

Review

Common Malignancies During Pregnancy: A Comprehensive Review

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Abstract. Malignant disease complicates pregnancy in up to 1 per 1,000-2,000 cases. Pregnancy itself does not constitute a predisposing factor for malignancy. Management and treatment of patients suffering from a malignancy during pregnancy still represents a challenge in everyday clinical practice. Recent advances in imaging, diagnostic and overall treatment modalities have tailored the management of patients, specifically those who wish to maintain the pregnancy. The aim of this review was to provide clinicians with concise information on the management of the most common malignancies during pregnancy. We performed a review of the current literature including review articles, original research articles and guidelines, which are used for the management of the most common malignancies during pregnancy. Breast, cervical and ovarian malignant tumours are the most common during pregnancy. However, the overall outcome and survival per stage for these cancers do not appear to be influenced by pregnancy. Ethical, emotional and treatment dilemmas may be encountered during treatment planning. Individualization of treatment planning should be made by a multidisciplinary team but the final decision rests with the parents.

Malignant disease complicates up to 1 per 1,000-2,000 pregnancies and its incidence is increased in developed countries due to advanced maternal age (1-3). Malignancies of the breast, cervix, ovary, thyroid, melanoma, and haematologic origin are the most common during pregnancy and those less frequent but associated with a worse prognosis are lung and gastric cancers (4-6).

Pregnancy itself does not constitute a predisposing factor for malignancies (2, 7). However, cancer diagnosis may often be delayed because some symptoms may be attributed to the pregnancy itself (2, 3). Management and treatment are unique challenges for the obstetrician who has to confront ethical, emotional and treatment dilemmas (2). Therefore, treatment planning has to be individualized with a multidisciplinary team (MDT) including a gynaecological oncologist, clinical and medical oncologist, radiologist and perinatologist since treatment decisions involve both the mother and the foetus (1). Thus, the decision for pregnancy termination or iatrogenic premature delivery is often quite laborious and requires extensive and detailed evaluation of the case by the tumour board (4, 8). The multidisciplinary team will further provide the appropriate advice to the parent(s) regarding the urgency of treatment initiation, the oncologic prognosis and different treatment options (4, 8).

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History, Examination and Investigations

Due to physiologic changes and symptoms occurring in pregnancy, time between the diagnosis of the disease and the treatment may be delayed (4). Thus, persistent symptoms of fatigue, anaemia, post-coital bleeding, vaginal bleeding, or discharge and breast tenderness or lumps should be thoroughly evaluated by clinical examination (1, 2). At the beginning of each pregnancy a detailed medical history must be taken and a clinical examination must be performed in

order to identify any predisposing genetic (strong family history of breast or ovarian cancer, BRCA1/BRCA2 mutation carrier status) or other risk factors for malignancy (9). A detailed inquiry about new signs or symptoms should be routine prior to attributing these to normal pregnancy changes (9). If there are certain symptoms, a thorough clinical examination should involve not only the breast, genitalia and the uterus but also the whole body including peripheral lymph nodes and skin (9). However, the overall outcome and survival at different stages of the disease do not seem to be influenced during pregnancy (2).

To avoid unnecessary examinations, imaging and possible exposure of the foetus to radiation or other harmful diagnostic techniques, an initial approach has to be made by the MDT to optimize the plan in a way to offer the maximum desirable outcome for both the mother and the foetus (10) (Table I).

Imaging Modalities

Non-ionizing scanning examinations, such as ultrasound (US) and magnetic resonance imaging (MRI), should be the first choice as long as they are suitable for assisting the diagnostic process (11, 12). When imaging techniques that involve exposure to radiation are to be used and cannot be avoided, such as computerized tomography (CT), foetal shielding is mandatory so as to minimize the harmful exposure (10, 12). Moreover, the radiation dose should be as low as possible (10). The use of radiopaque or gadolinium contrast agents, even though they do not appear to be teratogenic in animal models, should be avoided since the visualization of solid components within a cystic mass can be demonstrated with the use of gray-scale and doppler ultrasonography (10, 12). MRI is the gold standard for the accurate evaluation of cervical cancer but again stromal invasion, parametrial, and vaginal extension can be demonstrated without the use of gadolinium (13).

