



Educational Material

SHORT CASE VIGNETTE & HANDOUTS

“A woman born in 1967 presents with abdominal pain...”

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***** Please do not open this packet until instructed to do so. *****





Case Vignette

Mrs. Ellen Anderson, a white architect born in 1967, is a new patient to your primary care office. She presents with a 3-day history of right lower quadrant abdominal pain, which she describes as sharp, nonradiating, and intensifying. She rates its current severity as 8 on a scale of 10. When you ask whether the location of this pain has changed, she reports, “No.” She cannot cite any aggravating or ameliorating factors.

She denies associated fever or chills, malaise, nausea, or vomiting. She denies noticing blood in her stools, change in stool color, diarrhea, or constipation. She denies noticing any abdominal or groin masses. She denies any abdominal skin infections or rashes. She also denies abdominal trauma, pain on urination, blood-tinged urine, or increased urinary urgency or frequency.

1. What is your differential diagnosis (top eight candidates)?



Case Vignette

You perform a focused history and physical examination, from which you determine that Mrs. Anderson's last menstrual period was 8 weeks ago and was normal in timing and duration. Her menses typically occur every 28–30 days. Neither she nor her husband uses contraception. She denies any unusual vaginal discharge or bleeding, vaginal itching, extreme menstrual cramping, pain with intercourse, or vulvar lesions.

She reports no loss of appetite, recent weight change or change in sleeping habits. She denies any recent travel within or outside the country.

She denies any history of gastrointestinal or gynecologic maladies; and she denies any history of appendectomy or other abdominal or pelvic surgery.

Medical History

Mrs. Anderson had chicken pox as a child, denies any past surgeries, and has never been pregnant. She reports increased breast tenderness and “lumpiness” over the past two weeks, and recalls being told she has “fibrocystic breasts” but denies any other significant medical history, including malignancies.

Family History

Both of Mrs. Anderson's parents are alive. Her mother, born in 1944, has IDDM but is otherwise healthy. Her father, born in 1938, is hypertensive, but is also otherwise healthy. Mrs. Anderson's only sibling, a brother born in 1970, has no significant medical history.

Vital Signs: BP 140/90 (sitting) and 136/92 (standing)
HR 98 (sitting) and 104 (standing)
RR 16, T 99.0

Abdomen: Flat, soft, with normoactive bowel sounds; no palpable masses or organomegaly; no visible lesions, ecchymoses, or rash; no dyesthesia; no rebound tenderness, nor inguinal or femoral masses. Positive tenderness to light palpation and voluntary guarding of right lower quadrant.

Back: No costovertebral angle tenderness; no visible lesions, ecchymoses, or rash.

Rectal: Heme-negative, normal sphincter tone, brown stool of soft consistency, no hemorrhoids or other perianal lesions. Appendix nontender.



Case Vignette

Pelvic: Exocervix with 2–3 mm firm circumferential rim at peripheral margin. Rim pale pink and moist, without lesions or suspicious discharge, and nonfriable. Cervix central to rim projects 1 cm into vaginal cavity, is pale pink and moist, without lesions or suspicious discharge, and nonfriable. (See photograph in the Handout on page 4.) No cervical motion tenderness. Uterus nontender, slightly softened, upper range of normal size. Right adnexa extremely tender to palpation with slight fullness. Left adnexa unremarkable and without palpable masses.

Serum beta-HCG: Positive

2. What is your revised differential diagnosis (top four candidates)?



Case Vignette

You suspect Mrs. Anderson has an ectopic pregnancy and send her to the emergency department for evaluation. You also wonder whether her cervical lesion could somehow be related to the current situation or whether it's an incidental finding.

3. What are your next management steps?

4. What are known risk factors for ectopic pregnancy?

References 24–33

5. What is your differential diagnosis for Mrs. Anderson's cervical lesion?

References 34–39



Case Vignette

The pelvic ultrasound in the emergency department reveals a 4x4 cm gestational sac in Mrs. Anderson's right fallopian tube. Laparoscopic surgery is scheduled for that afternoon and proceeds without complication.

Note: Mrs. Anderson is treated with a right-sided salpingectomy, although more commonly she would receive chemotherapy (Methotrexate) or laparoscopic salpingostomy, removing the ectopic pregnancy and preserving the tube.

