35 Neoplasia in pregnancy

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Cancer complicates approximately 1 in 1000 pregnancies (1). The Third National Cancer Survey found that 12.8% of all cancers in women occur during the reproductive years, and the three most common cancers in decreasing order of frequency are thyroid, cervical, and melanoma of the skin (2). The most common malignancies actually encountered during pregnancy include cervical, breast, and hematologic malignancies (3).

Malignancy in pregnancy is a rare and distressing condition, which requires consideration of mother and fetus. Specific issues that complicate medical management of malignancy in pregnancy include the possible benefits of pregnancy termination to allow aggressive treatment, the effect of therapy on the developing fetus, the timing of delivery or termination with ongoing treatment, and the role of altered immune and hormonal status during pregnancy, which may affect the prognosis of the coexistent cancer. Most malignancies in females occur outside the reproductive age group; therefore, there are few large studies that adequately examine these issues in detail. However, in reviewing the composite literature, several general guidelines have emerged. First, the anatomic and physiologic changes of pregnancy can obscure the signs and symptoms of early malignancy. Patient complaints are often dismissed as simply symptoms of pregnancy, thereby delaying the performance of timely examination and diagnostic studies. Second, although immunosurveillance may be altered in pregnancy, stage-for-stage prognosis and survival data for malignancy in pregnancy when properly treated are not significantly different than those for the nonpregnant population. Finally, the risk of an anomalous fetus resulting from treatment depends upon the gestational age of the fetus, as well as the mode and intensity of therapy. Many cancers arising during pregnancy can be treated aggressively with surgery, chemotherapy, and even radiation, without necessarily requiring therapeutic abortion.

GYNECOLOGIC MALIGNANCIES

The following section details the gynecologic malignancies by disease site. Staging for the major gynecologic malignancies is presented in Tables 1–5 (4). Overall, endometrial cancer has the highest incidence among gynecologic malignancies for all age groups, followed by cervical and ovarian cancers. The incidence of gynecologic malignancies in the reproductive age group is altered, as cervical cancer far outranks ovarian cancer while endometrial carcinoma is the rarest, unless one considers gestational trophoblastic disease (GTD) in this group. A brief outline of etiology, epidemiology, diagnosis, and treatment of each disease site is presented, with specific reference to pregnancy.

Human Papillomavirus/Warts of Lower Genital Tract

The human papillomavirus (HPV) is the causative agent of genital warts, is related to a variety of skin diseases in humans,

and plays a role in the tumorigenesis of a variety of malignant tumors of the head, neck, anus, and lower genital tract. The discovery of its predominant role in the development of cervical cancer has allowed the development of a variety of screening and prevention protocols. To date, more than 100 HPV types have been identified. The prevalence of HPV in pregnancy has been reported anywhere from 6% to 70% (5) with the highest prevalence in women under the age of 26. It has also been suggested that the pregnant state may activate HPV expression, the mechanism of which is unclear, but likely involves a change in the immune status of the mother. HPV is of concern during pregnancy for several reasons. First, although it remains unclear the frequency of perinatal transmission, consensus holds that neonates can be exposed to maternal cervical HPV during pregnancy and birth. Studies have shown HPV to be causally related to recurrent laryngeal papillomatosis in children (6,7). Maternal history of genital warts in pregnancy has been shown to be the strongest predictive factor for respiratory papillomatosis in the child (8). A second concern is that the papillary lesions can proliferate and cause soft-tissue dystocia or potential hemorrhage upon attempted vaginal delivery.

Treatment during pregnancy is problematic, but when the lesions are occluding, the introitus and/or vagina are large and friable, treatment with trichloroacetic acid, and rarely laser or cryotherapy, may be attempted. Podophyllin and interferon are contraindicated in pregnancy. Without adequate resolution of obstructive or hemorrhagic papillomas, cesarean section is indicated. When smaller lesions or subclinical infections are present, the decision as to the route of delivery can be problematic. Recent evidence suggests that perinatal transmission of HPV may not be avoided by abdominal delivery, since transplacental in utero infection may be possible with intact membranes (9,10). Additionally, there is a lack of concordance of HPV types detected in newborns compared with their mothers, suggesting other routes of transmission that may occur postnatally (11). Other theories include acquisition via semen at fertilization, hematogenously, or via an ascending maternal infection. Overall, further studies are required to elucidate the mode of transmission and the potential benefits of cesarean section delivery over vaginal delivery to avoid maternal–fetal transmission.

Recently, investigative work has focused on the development of HPV vaccines as primary prevention of HPV infections and the subsequent development of cervical cancer (12–15). At this time, a quadrivalent vaccine is approved and a bivalent vaccine is undergoing phase III clinical trials both for both primary prevention and therapeutic benefits (14,15). As both vaccines target HPV 16 and 18 strains, they could potentially prevent 70% of future cervical cancer cases. At this time, controversy still exists as to what age groups should

Table 1 International Federation of Obstetrics and Gynecology Staging of Vulvar Carcinoma (3)

Stage 0 Tis	Carcinoma in situ, intraepithelial carcinoma
Stage I T1 N0 M0	Tumor confined to the vulva and/or perineum—2cm or less in greatest dimension. No nodal metastasis
Stage II T2 N0 M0	Tumor confined to the vulva and/or perineum—more than 2cm in greatest dimension. No nodal metastasis
Stage III T3 N0 M0	Tumor of any size with
Stage T3 N1 M0	1. adjacent spread to the lower urethra and/or the vagina, or the anus; and/or
Stage T2 N1 M0	2. unilateral regional lymph node metastasis
Stage IVA T1 N2M0	Tumor invades any of the following:
Stage T2 N2 M0	Upper urethra, bladder mucosa, rectal
Stage T3 N2 M0	mucosa, pelvic bone, and/or bilateral
Stage T4 any N M0	regional node metastasis

Table 2 International Federation of Obstetrics and Gynecology Staging for Vaginal Carcinoma (3)

Stage 0	Carcinoma in situ, intraepithelial carcinoma
Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue, but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IB	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV
Stage IVA	Spread of growth to adjacent organs and/or direct extension beyond the true pelvis
Stage IVB	Spread to distant organs

receive the vaccine, what methods should be employed to implement international public health policies regarding its use, and as to what marketing strategies against a sexually transmitted infection would be acceptable. Furthermore, these vaccines are currently contraindicated during pregnancy, and long-term data are necessary to evaluate their impact on overall mortality.

Cervical Neoplasia

The most common gynecologic neoplasia encountered during pregnancy arises from the cervix, including both invasive and preinvasive diseases. Although the mean age of diagnosis for carcinoma of the cervix is 50 years, this disease process has a bimodal peak incidence with age ranges of 35 to 39 years and 60 to 64 years (16). Clearly, this early peak corresponds with the reproductive age group. The incidence of preinvasive and invasive cancer of the cervix is estimated to be 1.3 and 0.45 to 1.0 per 1000 pregnancies, respectively (17).

Preinvasive Disease

Cervical intraepithelial neoplasia (CIN) arises in the transformation zone between squamous-lined ectocervix and columnar-lined endocervix and has a peak age in the mid to late

Table 3 International Federation of Obstetrics and Gynecology Staging for Cervical Carcinoma (3)

Stage 0	Carcinoma in situ, intraepithelial carcinoma
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
Stage IA	Preclinical carcinoma of cervix; that is, those diagnosed only by microscopy
Stage IA1	Minimal microscopically evident stromal invasion
Stage IA2	Clinical lesions detected microscopically that can be measured; depth 65mm from the base of the epithelium, either surface or glandular, from which it originates and horizontally spread
Stage IB	Clinical lesions confined to the cervix of preclinical lesions greater than IA
Stage IB1	Clinical lesions no greater than 4.0cm in size
Stage IB2	Clinical lesions greater than 4.0cm in size
Stage II	Carcinoma extends beyond the cervix, but not to pelvic wall. The carcinoma involves the vagina, but not as far as the lower third
Stage IIA	No obvious parametrial involvement
Stage IIB	Obvious parametrial involvement
Stage III	Carcinoma has extended to the pelvic wall or tumor involves the lower third of the vagina. Hydronephrosis or nonfunctioning kidneys are stage III, unless due to other causes
Stage IIIA	No extension to the pelvic wall
Stage IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
Stage IV	Spread of growth to adjacent organs (i.e., bladder or rectal mucosa)
Stage IVA	Spread to distant organs
Stage IVB	Spread to distant organs

Table 4 International Federation of Obstetrics and Gynecology Staging for Endometrial Carcinoma (3)

Stage IA, G123	Tumor limited to endometrium or invasion to less than one-half of the myometrium
Stage IB, G123	Tumor invasion to more than one-half of the myometrium
Stage II	Cervical stromal invasion
Stage IIIA, G123	Tumor invasion of serosa and/or adnexa
Stage IIIB, G123	Vaginal metastases
Stage IIIC1	Metastases to pelvic lymph nodes
Stage IIIC2	Metastases to para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IVA	Tumor invasion of bladder and/or bowel mucosa
Stage IVB	Distant metastases, including intra-abdominal and/or inguinal lymph nodes
Stage G1	5% or less of a non-squamous or non-morular solid growth pattern
Stage G2	6–50% of a non-squamous or non-morular solid growth pattern
Stage G3	>50% of a non-squamous or non-morular solid growth pattern

twenties. Over recent years, the integral role of that HPV plays in the genesis of CIN and subsequent transformation into malignant cells has been further elucidated. The progression of CIN to invasive disease does not appear to be accelerated by

Table 5 International Federation of Obstetrics and Gynecology Staging for Ovarian Carcinoma (3)

Stage I	Growth limited to ovaries
Stage IA	Growth limited to one ovary; no ascites present containing malignant cells; no tumor on external surfaces; capsule intact
Stage IB	Growth limited to both ovaries; no ascites present containing malignant cells; no tumor on external surfaces, capsule intact
Stage IC	Tumor involving one or both the ovaries either with tumor on external surfaces, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both the ovaries with pelvic extension
Stage IIA	Extension and/or metastases to uterus and/or tubes
Stage IIB	Extension to other pelvic tissues
Stage IIC	Tumor either stage IIA or IIB, but with tumor on surface of one or both the ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage III	Tumor involving one or both the ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. (Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.)
Stage IIIA	Tumor grossly limited to the true pelvis with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
Stage IIIB	Tumor of one or both the ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter; negative nodes
Stage IIIC	Abdominal implants greater than 2cm in diameter; negative and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both the ovaries, with distant metastasis. (If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.)

pregnancy, despite the possibility that pregnancy represents an immunocompromised state and may even activate HPV infections. As in the nonpregnant state, the screening method of choice for CIN is the Papanicolaou test, which should be performed at the first prenatal visit. Although not approved by the manufacturer for use in pregnancy, studies have shown that use of the standard cytobrush is safe and effective during pregnancy and can be routinely employed when obtaining cervical cells for evaluation. Although the pregnant cervix differs from the nonpregnant cervix with the appearance of greater inflammation, larger ectropion, and the presence of decidual cells (Arias-Stella reaction) that mimic atypical cells, evidence demonstrates that the accuracy of the Pap test in pregnancy remains unchanged. LaPolla and colleagues (18) reported a cytologic and histologic concordance rate of 84% in 248 pregnant patients with abnormal Pap tests who underwent

colposcopically directed biopsies and found no false-negative results after rigorous postpartum follow-up. Furthermore, in pregnancy, the transformation zone is expanded and, as such, a Pap test obtained during pregnancy that lacks endocervical cells should be repeated.

Abnormal Papanicolaou Results

The management of an abnormal cervical Pap test is a clinical dilemma often encountered during pregnancy. The algorithm for management of an abnormal Pap test is shown in Figure 1. Key points include that HPV triage of a Pap test showing atypical squamous cells of undetermined significance is acceptable in pregnancy. However, colposcopy may be deferred until the 6-week postpartum visit. Similarly, women with a result of a low-grade squamous intraepithelial lesion (LSIL) on Pap test may also defer colposcopy until the postpartum period. Those women who do undergo colposcopy antenatally and receive a histologic diagnosis of CIN I should have follow-up postpartum without any further treatment. To do otherwise is considered unacceptable. Patients with a high-grade squamous intraepithelial lesion by Pap test have a 1 in 100 chance of an invasive lesion. Most will have persistence of the high-grade lesion on postpartum follow-up without progression. Colposcopy with directed biopsies during pregnancy is recommended and should be performed by an experienced clinician. A result of atypical glandular cells on a Pap test in pregnancy should be managed in a fashion identical to that of a nonpregnant woman except that endometrial biopsy and endocervical curettage are contraindicated, and cold-knife conization is not advisable unless invasion is otherwise suspected. Postpartum evaluation may be negative as a high-grade lesion may commonly resolve after delivery. However, a thorough postpartum evaluation is necessary to determine whether the lesion is still present. Of note, patients with normal Pap tests but who are HPV positive for high-risk strains should have repeat testing 6 weeks postpartum as HPV infections are often transient during pregnancy.

Diagnostic Procedures in Pregnancy

In determining which diagnostic and therapeutic interventions to utilize for the assessment of an abnormal Pap test in pregnancy, maternal risk in the form of underdiagnosed invasive cancer, and thus inadequate or delayed treatment, must be balanced against fetal risk, in the form of premature rupture of membranes, chorioamnionitis, and spontaneous abortion from conization. As mentioned earlier, conservative management should be exercised with low-grade cervical lesions as these patients are highly unlikely to have an invasion lesion on pathologic examination (19). Additionally, Patsner (20) used serial evaluation of the Pap test, colposcopy, and directed biopsy to rule out occult or new malignancy in a large group of pregnant patients with mild dysplasia; the conclusion of this study was that patients with mild dysplasia require at most one antepartum colposcopy prior to thorough postpartum reevaluation, without significant increased risk of developing invasive cervical cancer. Some authors now suggest that it is neither cost-effective nor necessary to perform colposcopy on every patient with LSIL on Pap test (19). Advocacy of conservative management assumes that

Figure 1 Algorithm for the management of the abnormal Pap smear and cervical intraepithelial neoplasia (CIN) in pregnancy. Abbreviations: AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells favoring high grade; ASC-US, atypical squamous intraepithelial lesion of undetermined significance; HR-HPV, high-risk human papillomavirus testing; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade SIL. Source: From Ref. 42.

colposcopy is performed by an experienced operator, while cytology and histology are reviewed by a reliable laboratory. If these standards are not met, more frequent colposcopy and closer follow-up are probably necessary. Colposcopy with biopsies should always be performed for high-grade lesions and any lesion on repeat examination that appears to have progressed or is suspicious for invasive carcinoma.

Colposcopy During Pregnancy

The pregnant cervix is actually quite amenable to colposcopy, as the transformation zone tends to evert as pregnancy progresses and allows for optimal colposcopic visualization of the cervix. However, given the changes that occur within a gravid cervix compared with the nonpregnant state, it is imperative that the colposcopy be performed by a skilled physician with experience and training in advanced colposcopy. Colposcopic appearance of the pregnant cervix is highlighted by edematous and hyperemic changes secondary to increased vascularity and an underlying decidual stromal reaction. Increased friability with brisk bleeding upon cervical contact may be encountered during pregnancy and, if persistent, is an indication for evaluation. Acetic acid staining is often more intense during pregnancy, causing some minor abnormalities to be interpreted falsely as significant lesions. Nonetheless, aceto-white areas, especially those that have more opaque changes with mosaicism, punctuation, or frankly atypical vessels, deserve histologic evaluation by biopsy. Any gross lesion and the worst representative abnormal areas by colposcopic visualization should be biopsied regardless of gestational age unless delivery is imminent, whereby biopsy may be delayed up to several weeks. Cervical biopsy during pregnancy may cause increased bleeding, which is generally well controlled by silver nitrate sticks, ferric sulfate solution, or, rarely, suture placement. In a series of 100 pregnant

patients, Hacker and associates (17) reported a diagnostic accuracy of 99.5% and a complication rate of 0.6% for colposcopy with biopsies. No endocervical curettage should be performed on any patient with known or suspected pregnancy. The overall goal of a thorough colposcopic cervical examination in pregnancy is to exclude invasive disease, thus averting unnecessary conizations and allowing safe postponement of ablative therapy for CIN, including carcinoma in situ, until after delivery. Thus, the treatment of all forms of CIN in pregnancy is conservative, with required follow-up postpartum. It is imperative that all patients with histologically proven CIN 2 and 3 antenatally have repeat colposcopy with biopsies at the 6-week postpartum visit.

