Educational Material

INSTRUCTOR MATERIALS

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

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Instructor Materials

Guide for Instructors

This case presentation was designed as a problem-based learning curriculum for students in their first or second year of medical school, when they are beginning their exposure to clinical medicine. It also can be adapted for use by students with more clinical experience (whether in medical school or in training as a Physician's Assistant, Nurse Practitioner, or Nurse Midwife) by omitting the material on developing a good history and physical.

In its complete format, this case presentation is intended to be presented in two 2-hour sessions, with the students having the opportunity between sessions to conduct individual literature and Internet searches. If computers with Internet connectivity are available in the classroom, one 4-hour session also could be suitable. If more advanced students do not need to be taught the rudiments of clinical encounters, a shorter session of at least 2 hours should be allocated.

The case materials are divided into sections that should help the instructor decide the extent to which the materials can be omitted for any particular audience.

Note: This case is not suitable for presentation in a 1-hour time frame or for use in independent Web-based learning.

Navigation Hints

- The "story" is in the student's Case Vignette; the answers they should be able to generate are in these Instructor Materials.
- Both the student and the instructor need a copy of the Handout.
- Especially in the early stages when the students are likely to have a good knowledge base about general medicine, the instructor should caution the students to refrain from turning the pages of the Case Vignette or the Handout until the instructor is ready to move on to the next section.

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

Section A: History and Physical

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

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

What diagnostic information did your history and review of systems give you? What did it help rule in and out? What is your revised differential diagnosis? Mrs. Anderson told you her pain is in her right lower quadrant and has been there since it began 3 days ago. This information focuses you on the following possibilities:

Gastrointestinal:	appendicitis, incarcerated hernia
Genitourinary:	ectopic pregnancy, salpingitis, mittelchmertz, endometriosis, ovarian cyst (possibly rupturing), spontaneous or threatened abortion, adnexal or ovarian torsion, ovarian cancer, ureterolithiasis, cystitis
Musculoskeletal:	abdominal trauma
Dermatologic:	herpes zoster

Refer students to Table 1 on page 3 in the Handout for more detail on the characteristics of abdominal pain from various causes.

Appendicitis should be among the first diagnoses you consider, even though Mrs. Anderson's history of present illness differs from the so-called "classical presentation." The latter would include diffuse epigastric pain, slowly migrating to her right lower quadrant and becoming more focal. She most likely would describe concurrent nausea, vomiting, anorexia, and fever. However, Mrs. Anderson denies these associated symptoms and described focused pain from its initiation. Many cases of appendicitis, though, do not present in this so-called "classic" manner.[1,2] Persons with retrocecal appendices, for instance, describe persistently difficult-to-localize pain, which never migrates to McBurney's point.* Thus, until ruled out on physical exam, appendicitis must remain among your differential diagnoses.

**McBurney's point: One third the distance from the anterior superior iliac spine to the umbilicus.*[3]

Incarcerated hernia should be placed relatively low on your list of differential diagnoses. Mrs. Anderson reports a normal bowel movement this morning, indicating no intestinal obstruction. A partial, or Richter's hernia, could be present, thus allowing defecation. Yet if this were the source of her pain, Mrs. Anderson would be aware of a superficial mass and probably would present with associated nausea and vomiting.[4] A complete abdominal and groin exam confirming the absence of a such a painful palpable mass will assist in ruling out this possibility.

Ectopic pregnancy should be very high on your list of differential diagnoses. Mrs. Anderson has missed one of her periods, suggesting she may be pregnant, and now complains of steady, increasing pain in her right lower quadrant. This suggests an ectopic pregnancy in the right fallopian tube or ovary. However, there is no characteristic pain consistent with a diagnosis of ectopic pregnancy. The nature and location of the associated pain depends greatly on the size, position, and bleeding status of the pregnancy.[5] A pelvic exam will be necessary to help you determine whether Mrs. Anderson's uterus is gravid and whether her right tube or right ovary is abnormally enlarged and consistent with an ectopic gestational sac.

Salpingitis (infection of one or both fallopian tubes) is not likely, but should remain among your differential diagnoses until you have completed your physical exam. It typically presents with the gradual onset of pelvic or lower abdominal pain that slowly intensifies.[2] Mrs. Anderson's pain was more acute in onset than is typical of salpingitis. Furthermore, Mrs. Anderson denies a history of STDs and has been sexually monogamous with her husband. Unless she or her husband has not been monogamous, this diagnosis is unlikely.

Mittelchmertz is pain associated with monthly ovulation.[6,7] This pain is typically dull and achy, but may be sharp, even stabbing. It's often of rapid onset, lasting approximately 15 minutes to 1 day at most. The discomfort is believed to be secondary to peritoneal irritation following graffian follicle rupture and fluid release.[6,8] Mrs. Anderson's pain, however, has been building for 3 days with increasing intensity, a pattern dissimilar from that of mittelchmertz, which typically lasts fewer than 24 hours. This diagnosis, therefore, is highly unlikely.

Endometriosis develops in 5%–15% of premenopausal women, with the average age at diagnosis reported to be 28 years. Commonly asymptomatic, when symptomatic it causes dysmenorrhea, dyspareunia (especially with deep penetration), rectal pain (especially on defecation), backache, premenstrual spotting, or infertility.[9] Although Mrs. Anderson is within this condition's epidemiologic age bracket, her history does not parallel the presentation of endometriosis. Therefore, it need not remain among your differential diagnoses.

Section A: History and Physical

An ovarian cyst, especially if it is close to rupture, could cause Mrs. Anderson's pain. When large, these cysts tend to have an associated moderately severe, sharp, boring, and constant pain that slowly increases while the cysts enlarge to the point of rupture.[1,7,10] An ovarian cyst, therefore, should be kept relatively high among your differential diagnoses.

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.

