HHS Public Access

Author manuscript

Obstet Gynecol Surv. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Obstet Gynecol Surv. 2017 March ; 72(3): 184–193. doi:10.1097/OGX.0000000000000407.

Gynecologic Malignancies in Pregnancy: Balancing Fetal Risks with Oncologic Safety

Christina N. Cordeiro, MD[*] and **Mary L. Gemignani, MD, MPH**[†]

[*]Resident Physician, Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD

[†]Attending Surgeon, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Importance—Cancer occurs in 0.05 to 0.1% of all pregnancies.[1,2] Despite literature reporting good oncologic and fetal outcomes in women treated for cancer during pregnancy, as many as 44% of gynecologists would offer termination, and 37% would not administer chemotherapy or radiotherapy in pregnancy.[1]

Objectives—To summarize current recommendations for the treatment of cervical and ovarian cancers in pregnancy. To review updates on existing knowledge regarding the safety of surgical and chemotherapeutic treatments in pregnancy, including both oncologic and fetal outcomes.

Evidence Acquisition—A detailed literature review was performed on PubMed.

Results—The treatment of gynecologic malignancies during pregnancy mirrors that outside of pregnancy, with a balance between maternal versus fetal health. Fertility-sparing surgery can be offered to stage IA2 and low-risk IB1 cervical, stage I epithelial ovarian, germ cell ovarian or sex-cord stromal ovarian tumors.[1,9] Delayed treatment can be offered for stage IB1 cervical cancer.[1,3] Neoadjuvant and/or adjuvant chemotherapy can be given for advanced gynecologic cancers with good disease-free survival without significant adverse neonatal outcomes.[29–31,41,47,48]

Conclusions—A multidisciplinary approach and improved education of providers regarding the surgical and chemotherapeutic treatments in pregnancy is needed in order to fully inform patients regarding treatment options. Further research is needed to determine the safety of diagnostic and therapeutic procedures used in the non-pregnant woman in women who are pregnant.

Relevance—This article reviews and supports treatment of gynecologic cancer during pregnancy, calls for additional study and long-term follow-up, and justifies improved education of patients and providers regarding treatment options.

Target Audience

Obstetricians and gynecologists; gynecologic oncologists; medical oncologists ; family physicians

Correspondence requests to: Mary L. Gemignani, MD, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065. gemignam@mskcc.org; Telephone: 646 888 5359; Fax: 646 888 4921.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Introduction

Cancer is estimated to occur in 0.05 to 0.1% of all pregnancies. The most common gynecologic cancer presenting during pregnancy is cancer of the cervix.[2,3] The management of gynecologic cancer during pregnancy poses a number of unique challenges, particularly as they relate to the developing fetus, due to the direct relationship between the reproductive organ and the pregnancy itself. A multidisciplinary treatment approach is of the utmost importance in this setting to ensure all possible options are considered that will allow for appropriate treatment of the mother while accounting for any risks to the pregnancy.

Due to the nature of these challenges, many practitioners do not feel comfortable treating those patients who wish to continue their pregnancies. In 2013 Han et al conducted a survey of physicians belonging to professional societies in 14 European countries caring for pregnant and/or cancer patients. Forty-eight percent of physicians surveyed were gynecologic oncologists and 37% were general obstetricians/gynecologists. Overall, 44% of those surveyed stated that they would offer termination of pregnancy as a primary treatment recommendation when malignancy was diagnosed in the first or trimester of pregnancy, and 37% would not administer chemotherapy or radiotherapy when diagnosed in the third trimester of pregnancy.[1] This is in direct contrast to an increasing body of published literature reporting good oncologic and fetal outcomes in women who are treated during pregnancy.

The goal of this review will be to summarize current recommendations for the treatment of gynecologic malignancies in pregnancy. It will focus upon recent updates on existing knowledge regarding the safety of surgical and chemotherapeutic treatments in pregnancy, including both oncologic and fetal outcomes.

GENERAL TREATMENT CONSIDERATIONS

Currently, guidelines recommend avoiding elective surgery until the second or third trimester of pregnancy, [4] although these data are based upon retrospective reports from the 1970s of very-low- and low-birth-weight-infants as well as infants dying within 168 hours.[5] In fact, more recently, Ko et al. [6] reported safe management of complicated adnexal masses with laparoscopic surgery during the first trimester, supporting surgical treatment of cancer in pregnancy in any trimester. There is an increased risk of miscarriage associated with surgery in the first trimester of pregnancy; hence, if at all possible, elective surgery should be deferred to the second or third trimester.[4] Fetal monitoring (depending upon gestational age), deep venous thrombosis prophylaxis, tocodynamometry, left lateral tilt, and adequate pain control should be ensured, particularly in the third trimester.[4,7] The use of corticosteroids to accelerate fetal lung maturity can be considered 48 hours prior to surgery for fetuses less than 34 weeks of gestation in either patients who are intentionally delivered early, or in patients with spontaneous preterm labor resulting from surgery (reviewed in Grimm et al[4]).

