Gynecologic Cancers in Pregnancy: Guidelines of an International Consensus Meeting

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Background: Gynecologic cancer during pregnancy is a special challenge because cancer or its treatment may affect not only the pregnant women in general but directly involve the reproductive tract and fetus. Currently, there are no guidelines on how to deal with this special coincidence.

Methods: An international consensus meeting on staging and treatment of gynecological malignancies during pregnancy was organized including a systematic literature search, and interpretation followed by a physical meeting of all participants with intensive discussion. In the absence of large trials and randomized studies, recommendations were based on available literature data and personal experience thus representing a low but best achievable level of evidence.

Findings: Randomized trials and prospective studies on cancer treatment during pregnancy are lacking.

Gynecological cancer during pregnancy is a demanding problem, and multidisciplinary expertise should be available. Counseling both parents on the maternal prognosis and fetal risk is needed. When there is a firm desire to continue the pregnancy, gynecological cancer can be treated in selected cases. The staging and treatment should follow the standard approach as much as possible. Guidelines for safe pelvic surgery during pregnancy are presented. Mainly in cervical and ovarian cancer, chemotherapy and an alternative surgical approach need to be considered. Administration of chemotherapy during the second or third trimester may probably not increase the incidence of congenital malformations. Until now, the long-term outcome of children in utero exposed to oncological treatment modalities is poorly documented, but preterm birth on its own is associated with cognitive impairment. Delivery should be postponed preferably until after a gestational age of 35 weeks.

Interpretation: Further research including international registries for gynecologic cancer in pregnancy is urgently needed. The gathering of both available literature and personal experience allowed only suggesting models for treatment of gynecologic cancer in pregnancy.

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The estimation of worldwide cancer burden indicates that gynecological cancers (i.e., cancer of the vulva, vagina, cervix uteri, uterine corpus, ovary, and fallopian tube) account for 19% of the 5.1 million estimated new cancer cases and 2.9 million cancer deaths in 2002. They account for 22% of all new cancer cases among women in developing countries compared with 15% of all new cases among women in developed countries. Cancer of the cervix is the second most common cancer among women worldwide because it is the most common gynecological cancer in the developing world. In unscreened populations, the peak risk of invasive cervical cancers occurs earlier than for most adult cancers, peaking or reaching a plateau from about 35 to 55 years. The increase starts in the second and early in the third decade. This partial overlap with the reproductive era renders pregnant women susceptible to cervical cancer. Because information on the pregnant state is frequently missing in cancer registries, figures on cancer incidence during pregnancy are approximate only. Whereas abnormal cervical cytology complicates approximately 5% of pregnancies, the incidence of cervical cancer during pregnancy is estimated to be around 1/10,000. The incidence of adnexal masses during pregnancy varies between 2% and 4%. It is estimated that approximately 6% of all operated adnexal masses are malignant, including epithelial (49%-75%), sex cord stromal (9%-16%), and germ cell tumors (6%-40%). The incidence of ovarian cancer during gestation fluctuates around 1/10,000 to 100,000.

Cancer affecting the reproductive system during pregnancy is a complex situation that endangers at least 2 lives, the pregnant woman and the fetus. The tremendous therapeutic challenge implicated by this coincidence on one hand and the sparse experience of individual clinicians on the other hand demand clinical guidance. However, literature data on cancers of the pelvic female reproductive system during pregnancy mainly consist of anecdotal case reports or small series only. We expected that gathering and summarizing all available data could help to provide a useful tool in this situation. Therefore, we organized an International Consensus meeting on the 3rd of July 2008 in Leuven, Belgium.

Participants were selected based on their expertise, and all related fields were covered, gynecological oncology, medical oncology, clinical pharmacology, obstetrics, pediatrics, and radiation oncology. A basic manuscript and a CD-rom including 263 articles was sent to all participants before the meeting. These articles were identified during a PUBMED search looking for keywords including pregnancy, surgery, offspring, cancer, chemotherapy, radiotherapy, cervical, vulvar, endometrial, and ovarian. Articles before 1990 were only included if considered important. Some articles were hand searched based on reference lists. Endometrial cancer and cancers diagnosed in the postpartum are excluded. Malignant trophoblastic disease was not included.

All participants were assigned to comment and review the topic of their experience. This new manuscript served as a basis for discussion during the meeting. The discussion during the meeting resulted in a new version that circulated 6 times. All participants agreed with the final recommendations. Questions we sought to answer in particular include the identification of stages that exclude pregnancy preservation as a safe option, requirements for safe surgery for pelvic cancer during pregnancy, alternative surgical treatment options that aim to preserve the pregnancy, choice of chemotherapy, timing of delivery, and the neonatal outcome.

