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. ***

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

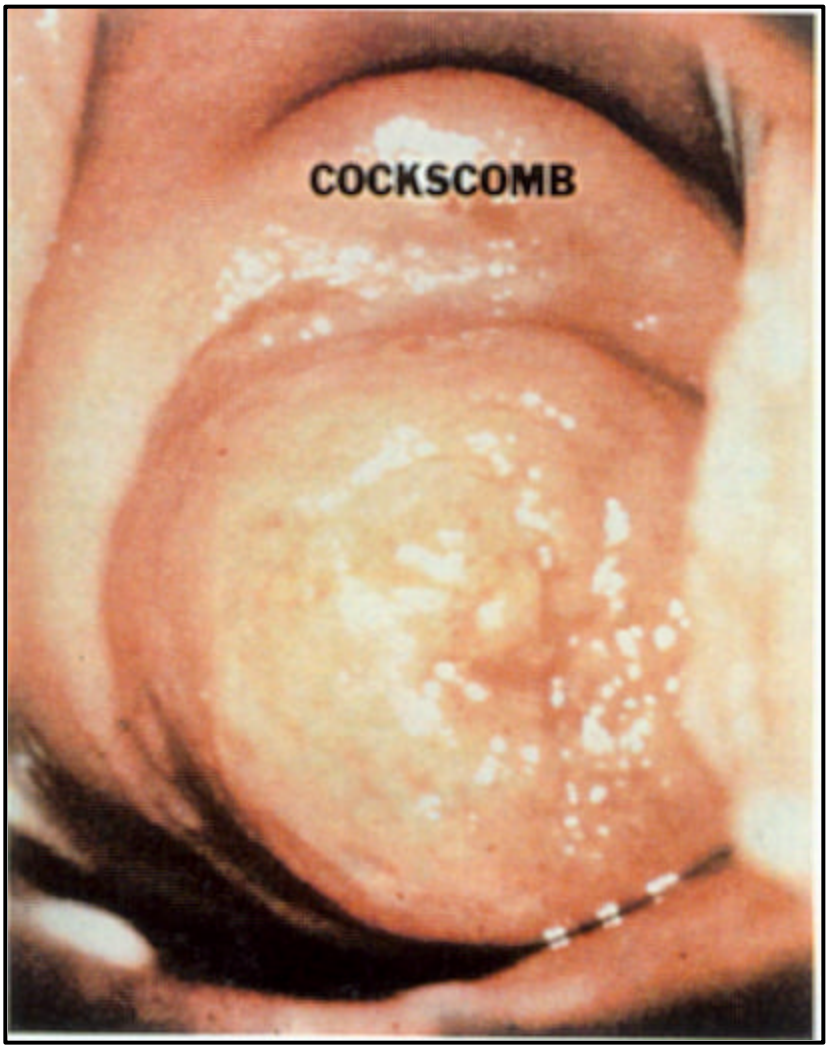


Table 2: Trade names under which DES and other nonsteroidal estrogens have been sold in the United States[41]

