Approaching the Adnexal Mass in the New Millennium

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Abstract

Adnexal masses are common dilemmas faced by practicing gynecologists. They affect women from before birth throughout life, yet considerable disagreement exists regarding their optimal management. Traditional management focused on avoiding undertreatment of a potentially malignant process. Advances in detection, diagnosis, and minimally invasive management make it necessary to review this practice to avoid unnecessary morbidity and mortality. The literature emphasizes a minimally invasive approach to the treatment of benign lesions without sacrificing the principles of oncologic surgery.

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The adnexal mass is one of the most common gynecologic pathologies, yet no consensus exists regarding its optimal management.[1–13] Improved radiologic detection, increased understanding and availability of serum tumor markers, emergence of screening protocols, and evolving laparoscopic techniques have combined to beg the question: what is the best approach to the adnexal mass?

To gauge the impact of evaluating and treating these lesions, consider that almost 1 in 10 women will have an ovarian neoplasm in her lifetime, and most of these patients will undergo surgical evaluation.[14] It is estimated that nearly 300,000 women are hospitalized annually for treatment of ovarian neoplasms and that as many 270,000 are evaluated surgically.[15] In contrast, fewer than 27,000 cases of ovarian cancer are diagnosed each year, indicating the potential cost of overtreatment.[16] Given these numbers, even marginal advancement in treatment of adnexal masses will yield amplified clinical benefits.

Reproductive-Age Women

Pelvic masses are common in women between menarche and menopause. They are usually functional, either follicular or corpus luteal, and most resolve without surgical intervention. Most of the remaining tumors are nonmalignant, with cystadenomas being most common. Malignancy occurs generally at the age extremes and reflects disease processes common in those groups. Thus germ cell and sex cord stromal tumors are most frequent in girls near menarche, and the frequency of epithelial ovarian cancers increases as women approach the postmenopausal margin.[14]

Evaluation of patients with adnexal masses begins with a thorough history and review of systems. Determining the duration, chronicity, and quality of symptoms often narrows the differential diagnosis considerably. Irregularities in the menstrual cycle can also be helpful in establishing a hormonally active tumor or ovarian dysfunction, which may in turn lead to a persistent hemorrhagic corpus luteum cyst or luteinized unruptured follicle. A review of sexual history and practices may be insightful when fallopian tube disease, acute infection, or ectopic pregnancy is a consideration. Assessment of recent gastrointestinal function is mandatory, as epithelial ovarian cancer most frequently causes vague abdominal or gastrointestinal complaints. A brief, open-ended review of

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systems is also recommended because isolated solid pelvic tumors of the reticuloendothelial, neural, urologic, musculoskeletal, dermatologic, and endocrine systems have been reported.[17–21] Semisolid or cystic masses in the pelvis may be associated with arteriovenous malformation, hematoma, bacterial and parasitic infections, and lymphoid malignancy, in addition to more common gynecologic pathologies.[22–26]

Review of family history is vital, as germ line mutations are implicated in up to 10% of ovarian cancers.[27] These patients tend to experience symptoms at an earlier age than those without such mutations (35–45 vs 65 yrs) and may have different clinical courses.[28] More than one first-degree relative with ovarian or breast cancer may be indicative of a germ line mutation or cancer-family syndrome. These patients can have up to a 70% lifetime chance of developing ovarian cancer.[29,30] A strong family history of colon cancer may indicate familial Lynch syndrome II (hereditary nonpolyposis colon cancer), which carries an increased risk of ovarian cancer, among other noncolonic malignancies.[31] The role of screening otherwise asymptomatic patients for germ line mutations such as BRCA1 and BRCA2 is unclear, as are treatment implications of diagnosing these disorders. Although it is often recommended that women with familial cancer syndromes undergo bilateral adnexectomy on completing reproduction or at age 35, firm criteria for prophylactic oophorectomy are not established.[32] As studies of these families mature, intervention strategies will no doubt be forthcoming.

A complete physical examination begins with assessment of general health including evidence of cancer-associated weight gain or loss. Evidence of masculinization should be investigated, although mild hirsutism is most often constitutional. Supraclavicular, axillary, and inguinal lymph nodes are examined to evaluate for metastatic disease. Ascites and pleural effusions are particularly ominous, although not irrevocably linked to cancer. The breast examination is important, as hormonally active tumors of the ovary may elaborate progesterone, estrogen, or ß-human chorionic gonadotropin (ß-hCG), exerting appreciable influence on the breasts. Conversely, metastasis of breast cancer to the ovary is well described, and at least 5% of ovarian malignancies are metastatic.[33]

Greatest attention is directed toward the pelvic bimanual examination to characterize tumor size, location, mobility, and tenderness. This examination can yield information regarding tumor surface and can differentiate a single mass extending across midline from bilateral masses that appear as one on radiologic evaluation. A rectovaginal examination should be performed to assess the pelvis for evidence of concomitant pathology such as myomas, endometriosis, and rectoanal disease.

Ultimately, few signs or symptoms are pathognomonic, and history and physical examination alone are often insufficient to make a conclusive diagnosis. Pelvic ultrasonography is a low-cost, noninvasive technique that reliably provides reproducible data, and is the recommended first step in radiologic assessment of adnexal masses. Strengths of ultrasound compared with computed tomography (CT) and magnetic resonance imaging (MRI) are greater availability, lower cost, ability to assess blood flow patterns, and improved resolution of both density and heterogeneity of masses. Traditional transabdominal ultrasound is increasingly giving way to the transvaginal approach because of improved resolution of gynecologic anatomy.