Large Loop Excision of the Transformation Zone

Inadequate colposcopic visualization of either the transformation zone or the entire proximal extent of a lesion is generally delayed during pregnancy and performed postpartum. In addition, endocervical curettage is not performed during pregnancy; thus, the primary indications for excisional procedures during pregnancy are histologic microinvasive disease or marked discordance between a Pap test suggestive of carcinoma and a histologic specimen with minimal abnormalities. Every effort should be made to reconcile such discordance by review of the cytologic interpretation and even repeat colposcopic biopsies to avoid unnecessary excisional procedures during pregnancy. Overall, a diagnostic excisional procedure should be considered only if the cytology, colposcopic impression, or cervical biopsies are suspicious for invasive carcinoma only. Treatment during pregnancy is otherwise unacceptable. When excision by large loop excision of the transformation zone (LLETZ) is required, it is best performed in the first or early second trimester when the risk of spontaneous abortion and bleeding from the increased

vascularity of the cervix are reduced. Current evidence demonstrates mixed results in regard to the impact of LLETZ on risk for premature rupture of membranes, preterm labor, and cesarean section (21–23). As such, it is considered acceptable to perform LLETZ with reasonable maternal safety if indicated. However, it should be performed by an experienced surgeon and ideally during the previable stage of pregnancy and when invasive cancer is highly suspected. These procedures should always be performed in the operating room with sufficient appropriately trained staff.

Cone Biopsy During Pregnancy

Averette and coworkers (24) collected the largest series of conizations during pregnancy with 180 patients and reported that 9.4% required a blood transfusion and 63% underwent a spontaneous abortion. Others have described less frequent but significant complications associated with cone biopsy in pregnancy, including cervical infection, stenosis, chorioamnionitis, preterm labor, thrombophlebitis, pulmonary embolism, and cervical laceration during labor. In an attempt to minimize bleeding and violation of the endocervical canal, DiSaia and colleagues (16) and others (25) have advocated excising a shallow “coin”-shaped biopsy rather than a “cone”-shaped specimen. Multiple hemostatic sutures can be placed at the vaginal reflection of the cervix and a vasoconstrictive agent can be used to infiltrate the cervical stroma in an attempt to decrease blood loss. Overall, the standard cone biopsy is not recommended during pregnancy due to the high complication rate associated with its use.

The so-called coin biopsy has been described as a safe method for performing diagnostic conization during pregnancy (26). The biopsy shape is usually smaller and shallower, resulting in an increased risk of residual disease with positive margins. The compilation of seven studies by Hacker and colleagues (17) showed 43.4% of cones for carcinoma in situ have residual disease upon repeat conization or hysterectomy. As such, this technique is considered diagnostic rather than therapeutic.

Invasive Cervical Carcinoma

More than 40% of cervical cancer cases occur in women of childbearing age, and up to 3% of all cases of cervical cancer are diagnosed during pregnancy (27–29). The incidence of invasive disease varies from 1 to 13 cases per 10,000 pregnancies (16,17). Pregnancy is not thought to play an etiologic role in the development of cervical carcinoma, since the age-adjusted incidence is the same in pregnant as in nonpregnant women. Despite increases in estrogen and progesterone levels, the natural history of cervical cancer is likewise unaffected by pregnancy, as the prognosis is the same in pregnant and nonpregnant patients (16,17,30). Precise survival data by stage for pregnancy complicated by invasive cervical carcinoma are difficult to ascertain, because more than 15 series reported a span greater than 30 years and their treatment, as well as staging, vary (31). Nonetheless, stage-for-stage, 5-year survival rates are the same for pregnant and nonpregnant patients, with rates approaching 100% for stage IA, 85% for IB, and 60% to 70% for stage II using aggregate data from more recent studies (17,32,33). The average age of patients with cervical cancer in pregnancy is 30 years, while the average parity is four, but neither variable has been shown to

Table 6 Cervical Carcinoma Associated with Pregnancy

	Trimester				Total	Average
	First	Second	Third	Postpartum		
Time of diagnosis	19.3	14.2	14.9	51.6	100	N/A
5-year survival	68.6	62.7	51.7	46.3	N/A	51.3
Stage						
IB	64.3	60.6	50.0	46.5	N/A	55.4
II	28.0	30.8	20.7	29.4	N/A	27.2
III/IV	7.7	8.6	29.3	24.1	N/A	17.4

Abbreviations: N/A, not applicable. *Source:* From Ref. 9.

be of prognostic value (17). Table 6 shows the breakdown by trimester (stage and 5-year survival) in cases of cervical cancer associated with pregnancy. Highlighted is the trend of decreased survival and increased likelihood of advanced stage at presentation as pregnancy progresses. Selection bias may influence the data. Patients who defer prenatal care and present later in pregnancy, or even during delivery, are more likely to ignore early symptoms of cervical cancer and not comply with regular cytologic screening. The distribution of histology is similar to the nonpregnant state; 95% or more are squamous cell carcinomas and 3% are adenocarcinomas.

The cornerstone of detection remains the Pap test. Biopsy is the requisite for diagnosis. Vaginal bleeding or abnormal discharge is the most frequent presenting symptom. Early-stage disease is often asymptomatic, but advanced disease may present with symptoms of urinary retention, pelvic pain, lymphedema, or weight loss. Once the diagnosis is made, thorough staging should be performed and may include cystoscopy, proctoscopy, and sigmoidoscopy. Imaging studies should be used judiciously; magnetic resonance imaging (MRI) may be the study of choice, as excellent soft-tissue delineation is obtained without ionizing radiation. Positron emission tomography (PET) imaging has newly recognized value in both the pretreatment and posttreatment management of nonpregnant cervical cancer patients (34–41). However, as the side effects the radioisotope required for the study may have on the developing fetus remains unclear, PET is considered contraindicated at this time during pregnancy. Single-exposure intravenous pyelography can be used and renal ultrasound may also be of value. Cervical malignancies tend to be understaged during pregnancy, because proper workup is oftentimes not performed and parametrial induration may be less prominent and more difficult to detect (32).

Although cervical cancer is not uncommonly found during pregnancy, the data regarding its treatment are limited secondary to the unique ethical considerations surrounding pregnancy that prevent many research methods. Treatment for invasive forms of cervical carcinoma depends on the stage of pregnancy and disease, as well as upon the wishes of the mother. It is also important to remember that most preinvasive lesions found during pregnancy do not progress and that oftentimes both high-grade lesions and low-grade lesions will regress during pregnancy and delivery to either low-grade lesions or normal appearance, respectively. As such, it is necessary to procure histologic confirmation of invasive carcinoma whenever feasible.

Treatment recommendations during pregnancy should be modified to the individual characteristics of the tumor and the patient's desires, and should involve multidisciplinary input. A thorough ultrasound should also be preformed to rule out any fetal anomalies that could influence treatment choice. In general, the patient may be offered the same standard of treatment outlined for all nonpregnant cervical cancer patients with the understanding that only treatment of very early lesions allows future fertility, and significant fetal risks are involved that would require termination of the pregnancy. However, some suggest that other treatment options exist based on a lower level of evidence (42). The limit of 20 weeks of gestation is often used as a cutoff for deciding treatment timing, with termination and immediate treatment reserved for a confirmed gestational age of less than 20 weeks.

Microinvasive tumors confirmed by conization are considered to be either stage IA1 or IA2 with invasion less than 3mm below the basement membrane and negative margins, no greater than 7mm of lateral spread and the absence or presence of lymphovascular space involvement as defining criteria. Previous data exist exploring fertility-sparing treatment in nonpregnant patients with microinvasive disease and demonstrates low incidence of recurrence with conization (43–45). However, rarely is an excisional conization procedure currently recommended during pregnancy given the high rate of complications. If conservative treatment is desired, it should be reserved for those patients with stage IA1 disease and squamous cell histology. Conservative treatment would involve repeat cytology and colposcopy to exclude regrowth of the tumor after conization is indicated (17). Patients with stage IA2 cervical cancer are not considered to be the candidates for the same fertility-sparing excisional procedures offered to IA1 patients. Outside of pregnancy, standard of care is radical hysterectomy. These patients may be offered the aforementioned purposeful delayed management strategy versus pregnancy termination with immediate treatment. New data in the literature also offer the possibility of radical trachelectomy as a new fertility-sparing treatment option in this particular group of patients (46). If treatment is delayed until after delivery, route of delivery should be based primarily on obstetric indications. If cesarean section is indicated, a cesarean extrafascial or radical hysterectomy can be performed at delivery. Close postpartum follow-up without surgery is advocated by some when future childbearing is desired in selected patients with minimal microinvasive disease (16).

Frankly, invasive tumors of the cervix demand prompt treatment, although slight delay of up to 6–8 weeks has been shown not to alter prognosis (17,33). For stage IB1 and selected IIA tumors early in pregnancy, treatment options include radiation therapy and chemotherapy or radical hysterectomy with bilateral pelvic lymphadenectomy. Surgery does allow ovarian preservation, but the patient should be counseled prior that certain risk factors could lead to adjuvant radiation or chemotherapy. This option can be effective therapy with the fetus in situ up to 18–20 weeks (47); thereafter, hysterotomy and uterine evacuation should be performed. Radiation is equally efficacious, and no hysterotomy is necessary prior to 20 weeks of gestation with radiation therapy. In general, spontaneous abortion occurs rapidly after exposure to radiation in early pregnancy (48,49).

Some authors now recommend using misoprostol to promote expulsion of the pregnancy if it does not occur within an expected time frame to avoid further complications. If the pregnancy is advanced, hysterotomy is required prior to intracavitary radiation. For IB and IIA tumors found in the third trimester, classical cesarean section can be followed by radical hysterectomy with pelvic and para-aortic lymph node dissection. If radiation is planned, lymph node dissection alone can be performed, which may guide subsequent therapy.

With cervical cancer beyond stage IIA, radiation is the treatment of choice with chemosensitization now being routinely performed with radiosensitizing chemotherapy (50,51). Commencement of treatment is immediate, with the exception of late second- or third-trimester pregnancies when treatment may be delayed until after the documentation of fetal pulmonary maturity and delivery. It must be emphasized that the impact of treatment delay on maternal and fetal health is uncertain. Overall evidence suggests that some amount of delay is reasonable without greatly affecting maternal outcome (49,51–59) and allowing potential small but significant gains in fetal outcomes. The literature suggests that prognosis is unchanged over many weeks and patients can be counseled as such allowing the opportunity to delay treatment if so desired. Clearly, these patients must be closely followed for any evidence of disease progression.

In patients with advanced-stage cervical cancer who strongly desire delay of treatment, neoadjuvant chemotherapy is considered a reasonable option. Limited data suggest that platinum agents in association with either bleomycin or paclitaxel when administered in the second and third trimesters appear to have no fetal toxicity or long-term sequelae (60–62).

Route of delivery has not been shown to be of prognostic significance. Recent studies suggest that there may be a slight advantage to delivery by cesarean section (63–66). However, at this point, choice of route should be based on obstetric indications, extent of cervical tumor involvement, and therapy planned. In general, early lesions allow for vaginal delivery if otherwise indicated, while advanced disease favors abdominal delivery because of the risk of cervical laceration and hemorrhage or infection. Additionally, it is important to note that vaginal delivery through a malignant cervix has been associated with cancer implantation and recurrence at previous episiotomy scar sites (67–75).

Vulvar Carcinoma

Carcinoma of the vulva represents only about 4% of gynecologic malignancies and is quite rare in pregnancy, because the vast majority of vulvar malignancies occur in postmenopausal patients. Approximately 15% of vulvar cancers are found in women less than 40 years of age. Of these, about 90% of the cases are squamous cell cancers. Other cell types include melanoma, adenocarcinoma, basal cell carcinoma, and sarcoma. Presenting symptoms are similar to those of the nonpregnant state and include itching, irritation, discharge, and occasionally bleeding. The etiology of vulvar cancer is unknown, but common patient characteristics include obesity, diabetes, hypertension, and perhaps less-than-optimal vulvar hygiene. Recent evidence suggests that HPV infection is a causative or associative factor in preinvasive

vulvar intraepithelial neoplasia as well as in invasive vulvar cancer. Examination of the vulva will demonstrate areas of ulceration, exophytic growth, hyper- or hypopigmentation, or red or white discoloration. The key to early diagnosis is biopsy. All abnormal areas of the vulva, including raised, depressed, discolored, or warty lesions, deserve consideration for biopsy. Biopsy may be performed in the office under local anesthesia by simple excision or by utilizing the Keyes punch biopsy instrument. Toluidine blue staining and colposcopy may be used as adjunctive procedures, but should not substitute for biopsies, even in lieu of pregnancy.

A review of pregnancy-associated vulvar cancers in the literature by Barclay (76) revealed only 31 reported cases. Since this review, several other small series have been added. The youngest reported patient was 17 years old, while the average age was 27. Such a small number of patients presenting with vulvar carcinoma during pregnancy limits the development of guidelines for prognosis and treatment; nonetheless, certain conclusions can be drawn. Prognostically, these patients appear to do as well stage-for-stage with proper treatment as their nonpregnant counterparts. Treatment for vulvar intraepithelial neoplasia should be conservative with multiple biopsies to rule out invasion and then close follow-up, including colposcopy, until definitive therapy can be carried out postpartum. Invasive disease should be treated as in the nonpregnant state during the first and second trimesters, with radical or modified radical resection and groin node dissection. Lesions less than 2 cm in diameter and with invasion of 1 mm or less that are confined to the vulva with no evidence of nodal involvement may be considered for radical local excision. Bilateral or multiple ipsilateral positive groin nodules require adjunctive radiation to the groin and pelvis. Even if radiation is given after the period of organogenesis, the risk of spontaneous pregnancy loss is great. Thus, depending on the wishes of the patient, radiation treatment may be delayed until after delivery (3,77). Alternatively, in this unusual circumstance, consideration may be given to a pelvic node dissection, which, if negative, might allow omission of pelvic irradiation. Positive or close margins of resection, while also treatable with radiation, may be considered for re-excision during pregnancy to avoid the deleterious effects of radiation.

Invasive lesions presenting late in pregnancy (third trimester) may be widely excised and definitive treatment delayed until after delivery. These patients must be informed that these alternative forms of therapy during pregnancy deviate from the standard of treatment and may carry an increased risk of recurrence. The route of delivery is generally not altered by treatment, including radical vulvectomy and groin node dissection. Marked vaginal constriction and perineal fibrosis rarely necessitate cesarean section delivery. After treatment for vulvar cancer, there is no contraindication to future pregnancies. Past studies have showed successful pregnancies following treatment for vulvar carcinoma, with surgery-pregnancy intervals ranging from 6 months to 4½ years (76,78).

Vaginal Carcinoma

The occurrence of vaginal cancer has limited demographic overlaps with the reproductive age group, as the vast majority of cases are diagnosed in patients beyond 50 years

of age (25). Less than 2% of gynecologic malignancies are of primary vaginal origin. Metastatic disease from the cervix or vulva is far more common and must always be excluded. Up to 95% of cases are of squamous cell origin, while melanomas, sarcomas, and adenocarcinomas, including clear cell histologies, are also found.

The incidence of squamous cell carcinoma of the vagina during pregnancy is very rare, with fewer than 20 reported cases (1). Symptoms of vaginal cancers are bleeding or discharge. More advanced disease may present with symptoms of bladder or bowel dysfunction, including frequent urinary tract infections, urinary retention, constipation, or tenesmus. While a persistently abnormal Papanicolaou (Pap) smear may rarely provide initial evidence of vaginal cancer, thorough speculum examination with biopsy of suspicious gross lesions provides definitive diagnosis. Preinvasive disease, vaginal intraepithelial neoplasia, which is far more common than invasive disease in the pregnant population, is best diagnosed with the use of colposcopic-guided biopsies. If biopsy confirms preinvasive disease, treatment with laser, 5-FU, or other ablative therapy can be postponed until completion of the pregnancy.

In the exceptional event that invasive cancer of the vagina is discovered during pregnancy, treatment is generally unaltered, except possibly during the late second or third trimester, when postponement of treatment until after delivery may be considered. Therapy is dependent upon the location and stage of disease, but the primary mode of treatment is radiation. Surgery is a viable option when early-stage disease is confined to the upper one-third of the vagina and is thus resectable with radical hysterectomy and upper vaginectomy. Disease localized to the distal portion of the vagina has been reported as resectable with lower vaginectomy. Utilizing radiation or surgery, fetal loss is inevitable. However, there is one case report of stage I squamous cell carcinoma of the vagina treated by wide local excision at 23 weeks (79). The patient then underwent cesarean section at 33 weeks with pelvic lymphadenectomy and a second wide local excision with no evidence of recurrence.

Surgery allows preservation of ovarian function in this young population with postoperative radiation indicated only for close or positive margins (80). Advanced-stage disease of any histology requires prompt treatment, which may necessitate hysterotomy for removal of products of conception, thus allowing initiation of radiation therapy. It is important to note that even in patients with early-stage disease (I–II), the risk of pelvic lymph node metastases is high (20–35%) (81).

Several histologic types of vaginal cancer, although rare, tend to occur more commonly than squamous cell carcinoma in women of reproductive age. Adenocarcinoma, usually of the clear cell variety, may develop after in utero exposure to diethylstilbestrol. The link between diethylstilbestrol exposure and clear cell adenocarcinoma of the lower genital tract, including the cervix, was well established by 1971, after which the use of diethylstilbestrol during pregnancy was discontinued. The risk of developing adenocarcinoma of the vagina or cervix is actually less than 1 in 1000 for those exposed to the transplacental carcinogen diethylstilbestrol. Approximately one-third of diethylstilbestrol-exposed patients develop adenosis, which may be a precursor to clear cell

carcinoma. Such diethylstilbestrol-linked malignancies rarely occur before 14 years of age or after 30 years of age. Thus, frequent cervical and vaginal cytology with careful colposcopic evaluation for abnormal findings are indicated beginning at menarche. Most clear cell adenocarcinomas are diagnosed early (stage I) and thus have a good prognosis with an 80% 5-year survival. In pregnancy, treatment is largely unaltered, as surgery is performed without fetal regard, unless in the final trimester, in which case delay until after delivery may be contemplated.

