Uterine Sarcomas; Secondary Amenorrhea; and Cologenital Fistulas

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Table of Contents

Preface ........................................... .ii
Case Studies in Uterine Sarcomas .................. .1
   Contributing Authors: Timothy J. McElrath, MD
                        Benjamin M. Schwartz, MD
                        Gary L. Goldberg, MD, FACOG

Case Studies in Secondary Amenorrhea:
Diagnostic and Therapeutic Approach .......... .12
   Contributing Author: Jamil A. Fayez, MD, FACOG

Case Studies in Cologenital Fistulas ............... .26
   Contributing Author: Norma Perez Veridiano, MD, FACOG

Cover Illustration by Jean Gardner
Phyiscian certification and recertification in the disciplines of medicine are required for privileges in most hospitals and for participation in most health care organizations. Physicians practicing obstetrics and gynecology are certified and recertified by the American Board of Obstetrics and Gynecology (ABOG). The candidates for ABOG certification are expected to have both clinical expertise and scientific knowledge of obstetrics, gynecology, and primary/preventive health care. Physicians receive board certification after successfully completing an ABOG-approved residency program and passing both the written and oral certification examinations given by the ABOG. Board recertification by the ABOG is required every 10 years.

The Hospital Physician Obstetrics and Gynecology Board Review Manual is a quarterly publication intended to supplement study material and provide a review for board certification candidates. Each board review manual covers anatomy, pathophysiology, principles and theories of disease, as well as clinical aspects of the diagnosis and treatment of pertinent obstetrical, gynecologic, and medical processes. The content of the board review manual is guided by the content specified by the Council on Resident Education in Obstetrics and Gynecology (CREOG) in the Educational Objectives: Core Curriculum for Residents in Obstetrics and Gynecology, 5th edition, 1996. Topics covered include:

- Antepartum care
- Basic science/mechanisms of disease
- Carcinoma of the breast
- Carcinoma of the uterus
- Cervical disorders
- Critical care
- Disorders of the breast
- Disorders of the urogenital tract
- Early pregnancy loss
- Gestational trophoblastic disease
- Gynecologic care
- Gynecologic procedures and complications
- Infertility
- Intrapartum care
- Management of nongynecological conditions
- Management of the climacteric period
- Medical complications of pregnancy
- Menstrual and endocrine disorders
- Obstetric complications
- Office procedures
- Oncology therapies
- Ovarian and tubal carcinoma
- Pediatric and adolescent gynecology
- Postpartum care
- Practice management
- Primary care
- Professional growth and development
- Vulvar and vaginal malignancies

The format of the Hospital Physician Obstetrics and Gynecology Board Review Manual is case-based clinical vignettes that are commonly encountered in the practice of obstetrics and gynecology. This format presents essential information in an easy-to-read, concise manner. The board review questions are intended for reader self-assessment and to direct the reader to pertinent information concerning the topics. The tables and figures are selected for their clarity, educational value, and ability to illustrate, highlight, and/or summarize essential facts and concepts that the candidate must know to successfully complete the Board examination. Coverage is not intended to be complete. Recommended reading and references are listed.

This manual has been developed without the involvement of the ABOG. The manual is based on the Series Editors’ and contributing authors’ clinical experiences, awareness of new developments, experiences as resident educators, and knowledge of the certification examinations in obstetrics and gynecology. The editors wish all the candidates success with their training and Board examinations and rewarding careers in obstetrics and gynecology.

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I. INTRODUCTION

Uterine tumors with a malignant mesenchymal component arise from either the myometrium or the endometrial stroma. These are a relatively rare group of tumors, comprising only 3% to 5% of all uterine malignancies.1 Uterine sarcomas are usually aggressive; they have a high probability of metastatic disease at the time of diagnosis and an increased risk of recurrent disease when compared with uterine epithelial malignancies. The pathologic subtypes of uterine sarcoma vary in their clinical presentation and their subsequent response to surgery, chemotherapy, and radiation.

CLASSIFICATION AND STAGING

Traditionally, uterine sarcomas have been classified using the Ober system, which divides sarcomas into pure (mesenchymal only) and mixed (mesenchymal and epithelial components) tumors (Table 1).2,3 The pure and mixed categories are further categorized into homologous and heterologous tumors. Homologous tumors are composed of tissues that are normally found in the uterus (ie, smooth muscle, endometrial stroma). Heterologous tumors are composed of tissues that are not normally found within the uterus (ie, striated muscle, bone, cartilage). More recently, the Gynecologic Oncology Group (GOG) has devised a clinically practical classification system that has become widely used. The system describes four main histologic categories that define the histology and therefore, to some degree, the clinical behavior of the given tumor (Table 2).4

Uterine sarcomas are surgically staged in the same way as other cancers of the uterus. This review uses the system devised by the International Federation of Gynecology and Obstetrics in 1989 for all references to stage.5 Three case patients are presented who have the three most
common sarcomas; their initial treatment and their follow-up are also described.

II. CASE PATIENT 1

INITIAL PRESENTATION

Patient 1 is a 60-year-old African-American woman who has been postmenopausal for more than 10 years; she presents for evaluation of daily vaginal spotting for the past 2 months. Her medical history is pertinent for non–insulin-dependent diabetes mellitus diagnosed 8 years ago (which is treated with an oral hypoglycemic agent) and for hypertension diagnosed 12 years ago (which is treated with a calcium-channel blocker). Patient 1’s most recent gynecologic examination was 2 years ago; at this time, both her Papanicolaou (Pap) smear and mammogram results were normal. She is not currently sexually active and denies using oral contraceptive pills or hormone replacement therapy.

Pertinent Physical Examination

Patient 1 is 64 in tall and weighs 90 lb. Her blood pressure is 150/90 mm Hg. Her abdomen is soft and nontender. An enlarged uterine fundus is palpated just above the symphysis pubis. No abdominal masses are evident. Her breasts are symmetrical; breast examination reveals no dominant masses, skin changes, nipple discharge, nipple retraction, or palpable lymph nodes. A pelvic examination reveals normal external female genitalia, with no vulvar masses or ulcers.

Speculum examination of her vagina shows moderate estrogen effect. A polypoid, necrotic mass is aborting through the cervical os. Her cervix appears normal to gross inspection. Rectal examination shows good tone with no masses, and a stool sample is negative for rectal blood (guaiac negative). A bimanual examination reveals a uterus that is 15 weeks in size, smooth, and boggy. It is mobile, and there are no palpable adnexal masses.

• What diagnostic procedures are appropriate in the initial evaluation of patient 1?

DIAGNOSIS AND EVALUATION OF PATIENT 1

A biopsy of the mass was performed along with an endometrial biopsy and endocervical curettage. The following tests were ordered for patient 1: mammography, chest radiography, liver function testing, cancer antigen 125 (CA-125) testing, and computed tomographic (CT) scanning of the abdomen and pelvis.

The biopsy of the mass was reported as a high-grade adenocarcinoma with suspicion of malignant stromal elements. This was confirmed by the endometrial biopsy. The endocervical curettage and the chest radiograph were negative. CA-125 levels were less than 35 U/mL. The CT scan found an enlarged uterus with areas of necrosis within the endometrial cavity. There was no evidence of enlarged retroperitoneal lymph nodes in the abdomen or pelvis on the scans. The mammogram was negative.

Surgical Exploration

Patient 1 was taken to the operating room with the preoperative impression of stage I disease. She underwent an exploratory laparotomy; total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAHBSO); pelvic and para-aortic lymph node dissection; omentectomy; and peritoneal washings. No obvious tumor bulk was noted during the laparotomy. The final pathology

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Table 1. Ober Classification of Uterine Sarcomas

<table>
<thead>
<tr>
<th>Homologous</th>
<th>Heterologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromal sarcoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>(endolymphatic</td>
<td></td>
</tr>
<tr>
<td>stromal myosis)</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>Liposarcoma</td>
</tr>
</tbody>
</table>

Table 2. Histologic Classification of Uterine Sarcomas from the Gynecologic Oncology Group

<table>
<thead>
<tr>
<th>Endometrial stromal sarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyosarcomas</td>
</tr>
<tr>
<td>Mixed heterologous müllerian sarcomas (mixed mesodermal sarcoma)</td>
</tr>
<tr>
<td>Mixed homologous müllerian sarcomas (carcinosarcoma)</td>
</tr>
<tr>
<td>Other uterine sarcomas</td>
</tr>
</tbody>
</table>

results for patient 1 found the tumor was 10 cm in its largest diameter; the tumor was invasive to greater than 50% of the myometrium. The cervix was not involved. Histologically, the tumor was a mixture of a clear-cell adenocarcinoma and a stromal sarcoma. Of pelvic lymph nodes, 3 of 17 were found to have metastatic disease. All of the para-aortic nodes, omentum, and peritoneal washings were free of disease. A portion of the tissue was sent for estrogen and progesterone receptor status, and these were noted to be weakly positive. The final diagnosis for patient 1 was a stage III malignant, mixed mesodermal tumor (MMMT) of the uterus.

∑ What is the most common presentation for patients with MMMT?

∑ What are the most common risk factors for MMMT?

MALIGNANT, MIXED MESODERMAL TUMORS

All sarcomas with a malignant epithelial and a malignant mesenchymal component, whether homologous or heterologous, belong to the category of MMMT. This group is the most common of the uterine sarcomas, accounting for 50% of the total. Patients usually present in their seventh decade, and the most frequent presenting symptom is vaginal bleeding. On physical examination, a symmetrically enlarged uterus is typically noted; in 30% to 50% of these patients, a tumor is noted to be aborting through the cervical os at the time of presentation. Endometrial biopsy usually reveals either MMMT or a high-grade adenocarcinoma.

The risk profile for patients with MMMT is similar to that of patients with endometrial cancer. They frequently have hypertension, 40% are obese, 15% have non-insulin-dependent diabetes mellitus, and 25% are nulliparous. A feature that distinguishes MMMTs from endometrial adenocarcinomas is a higher frequency of MMMTs in African-American women (Figure 1). Endometrial adenocarcinomas occur with a higher frequency in Caucasian women. Exposure to postmenopausal estrogen has not been implicated in the pathogenesis of MMMT. Of patients with MMMT, 10% have a history of previous pelvic radiation. The time course for the development of an MMMT after radiation exposure ranges from 2 to 20 years.

∑ What is the appropriate preoperative evaluation of a patient with a known MMMT?

DIAGNOSIS AND EVALUATION: GENERAL PRINCIPLES

The preoperative work-up should include a chest radiograph to evaluate for pulmonary metastasis, a CA-125 level to evaluate for possible extrauterine extension, and an abdominal or pelvic CT scan (or both) to evaluate metastatic disease and nodal disease (Figure 2). Although none of these tests can rule out metastatic spread, it is important to assess—before starting the procedure—the extent of surgery that may be necessary. The clinical assessment of disease stage is inaccurate in 50% of cases of MMMT.

Nodal metastases are found in 33% of cases at final review (Table 3). Peritoneal, omental, and ovarian metastases are found frequently on surgical exploration. The risk of extrauterine disease is related to the depth of invasion and cervical involvement but not to the presence or absence of heterologous elements.

Surgical Exploration

Primary surgery for MMMT should include an exploratory laparotomy, TAHBSO, pelvic and para-aortic lymph node sampling, peritoneal cytologic sampling, and debulking of any gross disease that is present. Pathologic review of the surgical specimen usually reveals that the endometrium is extensively involved and that the myometrium is deeply invaded. The epithelial component is commonly adenocarcinoma (endometrioid, serous, or clear-cell type). The sarcomatous portion may be either homologous or heterologous. The homologous types are usually high grade and of indeterminate histogenesis. Heterologous sarcomas may be rhabdosarcoma, chondrosarcoma, osteosarcoma, or liposarcoma. Despite the various embryonic lineages that may be displayed, it is currently believed that these malignancies arise from a common stem cell. Some MMMTs have estrogen or progesterone receptors, which may be useful when selecting therapy.

POSTOPERATIVE TREATMENT

Patients with MMMTs have various postoperative options. Those with extrauterine disease should be treated with chemotherapy and pelvic radiation. Patients known to have a small amount of residual disease may benefit from whole-abdominal radiation therapy and chemotherapy. The role of postoperative radiation is controversial in stage I and II disease. Pelvic radiotherapy reduces the rate of pelvic recurrences by up to 50% but does not affect the overall survival rate because the rate of distant metastasis is unaffected by pelvic radiation.