IMAGING AND ONCOLOGICAL TREATMENT MODALITIES DURING PREGNANCY

The risk of fetal damage (e.g., by surgery-related hypoxia, radiation, or chemotherapy) and hence the possibility to stage and treat cancer during pregnancy will largely depend on the exposure period in pregnancy. With regard to this, the pregnancy can be divided into 3 stages: fertilization/implantation, organogenesis, and the fetal phase.

During the first 10 days postconception (fertilization/implantation), cells are omnipotent and can develop in the 3 different embryological layers. Viability will depend on the number of cells that is killed during treatment, and this will result in an “all-or-nothing” phenomenon.

The most vulnerable phase expands from 10 days to 8 weeks after conception (organogenesis). The potential for fetal damage is the highest during this period but varies depending on the agents used. The use of radiation or cytotoxic drugs during the organogenesis will increase the risk for fetal malformations. Therefore, radiation or chemotherapy until 10 weeks gestational age (= duration of amnionea) is contraindicated. However, some systems including the eyes, genitals, haematopoietic system, and the central nervous system continue to develop afterward. We propagate a 2- to 4-week “safety period” in order to allow treatment from 12 to 14 weeks pregnancy (i.e., 10–12 weeks after conception). Proper dating is crucial to plan safe treatment. During the second and third trimesters, radiotherapy of the upper part of the body and limbs as well as chemotherapy can be administered safely. Chemotherapy is administered until a gestational age of 35 weeks or preferably an interval of at least 3 weeks before delivery is aimed for. When the interval is too short, there is a risk for delivery-related maternal/fetal infection or bleeding, whereas an inadequate elimination of cytotoxic drugs by the immature fetal organs may contribute to an increased fetal risk.

Imaging and Diagnosis During Pregnancy

Staging should be as comprehensive as in nonpregnant women. Ultrasoundography and magnetic resonance imaging are relatively safe and widely used during pregnancy. The safety for the latter, however, is not proven. In contrast to previous belief, also gadolinium-enhanced magnetic resonance imaging is possible during pregnancy. X-ray studies expose the fetus to radiation, and the highest dosages are generated by computed tomography (CT) (Table 1). Although the fetal dose does not reach the threshold dose for deterministic effects, stochastic effects need to be considered because fetuses have a high proportion of dividing cells. In children, this results in a higher lifetime risk for cancer after exposure to radiation. The risk for childhood cancer is highest after abdomino-pelvic imaging (but not other sites) with exposure during the third trimester. Positron emission tomography combined with CT exposed the fetus to 19 mGy and might be considered if it is the only tool to make a proper diagnosis. Staging examinations...
TABLE 1. Approximate fetal absorbed doses during imaging studies

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fetal dose, cGy</th>
<th>Procedure</th>
<th>Fetal dose, cGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray (posteroanterior and lateral)</td>
<td>0.00006</td>
<td>Lumbosacral spine</td>
<td>0.2–0.6</td>
</tr>
<tr>
<td>Abdominal x-ray</td>
<td>0.15–0.26</td>
<td>Mammography</td>
<td>0.01–0.04</td>
</tr>
<tr>
<td>Pelvic x-ray</td>
<td>0.2–0.35</td>
<td>CT thorax</td>
<td>0.01–1.3</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>0.4–0.9</td>
<td>CT abdomen</td>
<td>0.8–3</td>
</tr>
<tr>
<td>Barium enema</td>
<td>0.3–4</td>
<td>CT pelvis</td>
<td>2.5–8.9</td>
</tr>
<tr>
<td>Dorsal spine</td>
<td>&lt;0.001</td>
<td>TC bone scan</td>
<td>0.15–0.20</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.4–0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The threshold dose for fetal damage is estimated to vary between 10 and 20 cGy.

During pregnancy are possible, but fetal protection with abdominal shielding is advised.

The sentinel lymph node procedure with ⁹⁹mTc can safely be performed during pregnancy. Studies in breast cancer show that after injection of 18.5 MBq ⁹⁹mTc, the fetal dosage approximately ranges between 0.0 and 0.05 mGy which is far below the deterministic threshold dosage. This is mainly due to the low dosages that are administered and because ⁹⁹mTc is captured in the lymph nodes during a period during which radioactivity decreases considerably. The exposure after sentinel node procedure is in the same level as few day dosages of natural background irradiation. In vulvar cancer, a dosage of 60 or 80 MBq is often used to detect the sentinel lymph node. Approximately 80% of a theoretical dosage of 100 MBq remains in the pelvis (injection location and some lymph nodes). The distance from the fetus is at least 10 cm. In this situation, fetal exposure can be estimated to be 100 μSv (or 0.1 mGy). According to the International Commission on Radiological Protection, fetal risk starts from 100 mSv (or 10 mGy). The fetal exposure is thus 1000 times lower, and the fetal risk is negligible when a sentinel node procedure is used for vulvar cancer (after a personal communication with A. Van der Zee). Anaphylactic reaction to patent blue has been described. However, treatment of this side effect during pregnancy is hazardous, and fetal well being is put into danger. There are also reports of possible skeletal and neurologic defects in rat models. The use of patent blue for the detection of the sentinel node is therefore not recommended.