Adnexal or ovarian torsion also should be among your differential diagnoses. The pain associated with fallopian tube twisting can become excruciating, causing women to double over in pain, as the blood supply to the distal tube and ovary diminishes. This pain is sudden and constant and may crescendo.[11] Typically, an abscess or mass (e.g., an ovarian cyst or cancer, fibroid, or endometrioma) serves as the fulcrum about which the region twists;[1,8] however instances of idiopathic torsion have been reported in the literature.[12,13] The clinical presentation of torsion is similar to Mrs. Anderson's; therefore this diagnosis should be on your differential list.

Ovarian cancer is typically a disease of postmenopausal women, rather than women Mrs. Anderson's age. When diagnosed, it is usually well-advanced, with a nonspecific symptom complex: unexplained weight loss, malaise, nausea, dyspepsia, and altered bowel habits.[2] Rarely an ovarian tumor will become incarcerated in the pouch of Douglas, resulting in severe abdominal pain.[14] Equally rarely, an ovarian tumor will cause ovarian torsion (as noted above). Given Mrs. Anderson's age and her history, ovarian cancer is unlikely and need not remain among your differential diagnoses.

Ureterolithiasis ("kidney stones") may be moved to a lower position on your list. These patients present with sudden, severe flank pain that slowly migrates anteriorly and inferiorly as the stone progresses through the ureter to the bladder. When its associated pain peaks, patients move constantly to try to relieve their discomfort.[2] Mrs. Anderson, on the other hand, describes a constant, slowly increasing pain, which remained in a fixed, anterior location. Also, as you talked with her, you did not notice any fidgeting or urgency to move.

Cystitis typically presents with suprapubic discomfort, urinary frequency, urinary urgency, and dysuria (pain on urination).[15] In some instances, however, the pain may localize to one side of the abdomen, somewhat confusing the diagnosis. Yet without the triad of typical urinary symptoms, it is highly unlikely that Mrs. Anderson is experiencing cystitis.

Section A: History and Physical

Abdominal trauma may be placed somewhat lower on your differential given that Mrs. Anderson denied both trauma and domestic violence. However, until you perform your physical exam and can visibly rule out traumatic lesions and ecchymoses, your suspicion of domestic violence should remain. Many women are afraid to admit to domestic violence. Your job as a competent physician is to keep this among your differential diagnoses until absolutely proven otherwise.[16]

Herpes zoster ("shingles") may be a possibility because Mrs. Anderson had chicken pox as a child. She denies an abdominal rash (which would make zoster more likely); however, the pain of zoster often precedes its skin manifestations by several days. Patients often describe an "unpleasant, raw sensation" (dyesthesia) when the involved region is lightly stroked.[2] During your physical exam, you will need to determine whether Mrs. Anderson's pain is superficial and dermatomal (consistent with zoster) or whether it is focal and involves deeper structures (consistent with other diagnoses). Until you perform your examination, however, herpes zoster should remain among your differential diagnoses.

Top eight candidates:

1. Ectopic pregnancy
2. Appendicitis
3. Ovarian cyst
4. Salpingitis
5. Threatened or spontaneous abortion
6. Adnexal or ovarian torsion
7. Abdominal trauma, possibly secondary to domestic violence
8. Herpes zoster

⏩ Discuss with students what they should look for on a focused physical exam in a patient presenting with abdominal pain. Then have students read the physical findings in their Case Vignette, referring to the photograph of the cervix on page 4 in the Handout.

2. What should your physical exam consist of?

As with your history, your physical exam should be relatively complete. However, Mrs. Anderson has come to you for a problem-focused appointment. Your exam, therefore, should be tailored to her complaint rather than be a complete screening physical. A thorough neurologic exam, for instance, is not necessary under the circumstances.

General

How does she appear (well-developed, well-nourished, alert, fatigued, depressed, fidgety, in pain, in no apparent distress, "ill-appearing")? Your first impression is a useful diagnostic tool. On occasion, a patient will attempt to be stoic, describing his or her pain as mild when body language states otherwise. Pay attention to this discrepancy. Your general observations about Mrs. Anderson will help you assess the urgency and severity of her condition.

Weight and Height

What is Mrs. Anderson's weight? Is it significantly different from the last time she was weighed or weighed herself? Has she unintentionally lost more than 10 pounds in the last 6 months, thus causing you think more about a chronic or severe disease state?

Vital Signs

Temperature?

If Mrs. Anderson's temperature is elevated, you may consider an infectious process underlying her abdominal pain. Even a low-grade fever can be informative, suggesting a lesser infectious process or an inflammatory process. (For instance, the inflammation secondary to an ectopic pregnancy causes a low-grade fever in approximately 2% of cases.[17])

Blood pressure?

If Mrs. Anderson's blood pressure is significantly depressed, your first concern should be blood loss. A ruptured ectopic pregnancy can rapidly prove fatal secondary to hemorrhage.[1] A ruptured ovarian cyst, on the other hand, rarely has such serious consequences; although hemorrhagic cysts are not uncommon.[10]

Heart rate?

If Mrs. Anderson's heartbeat is elevated, this may be secondary to pain, anxiety, or stress. As with blood pressure, heart rate can also indicate of hypovolemia. When checking her blood pressure for orthostatis, also check her pulse.

Respiratory rate?

If Mrs. Anderson is tachypnic (more than 20 breaths per minute), many causes should be suspected. First, she may be taking frequent shallow breaths to minimize abdominal pain exacerbated with deeper breaths. Second, severe pain frequently increases patients' respiratory rates, especially as their anxiety rises. Third, if she is hypovolemic secondary to hemorrhage, she may be hyperventilating to increase her oxygen delivery to cells despite an insufficient RBC count. Fourth, if she has a fever, her respiratory rate will be elevated (on average) four breaths per minute per 1° F elevation.[3]

Cardiac Exam

Regular rhythm? Murmurs, rubs, clicks, or gallops? Displaced PMI? Normal rate?

Pulmonary Exam

Breath sounds symmetrically in all lobes? Wheezing, rhonchi, or rales?

Abdominal Exam

Contour (protuberant, flat, scaphoid, gravid)?