Ultrasonography is the most reliable means of ascertaining the density and heterogeneity of a mass, key determinants for the risk of malignancy. Individual cysts that are entirely simple have a low rate of neoplasia or cancer, whereas the presence of a solid mass or other nonsimple features, such as septations, nodularity, and excrescences, raises the possibility of neoplasia (Table 1).[6] Certain features, such as calcifications juxtaposed to fat in dermoid tumors, can be practically pathognomonic.[34] The presence and complexity of intraperitoneal fluid can also be assessed by ultrasound.

Because tumor growth is dependent on angiogenesis, many authors speculated that blood flow, measured by Doppler ultrasound, may be helpful in predicting malignancy. Poor reproducibility, high interobserver variability, and considerable overlap between normal and pathologic tissue limited the

TABLE 1. Ultrasound Characteristics of Adnexal Masses

Benign	Worrisome
Simple	Complex
Small	Septate
Unilocular	Partly solid
High pulsitility index	Low pulsitility index
Shrinking	Interval growth
	Ascites associated

usefulness of early Doppler studies. Internally corrected measurements of impedance such as the pulsitility index (PI) and resistance index were designed to standardize reporting. Some authors proposed that a high PI can exclude invasive carcinoma.[35,36] Problems with this technique are similar to those reported in the obstetric literature and include the need for high levels of expertise and subjectivity, and unknown effects of secondary conditions such as diabetes, hypertension, or pregnancy. At present, no data from comparative prospective trials indicate an increase in detection over transvaginal ultrasound. Furthermore, PI measurements frequently fail to differentiate between benign and nonneoplastic processes.[35]

Computed tomography is best suited to examine the abdomen primarily when metastasis is suspected. Magnetic resonance imaging is advocated by some, but in general provides information similar to that of CT at higher cost and with lower availability. The exception is in evaluating the pregnant patient, for whom efforts should be made to limit exposure to irradiation.[37,38]

Management

Pelvic masses in reproductive-age women can be broadly divided into two groups for the purpose of management: cystic and noncystic by ultrasound appearance. Masses that are entirely solid and those with both solid and fluid components are grouped together as noncystic. The simple cyst has no evidence of septations, nodularity (papillations), surface projections (excrescences), or associated pathology (ascites, bilateral lesions). Any of these features, or evidence of heterogeneity, should prompt management consistent with a noncystic mass.

Cystic Masses

In young women a single, simple cyst is traditionally observed through one to three menstrual cycles to allow for spontaneous resolution. Administration of oral contraceptive pills, as well as danazol, gonadotropin-releasing hormone analogs, and medroxyprogesterone, may expedite resolution of cystic and presumed functional cysts or endometriomas.[39,40] However, prospective studies failed to report improved outcome compared with expectant management.[39–42] In fact, between 50% and 90% of these lesions resolve without any intervention in less than two menstrual cycles. No adverse outcomes occurred when the observation period was prospectively extended to 6 months in a randomized study, but the authors failed to comment on the rate of resolution in later months.[43] Masses that are stable or increase in size over a period of weeks to months are unlikely to resolve spontaneously. Indications for intervention are as follows:

1. Size greater than 8 to 10 cm on two sequential scans performed at least 3 weeks apart
2. Growth on sequential scans
3. Pain or evidence of torsion
4. Worrisome family or personal history
5. Failure to resolve or size stable for more than 2 to 6 months
6. Patient desire for intervention
7. Incidental finding of cyst during surgery for another indication

Therapeutic options in the new millennium will range from minimally invasive procedures to traditional laparotomy. Percutaneous aspiration of cyst contents is reported to be effective for both diagnosis and primary therapy. Although it seems clear that it will provide symptomatic relief for many patients, its diagnostic and treatment benefits are suspect.[44] A poor correlation was seen between cytology and histology (sensitivity 25%, specificity 90%, false positive rate 73%, false negative rate 12%) even under optimal conditions.[45] Other studies support these results, finding similar low sensitivity and high false negative rates.[45–47] Some authors reported excellent detection rates of neoplasia by cyst aspiration; however, none demonstrated advantage over ultrasonography alone.[48] It should be noted as well that as many as 56% of aspirates may be devoid of diagnostic cells even in centers where this procedure is performed regularly.[45]

The therapeutic efficacy of cyst aspiration is controversial. Recurrence rates after aspiration range from 46% to 84%, comparable with those reported for observation alone.[43,49,50] Results improve with either tetracycline or alcohol sclerosis after aspiration of cyst contents, with success rates from 43% to 96%.[51,52] These reports are preliminary, and the number of subjects in all studies was small (Table 2). Long-term efficacy of postaspiration sclerosis, as well as its effects on fertility and ovarian function, is unknown with average follow-up much less than 1 year. The only randomized study comparing aspiration-sclerosis with expectant management failed to find a significant difference in outcome after 6 months.[43]

TABLE 2. Aspiration as Treatment of Ovarian Cysts

No. of Patients	Complex Cysts Included	Intervention	Follow-up (mo)	Success (%)
41[44]	Yes	Aspiration	1–24[a]	73
135[43]	No	Aspiration	6	46
143	No	Observation	6	45
31[49]	No	Aspiration	NR	16
25[51]	No	Aspiration, sclerosis	18	88
34[50]	Yes	Aspiration	12	47

[a]Only 30% had follow-up.