The effect of chemotherapy on final outcome remains unproved. A GOG study found a nonsignificant improvement in survival with doxorubicin treatment. It has been shown, however, that the combination of doxorubicin, cisplatin, and ifosfamide can produce a complete remission in 8% to 18% of patients with advanced or recurrent disease.
The individual activity levels of each of these agents differ: ifosfamide is the most active, with a 30% to 35% response rate. Cisplatin has an 18% to 40% response rate and doxorubicin has a 10% response rate. Other agents with known activity include cyclophosphamide and vincristine. Some MMMTs have estrogen and progesterone receptors and may respond to high-dose progestin. However, the beneficial effects of hormonal manipulation are usually transient in MMMTs.

Prognosis

The recurrence rates for stage I and II MMMTs range up to 50% (Table 4). In patients with negative lymph nodes and no parametral extension, overall 5-year survival is approximately 60% (Table 5). The most common recurrence sites are lung and abdomen. The pelvis is the first site of recurrence in only 21% of cases. When these tumors recur, it is very frequently the sarcomatous portion that recurs.

III. CASE PATIENT 2

INITIAL PRESENTATION

Patient 2 is a 50-year-old African-American woman, G2P2002, last menstrual period (LMP) postmenopausal for 1 year, who presents for evaluation of vaginal bleeding and discharge for 1 month. She reports pelvic pain for the previous 2 months with a subjective impression of a “lump” developing in her pelvis and of pressure on her bladder. Patient 2 reports no medical problems. She is currently sexually active and does not have a history of oral contraceptive use. Her most recent gynecologic examination was 1 year ago, and no uterine pathology was noted. Patient 2’s Pap smear and mammogram results at that time were normal.
Pertinent Physical Examination

No masses are palpated in patient 2’s abdomen. Her breasts are symmetrical; breast examination reveals no dominant masses, skin changes, nipple discharge, nipple retraction, or palpable lymph nodes. Pelvic examination reveals normal external female genitalia, with no vulvar masses or ulcers.

Speculum examination reveals atrophic, pale vaginal mucosa. No masses, active bleeding, or evidence of infection is seen. Both wet prepared and potassium hydroxide (KOH) tests are negative for infection. Rectal examination shows good tone with no masses and brown stool, and a stool sample is negative for rectal blood (guaiac negative). The uterine mass is easily palpable. A bimanual examination reveals a nontender uterus that is 12 weeks in size with a single dominant fundal mass approximately 8 ¥ 5 cm in size. The mass is firm and moves with the uterus on examination.

Diagnosis and Evaluation

An endometrial biopsy, Pap smear, and pelvic cultures were done. Patient 2 was scheduled for a sonogram to evaluate the endometrial cavity and the mass. A single fundal “fibroid” that was 7.5 ¥ 5 cm in size with areas of central necrosis was observed on the sonogram. No other fibroids were noted in the uterus. The endometrial biopsy was negative for diagnostic pathology. Her Pap smear, mammogram, and pelvic cultures were normal.

With the history of growth of a “fibroid” in this postmenopausal woman and with her pelvic discomfort, patient 2 was scheduled for an exploratory laparotomy and TAHBSO for diagnosis and treatment. Routine preoperative laboratory test results and a chest radiograph were obtained, and these were within normal limits.

Surgical Exploration

Patient 2 was taken to the operating room for a TAHBSO. The uterus and mass were removed; on gross inspection, the pathologist reported a 7.5 ¥ 5 cm soft fleshy mass with areas of hemorrhage and necrosis. On frozen section, the tissue was highly cellular with a high mitotic index and numerous areas of lymph vascular space involvement. The preliminary histopathologic diagnosis of leiomyosarcoma was made, and further surgery included a pelvic and para-aortic lymph node sampling, omentectomy, and peritoneal cytology.

∑ What are the most common presenting symptoms in patients with leiomyosarcomas (LMS) of the uterus?
∑ Of those patients with a presumed “fibroid uterus,” what percentage will be found to have an LMS at the time of hysterectomy?
∑ What is the appropriate surgical therapy for a patient with a known LMS?

LEIOMYOSARCOMAS

LMS are pure homologous sarcomas, accounting for 33% of all uterine sarcomas. LMS typically present in postmenopausal women in the sixth decade of life. Symptoms in these patients include a pelvic mass, vaginal bleeding, pelvic pain, or vaginal discharge.1 These sarcomas, like MMMTs, are more common in African-American than in Caucasian women (Figure 1).8 Of patients who are diagnosed with LMS, 20% are nulliparous. The diagnosis is made preoperatively in only 15% of cases, usually by a dilatation and curettage (D&C) specimen demonstrating sarcomatous elements.1

One of the distinctive features of an LMS on physical examination is that it may present as a single, solid tumor.1 This physical finding is supported by sonography that usually finds a single fundal mass with a necrotic heterogeneous core.29 This presentation is different from the typical myomatous uterus that has multiple, irregular

<p>| Table 3. Incidence of Lymph Node Metastasis in Uterine Sarcomas |
|-------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Type of Sarcoma</th>
<th>Positive Nodes, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT-HO</td>
<td>24/153 (16%)</td>
</tr>
<tr>
<td>MMT-HE</td>
<td>26/129 (20%)</td>
</tr>
<tr>
<td>LMS</td>
<td>2/53 (4%)</td>
</tr>
</tbody>
</table>

LMS = leiomyosarcoma; MMT-HO = mixed mesodermal, homologous; MMT-HE = mixed mesodermal, heterologous.


| Table 4. Recurrence Sites for Uterine Sarcomas |
|-------------------|-------------------|-------------------|
| Recurrence Sites   | MMT-HO (n = 165)  | MMT-HE (n = 134)  | LMS (n = 57) |
|-------------------|-------------------|-------------------|
| Pelvic only        | 9%                | 12%               | 7%           |
| Distant (especially lung and abdomen) | 33%    | 46%               | 56%          |
| None              | 58%               | 42%               | 37%          |

LMS = leiomyosarcoma; MMT-HE = mixed mesodermal, heterologous; MMT-HO = mixed mesodermal, homologous.

Considerable controversy exists among pathologists regarding the various diagnostic features of an LMS and their individual importance in predicting malignant behavior. Most pathologists agree on the good prognostic features of an LMS. Most pathologists agree that high mitotic index, coagulative necrosis, diffuse cellular atypia, and size greater than 5 cm are all important features, although different pathologists give each variable a different prognostic weight.

The classic approach to predicting malignant behavior has been to count mitotic figures (MF) and calculate a mitotic index (MF/10 high-power fields [HPF]). A tumor with an increased mitotic index (more than 10 MF per 10 HPF) was considered an LMS, regardless of other features. One immediate problem with this method is the large amount of interobserver and intraobserver variation among pathologists when counting MF. A second problem has recently come to light. There is a population of tumors with increased mitotic indices (as high as 20 MF/HPF) that behave in a benign fashion. These problems indicate that caution should be exercised when mitotic indices are used to predict malignant behavior. Mitotic indices are important, but as part of a group of variables, rather than as the single determining factor.

Table 5: Survival by Histologic and Clinical Stage for Patients with Uterine Sarcoma

<table>
<thead>
<tr>
<th>Histologic Stage</th>
<th>Total Cases (N)</th>
<th>Stage I n, %</th>
<th>Stage II n, %</th>
<th>Stage III n, %</th>
<th>Stage IV n, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGESS</td>
<td>65</td>
<td>55.89%</td>
<td>4.75%</td>
<td>6.67%</td>
<td>0.0%</td>
</tr>
<tr>
<td>HGESS</td>
<td>100</td>
<td>90.78%</td>
<td>1.0%</td>
<td>7.14%</td>
<td>2.0%</td>
</tr>
<tr>
<td>LMS</td>
<td>108</td>
<td>91.48%</td>
<td>3.67%</td>
<td>5.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>CS</td>
<td>399</td>
<td>245.36%</td>
<td>55.22%</td>
<td>69.10%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>

*Percentages refer to survival rates. Not all patients were followed for 5 years.

CS = carcinosarcoma; HGESS = high-grade endometrial stromal sarcoma; LGESS = low-grade endometrial stromal sarcoma; LMS = leiomyosarcoma.


nodular masses, creating an irregular uterine contour on sonogram and physical examination. Despite this presentation, the usual preoperative diagnosis is “fibroids” in patients found to have an LMS on final pathologic review. The incidence of finding an LMS when operating for symptomatic fibroids is less than 1%. If the diagnosis is made preoperatively, a chest radiograph to evaluate for pulmonary metastasis and a CT scan of the abdomen and pelvis are useful additions to the preoperative evaluation (Figure 3). The primary therapy for an LMS is an exploratory laparotomy, total abdominal hysterectomy, omentectomy, pelvic and para-aortic lymph node dissection, and peritoneal cytology. Finding gross extrauterine disease at the time of initial laparotomy is unusual (Table 3).

A GOG study found positive lymph nodes in only 3.5% of the cases; the adnexa was involved in 3.5% of cases, and the peritoneal cytologic results were positive 5% of the time. Sending tissue to evaluate estrogen and progesterone receptor status may help with subsequent therapeutic decisions.

On gross pathologic examination, an LMS appears to be soft and fleshy, with areas of hemorrhage and necrosis (Table 6). These tumors are thought to arise from the smooth muscle of the myometrium or the smooth muscle of the uterine blood vessels. Considerable controversy exists among pathologists regarding the various diagnostic features of an LMS and their individual importance in predicting malignant behavior. Most pathologists agree on the good prognostic features of an LMS. These features include a low mitotic index, pushing margins, hyalinization, absence of necrosis, and size less than 5 cm. It is more difficult to arrive at a consensus about the poor prognostic features of an LMS. Most pathologists agree that high mitotic index, coagulative necrosis, diffuse cellular atypia, and size greater than 5 cm are all important features, although different pathologists give each variable a different prognostic weight.

Table 7 shows the malignant potential of an LMS evaluated using two grading systems. The first system assesses the mitotic index and the degree of cellular atypia. If there are 1 to 4 MF/10 HPF, the tumor is classified as a fibroid (leiomyoma) regardless of the degree of cellular atypia. From 5 to 9 MF/10 HPF and grade I atypia, the tumor is considered to have undetermined malignant significance. From 5 to 9 MF/10 HPF and grade II to III atypia, the diagnosis of LMS is assigned. Tumors with more than 10 MF/10 HPF with any degree of atypia are considered an LMS.

The second grading system evaluates the mitotic index, the presence or absence of coagulative necrosis, and, if cytologic atypia is present, whether it is focal or diffuse (Table 7). Using this system, if there is no atypia and no necrosis then the tumor is a leiomyoma regardless of the cell count. In a tumor with no atypia and no necrosis, if there are more than 5 MF/10 HPF then the tumor is referred to as a leiomyoma with an increased mitotic index.

Tumors with diffuse atypia and no coagulative necrosis are subdivided into two groups. The first group have fewer than 10 MF/10 HPF and are considered atypical leiomyomas (low risk). The second group have more than 10 MF/10 HPF and are considered LMS.
with diffuse atypia and coagulative necrosis is automatically classified as an LMS. Tumors with no atypia but demonstrating coagulative necrosis are classified based on the mitotic index. Tumors with fewer than 10 MF/10 HPF are classified as atypical leiomyomas. If there are more than 10 MF/10 HPF, then the tumor is an LMS.

Tumors with focal atypia but not showing coagulative necrosis are classified as atypical leiomyomas, regardless of the mitotic index (Table 7). 28,29

### Tumor Recurrence Rate

Postoperative therapeutic options for LMS include chemotherapy, radiation, and hormone therapy (if the tumor contains estrogen and progesterone receptors).