One week later, Mrs. Anderson presents to your office for a follow-up visit. She is visibly distraught, commenting: "It's the abnormality on my cervix that made me lose the pregnancy, right?" You reassure her that the lesion does not appear to be cancerous but resembles a pseudopolyp. Associated with her ectopic pregnancy it makes you suspect that she may have been exposed to diethylstilbestrol (DES) in utero, as the gynecologist told her at the time of her surgery.

6. What is diethylstilbestrol (DES)? When was it used? What were and are DES's indications for use? Was it an effective agent for its initial indication? What is DES's mechanism of action? Refer to pages 11–13.

References 40–55

7. Caveats to consider...refer to pages 13–14.

8. What are DES's associated adverse effects in women exposed in utero (DES Daughters)? Refer to pages 14–23.

References 56–100

9. What is known about the effects of DES in men exposed in utero (DES Sons), women prescribed DES while pregnant, and the third generation (the offspring of DES Daughters and Sons)? Refer to pages 23–26.

References 101–136

10. What research is ongoing? Refer to pages 26.



Case Vignette

11. For a summary, refer to page 27. Review the information to be sure you fully understand the known effects of DES, as well as those that are disproven or still being investigated.

Mrs. Anderson is very interested in following up on your suspicions. She would like to see a specialist and collect more information for herself.

12. What are the current screening recommendations for people who have been exposed to DES? Refer to pages 28–30.

13. What are the current recommendations for referring DES Daughters to a specialist with DES experience? Refer to pages 30–31.

References 130-145

14. Where could you or Mrs. Anderson obtain additional information about DES? Refer to pages 32–34.

Handouts

Table 1: Lower abdominal pain presentation

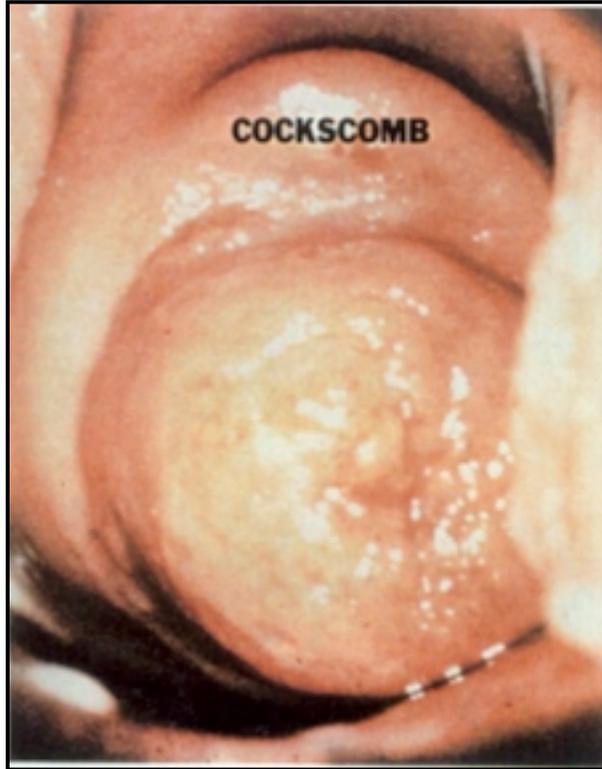
Diagnosis	Pain (Typical Characteristics)				
	Location	Quality	Radiation	Severity	Behavior over Time
Appendicitis	Initially diffuse, later RLQ focus	Crampy	Sometimes lower back or groin	Variable	Constant; may crescendo before rupture
Incarcerated hernia	Variable	Achy, crampy	—	Severe	Steady
Ectopic pregnancy	RLQ, LLQ, or suprapubic	Achy or sharp	Variable	Moderate to severe	Crescendos until point of rupture
Spontaneous abortion	Midline suprapubic	Achy, crampy	Variable	Variable	Variable
Salpingitis	RLQ or LLQ	Variable	—	Variable	Variable
Mittelschmerz	Midline suprapubic	Crampy, occasionally boring and sharp	Sometimes lower back or groin	Variable	Usually resolves after several days of declining severity
Endometriosis	RLQ, LLQ, or suprapubic	Crampy	Variable	Variable	Pain worst during menstrual period
Corpus luteum cyst	RLQ or LLQ	Initially crampy, later boring and sharp	Sometimes lower back	Moderate	Crescendos until point of rupture or leakage
Adnexal or ovarian torsion	RLQ or LLQ	Sharp, boring	Sometimes lower back	Severe	Steady; occasionally intermittent
Ovarian cancer	Variable	Variable	Variable	Variable	Variable
Ureterolithiasis	R or L flank	Sharp, colicky	Variable	Severe	Steady
Cystitis	Suprapubic and urethral	Burning	—	Moderate to severe	Pain worst on urination
Abdominal trauma	Variable	Variable	Variable	Variable	Variable
Herpes zoster	Variable (dermatomal)	Burning (especially with contact)	—	Variable	Pain precedes vesicular rash