Any therapeutic advantage gained by cyst aspiration, with or without sclerosis, must be weighed against the risk inherent in treating a mass neither seen directly nor examined histologically. Spillage of malignant cyst contents is cause for upstaging in the FIGO system from Ia to Ic and is presently accepted as prognostically detrimental, especially if there is also a delay in intervention. Spillage of tumor contents may also be problematic in benign conditions such as pseudomyxoma peritonei and chemical peritonitis, which may follow rupture of a mucinous cystadenoma and teratoma, respectively. Additional risks are a 2% chance of infection and increase in pelvic adhesion formation.[53,54] This approach seems most valuable for patients with persistent functional cysts, those with several previous surgeries in whom laparoscopy may be impractical, and women who refuse surgical intervention. Although some authors advocate aspiration of endometriomas, we believe that, at this time, aspiration of any lesion that does not conform to the strictest criteria of simple has a limited role. The possible exception is in documenting recurrence of a known cancer.[53]

Laparoscopy

Management of cystic ovarian lesions is presently the third most common indication for laparoscopy and the fourth most common cause of inpatient admission to a gynecology service. Outcomes after laparoscopy for smaller cysts, usually less than 8 to 10 cm, are almost uniformly favorable.[8,55] Proponents argue that low likelihood of ovarian cancer does not justify more aggressive intervention. In addition, if a mass appears suspicious on direct observation, no evidence suggests that conversion to laparotomy at the time of initial surgery adversely affects prognosis. Laparoscopy is associated with shorter hospital stay, shorter time to ambulation, and fewer complications (Table 3).[9,55] Financial savings from these reductions are offset in part by increased operating times; however, substantial evidence supports a steep learning curve for laparoscopy, indicating that these times are likely to be reduced as experience grows and techniques become standard.[56,57]

Operative treatment options for benign-appearing cysts include biopsy, aspiration, cystectomy, and oophorectomy. In reproductive-age women, the role of oophorectomy is limited in lesions that appear of low risk by direct visualization. Most of these patients can be treated successfully with cystectomy or cyst drainage with biopsy when the cyst is functional. The largest series of laparoscopically managed adnexal masses in reproductive-age women reported that the most reliable indicator of malignancy is the combination of laparoscopic visualization and frozen section analysis.[55] In most studies, both sensitivity and accuracy (positive predictive value) of frozen section examination in detecting benign and malignant processes were above 92%.[14,58–60] Two exceptions to this high accuracy are tumors that are very large (usually >1000 mg) and those that have borderline features.[59,60] In these cases accuracy decreases as a function of sampling bias.

Principles of cancer surgery should apply to the treatment of benign-appearing cysts, as up to one third of malignancies appear benign;[61] that is, efforts should be made to prevent spillage of cyst contents. For larger cysts, excision from the ovary followed by rupture in an intracorporeal sac may facilitate removal without peritoneal contamination or additional incisions. Occasionally, however, simple-appearing cysts exceed the size of even largest intracorporeal safe devices. Excellent outcomes were reported in such cases when minilaparotomy or colpotomy was

TABLE 3. Success Rates for Treatment of Adnexal Masses by Laparoscopy in the 1990s

Design	No. of Patients	Median Age (yrs)	Exclusion Criteria	Completed Therapy (%)	Benign (%)
Prospective[127]	44[a]	58	Ascites, overtly advanced disease	95	98
Prospective[126]	220	30	Nonsimple, >10 cm, CA 125 >35 U/ml	99	100
Retrospective[65]	160	52	Overt CA, mass above umbilicus	89	82
Retrospective[9]	199	11–88	Known CA	95	98
Retrospective[11]	188	33	Evidence of CA	95	98
Prospective[10]	138[b]	52	Ascites, upper abdominal mass	92	86
Retrospective[4]	34[c]	57	None	88	74
Retrospective[8]	757	36	Suspicious for cancer, >8 cm	94	97
Retrospective[55]	1011	11–54	Upper abdominal mass	99	99
Prospective[12]	25	63	Nonsimple, CA 125 >35 U/ml	88	100

[a]All were postmenopausal.
[b]All had abnormal ultrasound or CA 125.
[c]All had previous nongynecologic cancer.

performed.[62,63] Alternatively, internal aspirators are effective in reducing these masses to sizes manageable with a normal-size intracorporeal sac, although a small risk of spillage of cyst contents persists.[55]

Noncystic Masses

The role of laparoscopy in the management of suspicious masses has been perhaps the most controversial subject in gynecologic surgery over the last decade.[4,5,7–13] According to the American Association of Gynecologic Laparoscopists, most clinicians advocate mandatory laparotomy for nonsimple masses.[3] They maintain that laparoscopy leads to delay in diagnosis and definitive surgical management, increased rupture of early-stage tumors, and increased frequency of skin metastasis at port sites. Each of these complications is postulated to effect prognosis adversely.