Patients with extrauterine disease (stage III and IV) at the time of laparotomy should be considered for chemotherapy. Patients with stage I/II disease have a significant recurrence rate, up to 50% to 70%, and those patients without evidence of extraterine spread should be considered for adjuvant chemotherapy. 19 Chemotherapeutic agents that have been evaluated in patients with LMS include doxorubicin (Adriamycin), which yields a 25% response rate; ifosfamide, which yields a 14% response rate; and cisplatin, which yields a 0% response rate. 17,30,31 A GOG study of doxorubicin’s effect on outcome found no significant increase in survival. 30 No conclusive data have indicated that combination chemotherapy is superior to single agent therapy. Radiation to the pelvis has

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**Figure 3.** Work-up, diagnosis, and treatment for patients with leiomyosarcomas and stromal sarcomas. Numbered items are separate steps in the complete treatment of the patient; excluding any of the steps results in incomplete treatment. CA-125 = cancer antigen 125; D&C = dilatation and curettage; EMB = endometrial biopsy; MI = mitotic index (mitotic figures/10 high-power fields); RT = radiation therapy; TAHBSO = total abdominal hysterectomy, bilateral salpingo-oophorectomy. *Assessing whether estrogen and progesterone receptors are present. Adapted with permission from Morrow CP: Uterine sarcomas and related tumors. In Synopsis of Gynecologic Oncology, 4th ed. Morrow CP, Curtin JP, Townsend DE, eds. New York: Churchill Livingstone, 1993:193.

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### Preoperative Work-Up

1. EMB or D&C
2. Chest radiograph
3. Serum CA-125 level
4. Histology review
similarly poor results in preventing local pelvic recurrences and obviously has no effect outside the radiation field.

When recurrences occur in patients with stage I/II disease, fewer than 25% will be pelvic (Table 4). Once local recurrence is detected, a prompt search for occult distant metastasis should be performed. Isolated lung recurrences are unusual and require a careful metastatic workup.

### IV. CASE PATIENT 3

**INITIAL PRESENTATION**

Patient 3 is a 45-year-old Caucasian woman, G2P2002, LMP 3 weeks ago, who presents for evaluation of pelvic pain and increasing menorrhagia during the past 7 months. She reports using nine sanitary pads per day for 14 days of each cycle for the past 7 months. Patient 3’s most recent gynecologic examination was 1 year ago, and her Pap smear and mammogram results were normal at that time. She is sexually active and had a tubal ligation 15 years ago, after her second child. She denies any history of oral contraceptive pills.

**PERTINENT PHYSICAL EXAMINATION**

No masses are palpated in patient 3’s abdomen. Her breasts are symmetrical; breast examination reveals no dominant masses, skin changes, nipple discharge, nipple retraction, or palpable lymph nodes. Pelvic examination reveals normal external female genitalia, with no vulvar masses or ulcers.

Speculum examination shows a vagina that is moist, pink, and well-rugated. The cervix is normal in appearance, with no ulcers or masses. No bleeding or discharge is noted from the cervix. Rectal examination shows good tone with no masses, and a stool sample is negative for rectal blood (guaiac negative). A bimanual examination reveals a mobile uterus that is 12 weeks in size. It is mobile, firm, and symmetrically enlarged. No adnexal masses are palpated.

**DIAGNOSTIC TESTS AND SURGICAL EXPLORATION**

A sonogram was obtained to determine whether endometrial polyps were present. A Pap smear and endometrial biopsy were done. The Pap smear results were normal, and the sonogram showed diffuse enlargement of the uterus. The endometrial lining was thickened to 2 cm, but no clear evidence of endometrial polyps was noted. The endometrial biopsy was negative for malignancy, although it was described as containing suspicious pleomorphic stromal cells.

Patient 3 was taken to the operating room where a 12-week–sized uterus was noted. On gross inspection, a yellow-gray soft tumor mass protruded from the cut surface of the uterus. Pale yellow, “worm-like” extensions of the tumor were noted to be growing into the vessels of the broad ligament as it was divided. The frozen section indicated a low-grade endometrial stromal sarcoma (ESS). In view of the extrauterine extension of the tumor, the surgical procedure was expanded to a radical hysterectomy with a pelvic and para-aortic lymph node dissection, omentectomy, and peritoneal cytology.

**ENDOMETRIAL Stromal SARCOMA**

The presentation of an ESS does not typically suggest the diagnosis. Patients may be premenopausal or postmenopausal, usually in their fifth decade of life or later. A patient may present with vaginal bleeding, pelvic pain, or an abdominal/pelvic mass. The diagnosis is usually not made preoperatively, although an endometrial biopsy may show abnormal stromal tissue. Sonographic studies are similarly nonspecific, usually demonstrating a diffuse-ly enlarged uterus with no other definitive findings. If the diagnosis is suspected preoperatively, the work-up should include a chest radiograph and CA-125 level (to assess the possibility of extrauterine disease); strong consideration should be given to a pelvic and abdominal CT scan, to evaluate potential metastatic spread (Figure 3).

∑ In a patient with a known low-grade ESS, exploratory laparotomy reveals extension of the lesion beyond the uterus but still confined to the pelvis. What is the correct surgical intervention?

**Diagnosis**

Primary treatment of both high-grade and low-grade ESS includes a TAHBSO, pelvic and para-aortic lymph node dissection, omentectomy, and peritoneal cytology.
If extrauterine spread confined to the pelvis is noted intraoperatively, the procedure should be extended to a radical hysterectomy to remove all parametrial tissue.1 The fundamental diagnostic criterion for an ESS requires the cells forming the tumor to resemble those of the endometrial stroma during the proliferative phase of the menses.22 Pathologists divide these sarcomas into low-grade and high-grade types. Traditionally, the differentiation was based on mitotic index alone, with more than 10 MF/10 HPF indicating a high-grade tumor. Any tumor with fewer than 10 MF/10 HPF was described as a low-grade sarcoma.22 Recently, there has been concern that the division of high-grade versus low-grade tumors based solely on MF may no longer be valid. Evans and colleagues have extended the definition to require the presence of cytologic atypia for a tumor to qualify as a high-grade sarcoma.32 The source of the concern is that many tumors currently designated as high-grade sarcomas do not merit this classification. Evans and colleagues have suggested that these tumors would be best classified as undifferentiated uterine sarcomas.22 They characteristically respond poorly to treatment and are very aggressive in their growth and clinical behavior.22 If the undifferentiated tumors are excluded, there is no difference in prognosis between the remaining high-grade and low-grade tumors based on their mitotic index alone.23 In fact, a tumor diagnosed as a well-differentiated, high-grade ESS based on its mitotic index may actually behave like a leiomyoma with increased mitotic index (ie, behave in a benign fashion) if there is no cellular atypia (Table 7).33

The surgical presentation of ESS has several distinctive features. Two thirds of patients have disease confined to the uterus at the time of initial surgery.11 Extension beyond the uterus does occur with both high-grade and low-grade tumors. Lymph vascular space invasion and microscopic myometrial infiltration are as commonly noted with low-grade as with high-grade ESS.14 Low-grade ESS may be noted at the time of surgery to have yellow-gray, worm-like extensions into the venous structures of the parametria. Intra-abdominal and pulmonary lesions may be noted at the time of initial diagnosis.1

∑ What additional testing should be performed by the pathologist?

**Hormone Receptor Testing and Recurrence Rate**

Once the final pathology has been determined, a sample of tumor should be assayed to determine the estrogen and progesterone receptor status. ESS are frequently positive for these hormone receptors.1 The presence or absence of these receptors may help determine the patient’s postoperative therapy. No one adjuvant treatment is clearly superior to any other in the treatment of ESS. The most commonly used chemotherapeutic agent is doxorubicin. Low-grade tumors that have deep invasion (lymph-vascular invasion, are greater than

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Table 7. Grading System for Assessing Malignancy of Uterine Smooth Muscle Tumors*

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 to 5</th>
<th>5 to 10</th>
<th>10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No necrosis</td>
<td>Leiomyoma</td>
<td>Leiomyoma with increased mitotic count</td>
<td>Leiomyoma with increased mitotic count</td>
</tr>
<tr>
<td>No atypia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>Leiomyosarcoma</td>
<td>Leiomyosarcoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Diffuse atypia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No necrosis</td>
<td>Atypical leiomyoma</td>
<td>Atypical leiomyoma</td>
<td>Atypical leiomyoma</td>
</tr>
<tr>
<td>Diffuse atypia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>Atypical leiomyoma</td>
<td>Atypical leiomyoma</td>
<td>Leiomysarcoma</td>
</tr>
<tr>
<td>No atypia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No necrosis</td>
<td>Atypical leiomyoma</td>
<td>Atypical leiomyoma</td>
<td>Atypical leiomyoma</td>
</tr>
<tr>
<td>Focal atypia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HPF = high-power fields; MF = mitotic figures.

*Assessment depends on the mitotic count, the degree and extent of cytologic atypia, and the presence or absence of coagulative necrosis of tumor cells.

Adapted with permission from Fox H: Contemporary OB/GYN Sept 1996;41:157.
5 cm in size at diagnosis, and have estrogen and progesterone receptors are most commonly treated postoperatively using progestin with or without pelvic radiation therapy. High-grade tumors that have a well-differentiated cytologic appearance are treated using whole pelvic radiation and a progestin if they have estrogen and progesterone receptors. Poorly differentiated high-grade tumors are treated using chemotherapy with or without radiotherapy.1

ESS have a significant recurrence rate, as high as 50% in stage I disease.4 Most recurrences are local in the pelvis or vagina; however, extrapelvic metastases in the abdomen, brain, and lungs are not unusual. Late recurrences, from 5 to 10 years after initial diagnosis, are common.1

V. SUMMARY POINTS

GENERAL

∑ Uterine sarcomas usually have a nonspecific diagnostic work-up; they require a high index of suspicion to make a preoperative diagnosis.

∑ The most common presenting manifestations are vaginal bleeding, pelvic pain, pelvic mass, and vaginal discharge.

∑ Leiomyosarcomas and malignant, mixed mesodermal tumors (MMMTs) are more common in African-American women.

∑ Primary therapy is surgery in all classes of uterine sarcoma.

∑ Rates of tumor recurrence (both local and distant) are high for all histologic types, even those that are considered “low grade.”

MALIGNANT, MIXED MESODERMAL TUMORS

∑ MMMTs are made of any combination of malignant epithelial and malignant mesenchymal tissue.

∑ MMMTs are the most common uterine sarcoma, comprising up to 50% of the total.

∑ Patients are usually in their seventh decade of life.

∑ Risk demographics are similar to those for endometrial cancer (ie, obesity, hypertension, and diabetes).

∑ Of patients with MMMTs, 10% have a history of previous pelvic radiation.

∑ Of patients with MMMTs, 30% to 50% present with tissue aborting through the cervical os.

∑ Of patients with MMMTs, 50% are clinically understaged.

∑ Of patients with MMMTs, 33% have lymph node metastasis, and the risk is based on cervical involvement and depth of myometrial invasion.

∑ Active chemotherapeutic agents are doxorubicin, ifosfamide, and cisplatin.

∑ Pelvic radiotherapy decreases local recurrences but does not affect overall survival.

LEIOMYOSARCOMAS

∑ These tumors account for 30% of all uterine sarcomas.

∑ The average age at diagnosis is in the sixth decade of life.

∑ The most common presentation is vaginal bleeding, pelvic pain, and a single uterine mass.

∑ An endometrial biopsy or dilatation and curettage is diagnostic in 15% of cases.

∑ Extraterine disease at initial surgery is rare.

∑ Good prognostic features include low mitotic index, pushing margins, hyalinization, absence of necrosis, and tumor size less than 5 cm.

∑ Poor prognostic features include high mitotic index, coagulative necrosis, diffuse cellular atypia, and tumor size greater than 5 cm.

∑ Active chemotherapeutic agents include doxorubicin and ifosfamide.

∑ Pelvic radiation does not affect the rate of recurrence or survival.

∑ Recurrences are frequently outside of the pelvis.

ENDOMETRIAL STROMAL SARCOMAS

∑ These tumors are divided into high-grade and low-grade endometrial stromal sarcomas.

∑ Patients may be premenopausal or postmenopausal.

• Patients are usually in their fifth decade of life or older.

∑ Patients typically present with vaginal bleeding and pain.

∑ The diagnosis is usually not made preoperatively, although an endometrial biopsy or dilatation and curettage may show abnormal stromal cells.

∑ Two thirds of patients will have disease confined to the uterus at the time of surgery, although both high-grade and low-grade tumors are likely to have lymph vascular space invasion at the time of diagnosis.

∑ Sarcomas are frequently positive for estrogen and progesterone receptors, prompting the use of progestins as adjunctive therapy.

∑ Chemotherapy has not proven to be very useful in this disease. The most commonly used agent is doxorubicin.

∑ Most recurrences are local, in the pelvis and vagina.