Initial inspection of the contour of Mrs. Anderson's abdomen provides evidence of both her nutritional state and her pregnancy status, a very rough estimate of how long she has been so. For instance, early in pregnancy, you will see no contour change. As the pregnancy proceeds, the abdomen will progressively protrude.

Visible lesions, ecchymoses, or masses?

Does Mrs. Anderson's abdomen reveal any evidence of trauma, e.g., any abrasions, cuts, or ecchymoses (especially of varying ages)? If she has denied trauma or domestic violence, gently asking her about the source of these lesions may prompt a new response—or at least make her aware that you care about her welfare. Is any rash suggestive of herpes zoster visible overlying her right lower quadrant? Does she have any obvious masses that may suggest a hernia or tumor?

Bowel sounds (absent, hypoactive, hyperactive)?

Listening to Mrs. Anderson's bowel sounds will help you determine whether she has an intestinal obstruction. If her bowel sounds are hypoactive with high-pitched tinkles and peristaltic rushes in one area, obstruction should remain high among your differential diagnoses.[18]

Tenderness to light and deep palpation? Rebound tenderness? Masses?

Organomegaly?

If possible, the size of Mrs. Anderson's uterus also should be determined. If she is indeed pregnant and only in her first trimester, you are unlikely to be able to palpate her uterus abdominally. By 20–22 weeks, the fundus of her uterus would be at the level of her umbilicus. By 30 weeks, the fundus would reach her costal margin.[19]

Psoas or obturator signs?

Both of these maneuvers help you evaluate Mrs. Anderson's likelihood of appendicitis.

Back Exam

Costovertebral angle tenderness? Lesions or ecchymoses?

Once again, you are looking for signs of trauma or domestic violence, or for rashes.

Rectal Exam

Occult blood, stool color and consistency, presence of lesions or masses, sphincter tone?

A rectal exam is imperative when performing a physical on anyone with abdominal pain. Gross blood raises your suspicion of a lower GI bleed; occult blood detected with a heme test suggests an upper GI bleed.

Appendiceal tenderness?

If palpation of the appendix results in acute pain, appendicitis will clearly be elevated among your differential diagnoses.

Pelvic Exam

Vulvar, vaginal, or cervical lesions, masses, anatomic anomalies, foreign objects?

As with her perianal region, if Mrs. Anderson has visible warts, ulcerations, or unusual discharge, you should reconsider STDs as a source for her abdominal pain. A nonfriable (easily bleeding) cervix would further raise this suspicion.[20] Any masses should elevate the diagnosis of a genital cancer on your differential. If such a cancer has metastasized into her pelvic cavity, abdominal pain may indeed be her presenting symptom. Grossly apparent anatomic anomalies might clue you in to the possibility of other gynecologic malformations (for instance, uterine malformation or tubal strictures).[21] If Mrs. Anderson is pregnant, her risk for an ectopic pregnancy or spontaneous abortion may be elevated in this circumstance.

⏩ Refer students to Figure 1 of a cervical collar with pseudopolyp and cockscomb on page 4 in the Handout.

Uterine masses, tenderness, size?

If you can palpate a mass or thickening in Mrs. Anderson's uterus, five diagnostic possibilities should come to mind immediately. First, this may be a simple fibroid (especially if it is smooth).[22] Second, you may be appreciating a locus of endometriosis (endometrioma).[23] Third, this thickening could represent adenomyosis, the presence of endometrial glands and stroma within the myometrium. Fourth, this may be endometrial cancer (albeit unlikely given her age). Fifth, this mass may represent an interstitial ectopic pregnancy implanted in the uterine wall.[17] Uterine tenderness would raise your suspicion of an inflammatory process, infectious or other. Determining the size of Mrs. Anderson's uterus may assist you in determining the approximate gestational age of her fetus, if such is the case. Often the uteri of women with fibroids also are described on the basis of approximate gestational size.

Adnexal masses or tenderness?

If one (or both) of Mrs. Anderson's adnexa is (are) tender, your suspicion of salpingitis should again be entertained. Enlargement may simply be secondary to the inflammation of salpingitis, she may have formed a loculated abscess, or she may have an ectopic pregnancy in her tube.

Extremities Exam

Clubbing? Edema?

Lesions or ecchymoses?

Once again, you are looking for signs of domestic violence.

Cyanosis?

Peripheral cyanosis most typically presents in the setting of vasoconstriction, vascular occlusion, or reduced cardiac output. If you detect cyanosis when examining Mrs. Anderson's extremities, your primary concern should be hypovolemic shock secondary to severe internal hemorrhage.[3]

Section B: Developing a Working Diagnosis

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

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

Your previous differential diagnosis list was:

1. Ectopic pregnancy
2. Appendicitis
3. Ovarian cyst
4. Salpingitis
5. Threatened or spontaneous abortion
6. Adnexal or ovarian torsion
7. Abdominal trauma, possibly secondary to domestic violence
8. Herpes zoster

Ectopic pregnancy should remain extremely high among your differential diagnoses. Not only has Mrs. Anderson told you about missing her last menstrual period and having increased breast tenderness; but you now also have physical evidence of an enlarged, tender right fallopian tube. That her uterus is of nongravid size should not alter this consideration. Early in pregnancy you would not normally be able to detect manually any uterine enlargement.

Appendicitis can now be removed from you differential. Mrs. Anderson did not present with any of the expected findings, except right lower quadrant pain, and on physical exam, no appendiceal tenderness was demonstrated.

Ovarian cyst cannot yet be ruled out, because the ovaries are often difficult to palpate accurately on pelvic exam. Hemorrhagic corpus luteum cyst (with accompanying intrauterine pregnancy): 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.

Salpingitis remains low on your differential but should not yet be excluded. 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.

Spontaneous or threatened abortion, though less likely with such clear-cut findings in the right adnexa, still cannot be totally excluded.

Adnexal or ovarian torsion: This diagnosis alone would not explain Mrs. Anderson's missed menses.