A survey of the Society of Gynecologic Oncologists concluded that 31% of malignancies had four of four benign characteristics (unilocular, unilateral, <8 cm in diameter, cystic), implying that laparoscopic visualization may fail to identify cancer in up to one-third of cases.[61] It was acknowledged, however, that preoperative assessment and selection process were arbitrary and that frozen section diagnosis was requested in "a minority of cases." Whereas it is unequivocal that cancerous masses, particularly those of low malignancy potential, can appear benign, we believe that this survey supports liberal performance of frozen section diagnosis, rather than arguing for uniform laparotomy. The only evidence that laparotomy may improve detection of malignancy comes from a report in which 31 of 42 women who underwent laparoscopic oophorectomy had residual disease at the time of staging laparotomy.[64] It should be noted that the conclusions of this study and the AGO survey were based on retrospective data and should therefore be interpreted with caution. Moreover, both studies reported significant deviation from the standard of care advocated by most laparoscopists.[5,10,55] For example, 75% of patients ultimately proved to have malignancy were thought to have malignant or suspicious disease at the time of laparoscopy but did not have conversion to laparotomy; frozen section diagnosis was again done in only 26% of cases, even when malignancy was a concern of the surgeon.[64] We believe that these reports reflect failure to proceed appropriately, rather than failure of therapeutic strategy.

Despite these reports, the rarity of malignancy prompted many surgeons to perform laparoscopy in the initial evaluation of selected adnexal tumors. For example, 11% of 228 masses considered preoperatively to be low risk had one or more features of malignancy intraoperatively; all 26 women were spared unnecessary laparotomy by obtaining frozen section diagnosis of the excised adnexa.[58] More than 85% of 160 suspicious adnexal masses were managed successfully using only modest exclusion criteria.[65] All authors stressed importance of preoperative counseling, availability of frozen section, and surgical expertise.

Cyst Rupture and Port Site Metastasis

Intraoperative rupture of an apparently stage Ia malignancy mandates upstaging to Ic by FIGO definitions, and a difference in survival was shown between these substages. Much support for upstaging is based on retrospective, poorly controlled studies using surgical and radiation therapies known to be suboptimal.[66,67] A multivariate analysis observed no impact on survival when rupture occurred in properly staged patients.[68] These findings were confirmed in a retrospective study of properly staged patients in whom 5-year survival, with or without rupture, was 76% for those with stage I disease with negative washings.[69] Furthermore, evidence is increasing that patients with intraoperative rupture may have a different, improved survival pattern compared with women with stage Ic disease resulting from spontaneous preoperative rupture or involvement of the ovarian capsule.[68]

Aspiration of cyst contents even after extirpation yields malignant cells in only 26% to 44% of cases, causing some to postulate that absence of impact of spillage may be related to cyst biology.[45,70,71] The hypothesis is that the degree of shedding of malignant cells within the cyst may reflect intraperitoneal shedding. This would also explain why patients with preoperative rupture or positive washings fare worse than those with rupture after negative washings.

Cyst rupture is rarely anticipated. When it does occur, copious irrigation may decrease the risk of both tumor spread and chemical peritonitis. Controlled prospective data are unlikely to become available on this subject, but irrigating with several liters of normal saline carries no overt risk if care is taken to minimize retained fluid. When cyst rupture is imminent, prophylactic decompression can prevent gross contamination of the peritoneal cavity. Masses should be placed in an intracorporeal sac when possible and ruptured with a suction-aspiration device. After decompression, the cyst contents can be removed; the remaining adnexa can be washed thoroughly without removing it or disseminating cystic contents.

Abdominal wall metastases, also called port or wound site recurrences, may occur after laparotomy or laparoscopy. They are often symptomatic and disfiguring, and may be difficult to treat. Retrospective studies typically report a frequency of less than 1% after laparotomy and from 1% to 16% after laparoscopy.[72,73] The frequency of wound recurrence is sufficiently rare that prospective data in humans are essentially nonexistent, making comparisons between laparoscopy and laparotomy difficult. Many hypotheses have been put forward for the apparent increase in the rate of recurrence at port sites, but none has been prospectively studied in humans, and there are few convincing data in animal models.[74,75] Whereas these data may support laparotomy to avoid abdominal wall recurrence, one should recall the relatively low prevalence of ovarian cancer. Assuming conservatively that 25% of high-risk pelvic masses are malignant, this implies that between 30 and 400 laparotomies would be required to avoid 1 recurrence.[76] Abdominal wall metastasis is even less likely when low-risk patients are included in the analysis. More important, there is no prospective evidence that port site metastases worsen prognosis. The only retrospective study of the subject failed to find a significant survival difference between patients with and without abdominal wall metastasis after adjusting for common confounders age, stage, grade, and residual disease after primary debulking.

Prepubertal Girls

Pelvic neoplasms are rare before menarche, with large pediatric referral centers typically reporting fewer than 10 cases annually. Historically, the frequency of neoplasia in the pediatric population with an ovarian mass was in the range of 55% to 65%.[77–79] With improvements in ultrasound technique, the frequency appears to be decreasing, with studies reporting between 3% and 33%. The apparent change is most likely related to improved detection of functional pathology.