Several physiologic changes in pregnancy may lead to overall lower plasma levels of chemotherapeutic drugs; however, there is no evidence at present that dose adjustments are

necessary to improve efficacy.[4,8] Chemotherapy administered during the first trimester, specifically during the period of organogenesis (weeks 4 through 12), poses the highest risk of fetal teratogenesis, with an increased risk associated with multi-agent therapy.[9,10] Ebert et al[11] reported on 217 cases of myriad cancers (e.g., leukemia, malignant lymphoma, severe rheumatologic disease, gynecologic/breast cancer) treated with multiple different combination chemotherapeutic regimens (e.g., different combinations of alkaloids, purine analogs, cyclophosphamide, doxorubicin, bleomycin, vinblastine, vincristine, among others) during pregnancy, noting that only 18 newborns had congenital abnormalities and two had chromosome abnormalities. Of these, 15 were exposed during the first trimester.[11] These studies suggest the need to avoid administering chemotherapy during the first trimester. Thus, ideally, chemotherapy should be administered after the first trimester. Additionally, it is recommended that chemotherapy be discontinued three weeks prior to delivery due to risk of hematopoietic suppression in mother and newborn, and to prevent drug accumulation in fetus.[12]

Several studies have reported good neonatal outcomes associated with chemotherapy given during pregnancy. Overall, rates of congenital malformations associated with chemotherapy in pregnancy have been reported at 16%, 8%, and 6% in the first, second, and third trimesters, respectively.[13] During the second and third trimester, fetal effects associated with chemotherapy include intrauterine growth restriction, prematurity, and low birth weight. The toxicities associated with chemotherapy for the mother may also affect the fetus, including hair loss and myelosuppression (reviewed in Minig et al[9]).

Amant et al[7] reported on long-term follow-up of 70 children born at a median gestational age of 35.7 weeks who were followed for a median of 22.3 months after in utero exposure to chemotherapy for skin and inflammatory disease. Overall, neurocognitive outcomes were within normal limits; cognitive development scores were lower only for children who were born preterm as compared with those born at term. However, these children demonstrated a 39% discrepancy in verbal and performance IQ values as compared with 15% in the normal population, and they tended to have more behavioral problems than other children.[7] Second, although cardiac dimensions and function, behavior, general health, hearing, and growth were similar to what is reported in children who have not received chemotherapy in utero, clinically small but statistically significant differences were noted in ejection fraction, fractional shortening, and interventricular septum thickness. This suggests possible adverse fetal effects of chemotherapy in utero, although the clinical relevance of those effects is not known.

In each ensuing section, we review the published literature with respect to chemotherapeutic regimens used in pregnancy for women with cervical and ovarian cancers. Studies on long-term follow-up of children who receive chemotherapy in utero are limited, and further follow-up is necessary to establish the long-term safety of this approach.

CERVICAL CANCER IN PREGNANCY

Cervical cancer in pregnancy: introduction and diagnosis, including staging procedures

Cervical cancer is the most commonly diagnosed cancer during pregnancy, with an incidence of 1.5 to 12 per 100,000 pregnancies (cited in Hunter et al[14]). The 30-year survival of pregnant women diagnosed with cervical cancer is identical to age and disease-matched controls, suggesting that pregnancy does not affect survival.[15] Over the past few years, some general treatment recommendations have been put forth by national and international societies which are, for the most part, in agreement with each other with respect to the management of cervical cancer during pregnancy.[16–18]

Recommendations for screening and diagnosis are clearly defined.[3,19] A Pap smear should be performed at the first prenatal visit, and high-grade results should be followed up with intrapartum colposcopy and biopsies as clinically indicated. Endocervical curettage is contraindicated in pregnancy.[3]

In cases of biopsy-confirmed invasive cervical cancer, staging work up is indicated. For patients with stage IB1 cancer or greater, this may include a chest X-ray to evaluate for pulmonary metastases. Imaging of the urinary tract by ultrasound or MRI is generally recommended. Some authors have reported that pelvic MRI is “essential” for staging and management of these patients.[3,19]

The evaluation of lymph node status is critical to the prognosis and management of cervical cancer, particularly in the setting of pregnancy. Multiple authors have reported on the use of laparoscopy to perform lymphadenectomy as a part of surgical staging until at least 20 weeks gestation, without adverse fetal outcomes.[19] Vercellino et al[20] reported a large series of 32 patients undergoing laparoscopic pelvic lymphadenectomy for cervical cancer, with varied laparoscopic port and camera placements, as dictated by gestational age. There were no adverse obstetric or neonatal outcomes. Smaller studies have confirmed the safety of this technique in pregnancy.[21]

Sentinel lymph node (SLN) mapping for cervical cancer in pregnancy has not been well studied; Silva et al[22] published a case report of radioisotopic SLN mapping in a pregnant woman at 14 weeks gestation with a stage IB2, 6 cm cervical cancer. The authors reviewed the negligible risk of radiation exposure to the fetus and concluded that this procedure is feasible in pregnancy. Further study of the safety of this technique is needed. Mapping with blue dye in pregnancy is generally avoided because of the risk of anaphylactic reactions.

Cervical cancer in pregnancy: surgical treatment for stage IA

Early cervical cancer at a gestational age of greater than 22 to 25 weeks can be treated after delivery with no known adverse oncologic effects. However, for presentation at an earlier gestational age, intrapartum treatment is indicated. Stage IA1 disease is treated with cervical conization, while lymph node dissection is recommended as triage for stage IA2 cancer and above.[1,23]

Radical trachelectomy is associated with significant complications and a 32% rate of early pregnancy loss. Thus, recent recommendations from the European Society of Gynecologic Oncology task force on “Cancer in Pregnancy,” involving consultation with international experts during a consensus meeting, are for large conization for stage IA2 and IB1 tumors smaller than 2 cm with negative lymph nodes.[2] Significant complications have also been reported related to cervical conization in pregnancy, although less severe than those associated with trachelectomy. These include bleeding requiring transfusion, re-operation or readmission (6.2%), an increased rate of cervical laceration at time of vaginal delivery (18%), and an increased rate of fetal loss during second trimester conizations (19.1% abortion or fetal loss).[24] One promising option to decrease the morbidity associated with this procedure is loop-cone cerclage (i.e., a LEEP with top hat followed by McDonald cerclage placement). An analysis of 13 patients undergoing this procedure reported no cases of hemorrhage or pregnancy loss.[25] Further studies are needed to investigate the safety of this procedure as compared with a standard conization.