Melanomas are very rare as primary tumors of the vagina. The lower posterior one-third of the vagina is the most frequent site of origin. Sarcoma botryoides of the vagina generally occurs in infants and children and presents as a group of cystic masses. The occurrence of both vaginal melanomas and sarcomas is exceedingly rare and reportable in pregnancy. Both tumors have a very poor prognosis, and management must be individualized according to the stage of disease, desires of the patient, and gestational age.

Endometrial Carcinoma

Endometrial carcinoma in pregnancy is extremely rare. There are fewer than 10 well-documented cases in the world literature and great care is necessary to exclude misdiagnosis secondary to an intense Arias-Stella phenomenon. Diagnosis is usually made at dilatation and curettage for spontaneous or therapeutic abortion. Treatment is unaltered by pregnancy.

Ovarian Neoplasia

Adnexal/Pelvic Mass

Pelvic masses in pregnancy present difficult management problems, because one must also consider the fetus as well as the patient. Therefore, the proper treatment of this problem is not always clear and requires clinical judgment. Pregnancy complicated by a pelvic mass has been reported with an incidence varying from 1 in 79 pregnancies to 1 in 2489; the average of 21 publications in the literature is 1 in 800 (82–103). The wide range of reported incidences is likely due to different detection methods, study populations, and types of masses reported. Of those publications, approximately 1 in 16,000 pregnancies is complicated by a malignant adnexal mass.

Prior to the advent of ultrasound, fibroids, ectopic pregnancies, appendicitis, and pelvic kidneys were frequently included in the diagnosis of pelvic mass. These entities are now diagnosed more accurately with ultrasound, avoiding unnecessary laparotomy (104–106). In general, simple, unilateral ovarian masses smaller than 5cm during the first trimester are usually functional luteal cysts and oftentimes will resolve on ultrasound by 14 weeks of gestation. Those adnexal masses that are bilateral, greater than 5cm, growing rapidly or persisting into the second and third trimesters, with solid, septate, or multicystic components need further imaging and/or evaluation (107). Bernhard et al. showed that out of 423 adnexal masses found in pregnancy, only 25 persisted and were surgically treated of which 2 were confirmed malignancies by histologic diagnosis. Ultrasound has been shown to be less accurate in characterizing malignant lesions (102). As such, MRI is useful for follow-up imaging on patients with concerning adnexal masses

initially identified by ultrasound (108,109). Computed tomography should probably be avoided during pregnancy.

It is important to note that most masses found during pregnancy are benign (110). Only up to 5% of pelvic masses during pregnancy are malignant versus 20% in the non-pregnant state (16). The most common masses found during gestation are serous or mucinous cystadenoma, mature teratoma, or a miscellaneous array of simple cysts, fibroids, and theca luteal cysts. Masses over 15cm identified during pregnancy are seldom malignant (111–113). Of malignant pelvic masses found during pregnancy, the most common are germ cell tumors (45%), epithelial tumors (37.5%), sex cord-stromal tumors (10%), and other pathologies (7.5%) (114).

Masses discovered during pregnancy can be managed expectantly or surgically. Expectant management is frequently complicated by acute rupture, torsion, tumor previa, or malignancy. Grimes (115) reported that these complications occurred most commonly when masses were greater than 5cm. Acute rupture or torsion resulting in an acute abdomen occurred in 34% of patients expectantly managed. Tumor previa occurred about 5% of the time, while malignancy occurred only in about 4.5% of cases. Surgical management seeks to avoid these complications and removes the mass under more controlled and less emergent conditions. If possible, surgery should be postponed to 16 to 18 weeks, as this timing is associated with a reduced risk of spontaneous abortion, hormonal independence of the corpus luteum of pregnancy, and the resolution of functional cysts.

Ovarian Cancer

Although rare, ovarian malignancies are the second most common gynecologic cancer diagnosed during pregnancy after cervical cancer (116). They are usually found as an incidental finding during routine prenatal care via ultrasound (117–119) and, as such, are generally found at an earlier stage than in nonpregnant women (116,117,120). Once a malignant adnexal mass is suspected, extensive preoperative discussion with the patient and family is required prior to laparotomy, and management should be multidisciplinary in conjunction with a high-risk obstetrician, gynecologic oncologist, and medical oncologist specialized in gynecologic cancers. If a malignancy is found, the patient should be staged and treated as if she were not pregnant. Pelvic washings should be obtained, extent of disease be assessed, and appropriate surgery be performed. Conservative surgery to preserve fertility and the current pregnancy is attempted where appropriate. However, the patient may always alter her treatment based on her desire to preserve the fetus. Of note, ovarian tumors do not spread to the fetus, in contrast to certain other malignancies.

Germ cell tumors, both benign and malignant, occur primarily in young women (121). The two most common malignant types are dysgerminomas and endodermal sinus (yolk sac) tumors. As dysgerminomas are the most common malignant germ cell tumors and most often occur in young women, it is not surprising that they are the most common malignant adnexal mass found in pregnancy. Approximately 10% to 15% of dysgerminomas occur bilaterally. A review of 27 reported cases of dysgerminomas reported all patients presented with large-size tumors ranging from 12 to 28cm and most were stage IA (122). Because of their large size, obstetric

complications have been reported in association with dysgerminomas including obstructed labor and cesarean section (122). Surgical treatment is required as an initial management for all patients regardless of pregnancy status. Oftentimes, if appropriate, surgery will be postponed until 16 to 18 weeks when the risk for spontaneous abortion is minimized (83,123). Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and of the uterus is adequate for early-stage disease of both germ cell and epithelial cancers.

Treatment of more advanced stages is controversial. It has been suggested that if the uterus and other ovary appear free of metastatic disease, then adequate staging can be performed with omental and peritoneal biopsies and sampling of suspicious lymph nodes (122). Biopsy of the contralateral ovary is recommended only if it seems to be affected by disease (124). Ipsilateral lymph node dissection may be considered as this is the most common site of first metastases. Adjuvant chemotherapy is considered unnecessary for stage IA and possibly stage IB, as the risk for recurrence is low, and there is a high cure rate for recurrent disease (123,125). Of note, serum lactate dehydrogenase levels are unaffected by pregnancy and can be used for initial diagnosis and follow-up response to treatment.

Endodermal sinus tumors comprise approximately one-fifth of the ovarian germ cell tumors and are the second most common (126,127). They are much less frequently encountered during pregnancy, but may be suspected when a serum alpha fetoprotein level is much higher than expected. Treatment for these tumors is more aggressive as the 5-year survival rate is only 13% (128). The best treatment strategy is early surgical resection followed by multiagent adjuvant chemotherapy. Adequate surgical treatment can also be achieved usually with the preservation of the contralateral ovary and uterus. The most common chemotherapy regimen used consists of bleomycin, etoposide, and cisplatin (BEP). There are several reports of pregnant women treated with combination chemotherapy who delivered normal infants (122). However, fetal complications have been reported as well (129). Some suggest that, if the mother desires, chemotherapy can be postponed until after early delivery with confirmed fetal lung maturity (130).

Ovarian epithelial tumors are rare in pregnancy as they are usually a disease of the elderly. They are categorized into three groups: benign, borderline, or invasive cancer. Borderline tumors or low malignant potential tumors are a disease of younger women and are more likely to be encountered in pregnancy. Standard of treatment for invasive cancers is upfront surgical cytoreduction followed by adjuvant chemotherapy. Unfortunately, this surgical approach precludes continuation of pregnancy. There have been reports in the literature of patients with invasive epithelial ovarian tumors of at least a stage III who underwent initial unilateral salpingo-oophorectomy with the completion of the surgical debulking postponed until after the delivery of the fetus (122,131–133). These women received platinum-based chemotherapy during pregnancy. All infants were delivered without any gross abnormalities or significant complications. One woman died of recurrence 29 months later, and others were disease free with follow-up periods ranging from 6 to 36 months. Overall,

management must be discussed with the patient with the understanding of the limited evidence in regard to the delay of treatment. The overall prognosis for advanced-stage ovarian cancer is low at approximately 30% at 5 years (134).

Borderline tumors are distinguished from their invasive counterparts by the histologic findings of papillary epithelial proliferation and atypia, but lack of stromal invasion (135,136). Treatment is primarily surgical. However, given their favorable prognosis, surgery to preserve fertility can oftentimes be achieved. Adjuvant chemotherapy is usually given only in the presence of confirmed invasive implants and, as such, can frequently be avoided during pregnancy.

Other less commonly found ovarian cancers include sex-cord stromal tumors. These tumors usually present with abdominal pain, torsion, and increased abdominal girth. Most patients are diagnosed with stage I disease and require only conservative surgical intervention due to their low-malignant potential. In cases of more advanced disease, adjuvant chemotherapy should be considered and usually consists of BEP (137–141). Another tumor rarely found in pregnancy is carcinosarcoma of the ovary also known as a “malignant mixed mesodermal tumor.” The prognosis is poor even with aggressive treatment (142,143) and only three cases have been reported in the literature (144–146). Given the aggressive nature of carcinosarcomas and the fact that an optimal debulking procedure at the time of initial surgery is an important determinant of future outcomes, there is no role for conservative surgery in their management plan (147). Lastly, metastatic tumors to the ovary are always a consideration in the differential for malignant adnexal masses. They are not uncommon and the most frequently identified primary sites include colon, breast, and gastric cancers (123,148). Treatment is based on the type of primary malignancy and is usually individualized based on different factors such as histologic type, gestational week, and the patient’s wishes.

In general, several principles can help guide the management of ovarian malignancies in pregnancy. Hysterectomy should be performed during pregnancy only if it contributes significantly to tumor debulking (116,149) and overall prognosis. Additionally, chemotherapy is contraindicated in the first trimester due to high rate of abortion (150) and abnormal fetal development (151), but it is compatible in the second or third trimester (150,152). Platinum-based chemotherapy regimens have the most scientific data supporting their safe use in pregnancy (153). An interval of 3 to 4 weeks between the last chemotherapy administration and the delivery is optimal due to both maternal and fetal hematologic risks from treatment (3). The majority of adverse fetal outcomes are likely due to prematurity with few reports of congenital anomalies (150,154,155). In the postpartum period, breast-feeding should be discouraged while receiving cytotoxic agents (156,157). As always, treatment strategy must be case dependent, and the patient must remain fully informed at all times.

GTD

The term “gestational trophoblastic disease” comprises a wide variety of pathologic entities, from the benign hydatidiform mole to the highly malignant choriocarcinoma. Hydatidiform mole has been observed since the era of Hippocrates.

Table 7 International Federation of Obstetrics and Gynecology Prognostic Scoring System for Gestational Trophoblastic Neoplasia

Risk factor	Score ^a			
	0	1	2	4
Age	<39	>39		
Prior pregnancy	Mole	Abortion	Term	
Interval (months) ^b	4	4–6	7–12	>12
Pretreatment hCG (log)	<3	<4	<5	>5
Largest tumor (cm)	<3	3–4	≥5	
Site of metastases		Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases	0	1–4	5–8	>8
Prior failed chemotherapy agents			Single	Multiple

^aPrognosis is determined by summing the scores for each individual factor. Total score <7=low risk, >7=high risk. ^bInterval is the time between the termination of prior pregnancy and the start of chemotherapy. *Abbreviation:* hCG, human chorionic gonadotropin.

Richardson and Hertig provided the first account of a hydatid mole in 1638, while in 1827 the midwife Bolvin was the first to ascribe moles as products of gestational origin. In 1895, Felix Morchand finally demonstrated that hydatidiform moles and their malignant sequelae derived from trophoblast, but his concept was not widely accepted until 1903 (158,159).

Trophoblast may be regarded as the first organ of the developing embryo. Normal trophoblast is a unique tissue that bears several characteristics of cancer. Among these is the ability to invade the myometrium and to embolize into the maternal circulation. Whether the trophoblast is normal or neoplastic, it contains both syncytiotrophoblast and cytotrophoblast and secretes human chorionic gonadotropin (hCG) in proportion to its volume. This fact allows clinicians to monitor this disease and predict eradication of trophoblastic tissue from the host (160).

Abnormal trophoblastic proliferation is manifested in two entities: partial and complete hydatidiform mole. The complete mole consists of abnormal trophoblast of paternal origin with a karyotype of 46,XX. This entity presents with abnormal bleeding 95% of the time between the 6th and 16th week gestational age. Other manifestations of molar gestation include pre-eclampsia, hyperemesis, and hyperthyroidism. Rarely, patients can present with trophoblastic embolization and symptoms of congestive heart failure or pulmonary edema. hCG levels are usually markedly elevated above those appropriate for the gestational age of the pregnancy. The diagnosis is generally made with ultrasound. Histologically, complete hydatid moles are characterized by hydropic villi, proliferation of both syncytiotrophoblast and cytotrophoblast, absence of fetal vessels, and no definitive fetal structures (161,162).

By contrast, the diagnosis of partial mole is usually made at the time of curettage for a presumed missed or incomplete abortion. The clinical features are similar to those of a complete mole, but less severe. In addition, partial moles are usually of polyploid karyotype and associated with fetal structures.

The incidence of complete hydatidiform mole varies throughout the world from a high of 1 in 450 in Japan to 1 in 2500 in the United States (163). These data are based on population-based studies. The treatment of choice for a complete mole is suction curettage. Blood products, such as packed red blood cells, should be made available preoperatively,

Table 8 International Federation of Obstetrics and Gynecology Staging of Gestational Trophoblastic Neoplasia

I Disease confined to the uterus
II Disease extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
III Disease extends to the lungs with or without genital tract involvement
IV Disease involves other metastatic sites
(1) <i>Good prognosis</i>
(a) Serum hCG <40,000 mIU/mL (random) or urinary hCG <100,000 IU (24 hr)
(b) Symptoms present less than 4 months
(c) No brain or liver metastases
(d) No prior chemotherapy
(e) Prior pregnancy: a mole or abortion of ectopic pregnancy
(2) <i>Poor prognosis</i>
(a) Serum hCG >40,000 mIU/mL (random) or urinary hCG >100,000 IU (24 hr)
(b) Symptoms present more than 4 months
(c) Brain or liver metastases
(d) Failure of prior chemotherapy
(e) Antecedent-term pregnancy

as blood loss can be unexpectedly high. Furthermore, a substantial risk of post-evacuation pulmonary edema from trophoblastic deportation or rapid fluid replacement is possible. The incidence of malignant sequelae of complete moles is about 15%. The incidence of malignancy following a partial mole is much less. All moles require careful follow-up with weekly hCG levels. A rising level or one that plateaus requires immediate attention to staging and initiation of cytotoxic therapy (164,165).

The malignant sequelae of molar gestation, categorized as gestational trophoblastic neoplasia (GTN), include invasive mole, choriocarcinoma, and placental site trophoblastic tumors. The prognosis for these entities is excellent, exceeding 90%, with proper treatment. Patients diagnosed with GTN are categorized into risk groups based on the International Federation of Obstetrics and Gynecology (FIGO) staging and scoring system (166,167) (Tables 7,8). The scoring system is based on a modified version of the World Health Organization (WHO) prognostic factor scoring system. Once malignant trophoblastic disease is diagnosed, staging studies consisting of computed tomography scans of the head, abdomen, and

Table 9 Chemotherapy Regimens for Low-Risk Gestational Trophoblastic Neoplasia

1	MTX, 0.4mg/kg (maximum 25mg)/day, IV or IM for 5 days. Repeat every 14 days
2	MTX, 30–50mg/m ² , IM weekly ^a
3	MTX, 1mg/kg, IM days 1, 3, 5, and 7; folinic acid, 0.1mg/kg, IM days 2, 4, 6, and 8. Repeat every 15–18 days or as needed
4	MTX, 100mg/m ² , IVP, then 200mg/m ² in 500mL of D ₅ W over 12 hours. Folinic acid, 15mg IM or orally every 12 hours for four doses beginning 24 hours after starting MTX. Repeat every 18 days or as needed ^a
5	Act-D, 10–12µg/kg, IV every day for 5 days. Repeat every 14 days
6	Act-D, 1.25mg/m ² , IV every 2 weeks ^a
7	Alternating MTX/Act-D regimens 1 and 5

^aShould not be used for metastatic or resistant disease or choriocarcinoma. Abbreviations: Act-D, actinomycin-D; D₅W, 5% dextrose in water; IM, intramuscularly; IV, intravenously; IVP, intravenous push; MTX, methotrexate.

