Gynaecological oncology in pregnancy

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Summary

In this review current knowledge on prevalence, diagnosis, treatment and prognosis of gynaecological malignancies during pregnancy is discussed. After a general overview of surgery, chemotherapy and radiotherapy during pregnancy, tumour specific diagnosis and treatment options are described for breast, cervical, ovarian and vulvar cancer.

In contrast to previous belief, termination of pregnancy because of a concurrent malignancy does not result in an improved prognosis. Information on prognosis of cancer during pregnancy is often contradictory and evidence of the real influence of pregnancy on prognosis is weak. However, there is increasing belief that the prognosis per stage is similar to that of the non-pregnant patient and that the risk for impaired prognosis is most likely due to suboptimal diagnosis and treatment.

With the exception of pelvic surgery, most surgical techniques that are used in non-pregnant patients are also safe for pregnant patients. Radiotherapy proximal of the upper abdomen frequently is possible, while chemotherapy - depending on pregnancy trimester and type of chemotherapy - can usually be administered without much hazards. Indications for termination of pregnancy include an unwanted pregnancy, aggressive hematologic cancers and locally advanced cervical cancer. Fortunately, this group of patients is very small, suggesting that mostly foetal life can be saved.

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Introduction

Intra-uterine life can be affected by infections, teratogens, alcohol, drug and tobacco abuse as well as nutritional deprivation. Cytotoxic treatment regimens add to this list. In most West-European countries maternal age increases. It is expected that this increase in age will probably lead to an increased incidence of cancer occurring during pregnancy.

Breast cancers and cervical cancers constitute about 50% of cancer cases during pregnancy. It should be noted, however, that pre-invasive cervical cancer is included in this number (26%) and that the incidence of invasive cervical cancer is much lower. Patients with haematological malignancies (leukaemia and lymphoma) constitute approximately 25% of all cases during pregnancy. Cancers occurring less frequently during pregnancy include melanoma, thyroid cancer, ovarian cancer and colon cancer.[1]

Although most studies report that the prognosis of cancer during pregnancy is similar to prognosis in the non-pregnant state, these statements should be interpreted cautiously. These series are not large enough to control for all prognostic factors and to draw firm conclusions. Also reporting bias may occur with an overrepresentation of successful outcomes. Although therefore it is difficult to draw solid conclusions regarding the maternal prognosis, it seems important to avoid delays in treatment and to provide standard treatment.

In this review the effects of different treatment modalities when used during pregnancies, are discussed. Also, particular aspects of gynaecological organ pathology are reviewed.

Surgery during pregnancy

During 0.75 to 2% of pregnancies an operation is needed. Most common indications include cholecystitis, appendicitis and ovarian cysts. Literature data suggest that anaesthesia is safe during pregnancy provided physiologic adaptations are conside-

red.[2] Fetal effects after anaesthesia are more related to maternal hypotension or hypoxia, altered glucose metabolism or hypothermia, rather than to the use of anaesthetics.

Cohen-Kerem et al.[3] reviewed more than 12,000 cases of surgery during pregnancy. The data suggest that surgery does *not* increase the risk for miscarriage and congenital anomalies. Premature delivery occurred in 3.5% of cases, but this occurred mainly after abdominal surgery and peritonitis in the third trimester. Overall calculations demonstrate that 8.2% of women undergoing surgery during pregnancy will deliver prematurely. Adequate analgesia in the post-operative period is important since pain can induce premature contractions. Also thrombosis prophylaxis needs to be considered.[3] Non fractionated and low molecular weight heparins are used during pregnancy since coumarins are teratogenic in the first trimester and are associated with bleeding in the neonate when used in the third trimester. *Rizzo et al.*[4] described 11 cases of laparoscopic surgery during pregnancy between 16 and 28 weeks of pregnancy. Surgery was uneventful and children were healthy on interrogation 1 to 6 years after surgery. The safety issues were confirmed by *Mathevet et al.*[5] and *Yuen et al.*[6] in 48 and 67 patients respectively. It appears that laparoscopic surgery during pregnancy can be performed safely in experienced hands. Laparoscopic surgery offers many advantages but only limited data of these interventions during pregnancy are available. The CO_2 pneumoperitoneum and CO-production during electro-coagulation are not hazardous to the foetus as long as the maximal pressure (10 mmHg) and operation time (25 to 90 minutes) are respected. [4,5,6] Open laparoscopy (opening of the peritoneum under direct visualisation instead of using the Verres-needle) is mandatory in order to avoid uterine perforation.