Domestic violence is also among your differential diagnoses as a cause for her abdominal pain. Your physical exam revealed no evidence of trauma. Rather, it pointed to a gynecologic cause for her symptoms.

Herpes zoster, too, is low among your differential diagnoses. You noted no rash consistent with zoster. Mrs. Anderson's abdominal pain was focal, rather than dermatomal. Furthermore, your exam illustrated an adnexal source for her pain.

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)

4. What laboratory test(s) would you like to perform and why?

Pregnancy Test (B-hCG)
According to her history, Mrs. Anderson has missed one menstrual period, raising the possibility that she may be pregnant. Performing a pregnancy test in the office will assist with your differential and management plan.

Stat Complete Blood Count (CBC)
If Mrs. Anderson's WBC is elevated, your differential diagnoses may be redirected toward an infectious cause. If Mrs. Anderson's hematocrit is low, you should seriously consider rupture of an ectopic pregnancy.

⏩ ***Once students have come up with these answers, they can turn to the next page in their Case Vignette to find the next questions.***

5. What is your presumed diagnosis for Mrs. Anderson's abdominal pain?

Ectopic pregnancy.

Section C: Ectopic Pregnancy

6. What is your next management step?

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.

7. What study should be conducted to determine whether Mrs. Anderson has an ectopic pregnancy?

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]

8. What are known risk factors for ectopic pregnancy?

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 age[31]
- Developmental abnormalities of the tube (e.g., after exposure to diethylstilbestrol [DES] in utero)[27,32,33,89,90]
- Cigarette smoking[31]

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.

Section D: Lesions of the Cervix

9. What is your differential diagnosis for her 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 (refer to Figure 1)

These anomalies are not true polyps because they are not growths extending from the wall of the cervical canal. Rather, these are congenital variants seen in in-utero exposure to diethylstilbestrol (DES). A 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. This central tissue may be composed entirely of pale pink ectocervical cells, or it may include a visible region of darker pink, more granular endocervical cells. The presence of the cervical os in the center of this structure differentiates it from a true cervical polyp.[34] Also, this structure is much firmer than a polyp and is rarely friable (unless eroded or irritated secondary to infection) (see "Cervical polyps" below). Cervical pseudopolyps are asymptomatic but correlate 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. (See answer to question #13C for a complete discussion.)

Your pelvic exam findings match the textbook description of this lesion. Furthermore, Mrs. Anderson appears to have an ectopic pregnancy. This would make an elegant diagnosis, combining your findings on exam with her presenting complaint. Cervical pseudopolyp, therefore, should be top among your differential diagnoses; and you should screen Mrs. Anderson for DES exposure.

Cervical Condylomata

These lesions are caused by human papilloma virus (HPV), an STD. Lesions on the vulva and perianal region and in the vaginal vault tend to be clusters of small growths, appearing much like cauliflower—condylomata acuminata. They are typically asymptomatic, nonfriable, and similar in color to the tissue from which they emanate. Lesions on the cervix tend to present slightly differently. These are macular—flat condylomata.* They, too, are usually asymptomatic, nonfriable, and similar in color from the exocervix from which they extend.[9,20]

* Note: this is *not* the same as condyloma lata of secondary syphilis.

Neither Mrs. Anderson's gynecologic history nor physical exam supports this diagnosis. She has no known history of STDs nor a sexual history that would put her at significant risk for HPV. On physical exam, her lesion is single (versus multiple) and protuberant (versus macular). Certainly a variant presentation is possible; but too many details fail to match, thus making this an unlikely diagnosis.

Cervical Polyps

Cervical polyps are small, benign, pedunculated growths originating primarily from the endocervix. The most common etiology is presumed to be chronic papillary endocervicitis. This growth is 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. Those few polyps originating from the ectocervix are histologically more fibrous than their endocervical counterparts. Their gross appearance, too, is different, being flesh-colored, round or oblong, and rarely friable. On examination, both types of polyps are difficult to palpate, because they are often extremely soft. 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]

Mrs. Anderson's cervical lesion presents characteristics similar to those of an ectocervical polyp. On pelvic exam, however, her lesion was firm, rather the soft, making a polyp a more questionable diagnosis. Also, the presence of the cervical os in the center of her "polyp" makes this diagnosis extremely unlikely.

Cervical Cancer

Cervical cancer is the 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 and 90% are squamous (epidermoid) carcinomas. The mean age at presentation is approximately 50 years.[36] Established 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]

Three macroscopic presentations have been described: exophytic, endophytic, and ulcerative. Exophytic tumors occur most commonly, arising in the exocervix and extending into the vaginal canal. Their morphology can vary considerably, with a single polypoid mass, a multinodular appearance, or a single irregularly shaped mass. Endophytic tumors, as their name suggests, extend inward, distending and distorting the cervical meatus, resulting in a so-called "barrel" cervix. Ulcerative tumors present most dramatically, eventually replacing the cervix and the upper vagina with necrotic tissue.[9,35]

Section D: Lesions of the Cervix

The symptoms of cervical cancer also vary. Early on, most women are asymptomatic. 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]

Mrs. Anderson's presentation does not fit the typical epidemiologic profile for squamous cervical cancer; although this alone is not a reason to rule out this diagnosis entirely. Her lesion could be exophytic, presenting under atypical circumstances (younger age, no known previous HPV, or other risk factors). Her symptom complex, however, also does not direct you toward a diagnosis of cervical cancer. She denies vaginal bleeding, and her pain was acute and rapidly progressive. However, perhaps she has an atypical cervical cancer plus an unassociated ectopic pregnancy. Given the importance of accurately diagnosing her pain, your level of suspicion should remain elevated for now.

Clear cell adenocarcinoma (CCA) of the cervix also should be among your differential diagnoses. A rare form of cancer primarily in women older than 50 years of age, it also occurs in young women exposed to DES in utero (DES Daughters). Vaginal adenosis occurs in approximately 30%-35% of DES Daughters; therefore a high degree of suspicion in these women is mandatory.[37-39] Given Mrs. Anderson's age, she is a potential candidate for this cancer and, as noted above, should be screened for DES exposure. (See question #13 for a complete description.)