REFERENCES

Chapter 1—Case Studies in Uterine Sarcomas

Chapter 2—Case Studies in Secondary Amenorrhea: Diagnostic and Therapeutic Approach

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I. INTRODUCTION

Secondary amenorrhea is defined as lack of menses for more than 3 months. It may be caused by various disorders, and therapy is generally unproductive unless it is based on a specific diagnosis. Depending on this diagnosis, treatment may be simple or even unnecessary, but it is usually complicated and prolonged. It is useful to divide the causes of secondary amenorrhea into three major categories: common, less common, and rare (Table 8). This review outlines a practical approach to diagnosis and therapy that minimizes the time and tests required. Five case patients are presented along with recommended diagnoses and treatment, using detailed questions and answers, to illustrate the various manifestations of secondary amenorrhea.

II. COMMON CAUSES OF SECONDARY AMENORRHEA

PREGNANCY

This is the most frequent cause of secondary amenorrhea and should be ruled out before a more involved work-up is begun. A careful history, a complete physical examination, and perhaps a pregnancy test are sufficient to diagnose pregnancy. Once pregnancy takes place, the placenta starts to secrete human chorionic gonadotropin (hCG), which is a luteotropic hormone supporting the life of the corpus luteum. The latter continues to secrete estrogen and progesterone at approximately 10 weeks of gestation, a function that is taken over by the placenta.

HYPOTHALAMIC AMENORRHEA SYNDROME

Etiology

This syndrome is the second most frequent cause of secondary amenorrhea and, excluding pregnancy, accounts for some 50% to 60% of patients with secondary amenorrhea. Examples of this disorder include women who exercise vigorously (eg, ballet dancers), women experiencing stress from various causes, and women with pseudocyesis and anorexia nervosa. The common denominator in all these patients is inadequate hypothalamic function because of physical and emotional stress. In several surveys of ballet dancers, only one third were found to have regular menstrual cycles. In addition, when dancers increased their workload, more of them developed amenorrhea. In a survey of national collegiate championship athletes comparing runners and swimmers with cyclists, it was found that swimmers and cyclists had a steady 12% incidence of amenorrhea, but the runners had a 26% incidence. Only the runners showed an increase in the incidence of amenorrhea with increased training mileage. All the women who ran more than 55 miles per week and weighed less than 100% of their ideal body weight were amenorrheic.

Stress plays a major role in suppressing the hypothalamus, leading to amenorrhea. A study showed that 100% of women and men indicted for severe crimes and later executed developed gonadal atrophy. Without exception, the women became amenorrheic immediately after sentencing. Of women who entered military academies, 75% became amenorrheic 1 month after admission. This percentage decreased to 8% at the end of the first year.
Anorexia nervosa is another example of hypothalamic amenorrhea. Some studies have shown that 1 in every 100 female teenagers and young adults in North America has this problem; the incidence is 10% in males. The problems associated with anorexia focus on the hypothalamus. All processes controlled by the hypothalamus are affected (e.g., appetite, thirst and water conservation, temperature, and sleep). The endocrine changes are mediated through hypothalamic control mechanisms. Factors that interfere with the proper function of the hypothalamus affect the reproductive system. For example, as weight is lost, the pulsatile secretion of gonadotropin-releasing hormone (GnRH) is progressively decreased. As weight is regained, GnRH secretion gradually returns to normal.

**Diagnosis**

The diagnosis of hypothalamic amenorrhea is almost always made by exclusion. The patient’s history may suggest the presence of hypothalamic amenorrhea if a correlation can be found between the onset of amenorrhea and an acutely stressful event. Many patients admit to chronic stress—social, parental, or marital. Examination often reveals little more than a slender woman who is otherwise healthy. Frequently, although not invariably, pelvic examination shows relatively dry vaginal mucosa, probably because of a mild estrogen deficiency.

Clinically, the spectrum of hypothalamic amenorrhea ranges from mild to severe hypothalamic suppression. There are no specific guidelines regarding laboratory tests for these patients. When the hypothalamus is mildly suppressed, serum gonadotropin levels are usually in the low-to-normal range and the progesterone withdrawal bleeding test is positive. Most of these patients bleed within 7 days after receiving an intramuscular injection of 100 mg of progesterone in oil. A patient with severe hypothalamic suppression has very low gonadotropin levels and, therefore, her progesterone withdrawal test is negative.

**Treatment**

Sympathetic reassurance is the cornerstone of therapy for patients with hypothalamic amenorrhea because many of them will menstruate spontaneously. Patients who have a positive progesterone withdrawal test should benefit from an oral dose of 10 mg of medroxyprogesterone acetate daily for 7 days every other month. Consequent withdrawal bleeding usually provides reassurance and eliminates the remote possibility of endometrial hyperplasia development.

Patients who do not bleed after progesterone withdrawal should be given 0.3 mg/day of conjugated estrogen. This small dose of estrogen has a dual function: it serves as replacement hormonal therapy and stimulates hypothalamic-pituitary function. Medroxyprogesterone acetate treatment also is recommended every other month (10 mg daily for 7 days). Oral contraceptives to induce menses are contraindicated in patients with hypothalamic amenorrhea because these agents further inhibit an already suppressed hypothalamus. Agents that induce ovulation are indicated only if the patient wants to become pregnant. Inducing ovulation has not been shown to stimulate the return of normal menstrual function.

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**Table 8. Causes of Secondary Amenorrhea**

<table>
<thead>
<tr>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Hypothalamic amenorrhea</td>
</tr>
<tr>
<td>Androgenic disorders</td>
</tr>
<tr>
<td>Ovarian androgenic hyperfunction (polycystic ovary syndrome)</td>
</tr>
<tr>
<td>Adrenal androgenic hyperfunction (congenital adrenal hyperplasia)</td>
</tr>
<tr>
<td>Ovarian and adrenal androgenic hyperfunction</td>
</tr>
<tr>
<td>Galactorrhea-amenorrhea syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature ovarian failure</td>
</tr>
<tr>
<td>Pregnancy complications</td>
</tr>
<tr>
<td>Asherman’s syndrome</td>
</tr>
<tr>
<td>Sheehan’s syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rare causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders (outside the HPO axis)</td>
</tr>
<tr>
<td>Uncontrolled diabetes</td>
</tr>
<tr>
<td>Hyperthyroidism or hypothyroidism</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Chronic systemic and metabolic diseases</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Iatrogenic causes</td>
</tr>
<tr>
<td>Irradiation</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
</tbody>
</table>

HPO = hypothalamic-pituitary-ovarian.
Case Patient 4 Presentation

Patient 4 is a 29-year-old woman, G3P3, who has not had a menstrual period for 3 years. She claims that she is otherwise healthy. Her periods have been regular since menarche until she became pregnant with her last child, who was delivered 3 years ago. She experienced no menstrual flow after that last childbirth. Her normal vaginal delivery was uneventful, and she left the hospital in a good condition 48 hours after birth. Her son, who is now almost 3 years old, is developing normally. She mentions that her husband was killed in a car accident when her son was only 3 months old. She is a registered nurse and works 12 hours a day, sometimes 7 days a week, to support her three children.

Physical and gynecologic examinations are within normal limits. No hirsutism or galactorrhea is present. She is 5 ft 6 in tall and weighs 140 lb.

- What is the diagnosis of patient 4?
- How should patient 4 be treated?

Diagnosis and Treatment of Patient 4

Both Sheehan’s syndrome and Asherman’s syndrome can be ruled out by history because patient 4 did not have postpartum bleeding, postpartum dilatation, or infection (see pages 20 to 22 for descriptions of both syndromes). Her husband died 3 months after the birth of her last child, about the time her menstrual flow should have resumed. The loss of her husband must have caused severe stress, which continued because of her stressful hard work. This stress might have caused hypothalamic suppression, resulting in secondary amenorrhea. Physical examination ruled out pregnancy; excess androgen levels, or galactorrhea as the cause of patient 4’s secondary amenorrhea; therefore, by exclusion, the most probable diagnosis is hypothalamic amenorrhea.

To confirm this diagnosis, blood levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin need to be measured (Table 9). Patient 4 is given an intramuscular dose of 100 mg of progesterone in oil and told to return in 2 weeks. At her visit to review the laboratory results, she states that she had no withdrawal uterine bleeding. She did not bleed because her endometrium lacked the necessary estrogen stimulation. Both FSH and LH levels were low, and the prolactin level was slightly increased. These hormone levels rule out premature ovarian failure (POF) and confirm the diagnosis of hypothalamic amenorrhea (see pages 19 to 20 for a description of POF).

Therapy mainly consists of explaining to patient 4 what happened to her endocrine system after the death of her husband. She should be reassured that her menstrual periods will resume once her stress is alleviated. A low dose of conjugated estrogen, 0.3 mg daily, may be sufficient to estrogenize her estrogen-dependent organs. In addition, this low dose of estrogen may stimulate the hypothalamic-pituitary system to resume function sooner rather than later. Oral medroxyprogesterone acetate (10 mg daily for 7 days every other month) should be given to prevent the occurrence of endometrial hyperplasia. Both drugs should be continued until she resumes her normal menstrual cycles.

ANDROGENIC DISORDERS

These disorders are the third most frequent cause of secondary amenorrhea. In these patients, amenorrhea is almost always preceded by signs of androgenicity—excessive hair growth, acne, and menstrual dysfunction. The excess androgen secretion is caused by ovarian hyperfunction, adrenal hyperfunction, or both. Diagnostic evaluation of these patients requires determining levels of the following hormones: FSH, LH, prolactin, testosterone, and dehydroepiandrosterone sulfate (DHEAS).

Ovarian Androgenic Hyperfunction (Polycystic Ovary Syndrome [PCO])

The typical patient with this disorder has slightly increased testosterone levels but relatively abnormal pituitary gonadotropin levels (slightly depressed levels of FSH and increased levels of LH). Most patients with androgen-induced amenorrhea are in this category. The LH:FSH ratio is 2:1 or higher in approximately 50% of patients with PCO, depending on disease severity. Because approximately 50% of these patients do not have this increased ratio, this assay cannot be routinely
used for diagnostic purposes. Testosterone is produced primarily by the ovary and is usually slightly increased in patients with PCO. Therefore, patients can manifest signs of mild virilization (eg, acne, hirsutism). DHEAS is primarily produced by the adrenals, and levels are within normal limits in patients with PCO.

Treatment for amenorrhea with virilization consists of suppressing the secretion of ovarian androgens by cyclic use of a nonandrogenic combination oral contraceptive, such as norethynodrel and mestranol. These drugs increase testosterone and dihydrotestosterone binding and reduce the free amount available to act on the hair follicle. If the patient has amenorrhea alone and no hirsutism or acne, 10 mg of oral medroxyprogesterone acetate for the first 5 days of each month regulates the menstrual cycle and protects the endometrium from continuous estrogen stimulation. Patients who wish to conceive are excellent candidates for clomiphene citrate therapy either alone or combined with hCG.

Stromal Hyperthecosis

This disorder is characterized microscopically by the presence of nests of luteinized theca cells in the ovary; however, no follicular development is observed. Grossly, the ovaries are enlarged with thick tunica albuginea and no follicular cysts are seen on the surface. The testosterone level in these patients is usually high (approximately 200 ng/dL). Because of this high level, patients manifest signs of virilization. Suppression of testosterone secretion, using 2 months of oral contraceptive pills, rules out an ovarian tumor. The DHEAS level in these patients is usually within normal limits because it is produced primarily by the adrenal glands.

Adrenal Androgenic Hyperfunction (Congenital Adrenal Hyperplasia [CAH])

In these patients, excess androgen secretion is caused by a late onset of adrenal hyperplasia. Most patients have hirsutism, acne, or both in addition to secondary amenorrhea. DHEAS levels are increased, and the testosterone level is on the high end of normal. The most common type of CAH is caused by 21-hydroxylase deficiency. In most of these patients, the 17-OH progesterone level obtained in the morning is increased and diagnostic for 21-hydroxylase deficiency.

A 17-OH progesterone level of 800 ng/dL or more is diagnostic for CAH, whereas levels between 200 and 800 ng/dL are suggestive. In the latter case, an adrenocorticotropic hormone (ACTH) stimulation test is required. The patient is given dexamethasone (1 mg) at bedtime in order to suppress adrenal activity during the night. A 17-OH progesterone level is measured in the morning. Then 250 µg of corticotropin is given intravenously; and the 17-OH progesterone level is measured again in 1 hour. The second 17-OH progesterone level should be less than 400 ng/dL in the normal patient. Patients have CAH if their level is more than 800 ng/dL. Patients whose levels are approximately 1500 ng/dL have simple virilization, whereas those with levels around 3000 ng/mL have a salt-losing effect in addition to the virilization. CAH is rarely caused by 11-hydroxylase deficiency or 3β-hydroxysteroid dehydrogenase deficiency.