Chemotherapy during pregnancy

The risk of foetal damage and hence the possibility to treat cancer during pregnancy will largely depend on the exposure period in pregnancy. With regard to this aspect, the pregnancy can be divided into three stages: implantation, organogenesis and the fetal phase.

During the first 10 days of pregnancy (implantation) cells are omnipotent and can develop in the three 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. When sufficient cells remain, the embryo will unaffectedly result in a normal pregnancy. However, when too many cells are damaged, miscarriage will occur.

The most vulnerable phase is the phase of organogenesis which expands from 10 days until 8 weeks after conception. The potential for fetal damage is the highest during this period but varies depending on the agents used. Overall, taking into account a background risk of foetal malformation of 3%, the use of cytotoxic drugs during the organogenesis will increase the risk almost sixfold, to 17%; when folate antagonists are excluded the risk of fetal malformations doubles.[7] *Therefore, the administration of chemotherapy during this phase is contraindicated and administration should be postponed*. Since after organogenesis, the eyes, genitals, haematopoietic system and the central nervous system remain vulnerable, it is strongly recommended *to wait until 14 weeks have passed* before initiating chemotherapy. During the *second and third trimester*, chemotherapy can be administered relatively safely.[7]

- *Class of drugs and potential fetal damage: which drug to choose?*

The category of cytotoxic drugs with the highest potential of fetal damage are the folic acid antagonists with methotrexate as the most frequently used drug.[7]

The antitumour antibiotics doxorubicin and epirubicin can be used in pregnancy without much hazards for fetal development[7,8,] but fetal death has been reported after idarubicin exposure.[9] The latter can be explained by its more lipophylic properties and the higher affinity for DNA.[9] Therefore, idarubicin is no longer used during pregnancy.[7] The alkylating agents cyclophosphamide, cisplatin and carboplatin are also relatively safe to be administered. During pregnancy, preferably cisplatin, compared to carboplatin, is used, since carboplatin results in greater bone marrow toxicity and is less protein bound, possibly favouring transplacental transfer.[7] Based on 31 cases,[7,10-20] it could be calculated that cisplatin exposure resulted in 1/30 (3%) of patients in moderate bilateral hearing loss and in 1/30 (3%) in ventriculomegaly e causa ignota. This latter patient received one cycle of bleomycin, cisplatin and etoposide at a gestational age of 26 weeks. Apart from significant manipulation of the uterus and the development of a pelvic hematoma that might be associated with fetal hypoxia, requiring blood transfusion, a direct

neurotoxic effect must be taken into account.[19] In another case[20], maternal sepsis following bleomycin, cisplatin and etoposide administration occurred, resulting in preterm labour. The premature neonate (1190g) developed respiratory distress syndrome, myelosuppression, hearing impairment and alopecia. Although cisplatin might have contributed to the sensorineural hearing loss, prematurity and the postnatal treatment with gentamycin are confounding factors. From these data, absence of congenital anomalies and normal neurological development was observed in 28/30 (94%). It should be noted that follow-up of the offspring was short.

Carboplatin has been administered during pregnancy in eight cases (of which 4 in association with paclitaxel) and a normal neonatal outcome was noted in each case.[7,21-26]

Considering the antitubuline agents, eleven case reports were found documenting the outcome after the use of taxanes during pregnancy (6 on paclitaxel and 5 on docetaxel). Here, no fetal problems were reported.[15,23-32] In 9/11 cases, taxanes were administered after other cytotoxic drugs (to patients with breast cancer) or in combination with other cytotoxic drugs (to patients with ovarian or lung cancer).