The maximum dose of radiation during pregnancy is 0.5Gy (10, 12). The effects of radiation on the foetus (growth restriction, microcephaly, mental retardation, and foetal demise) are time- (stage of foetal development) and dose-dependent (10, 12). Pregnancy can be divided into 3 periods: pre-implantation (0-2 weeks after conception), organogenesis (2-8 weeks after conception) and foetal period (>8 weeks after conception) (8). The “all or nothing effect” will occur in the pre-implantation period, meaning that radiation exposure will either kill the embryo or not affect it at all (10). During the period of organogenesis, the most significant adverse effect is intrauterine growth restriction and a wide range of congenital structural deformities (10, 12). During the fetal period, the main risk of radiation exposure for the fetus is cognitive impairment and an increased risk for subsequent development of childhood

cancer and leukemia (8, 10). The foetus is usually exposed to much higher and most of the time lethal doses during radiation therapy (10). Application of pelvic radiotherapy during the first trimester will cause abortion and during the second trimester will lead to foetal death within a month (10, 12) (Table I).

Chemotherapeutic Agents

The most commonly used chemotherapeutic agents during pregnancy are vinca alkaloids, doxorubicin, and cisplatin (14, 15). Maternal gastrointestinal absorption of these drugs can be altered due to physiological changes in pregnancy (14, 15). Altered gastric secretion and motility, haemodynamic changes such as those resulting from increased plasma volume and increased renal clearance can all affect therapeutic concentrations of the active agent (14). When chemotherapy is administered during the first trimester the overall risk for foetal abortion, death, and malformations (toe, eyes, ears, palate) is approximately 6% using single agent chemotherapy and 17% with combination therapy (15, 16). After the first trimester the risk of congenital malformations is significantly diminished to a minimum but can still result in low birth weight and intrauterine growth restriction. In terms of long-term outcomes, the data is limited, but so far, the available studies do not show any significant impact on general health, cognitive development, and cardiac function as compared to the general population (15, 16). Therefore, concerns about long-term chemotherapy effects should not be a reason for withholding this treatment during pregnancy (Table I) (14, 16).

Surgery in Pregnancy

Surgery for gynecological malignancy during pregnancy has to be performed by a gynaecological oncologist in collaboration with an obstetrician and an anesthesiologist familiar with the management of pregnant patients (17). During surgery, the maternal haemodynamic condition should be optimized to avoid placenta hypoperfusion, hypoxia, hypotension, and hypoglycemia (17). Traditionally, because of difficulties in the manipulation of the uterus, laparotomy is usually chosen during the second trimester (17). After the 20th week of gestation positioning of the patient to the left lateral tilt position during surgery is preferred to alleviate the pressure upon the IVC from the gravid uterus (17). Nevertheless, there is an ever-extending variety of surgical techniques that can be employed safely using laparoscopy up to 28 weeks of gestation (17). Safety precautions for laparoscopy in pregnancy, apart from surgical expertise, include open trocar (Hasson's) entry, intra-abdominal pressure of less than 10-13 mmHg and a maximum operation time of 90 minutes (17). Pre and post-

Table I. Key points in the management of gynaecological malignancies during pregnancy.

At the beginning of each pregnancy a detailed medical history must be obtained and a thorough clinical examination must be completed. Non-ionizing scanning examinations, such as USS and MRI, should be the first choice during pregnancy. The maximum dose of radiation during pregnancy is 0.5Gy and the effects of radiation on the foetus (growth restriction, microcephaly, mental retardation, and foetal demise) are time (stage of foetal development) and dose dependent. When chemotherapy is administered in first trimester the overall risk for foetal abortion, death, and malformations (toe, eyes, ears, palate) range from 6% to 17% for single and combination therapy. When chemotherapy administered after the first trimester the risk of congenital malformations is minimum, but the risk of low birth weight and intrauterine growth restriction is significant.

Table II. Tips for clinical practice in Colposcopy during pregnancy (NHSCSP, document 20).