Table 10 Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine Chemotherapy for High-Risk Gestational Trophoblastic Neoplasia

Drug		Dosing
Day 1	Etoposide	100mg/m ² IV over 30 min
	Actinomycin-D	0.5mg IVP
	Methotrexate	100mg/m ² IVP, then 200mg/m ² in 500mL of D ₅ W over 12 hours
Day 2	Etoposide	100mg/m ² IV over 30 min
	Actinomycin-D	0.5mg IVP
	Folinic acid	15mg IM or orally every 12 hours for four doses starting 24 hours after starting MTX
Day 8	Cyclophosphamide	600mg/m ² IV
	Vincristine	1.0mg/m ² IVP

Abbreviations: D₅W, 5% dextrose in water; IM, intramuscularly; IV, intravenously; IVP, intravenous push; MTX, methotrexate.

pelvis, serum chemistries including liver and renal function studies, and quantitative beta-HCG need to be performed. A chest X-ray is mandatory. Computed tomography of the chest may identify low-risk patients who are likely to fail primary single-agent therapy (168). Cure for patients with non-metastatic (stage I) and low-risk metastatic GTN (stages II and III, score<7) disease approaches 100% in published studies (167). Patients classified as having high-risk metastatic GTN should receive multiagent chemotherapy plus adjuvant radiation or surgery to achieve survival rates of 80% to 90% (Tables 8,9). Of note, prior reports from the Brewer Center in Chicago, Illinois, have demonstrated the importance of having centralized trophoblastic disease centers to provide expertise in managing these patients. They noted that their successful secondary GTN treatment rates increased from 59% during 1962 to 1978 to 93% from 1979 to 2006 (169). They also noted that the most common reasons for unsuccessful GTN

treatment were using single-agent chemotherapy for high-risk disease and inappropriately using weekly methotrexate to treat patients with metastatic disease, FIGO scores ≥ 7, and/or non-postmolar choriocarcinoma. This highlights the importance of adhering to the FIGO staging and scoring system to administer chemotherapy regimens accordingly (Tables 9 and 10).

NONGYNECOLOGIC MALIGNANCIES

Breast Cancer

One in nine women will develop breast cancer during her lifetime, representing one-third of all cancers in women (170). Approximately 15% of breast cancers occur in women under the age of 41 years; 1 in 3000 pregnancies is complicated by breast cancer, with 3% of all breast cancer being diagnosed during pregnancy or lactation (1). The incidence of breast cancer in association with pregnancy is expected to continue to rise, owing to the trend toward delayed childbearing. It currently is the second most common malignancy diagnosed in pregnancy after cervical cancer (171).

Breast engorgement and hypertrophy during pregnancy may delay the detection of breast cancer. Some cases of inflammatory cancer, as well as some masses, can be confused with mastitis or other pregnancy-related changes. Most cases present with a painless lump often noted by the patient upon self-examination. If the woman is breast-feeding, she may note a “milk rejection sign” in which the infant refuses the breast affected by cancer (172). The initial prenatal visit should include a thorough breast examination with detailed instructions on breast self-examination.

More recent studies report an average delay in diagnosis of 1 to 2 months (173–177) although older studies noted delays of 6 months or greater (178–180). A 1-month delay in primary tumor treatment increases the risk of axillary metastases by 0.9% and a 6-month delay increases the risk by 5.1% (181). The presence of axillary metastases is a poor prognostic factor, and early detection despite pregnancy is essential.

Mammography should be limited during pregnancy to minimize radiation exposure. In addition, pregnancy changes, such as elevated water density, increase the rates of false-positive and false-negative mammographic examinations (182). Ultrasound is a recommended, good, inexpensive first step in the workup of a breast mass as it can distinguish between cystic and solid lesions in 97% of patients (175,176,183). For the diagnosis of metastases, MRI is preferred to ultrasonography especially for hepatic and brain imaging (184,185). Of note, gadolinium used during MRIs crosses the placenta, is associated with fetal abnormalities in rats, and its use during pregnancy should be limited to those cases where the benefits outweigh the risks to the fetus. Radioisotope bone scan, generally avoided during pregnancy, may be indicated only when metastases are clinically suspected. Adequate maternal hydration may increase fetal exposure to radiation.

For definitive diagnosis, any palpable mass should be biopsied. Stopping lactation beforehand reduces the risk for milk fistula formation. Fine-needle aspiration (FNA) has a specificity and sensitivity of about 95%, and no harmful effects upon the pregnancy have been reported (186). However, the accuracy of FNA is highly dependent on the pathologist’s experience with pregnancy-associated breast cancer and is

important to avoid a misdiagnosis of hyperproliferative changes (185,187). If FNA is unsuccessful, open biopsy, preferably under local anesthesia, is performed. Core needle biopsy may also be a more cost-effective method as studies in nonpregnant women have shown it to also have a high sensitivity and specificity (188–191).

In the nonpregnant state, wide local excision with axillary node dissection and radiation is the preferred treatment for small unifocal masses. This alternative is less attractive during pregnancy, as radiation with boost doses to the tumor bed would cause internal scatter, resulting in fetal radiation exposure above acceptable levels (186). As such, mastectomy with axillary node dissection is traditionally the procedure of choice for stage I or II disease during pregnancy, as nodal metastases are commonly found in pregnancy-associated breast cancers, and the procedure may eliminate the need for postoperative irradiation. Treatment may be modified by delaying radiation until after delivery if the diagnosis is made in the late second trimester or beyond, while carrying out lumpectomy and axillary dissection during pregnancy at the time of initial diagnosis.

Patients with either node-positive disease or node-negative disease, but tumor greater than 1 cm, should receive 4 to 6 months of chemotherapy. If the woman is far from term, breast-conserving surgery can be followed by chemotherapy after the first trimester and irradiation after delivery (185). Chemotherapy is usually withheld until the second trimester, as at least half of infants have no complications when their mothers are treated after the first trimester (150,192–194). The most common side effects of chemotherapy during pregnancy are preterm delivery, low birth weight, transient infant leukopenia, transient tachypnea of the newborn, and intrauterine growth restriction. Long-term effects of chemotherapy on the newborn are unknown.

Advanced disease calls for careful individualization of treatments. Delay of palliative treatment until achievement of fetal viability is a reasonable option when the diagnosis is made late in pregnancy. Otherwise, aggressive palliative treatment should be instituted without delay. Such treatment, which includes radiation, multiagent chemotherapy, and hormonal therapy, separately or in combination, poses considerable risk to the fetus. If such advanced disease is diagnosed early in pregnancy, termination may be considered. Therapeutic abortion does not appear to enhance maternal remission or survival in early-stage disease; however, it does allow for prompt initiation of therapy in advanced disease.

Prognosis for pregnancy-associated breast cancer has been traditionally deemed dismal based on early reports. More recent studies have shown that the prognosis for breast cancer, stage-for-stage, is unchanged by pregnancy. Prognosis is most influenced by maternal age with 5-year survival rates of 75% for women over 40 years of age, but only 55% for those under 40 years of age (195,196). Pregnancy-associated breast cancer tends to present at later stages with twice the rate of lymph node involvement (74% vs. 37%), even when controlled for age (195). This worse prognosis may be due to delayed diagnosis and treatment of pregnant patients. In addition, pregnancy-induced hormonal changes may alter the behavior of tumors. Over 70% of women with pregnancy-associated breast cancer had estrogen-receptor-negative tumors thought

to be secondary to the downregulation of receptor status during pregnancy (195).

The traditional recommendation to wait 2 years after breast cancer treatment prior to a subsequent pregnancy is arbitrary as little scientific evidence exists in regard to this topic. The prognosis, both maternal and fetal, appears unaltered by subsequent pregnancy (196). However, some data now show that those women who do establish future pregnancies tend to demonstrate a “healthy mother effect” with better 10-year survival rates (197,198). A recent large population-based study of over 10,000 women demonstrated a reduced risk of dying in women who had a full-term pregnancy subsequent to breast cancer treatment (199). There was no evidence that a pregnancy after treatment for breast cancer has a negative influence on prognosis. Overall, future pregnancies appear to be safe unless the mother has an ER-positive cancer that has not been cured (197, 200, 201, 202). By contrast, there have also been studies evaluating the prognosis of a new breast cancer diagnosed after a pregnancy (203,204). The authors suggest that a new diagnosis of breast cancer within 2 years of a prior pregnancy is associated with decreased survival. The negative effect no longer persisted if the diagnosis was made greater than 10 years after the last pregnancy (204).

Colorectal Carcinoma

Colorectal carcinoma (CRC), one of the leading causes of cancer death in females, occurs only in 1 in 50,000 to 1 in 100,000 pregnancies, with approximately 300 total reported cases. Most originate distally below the level of the peritoneal reflection (205,206). The mean age of diagnosis is 32 years (207). CRC represents a serious threat not only to the mother, but also to the fetus as one prior study showed that only 25 of 32 women diagnosed with CRC during pregnancy went on to have healthy live born infants (208). Additionally, CRC is uncommon in young women and, when diagnosed within this age group, is oftentimes associated with predisposing factors such as hereditary nonpolyposis CRC (Lynch syndrome), familial adenomatous polyposis, Gardner syndrome, and chronic history of ulcerative colitis (209).

Presenting symptoms include constipation, obstipation, abdominal pain, rectal or abdominal mass, rectal bleeding, nausea, and vomiting. Many of these signs and symptoms represent common complaints of normal pregnancy and therefore a delay in diagnosis until it has progressed to advanced-stage disease is common. Rectal bleeding of guaiac-positive stool is an alarming symptom, which requires full evaluation. Routine digital examination should be performed during prenatal evaluation. Distribution of lesions appears to be similar to that in the nonpregnant population, with 57% arising in the rectum, 20% in the sigmoid colon, and 23% in the remainder (207).

Workup of a colorectal lesion normally requires colonoscopy with biopsy, a serum carcinoembryonic antigen level, and abdominal imaging (210,211). However, little data exist for colonoscopy during pregnancy and is still considered experimental. As such, risks and benefits should be fully disclosed to the patient and oftentimes only a partial colonoscopy will be performed to confirm the diagnosis while minimizing risk. Barium enema should be avoided if possible. Levels of the serum tumor marker, carcinoembryonic antigen, are generally

Table 11 Dukes Staging for Colorectal Carcinoma

A	Penetration into, but not beyond, the bowel wall
B	Penetration through the bowel wall
C	Positive lymph node involvement
D	Distant metastasis

not affected in normal pregnancy and provide prognostic value (212,213). In regard to abdominal imaging during pregnancy, ultrasonography or MRI is the modality of choice.

Treatment during the first two trimesters is generally immediate surgery with limited regard for the pregnancy, although frequently the pregnancy is unharmed if cancer had not metastasized to other pelvic structures. Even distal tumors may be resected with primary re-anastomosis using automatic staplers and abdominoperineal or low anterior resection procedures. If optimal resection is prevented by the gravid uterus, hysterectomy may at times be necessary; such a possibility must be addressed with the mother prior to surgery. If tumor is not resectable, diverting colostomy for decompression and palliation is the treatment of choice to allow the pregnancy to progress toward term. During the third trimester, one can await fetal maturity and perform cesarean section with subsequent tumor excision or diverting colostomy, depending on the extent of the disease. If the tumor is discovered near term, vaginal delivery may be considered, provided that tumor is not obstructing the pelvic outlet. With advanced-stage and surgically unresectable tumor identified at any stage of pregnancy, consideration may be given to awaiting fetal maturity, thus delaying palliative treatment until after delivery (207). Irradiation for colorectal cancer during pregnancy has a limited role due to the colon’s close proximity to the uterus, with no evidence of prolonging survival. Chemotherapy is recommended for Dukes C and D CRC. Several studies have shown a survival advantage if chemotherapy is administered within 5 weeks of resection of Dukes C CRC (213). Recently, research into new chemotherapeutic agents has also demonstrated survival benefits for Dukes D CRC (213).

Pregnancy has not been shown to affect maternal prognosis or the natural source of colorectal cancer. The prognosis of pregnant women with CRC is dismal likely due to its delayed diagnosis. There are no reported 5-year survivors for colon cancer. Few with rectal carcinoma are reported, owing to the advanced stage at presentation. Over one-half of pregnant patients with CRC present with Dukes stage C or a more advanced stage (see Table 11 for staging) (206) and 25% of pregnant women with CRC have ovarian metastases compared with 3% to 8% in nonpregnant women (214,215). Theoretically, the estrogen-binding capacity of cells derived from CRCs may indicate accelerated cancer growth during pregnancy. However, survival data between pregnant and nonpregnant patients are comparable stage-for-stage. Information regarding fertility after CRC is limited and has focused on those cancers treated with 5-fluorouracil. The general consensus is to wait at least 1 to 2 years before pursuing a subsequent pregnancy to allow the body sufficient time to recover.

Melanoma

Melanoma represents 1% of all cancers diagnosed in the United States, with approximately 30% occurring in women of

reproductive age (216). It complicates pregnancy with an estimated incidence of 0.14 to 2.8 cases per 1000 pregnancies (217). In general, incidence rates have increased dramatically over recent decades in the United States (218) and, as such, could increase the incidence rates during pregnancy.

The majority of patients present with a change in the size and color of a preexisting nevus. More advanced melanomas may present with ulceration and bleeding. Excisional biopsy of the entire suspicious pigmented lesion is the diagnostic procedure of choice. Microscopic measurement of the actual tumor thickness, as outlined by Breslow, most accurately reflects the prognostic index and is of utmost importance in the clinical management of patients (219). The Clark level, which describes the anatomic level of invasion, should also be assessed. Following histopathologic evaluation of the biopsy, the patient should be clinically staged with a thorough history and complete physical examination. The most common clinical staging system defines stage I as local disease without clinically palpable regional lymph nodes, stage II as having suspiciously palpable regional lymph nodes, and stage III as having distant metastases (220). Further tests, such as serum liver function studies, or radionucleotide or computed tomography scans of the liver, bone, or brain, should be performed only for specific signs or symptoms suggesting metastatic disease.

Local excision with wide margins is the only effective cure for melanoma and this approach should not be influenced by pregnancy (221). Regional lymphadenectomy has not proven to be beneficial when lymph nodes are not palpable, but clinically involved lymph nodes should be excised. Distant metastatic disease may be treatable with systemic chemotherapy with a response rate of 20% to 25%. Metastatic melanoma is resistant to most forms of therapy. Immunotherapy or radiotherapy are unproven modalities during pregnancy.

Pregnancy-associated increases in pigmentation and melanocyte-stimulating hormone, presence of estrogen receptors on 46% of melanomas, reports of rapidly fatal courses in pregnancy, and reports of tumor regression postpartum or with hormonal therapy have led to the speculation that the course of malignant melanoma may be adversely affected by pregnancy (222). Additionally, incidence rates are higher in females compare with males only during the first four decades of life. However, two population-based studies showed that the number of incident melanoma cases diagnosed during pregnancy did not differ from the number expected based on current estimated prevalence rates (223,224). Overall, research has failed to demonstrate a clear association between estrogen and melanoma or between pregnancy-associated factors and subsequent development of melanoma (225).

Melanoma is one of the most unpredictable cancers. Extensive research had failed to provide conclusive evidence for either a beneficial or deleterious effect of pregnancy on its clinical course. Most recent studies that control for prognostic factors have demonstrated similar survival between pregnant and nonpregnant patients. When controlling of tumor site, age, Breslow thickness, and Clark level, an overall mortality of 25% in the pregnancy group was found during a 7-year mean follow-up period (226). For all patients, melanoma prognosis is closely related to Breslow thickness (the depth of the lesion from the granular cell layer of the epidermis to the deepest

identifiable tumor cells) (227,228) as well as anatomic site and presence of tumor ulceration (229).

Early-stage disease is managed surgically while more advanced-stage disease is often treated with combination chemotherapy. Although Reintgen and colleagues (216) reported no difference in survival for patients who developed melanoma during pregnancy or for those who became pregnant within 5 years of diagnosis, most clinicians advise patients to avoid a subsequent pregnancy for 2 to 5 years after diagnosis, since 60% to 86% of melanomas recur during this period (216,221).

In addition, when melanoma complicates pregnancy, both the fetus and the placenta should be examined closely after delivery because melanoma is the most common tumor metastasizing to the fetus and the placenta. The presence of metastases to the placenta is classified as stage IV disease, and all patients with placental metastases, except one, have died within 7 months (230). Overall, this phenomenon is exceedingly rare, with fewer than 20 reported cases. Termination of the pregnancy is not warranted, as infant survival, even with metastatic melanoma, is 75% (221,222). Of note, no cases of fetal metastases have been reported when the placenta did not demonstrate malignant transformation (225). Such information may prove useful in counseling couples after delivery.

Hematologic Malignancies

Hematologic malignancies are the third most common cancer complicating pregnancy (25% of cases) after cervical cancer and breast cancer (231–233). The three most common include Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia.

Leukemia

The development of leukemia during pregnancy is rare, with an incidence of 1 in 75,000 pregnancies (234). Acute and chronic leukemias occur with equal frequency, although acute leukemias are more frequently diagnosed during pregnancy (235,236). Among the acute forms, acute myelogenous leukemia (AML) is more common than acute lymphocytic leukemia (ALL). Ninety percent of the chronic leukemia cases are myelocytic, with the remainder being chronic lymphocytic leukemia (237).