At least eight cases of germ cell tumors that were treated with a combination of bleomycin, cisplatin and etoposide during pregnancy have been described.[16-19,33-35] Although reports describe a normal neonatal outcome, one child with a significant ventriculomegaly with cerebral atrophy was born (see discussion above).[19] Based on this case of poor neonatal outcome, *Hubalek et al.*[22] decided to use paclitaxel and carboplatin for stage III dysgerminoma. Vinca alkaloids are already in use for a long time and many reports cite that their use is considered relatively safe in pregnancy.[7]

- *Influence of pregnancy on pharmacodynamics and pharmacokinetics of chemotherapy*

Physiologic changes during pregnancy may interfere with the pharmacodynamics and pharmacokinetics of chemotherapy. An increase of the glomerular filtration rate can increase the clearance of drugs that are excreted by the kidney. Also, the metabolisation of drugs in the liver is increased during pregnancy and can influence the plasma levels of active drugs. During pregnancy, the entero-hepatic circulation increases. Active metabolites excreted in the colon, are therefore absorbed again and this might add to prolonged exposure and increased concentration. The increase of the plasma volume is likely to reduce plasma levels of cytotoxic drugs, while increased protein binding will also lead to decreased availability of active drugs. Amniotic fluid can act as third space for some drugs. Despite these changes, prospective pharmacokinetic studies on chemotherapy dosing are lacking, but are urgently needed. The scarce information on this subject has led to the current concept of dosing which is not different for pregnant compared to non-pregnant women and is based on height and weight.

Since haematological toxicity can put the mother as well as the foetus at risk for infections and bleeding complications during delivery, an interval of three to four weeks between the last chemotherapy administration and delivery is aimed for. *As a rule, chemotherapy should not be administered after 35 weeks of pregnancy.*

Targeted treatment

For gynaecological cancers, trastuzumab is the only antibody that currently is used in standard treatment regimens for breast cancer. This molecule blocks the ERBB2 receptor, a member of the epidermal growth factor receptor family. From three case reports, it appears that trastuzumab provokes renal insufficiency with oligohydramnios.[36] A fourth report did not show any harmful effect. At the same time, *Sekar and Stone*[37] reported on reversible anhydramnion when trastuzumab was used in combination with docetaxel. Thus, in 4/5 cases where trastuzumab was administered during pregnancy, oligo-or anhydramnion was noted. Possibly, the presence of ERBB2 in the fetal renal-tubule epithelial cells (and not in adult kidneys) can explain a decreased renal function.[38] The altered fetal renal function and unknown long term impact in the offspring suggest to limit the use of trastuzumab during pregnancy.

Neonatal and long-term outcome after in utero exposure to chemotherapy

The available literature data are limited due to the heterogeneity, retrospective nature of studies, short follow-up period and limited evaluation of the children. Nevertheless, some important conclusions can be drawn.

Echocardiographic follow-up data were provided by *Meyer-Wittkopf et al.*[39] who performed fetal echocardiograms every 2 weeks in a pregnant patient recei-

ving doxorubicin and cyclophosphamide, starting at 24 weeks. The left and right ventricles of the foetus developed normally during gestation. There were no significant differences between exposed and unexposed foetuses in systolic function, assessed using fractional shortening. Postnatal echocardiograms, repeated until 2 years of age, showed no myocardial damage.[39]