⏩ At this point a break is inserted for one of the following purposes, depending on the educational opportunity available:

- If 3-4 hours are allotted to the case presentation and discussion, use the next hour for students to conduct online literature searches or to review reference material handed out by the instructor.
- If the time available is two 1-hour sessions on different days, instruct the students to search the literature before the next class or to review reference material handed out by the instructor.
- If the opportunity available is an online course, this and other breaks can be inserted to permit the course instructor to answer student questions, give process instructions, and tailor the unfolding of the case over a period of several weeks.

Section E: Diethylstilbestrol (DES)

⏩ ***Ask students to list what they know about DES.***

⏩ ***Refer students to Table 2 on page 5 in the Handout and to the subsequent slides on pages 7–9, to supplement the facts they already know.***

10. What is diethylstilbestrol (DES)? When was it used?

*(**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.

11. What were and are DES's indications for use? Was it an effective agent for its initial indication?

Pregnancy

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 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] 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.

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. Consequently, an estimated 1–4.8 million pregnant U.S. women were given this compound.[9,41,46,47]

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

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

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

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.

12. What is DES's mechanism of action?

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] This turned out not to be the case, however, as evidenced by the work of Dieckmann and others.[43,45]

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]

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]

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]

Livestock

Akin to anabolic steroid use in humans, DES use in livestock feed led to increased lean muscle mass and decreased fat deposition.[55] Yet the exact mechanism through which DES and other estrogens affect anabolic results remains unknown.

Section E: Diethylstilbestrol (DES)

⏩ ***Before discussing the negative outcomes of DES exposure, make the following caveats known. Refer students to page 10 in the Handout where this table is abstracted.***

Caveats to consider when assessing a patient's health risks from DES exposure

- A majority of individuals who have been 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 current studies at that time for clinical practice.
- Research on DES is ongoing, and some animal studies have identified health effects that might yet occur.

Section F: DES Daughters

⏩ Refer students to slides on this topic, on pages 10–19 in the Handout, to supplement this discussion.

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

Neoplasms

A. Clear Cell Adenocarcinoma

Clear cell adenocarcinoma (CCA) of the vagina and cervix is a rare cancer that occurs more frequently in women exposed to DES in utero (DES Daughters) than in women not exposed to DES.[56,57] Clear cell adenocarcinoma (CCA) of the vagina (Figure 1) is more highly correlated with in utero DES exposure than is CCA of the cervix. The relative risk for CCA in DES Daughters is 40.7, compared with women not exposed to DES in utero.[57] The absolute risk for CCA in DES Daughters appears to be 1.0–1.5 in 1000 or less.[58] The peak incidence of CCA in DES Daughters appears to occur in the late teens and early 20s. However, a small number of CCA cases, confirmed or suspected as associated with DES exposure, have been reported in women in their 30s and 40s.[57,59] In the absence of DES exposure, CCA usually occurs in postmenopausal years. Most women enrolled in studies of DES Daughters are only now entering menopause. On the basis of current evidence, there is no age beyond which a provider can be certain CCA of the vagina and cervix will not occur.

⏩ Refer students to photographs on page 12 in the Handout of clear cell adenocarcinoma of the vagina.

B. Cervical Intraepithelial Neoplasia

The relation between in utero DES exposure and increased risk for cervical intraepithelial neoplasia (CIN) is uncertain. Some studies have suggested an increased risk on the order of a relative risk of 2.0.[60,61] Other studies have not found an association.

C. Breast Cancer

The relation between in utero DES exposure and increased risk for breast cancer continues to be studied. Several studies have demonstrated no increased risk;[62-65] however, a recent study provided initial results linking exposure to DES before birth with increased rates of breast cancer.[66]

Among study participants, DES Daughters were more likely to experience breast cancer than were unexposed women. Overall, DES Daughters had a relative risk of 1.4. However, the findings were not statistically significant. In participants over 40, DES Daughters were two-and-a-half times more likely than unexposed women to be diagnosed with breast cancer. Findings for DES Daughters over 40 were statistically significant. DES Daughters under 40 years of age did not experience an increased risk of breast cancer. The findings from this study are considered preliminary until confirmed and refined by other research.

D. Other Cancers

The average age of DES Daughters in reported studies is less than 40 years. Questions remain about the possibility of increased risk for age-related cancers.

Reproductive Tract Structural Differences

A. Vaginal Adenosis

This condition occurs in approximately 33% of DES Daughters.[37-39] Furthermore, studies have repeatedly shown that the greater the dose of DES the daughter was exposed to in utero, the greater her likelihood and the greater the extent of vaginal adenosis.[67] Almost invariably located in the upper one-third of the vagina, this lesion consists of glandular tissue abnormally situated in the vaginal wall. When palpated, the involved region feels unusually thickened. It can appear grossly as a small cystic lesion or as solid, red, granular epithelium.[38,68,69] As glandular tissue, it secretes varying amounts of mucus, causing many of these women to be misdiagnosed with vaginal infections.[68] Over time, these regions of adenosis are slowly replaced by squamous metaplasia, so that DES Daughters over 30 years of age rarely present with this finding.[70-72] In over 90% of diagnosed cases of CCA of the vagina and cervix, regions of vaginal adenosis have been found adjacent to the malignant tissue.[37,56,73] Therefore, the two are presumed to be somehow connected. However, no studies have yet demonstrated this hypothetical progression from adenosis to cancer.[74]

⏩ Refer students to photographs on page 14 in the Handout of benign vaginal adenosis.