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Figure 1: Cervical collar with pseudopolyp and cockscomb



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Table 2: Trade names under which DES and other nonsteroidal estrogens have been sold in the United States⁴¹

Nonsteroidal Estrogens		
Benzestrol	Fonatul	Palestrol
Chlorotrianisene	Gynben	Restrol
Comestrol	Gyneben	Stil-Rol
Cyren A.	Hexestrol	Stilbal
Cyren B.	Hexoestrol	Stilbestrol
Delvinal	Hi-Bestrol	Stilbestronate
DES	Menocrin	Stilbetin
DesPlex	Meprane	Stilbinol
Dibestil	Mestilbol	Stilboestroform
Diestryl	Microest	Stilboestrol
Dienestrol	Methallenestril	Stilboestrol DP
Dienoestrol	Mikarol	Stilestrate
Diethylstilbestrol dipalmitate	Mikarol Forti	Stilpalmitate
Diethylstilbestrol diphosphate	Milestrol	Stilphostrol
Diethylstilbestrol dipropionate	Monomestrol	Stilronate
Diethylstilbenediol	Neo-Oestranol I	Stilrone
Digestil	Neo-Oestranol II	Stils
Domestrol	Nulabort	Synestrin
Estilben	Oestrogenine	Synestrol
Estrobene	Oestromenin	Synthoestrin
Estrobene DP	Oestromon	Tace
Estrosyn	Orestol	Vallestril
	Pabestrol D	Willestrol
Nonsteroidal Estrogen-Androgen Combinations		
Amperone	Metystil	Tylosterone
Di-Erone	Teserene	
Estan	Tylandril	
Nonsteroidal Estrogen-Progesterone Combination		
Progravidium		
Vaginal Cream Suppositories and Nonsteroidal Estrogens		
AVC Cream with Dienestrol	Dienestrol Cream	

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What is Diethylstilbestrol?

- Synthetic nonsteroidal estrogen
- First produced in 1938
- Manufactured by over 267 companies under a wide variety of names
- Stilbestrol used most commonly
- Contained even in some prenatal vitamins



What are the Indications for Use?

- Pregnancy
 - Prevention of miscarriage, premature delivery, postmaturity, and toxemia in high-risk pregnancies
 - Infertility, morning sickness, and low-risk pregnancies
 - *No longer FDA approved*
- Postcoital Contraception
 - *No longer FDA approved*
- Breast and Prostate Cancer Treatment
- Livestock Fattening
 - *No longer FDA approved*



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When was DES Used?

- Became available in 1938
- In US, contraindicated for use in pregnancy in 1971
- Outside US, use continued after 1971



What is DES's Mechanism of Action?

- Pregnancy
 - Thought to induce placental hormone production, thus sustaining a viable pregnancy; later disproven^{43,45}
- Postcoital Contraception
 - Thought to decrease circulating progesterone levels, thus altering tubal motility and accelerating passage of ovum through oviduct
 - Inhibits synthesis of endometrial production of carbonic anhydrase, thus making implantation unfavorable⁴⁸



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What is DES's Mechanism of Action?

- Breast Cancer Treatment
 - At high doses, paradoxically inhibits growth of estrogen receptor positive tumors
 - Precise mechanism unknown⁵⁴
- Prostate Cancer Treatment
 - Inhibits pituitary production of luteinizing hormone, subsequently decreasing testicular androgen production⁵²
- Livestock Fattening
 - Increases lean muscle mass and decreases fat deposition
 - Precise mechanism unknown⁵⁵



Was DES Effective for Preventing Miscarriages?

