# Educational Material

## HANDOUTS

"A woman born in 1967 presents with abdominal pain…"

**Support materials for the Case Vignette**

Developed by MCP Hahnemann School of Medicine

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

*** The instructor will indicate when each page of this handout should be used. ****

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

CDC

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# *Handouts*

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## 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 |
| Mittelschmertz | 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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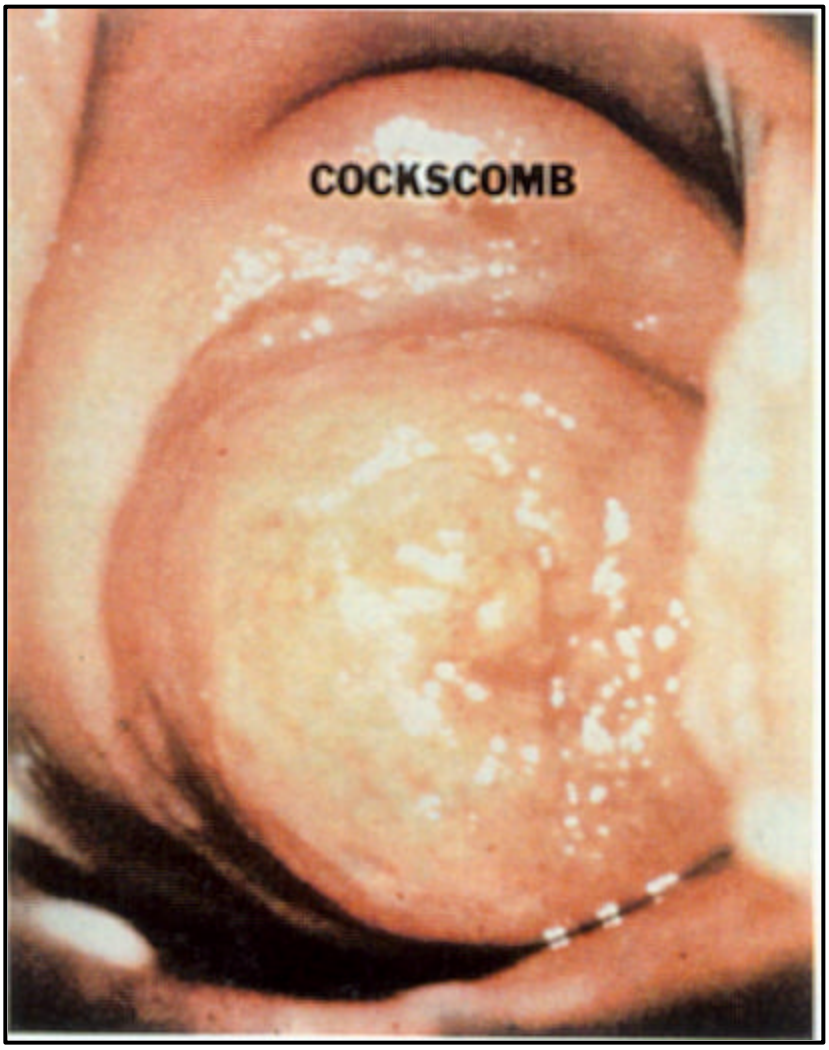
## Figure 1: Cervical collar with pseudopolyp and cockscomb



## Table 2: Trade names under which DES and other nonsteroidal estrogens have been sold in the United States[41]

| **Nonsteroidal Estrogens** | | |
|---|---|---|
| Benzestrol | Fonatol | 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 |
| Dienostrol | Methallenestril | Stilboestrol DP |
| Dienoestrol | Mikarol | Stilestrate |
| Diethylstilbestrol dipalmitate | Mikarol Forti | Stilpalmitate |
| Diethylstilbestrol diphosphate | Milestrol | Stilphostrol |
| Diethylstilbestrol diproprionate | 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 | |

## Advertisement from a 1957 medical journal[41]

## What is Diethylstilbestrol?

- Synthetic nonsteriodal 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*

## 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 unfavorable[48]

## What is DES's Mechanism of Action?

- Breast Cancer Treatment
  - At high doses, paradoxically inhibits growth of estrogen receptor positive tumors
  - Precise mechanism unknown[54]
- Prostate Cancer Treatment
  - Inhibits pituitary production of luteinizing hormone, subsequently decreasing testicular androgen production[52]
- Livestock Fattening
  - Increases lean muscle mass and decreases fat deposition
  - Precise mechanism unknown[55]

## Was DES Effective for Preventing Miscarriages?

# NO

- DES increased the rate of miscarriages, premature deliveries and neonatal mortality[43]