Prepubertal patients often have relatively fast-growing tumors, which can be more clinically symptomatic than tumors in adults.[1] Initial management should focus on differentiating gynecologic from nongynecologic etiology. Symptoms may be nonspecific; however, signs such as vaginal bleeding and masculinization can be helpful in narrowing the difference. Germ cell tumors are the most common ovarian malignancy of childhood, and combined with tumors of the sex cord stroma account for over 90% of malignancies diagnosed in the neonatal and early childhood periods. Epithelial ovarian malignancy does not contribute significantly until perimenarche, when it becomes more common, but still accounts for only 20% to 30% of ovarian tumors.

As with adults, ultrasonography is the first step in the evaluation. Whether to perform it transabdominally, transvaginally, or transrectally depends on the patient's habitus, ability to comply, and clinical situation, although in most cases a transabdominal approach in infants and young girls is adequate.[80,81] An intravenous pyelogram may be performed to evaluate for concomitant pathology in the urologic system and for symptoms of ureteral compression, if the ultrasound result is consistent with neoplasia or malignancy. When mullerian anomaly is suspected as a cause of an adnexal mass, MRI provides improved resolution of aberrant pelvic anatomy.

Serum tumor markers of potential value are ß-hCG, α-fetoprotein, and CA 125. They are nonspecific, but certain patterns of elevation are commonly associated with germ cell tumors (Table 4). Return of serum markers to normal values may indicate successful treatment, and elevations in surveillance measurements are used to detect recurrence.

Surgical therapy in children is directed toward preservation of endocrine, reproductive, and sexual function. Frozen section analysis should guide management when possible. In the event of benign pathology, conservative surgery is the rule. When the best available evidence indicates containment of the malignancy to a single ovary, as is most common with germ cell tumors, unilateral salpingo-oophorectomy with preservation of the uterus and contralateral ovary is indicated. In these cases, a staging operation, including pelvic washings, omentectomy or omental biopsies, and sampling of pelvic and periaortic lymph nodes should also be performed.

Whereas cosmesis and preservation of a positive self-image are important for the preadolescent girl, performance of adequate cancer surgery to provide the best chance for survival is the primary mandate. Numerous reports describe laparoscopy in evaluating pediatric adnexal masses.[82–84] Most are retrospective series and few describe long-term follow-up. Applying evidence obtained from studies in adults, laparoscopy in adolescents seems reasonable when the lesion is small and preferably cystic, the surgeon is skilled in advanced operative laparoscopy, and the patient and family understand the possibility of conversion to laparotomy.

Detection of an adnexal mass in utero presents a problem for both obstetrician and surgeon.[85] Largely, these cysts result from transplacental exposure of the fetal ovary to maternal estrogen. Their natural history is not well described, but it appears that most resolve spontaneously after delivery with discontinuation of maternal estrogen exposure. Torsion of the fetal ovary has been reported, and there is at least one report of in utero intervention by percutaneous needle aspiration. Two risks of untreated adnexal torsion are infarction and disseminated intravascular coagulation, but they must be weighed against the possibility of iatrogenically induced labor, chorioamnionitis, or other fetal injury. Needless to say, surgical correction should be attempted by only the most skilled and experienced obstetricians.

Postmenopausal Women

Ovarian size decreases with time after menopause, even with hormone replacement.[86] The finding of an enlarged adnexa therefore requires immediate investigation. When surgery is indicated, standard operative approach is exploratory laparotomy to ensure adequate exposure for treatment of ovarian cancer.[28] Reports beginning in the late 1980s began to

TABLE 4. Serum Tumor Markers in Ovarian Germ Cell Malignancies

	Tumor Marker				
Neoplasm	CA 125	CEA	AFP	LDH	ß-hCG
Endodermal sinus	+	+/-	+	+	+/-
Immature teratoma	+/-	+/-	+/-	+/-	+/-
Dysgerminoma	-	-	-	+	-
Embryonal	-	-	+	-	+
Choriocarcinoma	-	-	-	-	+

CEA = carcinoembryonic antigen; AFP = α–fetoprotein; LDH = lactic dehydrogenase; hCG = ß-human chorionic gonadotropin.
- rarely or never; +/- possible; + usually or always.

question this strategy, observing that even populations selected for higher risk had uniform a propensity for benign lesions.[87,88] Concomitantly, availability and understanding of serum CA 125 were increasing. Numerous studies indicated that when ultrasound evaluation reveals a simple cystic structure and CA 125 level is normal (usually >35 U/ml), positive predictive value for benignity approaches 100%.[12,89] With similar exclusion criteria, one group advocated conservative management with serial ultrasound examinations in selected postmenopausal women.[90]

Although evidence has mounted to support laparoscopy as the primary treatment of low-risk lesions in postmenopausal women, even in patients thought preoperatively to be at high risk (elevated CA 125, nonsimple appearance on ultrasound), up to 75% of tumors were histologically benign.[10,65,89] At present only one prospective study evaluated laparoscopy performed without attempt to stratify patients preoperatively. A cohort of reproductive-age and postmenopausal patients (average age 52.2 yrs) with adnexal masses was studied, excluding only those with masses above the umbilicus or with evidence of gross metastatic disease on radiologic examination.[65] Nearly 90% of patients were managed successfully by laparoscopy without appreciable increase in morbidity. It is notable that all procedures in that study were performed by gynecologic oncologists.