NO

- DES increased the rate of miscarriages, premature deliveries and neonatal mortality⁴³



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Caveats to Consider When Assessing Health Risks

- Most people who were exposed to DES have not experienced negative health consequences
- These case materials represent the state of DES research at the time of development and interpret studies current at that time for clinical practice
- Research on DES is ongoing, and some animal studies have identified health effects that might yet occur



DES Effects on Daughters

- Clear Cell Adenocarcinoma (CCA) of the Vagina and Cervix
 - Rare cancer, previously seen in women >50 years old
 - No premalignant lesion known



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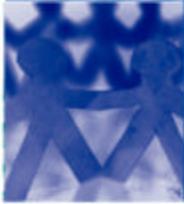
DES Effects on Daughters

- Clear Cell Adenocarcinoma (CCA) of the Vagina and Cervix
 - RR in DES exposed 40.7 compared with nonexposed;⁵⁷ absolute risk 1.0-1.5: 1000 in DES exposed⁵⁸
 - Peak incidence in late teens and early 20s; appears in DES Daughters as they reach 30s and 40s⁵⁷

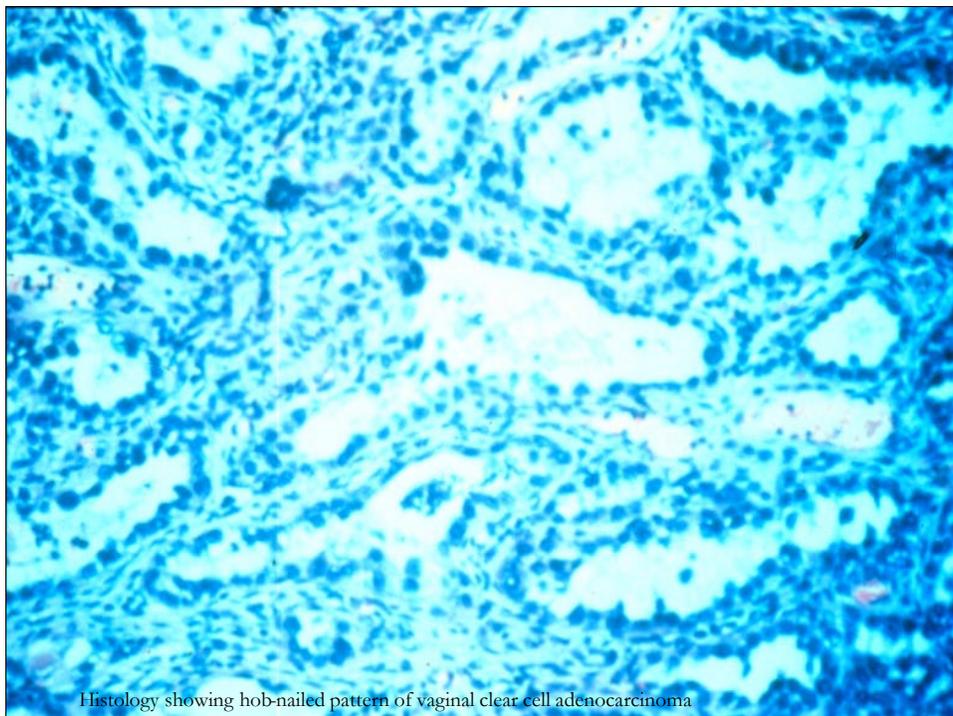
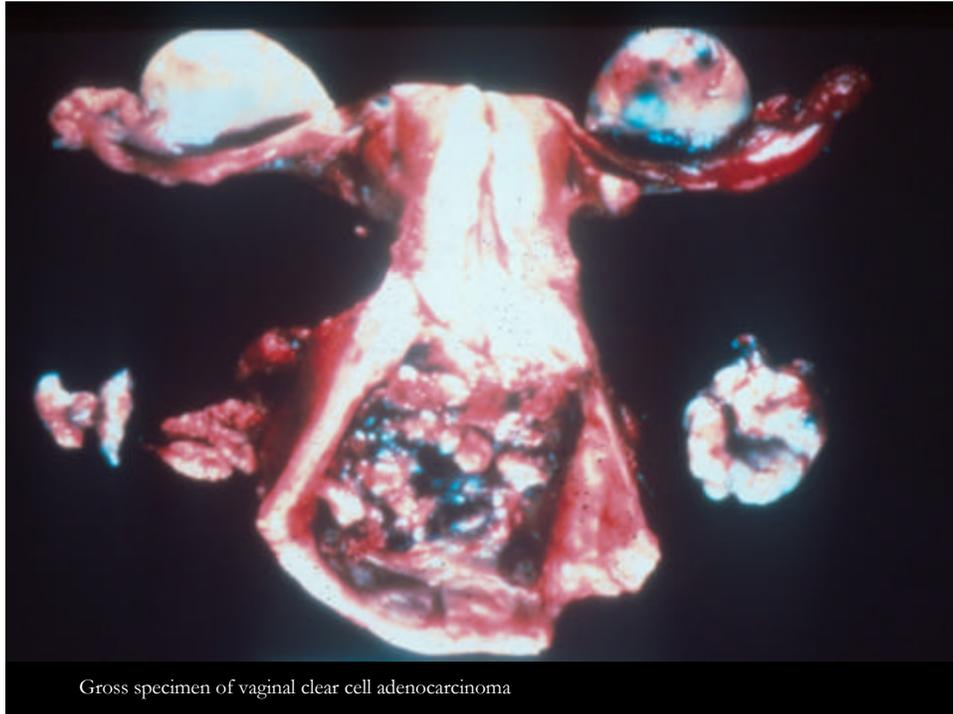


