GYNECOLOGIC CANCERS IN PREGNANCY: GUIDELINES BASED ON A THIRD INTERNATIONAL CONSENSUS MEETING

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Abstract:	OBJECTIVES We aimed to provide comprehensive protocols and promote effective management of pregnant women with gynecological cancers. New insights and more experience have been gained since the previous guidelines published in 2014. METHODS Members of the International Network on Cancer, Infertility and Pregnancy (INCIP), in collaboration with other international experts reviewed existing literature on their respective areas of expertise. Summaries were subsequently merged into a manuscript that served as a basis for discussion during the consensus meeting. RESULTS Treatment of gynecological cancers during pregnancy is attainable if management is achieved by collaboration of a multidisciplinary team of health care providers. This allows further optimization of maternal treatment, while considering fetal development and providing psychological support and long-term follow up of the infants. Non-ionizing imaging procedures are preferred diagnostic procedures, but limited ionizing imaging methods can be allowed if indispensable for the treatment plan. In contrast to other cancers, standard surgery for gynecological cancers often needs to be adapted according to cancer type and gestational age. Most standard regimens of chemotherapy can be administered after 14 weeks gestational age and are not recommended beyond 35 weeks. C-section is recommended for most cervical and vulvar cancers, whereas vaginal delivery is allowed in most ovarian cancers. Breast-feeding should be avoided with ongoing chemotherapeutic, endocrine or targeted treatment. CONCLUSIONS More studies that focus on the long-term toxic effects of gynecologic cancer treatments are needed to provide a full understanding of their fetal impact. In particular, data on targeted therapies that are becoming standard of care in certain gynecological malignancies is still limited. Furthermore, more studies aimed at the definition of the exact prognosis of patients after antenatal cancer treatment are warranted. Participation to existing registries (www.cancerinpregnancy.org) and the creation of national tumor boards with multidisciplinary team of care providers (supplementary box 1) is encouraged.

GYNECOLOGIC CANCERS IN PREGNANCY: GUIDELINES BASED ON A THIRD INTERNATIONAL CONSENSUS MEETING

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ABSTRACT

OBJECTIVES

We aimed to provide comprehensive protocols and promote effective management of pregnant women with gynecological cancers. New insights and more experience have been gained since the previous guidelines published in 2014.

METHODS

Members of the International Network on Cancer, Infertility and Pregnancy (INCIP), in collaboration with other international experts reviewed existing literature on their respective areas of expertise. Summaries were subsequently merged into a manuscript that served as a basis for discussion during the consensus meeting.

RESULTS

Treatment of gynecological cancers during pregnancy is attainable if management is achieved by collaboration of a multidisciplinary team of health care providers. This allows further optimization of maternal treatment, while considering fetal development and providing psychological support and long-term follow up of the infants. Non-ionizing imaging procedures are preferred diagnostic procedures, but limited ionizing imaging methods can be allowed if indispensable for the treatment plan. In contrast to other cancers, standard surgery for gynecological cancers often needs to be adapted according to cancer type and gestational age. Most standard regimens of chemotherapy can be administered after 14 weeks gestational age and are not recommended beyond 35 weeks. C-section is recommended for most cervical and vulvar cancers, whereas vaginal delivery is allowed in most ovarian cancers. Breast-feeding should be avoided with ongoing chemotherapeutic, endocrine or targeted treatment.

CONCLUSIONS

More studies that focus on the long-term toxic effects of gynecologic cancer treatments are needed to provide a full understanding of their fetal impact. In particular, data on targeted therapies that are becoming standard of care in certain gynecological malignancies is still limited. Furthermore, more studies aimed at the definition of the exact prognosis of patients after antenatal cancer treatment are warranted. Participation to existing registries (www.cancerinpregnancy.org) and the creation of national tumor boards with multidisciplinary team of care providers (supplementary box 1) is encouraged.

KEY MESSAGE

Recent studies have shown that treatment of gynecological cancers during pregnancy is attainable, although oncological treatment needs to be individualized to ensure optimal maternal care and minimize potential effects to the fetus, while meeting the psychosocial needs of the family.

INTRODUCTION

The lack of knowledge and the rarity of cancer in pregnancy spearheaded the creation of the International Network on Cancer, Infertility and Pregnancy (INCIP), that aims to contribute to the advancement of cancer management for pregnant women and facilitate large-scale studies. INCIP has grown remarkably in the past years and now consists of 62 medical centers in 25 countries, which have registered over 2000 patients with a cancer diagnosis during pregnancy. Since conception of the registration in 2005, our knowledge on how to manage gynecological cancers has increased tremendously. During this time, two international consensus meetings[1,2] with leading experts in the field were set up to create comprehensive protocols and to provide timely and effective guidance for pregnant cancer patients and healthcare providers. Despite all these efforts, however, many important questions are still not answered by evidence-based information. Therefore, the dissemination of expert's knowledge remains of outmost importance. The aim of this third consensus meeting was to disclose new evidence-based information and expert knowledge, to revise and strengthen the recommendations of the previous guidelines published in 2009[1] and 2014[2], to recommend appropriate techniques and to promote effective management of pregnant women with gynecological cancers, and their offspring. Details of the consensus meeting are depicted in Appendix 1.

1. EPIDEMIOLOGY

The rare combination of cancer and pregnancy is expected to rise, as already demonstrated by population-based studies[3–5]. This will be most significant in countries where women tend to delay childbearing and where Non-Invasive Prenatal Testing (NIPT), that may reveal asymptomatic malignancies[6], is easily available or reimbursed by insurances. Estimation of incidence of all antenatal cancers, including gynecological cancers is, however, a challenging task. This is mostly attributable to the fact that in most countries, obstetrical and oncological registries are not linked. Nationwide studies that combine obstetrical and oncological registries, in order to estimate the incidence of cancer during pregnancy, often lack information on miscarriage or termination of pregnancy, which can possibly result in an underestimation of the incidence. Furthermore, differences in the denominator used (pregnancies or live births) may lead to variation in reported incidence rates between studies. We present in table 1 (and in supplementary table 1 and 2) the incidences of cervical and ovarian cancer based on recent data. [3–5,7–12]. The relative risk of these malignancies is lower during pregnancy compared to non-pregnant women indicating either delay in diagnosis/detection, a true lower risk or a healthy mother effect. Solid data on how pregnancy affects the outcome of gynecological cancers is missing, although a few reports have shown that both cervical and ovarian cancer during pregnancy might not be associated with a poorer prognosis[13,14]. The gestational incidence of other malignancies of the female genital organs are low (table 1)[4,8,15–23].

2. IMAGING AND NUCLEAR MEDICINE DURING PREGNANCY

Imaging procedures in cancer diverge between pregnant and non-pregnant women, mainly due to the risk of teratogenicity and fetal death. The threshold for a significant risk for fetal damage is set at 100mGy[24]. X-rays with proper abdominal shielding are allowed as they carry a negligible fetal radiation exposure of <0.1mGy.

Ionizing imaging procedures should be avoided, if possible, as radiation could affect the viability and development of the fetus (see chapter on radiation therapy)[25]. Although Computerized Tomography (CT) scan is not recommended, it could be performed safely, with intravenous iodinated contrast, only when strictly necessary as there is no trustworthy literature about its safety. In these cases, fetal exposure will depend on proper use of abdominal shielding, tumor location and quality and settings of the CT instrumentation. CT can also be considered as second choice to Magnetic Resonance Imaging (MRI), reserved for cases should more information than the one provided by an MRI be required.

Concerning nuclear medicine procedures, adverse effects on the fetus differ regarding the type of radiotracer, the administrated dose and the weight of the fetus[26]. During the Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography /CT (^{18}FDG-PET/CT) scan proper hydration and a bladder catheter should be used to reduce fetal radiation exposure. Although sentinel node mapping using radioactive materials is contraindicated for cervical, it is not for vulvar cancer (see below). The use of sentinel mapping using indocyanine green is still experimental, and published case reports are insufficient to make any recommendation[27]. Thus, in sum, ionizing radiation techniques may be performed only after extensive discussion about indication and clinical relevance, in individual cases, under strict and specific precautions.