Treatment of stage IB or greater cervical cancer in pregnancy: treatment delay

Recently, new literature suggests that delayed treatment for stage IB1 cervical cancer, if lymph nodes are negative and gestational age is > 22 to 25 weeks, is an oncologically safe option.[1,2] In a review of 76 cases of stage IB1 cervical cancer with negative lymph nodes in which treatment was delayed until delivery (mean delay 16 weeks), the authors reported a 95% survival rate with no recurrence after a mean follow-up period of 37.5 months. An additional study by Takushi et al[26] also reported on delayed treatment for stage IB1 disease; in 21 patients with maximum a treatment delay of 32 weeks, two died of disease and no disease progression was reported among survivors.

Two additional reviews of stages IA and IB cancer further support delayed treatment for select cases of stage IB disease. Fukushima et al[27] reviewed 24 cases of pregnancy-associated cervical cancer. Expectant management for a mean length of 19.8 weeks was chosen for three patients with stage IA1 cancer and one with stage 1B cancer (seven weeks) with no cases of recurrence of or death from disease. Another study of 21 women with a tumor measuring less than 2 cm followed nine patients with treatment delay, five diagnosed during the first trimester and four diagnosed during the second trimester.[28] Five-year survival was not affected by a delay in treatment.[28]

Treatment of stage IB or greater cervical cancer in pregnancy: chemotherapy

For stage IB1 disease with positive lymph nodes or stage IB2 with a tumor measuring than 2 cm or higher, neoadjuvant chemotherapy is an option when pregnancy continuation is desired. However, no standard chemotherapy treatment regimens have been established. Current recommendations are for platinum-based chemotherapy with or without paclitaxel.[2].

Fruscio et al[29] report on the use of cisplatin monotherapy for stage IB cervical cancer, with good oncologic outcomes. However, a recent international report of guidelines for management of pregnancy-associated cervical cancer in France favor a combination approach with paclitaxel plus cisplatin over cisplatin alone based upon analyses statistically significantly improved outcomes as compared with cisplatin alone.[2] Of note, due to the risk

of fetal kidney damage associated with iphosphamide, this agent is not utilized in pregnancy (cited in Fruscio et al[29]).

With respect to oncologic and fetal outcomes of paclitaxel-based regimens used in cervical cancer during pregnancy, Li et al[30] reported on two cases of the use of paclitaxel plus platinum-based chemotherapy for stage IB2 cervical cancer in pregnancy resulting in a partial response (e.g., reduction in tumor size to 1.0 cm in greatest diameter) and a complete response for the two patients, respectively. There were no adverse fetal or neonatal outcomes after 12–21 months follow-up.

An alternative regimen is cisplatin with vincristine. A retrospective review of patients with FIGO stages IB1 and IB2 cervical cancer diagnosed in the first or second trimester reported on the use of cisplatin and vincristine followed by a median duration of therapy delay to delivery of 16 weeks, without any cases of spontaneous preterm birth.[29] All patients with stage IB1 cancer were alive at a median 65 months follow-up. Two patients treated with adjuvant radiation therapy had a recurrence, and one died. Neonatal outcomes were positive overall, with one case of intraventricular hemorrhage and one of mild respiratory distress syndrome, suspected to be secondary to prematurity.[29]

Few studies have reported on the use of neoadjuvant chemotherapy with delayed surgical treatment for cervical cancer of stage II or greater. Palaia et al[31] report a case of stage IIB cervical cancer diagnosed at 19 weeks, treated with neoadjuvant cisplatin plus paclitaxel for cycle 1, followed by cisplatin alone due to a paclitaxel-associated allergic reaction, with a good oncologic response of negative lymph nodes and a 2.5 cm tumor after hysterectomy at 35 weeks. Additionally, a recent review of 36 pregnant patients with stage IB1 through IIIB tumors, all of whom underwent neoadjuvant chemotherapy with delivery delay to radical hysterectomy, reported that the patients who died during follow-up (9/36) had stage IB2-IIIB cancer, many with negative prognostic factors such as positive lymph nodes and parametrial invasion. Therefore, the authors concluded that mortality is similar to that reported for cervical cancer outside of pregnancy and that chemotherapy to allow for continued pregnancy is oncologically safe in this population.[29] Overall, the survival associated with IB1 cancer is 94%, and with IB2 or higher is 70%, when patients are treated with chemotherapy with an average delay of delivery until 33.2 weeks.[2]

Cervical cancer in pregnancy: aspects of delivery

With respect to delivery, patients with stage IA1 without LVSI disease confirmed after conization of the cervix may undergo vaginal delivery at term, based upon a report that no invasive disease over CIN III was found in postpartum surgical specimens.[26] Typically, patients with stage IA2, IB, and IIA disease are delivered via Cesarean section due to the possibilities of infection, hemorrhage, obstructed labor, and dissemination of tumor cells via cervical dilation or at the episiotomy site, with conflicting data reported in various studies (reviewed in Sood et al[32]; Van Calsteren et al[33]). One matched case-control study of 56 women diagnosed with cervical cancer during pregnancy and 27 within 6 months of delivery, as compared with non-pregnant controls, 19 with stage I and 8 with stage IIA or higher, reported higher recurrence rates in women delivering vaginally (59%, n = 10) as compared with those delivering by Cesarean section (14%, n = 1). Vaginal delivery, as

compared with stage, diagnosis postpartum, smoking status, and histology, was the most significant predictor of recurrence (odds ratio [OR] 6.91, 95% confidence interval [CI] 1.45–32.8). Vaginal delivery was also associated with worse overall survival than by other delivery methods (p = 0.001).[32] During Cesarean section, some argue that a low transverse uterine incision is preferable to a classical incision to decrease blood loss, although abdominal wall metastases may occur if the placenta is anterior.[33]