Diagnosis of cervical pathology during pregnancy deserves special attention. Both cervical glands and stroma undergo physiologic alterations during pregnancy that alter cytologic and colposcopic interpretation. However, if the cytologist and colposcopist are aware of the pregnant state, their reliability is not decreased. Moreover, a colposcopic-guided biopsy should not be postponed because the colposcopic/cytologic concordance can be worse in the postpartum. Indications for colposcopy are the same as for nonpregnant patients and the same morphological alterations in case of abnormality are present. Progression or missed diagnosis of microinvasive disease until the postpartum period was noted in 0.0%, 1.1%, 2.4%, 8.0%, and 9.7% of cases. In the absence of progression to invasive cervical disease, no treatment of CIN 2-3 lesions during pregnancy is necessary. Diagnosis should be made by an experienced colposcopist. There is only very limited indication for conization in pregnancy in patients in whom the previously mentioned measures cannot rule out invasive disease. Then, conization refers to the excision of the transformation zone, and a thickness of at least 5 mm is recommended. In the presence of preinvasive disease, a vaginal delivery is allowed. However, this will not increase regression rates when compared with cesarean delivery.

Surgery During Pregnancy

Overall, 0.75% to 2% of pregnant women will undergo surgery during pregnancy. Surgery and anesthesia are safe during pregnancy if physiologic adaptations are considered. Adequate maternal monitoring is crucial in preventing hypoxia, hypotension, and hypoglycemia. Pregnant patients should be positioned in left lateral tilt to prevent caval compression. Perioperative fetal monitoring is always difficult to interpret and is only useful if clinically relevant. Fetal monitoring during surgery for gynecological cancers is mostly not feasible. A cardiotocography, Doppler, or ultrasound just before and after the surgery may be useful to exclude direct fetal damage timely associated with surgery. With regard to fetal resuscitation, the local policy needs to be followed.

Cohen-Kerem et al. reviewed over 12,000 cases of surgery during pregnancy. The data suggest that surgery does not increase the risk for miscarriage and congenital anomalies. Only in cases of preterm, fetal loss rate was increased. However, most of the reported surgeries did not include the reproductive tract or were indicated for cancer treatment. Therefore, conclusion should be interpreted cautiously.

Surgery might slightly increase preterm delivery but numbers are difficult to interpret because no comparison was made with a normal pregnant population.

There is no literature supporting the prophylactic use of tocolysis in cases of surgery during pregnancy. When preterm labor is diagnosed perioperatively, tocolytic agents like milodipine, atosiban, or indomethacin (<32 weeks) should be considered. Laparoscopic surgery during pregnancy is safe and effective when performed in experienced hands. The carbon dioxide pneumo-peritoneum and carbon monoxide production during electro-coagulation does not seem to be hazardous to the fetus as long as the maximal pressure (normal, 10–13 mm Hg; maximum, 15 mm Hg) and operation time (25–90 minutes) are respected. The use of a Verres needle puts the pregnant uterus at risk. An open laparoscopic procedure is safe from oncological point of view in the absence of malignant signs and in experienced hands that minimize the risk for spillage, ideally between 16th and 20th week of pregnancy.

Systemic Anticancer Treatment During Pregnancy

Most anticancer drugs exhibit a narrow therapeutic window with small margins between toxic and therapeutic exposure. Interindividual pharmacokinetic and pharmacodynamic variabilities are usually substantial and may be augmented by pregnancy. During pregnancy, multiple changes in physiology occur affecting the major pharmacokinetic processes of a drug: absorption, distribution, metabolism, and excretion. This may have therapeutic and toxic consequences for both the pregnant woman and the fetus. Because of the changes in pharmacokinetic processes the pregnant patient may be exposed to subtherapeutic or toxic drug levels, and an unwanted amount of drug may be delivered to the fetus. Only 1 report compared maternal doxorubicin levels during and after pregnancy. The results in a single case point to a lower drug exposure and decreased tissue toxicity when doxorubicin is administered during pregnancy. Despite the putative emerging pharmacokinetic changes of chemotherapeutics during pregnancy, there are, however, so far no indications that pregnant cancer patients who treated with standard height-weight based dosed
chemotherapy are at higher risk for reduced efficacy or more toxicity than nonpregnant patients treated with the same drugs and dosages.