Photographs and photomicrographs courtesy of Kenneth Noller, MD





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DES Effects on Daughters

- Additional Cancer Risks
 - None proven,⁵⁷ but average age of DES Daughters is 35-55 years
 - Relation with cervical intraepithelial neoplasia uncertain⁶⁵
 - Breast cancer risk a concern and still being investigated⁶²⁻⁶⁵
 - 2002 study links exposure to increased risks in Daughters over 40⁶⁶



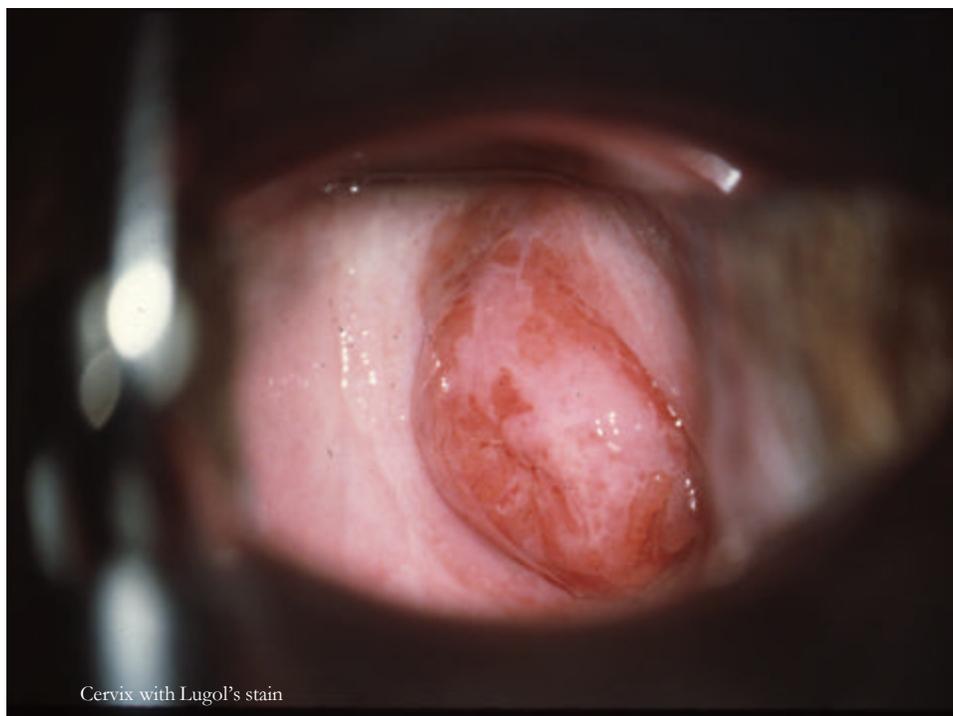
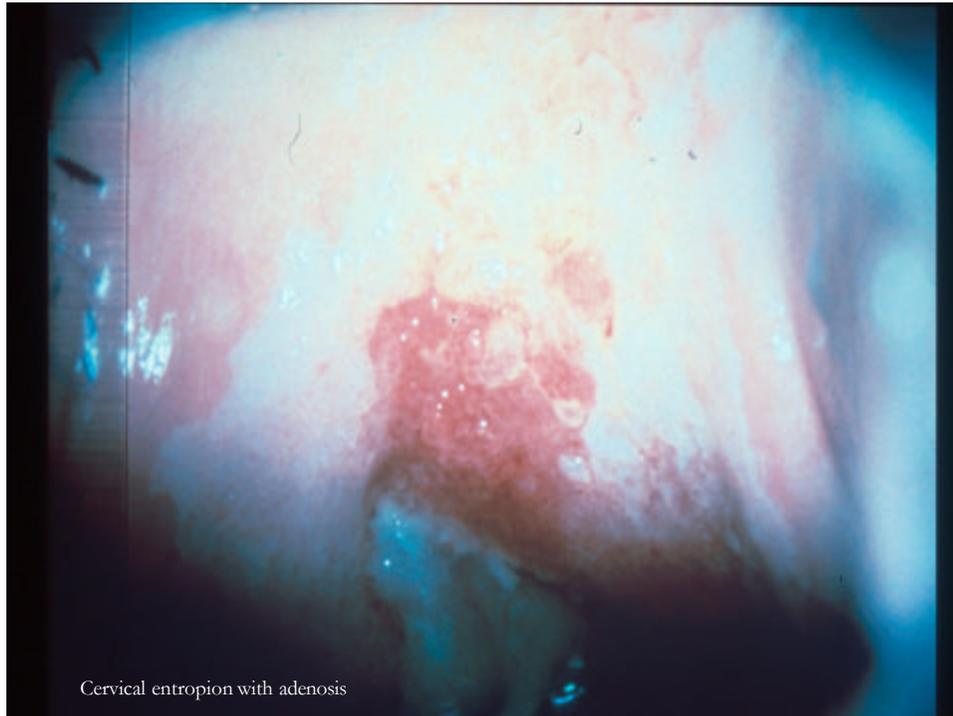
DES Effects on Daughters