The majority of pregnant women found to have leukemia are diagnosed during routine prenatal care. Signs and symptoms of acute leukemia include anemia, granulocytopenia, thrombocytopenia, splenomegaly, fatigue, fever, infection, and evidence of a bleeding diathesis. Physical exam may demonstrate pallor, petechiae, or ecchymoses. The diagnosis of leukemia oftentimes is confirmed by bone marrow examination. However, it can be initially suspected when a peripheral blood smear demonstrates a normocytic, normochromic anemia with a mild to severe thrombocytopenia. Blast cells are virtually always present despite a normal or low white blood cell count (238). Additionally, if the patient presents with a leukocytosis, flow cytometry and cytogenetics of a peripheral blood sample can be sufficient for diagnosis.

ALL in adults is seen in the 30- to 40-year-old age group. While anemia and splenomegaly are common, only 25% of patients will have white blood cell counts greater than

50,000/mm³ (239). By contrast, AML most commonly occurs in 30- to 60-year-old women and 75% will have white blood cell counts greater than 50,000/mm³. The usual age of presentation of acute leukemia during pregnancy ranges from 23 to 28 years (237). As such, it is not unexpected that AML is more commonly encountered during pregnancy (240).

Chronic leukemia usually presents with lymphadenopathy, splenomegaly, leukocytosis, and constitutional symptoms. Chronic myelocytic leukemia (CML) accounts for the majority of chronic leukemias complicating pregnancies, with a median age of 35 years (241). CML is generally indolent, with a median age onset of 60 years, which accounts for its relative rarity during gestation.

Treatment of acute leukemia with chemotherapy is based on the ultimate goal of eradicating all leukemic clone cells from the bone marrow with subsequent prevention of future emergence of resistant clone cells. As such, the treatment strategy is based on divided phases classified as induction, consolidation, and maintenance (242,243). For those patients who do not achieve remission, allogeneic hematopoietic stem cell transplant is an option. Common chemotherapy induction regimens for ALL include anthracyclines, cytarabine, and vincristine in combination with steroids and L-asparaginase. AML is treated with anthracyclines and cytarabine only. Additionally, induction-induced morbidities must be prevented and treated as needed, such as cotrimoxazole for *pneumocystis carinii* prophylaxis and fluconazole for prevention of *Candida albicans* infections.

Experience in the treatment of leukemia during pregnancy is limited. Without treatment, the median survival time for patients with acute leukemia is 2 months. With treatment, 65% to 75% of adults with ALL will gain complete remission; however, recurrence is common and only one-third of patients with ALL will be long-term survivors. A similar proportion of individuals less than 60 years of age treated for AML will achieve complete remission, with 40% of these experiencing eventual cure (241). Chronic leukemia is more indolent and can be successfully controlled with chemotherapy for a long period of time.

The patient diagnosed with acute leukemia during pregnancy poses a difficult problem. Due to the poor prognosis and rapid progression of this disease, immediate treatment is needed. Since there is no evidence that pregnancy alters the natural course of leukemia, terminating the pregnancy will not improve survival of the patient. Additionally, expert opinion holds that the outcome of pregnant patients with acute leukemia is adversely affected only when appropriate therapy is withheld for more than a few weeks (244).

Combination chemotherapy has become the therapeutic management of choice in patients with acute leukemia. Children who were exposed to chemotherapeutic agents in utero showed normal growth and development from 1 to 17 years of age (235). If given after the second trimester, chemotherapy is not associated with an increased rate of fetal malformations (240). Remission rates of pregnant women treated with combination chemotherapy compare favorably with those in comparable nonpregnant women. Standard anti-leukemic agents, such as cytarabine and anthracyclines, can be safely administered during the second and third trimesters. However, antifolates should be avoided during the first

trimester, owing to a 10% to 20% risk of congenital anomalies (245). Use of L-asparaginase during pregnancy should always been done with caution as it has been shown to decrease the levels of certain thrombosis inhibitors and is associated with a significantly increased risk of thromboembolism (246–249). It is important to note that evidence shows that delaying appropriate chemotherapy for more than a few weeks at any time other than the latter part of the third trimester is associated with excessive fetal mortality (235,250,251).

Intrathecal chemotherapy and whole-brain radiation may safely be performed during any trimester of pregnancy (252). There is an increased risk of infection, stillbirth, and spontaneous abortion associated with leukemia treatment (250). Patients diagnosed with leukemia during the first half of pregnancy have only a 50% to 60% chance of producing a healthy live infant. Intrauterine growth restriction is seen in approximately 8% of infants of mothers treated for leukemia during pregnancy (244).

Chronic leukemia is generally a more indolent disease and treatment should be withheld until after delivery if possible. As seen with acute leukemia, pregnancy does not appear to alter the natural course of chronic leukemia. Maternal and fetal outcomes are generally excellent, with survival rates of 96% and 84%, respectively (253), and are not significantly different from that expected for nonpregnant women. Interferon- α has been used in at least 10 cases of chronic leukemia-complicated pregnancy without adverse maternal effects with only one case of transient neonatal thrombocytopenia (254,255). The main goal of treating chronic leukemias during pregnancy is to control splenomegaly, leukocytosis, and constitutional symptoms.

Lymphoma

Lymphoma is a relatively common malignancy presenting during the reproductive years. It occurs in 1 in 1000 to 1 in 6000 pregnancies. Approximately 25% to 40% of lymphomas are Hodgkin's type, with the average age of onset being 32 years. Hodgkin's disease is the most common type of lymphoma associated with pregnancy (256).

The majority of women with lymphoma are asymptomatic. On physical examination, 80% will have superficial lymphadenopathy. Those with Hodgkin's disease are more likely to have localized lymphadenopathy, most often involving cervical, submaxillary, or axillary nodes. A small percentage of patients have fever, night sweats, weight loss, or pruritus, which are associated with poor prognosis. Biopsy is the "gold standard" of diagnosis. The histology of Hodgkin's lymphoma often shows multinucleated Reed–Sternberg cells with a pattern that is most commonly nodular sclerosing or lymphocytic. Histology is no longer thought to contribute to overall prognosis, as recent evidence demonstrates that the two most important prognostic factors are stage of disease and patient's age (244). Hodgkin's lymphoma is staged by the Ann Arbor staging system.

Patients with non-Hodgkin's lymphoma commonly present with high- or intermediate-grade diffuse histologic patterns and have a poorer prognosis than those with a nodular pattern (53). They are histologically distinguished from Hodgkin's lymphoma by the absence of Reed–Sternberg cells. They comprise a heterogeneous group of lymphoid

malignancies and differ in their presentation, stage at diagnosis, and prognosis. The classification system now used is based on the WHO classification system and uses morphologic, genetic, immunophenotypic, and clinical features. This has been shown to provide a higher degree of diagnostic accuracy and reproducibility (257).

The treatment of lymphoma depends on accurate staging, and minimal evaluation requires examination by the physician, chest radiographs, bone marrow biopsy with aspirate and core, and imaging of the abdomen usually with MRI. Abdominal ultrasound examination for retroperitoneal adenopathy or hydronephrosis may be helpful in staging. Lymphangiograms are rarely used in the current evaluation of lymphoma.

Once staging is complete, treatment generally should not be compromised because of the pregnancy. In the nonpregnant woman, nodal radiotherapy and combination chemotherapy result in cures for 70% of patients with Hodgkin's disease and 50% of patients with non-Hodgkin's lymphoma (256). Patients in the third trimester with localized Hodgkin's disease can be allowed to deliver prior to therapy (245). Treatment during the first and second trimesters and in patients with advanced disease or high-grade tumors is more complex. Localized disease above the diaphragm can be treated with radiotherapy with abdominal shielding. More extensive disease is best treated with combination chemotherapy to reduce the large fetal radiation exposure. The same considerations concerning combination chemotherapy as discussed with leukemia apply to lymphoma.

Placental metastases have been reported in both leukemia and lymphoma patients and, as such, the placenta should be closely examined after delivery as well as be sent to pathology for histologic evaluation. As a group, they account for 19% of the malignancies metastatic to the products of conception and 50% of those metastatic to the fetus (232,258). Postpartum contraception is important as many patients often require prolonged maintenance therapy. Breast-feeding should be avoided as little data exist regarding the specific chemotherapy agents used to treat these malignancies and their potential for neonatal adverse effects.

Thyroid Cancer

Thyroid cancer is the most frequently encountered cancer in the reproductive age group, with 50% of cases occurring in women of 15 to 44 years of age. In the general population, it is the most common endocrine cancer, with an estimated incidence of 9 per 100,000 (259). Approximately 10% of thyroid cancers that occur during the reproductive years are diagnosed during pregnancy or in the first year after birth (260,261). Some case-control studies suggest that hormonal factors may play an etiologic role in the development of thyroid cancer (262). This theory is supported by isolated studies showing an increased incidence in pregnancy and a decreased incidence, equal to that in males, following menopause. Clinically detectable thyroid nodules are three to four times more likely in pregnant women, and although most are benign, there are reports that up to 39% to 43% of these nodules are malignant (261). Thyroid stimulation is thought to be caused by the high levels of beta-hCG, which also has thyroid-stimulating activity. However, there is currently no

consensus about the impact of pregnancy on thyroid cancer, and the precise incidence of thyroid cancer in pregnancy is unknown (263).

The most common histologic type is papillary, followed by follicular and mixed papillary-follicular. These histologies have a favorable prognosis, whereas the less commonly occurring medullary and anaplastic patterns do not. The usual clinical presentation is that of a single thyroid nodule that has up to a 20% chance of being malignant. Rapid growth and fixation of the nodule to the surrounding structures or cervical lymphadenectomy are common findings for advanced disease. Risk factors for developing thyroid cancer are prior head or neck irradiation and a family history of multiple endocrine neoplasms.

Diagnosis is often made by palpation, but must be confirmed by biopsy. FNA has been shown to be a safe and effective technique in pregnant women, with false-positive results being exceedingly rare and false-negative results occurring in only 5% to 10% of cases (252). Some advocate fine-needle aspiration of all thyroid nodules prior to 20 weeks of gestation, and after 20 weeks, only those that grow during suppressive therapy should be sampled (264). Radioisotope nuclear scanning is contraindicated in pregnancy, because radioactive isotopes are taken up by the fetus. Other methods, such as ultrasound, can be used to distinguish solid-form cystic nodules. Thyroid function tests may also be helpful and can diagnose unsuspected thyroiditis. If medullary thyroid cancer is suspected, a calcitonin level should be checked as well. Normally, pregnancy witnesses a hypertrophy of the thyroid gland from follicular cell hyperplasia, and total triiodothyronine and thyroxine levels are elevated while triiodothyronine resin uptake is decreased secondary to increased thyroid-binding globulin. Thyroid-stimulating hormone is in the normal to slightly elevated range.

Treatment of choice for all primary carcinomas is surgery. Thyroidectomy is safe in the midtrimester and does not appear to increase the risk of adverse perinatal outcomes (265). Cancer discovered during the first or early second trimester should prompt immediate surgery (263). In the third trimester, a brief delay to allow fetal pulmonary maturity may be acceptable, and even malignant nodules diagnosed at any time after 20 weeks may be followed unless noted to be rapidly growing or of undifferentiated histology (261,266). Similarly, surgery for indeterminate findings on FNA can be delayed until after delivery as well unless the nodule is increasing in size (261). Well-differentiated forms of papillary and follicular histology are treated with subtotal thyroidectomy. Extensive neck dissection performed for cervical lymphadenectomy carries an increased incidence of spontaneous abortion. Poor prognostic medullary or anaplastic forms may present at very advanced stages, in which case regard for fetal development may predominate. Treatment with radioactive iodine, which is often used for adjuvant therapy in follicular thyroid cancers, is contraindicated, since it crosses the placenta and is trapped by the fetal thyroid.

Overall, prognosis during pregnancy appears unchanged when controlling for stage and histology; thus, abortion or prevention of subsequent pregnancy is unwarranted. When surgery is performed, vigilance for hypothyroidism and hypoparathyroidism should be maintained throughout

pregnancy as well as postpartum. After surgery and iodine treatment, hormonal replacement therapy is suggested to suppress thyroid-stimulation hormone. Thyroid hormone replacement is safe and effective in pregnancy. Subsequent pregnancy after treatment with radioactive iodine is safe as the gonadal impairment is only temporary and reversible, and there have been no reports of stillbirths, malformations, early deaths, or malignancies (267). In general, it is recommended to wait 1 year after treatment prior to pursuing another pregnancy to avoid all potential adverse side effects.

Bone and Soft-Tissue Sarcomas

Bone and soft-tissue sarcomas are relatively common malignancies in the reproductive age group. Their presence in association with pregnancy, however, is very rare, as there are less than 50 such recorded cases in the literature (268). The majority of these cases are osteosarcomas, followed by Ewing's sarcomas. Genital sarcomas of the cervix, vagina, and vulva include liposarcomas, histiocytomas, myosarcomas, and leiomyosarcomas, with and without peritoneal dissemination.

The majority of patients present with symptoms of localized pain or a mass. Diagnostic procedures commonly used to assess sarcomas include radiographs with abdominal shielding during pregnancy. Osteogenic sarcomas may require radioisotope bone scanning, which is thought to be of low risk to the fetus (269). Definitive diagnosis of any type of sarcoma requires biopsy. Although pregnancy has no proven deleterious effects on the natural course of sarcomas, delayed diagnosis results in postponed treatment. These tumors present at advanced stages, which may explain isolated reports of worsened prognosis for sarcomas in pregnancy (270). The aggressive biologic behavior of pelvic sarcomas may be enhanced by hypervascularity or hormonal stimulus; however, an impaired prognosis for most sarcomas associated with pregnancy remains unsubstantiated.

Owing to the diversity of histologic types, anatomic locations, stages of disease, and forms of treatment for different types of sarcomas, it is difficult to generalize treatment options. Since maternal prognosis for all types of sarcomas is poor, a combination of surgery, irradiation, and aggressive multiagent chemotherapy is warranted (271). Most clinicians recommend that the pregnant woman should be managed without regard for the pregnancy during the first two trimesters of gestation. In cases presenting in the third trimester, the fetus may be delivered vaginally or by cesarean section for obstetric indications as soon as pulmonary maturity is documented, so that aggressive treatment can be initiated. Although based on limited experience, more recent reports advocate the initiation of multiagent chemotherapy for control of systemic disease during any stage of gestation. Such therapy is based on the rationale that mortality in sarcomas often results from distant metastases and not local recurrence, and chemotherapy is relatively well tolerated by the fetus with the exception of the first trimester.

Tumors of the Central Nervous System

The Third National Cancer Study indicates that 21% of brain tumors affect women in the childbearing years (2); however, only 220 cases of central nervous system (CNS) tumors occurring during pregnancy have been reported in the world's

literature over the past 90 years (272). Intracranial tumors occur in pregnancy with a reported frequency of 3.6 per 10 (25) births (273). The most common neoplasms are glial neoplasms, followed by meningiomas and acoustic neuromas (274) and have similar frequencies in pregnant and nonpregnant women. Certain CNS tumors, such as meningiomas, pituitary adenomas, and vascular neoplasms, have a slightly increased incidence during pregnancy.

Although not well established, the fact that meningiomas predominate in women, enlarge rapidly during pregnancy, and express estrogen and progesterone receptors suggests a causal relationship between the tumors and pregnancy (275). Pregnancy normally results in pituitary enlargement secondary to hyperplasia of prolactin-secreting acidophilic cells and it also appears to stimulate the growth of pituitary microadenomas, making them clinically apparent (276). The relative frequency of CNS vascular tumors is also increased during pregnancy, with hemangioblastomas and spinal hemangiomas predominating. This increased incidence is attributed to retrograde engorgement of vascular channels in the tumor secondary to increased venous pressure from compression of the inferior vena cava in the gravid uterus, as well as an overall increased blood volume (277). These factors permit occult vascular tumors to become clinically apparent. Additionally, growth of residual lesions or recurrence is possible during pregnancy in previously treated patients (274).

Symptoms of brain tumors manifesting during pregnancy, such as nausea and vomiting, can be mistakenly attributed to the pregnancy. In addition, headache and visual disturbances commonly caused by brain tumors may be misinterpreted as signs of pre-eclampsia or optic neuritis. Spinal cord tumors cause symptoms of spinal cord compression, depending on the level involved. Early symptoms, such as fatigue, backache, and nerve-root irritation, may also be confused with common pregnancy-related complaints.

The diagnosis of CNS tumors can be established by radiographic studies, such as computed tomography scans, MRI, myelography, and angiography. Prolactin levels are useful in assessing pituitary tumors, and examination of the cerebrospinal fluid is helpful with spinal cord tumors. Definitive diagnosis of any tumor requires histologic examination. The coexistence of a CNS tumor and pregnancy should not preclude diagnostic studies.