The incidence of abnormal cytology during pregnancy is similar to non-pregnant, with rates 5-8% and the methods to diagnose cervical cancer include colposcopy, cervical biopsy and in selected cases where invasion is suspected cervical conization. If a woman has been called for routine screening and she is pregnant, the test should be deferred. If a previous test was abnormal and in the interim the woman becomes pregnant, then the test should not be delayed but should be taken in mid-trimester unless there is a clinical contraindication. If a pregnant woman requires colposcopy or cytology after treatment (or follow up of untreated CIN 1), her assessment may be delayed until after delivery. Unless there is an obstetric contraindication, however, assessment should not be delayed if a first follow up cytology or colposcopy is required following treatment for cervical glandular intraepithelial neoplasia, or treatment for CIN 2/3 with involved or uncertain margin status. A woman who meets the criteria for colposcopy should be examined in the colposcopy clinic even if she is pregnant. The primary aim of colposcopy for pregnant women is to exclude invasive disease and to defer biopsy or treatment until the woman has delivered. Women seen in early pregnancy may require a further assessment in the late second trimester at the clinician's discretion. If colposcopy has been performed during pregnancy, postpartum assessment of women with an abnormal cytology or biopsy proven CIN is essential (100%). Excision biopsy in pregnancy cannot be considered therapeutic and these women should be seen for colposcopy post-partum. If CIN 2 or 3 is suspected, repeat colposcopy at the end of the second trimester or, if the pregnancy has already advanced beyond that point, three months following delivery. If invasive disease is suspected, clinically or colposcopically, a biopsy adequate to make the diagnosis is essential (100%). Cone, wedge and diathermy loop biopsies are all associated with a risk of haemorrhage and such biopsies should be taken where appropriate facilities to deal with haemorrhage are available. Punch biopsy suggesting only CIN cannot reliably exclude invasion and "Tailored" treatment must be made when invasive cervical cancer is diagnosed.

operative management of the patient needs to be prepared in detail by the responsible obstetrician, the gynaecologist and the anesthesiologist (1). Special care should be taken for adequate and appropriate analgesia and tocolysis (9).

Management of the Most Common Malignancies and Preinvasive Lesions

Cervical intraepithelial neoplasia (CIN) and cervical cancer. The incidence of abnormal cervical cancer screening tests and cancer precursors in pregnancy is similar to that for non-pregnant women, with rates from 5 to 8% (18). It seems that pregnancy itself does not affect cervical lesions and when CIN lesions do occur during pregnancy the best approach is continued observation since progression to invasion is extremely rare (0-0.4%) (18).

Because physiological changes in the gestational cervix (increased vascularity, hypertrophy, hyperplasia of endocervical glands) may mimic CIN changes, colposcopy

should be carried out by an experienced colposcopist (19). Treatment of CIN during pregnancy is contraindicated (19). Loop cervical biopsy in pregnancy is indicated only in cases of persistent severe dyskaryosis likely to be invasive, minimal stromal invasion detected on the cervical biopsy, colposcopic appearance or inconclusive findings in colposcopy and/or by biopsy (20). Extensive counseling regarding possible haemorrhage, miscarriage, and pre-term labour risk need to be addressed prior to conization in pregnancy (19, 20) (Table II).

The incidence of cervical cancer is estimated to be between 3.3 and 11.1 per 100,000 deliveries (11). Diagnosis may be delayed if the level of suspicion is low since early cervical cancer symptoms may mimic pregnancy related changes (18, 21, 22). Staging of cervical cancer is carried out using a combination of clinical and imaging techniques and examination under anaesthesia may be necessary for macroscopic tumours and also for diagnostic biopsy for initial staging of suspected microscopic tumours (18, 21, 22).

Adjuvant imaging with MRI without contrast (safety of gadolinium is uncertain since it crosses the placenta and is excreted by the foetal kidney into amniotic fluid) is safe and allows assessment of tumour size and parametrium involvement (13). Management is stage dependent:

Stage IA1: A conization may be diagnostic and therapeutic at the same time and the ideal recommended time is between 14-20 gestational weeks with a placement of cervical cerclage if necessary (8, 9, 11, 18, 21-23). Vaginal delivery should be attempted and caesarean delivery should be kept only for obstetrical indications (8, 9, 11, 18, 21, 23).