We carefully studied the cardiac morphology and function of a series of children exposed to chemotherapy during intra-uterine life.[40] Echocardiographic quantification of cardiac function was performed using conventional as well as newer techniques. In all children, a normal cardiac performance could be observed. No morphological abnormalities could be demonstrated. Nevertheless, a trend towards a lower wall thickness and left ventricular mass was recorded.[40]We believe this could be due to chemotherapy, as this influences myocyte replication and growth. In contrast, *Avilés et al*[41] recently reported a normal cardiac function in 81 children who received anthracyclines during pregnancy.Whether the various measurements that were used, could account for the difference, is still subject of further study.
Previously (see above), this review described and discussed moderate bilateral hearing loss and ventriculomegaly that occurred after bleomycin, cisplatin and etoposide during pregnancy.[19,20] *Aviles and Neri*[42] described 84 cases of in utero exposure to chemotherapy for haematologic malignancies. The median follow-up period was 18 years (range 6 - 29 years) and the authors concluded that 84 children and 12 children from the second generation had a normal development. *Reynoso et al.*[9] described one twin pregnancy exposed to cyclophosphamide. One twin member was born with congenital malformations and developed thyroid cancer at the age of 11 and a neuroblastoma at the age of 14. The twin sister however, was healthy.

In the largest and most recent literature review on this topic, *Cardonic and Iacobucci*[7] described 376 cases of in utero exposure to chemotherapy. In this series 5% intra-uterine deaths, 1% neonatal deaths, 5% premature and 4% neonatal transient myelosuppression cases were registered. The authors encountered 11 cases of congenital malformation of which 9 were exposed to chemotherapy in the first trimester. More recent publications also described no particular problems when chemotherapy was administered *after* the first trimester.[43-44] *Hahn et al.*[45] described 57 patients that were treated for breast cancer during pregnancy. Telephone calls or mail were used to contact the parents/guardian or teacher.
Respiratory problems necessitating ventilation, were the most important neonatal complications (n=10). One child suffered from a subarachnoidal bleeding and three congenital anomalies were registered. In total, 40 children were followed until the age of 2 till 157 months. Of this group, 43% had no medical problems. Medical problems that were reported included allergy, eczema, asthma and upper respiratory interactions. Moreover, 2 of the 18 children who went to school, needed special attention.[45]

We reported on nine pregnant women (25-39 years) of whom one was having a twin pregnancy, and had been treated with chemotherapy for different malignant disorders.[40] Anti-neoplastic agents were administered between 15-35 weeks. Eight children were born before 37 weeks. Three babies had a birth weight below the 10th percentile. Children were 2-66 months of age when a neurological and cardiological examination was carried out. One child, born at 32 weeks, had a persistent asymmetric tonic neck reflex and delayed visual fixation at 10 weeks. One child, born at 28 weeks, had a minor delay in expressive language development at 21 months. A third child, member of a twin born at 33 weeks, had an autistic disorder, mental and mild motor retardation related to unilateral polymicrogyria. Although a cortical malformation in a twin member whose fraternal twin was normal remains enigmatic, morbidity after intrauterine exposure to cytotoxic drugs mainly appeared to be related to prematurity.[40]

The risk of neonatal cerebral haemorrhage and hyaline membrane disease decrease while the duration of pregnancy is advancing. Therefore, it is important to continue pregnancy as long as possible, preferentially until after 35 weeks. This strategy was shown to decrease prematurity.[44]

Thus, limited retrospective data are relatively reassuring and cannot show an increased risk of congenital malformations after intrauterine exposure to chemotherapy during the second and third trimester. However, long term follow-up is needed to provide more safety data on cognitive and cardiac function, fertility and the occurrence of secondary malignancies or germ cell mutations.

Radiotherapy during pregnancy

Although radiotherapy long has been considered to be non-compatible with pregnancy, a recent review supports its use during pregnancy, under strict conditions only.[46]

Radiotherapy should be planned and carefully executed, because leakage radiation and collimator scatter can damage the foetus. Fetal damage includes deterministic (cellular loss with impact on organ function) and stochastic (genomic damage that might lead to secondary cancers) effects and these depend on the pregnancy duration and fetal dose.

During implantation (first 10 days after conception), an all-or-nothing phenomenon occurs. Rarely malformations occur since either the foetus turn out to be normal (sufficient omnipotent cells that can restore cellular loss) or pregnancy ends in a miscarriage (insufficient omnipotent cells that are unable to cope with cellular loss).