- Reproductive Tract Structural Differences
 - Benign Vaginal Adenosis
 - Seen in approximately 33% of exposed women³⁷⁻³⁹
 - Present in 90% of cases with clear cell adenocarcinoma (CCA)⁵⁶
 - Not a proven premalignant lesion for CCA





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DES Effects on Daughters

- Reproductive Tract Structural Differences
 - Cervical Malformations
 - Seen in 25%-33% of exposed population^{34,75-79}
 - Cockscomb; hood; collar, and pseudopolyp



Large cockscomb cervix

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DES Effects on Daughters

- Reproductive Tract Structural Differences
 - Uterine Malformations
 - Up to 69% of DES Daughters²¹
 - T-shaped uterus most common
 - Variety of other abnormalities
 - Frequently associated with cervical lesions

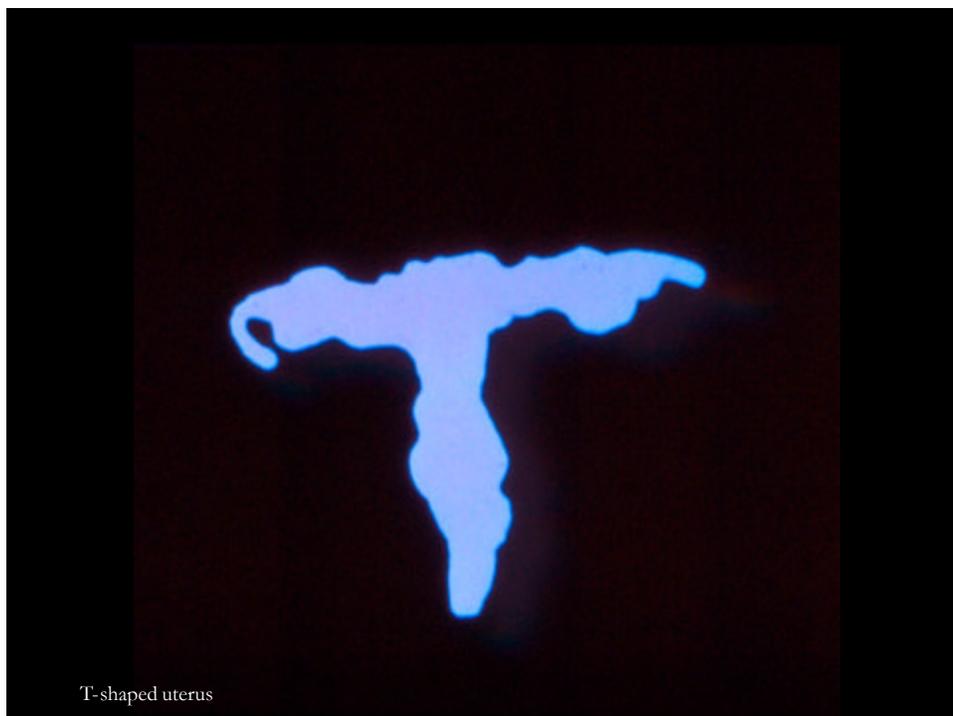


Illustrations courtesy of
DES Screening Program,
ProHEALTH Care Associates





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DES Effects on Daughters

- Additional Reproductive Risks
 - Infertility
 - Up to 33% in Dieckmann cohort vs. 14% in unexposed women^{80,81}
 - Adverse Pregnancy Outcomes⁸⁹
 - Ectopic pregnancy RR 3.84
 - Premature birth RR 2.9
 - Miscarriage RR 1.31, 1st trimester
RR 4.25, 2nd trimester
 - Risk higher in presence of reproductive tract abnormalities⁸⁹