Amenorrhea can be resolved and virilization gradually ameliorated by the use of oral dexamethasone, 0.5 mg at bedtime and 0.25 mg in the morning, daily for 1 year. Patients in this group who want to become pregnant can benefit from dexamethasone alone or a combination of dexamethasone and clomiphene citrate.

Ovarian and Adrenal Androgenic Hyperfunction

The ovaries and the adrenal glands are responsible for excess androgen secretion in these patients. Treatment consists of dexamethasone for 1 year (0.5 mg at bedtime and 0.25 mg in the morning, daily) and cyclic use of a nonandrogenic oral contraceptive (eg, norethynodrel and mestranol).

Case Patient 5 Presentation

Patient 5 is a 25-year-old woman, nulligravida, single, and not sexually active, who presents because of lack of menstrual periods for 11 months. She reports that her menarche occurred when she was 13 years old, and her menstrual cycles have been irregular since then (4 weeks to 12 weeks apart). Menstrual flow is described as prolonged and heavy. She started gaining weight at 21 years of age and at 23 years started to notice hair growth on her upper lip and chin. This patient is otherwise healthy and does not take any medication. She has no history of stress at home or at work. Her mother was overweight all her life and always had irregular periods but had no difficulty in getting pregnant; she had three children, and patient 5 is the youngest.

Physical examination reveals a rather healthy woman who is 5 ft 6 in tall and weighs 192 lb. The systemic examination is within normal limits except for mild scanty hair on her upper lip and chin. No galactorrhea is present. Her pelvic examination is normal. Patient 5 is given an intramuscular injection of 200 mg of progesterone in oil and is scheduled for another office visit in 2 weeks.
What is the cause of the secondary amenorrhea in patient 5?

How can an androgen-secreting tumor be ruled out as the cause of patient 5’s amenorrhea?

Can a tumor be the cause of hirsutism in patient 5?

How should patient 5 be treated?

Laboratory Testing for Patient 5

Medical history alone ruled out all the common causes of secondary amenorrhea in patient 5, including pregnancy, hypothalamic factors, and galactorrhea. Physical examination revealed that the patient is overweight and hirsute. Therefore, patient 5 most probably has PCO. To confirm the diagnosis and to rule out adrenal involvement, blood levels of FSH, LH, prolactin, testosterone, and DHEAS should be measured. Usually, but not always, the LH:FSH ratio in PCO is 2:1 or higher. Low levels of these two hormones rule out POF.

The prolactin level is usually on the high end of normal or slightly increased in patients with PCO. The testosterone level is on the high end of normal or slightly increased, but the DHEAS level is normal. Because testosterone is secreted mainly by the ovaries and DHEAS by the adrenal glands, these laboratory findings rule out adrenal involvement and confirm that the excess androgens are from the ovaries.

Diagnosis and Treatment of Patient 5

At her 2-week appointment, patient 5 states that she had withdrawal bleeding 1 week after the progesterone injection. The flow was moderate and lasted 5 days. This withdrawal bleeding confirms the diagnosis of PCO because all the other causes of secondary amenorrhea mentioned in Table 8 do not cause enough estrogen secretion to induce sufficient endometrium proliferation that will respond to progesterone.

Patient 5’s history indicated that hirsutism started 2 years ago, and her physical examination revealed mild hirsutism. These findings rule out a tumor because an androgen-secreting tumor causes rapid virilization, generally within months. Signs of rapid virilization include severe hirsutism, acne, temporal balding, decreased breast size, clitoromegaly, and deepening of the voice (Figure 4). However, PCO can cause mild hirsutism.

The testosterone level in patient 5 is on the high end of normal, and the DHEAS level is within normal limits. In patients with an androgen-secreting tumor, the testosterone blood level is greater than 200 ng/dL and the DHEAS level is greater than 700 ng/dL. Whenever an androgen-secreting tumor is suspected, a magnetic resonance imaging scan (MRI) of the abdomen is imperative. This MRI can localize the site of the tumor, ovarian or adrenal, and should distinguish a carcinoma from a simple adenoma. These testosterone and DHEAS levels are not suppressed when tested with oral contraceptive pills, dexamethasone, or both. Patient 5 should be treated with nonandrogenic combination oral contraceptive pills (such as norethynodrel and mestranol).

GALACTORRHEA-AMENORRHEA SYNDROME

In a nonpregnant woman, galactorrhea with amenorrhea is a pathologic condition often caused by a serious
organic disease. However, emission of a few drops of a clear, straw-colored fluid under periareolar pressure should not be considered galactorrhea. The fluid must be milk-colored for this diagnosis (Figure 5). The quantity of milky secretion or the involvement of one or both breasts is immaterial, and any galactorrhea requires evaluation. Although galactorrhea is not always associated with amenorrhea, when it is, the disorder is more serious. On average, hyperprolactinemia is present in 15% of women who are amenorrheic, 28% with galactorrhea who are eumenorrheic, and at least 60% with galactorrhea who are amenorrheic. The higher the level of basal prolactin, the greater the likelihood that the patient has a pituitary neoplasm.

Laboratory Tests

The prolactin level should be measured in the morning before breakfast and without breast manipulation. The prolactin level varies widely during the day and increases during sleep; the level can be increased by such diverse factors as medications, stress, and food. The galactorrhea-amenorrhea syndrome is believed to be mediated by hypothalamic hormones. If the normal secretion of GnRH, prolactin-inhibiting factor (PIF), or both is changed, then amenorrhea, galactorrhea, or a combination occurs because of unrestrained prolactin secretion by the pituitary, with minimal elaboration of FSH and LH.

The most common factors associated with galactorrhea-amenorrhea syndrome are: 1) frequent breast manipulation, especially suckling; 2) medications such as phenothiazines, reserpine, opiates, amphetamines, or oral contraceptives; 3) primary hypothyroidism that can be explained by the increased activity of thyrotropin-releasing hormone (TRH), which stimulates prolactin secretion; and 4) pituitary tumors that may be microadenomas (< 10 mm) or macroadenomas (≥ 10 mm).

Of all the possible factors involved in the galactorrhea-amenorrhea syndrome, it is essential to determine whether a pituitary tumor is present. A careful history and thorough physical examination will rule out the first three factors. Because any degree of hyperprolactinemia suggests the presence of a pituitary tumor, the author recommends screening all women with amenorrhea-galactorrhea syndrome for the magnitude of the plasma prolactin elevation. Imaging studies like MRI or CT scanning of the pituitary are of value in any woman with persistently increased prolactin levels (Figure 6).

Treatment

The first line of treatment for hyperprolactinemia is medical therapy. Dopamine agonists are the treatment of choice for patients with hyperprolactinemia disorders, including ovulatory dysfunction and microadenomas or macroadenomas. Bromocriptine and the newest dopamine agonist, cabergoline, inhibit prolactin synthesis as well as release and increase lysosomal degradation within the cell. Many studies showed that bromocriptine caused prolactin levels to normalize in approximately 80% of patients, menstrual flow to resume in approximately 50%, and ovulation to resume in 80% to 90%. Use of bromocriptine decreased the size of pituitary tumors by 50% or more in many patients (40%) and by 25% to 50% in some patients (25%)

Bromocriptine should be given in divided daily doses. Approximately 10% of patients experience adverse effects, including nausea, vomiting, dizziness, headache, and orthostatic hypotension. To reduce these symptoms, the starting dose should be low and dose increases should be gradual. In patients who cannot tolerate therapeutic doses, the route of administration can be changed from oral to vaginal. This treatment may be used for years to achieve the required shrinkage of the tumor.

Cabergoline is a long-acting ergot derivative administered once or twice weekly for treating hyperprolactinemia, either idiopathic or secondary to pituitary microadenomas or macroadenomas. A multicenter, prospective, randomized study of cabergoline compared with bromocriptine found cabergoline to be significantly more efficacious in suppressing prolactin.
levels and inducing ovulation while producing signifi-
cantly fewer adverse effects.10

Trans-sphenoidal resection of pituitary microadeno-
mas or macroadenomas is rarely indicated today. 
However, there are still a few important reasons why 
some patients should be seen by a neurosurgeon. 
Surgical candidates are primarily those who cannot tol-
erate or do not respond to medication, typically a 
dopamine agonist. Many such patients may have cystic 
tumors which are less likely to shrink in response to 
to medical therapy.

Case Patient 6 Presentation

Patient 6 is a 41-year-old woman, G4P4, who pre-
sents mainly because she has not menstruated for 
2 years. Her first three pregnancies and deliveries were 
eventful. She was 38 years old during her last preg-
nancy; the infant was 2 weeks overdue and was there-
fore induced. After the placenta was removed manual-
ly, patient 6 had severe uterine bleeding, controlled by 
intravenous oxytocin. Her hemoglobin level the next 
day was 8.5 g/dL; patient 6 was prescribed iron pills 
and was discharged on the second postpartum day. At 
her 6-week checkup, the hemoglobin level was 
10.0 g/dL and the pelvic examination was within nor-
mal limits.

Two years ago (at her annual routine checkup), 
patient 6 told her obstetrician that she had not had a 
menstrual period after her last childbirth. She breast-
fed her baby for 8 months. The obstetrician did not 
request any studies and advised her that lack of menses 
was probably caused by breast-feeding and that her 
menstrual flow should resume within the next few 
months. One year later (at her next annual checkup), 
patient 6 told her obstetrician that she still did not have 
menstrual periods and that she was concerned about 
the total absence of her menstrual flow; her obstetri-
cian then referred patient 6 to a reproductive endocri-
nologist.

• How should patient 6 be evaluated?
• What is the diagnosis for patient 6?

Differential Diagnosis of Patient 6

A complete history, thorough physical examination, 
and necessary work-up should be done. With the excep-
tion of the postpartum hemorrhage, patient 6’s obstetric 
history is insignificant. Medical, family, and social histo-
ries are unremarkable except that her mother under-
went menopause at 45 years of age. Patient 6’s physical 
examination is within normal limits. The differential 
diagnosis should include Asherman’s syndrome (be-
cause the manual removal of the placenta might have 
caused synechiae), Sheehan’s syndrome (because she 
bled heavily after removal of the placenta), ovarian fail-
ure (because her mother underwent early menopause), 
hypothalamic amenorrhea (because she could have 
been stressed and worried about approaching meno-
pause), and idiopathic pituitary dysfunction. Pregnancy 
is a remote possibility because of her age and the absence 
of her menstrual periods.

At her first office visit, a pregnancy test is negative, 
and a sonohysterogram shows a normal uterine cavity 
without synechiae. Sheehan’s syndrome can be ruled 
out because patient 6 breast-fed her baby for 8 months. 
FSH, LH, prolactin, and thyrotropin blood levels are 
measured. Patient 6 is given an intramuscular injection 
of 150 mg of progesterone in oil and is scheduled for 
afternoon office visit in 2 weeks.

At her 2-week visit, patient 6 states that she did not 
have withdrawal bleeding after her progesterone injec-
tion. This result was expected because her endometri-
um was not primed with estrogen. FSH and LH levels 
were on the low end of normal. The thyrotropin level 
was within normal limits; however, the prolactin level 
was increased (138 ng/mL).

• What is the next step for patient 6?
• How should patient 6 be counseled, and what type of 
treatment should she receive?

Diagnosis and Treatment of Patient 6

Patient 6 has prolactinemia, which could be caused 
by a pituitary adenoma. She admits that her husband 
manipulates and sucks her breasts during intercourse, 
but this act will never increase prolactin to a high level. 
She denies taking any medications. Patient 6 most prob-
ably has a pituitary adenoma, and therefore an MRI is 
scheduled. The next day, the MRI shows a pituitary 
tumor that is 0.8 ¥ 0.5 ¥ 0.6 mm.