At the time of delivery, the standard of treatment is radical hysterectomy. Important to note for providers treating patients with cervical cancer in pregnancy is the increased complication rate of radical hysterectomy in the setting of pregnancy.[34] Radical hysterectomy at time of Cesarean delivery has been associated with increased blood loss as compared with non-pregnant patients; in three women delivering nonviable fetuses (e.g., < 24 weeks gestational age) vaginally and four patients with combined Cesarean section-hysterectomy, transfusion rates for radical hysterectomy were 57%, as compared with 9% outside of pregnancy.[34]

Cervical cancer in pregnancy: conclusions

In summary, women with invasive cervical cancer and concurrent pregnancy can be faced with a difficult decision. A multidisciplinary treatment approach is necessary including the patient's obstetrician, a gynecologic oncologist, and/or a medical oncologist. Patients need guidance and information regarding outcomes and treatment issues regarding continuation of pregnancy. Particularly important in their decision making is balancing risks of prematurity for the infant and treatment delays for the patient, as well as the risks related to combined obstetrical and oncologic surgery.

Ovarian Masses and Cancer in Pregnancy

Ovarian cancer in pregnancy: introduction and diagnosis

Adnexal masses in pregnancy occur at a rate of 1/10,000 pregnancies, of which 3–6% are malignant.[35] The incidence of benign ovarian masses in pregnancy is as follows: benign cystic teratoma (7–37%), serous cystadenoma (5–28%), mucinous cystadenoma (3–24%), endometrioma (0.8–27%), parovarian cysts (< 5%) and leiomyoma (1–2.5%).[36] Although epithelial ovarian cancer is the most aggressive and common type of ovarian cancer outside of pregnancy, during pregnancy, germ cell tumors occur at the highest frequency, with only 35% of ovarian cancers diagnosed during pregnancy of epithelial origin (reviewed in Minig et al[9]). Adnexal masses are usually identified similarly to those outside of pregnancy, via physical examination and/or ultrasound.

Epithelial ovarian cancer in pregnancy: surgical treatment

Surgical management of ovarian masses is indicated for either a diagnostic concern for malignancy or for symptomatic relief (reviewed in Han et al[3]). Factors associated with increased risk of malignancy in pregnancy include a tumor diameter of 10 cm or more (OR 11.2) and a tumor growth rate of > 3.5 cm/week (OR 10.2).[37] Surgery may also be indicated to reduce the risk of ovarian torsion. In one retrospective study of 174 women with adnexal masses measuring 4 cm or greater during pregnancy, 14.8% experienced ovarian torsion with

an OR of 2.8 for masses measuring 6–8 cm. Sixty percent of torsion episodes occurred during the late first or second trimester.[37] Finally, a recent retrospective cohort of 13,677 live births reported on 41 women with a persistent adnexal mass, of whom 25 had a mass measuring > 5 cm. Large masses were associated with an increased likelihood of poor obstetric outcomes, specifically, preterm delivery (36.6 versus 38.2 weeks gestation) and lower birth weight (2,944 versus 3169g).[38] Collectively, these studies indicate that surgical management is indicated for masses greater than 4–5 cm in diameter, in order to reduce the risk of torsion and/or poor obstetric outcomes, or if there is concern for malignancy.

More recent advances in surgical technique have allowed for laparoscopic management of adnexal masses during pregnancy. Specifically, Friedman et al[39] report that laparoscopic surgery should be utilized in cases in which tumor size is less than 6–8 cm, in which there is no suspicion for advanced-stage ovarian cancer, and in which there is a possibility for complete intact removal of the mass using endo-catch bags.

When malignancy is suspected or known, surgical staging is indicated. Of note, the standard treatment for epithelial ovarian cancer is six cycles of carboplatin with paclitaxel following optimal debulking, including bilateral salpingo-oophorectomy and total hysterectomy. [40] In contrast, the most common approach to ovarian cancer in pregnancy typically consists of ovarian cystectomy or unilateral salpingo-oophorectomy with biopsies and possibly omentectomy, appendectomy, peritoneal biopsies, and pelvic and paraaortic lymphadenectomy (reviewed in Gilani et al[41]). Such retention of the uterus and contralateral ovary may be considered in stage IA epithelial ovarian cancer, grade 1–2, following the aforementioned surgical staging, in cases of non-clear cell histology (reviewed in Minig et al[9]).

Following surgery, if continuation of pregnancy is desired, two main treatment approaches can be considered for epithelial ovarian cancer—to delay chemotherapy until fetal lung maturity followed by delivery and postpartum chemotherapy, or to administer neoadjuvant chemotherapy (reviewed in Minig et al[9] and Stuart et al[40]). In advanced stage III or IV cancer, treatment is dependent upon trimester of pregnancy. Unless debulking with pregnancy sparing can be achieved, termination is necessary in the first trimester due to the risks of chemotherapy. In the second trimester, uni- or bilateral oophorectomy, radical omentectomy, peritoneal tumorectomy, and pelvic/paraaortic lymph node sampling, and appendectomy are performed followed by chemotherapy and delivery with immediate Cesarean/hysterectomy at term. In the third trimester, complete Cesarean hysterectomy and staging is recommended, followed by chemotherapy (reviewed in Minig et al[9]). With respect to mode of delivery, some authors have suggested administering several cycles of platinum-based chemotherapy delaying completion of surgery until a few weeks after spontaneous vaginal delivery, while others have suggested Cesarean section at the time of fetal lung maturity (reviewed in Modares Gilani et al[41])