The effect on the fetus is another aspect. The term "placental barrier" is a misnomer and a false notion because the placenta is not a true barrier for the transfer of most substances from mother to fetus. Instead the placenta is the entry through which the fetus is exposed to chemicals. Placental transfer of drugs from the maternal to the fetal side occurs predominantly via passive diffusion and to a lesser extent via active transport and facilitated diffusion. Concomitant administration of drugs that block these transporters or modulate the metabolizing enzymes, harbor the risk of leading to unintended exposure of the fetus to chemotherapy and thus alertness is advised when drug combinations are used. Specific cytotoxic drug effects are difficult to describe because combinations are frequently used and because co-medications including steroids, analgesics, antiemetics, and growth factors are administered as well. How chemotherapeutics should be dosed in pregnant women is uncertain and needs further research. Up till now, the same schemes are used as in nonpregnant women. Table 2 compares combinations used in nonpregnant and pregnant women.

Cytotoxic drugs used in gynecologic cancer include platin, paclitaxel, bleomycin, etoposide, and vinblastin.

Based on 37 reported cases, we calculate that cisplatin exposure resulted in moderate bilateral hearing loss in 1/37 (2.7%) and ventriculomegaly at the age of 26 weeks. Apart from significant manipulation of the uterus to remove the uterus and the development of a pelvic hematoma requiring blood transfusion that might have been associated with fetal hypoxia, a direct neurotoxic effect must be considered. In another case, maternal sepsis after bleomycin, cisplatin, and etoposide administration occurred, resulting in preterm labor. The premature neonate (1190 g) developed respiratory distress syndrome, myocardial depression, hearing impairment, and apnea. Although cisplatin might have contributed to the sensorineural hearing loss, prematurity and postnatal treatment with gentamicin were confounding factors. Taking these considerations into account, administration of cisplatin and cisplatin containing regimens during pregnancy resulted in absence of congenital anomalies and normal neurological development in 35 (95%) of 37 cases.

Carboplatin has been administered during pregnancy in 8 cases (of which 4 in association with paclitaxel) and a normal neonatal outcome was noted in each. Based on a better toxicity profile, we recommend carboplatin instead of cisplatin if evaluated in the respective tumor entity. Until more data are available on the pharmacokinetics during pregnancy, we recommend to dose as usual for ovarian tumors in nonpregnant women (area under curve, 5–7.5).

Area under curve is based on the glomerular filtration rate, with a safety upper limit of carboplatin of 800 mg. Dose escalations can be planned according to blood counts subsequently.

Twenty case reports were found documenting the outcome after the use of taxanes during pregnancy: 13 on paclitaxel and 7 on docetaxel. In 17 of the 20 cases, taxanes were administered after other cytotoxic drugs (patients with breast cancer) or in combination with other cytotoxic drugs (patients with ovarian or lung cancer). Except for 1 hydrocephalus in a patient given docetaxel with doxorubicin-cyclophosphamide but with normal outcome of the child after 28 months, no fetal or neonatal problems have been observed after the use of taxanes during pregnancy.

At least 9 cases of a combination of bleomycin, cisplatin, and etoposide (BEP) during pregnancy for treatment of germ cell tumors have been described. Although reports describe a normal neonatal outcome, 1 child with a significant ventriculomegaly with cerebral atrophy was born after 1 cycle of BEP and 1 case of hearing impairment (see discussion above). Based on this poor neonatal outcome and given the paclitaxel activity in germ cell tumors, paclitaxel and carboplatin can be administered. Vinca alkaloids are already in use for a long time, and many reports cite their use is relatively safe in pregnancy. In addition, vinblastin may replace etoposide because cisplatin-vinblastin-bleomycin has been used in 4 cases without maternal or fetal complications. Based on a possible fetal risk and the high risk of leukemia after etoposide administration, cisplatin-vinblastin-bleomycin or paclitaxel-cisplatin-carboplatin is advised in pregnant women with germ cell tumors (instead of BEP).

New targeted therapy is not recommended for pregnant patients with pelvic cancers because of the limited experience and because large randomized phase III trials are still awaited to prove their efficacy.

Radiotherapy During Pregnancy

Therapeutic pelvic irradiation induces severe or lethal consequences and is not consistent with preservation of the pregnancy.

Supportive Therapy and Symptom Control in the Pregnant Patient

Supportive treatment of chemotherapy can be given mainly according to the general recommendations. Regarding the use of corticoids, methylprednisolone and hydrocortisone are extensively metabolized in the placenta and little crosses into the fetal compartment. They are therefore preferred over dexamethasone. Repeated antenatal exposure to dexamethasone resulted in animal models in decreased body and brain weight, delay in the maturation timetable, and hormonal disturbances. This concern was raised subsequently in the National Institutes of Health Consensus. More children with attention problem and higher rates of cerebral palsy have been described.

Granulocyte colony-stimulating factor and erythropoetin have been used safely in pregnant patients, and their use should follow current guidelines for growth factor support during chemotherapy. A list of the most important supportive drugs and their safety profile is presented in Table 3.

