



Educational Material

SHORT INSTRUCTOR MATERIALS

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

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2001-2002

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Instructor Materials

Guide for Instructors

The material in this packet is intended to help the instructor lead the case participant through the discussion of the various questions. This “short” version of the case is intended for more advanced students and contains only a brief review of performing a focused history and physical.

The first six questions should be conducted in such a way as to provoke students to think about and come up with the answers. The details included in these Instructor Materials are intended as background material to assist the instructor in conducting this process, not as material that has to be imparted *in toto* to the participating students.

Because of the 1-hour time constraints, the subsequent questions, numbers 7–14, need to be addressed through a mini-lecture format, delivered by the instructor, with a question-and-answer period at the end.

Note also that much of the detailed information is included at the end of this document, to facilitate the discussions and to ensure that students take away relevant information.

Navigation Hints

▶ Special Instructor Prompts are included to assist with the navigation.

It is recommended that the following time limits be set, in order to ensure that the case is completed in the 1-hour allotted time:

Questions 1–5	5 minutes per question (20 minutes) ** Be sure to compile a list of potential diagnoses in answer to question 1; refine the list during the discussion of question 2.
Question 6	10 minutes
Question 7–14	20 minute PowerPoint presentation by instructor
Q&A	10 minutes



Section A: History and Physical

▶▶ ***Have students read the History from their Case Vignette & Handouts packet, then generate a list in answer to question 1.***

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

Gastrointestinal:	appendicitis, incarcerated hernia
Genitourinary:	ectopic pregnancy, threatened abortion, salpingitis, mittelschmerz, endometriosis, hemorrhagic corpus luteum cyst, adnexal or ovarian torsion, ovarian cancer, ureterolithiasis, cystitis
Musculoskeletal:	abdominal trauma
Dermatologic:	herpes zoster

▶▶ ***Refer students to Table 1 on page 8 in the Case Vignette & Handouts packet for more detail.***

▶▶ ***Ask students to review the physical findings in their Case Vignette & Handouts packet, and to view Figure 2 on page 9 of the packet. Then ask them to answer question 2.***

▶▶ ***Ask students to revise their original list now that they know the findings of the physical examination.***



Section B: Developing a Working Diagnosis

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

In order of decreasing likelihood, the top four candidates are:

1. Ectopic pregnancy
2. Hemorrhagic corpus luteum cyst (with accompanying intrauterine pregnancy)
3. Threatened or imminent spontaneous abortion
4. Salpingitis (with accompanying intrauterine pregnancy)

Ectopic Pregnancy

You know Mrs. Anderson is pregnant based on her history of one missed menstrual period as well as her positive pregnancy test. The quality and location of her abdominal pain are highly suggestive of a gestational sac in her right fallopian tube.

Hemorrhagic Corpus Luteum Cyst (with accompanying intrauterine pregnancy)

As these as these cysts enlarge, they tend to be associated with moderately severe, sharp, boring, constant pain that crescendos until rupture. After rupture, the pain may persist for several days secondary to peritoneal irritation.^{1,7,10} Mrs. Anderson's symptoms parallel those of cystic enlargement. An ultrasound would assist in ruling in or out this diagnosis.

Threatened or Imminent Spontaneous Abortion

The pain of a threatened or imminent abortion is typically dull and crampy and located in the suprapubic midline. As with most medical conditions, however, exceptions to this classic presentation occur frequently. Any abdominal pain in a woman known to be pregnant for 20 weeks or fewer may represent a spontaneous abortion and should be investigated further.

Salpingitis (with accompanying intrauterine pregnancy)

Fallopian tube infection typically results from ascending gonorrheal or chlamydial infection. Mrs. Anderson denies any history of STDs and reports a monogamous relationship with her husband. Her pelvic exam was unremarkable for signs of concurrent cervical disease. Thus, this diagnosis is highly unlikely; yet until disproven, it should still be entertained as a possibility.