DES Effects on Daughters

Overall pregnancy outcomes still good in most cases

Approximately 85% of pregnancies in DES-exposed women resulted in a live-born infant⁸⁹



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DES Effects on Daughters

- Other Disorders
 - Links have not been proven in
 - Immunologic diseases
 - Psychosexual disorders*

* But animal studies have raised concerns about effects on cognitive abilities differentiated by sex



DES Effects on Women Exposed While Pregnant

- Breast Cancer
 - RR is ~ 1.3 ¹⁰¹
 - Absolute risk 13.3% vs. 10.2% in unexposed¹⁰¹
 - No study has shown RR of 2 or greater, which would lead to changes in clinical screening
 - RR of family history of breast cancer 2.1¹⁰⁸
 - RR of 5 years of HRT 1.35¹⁰⁹



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DES Effects on Women Exposed While Pregnant

- Other Effects
 - Exposed women, now in 50s to 90s
 - Concerns about:
 - Using HRT
 - Other gynecologic disorders
 - Other cancers
 - None of these concerns yet verified through research studies



DES Effects on Sons

- Urologic Abnormalities
 - Increased risk for epididymal cysts¹¹¹
 - 20.8% exposed vs. 4.9% nonexposed
 - Increased risk for other genital abnormalities^{115,116}
 - Testicular hypoplasia
 - Undescended testicles
 - Microphallus



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DES Effects on Sons

- Testicular Cancer
 - Increased rates of testicular cancer, shown in a prospective study, not statistically significant;¹¹⁷ may reflect increasing rates overall in past 60 years
 - Several case-control studies have shown increased risk;¹¹⁸⁻¹²¹ others have shown none^{122,123}
 - Secondary risk exists for DES Sons with undescended and hypoplastic testes



DES Effects on Sons

- Other Abnormalities
 - No proven decrease in fertility,¹¹⁴ but concerns persist because of the problems with DES Daughters
 - Rates of cancer of rete testis and prostatic utricle are increased in mice¹²⁵⁻¹²⁷



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DES Effects on Third Generation

- Animal studies have generated concerns about uterine and rete testis tumors¹³¹⁻¹³³
- Only one published human study has demonstrated third-generation effects
- Sons of DES Daughters at increased risk for hypospadias¹³⁹



Ongoing Research on Health Effects in DES Sons, Daughters and Third Generation

- Baylor
- Boston University
- Dartmouth
- University of Chicago
- Tufts-New England Medical Center
- National Cancer Institute
- Netherlands Cancer Institute



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Table 3: Summary of effects of DES exposure

Group Exposed	Established Effects	Continuing Unproven Concerns
Daughters	Clear cell adenocarcinoma (RR ~ 40) Infertility (33% vs. 14%) Adverse pregnancy outcomes Cervical or uterine malformations	Immunologic disease Psychosexual disorders Other cancers, especially breast cancer
Women Exposed While Pregnant	Breast cancer (13.3% vs. 10.2%)	HRT use; gynecologic disorders; other cancers
Sons	Urogenital abnormalities Benign epididymal cysts (20.8% vs. 4.9%)	Other genital abnormalities; testicular cancer; prostatic utricle and rete testis tumors
Third Generation	—	Prostatic utricle and rete testis tumors seen in male mice; uterine cancer and ovarian tumors in female mice

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Screening Recommendations for DES Daughters

- Routine exams (annual breast and pelvic exam, including bimanual and rectal exams) and careful monitoring for clear cell adenocarcinoma (CCA), throughout life
- With presence of cervical intraepithelial neoplasia: routine monitoring with close follow up
- With vaginal adenosis: no specific change in monitoring



Screening Recommendations for DES Daughters

- With CCA: referral to gynecologic oncologist
- With uterine or cervical abnormalities: increased frequency of colposcopy and iodine staining
- When abnormalities are found: consultation with gynecologist experienced with DES
- Biopsy of any gross vaginal lesion



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Screening Recommendations for Women Prescribed DES While Pregnant