### TABLE 2. Recommended combinations of chemotherapy in nonpregnant and pregnant women

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>Paclitaxel-carboplatin</td>
<td>Paclitaxel-carboplatin</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Bleomycin-etoposide-cisplatin</td>
<td>Paclitaxel-carboplatin or Cisplatin-vinblastin-bleomycin</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Platin based</td>
<td>Paclitaxel-cisplatin</td>
</tr>
</tbody>
</table>

### MONITORING PREGNANCY AND NEONATAL OUTCOME

**Monitoring of the Pregnancy, Complicated With A Gynecological Cancer**

In general, the mother and fetus should be monitored with the standard prenatal care established for high-risk pregnancies.
TABLE 3. Most important supportive drugs and their fetal safety profile

<table>
<thead>
<tr>
<th>Supportive drugs</th>
<th>Fetal safety data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Metoclopramide can be used in all stages of pregnancy. Its methoxy-2-benzamide-derivate, alizapride, is probably also safe.</td>
</tr>
<tr>
<td>Metoclopramide/aliapride</td>
<td>Should not be withheld because of the pregnancy. Animal data suggest low risk. Case reports on ondansetron show its effectiveness in the control of vomiting in pregnancy and no adverse effects were observed in the children.</td>
</tr>
<tr>
<td>5-HT antagonists (granisetron, tropisetron, ondansetron)</td>
<td>Should not be withheld because of the pregnancy. No human data available, animal data suggest low risk. Can be used after the first trimester of pregnancy. Prednisolone or hydrocortisone are preferred if necessary.</td>
</tr>
<tr>
<td>NK1 antagonist (aprepitant)</td>
<td>Should not be withheld because of the pregnancy. Is crossing the placenta.</td>
</tr>
<tr>
<td>Corticoids</td>
<td>Should not be withheld because of the pregnancy. Is probably not crossing the placenta.</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Drug of preference (till 4 g/d)</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factors</td>
<td>Can be used between 12 and 32 weeks of gestation.</td>
</tr>
<tr>
<td>(pegfilgrastim, filgrastim, lenograstim)</td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td></td>
</tr>
<tr>
<td>Pain medication</td>
<td></td>
</tr>
<tr>
<td>Panacetamol</td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal inflammatory drugs</td>
<td></td>
</tr>
</tbody>
</table>

Pregnancy-related complications should be treated according to the standard obstetrical care. Delivery should take place in a hospital with a neonatal care unit. When possible, the delivery should be delayed until 35 to 37 weeks and beyond and preferably not before 32 weeks. Sequelae associated with preterm birth, of which neurodevelopmental impairments and cerebral palsy are the most important, increase with decreasing gestational age. The risk for long-term neurologic sequelae should be avoided if possible and discussed with the parents. When delivery is planned before 34 weeks, fotal lung maturation must be considered. The placenta should be examined for metastases, but fetal involvement has never been described for gynecological cancer. Breastfeeding during chemotherapy is contraindicated, as most of the agents used can be excreted in breast milk.

Neonatal and Long-Term Outcome After in Utero Exposure to Chemotherapy

Available studies on the outcome of the offspring lack either a detailed methodology or a systematic examination, therefore, data on the long-term outcome of these children are very limited. In the largest and recent literature review on this topic, Candonie and Iacoubi described 376 cases of in utero exposure to chemotherapy. In this series, 5% intra uterine deaths and 1% neonatal deaths were registered. All but 3 deaths occurred with maternal hematological malignant disease. Two of these 3 cases had been exposed to idarubicin for breast cancer. The authors encountered 11 cases of congenital malformation of which 9 cases were exposed to chemotherapy in the first trimester. More recent publications also described no particular problems when chemotherapy was administered after the first trimester. Hahn et al. described 57 patients that were treated for breast cancer during pregnancy. Although telephone call or mail was used to contact the parents/guardian or teacher, the outcome was encouraging. One small study applied systematically a battery of neuropsychological testing in 10 children. Morbidity after intrauterine exposure to cytotoxic drugs mainly appeared to be related to preterm neonates. If possible, delivery should be planned after 35 weeks gestational age. This strategy has shown to be beneficial.

Echocardiographic follow-up data suggest a normal cardiac function in children who were in utero exposed to cytotoxic drugs. In a small series, Van Calsteren et al. used echocardiographic quantification of cardiac function using both conventional and newer techniques. In all children, a normal cardiac performance without morphological abnormalities could be observed. However, a trend toward a lower wall thickness and left ventricular mass was recorded. The authors believe this could be due to chemotherapy as this influences myocyte replication and growth. Whether the different methodology that was used can explain the difference is subject for further study.

The limited data did not show an excessive increased risk for congenital malformations when compared with the background risk for fetal anomalies after intrauterine exposure to chemotherapy during the second and third trimester. However, long-term follow-up data are urgently needed.

ORGAN PATHOLOGY

Invasive Cervical Cancer

The treatment of cervical cancer during pregnancy is determined by the gestational age, stage of disease, and the wish of the patient to preserve the pregnancy.