Section C: Ectopic Pregnancy

► ***Guide students to the most likely diagnosis and then discuss questions 3 and 4.***

3. What are your next management steps?

Your top priority is to rule out anything life-threatening. In Mrs. Anderson's case, you're concerned she may have an ectopic pregnancy. If this were to rupture, the subsequent hemorrhage could prove fatal. Indeed, ruptured ectopic pregnancies are the leading cause of maternal death during the first trimester.²⁴ Mrs. Anderson should, therefore, be sent immediately to the nearest emergency department for evaluation.

Vaginal ultrasound is commonly recommended. Its higher resolution and closer proximity to the reproductive organs make it vastly superior to the standard transabdominal ultrasound. Using this technology, a pregnancy as early as 35 days can be detected, compared with an earliest detectable gestational age of 42 days with transabdominal ultrasound.⁵ However, vaginal ultrasound has, at best, only 80% sensitivity* because of the difficulty of finding an extrauterine pregnancy with this instrument.²⁵ It is 99%–100% specific,* though, when a pregnancy is detected.^{5,26} CT of the pelvis is NOT indicated.

* *Sensitivity: The percentage of subjects with the specified condition who are identified as such.*⁵

* *Specificity: The percentage of subjects without the specified condition who are identified as such.*⁵

4. What are known risk factors for ectopic pregnancy?

Below is a list of the seven most common risk factors for ectopic pregnancy in the United States are:

- History of salpingitis (50%–75% of all ectopic pregnancies)^{5,27,28}
- Peritubal adhesions (secondary to endometriosis, appendicitis, or puerperal infection)^{27,29}
- Previous ectopic pregnancy (probably secondary to #1)^{5,9,17,27}
- History of tubal surgery (either failed tubal ligation or surgery to restore patency)^{5,28,30}
- Increasing age³¹
- Developmental abnormalities of the tube (e.g., after exposure to diethylstilbestrol [DES] in utero)^{27,32,33,89,90}
- Cigarette smoking³¹



Section D: Lesions of the Cervix

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

Various lesions and anomalies will present with cervical growths. Below are descriptions of the four most common with presentations similar to Mrs. Anderson's cervical findings. They are listed in decreasing order of probability:

1. Cervical pseudopolyp
2. Cervical condylomata
3. Cervical polyp
4. Cervical cancer

Cervical Pseudopolyps

- Congenital variants seen in in-utero diethylstilbestrol (DES) exposure.
- Concentric band of cervical tissue forms a constricting ridge (collar) around the periphery of the cervix, causing the tissue central to this band to appear protuberant.
- The presence of the cervical os in the center of this structure differentiates it from a true cervical polyp.³⁴
- Asymptomatic, but correlates with increased rates of infertility and pregnancies with adverse outcomes. (This structural change does not appear to cause problems with pregnancy; but it is associated with a higher risk for uterine and fallopian tubes anomalies. These associated malformations appear to be responsible (in part) for pregnancy problems.)
- The combination of this cervical lesion with the clinical presentation of ectopic pregnancy increases the likelihood of diethylstilbestrol (DES) exposure.

Cervical Condylomata

- Caused by human papilloma virus (HPV), an STD.
- Condylomata acuminata: lesions on the vulva and perianal region and in the vaginal vault; tend to be clusters of small growths, appearing much like cauliflower.
- Flat condylomata: lesions on the cervix; tend to be macular in appearance. (Note: this is not the same as condyloma lata of secondary syphilis.)
- Typically asymptomatic, nonfriable, and similar in color to the tissue from which they emanate.^{9,20}

Cervical Polyps

- Small, pedunculated growths originating primarily from the endocervix.
- Most common etiology is presumed to be chronic papillary endocervicitis.
- Typically red, flame-shaped, and readily friable, ranging in size from only a few millimeters to 2–3 centimeters in length and width.
- Presenting symptoms commonly include postcoital and intermenstrual bleeding.