Non-ionizing imaging procedures, such as ultrasonography and MRI are preferred and can be used to determine tumor size, extent of invasion and lymph node involvement in any trimester of pregnancy. A recent study found that although gadolinium-enhanced MRI at any gestational age was not associated with a greater risk of congenital anomalies, it was associated to increased risk of a broad set of rheumatologic, inflammatory, or infiltrative skin conditions and risk of stillbirth or neonatal death[26]. Thus, the use of gadolinium for imaging in MRI, is not recommended during pregnancy. A recent study has shown that whole-body diffusion-weighted MRI (WB-DWI/MRI) could replace 18F-FDG-PET/CT as it presented equal efficacy in the detection of nodal and distant metastasis including bone metastasis both in solid tumors and lymphomas[28]. It also showed no adverse effects to the fetus. Therefore, WB-DWI/MRI could be used for staging and for tumor response evaluation in pregnant women with cancer[29]. One has to bear in mind that newer MRI scanners use significantly stronger magnets leading to fetal exposure to increasing amount of Tesla and research is mostly based on older MRI data. So, also in imaging, more studies on the consequences on pregnancy of new developments in imaging techniques are needed. Pineapple juice is used as a negative contrast for MRI (WB-DWI/MRI), allowing investigation of adhesions, peritoneal/intra-abdominal lesions; and is most frequently used in ovarian cancer. Pineapple juice is a very fitting contrast agent for cancer in pregnancy, since it helps patient comfort without compromising fetal health[30].

3. SURGERY

Surgery is the cornerstone in the treatment of most gynecologic cancers and can be performed safely during pregnancy. Postponing a procedure until postpartum can be considered in selected cases.

Surgery protocol

Physiological changes in pregnancy have consequences for the preoperative, peri-operative and postoperative care. Local or regional anesthesia are preferred. Although surgery is possible in all trimesters[31], it is preferably performed in the (early) second trimester when the risk of miscarriage is decreased and the size of the uterus still allows a certain degree of access. Although a “left lateral tilt” for elective cesarean delivery under spinal anesthesia appeared to have no effect on neonatal acid-base status, more vaso-active medication was needed to maintain hemodynamic stability when patients were not in left lateral tilt position for this short procedure[32]. Therefore, for oncologic procedures, the left lateral tilt position is still advised because of the longer operating time and the use of general anesthesia. Right lateral tilt can be used if this leads to improved exposure.

Laparoscopy in pregnancy is feasible, but depends on the gestational age, surgeon’s experience, type of procedure and the organs of interest.

A recent study comparing pregnant women undergoing laparotomy versus laparoscopy found that in pregnancy, laparoscopy was associated with less fetal adverse effects, shorter operative times and shorter hospital stays[33]. In addition, patients undergoing laparotomy for adnexal mass in pregnancy, experienced significantly more preterm contractions than women undergoing laparoscopy[34]. However, it is important to note that laparoscopic surgery can cause hypercapnia, perforation of the uterus, and reduced blood flow due to increased abdominal pressure and use of carbon dioxide. Thus, the recommendations for surgery during pregnancy are laparoscopic procedure (if possible), of

no longer than 90-120 minutes, with low intraabdominal pressure of 10-13mmHg, open introduction and an experienced surgeon[35–37].

During surgery, careful preparation and adequate monitoring of the maternal condition is mandatory for maternal and fetal well-being. Risks of surgery in a pregnant patient include preterm delivery, miscarriage, and fetal distress. Physiologic hemodynamic changes in pregnancy have consequences for peri-operative monitoring[38]. The same precautions of anesthesia as in non-pregnant women should be taken. The pregnancy-associated gastroesophageal reflux increases the risk of aspiration. Maternal hypotension causes a reduced blood flow to the placenta and fetal hypoxia will become apparent shortly after the occurrence of hemorrhage and hypovolemia. Fetal distress can occur before maternal deterioration[38]. Precautions are especially important since cardiotocography monitoring during pelvic surgery is impossible.

Peri-operative medication may display a significant transplacental transfer depending on lipophilicity, degree of ionization, molecular weight and protein-binding (supplementary table 3).

3.1 OVARIAN CANCER

Diagnostic procedures in pregnant patients with ovarian cancer are explained in supplementary box 2. Patients with apparent early stage malignant disease should be surgically treated and staged based on the histopathology report (low malignant potential, invasive or germ cell), of either definitive histology or by frozen section.

Staging procedures during pregnancy may include infracolic omentectomy, appendectomy, pelvic-peritoneal biopsies and lymph nodes dissection. A general recommendation is that, if the pelvic peritoneum and the pouch of Douglas cannot be reliably examined during surgery because of the enlarged dimension of the uterus and the limited possibility to manipulate it, restaging surgery should be planned postpartum. The expert panel believes an indicative threshold to perform an adequate gynecological surgical assessment could be proposed around 22 weeks of gestation. Based on a low risk of progression to invasive cancer, surgery might be postponed until postpartum if a tumor of low malignant potential is diagnosed during the second or the third trimester.

In cases with advanced stage epithelial ovarian cancer, termination of pregnancy should be considered when the diagnosis is made in the first half of the pregnancy.
In patients who are motivated for pregnancy preservation, a biopsy or an adnexectomy should be performed, followed by platinum-based chemotherapy. In these cases, cytoreductive surgery should be planned after delivery, as surgery to no residual disease cannot be performed during pregnancy.

3.2 CERVICAL CANCER

Surgery

Diagnostic procedures in pregnant patients with cervical cancer are explained in supplementary box 2. Lymphadenectomy can be performed by laparotomy or laparoscopy (supplementary table 4). Due to increased feasibility and safety, laparotomy should be reserved for cases over 14-16th week of gestation, whereas laparoscopy can often be performed below 14-16th week of gestation. Nodal resection is not recommended after the 22nd week of gestation, since insufficient number of nodes can be retrieved after this gestational age[39].
Several surgical procedures have been described in early stage cervical carcinomas (IA1-IB2, according to the most recent FIGO classification[39]) during pregnancy, such as large conization, simple trachelectomy and radical vaginal/abdominal/laparoscopic trachelectomy. As increasing number of studies in non-pregnant cervical cancer patients demonstrate that in case of negative pelvic lymph nodes, the risk of parametrial involvement is negligible, there is a growing support for large conization or simple trachelectomy only[40,41]. Supplementary table 5 presents the

cases of simple trachelectomy in pregnancy and shows the low number of major complications. Supplementary table 6 summarizes radical trachelectomy cases showing that this procedure results in a high rate of obstetrical and surgical complications and should not be recommended during pregnancy.

Management

Analysis of prognosis of cervical cancer during pregnancy shows no negative impact of pregnancy on the outcome of patients, therefore pregnancy-preserving management should be considered in the first place. Figure 3 summarizes the different treatment options based on stage and gestational age at diagnosis.

Pregnancy-preserving management

A cone biopsy may be used to treat stage IA1 tumors without lymphovascular space invasion. For stage IA1 with lymphovascular space invasion, IA2 and IB1, staging lymphadenectomy should be performed as a first step. This can be safely done up to the 22nd week of gestation. After the 22nd week of gestation delayed treatment after delivery with regular follow-up could be initiated. Alternatively, neoadjuvant chemotherapy (NACT) could be used to control the disease.

In stage IB2 less than the 22nd week of gestation, two options are available: a) pelvic lymphadenectomy as a first step followed by either chemotherapy or follow-up, and b) NACT and subsequent surgical staging of the disease after downstaging the tumor. In case of positive nodes (including micro metastases), we recommend termination of pregnancy. However, the panel believes that for those patients who refuse this option, chemotherapy could be considered. In these instances, patients should be informed of the possible negative impact on the prognosis and the lack of available data. Follow-up of IB1, IB2 and IB3 tumors after staging lymphadenectomy has been described in a systematic review of Morice et al[42], who collected 76 patients with a median follow-up of 37.5 months (mean 16 weeks of delay) and showed excellent oncological outcome). After the 22nd week of gestation, only NACT is an option.

In stage IB3 (according to the new FIGO 2018 classification[39]), the only pregnancy-preserving option is the application of NACT, although its efficiency has only been investigated in a small number of trials, and further research is warranted[43]. The role of staging lymphadenectomy is controversial[44]. Follow-up without therapy in such cases is likely to compromise the prognosis and is thus not recommended.

With increasing gestational age, a delay of definitive treatment is more commonly used, though NACT (until the 34-35th week of gestation) will prolong the duration of pregnancy until term delivery.

Pregnancy non-preserving management

Pregnancy non-preserving management is chosen in advanced disease (stage IIB or higher or lymph node metastases) or in cases when the patient chooses not to preserve her pregnancy (based on local legislation and usually until the 24th week of gestation). Treatment is thus planned without intention to preserve the fetus. In case of an operable disease (IA2-IB2), a radical hysterectomy with fetus in utero (during the 1st- or early-2nd trimester) or after hysterotomy (during the late 2nd trimester) can be performed.

In IB3 and higher stages, during first trimester chemoradiation can be applied with fetus in utero (the death of the fetus occurs within few days), while during second trimester a hysterotomy as a first step is advised. This reduces the risk of obstetrical complications (bleeding, rupture of the cervix, diffuse intravascular coagulation…) and psychological impact on the patient. Alternatively, before chemoradiotherapy is initiated, feticide can be considered for ethical and psychological reasons[45] .