The limited experience with an invasive cervical cancer diagnosed during pregnancy renders every treatment proposal other than established standard therapy for nonpregnant patients experimental. Radical hysterectomy of a pregnant uterus is possible. From the second trimester onward, surgical delivery by hysterotomy will improve the accessibility of the pelvis. The increased blood supply deserves an experienced surgeon. Alternatively, chemoradiation can be used. Radiation of the pelvis during the first trimester will result in spontaneous abortion. During the second trimester, abortion may be protracted and interfere with the radiotherapy. Prior uterine evacuation (hysterotomy or suction curettage) will facilitate subsequent chemoradiotherapy.

When maintenance of pregnancy is desired, the experimental nature of the cancer treatment during pregnancy and the potential risks should be discussed with the patient concerned. Treatment
lymphadenectomy, neoadjuvant chemotherapy (NACT), and trachelectomy during pregnancy can be considered.

A lymphadenectomy is performed during gestation when pregnancy or fertility saving surgery is possible. Pelvic lymphadenectomy is performed to identify high-risk disease that would exclude a pregnancy saving policy. A retroperitoneal laparoscopic approach or laparoscopy \(^{116,117}\) could potentially help to minimize uterine manipulation and hence contractility. The pathologist should be aware of the pregnant state, as decidual changes in the pelvic lymph nodes may mimic malignant disease. \(^{116-122}\)

Neoadjuvant chemotherapy during pregnancy can be used to stabilize or reduce the size of cervical cancer. \(^{89,91,127-129}\) A summary of 9 reported cases is presented in Table 4. It should be noted that 2 maternal deaths were treatment-related. The neonatal outcome was normal in all cases. Chemotherapy for cervical cancer should be platinum based but the addition of paclitaxel will increase response rates. \(^{130}\) During pregnancy, paclitaxel-carboplatin may be considered as alternative to cisplatin-based regimens because of its favorable toxicity profile as shown in small series. \(^{131,132}\) The number of cycles is guided by the presence of fetal maturity. When only 1 cycle of chemotherapy is needed to attain fetal maturity, a waiting policy is preferred.

Trachelectomy has been described as an abdominal \(^{133}\) or vaginal procedure. \(^{134}\) Experience during pregnancy is, however, very limited, and the technique requires sufficient surgical skills, may be associated with large volumes of blood loss (irrespective of the approach), and the risk of pregnancy loss is considerable. \(^{135}\) The experimental nature of this approach needs to be discussed.

These data suggest that lymphadenectomy, NACT, and trachelectomy can be used to treat cervical cancer during pregnancy. Their use depends on the stage of cervical cancer. An algorithm for stage IIA–IB1 less than 2 cm is presented in Figure 1. In the absence of nodal metastasis, NACT followed by conservative surgery (eg, trachelectomy) can be considered. Standard treatment depends on the local policy and is radical hysterectomy or chemoradiation (Fig. 1). An algorithm for stage IB1 2 to 4 cm tumors is presented in

**FIGURE 1.** Algorithm for treatment of cervical cancer stage IB1, less than 2 cm treated during the second trimester of pregnancy in patients wishing to preserve the pregnancy and fertility. NACT, neoadjuvant chemotherapy.

**FIGURE 2.** Algorithm for treatment of cervical cancer stage IB1, 2 to 4 cm treated during the second trimester of pregnancy in patients wishing to preserve the pregnancy and fertility. NACT, neoadjuvant chemotherapy.
FIGURE 3. Algorithm for treatment of cervical cancer stage IB2-IIB treated during the second trimester of pregnancy in patients wishing to preserve the pregnancy and fertility. NACT, neoadjuvant chemotherapy.

Figure 2. Lymphadenectomy is mandatory but can be performed after NACT. The potential to preserve the pregnancy depends mainly on the nodal status and the response to NACT. An algorithm for stage IB2-IIB is presented in Figure 3. For these tumors, fertility sparing surgery has not been sufficiently evaluated. Definitive treatment is performed after delivery. Neoadjuvant chemotherapy during pregnancy can be applied until fetal maturity, preferably longer than 35 weeks. Cesarean delivery precedes final treatment. If a good response to NACT (residual tumor < 4 cm), fertility sparing surgery can be considered in experienced hands though in an experimental setting. Alternatively, standard treatment is proposed. In selected cases, radical hysterectomy at the time of cesarean delivery may be indicated. Standard treatment is mandatory in nonresponder to NACT. Thus, for stage IB2-IIB, lymphadenectomy is postponed until after delivery, when radical trachelectomy or radical hysterectomy is opted for.

The route of delivery is determined by the presence or absence of tumor. When the cervix is cleared from tumor, a vaginal delivery is possible. In the presence of tumor, a cesarean delivery is the preferred route of delivery to prevent (fetal) recurrences in the epistomy scar. Because abdominal wall recurrences also have been described after a cesarean delivery, a wound protective system or a corporeal uterine incision might be useful when the tumor is large.

