women can make that decision with their physician."

This study also represents the first time cervical dysplasia rates have been studied in perimenopausal and postmenopausal DES Daughters. Because current DES Daughters are all 45 or older, it will take more time to gather enough data on cervical dysplasia rates at older ages. For now, however, these findings might provide a small amount of peace of mind that aging may provide a benefit when it comes to this particular DES risk. DES VOICE

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Pregnant Women in Clinical Trials: An Ethical Challenge

The ethics of pregnant women's involvement in scientific research has always been challenging. Including pregnant women in trials for new treatments could potentially cause harm to the fetus, but not testing treatments in pregnant women means possibly finding out the hard way in the general population that a treatment can harm a fetus—in women who never consented to research.

A recent article in the *Journal of Medical Ethics* discussed the ethics of special circumstances in which a woman has the option of joining a trial when her fetus has been diagnosed with a condition that cannot be treated beyond watchful waiting or termination. Author Maria Kreszentia Sheppard, from Queen Mary University London, explained why it's especially important that these women understand the risks of joining a clinical trial since their anxiety about their fetus may make it harder to assess whether they should join a study.

A woman "may be faced with the prospect of doing nothing and possibly losing her unborn child," Sheppard writes. "Where the trial potentially has benefits for the fetus, however minor, the woman may ignore any possible risks to herself, and may feel morally obliged to do the best for her 'unborn child' and focus solely on the glimmer of hope for its survival." Specifically, women might downplay risks to themselves if they believe their fetus could greatly benefit.

But the fetus may not benefit much at all—especially in phase I/II trials that test different dosages and efficacy levels—and women should understand that. Clinical care and clinical research have different goals, so Sheppard emphasized the importance of clear in-person communication between the researcher and the woman.

"The message should be clearly conveyed that the experiment is unlikely to benefit her unborn child and that there may be risks to her own health and possibly also to her fetus," Sheppard wrote. DES VOICE