Epithelial ovarian cancer in pregnancy: chemotherapy and neonatal outcomes

Several studies have reported on the use of standard chemotherapy–specifically, carboplatin and paclitaxel–during pregnancy, with good outcomes overall. Typically, chemotherapy is avoided in the first trimester, as previously discussed. Specifically, the risk of teratogenesis

has been reported to be close to 25% for carboplatin if administered in the first trimester, as compared to 1.3% if administered in the second and third trimesters.[13]

Single-agent platinum therapy

Platinum-based regimens are commonly recommended as treatment. Carboplatin is typically preferred over cisplatin due to the improved safety profile for the former in pregnancy. Reports in the literature using single-agent platinum regimens have been reported. Mir et al[42] reviewed 43 cases of women with cancer treated during pregnancy, of whom 28 had ovarian cancer. Thirty-six patients were treated with cisplatin alone and six women were treated with carboplatin alone. In this study, cisplatin was associated with several adverse outcomes: intrauterine growth restriction (8.3%), preterm birth (8.3%), oligohydramnios (5.6%), and polyhydramnios (2.8%), respiratory distress (8%), and neonatal anemia (5.6%).[42] In comparison with cisplatin, carboplatin was not associated with any fetal malformations, toxicities, or adverse neonatal effects.[42] Such data indicate this to be a rationale for the more commonly reported use of carboplatin than of cisplatin. Tabata et al[43] described the use of single-agent carboplatin for stage IC undifferentiated ovarian carcinoma diagnosed after bilateral salpingo-oophorectomy at 18 weeks gestation. The patient was treated with four courses of carboplatin, followed by Cesarean section, total hysterectomy, omentectomy, and pelvic and paraaortic lymphadenectomy at 33 weeks, followed by postoperative combined carboplatin/paclitaxel chemotherapy. The infant had normal development at one year follow-up, and the patient had no evidence of disease. Thus, the use of single-agent chemotherapy represents an appealing future direction to be studied in the management of pregnancy-associated cervical cancer, as it decreases the amount of exposure to the fetus to chemotherapeutic agents.

Taxane, combination chemotherapy, and surgery

Taxane use during pregnancy is most commonly cited in the literature on breast cancer in pregnancy, as reviewed above.[44] No specific fetal toxicities have been reported as associated with taxane use in pregnancy.[4] For combination treatment with paclitaxel and carboplatin during pregnancy, multiple authors have reported good oncologic and fetal outcomes. A recent literature review of ovarian masses managed in pregnancy from 1984 through 2009 noted that among six cases in which chemotherapy was administered during pregnancy, no adverse outcomes were reported.[45] Among the 198 patients diagnosed with ovarian cancer during pregnancy, adverse neonatal outcomes included preterm delivery (15.1%), neonatal death (2.5%), four spontaneous miscarriages, one intrauterine death. and one congenital anomaly.[45] Ramos et al[46] also reported on the use of the combination of paclitaxel and carboplatin during 16–36 weeks of gestation, resulting in a full-term live birth without evidence of neonatal abnormalities at birth or at two months follow-up.

Several case reports have documented the use of combined chemotherapy and surgical treatment for stage III ovarian cancer. Modares Gilani et al[41] reported a case of stage III ovarian cancer in pregnancy treated with unilateral salpingo-oophorectomy followed by carboplatin plus paclitaxel with a disease-free outcome after 6 months follow-up and no adverse fetal outcomes. One case report describes a woman with stage IIIC ovarian papillary serous cystadenocarcinoma diagnosed at five weeks gestation who was treated with six

cycles of paclitaxel and carboplatin were given beginning at 16 and 17 weeks gestation, followed by Cesarean hysterectomy and completion of surgical staging and postpartum chemotherapy. A good maternal outcome and no adverse fetal effects were reported at 15 months follow-up.[47] This fetus-sparing management with combined chemotherapy, followed by surgical staging, has been reported to be successful in several cases of advanced-stage epithelial ovarian cancer. Picone et al[48] also describe a case of stage IIIB ovarian epithelial carcinoma, in this case diagnosed at 22 weeks, treated with neoadjuvant carboplatin chemotherapy followed by Cesarean section at 34 weeks concurrent with a radical hysterectomy, staging, and postoperative carboplatin and paclitaxel, with complete remission and normal child development reported at 18 months follow-up. Of note, the authors described successful radical debulking surgery at the time of Cesarean delivery in this case. Similarly, Ramos et al[46] report a case of stage III ovarian cancer diagnosed in the fifteenth week of gestation, in which right salpingo-oophorectomy, lymph node dissection, and appendectomy were followed by adjuvant carboplatin and paclitaxel. A normal infant was born by Cesarean section with no evidence of physical or neurological anomalies at 2 months. In all of these cases, oncologic treatment was combined with Cesarean section.

Sood et al reported on the use of cisplatin and paclitaxel, in a case of stage IIIC papillary serous ovarian adenocarcinoma diagnosed at 27 weeks. The patient was treated with laparotomy, cytoreductive surgery, and three cycles of paclitaxel and cisplatin prior to Cesarean section, abdominal hysterectomy, and cytoreduction at 37 weeks.[49] She had three additional cycles of chemotherapy and recurred within six weeks of completing chemotherapy, ultimately dying 29 months after diagnosis. Her infant was reported to have normal growth and development at 30 months follow-up.[49] Further long-term follow-up of patients treated during pregnancy-associated breast cancer with preservation of pregnancy in regards to recurrence and long-term outcomes is needed.