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

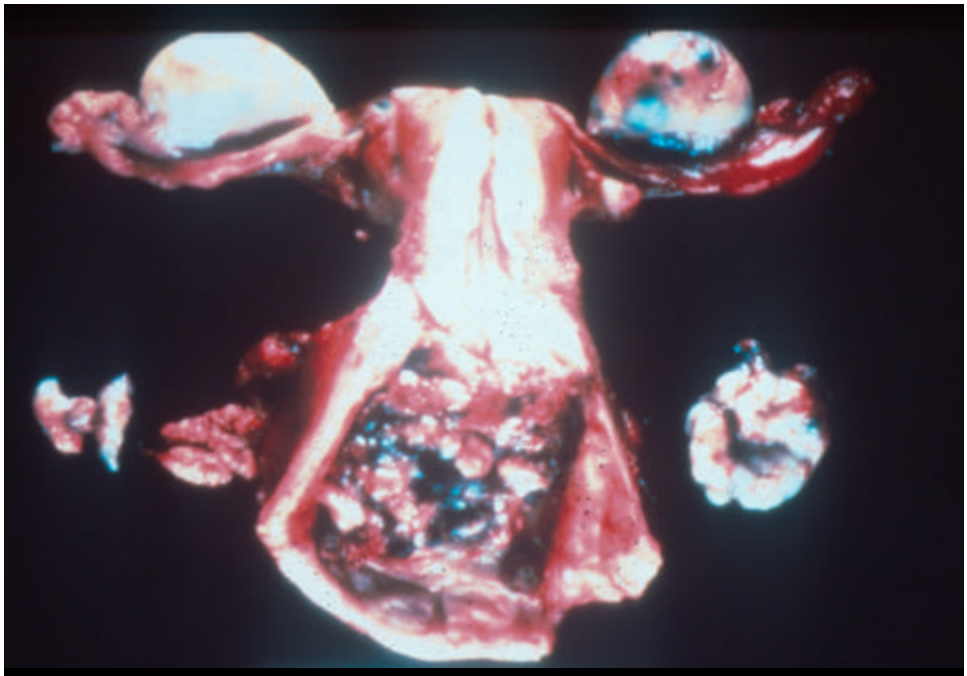
DES Effects on Daughters

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

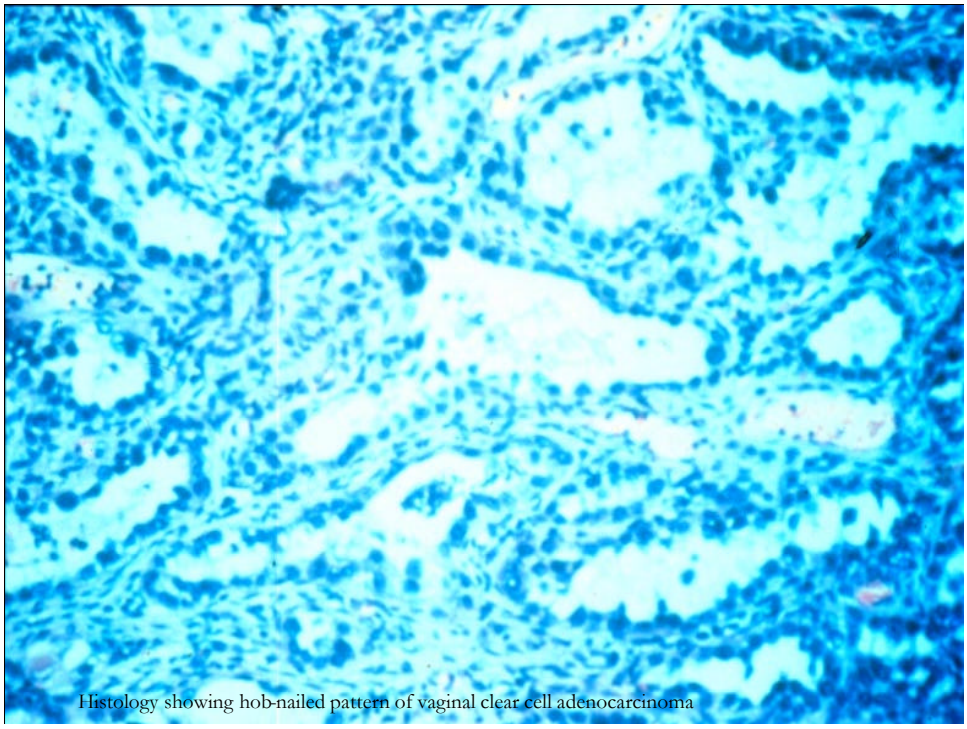
DES Effects on Daughters

- 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

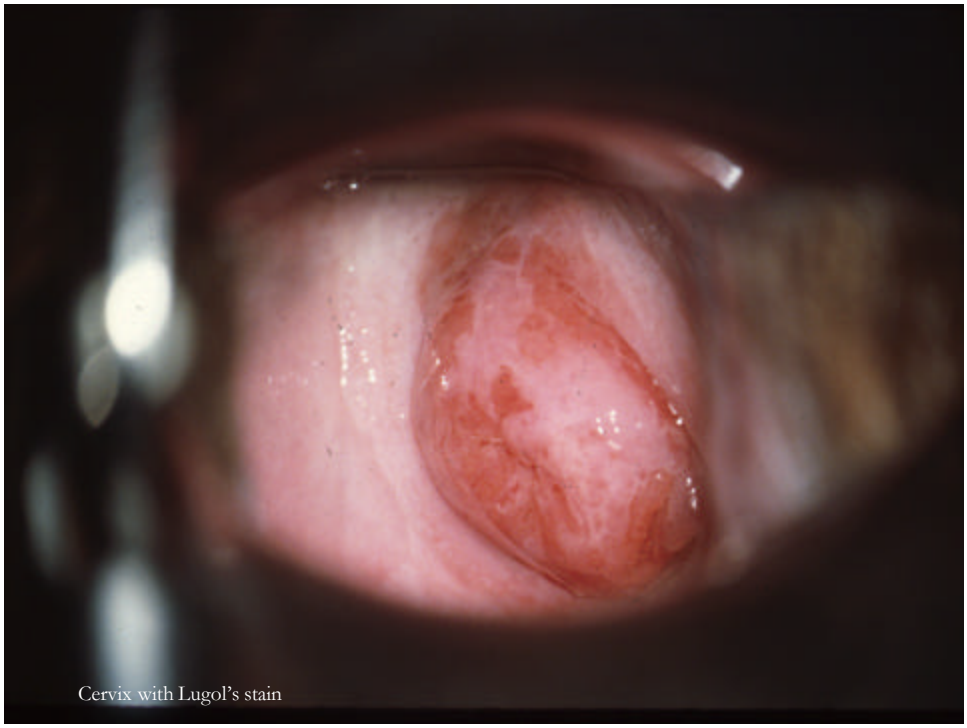
DES Effects on Daughters