Vulvar Cancer

Vulvar intraepithelial neoplasia can be treated with laser skinning or surgical excision at every stage of pregnancy. For invasive vulvar cancer, the potential to preserve the pregnancy depends on the nodal stage. Invasive (> 1mm) vulvar cancer with clinical negative nodes during pregnancy should be treated as in nonpregnant women with or without total vulvectomy and unilateral or bilateral inguinal-femoral lymphadenectomy or sentinel procedure. Recurrence during pregnancy has been described. Narrow margins should be avoided because postoperative radiotherapy to reduce recurrence rates during pregnancy is contraindicated. The increased vascularization of the pelvis during pregnancy increases the perioperative blood loss. After surgery for vulvar cancer, the route of delivery should be discussed with the gynecological oncologist. Problematic wound healing, important scarring, a periurethral or perineal scar are considered relative contraindications for a vaginal delivery.

The prognosis is poor if inguinal nodes are involved. Adequate treatment is needed without delay. Evidence for the benefit of chemotherapy is low. Termination of pregnancy with immediate treatment is advocated during the first and second trimester in patients with metastatic inguinal-femoral lymph nodes. During the third trimester, delivery followed by standard treatment is suggested in these patients. Given the potential for spilling in the epistomy wound and subsequent risk for an epistomy scar recurrence, a cesarean delivery is preferred.

Vulvar melanoma deserves the same treatment as in nonpregnant patients. Patients harboring poor prognosis disease should be informed about the high risk of relapse and death. Metastatic melanoma carries a risk for placental involvement with an approximate risk for fetal metastasis of 22%. We refer to tables 3 and 4 for more information.

Ovarian Neoplasm

Malignant ovarian tumors are more likely to present at early stage because of frequent obstetrical examinations in asymptomatic patients. Nonneoplastic neoplasms (germ cell, sex-cord stromal tumors) are usually stage I and can be treated during midline laparotomy with unilateral salpingo-oophorectomy, omentectomy, peritoneal

### TABLE 4. Summary of published reports on the use of NACT for cervical cancer during pregnancy

<table>
<thead>
<tr>
<th>Age</th>
<th>Stage</th>
<th>D (w)</th>
<th>Chemotherapy</th>
<th>Surgery (w)</th>
<th>FU (mts)</th>
<th>Outcome mother</th>
<th>Outcome child</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>IB1</td>
<td>17</td>
<td>75 mg/m² P (3 courses)</td>
<td>32</td>
<td>12</td>
<td>NED</td>
<td>NI</td>
</tr>
<tr>
<td>34</td>
<td>IA</td>
<td>16</td>
<td>1 mg/m² V, 50 mg/m² P (6 courses)</td>
<td>34</td>
<td>5</td>
<td>DOD*</td>
<td>NI</td>
</tr>
<tr>
<td>36</td>
<td>IB2</td>
<td>21</td>
<td>1 mg/m² V, 50 mg/m² P (4 courses)</td>
<td>32</td>
<td>24</td>
<td>NED</td>
<td>NI</td>
</tr>
<tr>
<td>26</td>
<td>IB</td>
<td>14</td>
<td>30 mg/m² B, 50 mg/m² P (2 courses)</td>
<td>38</td>
<td>12</td>
<td>DOD*</td>
<td>NI</td>
</tr>
<tr>
<td>28</td>
<td>IB1</td>
<td>17</td>
<td>75 mg/m² P (6 courses)</td>
<td>32</td>
<td>10</td>
<td>NED</td>
<td>NI</td>
</tr>
<tr>
<td>38</td>
<td>IA</td>
<td>19</td>
<td>1 mg/m² V, 50 mg/m² P (4 courses)</td>
<td>33</td>
<td>80</td>
<td>NED</td>
<td>NI</td>
</tr>
<tr>
<td>30</td>
<td>IIB</td>
<td>22</td>
<td>50 mg/m² P (2 courses)</td>
<td>28</td>
<td>10</td>
<td>DOD</td>
<td>NI</td>
</tr>
<tr>
<td>30</td>
<td>IB</td>
<td>20</td>
<td>75 mg/m² P (3 courses)</td>
<td>35</td>
<td>10</td>
<td>NED</td>
<td>NI</td>
</tr>
<tr>
<td>28</td>
<td>IB2</td>
<td>23</td>
<td>40 mg/m² P (6 courses)</td>
<td>33</td>
<td>14</td>
<td>NED</td>
<td>NI</td>
</tr>
</tbody>
</table>

*This patient developed an abdominal wound recurrence after surgical delivery.

*This patient refused further treatment.

Diagnosis (D), weeks (w), months (mts), follow-up (FU), normal (NI), dead of disease (DOD), no evidence of disease (NED).