Non-epithelial ovarian cancer in pregnancy: surgical treatment

Additional nuances with respect to the treatment of ovarian cancer in pregnancy are related to tumor type. The management of borderline ovarian tumors typically consists of unilateral salpingo-oophorectomy, presuming that a thorough inspection of the abdominal and peritoneal surfaces is performed.[35] Fauvet et al[50] retrospectively reviewed cases of borderline ovarian tumors during pregnancy and reported a high incidence of aggressive features such as a 21% incidence of intraepithelial carcinoma or microinvasion among mucinous tumors and a 45% incidence of micropapillary features, non-invasive implants, or microinvasion among serous tumors. Restaging was required in 52%, resulting in upstaging in 24%.[50] Thus, staging at time of unilateral salpingo-oophorectomy is recommended.

Similarly, due to the excellent prognosis of germ cell and sex-cord stromal tumors, fertility-sparing surgery is generally recommended.[35] In a recent review of 102 cases of malignant germ cell tumors, of which 76% were stage I, 67% of patients underwent unilateral salpingo-oophorectomy, and half underwent systemic chemotherapy. The overall five-year survival was 80.1%.[35] With respect to sex cord stromal tumors, one review of 46 cases reported that most patients in the second and third trimesters underwent unilateral salpingo-oophorectomy or node removal, with 69.4% of cases allowing for preservation of the

fetus.[51] Seventy-one percent of cases necessitated one debulking surgery, while 26.1% required multiple surgical debulking procedures.[51]

Non-epithelial ovarian cancer in pregnancy: chemotherapy and neonatal outcomes

Oncologic and neonatal outcomes have been reported in the treatment of non-epithelial ovarian cancers as well. In the previously described study of management of 46 patients with sex cord stromal tumors in which 69.4% of cases pregnancy was preserved, 13% of cases required chemotherapy intrapartum and 4.3% required postpartum radiation therapy.[51] Preterm labor was common (17.4%), although 60.9% of infants were born at term. Intrauterine fetal demise occurred in 6.5%, second trimester stillbirth and spontaneous abortion occurred in 2.2%. Overall, 95.2% of women were able to delay treatment for retention of pregnancy, although serious adverse events, including maternal shock/hemoperitoneum, recurrence during pregnancy, severe hypertension, maternal death, intrauterine fetal demise, stillbirth, fetal loss after surgery, neonatal death, and severe fetal brain damage occurred in a total of 40% of cases. Of note, adverse outcomes occurred only among patients with risk factors such as higher stage and older age.[51] Additionally, in the aforementioned study of treatment of malignant germ cell tumors, half of patients underwent chemotherapy, 76.9% of which was cisplatin with bleomycin.[52] Recurrence occurred in 6.9%, and overall five-year survival was 80.1%. Intrauterine growth restriction occurred in 22.8% of cases, without a significantly increased risk associated with intrauterine chemotherapy exposure.[52]

Ovarian cancer in pregnancy: conclusions

In summary, adnexal masses associated with pregnancy should be evaluated. Surgical intervention is important, particularly when suspicion of malignancy is high. For ovarian cancer associated with pregnancy, treatment options include surgery with fertility preservation and/or more radical surgery. Reports on neoadjuvant chemotherapy for both epithelial ovarian cancer and non-epithelial ovarian cancer have provided additional options for fetal preservation without delay in treatment. Standard regimens of carboplatin and paclitaxel are used for epithelial ovarian cancer and appear to be safe for the developing fetus in a series of mostly case reports in the literature. Further study and longer follow-up are needed to determine the oncologic safety of this approach.

Counseling Women with Cancer in Pregnancy

Given the data described above, we feel it is important to emphasize that providers provide patients with a detailed, broad-based, and empathetic approach to counseling on treatment options. Each patient should be informed to the best of the provider’s knowledge regarding the prognosis of her disease, the maternal and fetal risks of treatment during pregnancy, and the relative risks and benefits of early delivery. Providers should assess in detail each patient’s understanding of her illness as well as her priorities with respect to her own versus her fetus’ health.

Of note, in the preceding discussion regarding timing of delivery, it is emphasized that delivery should occur with a short delay after the most recent chemotherapy treatment to

avoid timing with the nadir of maternal and fetal blood counts; this does not mean that delivery should occur earlier in order to provide chemotherapy. One reasonable exception to this is a situation in which cancer is diagnosed very late in pregnancy, at a time when delivery would not result in significant adverse neonatal effects, in order to avoid fetal exposure to chemotherapy altogether.

Such nuances of treatment options should be individualized in all cases. Ultimately, the priority should be to maximize patient education and to fulfill her desires for her own and her future child's health while upholding the ethical principal of non-maleficence. Particularly, in advanced-stage cancer, questions of survivorship and mortality should be addressed, and providers should offer the support of patient cancer survivorship groups as well as therapeutic counseling resources as indicated.

Conclusions

The treatment of gynecologic malignancies during pregnancy mirrors that outside of pregnancy, with a few important differences dictated by the balance of maternal versus fetal health and oncologic versus obstetric outcome. Overall, surgical treatment, and neoadjuvant and/or adjuvant chemotherapy, is feasible in most cases. Intrapartum chemotherapy is particularly important to optimize oncologic outcomes if continuation of pregnancy is desired. Some of the most important differences in the treatment of these cancers in pregnancy include the possible need for delayed chemotherapeutic and/or radiation treatment when cancer is diagnosed during the first trimester and the possibility for fertility-sparing oncologic surgery in gynecologic cancers. Additionally, there is a strong need for further research to determine the safety of diagnostic and therapeutic procedures that are routinely used in the non-pregnant woman in women who are pregnant, including long-term data on their oncologic safety. Furthermore, although existing studies on the surgical and chemotherapeutic treatment of female reproductive malignancies in pregnancy report overall good fetal outcomes, long-term data on children treated with these agents in utero is warranted to truly understand the downstream effects of the treatments.. Finally, in order to provide the most timely and safe treatment to these patients, improved education of providers regarding the safety of various surgical and chemotherapeutic treatments in pregnancy, in order to fully inform patients of the risks and benefits of treatment options as well as a multidisciplinary approach to care, are needed.