3.3 VULVAR CANCER

Standard surgical treatment of this very rare condition in pregnancy, is radical local excision with unilateral or bilateral lymph node dissection or sentinel node procedure. Fetal exposure to locally injected technetium is small and can be further reduced by using a short treatment protocol and the lowest possible dose and performing the procedure 2 hours after injection. T½ of technetium is 6 hours, so the sooner the procedure is performed, the less delay has occurred and the smaller the dose that can be used. Because the technetium is captured in the node, there is little systemic exposure.

Also, nodal removal equals removal of exposure. The SPECT CT-scan that is often made in non-pregnant women, should be omitted. Also, blue dye should be omitted because of the chance of anaphylaxis. Treatment of patients diagnosed in the late third trimester might be delayed until the postpartum period. Surgical radicality should be aimed for, as vulvar radiotherapy is contraindicated during pregnancy. Increased gestational vulvar blood flow can lead to more peri-operative blood loss, which can be reduced by meticulous electrocautery.

Patients with sentinel node metastasis require additional inguinal treatment. In case of nodal involvement after inguinofemoral lymphadenectomy, depending on gestational age, pregnancy is advised to be terminated or delivery to be planned, and postpartum irradiation is subsequently advised. Delay of radiotherapy by 6 to 8 weeks is within the safety limits, based on data from other epithelial cancers[46]. When preoperative examinations suggest inguinal lymph node involvement, the prognosis is less favorable and inguinal radiotherapy to prevent local groin recurrence becomes vital. Immediate treatment is then mandatory, and termination of the pregnancy in the first and second trimester is indicated.

Regarding mode of delivery, in the third trimester a cesarean delivery is performed to prevent vulvar wound dehiscence. In case of smaller wounds that have already healed well, vaginal delivery is an option. NACT to reduce tumor size for locally advanced disease remains experimental.

3.4 VAGINAL CANCER

Since vaginal cancer occurs especially in postmenopausal women, only 12 cases of antenatal vaginal cancer have been reported in literature so far[21]. Depending on the location and tumor size, surgical resection can be done. When surgery is not an option, delay of radio(chemo)therapy or termination of pregnancy can be considered as shown in case reports.

4. SYSTEMIC TREATMENT

Pregnancy results in physiological changes that may influence the exposure and efficacy of systemic treatments, by influencing their pharmacokinetics with respect to distribution, metabolism and excretion of drugs. Current recommendations suggest to dose chemotherapeutic drugs during pregnancy based on actual pregnancy weight but not on ideal or pre-pregnancy body weight. These and other recommendations regarding systemic treatment are noted in table 2.

Chemotherapy

Chemotherapy is contra-indicated in the first trimester of gestation to avoid interference with organogenesis as early exposure has been associated with a 10-20% risk of major malformations[47]. Fetal benefit of treatment delay until the second trimester should be balanced against maternal risk. After 14 weeks of gestation, administration of a number of chemotherapy drugs is feasible, including taxanes, platinum agents, anthracyclines, etoposide and bleomycin. In several studies the rate of fetal malformations was comparable to the general population demonstrating the relative safety of chemotherapy beyond the first trimester [48–54]. Table 3 represents the chemotherapy regimens most commonly prescribed for gynecological cancers during pregnancy[55].

Chemotherapy is not recommended beyond a gestational age of 35 weeks since a 3-week window between the last cycle of chemotherapy and delivery is important to allow both maternal and fetal bone marrow recovery. This window is particularly important in preterm infants who lack the enzymes to metabolize chemotherapy adequately[56]. However, when weekly regimens are used, the panel recommends that administration should not go beyond 37-week gestational age.

Due to their relatively small molecular weight, most chemotherapeutic drugs can cross the placenta. For a detailed summary of the studies of placental transfer of chemotherapies used in gynecological cancers during pregnancy please refer to supplementary table 7.

Specific agents

A favorable fetal toxicity profile of weekly paclitaxel,3-weekly paclitaxel and docetaxel during the second and third trimesters of pregnancy was supported by pharmacological evidence[53]. Although substantial placental transfer has been described to platinum-based compounds, administration of carboplatin during pregnancy seems safe. Cisplatin carries the risk of dose-dependent ototoxicity in children that were exposed during pregnancy[57–59]. Carboplatin is therefore preferred for gynecological malignancies except for germ cell cancers, in which a cisplatin-based schedule is standard of care.
Etoposide remains relatively myelotoxic but its use during pregnancy in combination with cisplatin with or without bleomycin has been described and appears to be safe, although numbers of cases are limited[60–62].

The use of targeted therapies or supportive medication during pregnancy is explained in supplementary box 3.

5. RADIATION THERAPY (RT)

The influence of radiation on pregnancy in general may include fetal death, malformations and growth disturbances and may lead to carcinogenic effects, depending on gestational stage and radiation dose/dose rate (scheduling). We discriminate deterministic effects, occurring above a threshold dose with a severity related to the dose (e.g., teratogenesis), from stochastic effects, without a threshold, dose-related frequency and dose-independent severity (e.g., carcinogenesis)[24,63]. Overall, there is no role for RT during pregnancy for pelvic cancers, unless embryo-fetal death is considered unavoidable. Nevertheless, all reported cases of non pelvic RT during pregnancy describe healthy babies without RT-related side effects[64,65]. Possible treatment options need to be discussed in a shared decision-making process with patient and partner. General recommendations can be seen in table 4.

6. OBSTETRICAL CARE

All patients deserve referral to a high-risk dedicated well-equipped obstetric center for prenatal care.
After cancer diagnosis early in pregnancy or an inadvertent pregnancy during cancer treatment, it is important to obtain an accurate estimation of gestational age and assessment of the structural development of the fetus and placenta to exclude preexisting anomalies. In fact, during the first trimester the embryo is most vulnerable to teratogenic exposure. Standard screening and diagnostics for chromosomal and structural anomalies should be offered, and gestational complications should be assessed. In addition, folic acid supplementation and nutritional counseling is important to optimize the materno-fetal status.

If an agreement on intervention has been reached, fetal monitoring should be performed before and after surgery to detect fetal distress. In case of uterine manipulations during surgery, prophylactic use of tocolytics can be considered. After cervical conization, serial cervical length measurements are advised to assess cervical incompetence[66]. Vaginal progesterone administration is advised when the residual cervical length is < 25mm[67]. If there is no residual disease and limited residual cervical length, the panel believes a cerclage should be considered.

Abdominal and cervical surgeries are not associated with an increased likelihood of admission to neonatal intensive care unit (NICU) in comparison to pregnant cancer patients with or without other treatments[25]. In contrast, pregnant patients receiving chemotherapy seem to be at increased risk for having a fetus with IUGR, preterm premature rupture of membranes and preterm contractions[25]. In particular, platinum-based chemotherapy is associated with small for gestational age neonates, whereas taxanes are associated with NICU admission[25]. Thus, pregnant patients receiving antenatal chemotherapy should be monitored on a regular basis (2-4 weekly) with serial ultrasounds assessing interval growth, amniotic fluid and cervical length[25]. Further, the morphological development should be evaluated by ultrasonography. Fetal Doppler exams should be added in case of growth restriction or to evaluate fetal anemia via measurements of the peak systolic velocity (PSV) [68], this might be particular evident after platinum derivatives are used.

If possible, delivery should not be induced before 37 weeks in order to avoid acute neonatal morbidities and long-term prematurity-related sequelae. When a preterm delivery is inevitable, steroids for fetal lung maturation should be considered (supplementary table 3). Although the overall impact of mode of delivery on the oncological outcome of cervical cancer is controversial, vaginal delivery may result in tumor laceration, excessive bleeding and fatal implantation of malignant cells at the site of episiotomy[69–71]. In addition, cervical cancer can obstruct the birth canal. Thus, C-section is indicated for cervical and also for most vulvar cancers. As metastases can be found in the abdominal wound scar after surgery after C-section[72], a corporeal uterine incision is preferred to avoid surgical trauma of the lower uterine part harboring the cancer[27,72,73].
C-section could be combined with simple or radical hysterectomy. Usually, the C-section is performed under locoregional anesthesia, with conversion to general anesthesia for the hysterectomy. Lymph node dissection with or without sentinel node biopsy can be performed after delivery in case of nodal status was not assessed previously during pregnancy[27]. Meticulous surgery by an experienced gynecological oncologist is mandatory to minimize blood loss [73]. Patients with cervical cancer that was already completely excised during pregnancy and ovarian cancer have no oncologic indications for C-section[2].