Patient 6 should be assured that she has a slowly 
growing tumor that is usually benign, and therefore she 
should not be alarmed. However, her prolactin level 
should be checked annually, and any time the level is 
200 ng/mL or more a repeat MRI is mandatory. Patient 
6 should be advised that bromocriptine treatment will 
shrink the tumor and decrease the prolactin level and 
that she will resume her periods in 3 months from the 
beginning of treatment. The pros and cons of the sur-
gonal treatment should be discussed; however, surgery 
should be emphatically discouraged. Her serum pro-
lactin levels should be measured annually.
III. LESS COMMON CAUSES OF SECONDARY AMENORRHEA

PREMATURE OVARIAN FAILURE

This syndrome consists of primary or secondary amenorrhea, increased gonadotropin levels, and estrogen deficiency in women younger than 40 years. The condition is usually benign, but it has a marked emotional effect on women who want to conceive. POF occurs in 1% to 5% of women younger than 40 years. It affects 10% to 25% of women with primary amenorrhea and 5% to 15% with secondary amenorrhea. Ovarian function often begins to wane several years before menstrual periods cease.

Etiology

POF is due to an acceleration of the naturally occurring process of atresia of oocytes. This oocyte depletion may be associated with several other disorders, including thyroid dysfunction, diabetes mellitus, adrenal failure, hypoparathyroidism, and pernicious anemia (Table 10).

Clinical Picture

Gestational, neonatal, and childhood events are normal in most women who develop POF. All events of puberty, including menarche, usually occurred at a normal age. Several years of irregular menses may precede secondary amenorrhea. Approximately 10% of affected women have a family history of POF. The symptoms associated with POF are related to estrogen loss and include amenorrhea; vasomotor instability (e.g., hot flushes and night sweats); psychologic symptoms (e.g., anxiety, tension, mood swings, depression, and irritability); atrophy of the vaginal mucosa, vulva, and urethra causing bladder instability and coital discomfort; and osteoporosis.

Most studies showed that no ovarian follicles were present in patients who developed secondary amenorrhea and had serum FSH levels greater than 40 mIU/mL. However, most endocrinologists see a small group of patients who have clinical and laboratory signs of premature menopause yet whose ovarian biopsy specimens demonstrate follicles. Although these patients have POF, they have not undergone premature menopause because depletion of the ovarian follicles from atresia was not total. Therefore, increased FSH levels cannot be considered as absolute evidence of irreversible ovarian failure because some patients with presumptive POF have subsequently ovulated and even conceived.

<table>
<thead>
<tr>
<th>Table 10. Causes of Premature Ovarian Failure in Patients with Secondary Amenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune disorders</strong></td>
</tr>
<tr>
<td>Thyroid (e.g., Graves’ disease, Hashimoto’s thyroiditis)</td>
</tr>
<tr>
<td>Adrenal (e.g., Addison’s disease)</td>
</tr>
<tr>
<td>Parathyroid (e.g., hypoparathyroidism)</td>
</tr>
<tr>
<td>Pituitary (e.g., lymphocytic hypophysitis)</td>
</tr>
<tr>
<td>Blood (e.g., pernicious anemia, idiopathic</td>
</tr>
<tr>
<td>thrombocytopenic purpura)</td>
</tr>
<tr>
<td>Gastrointestinal (e.g., liver cirrhosis, Crohn’s disease)</td>
</tr>
<tr>
<td>Skin (e.g., alopecia areata, vitiligo)</td>
</tr>
<tr>
<td>Others (e.g., myasthenia gravis, diabetes mellitus, rheumatoid</td>
</tr>
<tr>
<td>arthritis, lupus erythematosus)</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong> (e.g., busulfan and cyclophosphamide)</td>
</tr>
<tr>
<td><strong>Radiation</strong> (e.g., for Hodgkin’s disease)</td>
</tr>
<tr>
<td><strong>Infection</strong> (e.g., mumps at puberty)</td>
</tr>
<tr>
<td><strong>Metabolic disorders</strong> (e.g., galactosemia)</td>
</tr>
</tbody>
</table>

Diagnosis

When a thorough history and careful physical examination raise the suspicion of POF, certain laboratory tests should be requested to confirm the diagnosis. When other endocrinopathies are suspected, pertinent hormonal tests should be ordered such as fasting glucose levels, serum cortisol levels in the morning, and a thyroid panel. The serum concentration of estradiol-17β needs to be measured; an E2 value greater than 50 pg/mL confirms that estrogen production is adequate. FSH and LH levels need to be measured to distinguish ovarian failure from a hypothalamic-pituitary dysfunction. Increased levels of FSH and LH and a decreased E2 level confirm the diagnosis of POF. For women with POF who want to conceive, it is worthwhile to perform an ovarian biopsy looking for primordial follicles. If follicles are present, these follicles may respond to gonadotropin treatment. However, laparoscopic ovarian biopsy has risks, such as problems associated with general anesthesia and major surgery along with the possibility of postoperative tubo-ovarian adhesions. In addition, the tissue removed may not be representative of the histologic appearance of the ovary. It is the author’s opinion that if endocrine evidence indicates no follicular activity, the ovarian biopsy is not warranted.

Treatment

The treatment of patients with POF depends on whether the patient wants to become pregnant and on
the etiology. In patients without ovarian follicles who are not interested in pregnancy, combined estrogen-progestin replacement therapy is essential. This therapy will relieve hot flushes and other symptoms, reverse urogenital atrophy, and retard the progress of osteoporosis.

It is adequate to administer oral doses of 0.625 mg of conjugated estrogens daily for 25 days each month in addition to 10 mg of oral medroxyprogesterone acetate daily from day 16 through day 25. Patients with associated diseases (ie, thyroid or adrenal dysfunction, autoimmune disease, or metabolic disturbances) should be counseled thoroughly and referred to appropriate consultants.

Case Patient 7 Presentation

Patient 7 is a 23-year-old woman, nulligravida, single, and not sexually active, who presents with a chief symptom of no menstrual periods for 2 years. Menarche occurred at 14 years of age; menstrual cycles were regular (every 28 days) and the flow lasted 5 days until 19 years of age, when her cycles became irregular (occurring at 2- to 3-month intervals). When she was 21 years old, her menstrual flow ceased completely.

Medical history revealed that she had laparotomy and right oophorectomy when she was 3 years old. The oophorectomy was done because of a large right ovarian tumor, the pathology of which the patient did not know. However, she states that she had pelvic irradiation after the laparotomy. She works as a policewoman, smokes one pack of cigarettes per day, and does not drink alcohol. She denies any stress at home or at work.

Physical examination reveals a midline scar secondary to her laparotomy incision at 3 years of age. Systems review is within normal limits. Pelvic examination reveals slight tenderness, and a small retroverted uterus is easily felt.

- How should patient 7 be evaluated?
- What is the diagnosis for patient 7?

Differential Diagnosis of Patient 7

Patient 7 obviously has had secondary amenorrhea for 2 years. Before the cessation of menses, her menstrual cycles started to occur less frequently until they stopped completely when she was 21 years old. Pregnancy is ruled out because patient 7 denies intercourse; hypothalamic amenorrhea is probably ruled out because she denies a history of stress. The galactorrhea-amenorrhea syndrome is ruled out because a breast examination does not elicit any secretion. Endocrinopathies can be easily ruled out because her systems review was within normal limits. Pregnancy complications should not be included in the differential diagnosis because she has never been pregnant.

Physical examination reveals a midline scar secondary to the laparotomy and right oophorectomy, which was followed by pelvic irradiation. The irradiation must have affected the follicles in the remaining left ovary; however, some follicles probably continued to secrete estrogen until she was 21 years old. Therefore, the most probable diagnosis is POF caused by the destruction of the ovarian follicles by irradiation.

- What laboratory tests should be ordered to confirm the diagnosis for patient 7?
- How should patient 7 be counseled?
- How should patient 7 be treated?

Diagnosis, Counseling, and Treatment of Patient 7

Blood levels of FSH, LH, and prolactin are measured. Patient 7 is given a prescription for 10 mg of medroxyprogesterone acetate to be taken daily for 1 week. A return appointment is scheduled in 3 weeks to discuss the tests results and to provide further counseling. Patient 7 does not have withdrawal bleeding. At her return visit, patient 7 is told that she has POF; her FSH level is 82 mIU/mL, LH level is 66 mIU/mL, and prolactin level is normal. Patient 7 asks if she can become pregnant in the future.

Patient 7 is told that most likely irradiation destroyed all her ovarian follicles; therefore, she should probably use a donated egg and in vitro fertilization to conceive. However, laparoscopic ovarian biopsy can determine whether her follicles are present or absent. Patient 7 requests laparoscopy, which reveals a completely sclerosed left ovary without any follicles; the right adnexa is missing. If patient 7 is not interested in pregnancy, combined estrogen-progestin replacement therapy is essential. This therapy will relieve hot flushes and other symptoms, reverse urogenital atrophy, and retard the progress of osteoporosis. It is adequate to administer oral doses of 0.625 mg of conjugated estrogens daily for 25 days each month in addition to 10 mg of oral medroxyprogesterone acetate daily from day 16 through day 25.

ASHERMAN’S SYNDROME

In this syndrome, intrauterine adhesions develop after trauma, usually a postabortion or postpartum curettage. Intrauterine adhesions may also occur without trauma (eg, can be caused by tuberculosis). Myomectomy, diagnostic curettage, and pelvic irradiation are rare causes. A predisposing factor is a diminished hormonal status at the time of the operation. Hypogonadalotrophic hypogonadism has been shown to be associated with extensive
formation of intrauterine adhesions. Women who breast-feed their babies may be at a higher risk for the development of intrauterine adhesions after a postpartum curettage because they remain estrogen deficient for a prolonged time. Women with congenital uterine malformation are prone to have spontaneous abortions, which are treated with dilatation and curettage (D&C); therefore, they are at increased risk for the development of intrauterine adhesions. The incidence of intrauterine adhesions ranges from 4% of all infertile patients to 68% of all infertility patients who have had two or more postabortion curettages.

### Signs and Symptoms

Most patients with intrauterine adhesions are symptomless. Approximately one third have menstrual dysfunction (hypomenorrhea, oligomenorrhea, or amenorrhea). The menstrual pattern does not always correlate with the extent of scarring. Rarely, patients with amenorrhea have associated cyclic pain, probably due to cervical canal obstruction causing hematomata.

The real problem for patients with intrauterine adhesions is infertility. This may present in many forms such as secondary infertility, repeated early abortions, premature labor, and fetal death in utero.

### Diagnosis

The key to establishing the diagnosis is a high index of suspicion. All patients with a history of previous curettages after abortion or delivery must be considered to be at risk of having intrauterine adhesions. Nonpregnant patients with secondary amenorrhea who do not have progestin-induced withdrawal bleeding should be suspected of having intrauterine adhesions. Failure to induce menstrual flow after sequential estrogen-progestin treatment is strongly suggestive of the diagnosis. If bleeding does occur, intrauterine adhesions may still be present. Thus, withdrawal bleeding can be used to support but not to rule out the diagnosis of intrauterine adhesions. Visualization of intrauterine adhesions is achieved by either hysterosalpingogram or hysteroscopy.

The main characteristic on radiographs of intrauterine filling defects caused by intrauterine adhesions is that they do not change in form or size when the pressure of the distension of the contrast medium is increased or the position of the patient is changed (Figure 7). This characteristic may make it relatively easy to distinguish intrauterine adhesions from other intrauterine pathology that appears on the hysterosalpingogram, like endometrial polyps or submucous myomas. Hysteroscopy allows direct inspection of the uterine cavity with assessment of both the extent and the location of the scar. Intrauterine adhesions are divided into three classes according to the extent of the adhesions and whether the ostia of the tubes are visible or not (Table 11). These adhesions can be endometrial, fibrous, or muscular.

### Treatment

Mechanical division of the synechiae is the logical treatment of intrauterine adhesions. After the advent of hysteroscopy, lysis of the adhesions under direct vision became the method of choice and the old methods of blind curettage or hysterotomy became obsolete. Direct visualization enables the surgeon to cut only scar tissue and to spare normal endometrium and myometrium. The author uses the operating hysteroscope with rigid scissors and Hyskon as the distension medium.

### Table 11. Classification of Intrauterine Adhesions in Patients with Asherman’s Syndrome

<table>
<thead>
<tr>
<th>Classification (Incidence)</th>
<th>Severity</th>
<th>Intrauterine Adhesions</th>
<th>Ostia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (20%)</td>
<td>Slight</td>
<td>In &lt; one third of cavity</td>
<td>Both ostia visible</td>
</tr>
<tr>
<td>Class II (42%)</td>
<td>Medium</td>
<td>In one third to one half of cavity</td>
<td>One ostium visible</td>
</tr>
<tr>
<td>Class III (38%)</td>
<td>Severe</td>
<td>In one half or more of cavity</td>
<td>No ostium visible</td>
</tr>
</tbody>
</table>

Figure 7. A hysterosalpingogram showing intrauterine adhesions, thus proving the diagnosis of Asherman’s syndrome.
Complete lysis of adhesions can be achieved even in women with extensive scarring. The strokes of the hysteroscope sheath can be used successfully to disrupt the endometrial type of adhesions. For the fibromuscular type of synechiae, rigid scissors are more suitable. The adhesiolysis is begun inferiorly and carried cephaladly until the uterine architecture has been normalized.