- 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

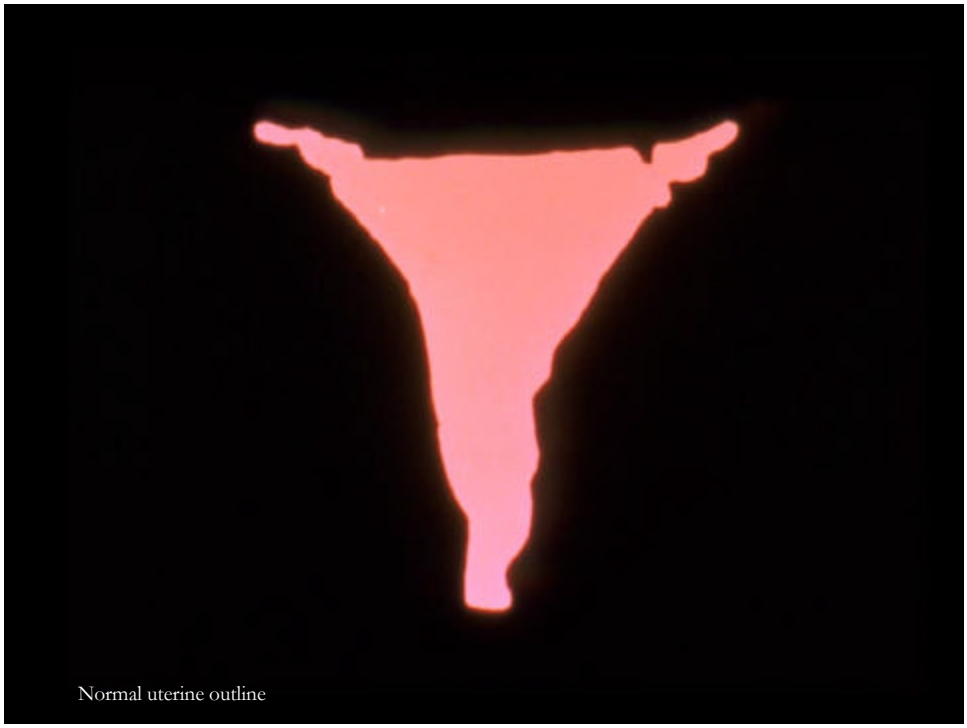
Large cockscomb cervix

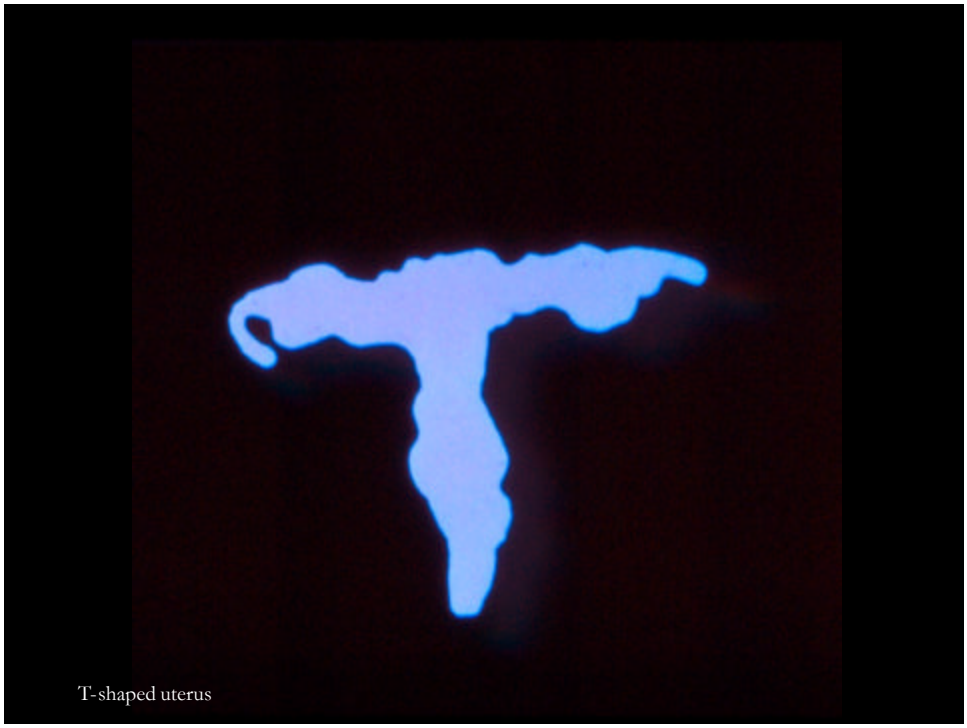
DES Effects on Daughters

- 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.

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

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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