Both the pregnancy/postpartum period and malignancy are risk factors for venous thromboembolism. Therefore, thromboprophylaxis with low molecular weight heparin (LMWH) should be considered[74], especially in post-operative setting or in case of immobilization. Oncological treatment can be continued immediately after vaginal delivery, and one week after uncomplicated C-section. It is also important to discuss postpartum contraception if fertility is maintained[75].

Breastfeeding is allowed if there is no ongoing chemotherapy or targeted therapy and the time since last administration is at least three weeks[76].

The placenta should be examined for metastatic disease[77–81]. In the rare case that the placenta showed metastases, three monthly clinical follow-up of the child is recommended by a specialized cancer in a pediatric oncology center. Metastasis to the fetus in gynecological cancers is exceptional[82].

7. NEONATAL AND PEDIATRIC CARE

The neonate needs to be examined thoroughly by a neonatologist or pediatrician. After exposure to chemotherapy, hematological parameters, liver and renal function should be checked. Preterm and small for gestational age (SGA) infants require specific neonatal follow up care. In case of cardiotoxic treatment (e.g. anthracyclines) administered during pregnancy, an echocardiogram in the first weeks is advisable. After platinum exposure, special attention for hearing function is needed throughout infancy[58]. It is anticipated, based on animal models as well as childhood cancer studies, that combining platinum exposure with aminoglycosides or furosemide is adding to the risk [83,84].

Long-term toxicity data after chemotherapy exposure in young children with childhood cancer has shown cardiotoxicity, hearing loss, neurocognitive problems, endocrine impairment, secondary malignancy and general burden of disease [85–88]. In particular, anthracyclines are notorious for long-term cardiotoxicity in cancer survivors, and cisplatin for irreversible hearing loss[87,88]. Based on these findings surveillance guidelines have been developed for life-long follow up of young cancer survivors[89].

Although it is still unclear whether the effects of *in utero* chemotherapeutic exposure are similar to the effects of exposure in young children with cancer, it is important to address the same short- and long-term toxic effects. Several important large-scale studies have addressed the outcome of children born to mothers diagnosed with cancer, but none have specifically investigated outcome in gynecological cancers. These studies have shown that middle- and long-term

cognitive and physical outcomes of children prenatally exposed to chemotherapy appear reassuring till now[25,57,90–94], although neurocognitive problems and cardiotoxicity may become more apparent later in life. In addition, in prenatally platinum exposed children, irreversible hearing loss has been described[11,58,95]. Thus, we recommend a long-term follow up of children exposed antenatally to chemotherapy every three years, in case of cisplatin or anthracycline *in utero* exposure. Additionally, we recommend an auditory evaluation and echocardiographic follow up, respectively (table 5).

Furthermore, a consultation shortly after birth as a standard of care, to (ideally) confirm that the newborn is healthy, to inform the families regarding follow-up, and to support them by giving information and access to specialized medical surveillance and psychosocial family care, is recommended. This is further underscored by the fact that, in the following years a probability exists that the child will lose the mother at an early age; hence the team can anticipate that psychosocial support may be offered, when desired.

8. PSYCHOLOGY

A cancer diagnosis during pregnancy is a challenging life event. This can cause prenatal maternal stress and disruptions in mother-child interaction. In healthy women, stress and anxiety during pregnancy have been associated with adverse birth outcomes, developmental and cognitive impairments and psychopathology in the offspring. There is an increased risk of spontaneous abortion, preterm labor, malformations, growth restriction and low birth weight[96,97]. Further, women confronted with this situation often do not feel completely understood by others. Treatment for gynecological cancers (e.g., hysterectomy, radiotherapy of the pelvis, bilateral oophorectomy) may also induce other psychological effects including depression, but may also induce sexual dysfunctions such as dyspareunia or loss of sexual desire and arousal[98]. The psychological impact of such a devastating and threatening life event on the partner is often ignored, which can also compromise the partnership and the father-child relationship[99].

A recent study has shown that an extensive education about necessary medical steps and their implication on the outcome of the pregnancy and long-term effects on the physical and cognitive health of the offspring might alleviate the fear of harming the child, thus reducing guilt and anxiety[99]. Thus, pregnant cancer patients deserve a careful continuous assessment and support of their psychological wellbeing on a routine basis with follow up in the postpartum period[25]. General recommendations are provided in table 6.

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FIGURE LEGENDS

Figure 1: Flowchart for management of epithelial OC tumors. Staging refers to surgical staging.
Abbreviations: CT=chemotherapy; gw=gestational weeks;
*=according to ESMO guidelines;
**=CT administered according to restaging surgery findings.

Figure 2: **Flowchart for management of non-epithelial OC tumors.** Staging refers to surgical staging.
Abbreviations: CT=chemotherapy; gw=gestational weeks;
*=according to ESMO guidelines;
**=CT administered according to restaging surgery findings.

Figure 3: Flowchart for cervical cancer management during pregnancy. Abbreviations: PLND=pelvic lymph node dissection; NACT=neoadjuvant chemotherapy; AC=adjuvant chemotherapy; TOP=termination of pregnancy; ST=simple trachelectomy; DTAD=delayed treatment after delivery.
*FIGO 2018 for cervical cancer is used (reference 39).

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Malignancy	Incidence (cases/pregnancies)	Comments	References
Cervical cancer	1.4 to 4.6 per 100,000	The variation in incidence during pregnancy is likely to reflect differences in underlying cervical incidence rates across population and screening programs.	3-5, 7-12
Ovarian Cancer	0.2 to 3.8 per 100,000		11,12
Ovarian masses with low malignant potential	1.1 to 2.4 per 100,000		11,12
Vulvar cancer	0.1 per 0.5 in 100,000	Rare, only 38 case reports in literature.	4,8, 15-20
Vaginal cancer	0.1 per 0.5 in 100,000	Rare, only 12 case reports in literature.	4,8, 15-20

Table 1: Incidences Gynecological cancers during pregnancy. Numbers are based on recent data. Vulvar cancer during pregnancy is rare, reflecting the general low incidence of the disease before the age of 40-45 years. Also, endometrial cancer is very rare among premenopausal women and to our knowledge only 39 cases in association with pregnancy have been published, usually diagnosed after curettage for miscarriage. As endometrial cancer is mostly diagnosed after delivery or miscarriage, standard treatment can then be applied. Adapted procedures for the other gynecological cancers are described in the text.

Table 2: Recommendations for systemic treatment and supportive medication

- Dosing of chemotherapeutic drugs during pregnancy should be based on actual weight.
- The same dose/m^2 or dose/kg^2 should be used as in non-pregnant patients.
- Chemotherapy is contra-indicated in the first trimester of gestation to avoid interference with organogenesis; fetal benefit of treatment delay until the second trimester should be balanced against maternal risk.
- After 14 weeks of gestation, administration of a number of anticancer drugs is feasible including taxanes, platinum agents, anthracyclines, etoposide and bleomycin.
- Chemotherapy is not recommended beyond 35 weeks: it is important to give a 3-week window between the last cycle of chemotherapy and delivery to allow both maternal and fetal bone marrow to recover.
- Anti VEGF and other antiangiogenic drugs are contraindicated during pregnancy.
- Until safety data are available, targeted therapies should be avoided during pregnancy.
- Metoclopramide, 5HT3 antagonists, ranitidine, proton pump inhibitors, methylprednisolone, prednisolone or hydrocortisone can be used if necessary.

Tumor type	Preferred regimen
Cervical cancer	Paclitaxel / carboplatin weekly or 3-weekly
Epithelial ovarian cancer	Paclitaxel / carboplatin 3 weekly
Non epithelial ovarian cancer	(Bleomycine/) etoposide/ cisplatin (BEP or EP)

Table 3: Chemotherapy regimens used for cancer during pregnancy. Abbreviations: BEP=Bleomycin, etoposide and platinum; EP=Etoposide and cisplatin

Table 4: Recommendations for radiation oncology teams treating pregnant gynecological cancer patients

- Any radiation treatment to the pelvic region will deliver a significant dose to the fetus and should therefore be avoided if pregnancy is to be continued.
- Doses in the therapeutic range, starting from the first fraction, will lead to fetal death.
- The probability for a new pregnancy after successful cancer treatment decreases with the delivered radiation dose to the uterine structures.
- If radiation therapy is indicated after termination of pregnancy, it is advised that the ovaries are marked with radiological visible clips to guide ovary-sparing radiation therapy to decrease the risk of premature menopause.