Fetal malformations mainly occur during organogenesis (2-8 weeks after conception) and are reported when the fetal exposure exceeds 100-200 mGy.[46] During organogenesis and until 25 weeks after conception, the CNS remains susceptible to radiation. Mental retardation and decrease of intelligence quotient may point towards cognitive impairment. After 25 weeks, the CNS appears to be less sensitive to radiation.

Utilization of fetal irradiation without protection depends on the total dose and field size used as well as the distance between the foetus and the irradiation field.

Several cases have been reported where radiotherapy was applied during pregnancy for cancers of the upper body. Although the children born did not have major problems, the follow-up was only short and the outcome description limited. These mathematical considerations in combination with the clinical data show that radiotherapy can be used for breast cancer treatment during pregnancy. The fetal dose depends on target dose, proper shielding and the gestational age (or distance between target field and foetus) and the predicted effect should be calculated and discussed on an individual basis.

In contrast, cancers in the pelvis cannot be treated adequately with radiation during pregnancy without severe or lethal consequences for the foetus. Irradiation of the pelvis always results in loss of foetal life. Alternatives, such as administration of neoadjuvant chemotherapy, or postponed radiotherapy until delivery, can be discussed with the patient on an individual basis.

Prenatal irradiation with a fetal dose of 100mGy will increase the incidence for childhood cancer and leukaemia (stochastic effect) from a background risk of 2-3/1000 to 3-4/1000.

The sentinel lymph node procedure with upper score $^{99\,m}$Tc can safely be performed during pregnancy. Studies in breast cancer show that after injection of 18,5 MBq ^{99m}Tc the foetal dosage varies between approximately 0,0-0.05 mGy which is far below the deterministic threshold dosage.[47,48] This is mainly due to the low dosages that are administered and due to the fact that ^{99m}Tc is captured in the lymph nodes during a period in which radioactivity decreases considerably.The exposure after sentinel node procedure is of the same level as few day dosages of natural background irradiation.[47-49]

Diagnostic imaging of body parts at distance from the foetus can be executed safely since the fetal dose is lower than 1 mGy. Computer tomography of the pelvis exposes the foetus to 10-40 mGy.[50] Alternatives including sonography or magnetic resonance imaging should be aimed for. Should computer tomography be necessary, only the area of interest should be investigated with as limited number of sections as possible.

Breast cancer

The diagnosis of breast cancer during pregnancy is based on clinical examination, mammography, breast ultrasound and a core biopsy. A dose of 200-400 mGy is delivered by standard bilateral mammography, resulting in a fetal exposure of less than 0.5 µGy, being far below the threshold dose.[51] However, sensitivity of mammography is low due to increased density of the breast during pregnancy, and therefore ultrasonography is a more sensitive technique to find malignancies in the breast.[52] Magnetic resonance imaging probably also is regarded as a less sensitive technique due to an increased blood flow through the breast. There is a potential risk for the fetus due to heating, and the use of

gadolinium may increase this risk, because it passes the placenta and has been shown teratogenic in rats, and reluctance to use it is therefore appropriate. Adequate staging is important and should be planned as in the non-pregnant patient. Computer tomography can be replaced by sonography. Provided a bladder catheter is placed, bone scintigraphy during pregnancy is possible.Surgical treatment of breast cancer is similar as in the non-pregnant setting. Traditionally, mastectomy was the preferred surgical treatment because radiotherapy was considered to be contra-indicated. Nowadays radiotherapy for the breast during pregnancy is feasible.[46] For a breast cancer treatment course delivering 50 Gy to the tumor bed, a fetal exposure during the first trimester of 21-76 mGy using anthropomorphic phantoms was calculated.[53] The corresponding dose ranges to the foetus during the second and third trimesters of gestation were 22-246 mGy and 22-586 mGy, respectively.[53]

Proper shielding can reduce this fetal exposure with a factor 2 to 4, thus below the threshold dose.With fetal protection, the fetal dosage varies from 0.3 - 143 mGy depending on the duration of the pregnancy (until 36 weeks).[54] Especially after 28 weeks, a cephalic position is advisable. After 36 weeks of pregnancy, 3-4% of the target dose is received by the foetus and in this stage irradiation should be postponed until after delivery.[54] As most patients will need chemotherapy after surgery, radiotherapy is most frequently postponed until the postpartum.