Most surgeons recommend placing a large intrauterine device into the uterine cavity and retaining it for 2 months. They assume that postoperative use of an intrauterine device may keep the raw dissected surfaces separated during the initial healing phase and may reduce the chance that they will re-adhere to one another. The author doubts the efficacy of the intrauterine device and therefore has never used it. In patients with class I and II disease, the author does not use any intrauterine splint except a Foley catheter for 8 hours postoperatively. In patients with class III disease, the author uses a Foley catheter for 48 hours. Hysteroscograms 2 months after the hysteroscopic lysis of the synechiae have showed excellent results using these techniques (Figure 8).

Hormonal treatment is also typically prescribed because it is believed that a lush endometrium will be formed under the influence of estrogens or cyclic estrogen and progesterone, thereby preventing reformation of the adhesions. Oral conjugated estrogens (5 mg daily) are typically given for 60 consecutive days, and oral medroxyprogesterone acetate (10 mg) is added during the last 5 days of estrogen therapy. However, the author does not totally concur with this notion and does not prescribe estrogens to those patients with class I and II disease who have endogenous estrogens. For patients with class III disease, the author prescribes hormonal treatment but only for 30 days.

Perforation and infection are very rarely reported (ranging between 0% and 2.2%). Neither of these complications usually has any deleterious effects on the final results.

**SHEEHAN'S SYNDROME**

**Etiology**

Pituitary enlargement with the formation of large chromophobe pregnancy cells has long been known to occur during pregnancy; lactotroph hyperplasia occurs as well. Accompanying these morphologic changes in the pituitary during pregnancy, serum prolactin levels begin to increase at 8 weeks of gestation; at term, serum prolactin levels are 10 times the nonpregnant level. After delivery, prolactin levels decrease rapidly, reaching baseline within 2 weeks in nonlactating women. Maternal serum FSH and LH levels are decreased to undetectable levels and the pituitary response to GnRH is blunted or absent during pregnancy. The decreased gonadotropin synthesis and secretion are secondary to the feedback inhibition of the increased estrogen, progesterone, prolactin, and inhibin levels at the pituitary level during pregnancy.

The volume of the anterior pituitary (adenohypophysis) increases during pregnancy by approximately one third, resulting in an upward convexity of the superior surface on radiography. The size of the posterior pituitary (neurohypophysis) does not increase and is actually not visualized during the third trimester. The hypertrophied pituitary gland of pregnant women is very susceptible to a compromised blood supply through the low-pressure sinusoidal system that accompanies postpartum hemorrhage. Pituitary insufficiency secondary to ischemia and infarction, which appears as a late sequela to obstetric hemorrhage, is known as Sheehan's syndrome (hypogonadotropic hypogonadism amenorrhea).

**Clinical Picture**

Classically, patients with Sheehan's syndrome present with rapid breast involution and failure to lactate, resume menses, and regrow shaved pubic or axillary hair. Pituitary necrosis accompanying Sheehan's syndrome is frequently partial, with selective loss of hormone secretion. The first cells to be affected are the gonadotrophs and lactotrophs, resulting in loss of FSH, LH, and prolactin secretion. Thyrotrophs and corticotrophs are usually not affected unless more than 95% of the pituitary gland is destroyed by infarction. Diagnosis is usually highly suggested by history and physical examination but is confirmed by measuring blood levels of the anterior pituitary hormones (e.g., FSH, LH, prolactin, TSH, and ACTH). Treatment with...
hormone replacement therapy (eg, estrogen, progesterone) is usually very satisfactory.

**Case Patient 8 Presentation**

Patient 8 is a 27-year-old woman, G2P2, with absence of menstrual flow since she became pregnant 18 months ago. Her periods had been always regular. Her first childbirth was at 24 years of age; pregnancy and delivery were uneventful. She breast-fed her baby boy for 6 months and decided not to use any type of contraception except the rhythm method. Patient 8 had amenorrhea while she was breast-feeding; however, once she stopped nursing, her menstrual cycles became regular and occurred on a monthly basis.

Patient 8 became pregnant 5 months after she weaned her first baby. Her second pregnancy progressed normally until she failed to go into spontaneous labor at her expected date. A week after the expected date of confinement, labor was induced with oxytocin, and patient 8 vaginally delivered a baby boy. The infant weighed 9 lb 9 oz, and his Apgar scores were 8 and 10 after 1 and 2 minutes, respectively. Patient 8's placenta was expelled spontaneously, and she was sent to the recovery room in a good condition.

Thirty minutes later, severe vaginal bleeding with large clots was noticed. Massage of the atonic uterus and use of oxytocin drip failed to induce uterine contractility. Her blood pressure decreased to 80 mm Hg systolic and 40 mm Hg diastolic. A blood transfusion was started, and she was taken to the delivery room in a state of impending shock. Manual exploration of the uterine cavity revealed that a large piece of the placenta was retained and attached to the posterior uterine wall. This retained placenta was extracted manually but the bleeding continued, although to a lesser extent. Therefore, curettage with a blunt and later with a sharp curette was performed. Patient 8 was kept in the delivery room for more than 1 hour. When her blood pressure normalized (increased to 100/60 mm Hg), and when the bleeding slowed down substantially, she was returned to the recovery room. Antibiotic treatment was started, and patient 8 was given 4 pints of blood. After this treatment, her recovery went smoothly, and she was sent home on the third postpartum day.

At her 6-week postpartum visit, patient 8 stated that her milk supply was not sufficient to breast-feed her baby and that she had to supplement with bottle feeding. Physical examination including bimanual breast examination was within normal limits except that the obstetrician could not elicit any milk from her breasts. The obstetrician told patient 8 that milk dryness happens occasionally and that she should not be concerned. However, patient 8 had to depend totally on bottle feeding for her second baby, although she had successfully breast-fed her first baby. Nine months postpartum, she realized that she had never resumed her menstrual periods and noticed that her pubic and axillary hair was getting thinner. She went to see her obstetrician who confirmed all her observations. Therefore, her obstetrician referred patient 8 to a reproductive endocrinologist.

- How can the proper diagnosis be reached?
- What treatment should patient 8 receive?

**Diagnosis of Patient 8**

The pertinent event in patient 8's history was the postpartum uterine bleeding causing impending shock. Patient 8 required 4 pints of blood to save her from an irreversible shock; thus, she lost a large amount of her blood. Her blood pressure decreased, producing generalized vasoconstriction. The pituitary gland is enlarged during pregnancy; vasoconstriction deprives the pituitary of an adequate blood supply, resulting in partial or total necrosis. Therefore, measuring blood levels of pituitary hormones is essential to rule out Sheehan's syndrome.

In addition, patient 8 had manual removal of part of her placenta followed by curettage. This procedure could have caused intrauterine adhesions, leading to secondary amenorrhea. A hysterosogram or a sonohysterogram is essential to rule out intrauterine synechiae.

Physical examination reveals thinning of the pubic and axillary hair; therefore, patient 8 most probably has Sheehan’s syndrome.

**Laboratory Tests for Patient 8**

A sonohysterogram in the office shows that patient 8 has a normal uterine cavity, which rules out Asherman's syndrome. The progesterone-withdrawal test is negative because patient 8 did not notice vaginal bleeding 2 weeks after an intramuscular injection of 150 mg of progesterone in oil.

Serum levels of FSH, LH, and prolactin were very low, whereas thyrotropin and ACTH levels were normal. These levels confirm the diagnosis of partial pituitary necrosis resulting in the lack of secretion of the gonadotropins and prolactin. Thus, patient 8 has hypogonadotropic hypogonadism amenorrhea.

**Treatment of Patient 8**

Patient 8 should be counseled regarding what caused her amenorrhea and hair thinning. In addition, she
should be advised that she could become pregnant in the future by inducing ovulation using gonadotropins and hCG injections. She has to understand that her estrogen-dependent organs should be kept well-estrogenized to keep them healthy and to avoid osteoporosis; therefore, she needs to take hormone replacement therapy (eg, estrogen, progesterone). She can use sequential estrogen and progesterone pills or the combined form. The author prefers the combined form and therefore usually prescribes oral contraceptive pills.

IV. RARE CAUSES OF SECONDARY AMENORRHEA

ENDOCRINE DISORDERS OUTSIDE THE HYPOTHALAMIC-PITUITARY-OVARIAN (HPO) AXIS

Hyperthyroidism, hypothyroidism, Cushing’s syndrome, Addison’s disease, and uncontrolled diabetes are also associated with amenorrhea. With any of these disorders, amenorrhea is of secondary importance, and all efforts should be directed to diagnosing and managing the primary disease. History and physical examination, along with pertinent laboratory tests, usually achieve a definite diagnosis. Treatment consists of long-term estrogen-progesterone replacement therapy with careful titration of dosage. Appropriate therapy should result in the resumption of normal menstrual periods.

Chronic Systemic and Metabolic Diseases

Chronic diseases such as liver cirrhosis, tuberculosis, obesity, and malnutrition may cause secondary amenorrhea. Treatment is directed at the underlying cause.

Iatrogenic Causes

These are extremely rare causes of secondary amenorrhea. A careful history detecting irradiation or surgical removal of the ovaries at a young age is all that is needed to make the diagnosis (see patient 7 on page 20). Estrogen-progesterone replacement therapy will induce menstruation.

V. SUMMARY POINTS

• Thorough history and complete physical examination are essential in patients with secondary amenorrhea so that only the most pertinent laboratory tests are ordered.
• Diagnosis can be easily reached when history, physical examination, and laboratory tests are combined to rule in or rule out the suspected diseases causing the amenorrhea.
• Therapy should be updated because it may change from one year to another.
• Pregnancy, the hypothalamic amenorrhea syndrome, androgenic disorders, and the galactorrhea-amenorrhea syndrome are among the most common causes of secondary amenorrhea.
• Pregnancy is the most frequent cause of secondary amenorrhea and should be ruled out before a more involved work-up is begun.
• The hypothalamic amenorrhea syndrome is typically caused by physical and emotional stress, which lead to inadequate hypothalamic function.
• A patient with severe hypothalamic suppression has very low gonadotropin levels, and therefore, her progesterone withdrawal test is negative.
• Diagnostic evaluation of patients with androgenic disorders requires determining levels of the following hormones: follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone, and dehydroepiandrosterone sulfate (DHEAS).
• In a nonpregnant woman, galactorrhea with amenorrhea is a pathologic condition often caused by a serious organic disease. The higher the level of basal prolactin, the greater the likelihood that the patient has a pituitary neoplasm.

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Chapter 3—Case Studies in Cologenital Fistulas

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I. INTRODUCTION

Genital fistulas that complicate diverticular disease of the sigmoid colon may no longer be considered a rare phenomenon. Most patients who have these lesions present to their gynecologists with a foul smelling, sometimes purulent, and occasionally blood-tinged vaginal discharge. This review discusses the topic of cologenital fistulas using three case patients to illustrate the typical presentation, pertinent medical history, laboratory testing, diagnosis, and treatment of patients with these conditions.

II. CASE PATIENT 9

PRESENTATION

Patient 9 is a 64-year-old multiparous woman who states that she has had a brown vaginal discharge for 7 days. Her medical history includes a total abdominal hysterectomy at 34 years of age and rectal bleeding at 52 years of age. The bleeding had been ascribed to sigmoid diverticulosis and was diagnosed by barium enema series.

Σ Based on patient 9’s history, what is the likely source of the brown vaginal discharge?
Σ What diagnostic test(s) will help locate the source of the vaginal discharge?

DISCUSSION

Brown vaginal discharge in a postmenopausal woman who has a history of total abdominal hysterectomy may have several possible sources. A malignant lesion from the vagina, either primary or metastatic, should be suspected. The history of diverticular disease should alert the clinician to the possibility of a cologenital fistula. A careful examination, with or without the aid of the colposcope, will help the clinician to eliminate or establish the diagnosis. Atrophy of the vagina is another possible cause of this condition.