Cancer in pregnancy	Screening of children with intra-uterine chemotherapy / radiotherapy during pregnancy because of maternal gynecological cancer (including cervix carcinoma, ovarian cancer and breast cancer)													
Birth														
Examination of placenta	X													
Examination of neonate	X													
Registration of family (mother and child) (signed informed consent)	X													
Follow-up/Check-up (Care)		X / X*						X	X	X	X	X	X	X
Blood count (morphology, differentiation)**	X													
Evaluation of auditory function***		X								X				
EKG and echocardiogram****		X				X		X	X	X		X		X
Neurocognitive development (psychologist)		X						X	X	X	X	X	X	X
Neuromotor development (qualified physiotherapist/neurologist or pediatrician)		X						X	X	X	X	X	X	
Genetic consultation offered		X												
Time														
Months	**at birth**	**1-6**	**8**	**9**	**10**	**12**	**15**	**18**						
Years						**1**			**3**	**6**	**9**	**12**	**15**	**17**

Table 5: Follow-up of children born, after gynecological cancer in pregnancy.

* Intensive follow-up when indicated: placenta positive for micrometastasis or when neonatal abnormalities suspicious for metastasis are identified at birth.

** Diagnostic tests: i) laboratory tests will include complete blood count when chemotherapy was administered <4 weeks prior to the birth (risk of bone marrow depression) or complete blood count plus analyses of transaminases and Lactic Acid Dehydrogenase (LDH) (when the placenta contains metastasis or when neonatal abnormalities suspicious for metastasis are found); ii) abdominal ultrasound when the placenta contains metastasis (in the first week of life), or when neonatal abnormalities suspicious for metastasis are identified (urgently in the first days postpartum)

*** After intra-uterine exposure to platin-based treatment: Evaluation of auditory function by ALGO/OAE: until 6 years. Beyond the age of 6 years a tone audiogram is advised.

**** Echocardiogram and Electrocardiogram: after intra-uterine anthracycline exposure.

The expert panel recommends the following roles for the multidisciplinary team involved in the follow-up:
-Gynecologist: Sends placenta for extensive pathological/histological examination (explicitly asks to examine for metastasis of maternal malignancy). Asks consultation of neonatologist. Consultation form: malignancy mother, moment of diagnosis, stage of the disease, metastasis, type, TCD and time of treatment.
-Neonatologist: Physical examination of the neonate, explanation of risk of metastasis and necessity to examine the placenta, reasons for follow-up. Monitor outcome of placental examination, contact parents with result, and perform additional diagnostic tests if indicated. Contact pediatrician experienced in chemo related toxicity, connected to INCIP.
-Pediatrician experienced in chemo related toxicity, connected to INCIP: Further follow-up child. Perform surveillance including additional diagnostic.
Abbreviations: OAE = oto-acoustic emissions; ALGO = automatic BERA; BERA = brainstem evoked response audiometry; TCD= total cumulative dose

Table 6: Recommendations for psychosocial caregivers treating pregnant cancer patients and their families

- Psychologists should be included in the interdisciplinary team of caregivers for pregnant cancer patients.
- Counseling should be offered to both the affected woman and her partner.
- An extensive education about necessary medical steps and their implication on the outcome of the pregnancy and long-term effects on the physical and cognitive health of the offspring should be provided.
- Contact with other families who have experienced cancer during pregnancy should be encouraged as it might help to cope more easily with own emotions, thoughts, and concerns.
- In gynecological cancers hysterectomy and bilateral oophorectomy can be performed. Thus, the interdisciplinary team should be aware of the possible psychological effects of this surgery, including depression, loss of sexual pleasure and future childbearing.

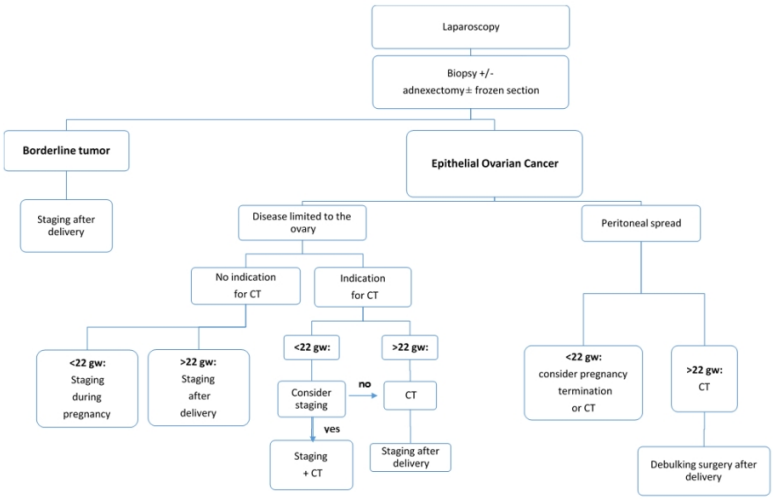

Figure 1: Flowchart for management of epithelial OC tumors. Staging refers to surgical staging.
Abbreviations: CT=chemotherapy; gw=gestational weeks;
*=according to ESMO guidelines;
**=CT administered according to restaging surgery findings.

338x190mm (96 x 96 DPI)

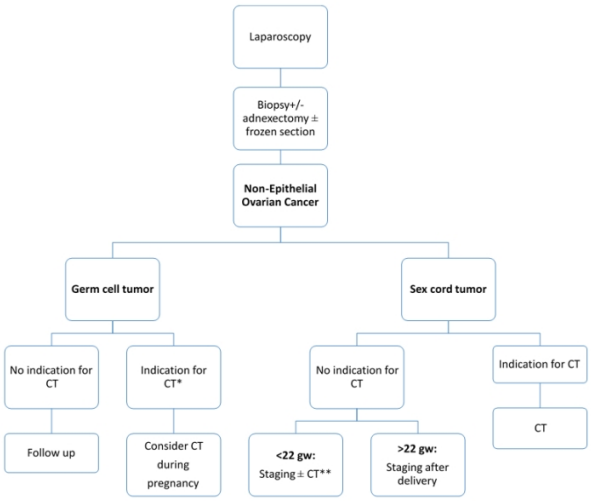

Figure 2: Flowchart for management of non-epithelial OC tumors. Staging refers to surgical staging.
Abbreviations: CT=chemotherapy; gw=gestational weeks;
*=according to ESMO guidelines;
**=CT administered according to restaging surgery findings.

338x190mm (96 x 96 DPI)

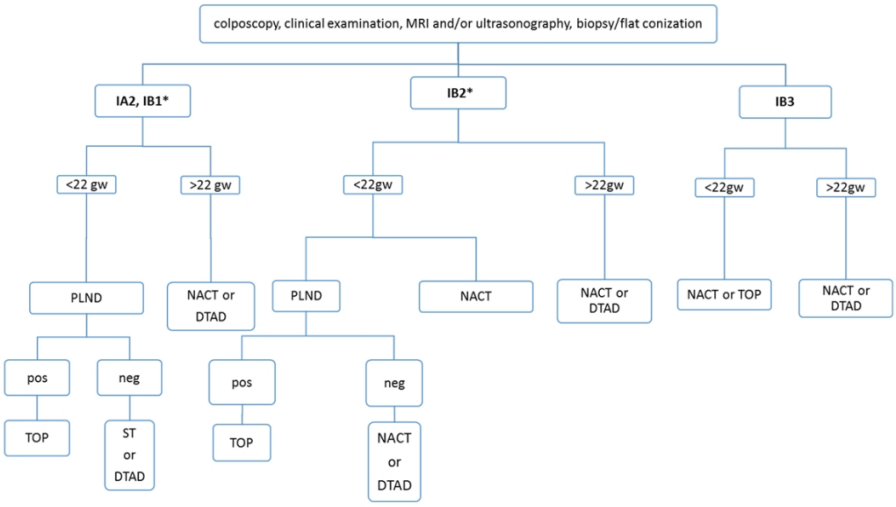

Figure 3: Flowchart for cervical cancer management during pregnancy. Abbreviations: PLND=pelvic lymph node dissection; NACT=neoadjuvant chemotherapy; AC=adjuvant chemotherapy; TOP=termination of pregnancy; ST=simple trachelectomy; DTAD=delayed treatment after delivery. *FIGO 2018 for cervical cancer is used (reference 39).

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Appendix 1:

Members of the International Network on Cancer, Infertility and Pregnancy (INCIP), were selected based on their expertise. Fields that were covered include oncology, medical oncology, clinical pharmacology, obstetrics, pediatrics, psychology and radiation oncology. All participants were assigned to draft a section on the topic of their experience. All the sections were merged into a new manuscript, which was remotely discussed two times. The final version served as the basis for the discussion during the meeting, which took place in Madrid on the 23rd December 2018. Discussions during the meeting resulted in a new version that circulated 2 times. All participants agree with the final recommendations.