Acknowledgments

Source of Funding: This report was funded in part by NIH/NCI Cancer Center Support Grant No. P30 CA008748.

References

1. Han SN, Kesic VI, Van Calsteren K, et al. Cancer in pregnancy: a survey of current clinical practice. Eur J Obstet Gynecol Reprod Biol. 2013; 167(1):18–23. [PubMed: 23182070]
2. Amant F, Halaska MJ, Fumagalli M, et al. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. Int J Gynecol Cancer. 2014; 24(3):394–403. [PubMed: 24445819]
3. Han SN, Verheecke M, Vandenbroucke T, et al. Management of gynecological cancers during pregnancy. Curr Oncol Rep. 2014; 16(12):415. [PubMed: 25344340]

4. Grimm D, Woelber L, Trillsch F, et al. Clinical management of epithelial ovarian cancer during pregnancy. Eur J Cancer. 2014; 50(5):963–71. [PubMed: 24462638]
5. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol. 1989; 161(5):1178–85. [PubMed: 2589435]
6. Ko ML, Lai TH, Chen SC. Laparoscopic management of complicated adnexal masses in the first trimester of pregnancy. Fertil Steril. 2009; 92(1):283–7. [PubMed: 18692789]
7. Amant F, Van Calsteren K, Halaska MJ, et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol. 2012; 13(3):256–64. [PubMed: 22326925]
8. Amant F, Brepoels L, Halaska MJ, et al. Gynaecologic cancer complicating pregnancy: an overview. Best Pract Res Clin Obstet Gynaecol. 2010; 24(1):61–79. [PubMed: 19740709]
9. Minig L, Otano L, Diaz-Padilla I, et al. Therapeutic management of epithelial ovarian cancer during pregnancy. Clin Transl Oncol. 2013; 15(4):259–64. [PubMed: 23180347]
10. Salani R, Billingsley CC, Crafton SM. Cancer and pregnancy: an overview for obstetricians and gynecologists. Am J Obstet Gynecol. 2014; 211(1):7–14. [PubMed: 24316272]
11. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. Pharmacol Ther. 1997; 74(2):207–20. [PubMed: 9336023]
12. Zagouri F, Sergentanis TN, Chrysikos D, et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013; 137(2):349–57. [PubMed: 23242615]
13. Doll DC, Ringenberg QS, Yarbro JW. Management of cancer during pregnancy. Arch Intern Med. 1988; 148(9):2058–64. [PubMed: 3046546]
14. Hunter MI, Tewari K, Monk BJ. Cervical neoplasia in pregnancy. Part 2: current treatment of invasive disease. Am J Obstet Gynecol. 2008; 199(1):10–8. [PubMed: 18585521]
15. Zemlickis D, Lishner M, Degendorfer P, et al. Maternal and fetal outcome after invasive cervical cancer in pregnancy. J Clin Oncol. 1991; 9(11):1956–61. [PubMed: 1941053]
16. Morice P, Narducci F, Mathevet P, et al. French recommendations on the management of invasive cervical cancer during pregnancy. Int J Gynecol Cancer. 2009; 19(9):1638–41. [PubMed: 19955951]
17. Morice P, Uzan C, Gouy S, et al. Results of conservative treatment of epithelial ovarian tumor. Gynecol Oncol. 2009; 112(3):673–4. author reply 4. [PubMed: 18986689]
18. Morice P, Uzan C, Gouy S, et al. Cancer during pregnancy: the time has come for a prospective program. J Clin Oncol. 2009; 27(13):2298. author reply 9. [PubMed: 19307492]
19. Morice P, Uzan C, Gouy S, et al. Gynaecological cancers in pregnancy. Lancet. 2012; 379(9815): 558–69. [PubMed: 22325661]
20. Vercellino GF, Koehler C, Erdemoglu E, et al. Laparoscopic pelvic lymphadenectomy in 32 pregnant patients with cervical cancer: rationale, description of the technique, and outcome. Int J Gynecol Cancer. 2014; 24(2):364–71. [PubMed: 24424374]
21. Alouini S, Rida K, Mathevet P. Cervical cancer complicating pregnancy: implications of laparoscopic lymphadenectomy. Gynecol Oncol. 2008; 108(3):472–7. [PubMed: 18201752]
22. Silva LB, Silva-Filho AL, Traiman P, et al. Sentinel node mapping in a pregnant woman with cervical cancer: a case report. Int J Gynecol Cancer. 2006; 16(3):1454–7. [PubMed: 16803548]
23. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013; 31(20):2532–9. [PubMed: 23610117]
24. Hannigan EV, Whitehouse HH 3rd, Atkinson WD, et al. Cone biopsy during pregnancy. Obstet Gynecol. 1982; 60(4):450–5. [PubMed: 7121932]
25. Dunn TS, Ginsburg V, Wolf D. Loop-cone cerclage in pregnancy: a 5-year review. Gynecol Oncol. 2003; 90(3):577–80. [PubMed: 13678727]
26. Takushi M, Moromizato H, Sakumoto K, et al. Management of invasive carcinoma of the uterine cervix associated with pregnancy: outcome of intentional delay in treatment. Gynecol Oncol. 2002; 87(2):185–9. [PubMed: 12477449]