Stage IA2-IIA: Cone biopsy and laparoscopic pelvic lymphadenectomy can be offered for stage IA2 tumours in early pregnancy (8, 9, 11, 18, 21, 23). When termination of pregnancy has been decided immediate treatment with radical hysterectomy and lymphadenectomy with or without the presence of the foetus in utero is generally proposed (8, 9, 11, 18, 21-23). Nevertheless, in IB stage cervical carcinoma with a tumour size <2 cm, pelvic lymphadenectomy may be performed and if negative a wait and see policy can be chosen (especially late in the 2nd trimester) or treatment with a large cone or simple trachelectomy (8, 9, 11, 18, 21-23). Also, in these cases and higher stages (IB with tumour size >2 cm), where maintenance of pregnancy is desirable, neoadjuvant chemotherapy (cisplatin 75 mg/m² with paclitaxel 175 mg/m²) is an option until foetal maturity achieved and then followed by radical hysterectomy and lymphadenectomy at the time of caesarean section (8, 9, 11, 18, 21-24).

Stage IIB-IV: For these cases the recommended treatment is radiation with concomitant sensitizing chemotherapy (8, 9, 11, 18, 21, 23, 24).

Ovarian Cancer

Ovarian neoplasms can be detected in up to 2% of all pregnancies with ovarian cancer being a rare entity with an estimated incidence at 0.018 to 0.11 per 1000 pregnancies. Most of these cancers are detected at Stage I during routine ultrasonic screening (9, 25, 26).

The majority of the adnexal masses found in pregnancy are benign and most of them are functional cysts and 70% of them are resolved by the second trimester (25, 27). The use of Ca125 as a prognostic factor for cancer has limited value because it can vary throughout pregnancy whereas lactate dehydrogenase (LDH) remains unchanged during pregnancy and it is useful for the diagnosis of dysgerminomas (9, 25, 27). A surgical approach is indicated in the second trimester for a persistent cyst of greater than 6-8 cm mass, that rapidly increases in size and with complex characteristics such as the presence of solid components and bilaterality (9, 25-27).

Germ cell tumours are the most common ovarian neoplasms with ovarian mature teratoma (dermoid cyst)

being the most common histologic type (1, 2, 9). Dysgerminomas is the most common malignant type of germ cell tumours representing approximately 30% of all ovarian malignancies found during pregnancy followed by serous cystadenomas (1, 2, 9).

Borderline tumours: Atypical proliferative tumours, also known as borderline tumours, have a benign behavior when limited to the ovary and are diagnosed histologically, in the majority of cases, after an incidental finding at the time of caesarean section (27). When suspected in pregnancy, surgical treatment with peritoneal washings, unilateral salpingoophorectomy, omentectomy, and peritoneal biopsies are employed (27).

Early stage invasive epithelial ovarian cancer: If the patient wishes to preserve the pregnancy, the best approach is unilateral salpingoophorectomy with peritoneal washings, omentectomy, peritoneal biopsies including pelvic and para-aortic lymphadenectomy following frozen section detection (9, 25-27). Adjuvant chemotherapy treatment may be necessary (9, 25, 27).

Advanced stage invasive epithelial ovarian cancer: Typical treatment is not achievable when preservation of pregnancy is desired, so poor maternal outcome makes pregnancy termination a logical choice (9, 25, 27). However, if pregnancy is desired, the only approach is neoadjuvant chemotherapy until fetal maturity is achieved followed by interval debulking surgery after delivery (1, 8, 9, 14, 25-27).

Germ cell and sex-cord stromal tumours: These types of tumours are at Stage I when found in pregnancy (27). Therefore, the best treatment is unilateral salpingoophorectomy and surgical staging without lymphadenectomy (9). Adjuvant chemotherapy should be given if there are indications of the presence of tumour as in the case of non-pregnant women with paclitaxel-carboplatin or cisplatin-vinblastine-bleomycin being the most common regimens (8).

Breast Cancer

Breast cancer is the most common malignancy in women, affecting 5000 women of reproductive age in the United Kingdom annually (28, 29). Thus, young women with breast cancer often need fertility sparing and a pregnancy and lactation plan during consultation (6, 29, 30).