Supplementary Box1: International and national organization of cancer in pregnancy research and clinical care

The most recent INCIP-supported studies have led to the understanding that management of cancer in pregnancy requires a specialized multidisciplinary care of not only physicians within the oncology field but also in gynecology, obstetrics, perinatology and psychology[1,2]. However, as cancer in pregnancy is a rare event, most physicians worldwide are rarely confronted with pregnant women with cancer and therefore, lack the expertise to manage these cases. Moreover, many geographical and logistic barriers might impede community-based hospitals and/or patients access to multidisciplinary tumor boards in referral hospitals. This results in a staggering number of patients that are treated with suboptimal care.

As a result of these limitations, two national "Advisory Board on Cancer in Pregnancy" have been created in France and in The Netherlands. These email-based tumor advisory boards are composed of a highly integrative teams of specialized physicians that remotely discuss cases of cancer in pregnancy and provide advice to physicians (national or from abroad) that lack the expertise to manage these patients. It is our recommendation, to encourage the creation of such multidisciplinary national tumor boards worldwide.

Supplementary Box 2. Diagnostic procedures for ovary and cervical cancer during pregnancy.

Ovarian Masses

Adnexal masses found in pregnancy are often incidental findings, mostly benign or functional and of little clinical significance[3]. However, as approximately 1-6% of ovarian masses are malignant, assessment using ultrasound and MRI can allow the distinction between benign and malignant lesions[4]. A wait-and-see strategy is advised for an ovarian cyst with benign features[5].

The use of tumor markers to detect cancer during pregnancy should be performed carefully as some might be elevated during pregnancy[6,7]. Knowledge of the physiological variations of these markers during pregnancy is clinically important during the diagnostic phase of gynecological cancers. Some markers, such as α-fetoprotein and the β subunit of human chorionic gonadotropin, are abundantly increased during pregnancy and cannot be used. In contrast, levels of lactate dehydrogenase (LDH), anti-mullerian hormone (AMH) and Inhibin B, remain below normal cut-off values. CA125 and HE4 are often elevated in pregnancy or in obstetrical complications. As HE4 blood levels have been recently found to be more stable during pregnancy than the ones from CA125, HE4 might represent a more reliable marker for ovarian cancer during pregnancy in comparison to CA125.
In case of suspected ovarian masses, an active management with surgical planning is recommended (figure 1 and 2), to obtain histological definition of the lesion and to avoid complications such as torsion or rupture, as they should be prevented specially during pregnancy[8]. Laparoscopy is preferred to laparotomy for ovarian cysts treatment[9], and unilateral salpingo-oophorectomy is preferred to cystectomy to avoid cyst rupture in case of suspicious mass. In case a bilateral adnexectomy is required, surgery should be scheduled after the 14th week of gestation when the placenta is capable of sufficient hormonal supply. If surgery is required before the 14th week of gestation, hormonal supply (Agolutin (Progesteron) 60-120 mg i.m/day or Utrogestan (Progesteron) 300–600 mg i.vag/p.o./day) should be administered since placental function is not developed enough at this stage. A conservative approach (observation instead of operation) needs to be balanced to the risk of torsion, rupture or discomfort[10].

Cervical Cancer

Due to more frequent gynecological examinations, the majority of pregnant cervical cancer patients are diagnosed at an early stage[11]. Diagnostics in pregnant women are similar to those in non-pregnant women, including cytology and colposcopy. Several physiological changes due to pregnancy make colposcopy to be more challenging (e.g., increased vascularization, stromal edema, hyperplasia of the glandular cells). On the other hand, eversion of the transformation zone helps to better recognize colposcopic visible changes[12].
In case of suspicion of microinvasion, a large loop excision of the transformation zone (LLETZ) is indicated while in more advanced tumors a biopsy is preferred. Optimal timing for LLETZ in terms of safety is between the 12th and 20th week of gestation[13,14].
Staging is done by clinical examination, ultrasonography and MRI[15].

Supplementary Box 3. Additional treatments during pregnancy.

Targeted therapy

Limited preclinical data and only few case reports or case series in humans are available respective to the use of targeted therapy during pregnancy[15,16]. Two main considerations should be made on this regard[16]. First, there are different classes of drugs with different pharmacological properties: 1) large molecules such as monoclonal antibodies that require an active transport via the placenta to reach the fetus (mechanism not present before the 14th week of gestation); and 2) small molecules such as Poly(ADP-ribose) polymerase (PARP) inhibitors and tyrosine kinase inhibitors (TKIs), which have the potential to cross the placenta throughout the whole pregnancy period. Second, these therapies are by definition "targeted" against specific tumor-related features that may have a physiological role in fetal development.

Animal experiments with targeted therapies currently used in gynecological malignancies showed their potential embryotoxicity and risk of adverse fetal outcomes[17]. Angiogenesis inhibitors such as bevacizumab are teratogenic and have been shown to induce pregnancy loss, skeletal malformation and intrauterine growth restriction (IUGR) in animal models, due to the fact that angiogenesis is crucial for the normal development of placenta and fetus. Thus, anti-VEGF and other antiangiogenic drugs are contraindicated during pregnancy.

No case reports of systemic administration of PARP inhibitors, other targeted agents or immunotherapy in pregnant patients with gynecological malignancies have been reported so far.
PD1/PD-L1 and CTLA-4 interactions appear to play key roles in maintaining normal fetal tolerance, and thus, immune checkpoint inhibitors such as anti-PD1/PD-L1 agents have shown to increase the rate of spontaneous abortions in animals[18]. However, few case reports have been reported in pregnant melanoma patients without miscarriage[19,20]. Based on the limited evidence available so far, the use of targeted therapies commonly administered for the management of gynecological malignances is not supported during pregnancy and should be postponed until after delivery. Nevertheless, accidental short-term exposure to biologic agents during the first trimester does not justify termination of pregnancy per se.

Supportive medication

Safety data on the use of antiemetics during pregnancy generally comes from the treatment of hyperemesis gravidarum. The frequently used metoclopramide and 5HT3 antagonists are not associated with birth defects[21,22]. Ranitidine and proton pump inhibitors can also be used if necessary[23].

Methylprednisolone, prednisolone or hydrocortisone are preferred as premedication instead of betamethasone or dexamethasone because the latter are preferentially distributed to the fetus and thus best to be avoided[24,25]. From clinical experience, it seems that chemotherapy-induced nausea and vomiting is usually milder during pregnancy, allowing the use of antiemetics only if needed depending on the type of chemotherapy.
The use of growth factors granulocyte colony stimulating factor (G-CSF) and erythropoietin has been shown to be feasible during pregnancy[26,27,28]. Supplementary table 3 shows medication that can be used during oncologic treatment in pregnancy.

Study / References	Year Journal	Country	Years	PAC definition	CxCa definition	Total PAC: CxCa	N (Incidence): Pregn + 1y postpartum Pregnancy 1y postpartum	Denominator used in incidence
Cottreau et al[29]	2018 J Women's Health	US, 5 states	2001-2013	Pregn+1y	"cervical cancer" no ICD given	74 CxCa	74 (9.5/100,000)[a] 25 (3.2/100,000)[a] 49 (6.3/100,000)[a]	775,709 Births
Parazzini et al [30]	2017 Int J Gynecol Cancer	Lombardia, Italy	2001-2012	Pregn+1y	ICD9:180	66 CxCa	66 (5.4/100,000) 17 (1.4/100,000) 49 (4.1/100,000)	1,200,263 Pregnancies
Andersson et al[31]	2015 Cancer	Sweden	1963-2007	Pregn+1y[b]	ICD7: 171	502 CxCa	502 (11.1/100,000)[b] 139 (3.1/100,000) [b] 363 (8.1/100,000) [b]	4,508,005 Live deliveries
Eibye et al[32]	2013 Obstet Gynecol	Denmark	1977-2006	Pregn+1y	*cervical cancer No ICD given	96 CxCa	96 (4.0/100,000 pregnancies) 70 (3.8/100,000 live births) *Diagnosis during pregnancy/postpartum not separately reported*	2,427,670 Pregnancies/ 1,858,619 Live births
Lee et al[33]	2012 BJOG	Australia, New South Wales	1994-2008	Pregn+1y	"cervical cancer" no ICD given	110 CxCa	110 (8.4/100,000) 24 (1.8/100,000) 86 (6.56/100,000)	1,309,501 "Maternities"
Dalrymple et al[34]	2005 J.Maternal and neonatal medicine	California	1990-1999	Pregn+1y[b]	Invasive cervical cancer, No ICD given	434 CxCa	434 (9./100,000)[c] 136 (2.8/100,000)[c] 298 (6.1/100,000)[c]	4,846,505 Births beyond 20 weeks
Smith et al[35]	2003 Am J Obstet Gynecol	California	1991-1999	Pregn+1y	"cervical cancer" no ICD given	580 CxCa	580 (12.0/100,000) 223 (4.6/100,000) 357 (7.3/100,000)	4,846,505 Births beyond 20 weeks
**Haas[36]	1984 Int J Cancer	Germany	1970-1979	During pregnancy	"invasive carcinoma of the cervix"	231 CxCa	**Only pregnancy** 231 (11.0/100,000)	2,103,112 Live births

Supplementary table 1. Population-based studies of pregnancy-associated cervical cancer incidence during pregnancy and 1 year post-partum (CxCa=cervical cancer, PAC=pregnancy-associated cancer). Abbreviations: PAC=Pregnancy-associated cancer; CxCa=Cervical Cancer; Pregn +1y=Diagnosis during pregnancy or within 1 year after delivery.

