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

Support materials for the Case Vignette
Developed by MCP Hahnemann School of Medicine

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# Table 1: Lower abdominal pain presentation

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

Developed by: Elizabeth Tillman, MD
Reviewed by: Ana Nunez, MD
Shahab Minassian, MD
Glenda Donoghue, MD
MCP Hahnemann School of Medicine
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

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**Nonsteroidal Estrogen-Androgen Combinations**

<table>
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<tr>
<th>Amperone</th>
<th>Metystil</th>
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<tr>
<td>Di-Erone</td>
<td>Teserene</td>
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<td>Estan</td>
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**Nonsteroidal Estrogen-Progesterone Combination**

| Pro gravidium  |           |           |

**Vaginal Cream Suppositories and Nonsteroidal Estrogens**

| AVC Cream with Dienestrol | Dienestrol Cream |
Advertisement from a 1957 medical journal
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
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\(^{45}\)
What is DES’s Mechanism of Action?

- Breast Cancer Treatment
  - At high doses, paradoxically inhibits growth of estrogen receptor positive tumors
  - Precise mechanism unknown

- Prostate Cancer Treatment
  - Inhibits pituitary production of luteinizing hormone, subsequently decreasing testicular androgen production

- Livestock Fattening
  - Increases lean muscle mass and decreases fat deposition
  - Precise mechanism unknown

Was DES Effective for Preventing Miscarriages?

**NO**

- DES increased the rate of miscarriages, premature deliveries and neonatal mortality
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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
DES Effects on Daughters

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

Photographs and photomicrographs courtesy of Kenneth Noller, MD
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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, but average age of DES Daughters is 35–55 years
  - Relation with cervical intraepithelial neoplasia uncertain
  - Breast cancer risk a concern and still being investigated
    - 2002 study links exposure to increased risks in Daughters over 40

- Reproductive Tract Structural Differences
  - Benign Vaginal Adenosis
    - Seen in approximately 33% of exposed women
    - Present in 90% of cases with clear cell adenocarcinoma (CCA)
    - Not a proven premalignant lesion for CCA
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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\textsuperscript{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
Handouts

Normal uterine outline

T-shaped uterus
DES Effects on Daughters

• Additional Reproductive Risks
  – Infertility
    • Up to 33% in Dieckmann cohort vs. 14% in unexposed women80,81
  – 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
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\textsuperscript{101}
  - Absolute risk 13.3% vs. 10.2% in unexposed\textsuperscript{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\textsuperscript{108}
  - RR of 5 years of HRT 1.35\textsuperscript{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;\textsuperscript{117} may reflect increasing rates overall in past 60 years
  – Several case-control studies have shown increased risk;\textsuperscript{118-121} others have shown none\textsuperscript{122,123}
  – Secondary risk exists for DES Sons with undescended and hypoplastic testes

• Other Abnormalities
  – No proven decrease in fertility,\textsuperscript{114} but concerns persist because of the problems with DES Daughters
  – Rates of cancer of rete testis and prostatic utricle are increased in mice\textsuperscript{125-127}
**Handouts**

**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
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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

Clinician Handouts, CDC's DES Update, www.cdc.gov/DES
Handouts

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

American Cancer Society Web site

Clinician Handouts, CDC’s DES Update, www.cdc.gov/DES
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](http://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](http://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](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](mailto:desaction@earthlink.net)  
[http://www.desaction.org](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.
Handouts

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

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


100. Felton BS. The lingering tragedy of DES. RN 1990:8;36–40.