Section D: Lesions of the Cervix

- Difficult to palpate given soft consistency.
- Ninety-nine percent will remain benign, and 1% eventually evidence neoplastic change. For this reason, all cervical polyps should be removed and examined for malignant characteristics.^{9,20,35}

Cervical Cancer

- Sixth most common cancer in women and the third most common cancer of the female genital tract (after endometrial and ovarian cancer).
- Most cases arise from dysplastic lesions secondary to prior infection with HPV.
- Ninety percent are squamous (epidermoid) carcinomas.
- Mean age at presentation is approximately 50 years.³⁶
- Risk factors include (1) HPV, (2) first intercourse before 17 years of age, (3) multiple sex partners, (4) high-risk male partners, (5) HSV type 2, and (6) cigarette smoking.^{9,35}
- Early on, most women are symptomatic. Over time, irregular vaginal bleeding occurs, especially postcoitally. Daily serosanguinous spotting eventually occurs, sometimes leading to frank hemorrhage. Associated pain indicates advanced disease, with pain typically sciatic.³⁵
- Clear cell adenocarcinoma (CCA) of the vagina and cervix, previously rare and seen mostly in women older than 50 years of age, appears in young women exposed to diethylstilbestrol (DES) in utero (DES Daughters).



Section E: Diethylstilbestrol (DES)

- ▶ *Have students read the continuing history in their Case Vignette & Handouts packet, and then proceed with questions 6–9.*
 - ▶ *Ask students to list what they know about DES.*
 - ▶ *Refer them to Table 2 and to the slides on pages 10–14 in their Case Vignette & Handouts packet to add facts they do not know already.*
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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?
(Di-e-thil-stil-bes-trol)

DES is a synthetic, nonsteroidal estrogen, first produced in 1938 by Charles Dodds and colleagues in London. It was and still is inexpensively produced and available in an oral preparation. Because it was never patented, 267 pharmaceutical companies in the United States alone manufactured this product and other similar nonsteroidal estrogens thought to have parallel adverse effects. The result was a plethora of various trade names. Stilbestrol was by far the most commonly used.

Background Information for the Instructor

Pregnancy

During the first half of the 20th century, researchers and physicians believed that miscarriages resulted largely from decreased levels of placental hormones. The theory behind prescribing DES, therefore, was that if the maternal estrogen level could be artificially elevated, the placenta would produce more of the hormones necessary to maintain a viable pregnancy.⁴⁰

Starting in 1938, DES was indicated for women at high risk for miscarriage, premature delivery, postmaturity, and toxemia.⁴⁰ Under increasing pressure from the multitude of companies manufacturing DES, however, the FDA eventually widened the medication's indications for use. Soon DES was being prescribed for morning sickness, infertility, and



Section E: Diethylstilbestrol (DES)

various gynecologic infections and for use during low-risk pregnancies. Its most common uses were:

- To prevent spontaneous abortion in women with a history of miscarriage
- To prevent premature delivery

Even some prenatal vitamin preparations contained DES.⁴¹

In 1953, however, Dieckmann and his colleagues studied the efficacy of DES in pregnant women. They found that DES was entirely ineffective.⁴² In fact in 1974, Noller and Fische concluded that DES actually was associated with increased rates of miscarriage, premature delivery, and neonatal mortality.^{44,45} Yet despite this information, the FDA did not warn against the use of DES in pregnancy until 1971, when additional adverse effects were noted. An estimated 5–10 million people were exposed to DES in the United States during 1938–1971. This estimate includes women who were prescribed DES while pregnant and the children born of these pregnancies. The women and the children are both considered “DES exposed.”⁴² The women exposed during pregnancy are (in 2002) in the 50- to 90-year age range. The children are now 30 years old or older.

Women born outside the United States may have been prescribed DES after 1971.⁴⁶ Some countries did not ban DES until the 1980s, and anecdotal reports indicate DES may be still used by pregnant women in some parts of the world.