Intraoperative management should proceed in a similar fashion whether laparotomy or laparoscopy is performed. If disease is not visibly disseminated, peritoneal and serosal surfaces are surveyed for evidence of metastatic disease. Washings are taken from diaphragms, paracolic gutters, and pelvis before additional surgical intervention. Unilateral adnexectomy can be performed when no additional disease is appreciated in the pelvis or abdomen. The entire adnexa should be removed intact, preferably in a surgical sac, and delivered for frozen section analysis. Cystectomy in the postmenopausal woman is unwarranted, as the risks of malignancy and prolongation of operating time invariably outweigh benefits of more conservative surgery.[27] A normal-appearing contralateral ovary in these patients should be removed according to preoperative consultation, medical and family history, and women's wishes when pathology is benign.

Preliminary data suggest that in selected early ovarian cancers, an experienced laparoscopist can perform complete endoscopic staging without compromising outcome.[10,65] Data on long-term outcome and comparative trials of endoscopic versus open staging are not available.

When extensive overt disease is present, resectability must be assessed. Laparotomy, hysterectomy, bilateral salpingo-oophorectomy, and staging with debulking should be performed when optimal cytoreduction is considered possible. If the intraabdominal tumor burden is believed not to be resectable at laparoscopy, tissue should be obtained for definitive diagnosis and laparoscopy discontinued. Neoadjuvant chemotherapy followed by secondary cytoreductive surgery (end staging) may decrease morbidity in this setting.

It is crucial that all women be counseled that definitive surgery at initial diagnosis of ovarian cancer imparts a distinct survival advantage. Unfortunately, the differential diagnosis of an adnexal mass in postmenopausal women must always include ovarian cancer. Thus, patients should uniformly give consent for debulking and staging to avoid misunderstanding between them and physicians.

Patients with Previous Nongynecologic Cancer

Periodically the clinician will be faced with an adnexal mass in a patient who was previously diagnosed with a nongynecologic malignancy.[91] The primary question in such cases is whether the lesion represents a metastasis, a new primary neoplasm, or a benign tumor. In 34 women in whom the a priori risk for cancer appeared high, 71% had nonmalignant pathology.[4] These data are supported by others.[65] Conversely, almost one-third of patients with this history will have malignancy, and some will be new ovarian primaries; expectant or medical management is therefore not an option.

Optimal preoperative evaluation of these patients is controversial. Serum CA 125 levels can be elevated in the presence of ovarian cancer; however, elevations are also seen in disease metastatic to the ovary and in benign lesions, leading to high false positive rates. The utility of ultrasound after the diagnosis of adnexal mass is also unclear. For example, nearly two-thirds of women with benign pathology had complex cystic masses on preoperative ultrasound.[4] Computed tomography may be of greater value in this setting because it allows for a more comprehensive metastatic evaluation. The presence of diffuse or nodal

disease should prompt evaluation by fine-needle aspiration, obviating the need for laparotomy or laparoscopy in some cases.

When fine-needle aspiration is not diagnostic or not appropriate, either laparoscopy or laparotomy must be performed. No prospective studies evaluated the relative risks and benefits of laparoscopy in this setting; however, retrospective reports indicate that first approaching these masses by laparoscopy decreases the number of laparotomies performed for benign disease.[4,65] This should translate to decreased morbidity and shorter hospitalization, although these benefits have yet to be reported convincingly.

Adnexal Masses in Torsion

Torsion of the uterine adnexa is a relatively rare cause of a painful mass resulting from twisting of the ovary, fallopian tube, or both. Strangulation of the adnexa by pedunculated paratubal or paraovarian cysts may mimic torsion clinically. Torsion is commonly a disease of reproductive-age women, but is not restricted to this group, with cases reported from before birth through the ninth decade of life.[92,93]

The diagnosis should be entertained in any woman with acute onset of lateralizing low abdominal pain. Often, the patient first experiences several episodes of intermittent sharp pain. Torsion is suggested when Doppler examination shows evidence of compromised blood flow to and from the adnexa. The positive and negative predictive values of Doppler are, however, unknown, and case series in the radiology literature are in general too small to allow for strong conclusions.[94–96]

Management should be guided by the desire to maintain fertility and hormone function. Since the first report of conservative management of ovarian torsion with untwisting, traditional treatment by laparotomy and salpingo-oophorectomy has slowly given way to less aggressive, adnexa-sparing therapies. In a review of over 100 cases of torsion, laparoscopy with conservative intervention (cystectomy, cyst drainage, untwisting) was employed in 20%.[93] Criteria for determining which adnexa to attempt to untwist are unclear, but success was reported in even black-bluish ovaries.[97]

Most torsed lesions arise in the setting of functional cysts or benign neoplasms. Historically, malignancy was reported in 1% to 28% of torsions, with most recent series reporting less than 1% to 2%. Embolic phenomenon, a theoretical risk attributed to detorsing, is exceedingly rare.[98] In fact, according to a review of nearly 1000 cases, embolism was noted in only 2, 1 each after excision and untwisting.[99]

Pregnant Women

Management of adnexal masses during pregnancy is among the most challenging in obstetrics. Ovarian masses in early pregnancy are common, but most resolve in the first trimester. Persistence of a mass occurs in about 1 in 500 pregnancies.[100,101] However, with increasing sensitivity of ultrasound, detection of incidental masses is certain to increase.