Vaginal examination of patient 9 revealed stool extruding from a left vaginal apical defect. The universal presenting symptom of patients with cologenital fistula is a foul vaginal discharge, often fecal in nature, sometimes accompanied by passage of flatus from the vagina. Occasionally, the discharge is preceded by lower abdominal discomfort, which disappears when the discharge becomes evident. Not infrequently, a bloody discharge precedes the advent of the more prominent purulent or fecal material.

Diverticular Disease

This is a general term referring to the outpouching of the colon, diverticulosis, and diverticulitis (inflammation of a diverticulum). Diverticular disease is a disease of advancing age; it is uncommon in persons younger than 40 years. This colon disease becomes increasingly more common with advancing age until 50% of persons older than 80 years are afflicted; it is more common in men. The sigmoid is involved in 95% to 98% of patients with diverticulosis (the presence of pouches or diverticula in the colon without inflammation).1

The longer that diverticulosis is present, the greater is the likelihood that the person develops diverticulitis. The latter develops in 10% of persons with diverticulosis after 5 years, 25% after 10 years, and 35% after 20 years.2 As in patient 9, the diagnosis of diverticulosis should be suspected in a woman aged 50 years or older.
who has vaginal discharge and a history of total abdominal hysterectomy.

**Diagnostic Tests**

A **barium enema** series is the simplest but the least dependable test in locating the communication between the vagina and the colon. The barium solution is often too thick and the retrograde pressure gradient is too weak to force the barium through the fistulous tract into the genital organ. Also, the loops of bowel filled with barium tend to obscure the fistula, if it is filled and otherwise visible.

**Sigmoidoscopy** is also not reliable unless the opening in the colon is large enough. Demonstration of the fistula usually requires a **retrograde dye transmission study** using a water-soluble medium. In patient 9, a **vaginogram** was used to identify the connection between the sigmoid colon and the vagina. The diverticular process and its extent were also shown on the vaginogram (Figure 9).

Coe³ in 1963 and Tancer in 1964⁴ described retrograde dye transmission. Tancer used the Bardex bag to obtund the vagina and thus increase the positive pressure of the infused dye. In dye studies done under image intensification, the dye may be seen to progressively fill the involved genital organ, outline the fistula, and enter the sigmoid where diverticula are subsequently visualized. A **fistulogram** can be used in areas in which the vaginal opening is so small that a vaginogram may fail to demonstrate communication between the two organs.

Other infrequently used diagnostic methods include the charcoal test in which charcoal taken orally appears in the vagina after 24 hours.⁵ When this test is positive, it indicates a fistula but fails to identify the area of bowel involved. Kuhlman and Fishman⁶ have used computed tomography (CT) evaluation for the same purpose. Adams and Perry⁷ have used a flexible sigmoidoscope and a gastroscope simultaneously in the vagina to find a tract through which to pass a soft-tipped device to demonstrate a sigmoidovaginal fistula.

∑ What treatment would you recommend for patient 9?

**TREATMENT**

Diverticulitis has always been considered a medical disease and one to be treated expectantly. The procedure of choice for therapy depends on the degree of inflammation found at laparotomy. The two considerations in the treatment of cologenital fistula are **concern for the genital organ involved** and **concern for the degree of diverticular disease**. Full consent should be obtained from the patient for both resection and temporary colostomy. The patient should have a thorough bowel preparation before exploration. If, at exploration, the bowel is found to be minimally involved, **fistulectomy** is adequate. Otherwise, **primary resection and anastomosis** are carried out. Staged procedures are rarely necessary in acute cases.

### III. CASE PATIENT 10

**PRESENTATION**

Patient 10 is a 60-year-old woman who states that for 4 years she has had a brown, foul smelling vaginal discharge after meals. Her medical history includes two cesarean section deliveries. Both in-office and in-hospital endometrial sampling were carried out, revealing benign findings. A barium enema, colonoscopy, and small bowel series demonstrated sigmoid diverticular disease, but no fistula was noted. The only abnormality found during pelvic examination was a fecaloid odor emanating from the vagina. An endometrial aspirate revealed food particles, and a diagnosis of cologenital fistula was entertained.

∑ What types of fistulas can complicate diverticular disease of the colon?

∑ How can you confirm the presence of the different types of fistulas?
DISCUSSION
Complications of Diverticulitis

Of patients with diverticulitis, 20% require surgical intervention for complications such as abscess formation or rupture, bowel obstruction, or fistula formation. Fistulas most often involve other loops of bowel or pelvic viscera, such as the urinary bladder or female genital organs. Sigmoidovesical fistulas secondary to diverticulitis have been known since Jones9 reported the first proven case in 1859.

The most common cologenous fistula to complicate diverticular disease is the sigmoidovaginal fistula. There are two varieties of this fistula, as follows. 1) The less common fistula occurs in the presence of a uterus or retained cervix, as in patient 10. This happens when a diverticular abscess in the cul-de-sac burrows through the posterior vaginal fornix. 2) In the more common fistula, the sigmoidovaginal fistula perforates the apical vaginal scar some years after a total hysterectomy, as in patient 9. The latter fistula is three times more common than the former. The increased incidence may be ascribed to several factors.

By 1960, supracervical hysterectomy had been replaced by total hysterectomy. Since 1965 alone, more than 500,000 hysterectomies have been performed yearly in the United States. Therefore, increasing numbers of women with a prior hysterectomy are entering their 8th and 9th decades of life—the period when 60% of the population is likely to have diverticular disease.

Additional Defects

When pelvic examination reveals that the uterus or retained cervix is present (as in case patient 10), the vagina is otherwise intact, and the discharge is coming from the cervix, further study is indicated to visualize a cervical, fundal, or tubal lesion involving the sigmoid.

With a uterus or a retained cervix, a posterior cul-de-sac defect is typically noted through which the discharge has passed. It is not uncommon to appreciate a left adnexal mass or thickening representing the diseased sigmoid. If a pelvic examination reveals a total absence of uterus, an apical defect is typically found through which passage of the discharge can be viewed.

Occasionally, the defect may be too small to be palpated or seen or is hidden in an apical granulation. In either case, it is considered necessary to demonstrate the fistula. It is not uncommon for evidence of acute diverticulitis or palpable chronic disease to be absent, in which case the fistula is described as “silent.”

Among the various genital fistulas that complicate diverticulitis, the least common is the sigmoidocervical lesion, which involves the retained cervix in a patient who has undergone a supracervical hysterectomy some years previously. Only four such cases have been reported.

Diagnostic Tests

Diagnosis of sigmoidovaginal fistula can be confirmed by retrograde dye studies such as a vaginogram in the case of a sigmoidovaginal or sigmoidocervical fistula, a hysterogram in the case of a sigmoidouterine fistula, and a hysterosalpingogram in the case of a sigmoidotubal fistula. A cystogram can confirm a diagnosis of sigmoidovesical fistula.

∑ What is the appropriate treatment for patient 10?

TREATMENT

Surgery is the treatment of choice for cologenous fistula. Surgery not only eradicates the fistula and its symptoms, it also provides an opportunity for the surgeon to treat bowel disease that has already demonstrated its propensity for abscess formation. The different surgical approaches vary from a conservative excision of the fistula to the more aggressive resection of the affected sigmoid colon and closure of the vagina. In a sigmoidouterine lesion, the uterus may or may not be removed if the affected sigmoid is resected. Patient 9 was treated by sigmoid resection and closure of the fistula; patient 10 had a fistulectomy.

IV. CASE PATIENT 11

PRESENTATION

A 32-year-old woman states that she has vaginal seepage of gas and liquid stool, which started about 4 months after the birth of her daughter who is now 3 years old. More recently, the patient noted feces coming from her vagina. Vaginal examination revealed a 1.5-cm fistula in the posterior wall of the vagina approximately 3.5 cm from the anal orifice. The anal sphincter is intact.

∑ What are the possible causes of rectovaginal fistula?
∑ What is the cause of patient 11’s fistula?
∑ What are the clinical manifestations of rectovaginal fistula?

DISCUSSION

Causes

The most common cause of rectovaginal fistula is failed repair of a fourth-degree laceration of the vagina during childbirth. The anal sphincter may or may not be intact. A fistula adjacent to the sphincter is called an anovaginal fistula, and an opening more than 3 cm from the sphincter is called a rectovaginal fistula, as in patient 11. A rectovaginal fistula may also occur because of the...
 clinician’s failure to recognize a rectal extension of the episiotomy or because of inadvertent placement of the suture in the rectal mucosa. Fistulas may also occur after rectal injury during a posterior vaginal wall repair. Perforation of a rectal abscess into the vagina can result in a rectovaginal fistula. Patient 11 had a rectal extension of the episiotomy that was not recognized.

Less common causes of rectovaginal fistulas are malignancy of the rectum or vagina, radiation therapy for malignancy of the cervix or vagina, and inflammatory bowel disorders (such as Crohn’s disease). Systemic lupus erythematosus can also predispose women to rectovaginal fistula formation.

Clinical Manifestations

A small rectovaginal fistula may be asymptomatic. Sometimes the only symptom is slightly foul smelling discharge when the woman has diarrhea. Fecal incontinence is the most distressing symptom. Rectovaginal fistulas resulting from Crohn’s disease are usually tender, and multiple perianal and perirectal fistulas may also be present.

The diagnosis of a large rectovaginal fistula is very simple. The difficulty is encountered when the fistula is small and when extensive scarring from previous surgery obscures the opening. Use of a silver probe is usually very helpful. Examination with the patient under anesthesia is helpful in this situation.

Σ How should patient 11 be treated?

TREATMENT

Surgical repair is the treatment of choice for the patient with rectovaginal fistula. Whether surgery is successful depends on the condition predisposing the patient to the fistula formation. Repair of rectovaginal fistula secondary to obstetric trauma is the most successful, as in patient 11. Fecal diversion is not necessary. This type of repair can be accomplished with either a fistulectomy or conversion of the fistula into a fourth-degree tear. The location and size of the fistula determine the type of surgical approach. Patient 11 underwent fistulectomy under epidural anesthesia. The procedure is as follows: an incision is made on the vaginal mucosa surrounding the fistula opening. Adequate dissection of the vaginal mucosa is carried out to mobilize the rectum. Vertical mattress sutures are placed on the pararectal tissue to close and imbricate the rectal opening. A second layer of sutures is placed to reinforce the first set. The vaginal mucosa is then closed.

The timing of the repair is important. Although most older gynecologists prefer to wait 3 months or longer after diagnosis before surgical correction is attempted, some recent literature suggests that early repair can accomplish a similar result. Surgical correction is attempted only after the inflammation surrounding the fistula has healed; this process takes several weeks. Wide mobilization of both the rectal and vaginal mucosa is desirable for optimal outcome. Prevention of hematoma formation by controlling hemostasis and closure of dead space is of equal importance.

Preoperative and postoperative care of the bowel are just as important as the surgical procedure in ensuring a successful repair. Preoperative mechanical bowel preparation using GoLYTELY is started the day before surgery, and the patient is placed on a clear liquid diet the same day. The patient is given a high colonic enema on the morning of surgery, and an antibiotic is administered intravenously before incision. Postoperatively, the patient should be given a liquid diet until she has a bowel movement. She should be discharged home on a low-residue diet and stool softener for 6 months.

Fecal diversion is often necessary before repair of a fistula resulting from radiation, a difficult hysterectomy (due to endometriosis), or a perforated abscess. Use of the Martius bulbocavernousus transplantation operation has improved the results of fistula repair. Surgical repair of fistulas resulting from Crohn’s disease is usually not successful.

Σ

SUMMARY POINTS

- The diagnosis of cologenous fistula should be considered when a patient older than 50 years has a fecal or fecaloid vaginal discharge. The level of suspicion should be raised if the patient has had a total abdominal hysterectomy with or without a history of diverticulitis.
- Demonstration of the fistula usually requires a retrograde dye transmission study using a water-soluble solution.
- Surgical correction is the treatment of choice for cologenous fistulas. The different surgical approaches vary from a conservative excision of the fistula to the more aggressive resection of the affected sigmoid colon and closure of the vagina.
- Surgical correction is the treatment of choice for rectovaginal fistulas. This type of repair can be accomplished with either a fistulectomy or conversion of the fistula into a fourth-degree tear. The location and size of the fistula determine the type of surgical approach. It is rarely necessary to divert the feces before repairing a rectovaginal fistula.
REFERENCES