The management of CNS tumors must be considered on an individual basis. In general, immediate treatment is necessary when symptoms are severe or progressive. Once the diagnosis of a CNS tumor is established, the patient should be closely observed for sudden increase in intracranial pressure, loss of visual fields, or progressive neurologic deficits. The treatment of choice for most CNS tumors, including meningiomas and spinal cord tumors, is surgery. Other tumors may respond to radiation therapy, which is not contraindicated during pregnancy provided the tumor is above the thoracic region and the fetus can be appropriately shielded. Prolactinomas can be treated with bromocriptine even during pregnancy, but surgical management is still preferred. When symptoms are mild or occur during the third trimester, careful observation with conservative medical treatment aimed at reducing intracranial pressure until fetal maturity is suggested (278). When symptoms are severe, treatment is mandatory without

regard to the pregnancy to prevent further neurologic deficits or death. Neurosurgery is particularly safe in the third trimester. The best mode of delivery in the presence of increased intracranial pressure remains to be determined.

CHEMOTHERAPY IN PREGNANCY

Oftentimes, chemotherapy treatment cannot be delayed until after delivery for pregnant women diagnosed with certain cancers. Most chemotherapeutic agents have been associated with adverse fetal side effects (279). However, safe use of chemotherapy has also been reported in the second and third trimesters with little evidence for adverse neonatal outcomes. The risks regarding chemotherapy use during pregnancy depend on the timing of exposure, the dose, and the characteristics affecting placental transfer. Those factors that most readily affect placental transfer from mother to fetus are high lipid solubility, low molecular weight, and loose binding to plasma proteins. It is also thought that genetic predisposition to teratogenicity might explain why some women have increased susceptibility compared with others (279). Risks of chemotherapy vary depending on the gestational age. Use of chemotherapy in the first trimester carries the risk of spontaneous abortion, fetal death, and major malformations. The gestational weeks 2 to 8 comprise the period of organogenesis and, as such, represent the time when the fetus is most vulnerable to teratogenic insults. Chemotherapy administered during the second and third trimesters increases the risk for intrauterine growth restriction and low birth weight. Unfortunately, transplacental studies have been unsuccessful in effectively monitoring fetal exposure to the administration of chemotherapeutic agents to the mother (280).

Pharmacokinetic changes associated with pregnancy are largely unknown, and pregnant women receive similar weight-based doses as those who are not pregnant. Given the increased blood volume and renal clearance that occurs with pregnancy, these women may receive decreased doses of the active agent. There is also a thought that a faster hepatic mixed-function oxidase system combined with decreased plasma albumin levels may also affect drug absorption. Currently, no pharmacokinetic studies have been done in pregnant women receiving chemotherapy.

Overall, delivery should be avoided during the maternal nadir period, which occurs 2 to 3 weeks after treatment. Chemotherapy should not be administered after 35 weeks of gestation as spontaneous delivery could occur before the bone marrow has recovered. The ability of an agent to cross the placenta correlates poorly with its ability to pass into breast milk, and breast-feeding is considered contraindicated while undergoing chemotherapy. As always, the decision to use chemotherapy in pregnancy must be weighed against the effect of treatment delay on maternal survival and the overall risk to the fetus.

REFERENCES

1. Donegan WL. Cancer and pregnancy. *Cancer* 1983; 33: 194–214.
2. Third National Cancer Survey. Incidence data NCI. Monogr 1975; 41: 108–11.
3. Amant F, Calsteren KV, Vergote I, Ottevanger N. Gynecologic oncology in pregnancy. *Crit Rev Oncol Hematol* 2008; 67: 187–95.

4. Creasman WT. New gynecologic cancer staging. *Obstet Gynecol* 1990; 75: 287.
5. Arena S, Marconi M, Uberty M, et al. HPV and pregnancy: diagnostic methods, transmission, and evolution. *Minerva Gynecol* 2002; 54: 225–37.
6. Wood C. Laryngeal papillomas in infants and children. Relationship to maternal venereal warts. *J Nurse Mid* 1991; 36: 297–302.
7. Lee JH, Smith RJ. Recurrent respiratory papillomatosis: pathogenesis to treatment. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13: 354–9.
8. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. *Obstet Gynecol* 2003; 101: 645–52.
9. Rombaldi RL, Serafini EP, Mandelli J, Zimmermann E, Losquiavo KP. Transplacental transmission of human papillomavirus. *Virol J* 2008; 5: 106.
10. Deng D, Wen L, Chen W, Ling X. Asymptomatic genital infection of human papillomavirus in pregnant women and the vertical transmission route. *J Huazhong Univ Sci Technolog Med Sci* 2005; 25: 343–5.
11. Syrjänen S, Puranen M. Human papillomavirus infection in children: the potential role of maternal transmission. *Crit Rev Oral Biol Med* 2000; 11: 259–74.
12. Nardelli-Haeffliger D, Wirthner D, Schiller JT, et al. Specific antibody levels at the cervix during the menstrual cycle of women vaccinated with human papillomavirus 16 virus-like particles. *J Natl Cancer Inst* 2003; 95: 1128–37.
13. Koutsky LA, Ault KA, Wheeler CM, et al.; Proof of Principle Study Investigators. A controlled trial of a human papilloma virus type 16 vaccine. *NEJM* 2002; 347: 1645–51.
14. Jansen KU, Shaw AR. Human papilloma virus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; 55: 319–31.
15. Billich A. HPV vaccine MedImmune/GlaxoSmithKline. *Curr Opin Investig Drugs* 2003; 4: 210–13.
16. DiSaia PJ, Creasman WT. Cancer in pregnancy. In: DiSaia PJ, Creasman WT, eds. *Clinical gynecologic oncology*. St. Louis, MO: CV Mosby, 1989.
17. Hacker NF, Berek JS, Lagasse LD. Carcinoma of the cervix associated with pregnancy. *Obstet Gynecol* 1982; 59: 735–46.
18. LaPolla JP, O'Neill C, Wetrich D. Colposcopy management of abnormal cervical cytology in pregnancy. *J Reprod Med* 1988; 33: 301–6.
19. Jain AG, Higgins RV, Boyle MJ. Management of low-grade squamous intraepithelial lesions during pregnancy. *Am J Obstet Gynecol* 1997; 177: 298–302.
20. Patsner B. Management of low grade cervical dysplasia during pregnancy. *South Med J* 1990; 83: 1405–12.
21. Robinson WR, Webb S, Tirpack J, Degefu S, O'Quinn AG. Management of cervical intraepithelial neoplasia during pregnancy with LOOP excision. *Gynecol Oncol* 1997; 64: 153–5.
22. Mitsuhashi A, Sekiya S. Loop electrosurgical excision procedure (LEEP) during first trimester of pregnancy. *Int J Gynaecol Obstet* 2000; 71: 237–9.
23. Dunn TS, Ginsburg V, Wolf D. Loop-cone cerclage in pregnancy: a 5-year review. *Gynecol Oncol* 2003; 90: 577–80.
24. Averette HE, Nasser N, Yankow SL, Little WA. Cervical conization in pregnancy. *Am J Obstet Gynecol* 1970; 106: 543–8.
25. Lutz MH, Underwood PB, Rozier JC, Putney FW. Genital malignancy in pregnancy. *Am J Obstet Gynecol* 1977; 129: 536–42.
26. Goldberg GL, Ataras MM, Block B. Cone cerclage in pregnancy. *Obstet Gynecol* 1991; 77: 315–17.
27. Smith LH, Dalrymple JL, Leiserowitz GS, Danielsen B, Gilbert WM. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. *Am J Obstet Gynecol* 2001; 184: 1504–12; discussion 1512–13.
28. Smith H, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol* 2003; 189: 1128–35.
29. Demeter A, Sziller I, Caspo Z, Szantho A, Papp Z. Outcome of pregnancies after cold-knife conization of the uterine cervix during pregnancy. *Eur J Gynaecol Oncol* 2002; 23: 207–10.
30. Jacob JH, Stringer CA. Diagnosis and management of cancer during pregnancy. *Semin Perinatol* 1990; 14: 79–87.
31. Zemlickis D, Lishner M, Degendorfer P, et al. Maternal and fetal outcome after invasive cervical cancer in pregnancy. *J Clin Oncol* 1991; 9: 1956–61.
32. Yagizi R, Cunningham FG. Cancer and pregnancy. *Williams Obstet* 1990; 4(Suppl): 1–15.
33. Lee RB, Neglia W, Park RC. Cervical carcinoma in pregnancy. *Obstet Gynecol* 1981; 58: 584–9.
34. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol* 2001; 19: 3745–9.
35. Grigsby PW, Dehdashti F, Siegel BA. FDG-PET evaluation of carcinoma of the cervix. *Clin Pos Imag* 1999; 2: 105–9.
36. Rose PG, Adler LP, Rodriguez M, et al. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol* 1999; 17: 41–5.
37. Wong TZ, Jones IL, Coleman RE. Positron emission tomography with 2-deoxy-2-[(18)F]fluoro-D-glucose for evaluating local and distant disease in patients with cervical cancer. *Mol Imag Biol* 2004; 6: 55–62.
38. Miller TR, Grigsby PW. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. *Int J Radiat Oncol Biol Phys* 2002; 53: 353–9.
39. Miller TR, Pinkus E, Dehdashti F, Grigsby PW. Improved prognostic value of 18F-FDG PET using a simple visual analysis of tumor characteristics in patients with cervical cancer. *J Nucl Med* 2003; 44: 192–7.
40. Grigsby PW, Siegel BA, Dehdashti F, Rader J, Zoberi I. Posttherapy [(18)F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol* 1999; 17: 41–5.
41. Brooks RA, Rader JS, Dehdashti F, et al. Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer. *Gynecol Oncol* 2009; 112: 104–9.
42. Hunter MI, Tewari K, Monk BJ. Cervical neoplasia in pregnancy. Part 2: current treatment of invasive disease. *Am J Obstet Gynecol* 2008; 199: 10–18.
43. Diakomanolis E, Haidopoulos D, Rodolakis A, et al. Laser CO(2) conization: a safe mode of treating conservatively microinvasive carcinoma of the uterine cervix. *Eur J Obstet Gynecol Reprod Biol* 2004; 113: 229–33.
44. Itsukaichi M, Kurata H, Matsushita M, et al. Stage Ia1 cervical squamous cell carcinoma: Conservative management after laser conization with positive margins. *Gynecol Oncol* 2003; 90: 387–9.
45. Okamoto Y, Ueki K, Ueki M. Pathological indications for conservative therapy in treating cervical cancer. *Acta Obstet Gynecol Scand* 1999; 78: 818–23.
46. Van De Nieuwenhof HP, Van Ham MAPC, Lotgering FK, Massugar LFAG. First case of vaginal radical trachelectomy in a pregnant patient. *Int J Gynecol Cancer* 2008; 18: 1381–5.
47. Sivanesaratnam V, Jayalakshmi P, Loo C. Surgical management of early invasive cancer of the cervix associated with pregnancy. *Gynecol Oncol* 1993; 48: 68–75.
48. Sood AK, Sorosky JL, Mayr N, et al. Radiotherapeutic management of cervical carcinoma that complicates pregnancy. *Cancer* 1997; 80: 1073–8.
49. Prem KA, Makowski EL, McKelvey JL. Carcinoma of the cervix associated with pregnancy. *Am J Obstet Gynecol* 1966; 95: 99–108.
50. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; 340: 1144–53.
51. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; 340: 1137–43.
52. Duggan B, Mudderspach LI, Roman LD, et al. Cervical cancer in pregnancy: Reporting on planned delay in therapy. *Obstet Gynecol* 1993; 82: 598–602.
53. Sorosky I, Squatrito R, Ndubisi BU, et al. Stage I squamous cell cervical carcinoma in pregnancy: planned delay in therapy awaiting fetal maturity. *Gynecol Oncol* 1995; 59: 207–10.
54. Monk BJ, Montz FJ. Invasive cervical cancer complicating intrauterine pregnancy: treatment with radical hysterectomy. *Obstet Gynecol* 1992; 80: 199–203.
55. Sood AK, Sorosky JL, Krogman S, et al. Surgical management of cervical cancer complicating pregnancy: a case-control study. *Gynecol Oncol* 1996; 63: 294–8.