Pelvic masses in pregnant women are rarely malignant, with most series reporting that less than 5% of persistent adnexal masses are cancerous, and most of these are borderline tumors.[102–105] When diagnosed in the first trimester, the likelihood of functional etiology is high, as is the probability of spontaneous resolution. Given the high obstetric risk during this period of organogenesis, management in the first trimester is almost uniformly expectant when the clinical examination is benign or subacute.[106] Similarly, intervention in the third trimester is typically deferred until delivery, as the risk of delaying therapy rarely outweighs the risk of surgery to mother and fetus.[101,107] When necessary and feasible, surgery should be scheduled for the early portion of the second trimester, when organogenesis is complete and most spontaneous abortions have occurred, but before later risks of technical difficulties and premature labor.

The decision to operate must be tempered by understanding of the risks of intervention to both mother and fetus. Many physiologic changes occur during pregnancy that increase potential maternal morbidity both during surgery and postoperatively, especially as pregnancy progresses:

1. Increased oxygen demand
2. Decreased gastric motility and lower esophageal sphincter tone
3. Decreased venous return as a result of inferior vena cava compression
4. Inability to tolerate hypercarbia
5. Hypercoagulability
6. Increased blood flow to the pelvic organs
7. Distortion of pelvic and abdominal anatomy

In addition, risks of adverse perinatal outcome (preterm delivery, perinatal death) increase significantly when surgical intervention is performed in the late

second or third trimester.[101,107] In general, surgery is reserved for patients with acute symptoms (as with torsion), masses persistent or growing on serial scans, or tumors with solid elements.

Traditionally, pregnancy was considered a contraindication for laparoscopy, and when surgery was indicated laparotomy was uniformly performed. Since the early 1990s, however, well over 100 reports of successful laparoscopic surgery have been published (Table 5). Two reviews described favorable outcomes in 15 women treated by laparoscopy, and an additional 100 cases in the literature indicated no untoward effect on mother or fetus.[100,108] Future prospective data and large retrospective series are required to confirm these findings.

Theoretical disadvantages specific to laparoscopy are uterine trauma associated with port placement, increased exposure to carbon dioxide (CO_2), and the effect of increased intraabdominal pressure. None of these poses significant increased risks to mothers. Uterine perforation, although potentially horrific, remains essentially unreported. Open laparoscopy technique or use of alternative sites for initial port placement should keep this complication infrequent. Increased intraabdominal pressure may affect venous blood flow at the level of the umbilical vein, uterine vein, or vena cava, and thus affect maternal cardiac output. Animal models showed increased intrauterine pressure during pneumoperitoneum, which in turn was associated with fetal hypoxia, which may increase the risk of premature rupture of membranes.[109] These reports cannot be confirmed in humans using available technology.

Operating time is an indirect measure of fetal exposure to CO_2, inhalational anesthetics, and analgesics. Two of three case control studies comparing operating times for appendectomy and cholecystectomy during pregnancy found no significant difference between laparoscopy and laparotomy.[110–112] Median operating time was 37 minutes in six laparoscopic adnexectomies in the second trimester.[108] In addition to these exposures, decreasing operating times reduces risk of infection, frequency of deep vein thrombosis, and cost. Additional advantages of laparoscopy in the pregnant patient are prompt resumption of diet, decreased postoperative narcotic requirement, and shorter postoperative recovery and immobilization period compared with laparotomy, potentially yielding a decrease in the frequency of deep vein thromboses.

Fetal regulation of CO_2 is a highly gradient-dependent phenomenon; therefore, maternal hypercapnia could impede fetal down-loading of CO_2. Carbon dioxide pneumoperitoneum in the gravid ewe resulted in increased intrauterine pressure, decreased uterine blood flow, and maternal and fetal acidosis, although no deleterious effects on long-term fetal well-being were seen.[112] Preliminary evidence in humans, however, indicates that, with monitoring of end-tidal CO_2, operative laparoscopy has little effect on maternal blood gases.[113,114] A technique of gasless laparoscopy during pregnancy may obviate both

TABLE 5. Outcomes after Laparoscopy During Pregnancy

No. of Patients	Mean Gestational Age	Surgical Approach	IUFD, Miscarriage, Neonatal Death	Preterm Delivery	Malignancy Rate (%)	Converted to Laparotomy (%)
130[101]	18[a]	Laparotomy	3	12	6.1	
17[110]	14	Laparoscopy	0	0	0	0
18	14	Laparotomy	1	0	0	
19[125]	NR	Laparoscopy	0	1	0	11
11[111]	12	Laparoscopy	2	NR	NA	0
9	25	Laparotomy	0	NR	NA	
9[100]	14	Laparoscopy	0	0	0	0
6[108]	14	Laparoscopy	0	0	0	0
19[123]	NR	Laparoscopy	0	0	NA	16
18	NR	Laparotomy	0	0	NA	
15[124]	19	Laparoscopy	0	0	0	0
8	17[a]	Laparotomy	0	0	NA	

IUFD = intrauterine fetal death; NR = not reported; NA = not applicable.
[a]Estimated.

the problem of increased pressure and possible hypercapnia.[110]

We believe that in experienced hands laparoscopy is feasible, especially before 20 weeks' gestation. Preoperative management of pregnant women is similar to that for nonpregnant patients. They should be allowed no oral intake for a minimum of 8 to 12 hours, as gastric emptying is delayed in pregnancy. Positioning in the operating room includes left uterine displacement to maximize blood flow to the placenta and to decrease compression of the inferior vena cava. The primary laparoscopy port may be placed in midline at or above the umbilicus, depending on gestational age, or in the left upper quadrant. Secondary cannula sites are chosen based on the size and location of pathology. The decision to proceed by laparotomy or laparoscopy should be based on pathology, gestational age, surgeon's experience with advanced laparoscopic technique, and patient's body habitus.