Breast cancer usually presents as a painful lump felt by these women (8, 28, 31). Thus, referral to a breast specialist team is mandatory (8, 28, 31). Breast cancer in pregnancy is usually found in a more advanced stage due to breast gestational changes (hypertrophy, engorgement, nipple discharge) (8, 28, 31). The "gold diagnostic choice" during pregnancy is breast ultrasonography by which differential diagnosis between solid vs. cystic mass and lymph node assessment can be made with high sensitivity and specificity (6, 29). If necessary, mammography can be employed with

Table III. *Tips for clinical practice for the management of breast cancer during pregnancy (RCOG Green-top Guideline No. 12).*

<p>Women presenting with a breast lump during pregnancy should be referred to a breast specialist team and any imaging or further tests should be conducted in cooperation with the multidisciplinary team.</p> <p>Bone scanning and pelvic X-ray computed tomography are not recommended because of the possible effect of irradiation on the fetus.</p> <p>The decision to continue the pregnancy should be based on careful discussion of the cancer prognosis, treatment and future fertility with the woman, her partner and the multidisciplinary team.</p> <p>Tamoxifen and trastuzumab are contraindicated in pregnancy and should not be used.</p> <p>The birth of the baby should be timed after discussion with the woman and the multidisciplinary team.</p> <p>Women should not breastfeed when taking trastuzumab (Herceptin®, Roche) or tamoxifen, as it is unknown whether these drugs are transmitted in breast milk.</p> <p>Women can be reassured that long-term survival after breast cancer is not adversely affected by pregnancy.</p>
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abdominal shielding and histologic diagnosis made with a core biopsy under local anaesthesia (8, 28, 31). To rule out metastases, chest X-ray, liver ultrasound, and skeletal MRI without contrast is suggested (8, 28, 31).

The decision for pregnancy preservation and methods of treatment must be made between the parents and the MDT. Surgical treatment including loco-regional clearance can be performed in all trimesters (2, 6, 8, 28-32). Those women who had a negative preoperative axillary US and needle biopsy are candidates for sentinel lymph node sampling with radioisotope scintigraphy but excluding blue dye since its effect upon the fetus is not well described (2, 6, 8, 28-32). The proposed chemotherapy regimens for adjuvant or neoadjuvant treatment in second or third trimester are fluorouracil-epirubicin/doxorubicin-cyclophosphamide and taxanes (paclitaxel every 1-3 weeks or docetaxel every 3 weeks) (2, 6, 8, 28-32). Tamoxifen and trastuzumab should not be used in pregnancy as it is not known whether these drugs are secreted in breast milk. Radiotherapy is not indicated until delivery (2, 6, 8, 28-32) (Table III).

Vulval Cancer

Vulval irritation, pruritis, and vulval mass are the most common signs of vulval cancer (1, 8). Once diagnosis is made, surgical techniques and indications for groin lymphadenectomy should follow the same guidelines as in non-pregnant patients (1, 8). To minimize surgical morbidity, groin dissection is usually left until after delivery, with sentinel lymph node being another option if necessary (1, 8).

Malignant Melanoma and Haematological Malignancies

Even though skin changes occur in pregnancy, any suspicious lesion should be fully evaluated (33, 34). Treatment for early-stage melanoma is surgical excision with lymphadenectomy performed only if it is absolutely

necessary (33, 34). Thorough histologic investigation of the placenta must be made because of the great potential for metastasis to the placenta (33, 34).

With an incidence of 1 per 6,000 pregnancies, Hodgkin lymphoma is the most common haematological malignancy in pregnancy followed by non-Hodgkin lymphoma and leukemia (1 per 75,000-100,000 pregnancies) (35, 36). Treatment of lymphoma is the same as for non-pregnant women and if chemotherapy is compulsory during the first trimester, termination of pregnancy is suggested (35, 36). Treatment of leukemia should be started immediately regardless of gestational age since maternal outcome worsens if treatment is delayed (35, 36).

Conclusion

Malignancies of the cervix and ovary are the most common of gynaecological origin. "Tailored" treatment should be employed when invasive cervical cancer is diagnosed, including stage, and factors such as pregnancy preservation, foetal viability and maturity taken into consideration. Epithelial tumours of the ovary are the most common type in pregnancy followed by germ cell tumours, with adjuvant chemotherapy treatment delayed for these tumours after the first trimester. Breast cancer usually presents as a painful lump felt by women and treatment includes loco-regional clearance which can be carried out in all trimesters. Hodgkin lymphoma is the most common haematologic malignancy in pregnancy followed by non-Hodgkin lymphoma and leukemia. Ethical, emotional and treatment dilemmas may impact on the treatment plan. Individualization of treatment planning should be made by a multidisciplinary team but the final decision rests with the parent(s).

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

EK: main author; NV: co-author, reviewed the manuscript; TK: reviewed the manuscript; MG: co-author, reviewed the manuscript.

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