[a] For Cottreau et al: We have calculated the incidence for pregnancy window using the total PAC incidence for pregnancy x proportion of PAC which are CxCa during pregnancy (25/74*9.5=1.9), and similarly for postpartum (49/74*9.5=3.8)
[b] For Andersson et al: Study used pregnancy+2 years PAC window, we have re-calculated numbers for pregnancy+1year using numbers given in the tables in the article. We have also calculated incidence using the reported number of live deliveries (4,508,005). E.g. total incidence is calculated as 363/4,508,005=8.05/100,000.
[c] For Dalrymple et al: Incidence based on linkage California Cancer registry (CCR) and obstetric registry (all births beyond 20 weeks); 434 cases identified; Additional 146 cases with cervical cancer identified from discharge reports excluded from analysis; aim of study was to describe obstetric outcome and they excluded cases were cancer diagnosis was uncertain (not registered in CCR); so probably underestimation of incidence
**For final analysis only recent data were included. The higher incidence of cervical cancer during pregnancy in Haas et al. might be explained by the introduction of screening for cervical cancer during the study period.

ICD9:180; International Statistical Classification of Diseases and Related Health Problems: revision 9 (1977)- Malignant neoplasm of cervix uteri
ICD7:171; ; International Statistical Classification of Diseases and Related Health Problems: revision 7 (1955) -Malignant neoplasm of cervix uteri

Study/References	Year Journal	Country	Years	PAC definition	OvCa definition	Total PAC: OvCa	N (Incidence): pregn+1y postpartum pregn 1y postpartum	Denominator used in incidence
Cottreau et al[29]	2018 J Women's Health	US, 5 states	2001-2013	Pregn+1y	"ovary" no ICD given	44 OvCa	44 (5.7/100,000) 29 (3.8/100,000)[a] 15 (1.9/100,000)[a]	775,709 Births
Parazzini et al[30]	2017 Int J Gynecol Cancer	Lombardia, Italy	2001-2012	Pregn+1y	ICD9:183.x	45 OvCa	45 (3.7/100,000) 14 (2.6/100,000) 31 (1.2/100,000)	1,200,263 Pregnancies
Andersson et al[31]	2015 Cancer	Sweden	1963-2007	Pregn+1y[b]	ICD7: 175	166 OvCa	166 (3.6/100,000)[b] 54 (1.2/100,000) [b] 112 (2.4/100,000) [b]	4,580,005 live births
Nazer et al[37]	2015	US	2003-2011	Pregn	"malignant adnexal masses" ICD-9 183.0, 183.2, 183.8, 183.9), including ovarian mass with LMP	93 OvCa 87 LMP	**Only pregnancy:** 93 OvCa (1.2/100,000) 87 LMP (1.1/100,000)	7,785,583 births
Lee et al[33]	2012 BJOG	Australia, New South Wales	1994-2008	Pregn+1y	"ovarian cancer" no ICD given	47 OvCa	47 (3.6/100,000) 19 (1.5/100,000) 28 (2.1/100,000)	1 309 501 Maternities (births)
Leisorowitz et al[38]	2006	California registrybased	1991-1999	Pregn	"ovarian mass"	87 OvCa 115 LMP	**Only pregnancy:** 87 OvCa (1.8/100,000) 115 LMP (2.4/100,000)[c]	4,846,505 deliveries
Smith et al[35]	2003 Am J Obstet Gynecol	California	1991-1999	Pregn+1y	"ovarian" no ICD given	253 OvCa	253 (5.2/100,000) 171 (3.6/100,000) 82 (1.7/100,000)	4,846,505 births

Supplementary table 2. Population-based studies of pregnancy-associated ovarian cancer incidence during pregnancy and 1 year post-partum (OvCa=ovarian cancer, PAC=pregnancy-associated cancer). Abbreviations: PAC=Pregnancy-associated cancer; OvCa=Ovarian Cancer; Pregn +1y=Diagnosis during pregnancy or within 1 year after delivery; LMP=Low Malignant Potential.

[a] For Cottreau et al: We have calculated the incidence for pregnancy window using the total PAC incidence for pregnancy x proportion of PAC which are OvCa during pregnancy (29/44*5.7=3.8), and similarly for postpartum (15/44*5.7=1.9).
[b] For Andersson et al: Study used pregnancy+2 years PAC window, we have re-calculated numbers for pregnancy+1year using numbers given in the tables in the article. We have also calculated incidence using the reported number of live deliveries (4,508,005). E.g. total incidence is calculated as 66/4,508,005=3.6/100,000.
[c] For Leiserowitz et al: Incidence of LMP was calculated as 115/4,846,505 deliveries=2.4/100,000.

ICD9:183.0/ 183.2/ 183.8/ 183.9; International Statistical Classification of Diseases and Related Health Problems: revision 9 (1977) - Malignant neoplasm of ovary/ Malignant neoplasm of fallopian tube/ Malignant neoplasm of other specified sites of uterine adnexa/ Malignant neoplasm of uterine adnexa, unspecified site
ICD7:175; International Statistical Classification of Diseases and Related Health Problems: revision 7 (1955)-

	Agents	Additional information
Anti-emetics	Metoclopramide Ondansetron Granisetron	
Pain medication	Paracetamol Morphine Sufentanil Lidocain Ketamine Tramadol-short term use	Maximum of 30 ug For local injection
Sedatives	Desflurane Propofol Rocuronium Suxamethonium	
Hematological support	Erythropoietin G-CSF (granulocyte colony stimulating factor)	
Steroids	Methyl prednisolone Hydrocortisone Prednisolone Hydrocortisone Dexamethasone	preferred because of active metabolisation in the placenta and lower concentrations in the fetus
Antacid	Omeprazol Pantoprozol Ranitidine	Premedication for chemotherapy
Anti-histaminic	Clemastine	Premedication for chemotherapy
Anti-coagulant	Low-molecular-weight heparin	Thromboprophylaxis

Supplementary table 3: List of medications that can be used during oncologic treatment in pregnancy

Author/Reference	year	stage (type)	surgery	week of pregnancy	delivery	follow up (month)	outcome
Ben Arie et al[39]	2004	IA2 (spinocellular)	simple trachel. + LAP	17	39	36	NED
van Calsteren et al.[40]	2008	IB1 (adenoca)	simple trachel. + LAP	15	38	20	NED
Herod et al.[41]	2010	IA2 (adenosquam.)	cone biopsy + LAP	9	36	28	NED
Herod et al.[41]	2010	IB1 (adenoca)	cone biopsy + LAP	11	41	31	NED
Salas et al [42]	2015	IB2 (adenoca)	simple trachel.	29	34	22	NED
Moreno-Luna et al.[43]	2016	IA1 (spinocelullar)	simple trachel.	20	37	17	NED
Salvo et al[42]	2018	IB1(adenocarcinoma)	simple trachel. + LAP	17	37	168	NED
Salvo et al[42]	2018	IB1(adenocarcinoma)	simple trachel. + LAP	15	39	102	NED
Salvo et al[42]	2018	IB1(squamous)	simple trachel. + LAP	19	37	75	NED
Salvo et al[42]	2018	IB1(adenocarcinoma)	simple trachel. + LAP	16	40	65	NED
Salvo et al[42]	2018	IB1(squamous)	simple trachel. + LAP	12	28	18	NED

Supplementary table 4. Cases of lymphadenectomy in cases of cervical cancer during pregnancy. Abbreviations: LAP= Laparoscopy; NED=No evidence of Disease; NA= Not applicable