B. Cervical Malformations

Twenty-five percent to 33% of DES Daughters exhibit cervical deformities, including: cockscomb cervices, cervical hoods, cervical collars (rims), pseudopolyps, and cervical septae.[21,34,75-79]

Cockscomb cervices result when stromal abnormalities of the cervical tissue result in a firm ridge or collection of ridges in the anterior vaginal fornix or upper ectocervix. This anomaly resembles the comb of a rooster's head, hence its name.[35,68] It is both benign and asymptomatic.

Cervical hoods also are stromal anomalies. A small ledge of firm but otherwise normal-appearing tissue forms on the anterior edge of the ectocervix. Some of these women consequently describe difficulty using diaphragms.[35,72]

Cervical collars (rims) are bands of tissue encircling the periphery of the cervix.[34]

Pseudopolyps, as noted earlier, comprised the cervical tissue, which appears to protrude from the center of cervical collars.[35]

⏩ Refer students to photograph of a large cockscomb cervix on page 15 in the Handout.

⏩ Refer students to previously shown photograph of pseudopolyp on page 4 in the Handout.

C. Uterine Malformations

Abnormal hysterosalpingogram occurs in up to 69% of DES Daughters.[21] The most common anomaly is the T-shaped uterus. Other abnormalities include small uterine cavity, T-shaped uterus with constriction, and constriction rings. DES Daughters with grossly misshapen cervices are five times more likely to have these uterine anomalies than are daughters without externally apparent malformations.[21]

⏩ Refer students to uterine abnormalities demonstrated in DES Daughters on page 17 in the Handout.

Section F: DES Daughters

Infertility and Adverse Pregnancy Outcomes

A. Infertility

Several studies have found that incidence of primary infertility is increased in DES Daughters. In the Dieckmann cohort, rates as high as 33% were reported,[80,81] compared with 14% in unexposed women, although other studies have not confirmed this.[81,82] The proposed mechanisms for infertility are still being investigated. Possible explanations[84] have included direct effect from the structural abnormalities;[85] elevated testosterone and prolactin;[86-88] and failure of implantation or alterations in ovarian steroidogenesis. Earlier studies of the DESAD cohort found no effect on infertility in DES Daughters. However, these studies evaluated women still in the early years of their reproductive life.[82-83]

B. Adverse Pregnancy Outcomes

Pregnancy outcome for DES Daughters will most frequently be to carry a normal pregnancy to term.[89] However, an increased risk for abnormal pregnancy outcomes has been consistently documented:

- Rates for ectopic pregnancy range from 3.7 to 8.6 higher than for unexposed women. RR has been assessed at 3.84.[89,90]
- Premature birth rates range from 2.6 to 4.7 times higher than for unexposed women. RR has been assessed at 2.9.[89,90]
- Rates of miscarriage, especially those in the second trimester, range from 1.8 to 4.4 times higher than for unexposed women. The RR has been assessed at 1.31 for the first trimester and 2.93 for the second trimester.[89,90]
- With reproductive tract abnormalities, rates for ectopic pregnancy, premature births, and miscarriage in DES Daughters are even higher (13.5; 9.6; 2.6, respectively).[90]

Other Disorders

A. Immune Function

Animal studies of in utero DES exposure in female mice suggest increased risk for autoimmune disease for female mice. Yet studies in humans have yielded conflicting results. One study indicated that the incidence of autoimmune diseases was higher in DES Daughters.[91] However, no single autoimmune disease had a statistically significant association with in utero DES exposure.

B. Psychosexual

Some animal studies have suggested links and have raised concern in those humans who have been exposed. They suggest links between prenatal exposure to androgens or estrogens and cognitive abilities differentiated by sex.[92,93] However, no human studies have documented consistent findings linking DES exposure in utero to any psychological/psychiatric condition or to any sexual dysfunction,[94,95] although Vessay showed a slight increase in rates of depression.

14. What are the treatment options and prognosis for clear cell adenocarcinoma (CCA)?

Women with stage I CCA have traditionally been treated with radical hysterectomy (removal of the uterus, fallopian tubes, and one or both ovaries) and pelvic lymphadenectomy.[96] Vaginectomy (removal of part or all of the vagina) is added when vaginal tumors are present. More recently, an alternative treatment has been instituted for women desiring preservation of their reproductive function. In this instance, the surgical treatment includes wide local excision and staging laparotomy with retroperitoneal lymph node dissection followed by local radiation treatment.[97] Patients with stage II and stage III disease are treated with radical hysterectomy, pelvic lymphadenectomy, and radiation therapy (both internal and external). Pelvic exenteration* or palliative therapies are reserved for patients with stage IV disease.[96] Chemotherapy has proven an ineffective adjuvant modality.[96]

In most women (>90%), this cancer has been diagnosed during either stage I or stage II of the disease.[98] For women with stage I disease, their 10-year survival rate has approached 90%.[46,98] On the other hand, none of the women diagnosed with stage IV disease has survived even 5 years.[46] Recurrences of disease have been reported, albeit uncommonly. Several of these recurrences have occurred approximately 20 years after initial diagnosis. Clinicians, therefore, must remain vigilant to this possibility.[46]

In his report to the NIH in 1999, Herbst also noted that treatment of CCA does not end simply when this lesion is "cured." He reported the unpublished findings of Siston and colleagues, who found that 85% of CCA survivors in their study experienced problems with sexual function, 58% experienced medical or anatomic problems related to vaginal reconstruction, and 33% experienced psychological problems after their illness (e.g., anxiety and depression).[46] Therefore, when analyzing prognosis, you should review not only mortality statistics but also morbidity data.

* **Pelvic exenteration:** The surgical removal of all pelvic organs and adjacent structures. [Anderson 1994]

Section G: Women Prescribed DES While Pregnant

Refer students to slides on this topic, on pages 19-20 in the Handout, to supplement this discussion.