Postcoital Contraception

As postcoital contraception, its mechanism of action is thought to be twofold. First, by decreasing circulating progesterone levels, it is thought to alter fallopian tube motility so that transit of the ovum through the tube is accelerated. Second, it inhibits the synthesis of carbonic anhydrase in the endometrium, making it unfavorable for implantation.^{48,49}

DES was the first hormonal preparation used for postcoital contraception. It was given within 72 hours of intercourse, 25 mg BID PO for 5 days.⁴⁸ It is no longer favored for this purpose because its many side effects (e.g., pulmonary emboli, fluid retention, potential adverse effects on fetus if the abortion is unsuccessful). Indeed, postcoital contraception is no longer an FDA-approved indication.⁴⁹

Breast Cancer

Naturally occurring estrogens are lipophilic and thereby diffuse through cell membranes, eventually binding to nuclear estrogen receptors. There, they stimulate various transcriptional processes, which in the setting of breast cancer, augment the tumor’s growth. Therefore DES should behave in the same manner. Yet, paradoxically, DES inhibits the growth of estrogen receptor positive tumors. The large doses of DES used in this setting appear to elicit a different response than the much smaller naturally occurring estrogen concentrations. The precise mechanism, however, is unknown.⁵⁴



Section E: Diethylstilbestrol (DES)

For many years, DES was used in the palliative treatment of estrogen receptor-positive breast cancers in postmenopausal women.⁵⁰ It was not recommended for premenopausal women because of the greater risk for tumor growth than resolution in this population.⁴⁹

Tamoxifen has largely replaced DES in this arena, however, because of DES's side-effect profile (which includes exacerbation of underlying ischemic heart disease in this population).⁵¹

Prostate Cancer

Triggering the negative-feedback system, DES inhibits luteinizing hormone release from the pituitary. This, in turn, reduces the testicular androgen formation that had previously accelerated the growth of this testosterone-dependent tumor.⁵²

DES is no longer as popular as it once was for this indication, again because of its numerous side effects (which include impotence, gynecomastia, and other feminizing effects).^{51,52}

Livestock

Throughout much of the 20th century, DES was used to fatten livestock. In 1959, the FDA banned its use in chickens and lambs, citing adverse effects in farmers and consumers (sterility and gynecomastia).³² The powerful cattle industry fought the DES ban successfully until 1979, when the FDA finally banned this chemical.⁵³ However, evidence of covert use has been reported through July of 1999.⁵³ In the latter instance, Switzerland detected DES in two samples of supposedly hormone-free U.S. beef exported to that country. (The USDA ceased DES testing in 1991.)

DES currently is used for veterinary and human clinical trial purposes only.



Section F: DES Effects

7. Before proceeding to question 8, review the Caveats on page 14 in the Case Vignette & Handouts packet.

8. What are DES's associated adverse effects in women exposed in utero (DES Daughters)?

▶▶ During this discussion, refer students to pages 14–23 in their Case Vignette & Handouts packet where slides on the effects on DES Daughters are detailed.

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

▶▶ Refer students to pages 23–26 to supplement this discussion.



Section G: Ongoing Research and Summary

▶▶ ***Refer students to page 26 of their Case Vignette & Handouts packet.***

10. What research is ongoing?

▶▶ ***Using Table 3 on page 27 of the Case Vignette & Handouts packet, summarize the outcomes of DES exposure to be sure students understand what is currently known, what has been disproven, and what is still under investigation.***

11. Summary



Section H: Screening and Referral Recommendations

▶ ***Present the factual material on pages 28–31 of the Case Vignette & Handouts packet.***

12. What are the current screening recommendations for people who have been exposed to DES?

13. What are the current recommendations for referring DES Daughters to a specialist with DES experience?

▶ ***Refer students to pages 32–34 of the Case Vignette & Handouts packet.***

14. Where could you or Mrs. Anderson obtain additional information about DES?