## 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

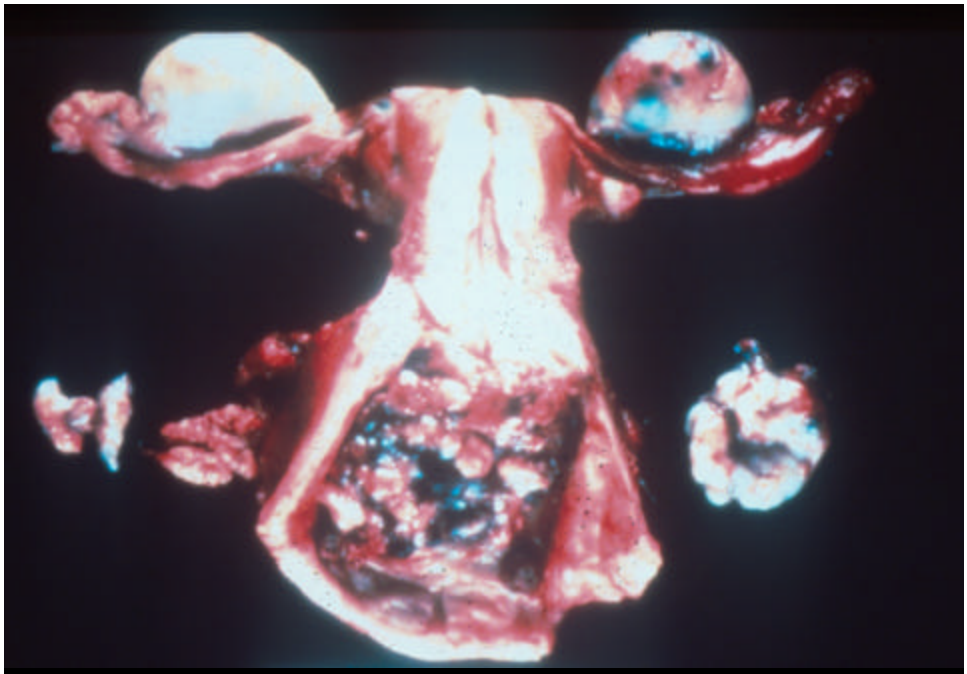
## DES Effects on Daughters

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

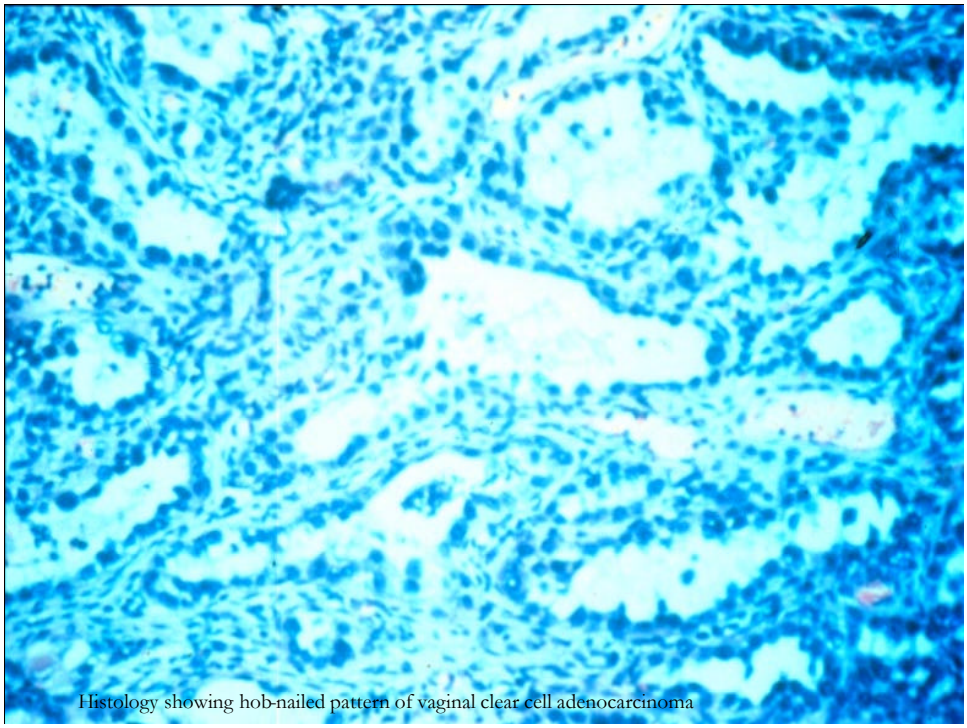
## DES Effects on Daughters

- 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 exposed[58]
  - Peak incidence in late teens and early 20s; appears in DES Daughters as they reach 30s and 40s[57]