Currently, breast sparing surgery with lymph node resection is more frequently used. Sentinel node resection using ^{99m}Tc is safe during pregnancy (see above) and can be used in selected cases.[47-49]

Adjuvant treatment depends on the pathological findings, including prognostic markers. Indications for subsequent treatment are identical as for non-pregnant patients. Given the young age and mostly large tumours, most frequently chemotherapy will be indicated. Cyclophosphamide and doxorubicin with or without 5-fluorouracil is the preferred combination treatment for breast cancer during pregnancy.[7] Although a large series including 85 women who became pregnant during tamoxifen intake, did not show an increased risk for fetal malformations[55], its use is not advocated based on later reported birth defects including Goldenhar syndrome[56] and ambiguous genitalia.[57]

Pre-invasive cervical cancer

Although the interpretation of the cytology in pregnant patients is more difficult, an experienced pathologist who is aware of the pregnant state is able to determine the cells adequately. Indications for colposcopy are the same as for non-pregnant patients and also the same morphological alterations in case of abnormality are present. However, the interpretation of the colposcopic findings is more difficult due to the increased cervical volume, stromal oedema, glandular hyperplasia and the increased vascularisation. A punch biopsy should be taken if a lesion appears to be invasive at colposcopy. *Ackerman et al.*[58] described in 70 cases the evolution of a cervical intraepithelial neoplasia III (CIN-III) lesion until the postpartal period. In 27% of the cases postpartally a normal biopsy was diagnosed, in 2.5% a CIN-I lesion, in 3.8% a CIN-II lesion and in 63% the diagnosis remained CIN-III. In only 2 patients (2.5%) a progression towards invasive cervical cancer was observed. According to 4 papers on this subject, biopsy proven CIN II-III lesions during pregnancy can progress to invasive cancer in 0-10% of the cases.[58-61] We estimate that probably less than 5% of all cases with a CIN-III lesion will progress to invasive cancer. Based on these data, CIN lesions during pregnancy can be treated conservatively and re-evaluated in the postpartum period. Nevertheless, control colposcopy every 2 to 3 months during pregnancy is advocated in order to timely diagnose possible invasive cancer. This diagnosis can influence the way of delivery, since recurrences - including fatal - in episiotomy scars have been described.[62] In case of doubt, an elected caesarean section is advisable.

Invasive cervical cancer

In case of doubt on the diagnosis of cervical cancer or as a treatment for stage Ia disease a conisation is indicated.[62] A flat cone is usually sufficient since the exocervix is better visible during pregnancy. This technique is also advocated to reduce complications related to the treatment.

Traditionally, when cervical cancer was diagnosed before 20 weeks, termination of pregnancy with immediate cervical cancer treatment used to be offered. When the diagnosis was made after 20 weeks of pregnancy, fetal maturation was attended to.[62] At that stage caesarean section followed by final treatment was proposed.

Addendum: call for patients

Prospective study on cancer during pregnancy

Although retrospective data are relatively reassuring, we currently need more solid data regarding farmacokinetics and maternal/neonatal outcome in order to be able to inform patients adequately about the risk of administering chemotherapy/radiotherapy during pregnancy.

This provides the rationale for the initiation of a *prospective study* with the intention of determining the distribution of cytotoxic drugs during pregnancy and/or evaluating the neonatal and long term outcome after oncological treatment. **This trial is currently open for inclusion.** All types of cancer can be included. Also older children that have grown up and previously were exposed, can be included. The oldest participant now is 16 years of age. More information is available on: www.cancerinpregnancy.org.