15. What are the adverse effects in women prescribed DES while pregnant?

Breast Cancer

Exposure to DES while pregnant is associated with a modestly increased risk (30%) for breast cancer. The relative risk is approximately 1.3. The risk does not increase as women age. The absolute risk is 13.3% in exposed women and 10.2% in unexposed women.[101]

- Several prospective follow-up case-control studies have shown an increased risk for breast cancer over the lifetime of cancer patients. Reported relative risk is approximately 1.3.[101-105]
- Not all studies have shown an increased risk for breast cancer, perhaps because of differing ages of study participants or methods of analysis.[106,107]
- To contextualize the increased risk from DES exposure, one should compare the relative risk to other risk factors, such as family history of breast cancer, where the relative risk is 2.1;[108] and HRT use over 5 years or more, where the relative risk is 1.35. [109]

Other Effects

A number of health risks to women from DES exposure during pregnancy have been disproven. (Audience research has identified worries and concerns of DES-exposed persons, that providers should be prepared to discuss, the relation between DES exposure and HRT, and worries about other gynecologic cases. Providers should be able to reassure patients that no evidence exists of increased risk for other cancers.[101])

Section H: DES Sons

Refer students to slides on this topic, on pages 20–21 in the Handout, to supplement this discussion.

16. What are the adverse effects of DES in men exposed in utero (DES Sons)?

In general, much less is known about the adverse effects of DES in sons than daughters. The few studies that have focused on the health of DES-exposed men have addressed development of genitourinary tract abnormalities or neoplasms. Because of the small numbers of studies, potential for selection bias in some studies, limits of statistical power caused by small samples in some studies, and the "loss to follow up" in some cohort studies, few firm conclusions about the risks of health effects in DES Sons can be drawn from the studies. Comparisons between studies are further complicated by differences in, and lack of information about, DES timing and dosage in various cohorts. However, providers should be aware that known-exposed sons and their families have followed the ongoing studies and are concerned about uncertain health effects. In addition, providers will want to be aware of potential health effects to effectively monitor DES Sons on the basis of current, and ongoing, follow-up research on this cohort.

Urologic Anomalies

DES Sons have an increased risk for benign epididymal cysts.[110-114] One study reported incidences of 20.8% exposed vs. 4.9% unexposed.[111]

Increased risks for other genital abnormalities (testicular hypoplasia, cryptorchidism, and microphallus) have been associated with DES exposure in males in a smaller number of studies.[111,114] Other studies have shown no increased risk for genital abnormalities among DES Sons.[115,116] Differences in findings may result from rate of follow-up with participants, method of analysis, or total DES dose received.

Testicular Cancer

An increased risk for testicular cancer in DES Sons has not been ruled out or confirmed. Studies on the risk for testicular cancer in DES Sons have yielded conflicting findings.

- The most definitive study of the association between in utero exposure to DES (a prospective study of 3,613 men in four DES cohorts) found elevated levels of testicular cancer among DES Sons than among the control group (RR 3.05; 95% CI = 0.65–22.0) and among men in population-based rates (RR 20.4; 95% CI = 0.82–4.20).[117] However, the increases were not statistically significant. The authors concluded that "it is highly unlikely that DES exposure plays a major role in the increases in testicular cancer rates that have been observed in developed countries over the past 60 years." Nonetheless, they concluded that the findings of

the study did "lend support to the hypothesis that the prenatal hormonal environment may influence the development of testicular cancer in adults."

- Four case-control studies have provided evidence of increased risk for testicular cancer among men prenatally exposed to either DES or estrogen analogues. [118-121]

- Two other case-control studies failed to identify an association between prenatal DES exposure and testicular cancer risk.[122,123] Providers will know that testicular cancer is a secondary risk for those with undescended and hypoplastic testes (a few studies have identified DES Sons as having higher risk for these abnormalities than nonexposed men).

- Testicular cancer is a secondary risk for DES Sons with undescended testis. A few studies have identified DES Sons as having a higher risk of these abnormalities than nonexposed men.[111,114]

Infertility

Many DES Sons are concerned that their exposure will lead to infertility. They may base their concerns on studies reporting higher incidence of infertility in DES Daughters or animal studies reporting increased rates of infertility in DES-exposed male mice. However, DES Sons have not been found to have increased risk for infertility, despite the belief by some of these men that their infertility stems from their in utero DES exposure. A 40-year follow up of the participants in Dieckmann's prospective, blinded, placebo-controlled study[124] indicated no de facto impairment of fertility.[114]

Other

DES Sons are sometimes concerned about the findings of animal studies. Several animal studies have demonstrated a significant relation between in utero exposure to DES and subsequent development of tumors of the rete testis and significant metaplastic, dysplastic, and neoplastic changes in the prostatic utricle.[125-130] These studies further demonstrated the development of rete testis cancer at an older age in DES-exposed animals than has yet been reached by the human DES male cohort. As a result, a possibility exists of increased risk for men as they age. In addition, prostatic cancers typically become more prevalent in men older than the current age of the DES Sons cohort. Thus, animal studies raise concerns about a possible human correlate developing as the DES-exposed population ages. Prostatic utricle cancer presents as occult blood in the urine, unexplained by infection.

Section I: Third Generation

⏩ ***Refer students to slide on this topic, on page 22 of the Handout, to supplement this discussion.***

17. What is the impact of DES on the third generation (the offspring of DES Daughters and Sons)?

Animal studies showing increased risk for reproductive tract tumors in "third-generation" mice have generated concern. These tumors include uterine adenocarcinoma, uterine sarcomas, benign ovarian tumors, and lymphomas in female mice, and tumors of the rete testis and other reproductive tract tissues in male mice. Such studies suggest possible genetic changes imprinted at the molecular level.[131-136]

Two human studies of third-generation effects in females have been published. Neither found evidence of increased health risks or abnormalities.[137,138] One study of health risks in third-generation males has been published, showing an increased risk of hypospadias.[139]

The children of DES Sons and Daughters range in age from newborn to 40 years. As a result, any increased health risks related to third-generation DES effects might not emerge for decades. Further study will be required to determine whether these persons are at increased risk for health problems related to DES exposure.

Section J: Screening and Referral Recommendations

Refer students to slides on this topic, on pages 23–25 in the Handout, to supplement this discussion.