- Women aged 20 and older: monthly breast self-exams
- Women aged 20-39: clinical breast exam by a health professional every 3 years
- Women aged 40 and older: annual clinical breast exam by a health professional
- Women aged 40 and older: annual mammogram

American Cancer Society Web site¹⁴⁴



Women who know they were exposed
to DES while pregnant should be
strongly encouraged to share this
information with their children



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Screening Recommendations for DES Sons

- Annual clinical testicular exam by a health professional
- Education regarding proper testicular self-exam technique and prompt medical evaluation if any abnormalities are found
- Monthly testicular self-exam for men with certain risk factors: cryptorchidism, previous germ cell tumor on one side, or family history of testicular cancer

American Cancer Society Web site¹⁴⁵



Indications for Referral to an OB/GYN

- Preconception counseling, including discussion of increased risks for infertility, ectopic pregnancy, miscarriage, premature labor, and premature birth
- Consideration of diagnostic testing, including
 - Pelvic exam to assess for cervical anomalies
 - Hysterosalpingogram to assess for upper genital tract anomalies
 - Endometrial biopsy to diagnose luteal phase defect
 - Early diagnosis of pregnancy with close monitoring for ectopic pregnancy



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Screening of DES Daughters by OB/GYN

- Preconception counseling
- Pelvic exam
- Hysterosalpingogram
- Close monitoring for early pregnancy
- Referral to an MFM specialist





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Resources for consumers and health care providers

U.S. Government Resources

Centers for Disease Control and Prevention

CDC's DES Update

888-232-6789 (toll-free phone)

www.cdc.gov/DES

A national education program for consumers and health care providers based on the latest research on DES-related health risks and treatment options.

National Cancer Institute

Cancer Information Service

800-4-CANCER (800-422-6237) (toll-free phone)

www.cancer.gov

A national service providing the latest cancer information to patients, families, health professionals, and the general public.

National Cancer Institute

Questions & Answers About DES

http://cis.nci.nih.gov/fact/3_4.htm

A national service providing the latest DES information to patients, families, health professionals, and the general public.

Consumer Organizations

DES Action USA

610 16th Street, Suite 301

Oakland, CA 94612

510-465-4011 (phone)

800-DES-9288 (800-337-9288) (toll-free phone)

510-465-4815 (fax)

desaction@earthlink.net

<http://www.desaction.org>

A national organization representing DES mothers, daughters, and sons. Mission includes promoting research and educating both public and medical professionals about DES consequences and subsequent treatment options. Services include website; physician referrals; DES publications; and a quarterly newsletter, DES Action Voice.



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DES Cancer Network

P.O. Box 220465
Chantilly, VA 20153-0465
202-628-6330 (phone)
800-DESNET4 (800-337-6384) (toll-free phone)
202-628-6217 (fax)
desnetwrk@aol.com
<http://www.descancer.org>

A national network for DES mothers and offspring. Mission includes research advocacy, educational of both public and medical professionals, and peer support. Services include website; educational programs for DES-exposed people with cancer; medical referrals; and a newsletter, DES Issues.

DES Daughters Listserv and Online Support Group

http://www.surrogacy.com/online_support/des/

An online support group to promote discussion, support, and sharing of information among DES Daughters.

DES-Family Listserv

An online listserv for all DES-exposed people, their families and friends, designed to promote mutual support and sharing of information. To subscribe, send an e-mail to listserv@sact.com. In the body of your message, write only “subscribe des-family” (without the quotation marks).

DES Sons Network

104 Sleepy Hollow Pl.
Cherry Hill, NJ 08003
609-795-1658 (phone)
msfreilick@hotmail.com

The DES Sons Network is a national network providing information and support for men exposed to DES before birth, and counseling for men with testicular cancer.

DES Sons Discussion Network

<http://groups.yahoo.com/group/des-sons/>

A private, professional health information and support network for DES Sons.



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National Women's Health Network

514 10th St., NW, Ste. 400

Washington, DC 20004

202-347-1140 Administration

202-628-7814 Health Information

<http://www.womenshealthnetwork.org>

A coalition of women's health organizations that lobbies Congress for women's health issues and provides an information clearinghouse on various women's health topics, including DES.

Resolve

National Office:

1310 Broadway

Somerville, MA 02144-1731

617-623-0744 (phone)

Philadelphia Office:

821 Westview St.

Philadelphia, PA 19119

215-849-3920 (phone)

<http://www.resolve.org>

A national infertility organization with regional offices that provides support groups, publications, and a newsletter.



Handouts

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Handouts

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Handouts

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