56. Takushi M, Moromizato H, Sakumoto K, Kanazawa K. Management of invasive carcinoma of the uterine cervix associated with pregnancy: outcome of intentional delay in treatment. *Gynecol Oncol* 2002; 87: 185–9.
57. Tewari K, Cappuccini F, Gambino A, et al. Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy. *Cancer* 1998; 82: 1529–34.
58. Greer BE, Easterling TR, McLennan DA, et al. Fetal and maternal considerations in the management of stage I-B cervical cancer during pregnancy. *Gynecol Oncol* 1989; 34: 61–5.
59. Lee RB, Neglia W, Park RC. Cervical carcinoma in pregnancy. *Obstet Gynecol* 1981; 58: 584–9.
60. Marana HR, de Andrade JM, da Silva Mathes AC, et al. Chemotherapy in the treatment of locally advanced cervical cancer and pregnancy. *Gynecol Oncol* 2001; 80: 272–4.
61. Sood AK, Shahin MS, Soroski JJ. Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; 83: 599–600.
62. Mendez LE, Mueller A, Salom E, Gonzales-Quintero VH. Paclitaxel and carboplatin chemotherapy administered during pregnancy for advanced epithelial ovarian cancer. *Obstet Gynecol* 2003; 5: 1200–2.
63. Barber HR, Brunschwig A. Gynecologic cancer complicating pregnancy. *Am J Obstet Gynecol* 1963; 85: 156–64.
64. Mikuta JJ. Invasive carcinoma of the cervix in pregnancy. *South Med J* 1967; 60: 843–7.
65. Cliby WA, Dodson MK, Podratz KC. Cervical cancer complicated by pregnancy: episiotomy site recurrences following vaginal delivery. *Obstet Gynecol* 1994; 84: 179–82.
66. Gordon AN, Jensen R, Jones HW 3rd. Squamous carcinoma of the cervix complicating pregnancy: recurrence in episiotomy after vaginal delivery. *Obstet Gynecol* 1989; 73: 850–2.
67. Baloglu A, Uysal D, Aslan N, Yigit S. Advanced stage of cervical carcinoma undiagnosed during antenatal period in term pregnancy and concomitant metastasis on episiotomy scar during delivery: a case report and review of the literature. *Int J Gynecol Cancer* 2007; 17: 1131–71.
68. Burgess SP, Waymont B. Implantation of a cervical carcinoma in an episiotomy site. *Br J Obstet Gynaecol* 1987; 94: 598–9.
69. Copeland LJ, Saul PB, Snieg N. Cervical adenocarcinoma: tumor implantation in the episiotomy sites of two patients. *Gynecol Oncol* 1987; 28: 230–5.
70. Gordon AN, Jensen R, Jones HW 3rd. Squamous carcinoma of the cervix complicating pregnancy: recurrence in episiotomy after vaginal delivery. *Obstet Gynecol* 1989; 73: 850–2.
71. Van Dam PA, Irvine L, Lowe DG, et al. Carcinoma in episiotomy scars. *Gynecol Oncol* 1992; 44: 96–100.
72. Khalil AM, Khatib RA, Mufarrij AA, Tawil AN, Issa PY. Squamous cell carcinoma of the cervix implanting in the episiotomy site. *Gynecol Oncol* 1993; 51: 408–10.
73. Cliby WA, Dodson MK, Podratz KC. Cervical cancer complicated by pregnancy: episiotomy site recurrences following vaginal delivery. *Obstet Gynecol* 1994; 84: 179–82.
74. Goldman NA, Goldberg GL. Late recurrence of squamous cell cervical cancer in an episiotomy site after vaginal delivery. *Obstet Gynecol* 2003; 101: 1127–9.
75. Amanie J, Pearcey RG, Honore L, Sloboda R. Metastatic adenocarcinoma of the cervix in a delivery-induced traumatic lower vaginal tear. *Gynecol Oncol* 2005; 96: 857–9.
76. Barclay DL. Surgery of the vulva, perineum, and vagina in pregnancy. In: Barber HRK, Braber EA, eds. *Surgical Disease in Pregnancy*. Philadelphia: WB Saunders, 1974.
77. Arena S, Marconi M, Ubertosi M, et al. HPV and pregnancy: diagnostic methods, transmission, and evolution. *Minerva Gynecol* 2002; 54: 225–37.
78. Monaghan JM, Lindeque G. Vulvar carcinoma in pregnancy [editorial]. *Br J Obstet Gynaecol* 1986; 93: 785–6.
79. Fujita K, Aoki Y, Tanaka K. Stage I squamous cell carcinoma of vagina complicating pregnancy: successful conservative management. *Gynecol Oncol* 2005; 98: 513–15.
80. Stock RG, Chen ASJ, Seski J. A 30-year experience in the management of primary carcinoma of the vagina: analysis of prognostic factors and treatment modalities. *Gynecol Oncol* 1995; 56: 43–52.
81. Davis KP, Stanhope CR, Garton GR, Atkinson EJ, O'Brien PC. Invasive vaginal carcinoma: analysis of early-stage disease. *Gynecol Oncol* 1991; 42: 131–6.
82. Grimes WH, Bartholomew RA, Colvin ED, Fish JS, Lester WM. Ovarian cyst complicating pregnancy. *Am J Obstet Gynecol* 1954; 68: 594–605.
83. Struyk APHB, Treffers PE. Ovarian tumors in pregnancy. *Acta Obstet Gynecol Scand* 1984; 63: 421–4.
84. Booth RT. Ovarian tumors in pregnancy. *Obstet Gynecol* 1963; 21: 189–92.
85. White KC. Ovarian tumors in pregnancy. *Am J Obstet Gynecol* 1973; 116: 544–50.
86. BATTERY BW, Beisher NA, Fortune DW, Macafee CA. Ovarian tumors in pregnancy. *Med J Aust* 1973; 1: 345–9.
87. Hess W, Peaceman A, O'Brien WF, et al. Adnexal mass occurring with intrauterine pregnancy: report of fifty-four patients requiring laparotomy for definitive management. *Am J Obstet Gynecol* 1988; 158: 1029–34.
88. Thornton JG, Wells M. Ovarian cysts in pregnancy: does ultrasound make traditional management inappropriate? *Obstet Gynecol* 1987; 69: 717–21.
89. Tawa K. Ovarian tumors in pregnancy. *Am J Obstet Gynecol* 1964; 90: 511–15.
90. Hill LM, Johnson CE, Raymond AL. Ovarian surgery in pregnancy. *Am J Obstet Gynecol* 1975; 122: 565–9.
91. Hasan A, Amr S, Issa A, Bata M. Ovarian tumors complicating pregnancy. *Int J Gynaecol Obstet* 1983; 21: 279–82.
92. Ballard CA. Ovarian tumors associated with pregnancy termination patients. *Am J Obstet Gynecol* 1984; 149: 384–7.
93. Hopkins MP, Duchon MA. Adnexal surgery in pregnancy. *J Reprod Med* 1986; 31: 1035–7.
94. Nelson MJ, Cavalieri R, Graham D, Sanders RC. Cysts in pregnancy discovered by sonography. *J Clin Ultrasound* 1986; 14: 509–12.
95. Askenazy M, Kessler I, Czernobilsky B, Nahshoni A, Lancet M. Ovarian tumors in pregnancy. *Int J Gynaecol Obstet* 1988; 27: 79–83.
96. Tchabo JG, Stay EJ, Limaye NS. Ovarian tumors in pregnancy: a community hospital's five year experience. *Int Surg* 1987; 72: 227–9.
97. Koonings PP, Platt LD, Wallace R. Incidental adnexal neoplasms at cesarean section. *Obstet Gynecol* 1988; 72: 767–9.
98. Sunoo CS, Terada KY, Kamemoto LE, Hale RW. Adnexal masses in pregnancy: occurrence by ethnic group. *Obstet Gynecol* 1990; 75: 38–40.
99. el-Yahia AR, Rahman J, Rahman MS, al-Suleiman SA. Ovarian tumours in pregnancy. *Aust NZ J Obstet Gynaecol* 1991; 31: 327–30.
100. Platek DN, Henderson CE, Goldberg GL. The management of a persistent mass in pregnancy. *Am J Obstet Gynecol* 1995; 173: 1236–40.
101. Ueda M, Ueki M. Ovarian tumors associated with pregnancy. *Int J Gynaecol Obstet* 1996; 55: 59–65.
102. Bromley B, Benacerraf B. Adnexal masses during pregnancy: accuracy of sonographic diagnosis and outcome. *J Ultrasound Med* 1997; 16: 447–52.
103. Whitecar MP, Turner S, Higby MK. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. *Am J Obstet Gynecol* 1999; 181: 19–24.
104. Gustafson GW, Gardener SH, Stout FE. Ovarian tumors complicating pregnancy: a review of 45 surgically proved cases. *Am J Obstet Gynecol* 1954; 67: 1210–23.
105. Levine W, Diamond B. Surgical procedures during pregnancy. *Am J Obstet Gynecol* 1961; 81: 1046–52.
106. Child CG, Douglas RG. Surgical problems arising during pregnancy. *Am J Obstet Gynecol* 1943; 47: 213–28.
107. Bernhard LM, Klebba PK, Gray DL, Mutch DG. Predictors of persistence of adnexal masses in pregnancy. *Obstet Gynecol* 1999; 93: 585–9.
108. Curtis M, Hopkins MP, Zarlingo T, et al. Magnetic resonance imaging to avoid laparotomy in pregnancy. *Obstet Gynecol* 1993; 82: 833–6.
109. Chiang G, Levine D. Imaging of adnexal masses in pregnancy. *J Ultrasound Med* 2004; 23: 805–19.
110. Beischen HA, BATTERY BW, Fortune DW, McCafee CAJ. Growth and malignancy of ovarian tumors in pregnancy. *Aust NZ J Obstet Gynecol* 1971; 11: 208–20.
111. Dougherty CM, Lund CJ. Solid ovarian tumors complicating pregnancy: a clinicopathologic study. *Am J Obstet Gynecol* 1950; 60: 261–72.
112. Chung A, Birnbaum SJ. Ovarian cancer associated with pregnancy. *Obstet Gynecol* 1977; 41: 211–14.

113. Bitson JR, Golden ML. Cancer and pregnancy. *Am J Obstet Gynecol* 1961; 85: 345–54.
114. Copeland LJ, Landon MB. Malignant disease in pregnancy. In: Gabbe SG, Niebyl JR, Simpson JL, eds. *Obstetrics, normal and problems pregnancies*, 3rd edn. New York: Churchill Livingstone, 1996: 115–118.
115. Grimes DA. Epidemiology of gestational trophoblastic disease. *Am J Obstet Gynecol* 1984; 150: 309–18.
116. Zanotti KS, Belinson JL, Kennedy AW. Treatment of gynecologic cancers in pregnancy. *Semin Oncol* 2000; 27: 686–98.
117. Zhao XY, Huang HF, Lian LJ, Lang JH. Ovarian cancer in pregnancy: a clinicopathologic analysis of 22 cases and review of the literature. *Int J Gynecol Cancer* 2006; 16: 8–15.
118. Hermans RH, Fischer DC, Van Der Putten HW, et al. Adnexal masses in pregnancy. *Onkologie* 2003; 26: 167–72.
119. Takeuchi T, Suzuki S, Hayashi Z, Shinagawa T, Araki T. Primary ovarian tumor undergoing surgical management during pregnancy. *J Nippon Med Sch* 2002; 69: 39–42.
120. Partridge EE, Phillips JL, Menck HR. The National Cancer Data Base report on ovarian cancer treatment in the United States hospitals. *Cancer* 1996; 78: 2236–46.
121. Zalel Y, Piura B, Elchalal U, et al. Diagnosis and management of malignant germ cell ovarian tumors in young females. *Int J Gynaecol Obstet* 1996; 55: 1–10.
122. Sayar H, Lhomme C, Verschraegen CF. Malignant adnexal masses in pregnancy. *Obstet Gynecol Clin N Am* 2005; 32: 569–93.
123. Disaia PJ, Creasman WT. *Clinical gynecologic oncology*, 6th edn. St. Louis, Missouri: Mosby, 2002.
124. Buller RE, Darrow V, Manetta A, Porto M, Disaia PJ. Conservative surgical management of dysgerminoma concomitant with pregnancy. *Obstet Gynecol* 1992; 79: 887–90.
125. Oehler M, Wain G, Brand A. Gynaecological malignancies in pregnancy: a review. *Aust NZ J Obstet Gynaecol* 2003; 43: 414–20.
126. Kumar V, Fausto N, Abbas A. *Pathologic basis of disease*, 7th edn. St. Louis, Missouri: WB Saunders/Elsevier, 2005.
127. Fujita M, Inoue M, Tanizawa O, et al. Retrospective review of 41 patients with endodermal sinus tumor of the ovary. *Int J Gynecol Cancer* 1993; 3: 329–35.
128. Tewari K, Cappuccini F, Disaia PJ, et al. Malignant germ cell tumors of the ovary. *Obstet Gynecol* 2000; 95: 128–33.
129. Elit L, Bocking A, Kenyon C, Natale R. An endodermal sinus tumor diagnosed in pregnancy: case report and review of the literature. *Gynecol Oncol* 1999; 72: 123–7.
130. Shimizu Y, Komiyama S, Kobayashi T, Nakata K, Iida T. Successful management of endodermal sinus tumor of the ovary associated with pregnancy. *Gynecol Oncol* 2003; 88: 447–50.
131. Ferrandina G, Distefano M, Testa A, de Vincenzo R, Scambia G. Management of an advanced ovarian cancer at 15 weeks of gestation: case report and review of the literature. *Gynecol Oncol* 2005; 97: 693–6.
132. Modares Gilani M, Karimi Zarchi M, Behdash N, et al. Preservation of pregnancy in a patient with advanced ovarian cancer at 20 weeks of gestation: case report and review of the literature. *Int J Gynecol Cancer* 2007; 17: 1131–71.
133. Mantovani G, Mais V, Parodo G, Carrucci GM. Use of chemotherapy for ovarian cancer during human pregnancy: case report and literature review. *Eur J Obstet Gynecol Rep Biol* 2007; 131: 235–45.
134. Picone O, Lhomme C, Tournaire M, et al. Preservation of pregnancy in a patient with a stage IIIB ovarian epithelial carcinoma diagnosed at 22 weeks of gestation and treated with initial chemotherapy: case report and literature review. *Gynecol Oncol* 2004; 94: 600–4.
135. Russell P. Surface epithelial-stromal tumors of the ovary. In: Kurman RJ, ed. *Blaustein's pathology of the female genital tract*, 4th edn. New York: Springer Verlag, 1994: 705.
136. Morice P, Camatte S, Wicart-Poquet F, et al. Results of conservative management of epithelial malignant and borderline ovarian tumours. *Hum Reprod Update* 2003; 9: 185–92.
137. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. *J Clin Oncol* 2003; 21: 1180–9.
138. Williams SD, Birch R, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med* 1987; 316: 1435–40.
139. Gershenson DM, Morris M, Burke TW, et al. Treatment of poor prognosis sex-cord stromal tumors of the ovary with combination of bleomycin, etoposide, and cisplatin. *Obstet Gynecol* 1996; 87: 527–31.
140. Savage P, Constenla D, Fisher C, et al. Granulosa cell tumors of the ovary: demographics survival and the management of advanced disease. *Clin Oncol (R Coll Radiol)* 1998; 10: 242–5.
141. Homesley HD, Bundy BN, Hurteau JA, Roth LM. Bleomycin, etoposide and cisplatin combination therapy of ovarian granulosa cell tumors and other stromal malignancies: a Gynecologic Oncology Group study. *Gynecol Oncol* 1999; 72: 131–7.
142. Hanjani P, Petersen RO, Lipton SE, Nolte SA. Malignant mixed mesodermal tumors and carcinosarcoma of the ovary: report of eight cases and review of the literature. *Obstet Gynecol Surv* 1983; 38: 37–545.
143. DiSilvestro PA, Gajewski WH, Ludwig ME, et al. Malignant mixed mesodermal tumors of the ovary. *Obstet Gynecol* 1995; 86: 780–2.
144. Kowalski MS. Case of primary sarcoma of the ovary in pregnancy. *Pol Tyg Lek (Wars)* 1854; 9: 12–14.
145. Schroder H. Sarcoma and carcinoma of ovary in pregnancy. *Zentralbl Gynakol* 1966; 88: 1047–51.
146. Bonevat N, Sophonn S, San LK, Samban M. Ovarian sarcoma and pregnancy (apropos of a personal case). *Bull Fed Soc Gynecol Obstet Lang Fr* 1967; 19: 214–15.
147. Brown E, Stewart M, Rye T, et al. Carcinosarcoma of the ovary: 19 years prospective data from a single center. *Cancer* 2004; 100: 2148–53.
148. Yada-Hashimoto N, Yamamoto T, Kamiura S, et al. Metastatic ovarian tumors: a review of 64 cases. *Gynecol Oncol* 2003; 89: 314–17.
149. Boulay R, Podczaski E. Ovarian cancer complicating pregnancy. *Obstet Gynecol Clin N Am* 1998; 25: 385–99.
150. Zemlicks D, Lishner M, Degendorfer P, et al. Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med* 1992; 152: 573–6.
151. Randall T. National registry seeks scarce data on pregnancy outcomes during chemotherapy. *JAMA* 1993; 269: 323.
152. Doll DC, Ringenberg QS, Yarbrow JW. Antineoplastic agents and pregnancy. *Semin Oncol* 1989; 16: 337–46.
153. Otton G, Higgins S, Phillips KA, Quinn M. A case of early-stage epithelial ovarian cancer in pregnancy. *Int J Gynecol Cancer* 2001; 11: 413–17.
154. Bakri YN, Ezzat A, Akhtar M, Dohami H, Zahrani A. Malignant germ cell tumors of the ovary. Pregnancy considerations. *Eur J Obstet Gynecol Reprod Biol* 2000; 90: 87–91.
155. Karlen JR, Akbari A, Cook WA. Dysgerminoma associated with pregnancy. *Obstet Gynecol* 1979; 53: 330–5.
156. Briggs GG, Freeman RK, Yaffe SJ. *A Reference Guide to Fetal and Neonatal Risk: Drugs in pregnancy and lactation*. Baltimore: Williams and Wilkins, 1994.
157. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 1994; 93: 137.
158. Obner WB. Choriocarcinoma: historical notes. In: Szulman AE, Buschbaum J, eds. *Gestational Trophoblastic Disease*. New York: Springer Verlag, 1987.
159. Dehner LP. Gestational and nongestational trophoblastic disease. *Am J Surg Pathol* 1980; 4: 43–58.
160. Vaitukaitis JL, Braunstein GD, Ross GT. A radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone. *Am J Obstet Gynecol* 1972; 113: 751–8.
161. Voss IP, Riottmanm G, Kazii T. Hydatidiform mole: two entities. *Am J Obstet Gynecol* 1977; 127: 167–70.
162. Lawler SD, Fisher RA, Dent J. A prospective genetic study of complete and partial hydatidiform moles. *Am J Obstet Gynecol* 1991; 164: 1270–7.
163. Grimes DA. Epidemiology of gestational trophoblastic disease. *Am J Obstet Gynecol* 1984; 150: 309–18.
164. Kahan EI. Clinical management and the neoplastic sequelae of trophoblastic embolization associated with hydatidiform mole. *Obstet Gynecol Surv* 1987; 42: 484–8.
165. Berkowitz RJ, Goldstein DP, DuBeshten B, Bernstein MR. Management of complete molar pregnancy. *J Reprod Med* 1987; 32: 634–9.
166. Bageshawe KD. Risk and prognostic factors in trophoblastic neoplasm. *Cancer* 1976; 58: 1373–85.
167. Hammond CB, Berchert LG, Tyrey L, Creasman WT, Parker RT. Treatment of metastatic trophoblastic disease: good and poor prognosis. *Am J Obstet Gynecol* 1973; 115: 451–7.