Author / Reference	Stage	Size	Type	Surgery	Week	Delivery	Complication	Outcome	Follow-up
Ungar, 2006 [45]	IB1	NA	squamous cell	ART+PLND	7	AB	abortion at the 1st postop day	NED	NA
Ungar, 2006 [45]	IB1	NA	squamous cell	ART+PLND	8	AB	abortion at the 1st postop day	NED	NA
Ungar, 2006 [45]	IB1	NA	squamous cell	ART+PLND	9	38	0	NED	20
Ungar, 2006 [45]	IB1	NA	squamous cell	ART+PLND	13	AB	abortion at the 16th postop day	NED	NA
Abu-Rustum, 2010 [46]	IB1	12	lympho-epithelial	ART+PLND	15	39	3.5 hours, blood loss 1600 ml, ureter lesion	NA	NA
Enomoto, 2011 [47]	IB1	NA	squamous cell	ART+PLND	15	37	7.5 hours, blood loss 960 ml	NED	6
Aoki, 2014 [48]	IB1	20	squamous cell	ART+PLND	17	38	6.5 hours, blood loss 2510 ml	NED	40
Capilna, 2016[49]	IB1	NA	squamous cell	ART+PLND	17	38	6 hours	NA	NED
Ungar, 2006 [45]	IA2	NA	squamous cell	ART+PLND	18	39	0	NED	72
Mandic, 2009 [50]	IB1	4	squamous cell	ART+PLND	19	36	5 hours, blood loss 450 ml	NED	12
Karateke, 2010 [51]	IB2	50	squamous cell	ART+PLND	22	AB	4 hours, abortion 4 hours postop	NA	NA
Ferriaoli, 2012 [52]	IA2	4	adenocarcinoma	VRT+PLND	5	35	0	NED	120
Ferriaoli, 2012 [52]	IA2	10	squamous cell	VRT+PLND	11	AB	abortion on the 7th postop day	NED	240
Bravo, 2012[53]	IB1	35	squamous cell	VRT+PLND	11	36	0	NED	160
Alouini, 2008[54]	IB1	20	squamous cell	VRT+PLND	12	AB	abortion on the 2nd postop day	NED	132
Alouini, 2008[54]	IB1	25	adenocarcinoma	VRT+PLND	12	30	0	DOD	18
Sioutas, 2012[55]	IA2	3.6	squamous cell	VRT+PLND	12	37	0	NED	26
Sioutas, 2010[55]	IB1	NA	adenocarcinoma	VRT+PLND	13	37	0	NED	47
Sioutas, 2011[55]	IB1	NA	adenocarcinoma	VRT+PLND	13	29	0	NED	33
Iwami, 2011[56]	IB1	NA	adenocarcinoma	VRT+PLND	16	37	0	NED	14

Kolomainen, 2013[57]	IB2	42	adenocarcinoma	VRT	16	26	PROM 8 weeks after surgery, NEC	NED	184
van de Nieuwenhof, 2008[58]	IB1	8	squamous cell	VRT+PLND	18	36	6.5 hours, blood loss 1550 ml	NED	9
Saso, 2015[59]	IB1	4	squamous cell	VRT	19	36	0	NED	64
Ferriaoli, 2012[52]	IB1	27	adenocarcinoma	VRT+PLND	22	31	IVH on the 2nd postop day	DOD	48
Papadia, 2015[60]	IB1	30	squamous cell	LRT+PLND	14	35	0	NED	24
Kyrgiou,2015[61]	IB1	10	adenocarcinoma	LRT+PLND	14	36	4 hours	NED	9
Papadia, 2015[60]	IB1	8	adenocarcinoma	LRT+PLND	21	39	0	NA	NA

Supplementary table 5. Cases of simple trachelectomy in pregnancy complicated with cervical cancer. Abbreviations: ART= abdradical trachelectomy; VRT= vaginal radical trachelectomy; PLND= Pelvic Lymph Node Dissection; AB= Abortion; NED=No evidence of Disease; DOD= Death of disease; NA= Not applicable

Author	Number	Stage	Surgery	Gestational age	Number of LNs	Positive LNs	Follow-up	Follow-up
		(range)		(weeks, range, median)	(median)	(%)		(months, median)
Ungar, 2006[45]	5	IA2-IB1	Laparotomy	7-18 (9)	NA	NA	5xNED	22
Mandic, 2009[50]	1	IB1	Laparotomy	19	NA	0	NED	12
Karateke, 2010[51]	8	IB2	Laparotomy	22	NA	0	NA	NA
Abu-Rustum, 2010[46]	1	IB1	Laparotomy	15	9	0	NA	NA
Enomoto, 2011[47]	1	IB1	Laparotomy	15	16	0	NED	6
Aoki, 2014[48]	1	IB1	Laparotomy	17	13	0	NED	40
Capilna, 2016[49]	1	IB1	Laparotomy	17	38	0	NED	NA
Muallem, 2017[64]	1	IB1	Laparotomy	26	62	0	NED	26
Stan, 2005[65]	1	IB2	Laparoscopy	16	72	0	NED	48
Alouini, 2008[54]	8	IB1-IIIA	Laparoscopy	12-32 (20)	18	37.5	5xNED, 3xDOD	64
van de Nieuwenhof, 2008 [58]	1	IB2	Laparoscopy	18	19	0	NED	9
Sioutas, 2011[55]	1	IB1	Laparoscopy	13	18	0	NED	30
Sioutas, 2011[55]	1	IA2	Laparoscopy	12	28	0	NED	27
Carillon, 2011[62]	1	IB1	Laparoscopy	13	NA	0	NED	12
Iwami, 2011 [56]	1	IB1	Laparoscopy	16	NA	0	NED	14
Ferriaoli, 2012 [52]	1	IB1	Laparoscopy	22	18	11.1	DOD	48
Bravo, 2012 [53]	1	IB1	Laparoscopy	11	22	0	NED	40
Ferriaoli, 2012[52]	1	IA2	Laparoscopy	7	13	0	NED	120
Ferriaoli, 2012[52]	1	IA2	Laparoscopy	13	30	0	NED	240
Vercellino, 2014[63]	32	IA1-IIA	Laparoscopy	6-25 (17,5)	14	16.7	32xNED	42.5
Papadia, 2015[60]	2	IB1	Laparoscopy	14-21 (17,5)	38.5	0	NED	24
Kyrgiou,2015[61]	1	IB1	Laparoscopy	14	NA	0	NED	9

Supplementary table 6. Radical trachelectomy in cases of cervical cancer during pregnancy. Abbreviations: NED=No evidence of Disease; DOD= Death of disease; NA= Not applicable; LNs= Lymph nodes.

CT AGENTS					EXPERIMENTAL MODELS OF PLACENTAL TRANSFER			
	Molecular weight (g/mol)	**Predicted lipophilicity (logP)***	**Protein binding (%)**	**T1/2 (of unbound fraction)**	**Mouse/rat**	**Baboon**	**Human Placenta Perfusion Model**	**Human in Vivo data**
Cisplatin	300.05	0.014 (+/-)	>90	10-20 minutes (initial phase) – 32 to 53 minutes (later phase)	Transfer is gestational-age-dependent[66]	No data	9.0 ± 0.5% (bolus)[67] 2-24%	Platinum-DNA adducts in AF, placental tissues, cord blood and maternal blood[68-71]
Carboplatin	373.27	0.14 (+/-)	29 (first 4 hours), 85-98 after 24 hours	1.1 to 2 hours (initial phase) – 2.6 to 5.9 hours (later phase)	117%[72]	57.5%[73]	9.0 ± 0.5% (bolus)[74]	Platinum-DNA adducts in AF, placental tissues, FCB (lymphocytes) and maternal blood[75,80]
Docetaxel	907.89	2.4 (++)	>95	11.1 hours, dose dependent	/	Undetectable[73]	4.0%[75]	/
Paclitaxel	853.92	3.2-3.5 (++)	89-98	3-52.7 hours depending on dose and infusion rate	0%-0.01%[72]	1.5%[73]	1.7 – 4.3%[75,76] 3.9 ± 0.3[77] may modulate the expression of placental drug transporters involved in the disposition of various anticancer agents.[13]	Two cases (lower limit of quantification: 1.2 ng/ml) Case 1: 0.2 ng/ml (delivery 7 days after administration, 80mg/m^2) Case 2: 0 ng/ml (21 days after administration, 80 mg/m^2) [77]
Gemcitabine	263.20	-1.4 (-)	<10 (low)	42-94 minutes	4.0–6.4 times the maternal concentration in rats[78]	/	/	/
Bleomycin	1415.56	-9.7 to -0.52 (-)	1 (low)	115 minutes	/	/	/	/

Ifosfamide	261.08	0.86 (+/-)	low	7-15 hours, dose dependent	/	/	/	Ifosfamide undetectable in amniotic fluid and cord blood[79]

Supplementary table 7: Overview of experimental models and in vivo human data of transplacental transfer of anticancer drugs used in gynaecological cancers.
Abbreviations: CT=chemotherapeutics, FT=Fetal tissue, FP=Fetal Plasma, AF=Amniotic Fluid, CSF=Cerebrospinal Fluid, FCB=Fetal Cord Blood
*The higher the predicted lipophilocity (logP), the more likely a drug is able to cross the placenta
References: PUBCHEM[81] and drugbank.ca[82]

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