Photographs and photomicrographs courtesy of Kenneth Noller, MD



Gross specimen of vaginal clear cell adenocarcinoma



Histology showing hob-nailed pattern of vaginal clear cell adenocarcinoma

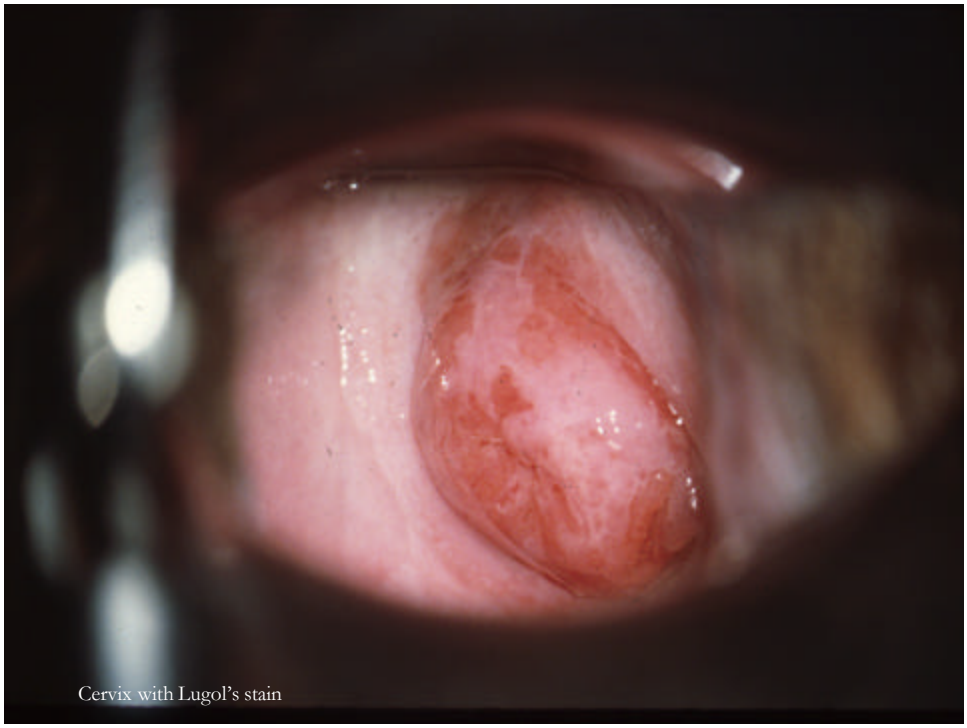
## DES Effects on Daughters

- Additional Cancer Risks
  - None proven,[57] but average age of DES Daughters is 35–55 years
  - Relation with cervical intraepithelial neoplasia uncertain[65]
  - Breast cancer risk a concern and still being investigated[62-65]
    - 2002 study links exposure to increased risks in Daughters over 40[66]

## DES Effects on Daughters

- Reproductive Tract Structural Differences
  - Benign Vaginal Adenosis
    - Seen in approximately 33% of exposed women[37-39]
    - Present in 90% of cases with clear cell adenocarcinoma (CCA)[56]
    - Not a proven premalignant lesion for CCA