168. Mutch DG, Soper JT, Baker ME, et al. Role of computer axial tomography of the chest in staging patients with nonmetastatic gestational trophoblastic disease. *Obstet Gynecol* 1986; 68: 348–52.
169. Morgan JM, Lurain JR. Gestational trophoblastic neoplasia: an update. *Curr Oncol Rep* 2008; 10: 497–504.
170. American College of Obstetricians and Gynecologists. Carcinoma of the Breast. Technical bulletin no. 158. ACOG, 1991.
171. Antonelli NM, Dotters DJ, Katz VL, Kuller JA. Cancer in pregnancy: a review of the literature: part I. *Obstet Gynecol Surv* 1996; 51: 125–34.
172. Gallenberg M, Loprinzi C. Breast cancer and pregnancy. *Semin Oncol* 1989; 16: 369–76.
173. King R, Welch J, Martin JJ, Coulam C. Carcinoma of the breast associated with pregnancy. *Surg Gynecol Obstet* 1985; 160: 228–32.
174. Tretli S, Kvalheim G, Thoresen S, Host H. Survival of breast cancer patients diagnosed during pregnancy or lactation. *Br J Cancer* 1988; 58: 382–4.
175. Ishida T, Yokoe T, Kasumi F, et al. Clinicopathological characteristics and prognosis of breast cancer patients associated with pregnancy and lactation: analysis of case-control study in Japan. *Jpn J Cancer Res* 1992; 83: 1143–9.
176. Liberman L, Giess C, Dershaw D, Deutch B, Petrek J. Imaging of pregnancy-associated breast cancer. *Radiology* 1994; 191: 245–8.
177. Bonnier P, Romain S, Dilhuydy J, et al. Influence of pregnancy on the outcome of breast cancer: a case-control study. *Int J Cancer* 1997; 72: 720–7.
178. Byrd BJ, Bayer D, Robertson J. Treatment of breast cancer associated with pregnancy and lactation. *Ann Surg* 1962; 155: 940–7.
179. Bunker M, Peters M. Breast cancer associated with pregnancy or lactation. *Am J Obstet Gynecol* 1963; 85: 312–21.
180. Applewhite R, Smith L, DiVincenti F. Carcinoma of the breast associated with pregnancy and lactation. *Am Surg* 1973; 39: 101–4.
181. Nettleton J, Long J, Kuban D, et al. Breast cancer during pregnancy: quantifying the risk of treatment delay. *Obstet Gynecol* 1996; 87: 414–18.
182. Gallenberg MM, Loprinzi CL. Breast cancer and pregnancy. *Semin Oncol* 1989; 16: 369–76.
183. Samuels T, Liu F-F, Yaffe M, Haider M. Gestational breast cancer. *Can Assoc Radiol J* 1998; 49: 172–80.
184. Nicklas A, Baker M. Imaging strategies in pregnant cancer patients. *Semin Oncol* 2000; 27: 623–32.
185. Gwyn K, Theriault R. Breast cancer during pregnancy. *Oncology (Huntingt)* 2001; 15: 39–46.
186. Hoover HC. Breast cancer during pregnancy and lactation. *Surg Clin North Am* 1990; 70: 1151–63.
187. Novotny D, Maygarden S, Shermer R, Frable W. Fine needle aspiration of benign and malignant breast masses associated with pregnancy. *Acta Cytol* 1991; 35: 676–86.
188. Westenend PJ, Sever AR, Beekman-De Volder JH, Leim SJ. A comparison of aspiration cytology and core needle biopsy in the evaluation of breast lesions. *Cancer* 2001; 93: 146–50.
189. Shannon J, Douglas-Jones AG, Dallimore NS. Conversion of core biopsy in preoperative diagnosis of breast lesions: is it justified by results? *J Clin Pathol* 2001; 54: 762–5.
190. Poniacka AW, Krasuski P, Gal E, et al. Granulomatous inflammation of the breast in a pregnant woman: report of a case with fine needle aspiration diagnosis. *Acta Cytol* 2001; 45: 797–801.
191. Brenner RJ, Bassett LW, Fajardo LL, et al. Stereotactic core-needle breast biopsy: a multi-institutional prospective trial. *Radiology* 2001; 218: 866–72.
192. Glacalone P-L, Laffargue F, Benos P. Chemotherapy for breast carcinoma in pregnancy: a French national survey. *Cancer* 1999; 86: 2266–72.
193. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther* 1997; 74: 207–20.
194. Nicholson HO. Cytotoxic drugs in pregnancy: review of reported cases. *J Obstet Gynaecol Br Commonw* 1968; 75: 307–12.
195. Nugent P, O'Connell TX. Breast cancer and pregnancy. *Arch Surg* 1985; 120: 1221–4.
196. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer* 1991; 61: 869–72.
197. Gelber S, Coates A, Goldhirsch A, et al.; Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 2001; 19: 1671–5.
198. Sankila R, Heinvaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: healthy mother effect. *Am J Obstet Gynecol* 1994; 170: 818–23.
199. Kroman N, Jensen M-B, Wohlfahrt J, Ejlersen B. Pregnancy after treatment of breast cancer – a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol* 2008; 47: 545–9.
200. Ariel I, Kempner R. The prognosis of patients who become pregnant after mastectomy for breast cancer. *Int Surg* 1989; 74: 185–7.
201. Petrek J. Pregnancy safety after breast cancer. *Cancer* 1994; 74: 528–31.
202. Malamou N, Stathopoulos G, Keramopoulos A, Papadiamantis J, Vassilaros S. Pregnancy and offspring after the appearance of breast cancer. *Oncology* 1996; 53: 471–5.
203. Whiteman MK, Hillis SD, Curtiss KM, et al. Reproductive history and mortality after breast cancer diagnosis. *Obstet Gynecol* 2004; 1: 146–54.
204. Kroman N, Mouridsen HT. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *Breast* 2003; 12: 516–21.
205. Gonsoulin W, Mason B, Carpenter RS. Colon cancer in pregnancy with elevated maternal serum a-fetoprotein level at presentation. *Am J Obstet Gynecol* 1990; 163: 1172–3.
206. Nesbitt JC, Moise KJ, Sawyers JL. Colorectal carcinoma in pregnancy. *Arch Surg* 1985; 12: 636–40.
207. Hill JA, Kassam SH, Talled OE. Colonic cancer in pregnancy. *South Med J* 1984; 77: 375–8.
208. Woods JB, Martin JN Jr, Ingram FH, et al. Pregnancy complicated by carcinoma of the colon above the rectum. *Am J Perinatol* 1992; 9: 102–10.
209. Minter A, Malik R, Ledbetter L, et al. Colon cancer in pregnancy. *Cancer Control* 2005; 12: 196–202.
210. Cappell MS. Colon cancer during pregnancy. *Gastroenterol Clin North Am* 1998; 27: 225–56.
211. Balthazer EJ, Megibow AJ, Hulnick D, Naidich DP. Carcinoma of the colon: Detection and preoperative staging by CT. *AJR Am J Roentgenol* 1988; 150: 301–6.
212. Fletcher RH. Carcinoembryonic antigen. *Ann Intern Med* 1986; 104: 66–73.
213. Saif MW. Management of colorectal cancer in pregnancy: a multi-modality approach. *Clin Colorectal Cancer* 2005; 5: 247–56.
214. Knoepp LF Jr, Ray JE, Overby I. Ovarian metastases from colorectal carcinoma. *Dis Colon Rectum* 1973; 16: 305–11.
215. Mason MH, Kovalcik PJ. Ovarian metastases from colon carcinoma. *J Surg Oncol* 1981; 17: 33–8.
216. Reintgen DS, McCarty KS, Vollmer R, Cox E, Seigler HF. Malignant melanoma and pregnancy. *Cancer* 1985; 55: 1340–4.
217. Allen HH, Nisker JA. Cancer in Pregnancy: Therapeutic Guidelines. Mt. Kisco, NY: Futura, 1986.
218. Ries LAG, Eisner MP, Kosary CL, et al., eds. SEER cancer statistics review, 1975–2002. National Cancer Institute, Bethesda, MD. [Available from: http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER website 2005]. Accessed 1 May 2005.
219. Balch CM, Murad TM, Soong SJ, et al. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. *Ann Surg* 1978; 188: 732–42.
220. Ho VC, Sober AJ. Therapy for cutaneous melanoma: an update. *J Am Acad Dermatol* 1990; 22: 159–76.
221. Wong DJ, Strassner HT. Melanoma in pregnancy. *Clin Obstet Gynecol* 1990; 33: 782–90.
222. Colbourn DS, Nathanson L, Belilos E. Pregnancy and malignant melanoma. *Semin Oncol* 1989; 16: 377–87.
223. Lambe M, Ekblom A. Cancers coinciding with child bearing: delayed diagnosis during pregnancy? *BMJ* 1995; 311: 1607–8.
224. Haas JF. Pregnancy in association with a newly diagnosed cancer: a population-based epidemiologic assessment. *Int J Cancer* 1984; 34: 229–35.
225. Wiggins CL, Berwick M, Newton Bishop JA. Malignant melanoma in pregnancy. *Obstet Gynecol Clin N Am* 2005; 32: 559–68.
226. Slingliff LL, Reintgen DS, Vollmer RT. Malignant melanoma arising during pregnancy: a study of 100 patients. *Ann Surg* 1990; 211: 552–9.
227. Balch CM, Soong SJ, Gershenwald JE, et al. A prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint

- Committee on Cancer melanoma staging system. *J Clin Oncol* 2001; 19: 3622–34.
228. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970; 172: 902–8.
 229. Stadelmann WK, Rapaport DP, Soong SJ, et al. Prognostic, clinical, and pathologic features. In: Balch CM, Houghton AN, Sober AJ, et al., eds. *Cutaneous melanoma*, 3rd edn. St. Louis: Quality Medical Publishing, 1998: 11–35.
 230. Altman JF, Lowe L, Redman B, et al. Placental metastases of maternal melanoma. *J Am Acad Dermatol* 2003; 49: 1150–3.
 231. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol* 2003; 189: 1128–35.
 232. Dildy GA, Moise KJ, Carpenter RJ Jr, Klima T. Maternal malignance metastatic to the products of conception: a review. *Obstet Gynecol Surv* 1989; 44: 535–40.
 233. Pavlidis NA. Coexistence of pregnancy and malignancy. *Oncologist* 2002; 7: 279–87.
 234. McLain CR. Leukemia in pregnancy. *Clin Obstet Gynecol* 1974; 17: 185–94.
 235. Reynoso EE, Shepherd FA, Messner HA, et al. Acute Leukemia during pregnancy: the Toronto Leukemia Study Group experience with long-term follow-up of children exposed in utero to chemotherapeutic agents. *J Clin Oncol* 1987; 5: 1098–106.
 236. Kuzel TM, Benson AB. Non-Hodgkin's lymphoma. In: Gleicher N, ed. *Principles and practice of medical therapy in pregnancy*, 2nd edn. East Norwalk (CT): Appleton and Lang, 1992: 1078–80.
 237. Juarez S, Cuarado Pastor JM, Feliu J, et al. Association of leukemia and pregnancy: clinical and obstetric aspects. *J Clin Oncol* 1988; 11: 159–65.
 238. Hoelzer D, Gokbuget N. Acute lymphocytic leukemia and Klinefelter's syndrome. *Pediatr Hematol Oncol* 1992; 9: 81–5.
 239. Wiernek PH. Acute leukemia in adults. In: DeVita VT, ed. *Cancer: Principles and Practice of Oncology*, 3rd edn. Philadelphia: JB Lippincott, 1989.
 240. Chelghoum Y, Vey N, Raffoux E, et al. Acute leukemia during pregnancy: a report on 37 patients and a review of the literature. *Cancer* 2005; 104: 110–17.
 241. Koren G, Weiner L, Lishner M, Zemelickes D, Finegen J. Cancer in pregnancy: identification of unanswered questions on maternal and fetal risks. *Obstet Gynecol Surv* 1990; 45: 509–14.
 242. Hoelzer D, Gokbuget N. Acute lymphocytic leukemia in adults. In: Hoffman R, Benz EJ, Shattil SJ, eds. *Hematology: basic principles and practice*, 4th edn. Philadelphia: Elsevier, 2005: 1177.
 243. Todeschini G, Tecchio C, Meneghini V, et al. Estimated 6-year event-free survival of 55% in 60 consecutive adult acute lymphoblastic leukemia patients treated with an intensive phase II protocol based on high induction dose of daunorubicin. *Leukemia* 1998; 12: 144–9.
 244. Hurley TJ, McKinnell JV, Irani MS. Hematologic malignancies in pregnancy. *Obstet Gynecol Clin N Am* 2005; 32: 595–614.
 245. Williams SF, Bitran JD. Cancer and pregnancy. *Clin Perinatol* 1985; 12: 609–23.
 246. Elliot MA, Wolf RC, Hook CC, et al. Thromboembolism in adults with acute lymphoblastic leukemia during induction with L-asparaginase-containing multi-agent regimens: incidence, risk factors, and possible role of antithrombin. *Leuk Lymphoma* 2004; 45: 1545–51.
 247. Beinant G, Damon L. Thrombosis associated with L-asparaginase therapy and low fibrinogen levels in adult acute lymphoblastic leukemia. *Am J Hematol* 2004; 77: 331–5.
 248. Mauz-Körholz C, Junken R, Göbel U, Nowak-Göttl U. Prothrombotic risk factors in children with acute lymphoblastic leukemia treated with delayed E. coli asparaginase (CCOALL-92 and 97 protocols). *Thromb Haemost* 2000; 83: 840–3.
 249. Jaime-Perez JC, Gomez-Almaguer D. The complex nature of the prothrombotic state in acute lymphoblastic leukemia of childhood. *Haematology* 2003; 88: ELT 25.
 250. Caligiuri MA, Mayer RJ. Pregnancy and leukemia. *Semin Oncol* 1989; 16: 338–96.
 251. Greenlund LJS, Letendne L, Tefferi A. Acute leukemia during pregnancy: a single institutional experience with 17 cases. *Leuk Lymphoma* 2001; 41: 571–7.
 252. Jacob JH, Stringer CA. Diagnosis and management of cancer during pregnancy. *Semin Perinatol* 1990; 14: 79–87.
 253. Sadural E, Smith LG. Hematologic malignancies during pregnancy. *Clin Obstet Gynecol* 1995; 38: 525–46.
 254. Mesquita M, Pestana A, Mota A. Successful pregnancy occurring with interferon-alpha therapy in chronic myeloid leukemia. *Acta Obstet Gynecol* 2005; 84: 300–1.
 255. Mubarak AA, Kakil ER, Awidi A, et al. Normal outcome of pregnancy in chronic myeloid leukemia treated with interferon-alpha in 1st trimester: report of 3 cases and review of the literature. *Am J Hematol* 2002; 69: 115–18.
 256. DeVita VT, Hellman S, Rosenberg SA. Hodgkin's disease and the non-Hodgkin's lymphomas. In: DeVita VT, ed. *Cancer: Principles and Practice of Oncology*, 3rd edn. Philadelphia: JB Lippincott, 1989.
 257. Weinschel EL, Peterson BA. Hodgkin's disease. *CA Cancer J Clin* 1993; 43: 327–45.
 258. Walker JW, Reinisch JF, Monforte HL. Maternal pulmonary adenocarcinoma metastatic to the fetus: first recorded case report and literature review. *Pediatr Pathol Mol Med* 2002; 21: 57–69.
 259. Yasmeen S, Cress R, Romano PS, et al. Thyroid cancer in pregnancy. *Int J Gynecol Obstet* 2005; 91: 15–20.
 260. SEER cancer statistics review. National Cancer Institute Surveillance, Epidemiology, and End Results; 1975–2000. [Available from: http://seer.cancer.gov/csr/1975_2000/results/merged/sect_16_thyroid_cancer.pdf] Accessed January 2005.
 261. Morris PC. Thyroid cancer complicating pregnancy. *Obstet Gynecol Clin* 1998; 25: 401–6.
 262. Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Cancer* 1987; 55: 191–5.
 263. Rosen IB, Walfish PG. Pregnancy as a predisposing factor in thyroid neoplasia. *Arch Surg* 1986; 121: 1287–90.
 264. Mazzaferri E. Evaluation and management of common thyroid disorders in women. *Am J Obstet Gynecol* 1997; 176: 507.
 265. Hamer CL, McCreedy VR. Thyroid cancer: differentiated carcinoma. *Cancer Treat Rev* 1996; 22: 161–77.
 266. Doherty C, Shindo M, Rice D, Montero M, Mestman JH. Management of thyroid nodules during pregnancy. *Laryngoscope* 1995; 105: 251–5.
 267. Casara D, Rubello D, Saladini G, et al. Pregnancy after high therapeutic doses of iodine-131 in differentiated thyroid cancer: potential risks and recommendations. *Eur J Nucl Med* 1993; 20: 192–4.
 268. Yutaka K, Kenji I, Tadayuki A. Sarcoma associated with pregnancy. *Am J Obstet Gynecol* 1989; 161: 94–6.
 269. Simon MA, Phillips WA, Bonfiglio M. Pregnancy and aggressive or malignant bone tumors. *Cancer* 1984; 53: 2564–9.
 270. Huvos AG, Butler A, Bretsky SS. Osteogenic sarcoma in pregnant women. *Cancer* 1985; 56: 2326–31.
 271. Haerr RW, Pratt AT. Multiagent chemotherapy for sarcoma diagnosed during pregnancy. *Cancer* 1985; 56: 1028–33.
 272. Roelvink NC, Kamphorst W, van Alphen H, Rao BR. Pregnancy related primary brain and spinal tumors. *Arch Neurol* 1987; 44: 209–15.
 273. Haas JF, Janisch W, Stanecz W. Newly diagnosed primary intracranial neoplasms in pregnant women: a population based assessment. *J Neurol Neurosurg Psychiatry* 1986; 49: 874–80.
 274. Johnson N, Sermer M, Lausman A, Maxwell C. Obstetric outcomes of women with intracranial neoplasms. *Int J Gynecol Obstet* 2009; doi: 10.1016/j.jigo.2008.11.037 105: 56–9.
 275. Wan WL, Geller JL, Feldon SE, Sadun AA. Visual loss caused by rapidly progressive intracranial meningiomas during pregnancy. *Ophthalmology* 1990; 97: 18–21.
 276. Magyar DM, Marshall JR. Pituitary tumors and pregnancy. *Am J Obstet Gynecol* 1978; 132: 739–49.
 277. Apuzzo J, Peliosio MA, Ganesh VV, Caterini H, Iffy L. Spinal cord tumors during pregnancy. *Int J Gynecol Obstet* 1980; 17: 608–10.
 278. Simon RH. Brain tumors in pregnancy. *Semin Neurol* 1988; 8: 214–21.
 279. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; 5: 283–91.
 280. Roboz J, Gleicher N, Wuk K, et al. Does doxorubicin cross the placenta? *Lancet* 1979; 2: 1382–3.