During this prospective research we welcome patients to be informed about the risks and propose to perform non-invasive neurologic and cardiologic investigations on their offspring. Our experience learns that parents feel endorsed when their children receive professional attention. The examinations are free of charge and are performed by pediatricians in Leuven. For further information, please contact: frederic.amant@uz.kuleuven.ac.be

However, preservation of pregnancy has gained interest and more published data on new treatment modalities have become available in the meantime.

The explicit wish to preserve the pregnancy, the potential to conservatively treat early cervical cancer and the preoperative prognostic tumor biology will determine the potential to preserve the pregnancy.

The limited experience with an invasive cervical cancer that is diagnosed during pregnancy renders every new treatment proposal as experimental. Since cancer is a life threatening condition, the potential risks associated with cancer treatment during pregnancy should be discussed with the patient concerned. A conservative approach will be considered only if a firm desire exists to continue the pregnancy, and if there is sufficient evidence that such an approach will not harm the mother.

The decision to preserve the uterus in case of cervical cancer is based on prognostic factors with respect to oncological and obstetrical outcomes. Safety guidelines for pregnancy-sparing treatments are very much the same as those established in the guidelines for fertility-sparing surgery. The obstetrical outcome is mainly determined by the residual cervical length and prognostic factors therefore include the stromal invasion and largest tumor diameter detected.[63]

Tumour biology determines the oncological outcome and hence the potential to maintain the pregnancy. Although tumour differentiation and lymph vessel invasion reflect tumour biology, the pelvic nodal status is the most important prognostic factor in early stage cervical cancer.[63] The documentation of a negative nodal status is necessary to accept a conservative approach. The presence of positive nodes would indicate high risk disease necessitating standard treatment for cervical cancer at the cost of pregnancy. It should be noted that the interpretation of lymph nodes during pregnancy requires pathological expertise.When pathologic examination on lymph nodes is performed for cervical cancer, the pathologist should be aware of the pregnant state, as decidual changes in the pelvic lymph nodes may mimic malignant disease.[64,65,66,67,68]

Conisation, cervical amputation (large cone) and radical trachelectomy have been described as fertility-conserving surgery and can also be applied when maintenance of pregnancy is aimed for. Conisation is the standard treatment for stage Ia1 cervical cancer in non-pregnant women who want to preserve

their fertility and can indeed be applied during pregnancy as well. The most frequent complications of a conisation during pregnancy are haemorrhage (5-10%), miscarriage (25%), preterm labour and delivery as well as infection. The risk of severe bleeding increases with the duration of pregnancy and has an insignificant incidence in the first trimester, 5% incidence in the second trimester and 10% incidence in the third trimester. Miscarriage has been observed in 7-50% of the cases. In 12% of the cases preterm delivery has been observed, especially in cases where conisation is done late in pregnancy.To minimize the risk of miscarriage and blood loss, the optimal time for cervical conisation is the second trimester, preferably between week 14 and 20 of gestation.[62]
For larger lesions, individualization is necessary and mainly two options have been described. Radical trachelectomy during pregnancy has been described by *Ungar and colleagues*[69], but the procedure is technically hazardous, and is associated with large volumes of blood loss and a considerable risk of pregnancy loss. Neoadjuvant chemotherapy during pregnancy has been described but remains experimental.[11,70,71] Literature data suggest chemosensitivity of cervical cancer varying from 78 to 95% when platin-based chemotherapy is used. This treatment can also be administered during pregnancy. Once fetal maturation has been reached, caesarean section followed by final treatment can be advised. A caesarean section is the preferred route of delivery to prevent (fatal) recurrences in the episiotomy scar.[13,62,72]

Vulvar cancers

HPV-related vulvar intra-epithelial neoplasia is mainly recognized in younger women and is the most frequent oncological vulvar pathology during pregnancy.The same treatment modalities as used in the non-pregnant patient, including laser vaporisation, laserskinning or surgical excision, are possible. Although the safe use of imiquimod during pregnancy has been described in a single case[73], the application of podophylline and imiquimod remains contraindicated.