Intraoperative manipulation of the uterus should be minimized, as trauma may predispose to premature labor, placental abruption, or rupture of amniotic membranes. Measurement of fetal heart rate during or after surgery is unnecessary in the previable fetus, although measurement of uterine activity may be useful in initiating tocolysis in all patients. Some measurement of uterine activity and fetal well-being should be performed after surgery in the viable fetus; however, no prospective studies are available to validate this recommendation. The patient must understand before intervention that fetal demise or miscarriage is always a risk.

When counseling a pregnant woman with a pelvic mass, the surgeon must relate that the likelihood of malignancy is low in nonsolid tumors, and that risks to the fetus include acute, severe effects such as abortion or spontaneous rupture of membranes, as well as subacute problems such as premature labor, infection, and possible transient hypoxia and hypercapnia. Maternal risks, as discussed, also should be made clear. In late pregnancy, the possibility of exploratory surgery at the time of delivery or during a planned cesarean section should also be discussed in advance.

Screening

Because prognosis in ovarian cancer is strongly linked to stage at discovery, efforts are constantly being made to improve early detection. Primary modalities include yearly physical examination, radiologic studies, tumor markers, and genetic screening. Whereas success has been reported with each modality, inconsistencies among studies are common, and there is still no accepted screening standard.[115]

The role of tumor markers seems bound to increase in the new millennium with new markers discovered at increasing rates. Whereas CA 125, the most commonly used marker, is expressed in more than 80% of nonmucinous epithelial ovarian cancers, levels are also elevated in cases of endometriosis, adenomyosis, fibroids, salpingitis, pregnancy, and normal menstruation. Elevated levels also result from nongynecologic pathology such as inflammatory or infectious peritonitis and hepatic and renal disease.[1] At present the only recommendation for CA 125 testing in premenopausal women is annual screening, starting at age 25 to 30, for women thought to be at high risk by family history or known to carry a mutation in the BRCA gene. In postmenopausal women incidental elevations of CA 125 are less common; however, sensitivity and specificity remain too low, in light of the low prevalence of the disease, to use the marker as an effective screening tool.[30]

Serum CA 125 level is most useful in the detection of recurrence in patients with diagnosed and treated ovarian cancer, in whom it facilitates detection at a median of 3 months before conventional noninvasive techniques.[116] There also is a role for α-fetoprotein, carcinoembryonic antigen (CEA), and ß-hCG in differentiation on follow-up of stromal and germ cell tumors. Serum ovarian cancer markers, such as CEA, α-fetoprotein, OVXI, inhibin, NB/70K, UGP, LPS, and CA 19-9, among others, have been used alone or in combination with CA 125 and ultrasound, but none has yet proved both cost-effective and accurate for screening.[117–119]

Screening protocols employing pelvic ultrasonography reported favorable and unfavorable detection of malignancy. These studies were plagued by relatively high cost and high false positive rates. Doppler flow may add accuracy to standard ultrasonography, but reports are inconsistent, likely owing to differences in technique and to wide overlap in values for malignant and nonmalignant tumors. Results of large-scale, prospective, randomized screening protocols in the last decade are summarized in Table 6. Unfortunately, given the low prevalence of cancer, detecting a beneficial effect from an imperfect screening process requires study populations in the tens of thousands.

TABLE 6. Prospective Screening Trials for Early Detection of Ovarian Cancer in the 1990s

Primary Modality	Secondary Modality	No. of Patients	Mean Age (yrs)	Sensitivity, Specificity	PPV (%)	Required Surgery	Cancer	Stage I Disease
CA 125[128]	TVS	10,958	>45	38, 99.6	21	29	6	3
TVS[130]	CA 125	6,470	>30[a]	86, 99	7	90	6	5
TVS, TAS[131]	Doppler	1,364	59	100, 88	<1	3[b]	1	1
PE, CA 125[122]	TVS	2,000	58	100, 99.7	6	34	2	2
PE, CA 125[120]	TVS	2,550	51	100, 99	6	17	1	0
TAS[121]	FNA	3,541	>50	100, 99.5	10	19	2	0
CA 125[129]	TAS	22,000	>45	58, 100	27	41	11	3

PPV = positive predictive value; TVS = transvaginal ultrasound; TAS = transabdominal ultrasound; PE = physical examination; FNA = fine needle aspiration.
[a]Several subpopulations.
[b]Two additional patients had ultrasound-guided cyst aspirations.

Conclusion

Management of adnexal masses in the twenty-first century will be most notable for a shift in paradigm from maximum intervention, with emphasis on avoiding undertreatment, to evidence-based management designed to minimize overtreatment without sacrificing principles of oncologic surgery. Intervention at progressively earlier points in the natural course of the process seems inevitable with improving methods of detection and evaluation. Ultimately we should be able to realize decreases in morbidity, mortality, and cost without compromising the care of patients with adnexal malignancy.

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