18. What are the current screening recommendations for DES Daughters? [140]

- In 1995 the National Cancer Institute (NCI) sponsored the National DES Education Project, which recommended the following procedures as routine screening for DES Daughters:
    - An annual examination, including clinical breast examination
    - Inspection of the vulva, vagina, and cervix
    - Vaginal and cervical cytology
    - Digital vaginal and cervical palpation
    - Bimanual examination, including rectal examination[140]

- Pap smear screening has detected some cases of clear cell adenocarcinoma (CCA) of the vagina and cervix, but smears have been negative in other cases. The mechanism of efficacy of Pap smear screening for squamous cell carcinoma in DES Daughters may differ from that for CCA. Data are lacking on which to make a firm conclusion.

- Increasing the frequency of examinations and the use of colposcopy and Lugol's iodine staining may be recommended depending on structural abnormalities or changes.[140]

- When abnormalities are found in routine gynecologic examinations, providers should consult with a gynecologist experienced in evaluating DES Daughters.[140]

- CCA of the vagina and cervix is diagnosed by biopsy of any grossly abnormal vaginal lesion. The standard of care for management of all grossly visible vaginal lesions is biopsy.

- Known or suspected DES Daughters should be monitored for development of CCA throughout their lifetimes. Although the risk of developing CCA beyond age 30 appears to be small, it should not be dismissed.[42]

- The evaluation and management of cervical intraepithelial neoplasia (CIN) is not altered in the presence of DES exposure. Untreated cases of CIN require close follow up.

- Although the presence of vaginal adenosis suggests DES exposure, no specific treatment is necessary.[141-143]

- Patients presenting with indications of CCA of the vagina or cervix should be referred to a gynecologic oncologist for further evaluation and treatment.

19. What are the current screening recommendations for women prescribed DES while pregnant?

The current screening recommendations for women prescribed DES while pregnant do not differ from those for the general female population because their risk for breast cancer is only mildly elevated above that of their peers. The American Cancer Society Guidelines for Breast Cancer Screening are as follows:[144]

- Women aged 20 and older should perform monthly breast self-exams.
- Women aged 20–39 years should have a clinical breast examination by a health professional every 3 years.
- Women aged 40 and older should have a clinical breast examination by a health professional annually.
- Women aged 40 and older should have an annual mammogram.

**** Women who know they were exposed to DES during pregnancy should be strongly encouraged to share the information with their children.****

20. What are the current screening recommendations for DES Sons?

The current screening recommendations for DES Sons do not differ from the general male population. The American Cancer Society recommends the following testicular cancer screening guidelines:[145]

- Annual clinical testicular exam by a health professional.
- Education regarding proper testicular self-exam technique and prompt medical evaluation any abnormalities found on exam.

- Monthly testicular self-exam for men with certain risk factors: cryptorchidism, previous germ cell tumor on one side, or family history of testicular cancer.

- Instructions for testicular self-exam can be found at http://www.cancer.org (American Cancer Society).

21. When should a primary care provider refer a DES Daughter to a specialist with DES experience? What services should the obstetrician/gynecologist provide?

Referral to an obstetrician/gynecologist is appropriate for consultation to perform preconception counseling and screening for reproductive tract abnormalities for DES Daughters contemplating pregnancy or who are pregnant.

Because individual presentation of DES-related abnormalities varies, obstetric/gynecologic management will likewise vary accordingly but may include:

- Preconception counseling, including a discussion of increased risks for infertility, ectopic pregnancy, miscarriage, premature labor, and premature birth.

- Consideration of diagnostic testing and therapeutic options, including:
  - Pelvic examination to assess for cervical anomalies
  - Hysterosalpingogram to assess for upper genital tract anomalies when infertility is an issue.
  - Early diagnosis of pregnancy with close monitoring for ectopic pregnancy

- Consideration of referral to a maternal-fetal medicine specialist.

22. What DES advocacy and information resources are available for patients and health care providers?

⏩ Refer students to an annotated list of resources in the Handout on pages 26–28.

23. What research on DES is being conducted?

⏩ Refer students to the slide that summarizes ongoing research on page 29 in the Handout.

Studies of DES combined cohorts continue to follow health outcomes in DES Sons and to track DES Daughters; these health outcomes include age at menopause, osteoporosis, and autoimmune diseases (such as rheumatoid arthritis and lupus). Studies are being conducted at Baylor College of Medicine (Raymond Kaufman, MD), Boston University (Julie Palmer, ScD), Dartmouth Medical School (Linda Titus-Ernstoff, MD), University of Chicago (Arthur L. Herbst, MD), Tufts-New England Medical Center (Kenneth Noller, MD), and the National Cancer Institute (Robert Hoover, PhD). NCI and the Netherlands Cancer Institute are sponsoring studies on third-generation effects on females and males, respectively.[114]

Section L: Concluding Discussion

Epilogue

Mrs. Anderson calls you later that evening to tell you her mother is not sure whether she was prescribed DES. You suggest that Mrs. Anderson assist her mother in tracking down this information by contacting the family physician that may have prescribed the medication. He may no longer be practicing, you acknowledge, but the office may still have access to her mother's medical records.

One month later, Mrs. Anderson calls to confirm that her mother was prescribed desPlex throughout her pregnancies with both herself and her brother.

Several months later, you receive a letter from Dr. Adams in which she describes the results of Mrs. Anderson's formal fertility work-up. A hysterosalpingogram indicated that Mrs. Anderson has almost complete stenosis of her left fallopian tube, in addition to the complete obstruction of her right fallopian tube (which was removed earlier in surgery). Her uterus appears to be of normal morphology on the basis of this study. Dr. Adams has recommended in vitro fertilization to Mrs. Anderson. Mrs. Anderson is considering this option but has not yet made a final decision.

Summary

⏩ ***Refer students to Table 3 for a summary in the Handout on page 30.***

References

⏩ ***Refer students to the references that conclude the Handout on pages 31–43.***