27. Fukushima K, Ogawa S, Tsukimori K, et al. Can we diagnose invasive cervical cancer during pregnancy as precise as in nonpregnant women?: maternal and perinatal outcome in pregnancies complicated with cervical cancers. Int J Gynecol Cancer. 2009; 19(8):1439–45. [PubMed: 20009904]
28. Germann N, Haie-Meder C, Morice P, et al. Management and clinical outcomes of pregnant patients with invasive cervical cancer. Ann Oncol. 2005; 16(3):397–402. [PubMed: 15668263]
29. Fruscio R, Villa A, Chiari S, et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. Gynecol Oncol. 2012; 126(2):192–7. [PubMed: 22555106]
30. Li J, Wang LJ, Zhang BZ, et al. Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two case report and literature review. Arch Gynecol Obstet. 2011; 284(3):779–83. [PubMed: 21691768]
31. Palaia I, Pernice M, Graziano M, et al. Neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer during pregnancy: a case report. Am J Obstet Gynecol. 2007; 197(4):e5–6.
32. Sood AK, Sorosky JI, Mayr N, et al. Cervical cancer diagnosed shortly after pregnancy: prognostic variables and delivery routes. Obstet Gynecol. 2000; 95(6 Pt 1):832–8. [PubMed: 10831976]
33. Van Calsteren K, Vergote I, Amant F. Cervical neoplasia during pregnancy: diagnosis, management and prognosis. Best Pract Res Clin Obstet Gynaecol. 2005; 19(4):611–30. [PubMed: 15886059]
34. Leath CA 3rd, Bevis KS, Numnum TM, et al. Comparison of operative risks associated with radical hysterectomy in pregnant and nonpregnant women. J Reprod Med. 2013; 58(7–8):279–84. [PubMed: 23947076]
35. Mancari R, Tomasi-Cont N, Sarno MA, et al. Treatment options for pregnant women with ovarian tumors. Int J Gynecol Cancer. 2014; 24(6):967–72. [PubMed: 24978707]
36. Hoover K, Jenkins TR. Evaluation and management of adnexal mass in pregnancy. Am J Obstet Gynecol. 2011; 205(2):97–102. [PubMed: 21571247]
37. Yen CF, Lin SL, Murk W, et al. Risk analysis of torsion and malignancy for adnexal masses during pregnancy. Fertil Steril. 2009; 91(5):1895–902. [PubMed: 18359024]
38. Gholson R. Adnexal Masses in Pregnancy: Does Magnitude Matter? Obstetrics & Gynecology. 2014; 123(suppl 1):192S–3S.
39. Friedman JD, Ramsey PS, Ramin KD, et al. Pneumoamnion and pregnancy loss after second-trimester laparoscopic surgery. Obstet Gynecol. 2002; 99(3):512–3. [PubMed: 11864684]
40. Stuart GC, Kitchener H, Bacom M, et al. Participants of the 4th Ovarian Cancer Consensus Conference (OCCC), Gynecologic Cancer Intergroup. 2010 Gynecologic Cancer Intergroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer: Report From the Fourth Ovarian Cancer Consensus Conference. International Journal of Gynecological Cancer. 2011; 21(4):750–55. [PubMed: 21543936]
41. Modares Gilani M, Karimi Zarchi M, Behtash N, et al. Preservation of pregnancy in a patient with advanced ovarian cancer at 20 weeks of gestation: case report and literature review. Int J Gynecol Cancer. 2007; 17(5):1140–3. [PubMed: 17433066]
42. Mir O, Berveiller P, Ropert S, et al. Use of platinum derivatives during pregnancy. Cancer. 2008; 113(11):3069–74. [PubMed: 18985677]
43. Tabata T, Nishiura K, Tanida K, et al. Carboplatin chemotherapy in a pregnant patient with undifferentiated ovarian carcinoma: case report and review of the literature. Int J Gynecol Cancer. 2008; 18(1):181–4. [PubMed: 17466045]
44. Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. Obstet Gynecol. 2012; 120(6):1267–72. [PubMed: 23168749]
45. Aggarwal P, Kehoe S. Ovarian tumours in pregnancy: a literature review. Eur J Obstet Gynecol Reprod Biol. 2011; 155(2):119–24. [PubMed: 21194826]
46. Ruiz Ramos J, Roma E, Palomar L, et al. Paclitaxel and carboplatin treatment for advanced ovarian cancer during pregnancy. Chemotherapy. 2013; 59(5):344–5. [PubMed: 24820861]

47. Mendez LE, Mueller A, Salom E, et al. Paclitaxel and carboplatin chemotherapy administered during pregnancy for advanced epithelial ovarian cancer. Obstet Gynecol. 2003; 102(5 Pt 2):1200–2. [PubMed: 14607056]

48. 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(2):600–4. [PubMed: 15297214]

49. Sood AK, Shahin MS, Sorosky JI. Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. Gynecol Oncol. 2001; 83(3):599–600. [PubMed: 11733979]

50. Fauvet R, Brzakowski M, Morice P, et al. Borderline ovarian tumors diagnosed during pregnancy exhibit a high incidence of aggressive features: results of a French multicenter study. Ann Oncol. 2012; 23(6):1481–7. [PubMed: 22003244]

51. Blake EA, Carter CM, Kashani BN, et al. Feto-maternal outcomes of pregnancy complicated by ovarian sex-cord stromal tumor: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol. 2014; 175:1–7. [PubMed: 24439718]

52. Kodama M, Grubbs BH, Blake EA, et al. Feto-maternal outcomes of pregnancy complicated by ovarian malignant germ cell tumor: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol. 2014; 181:145–56. [PubMed: 25150953]

Learning Objectives

After completing this activity, the learner will be better able to

1. Review general principles in the management and treatment of gynecologic cancers in pregnancy
2. Review the diagnosis and treatment of cervical cancer in pregnancy
3. Review the diagnosis and treatment of ovarian cancer in pregnancy