Cervical entropion with adenosis



Cervix with Lugol's stain

## 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

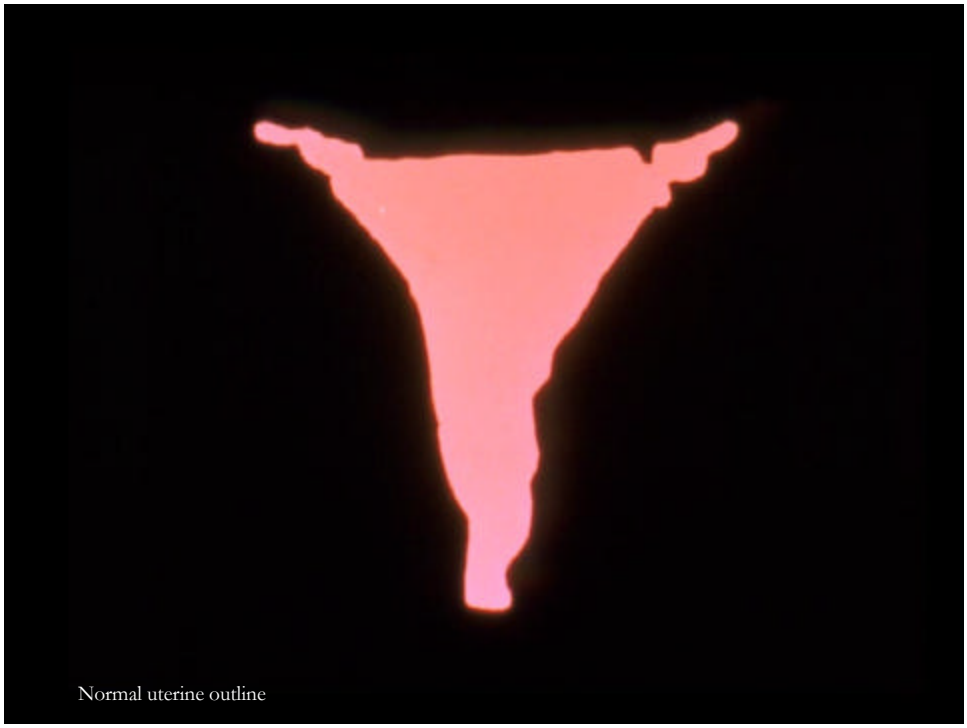
Large cockscomb cervix

## DES Effects on Daughters

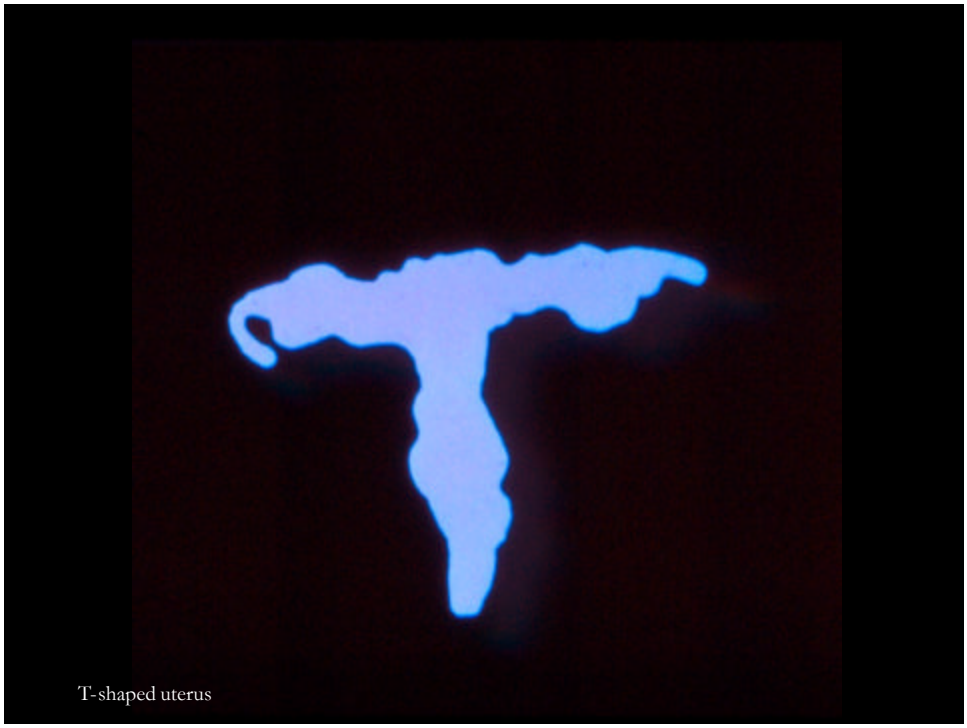
- Reproductive Tract Structural Differences
  - Uterine Malformations
    - Up to 69% of DES Daughters[21]
    - T-shaped uterus most common
    - Variety of other abnormalities
    - Frequently associated with cervical lesions

Illustrations courtesy of

DES Screening Program,
ProHEALTH Care Associates



Normal uterine outline



T-shaped uterus

## DES Effects on Daughters

- Additional Reproductive Risks
  - Infertility
    - Up to 33% in Dieckmann cohort vs. 14% in unexposed women[80,81]
  - Adverse Pregnancy Outcomes[89]
    - 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 abnormalities[89]

## 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 infant[89]

## 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 unexposed[101]
  - No study has shown RR of 2 or greater, which would lead to changes in clinical screening
  - RR of family history of breast cancer 2.1[108]
  - RR of 5 years of HRT 1.35[109]

## 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 cysts[111]
    - 20.8% exposed vs. 4.9% nonexposed
  - Increased risk for other genital abnormalities[115,116]
    - Testicular hypoplasia
    - Undescended testicles
    - Microphallus

## 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 mice[125-127]

## DES Effects on Third Generation

- Animal studies have generated concerns about uterine and rete testis tumors[131-133]
- Only one published human study has demonstrated third-generation effects
- Sons of DES Daughters at increased risk for hypospadias[139]

## 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

## Screening Recommendations for Women Prescribed DES While Pregnant

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

*American Cancer Society Web site*[144]

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

## 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: cryptochidism , previous germ cell tumor on one side, or family history of testicular cancer

*American Cancer Society Web site*[145]

## 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

## Screening of DES Daughters by OB/GYN

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

## 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.

# Handouts

***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.

***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.


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
CDC

## Table 3: Summary of effects of DES exposure

| Group Exposed | Established Effects | Continuing Unproven Concerns |
|---|---|---|
| **Daughters** | Clear cell adenocarcinoma (RR ~ 40)<br>Infertility (33% vs. 14%)<br>Adverse pregnancy outcomes<br>Cervical or uterine malformations | Immunologic disease<br>Psychosexual disorders<br>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<br>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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