Invasive (>1 mm) vulvar cancer during pregnancy is uncommon. *Bakour et al.* [74] summarize 27 cases and state that definitive surgical treatment is recommended before 36 weeks of pregnancy. From a technical point of view, we learned that increased vascularisation of the pelvis during pregnancy increases the peroperative blood loss and meticulous haemostasis should be aimed for. Adequate thrombosis prophylaxis should be provided given the procoagulative status in pregnancy and with cancer. Postoperative follow up is necessary since recurrence during pregnancy has been described.[75] With regard to the mode of delivery, caesarean section is only indicated for obstetrical indications.

Fatal vulvar melanoma also has been described. Despite the occurrence of placental metastasis, a healthy unaffected baby was born.[76]

Ovarian cancer

Similar to the non-pregnant state, during pregnancy a midline staging procedure after the first trimester is mandatory. Since early stage disease is most common (especially in germ cell tumors), frequently the procedure will consist of sampling cytology, adnexectomy, omentectomy and peritoneal biopsies. Uterine manipulations should be limited in order to prevent premature contractions. The exploration of the Douglas and pelvis frequently proves suboptimal, depending on the uterine volume. Pathology type and the prognostic factors should guide the decision on using additive chemotherapy during pregnancy.

When advanced stage epithelial ovarian cancer is diagnosed during pregnancy, the extent of the disease, the duration of the pregnancy at diagnosis and the surgical experience of the gynaecological oncologist will determine the treatment strategy. As such, primary debulking including termination of pregnancy[14], expectant management[14], surgery during pregnancy followed by postpartal chemotherapy[14], surgery (including cytoreductive surgery) followed by chemotherapy during pregnancy with final surgery during/after delivery[12,13,23-29,77] have been described. Final surgery is performed after vaginal delivery or at the same time as the execution of a caesarean section.

Conclusion

Although cancer complicating pregnancy seldomly occurs, data are available that suggest that the cancer can be treated successfully without harming the foetus. A multidisciplinary approach and extensive information of the parents is necessary. Termination of pregnancy will not improve the maternal outcome. However, in order not to jeopardize maternal

Key messages for clinical practice

1. Termination of pregnancy does not improve the prognosis.
2. The maternal prognosis is not impaired by the pregnancy, provided standard treatment is applied without a delay
3. Oncological treatment modalities including surgery, radiotherapy of the upper body part and chemotherapy are relatively safe when administered after the first trimester.
4. Since haematological toxicity can put the mother as well as the foetus at risk for infections and bleeding complications during delivery, an interval of three to four weeks between the last chemotherapy administration and delivery is aimed for. As a rule, chemotherapy should not be administered after 35 weeks of pregnancy.
5. The category of cytotoxic drugs with the highest potential of fetal damage are the folic acid antagonists with methotrexate as the most frequently used drug.
6. The antitumour antibiotics doxorubicin and epirubicin can be used in pregnancy without much hazards for fetal development. Fetal death has been reported after idarubicin exposure. Therefore, idarubicin is no longer used during pregnancy. The alkylating agents cyclophosphamide, cisplatin and carboplatin are also relatively safe to be administered. Vinca alkaloids are already in use for a long time and many reports cite that their use is considered relatively safe in pregnancy.
7. Pharmacological data of cytotoxic drugs during pregnancy are not available.
8. Provided prematurity is avoided, the neonatal outcome after cytotoxic treatment is reassuring and not associated with congenital abnormalities.
9. Further research is needed to delineate the long term outcome of the offspring.

chances, standard cancer treatment should be aimed for. Oncological treatment modalities including surgery, radiotherapy and chemotherapy can safely be performed after the first trimester. Continuation of pregnancy until full term is advocated in order to prevent neonatal problems induced by prematurity.

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