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cytology, and blind biopsies during pregnancy. Uterine manipulations should be limited in order to prevent preterm contractions. Lymphadenectomy is not indicated, unless enlarged nodes were noticed during staging or intraoperatively. Adjuvant chemotherapy is not indicated for FIGO stage I grade 1 immature teratoma or FIGO stage I dysgerminoma. For higher stages or nondysgerminoma tumors adjuvant chemotherapy is needed. Close surveillance instead of adjuvant chemotherapy has been propagated, however, tumor markers during pregnancy are less reliable. If continuation of pregnancy is desired, tumor markers are not useful to determine the number of cycles and 6 cycles of paclitaxel-carboplatin are recommended (bleomycin-etoposide-cisplatin second choice) (see paragraph on chemotherapy). Restaging after delivery should be considered based on imaging findings and tumor markers.

Borderline epithelial cancers during pregnancy are likely to be stage I and can be treated during pregnancy. Staging laparotomy with unilateral salpingo-oophorectomy, omentectomy, and peritoneal biopsies is needed. In selected cases, a laparoscopic procedure can be executed. For higher stages, removal of the adnexa during pregnancy is aimed for with completion of the surgery after delivery. A vaginal delivery is allowed.

For invasive epithelial ovarian carcinoma, the potential to preserve the pregnancy and the type of surgery and chemotherapy depend on the stage and grade. For stage IA, grade 1 surgical staging is similar to borderline tumors. Postdelivery restaging may be considered because staging during pregnancy is not complete. For stage IA grade 2–3, IB, IC and IIA, additionally, a lymphadenectomy and adjuvant platinum-based chemotherapy is mandatory. If the patient is upstaged, chemotherapy during pregnancy and final surgery after delivery are needed.

Advanced stage ovarian cancer during pregnancy was treated with different treatment strategies, including primary debulking with termination of pregnancy, or delivery, followed by expectant management, surgery during pregnancy followed by postpartum chemotherapy, surgery (including cytoreductive surgery) followed by chemotherapy during pregnancy with final surgery during/after delivery. These case reports show that ovarian cancer treatment during pregnancy is an option. After considering the maternal prognosis and wish to preserve the pregnancy, stage of disease and the gestational age will determine the treatment plan. Advanced stage ovarian cancer before 20 weeks is mostly incompatible with maintenance of pregnancy. Debulking surgery with removal of the pregnancy and subsequent chemotherapy are recommended. After 20 weeks, preservation of pregnancy is experimental though possible. Surgery should be limited to establish the diagnosis. Any debulking procedure would be incomplete when preservation of the pregnancy is aimed for. Incomplete debulking during pregnancy should be avoided because the fetus would be exposed unnecessarily to major surgery not accomplishing the goal of complete resection of the tumor. Paclitaxel-carboplatin chemotherapy until fetal maturity is the regimen of choice for pre-operative chemotherapy. Vaginal delivery followed by final surgery in the postpartum period or planned laparotomy for cesarean delivery and (interval)-debulking may be considered.

Psychosocial and Ethical Concerns of Cancer Diagnosis During Pregnancy

Most pregnant women diagnosed with cancer experience high emotional distress and even long-term emotional sequelae. Cancer diagnosis brings fear of death, worry about continuation of the pregnancy, anxiety about the impact of cancer treatment on the fetus, fear for not being able to raise the child into adulthood, and anxiety about future fertility. Emotional and psychological support is imperative. It is advisable to engage the expertise of other members of the health care team such as psychologists, social workers, and depending on patient's religion, a pastoral worker, especially while treatment decisions are being made. Such a decision comprises a balance between the (dis)advantages for mother and child. The prognosis, treatment modalities, gestational age, and the patient's preference are pivotal in the decision making process on treatment during pregnancy or termination of pregnancy. Although most studies report that the prognosis of cancer during pregnancy is similar to the nonpregnant state, these statements should be interpreted cautiously. The series are not large enough to control for all prognostic factors and to draw firm conclusions. Ethically, a delivery before 28 weeks is an undue risk for the fetus but a suboptimal treatment is an undue risk for the mother. The parents should be informed about the different treatment options and the possible consequences for the patient and the fetus.

CONCLUSIONS

Individualization is crucial when gynecological cancer is diagnosed during pregnancy. Oncological surgery and chemotherapy after the first trimester seem to be relatively safe from a fetal point of view. In any case, oncolgic treatment close to the standard should be offered. Unnecessary delay in treatment should be avoided. Continuation of pregnancy until 35 to 37 weeks of gestational age is advocated to prevent neonatal and long-term cognitive problems induced by preterm birth. When confronted with a cancer case during pregnancy, there is no reason to overreact and to take urgent decisions. The pros and cons of continuing or terminating the pregnancy should be weighed from the physical and psychological well being of both the parent(s) and the child. The time needed for consulting an expert is not worsening prognosis.

REFERENCES


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