Difficulties with diagnosis of malignancies in pregnancy

J. de Haan (MD)[a,b], V. Vandecaveye (MD, PhD)[c], S.N. Han (MD, PhD)[d], K.K. Van de Vijver (MD, PhD)[e], F. Amant (MD, PhD)[a,d,f].

[a] Division of Oncology, KU Leuven, Leuven, Belgium.

[b] Department of Obstetrics and Gynaecology, VU University Medical Centre, Amsterdam, The Netherlands.

[c] Department of Radiology, University Hospitals Leuven, Leuven, Belgium.

[d] Division of Gynaecologic Oncology, University Hospitals Leuven, Leuven, Belgium.

[e] Divisions of Diagnostic Oncology and Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

[f] Department of Gynaecologic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

Corresponding author:

F. Amant, MD, PhD

University Hospitals Leuven

Gynaecologic Oncology

Herestraat 49

B-3000 Leuven

Belgium

Email: Frederic.amant@uzleuven.be

Abstract

Diagnosis and staging of cancer during pregnancy may be difficult due to overlap in physical signs, uncertainties on safety and accuracy of diagnostic tests and histopathology in pregnant women. Tumour markers should be used with caution due to pregnancy-induced elevation. Ionizing imaging and staging techniques like CT- or PET-scans and sentinel node procedures are safe during pregnancy when fetal radiation threshold of 100 mGy is maintained. Ionizing imaging techniques can increasingly be avoided with the technical evolvement of non-ionizing techniques like MRI, including whole body MRI and diffusion-weighted imaging which hold potentially great opportunities for the diagnostic management of pregnant cancer patients. Pathological evaluation and establishing a diagnosis of malignancy can be difficult in pregnant women and a note to the pathologist of the pregnant status is essential for accurate diagnosis. This chapter will give an overview of possibilities and difficulties in diagnosing pregnant women with cancer.

Keywords: Neoplasms; pregnancy; diagnostic tests; diagnostic imaging; pathology.

Introduction

For patients with symptoms that might be caused by a malignancy; quick and proper diagnosis is of utmost importance. Some tumours, especially in the case of a visible or palpable mass, are more easily to when compared to more internally localised cancers. The physiologic gestational changes may contribute to this masking of cancer symptoms. Since cancer during pregnancy is relatively rare with an estimated incidence of 1 in 1000 pregnancies, it might not high on the list of different potential diagnoses.[1] It has been reported that due to pregnancy delay in diagnosis occurs, leading to higher stage of disease at diagnosis.[1] Pregnant women with cancer enface an even more complex problem since standard interventions in diagnosing, staging and treatment of cancer may be harmful for the unborn child. But as these interventions are standard patient management, alternatives should be applied with caution in order to accurately assess the maternal condition.[1] In this review we will focus on the difficulties of diagnosing and staging pregnant women with cancer.

Clinical presentation

Symptoms of normal pregnancy can be vague and diverse and most of these complaints are self-limiting. Primary caretakers who are confronted with pregnant women easily consider them as pregnancy-related. A malignancy may not be the most obvious cause but it has the greatest impact on the mother and unborn child. Table 1 shows the most common overlapping symptoms. This big overlap makes it more understandable that both patient's delay and doctor's delay may occur.[2–4] Andersson et al.[5] found fewer new cancer diagnoses during pregnancy then expected based on population-based numbers with a ratio of 0.46 (95% CI 0.43-0.49). A subsequent rebound effect postpartum for melanoma, nervous system malignancies, breast cancer and thyroid cancer was also observed, which might be

caused by the delay in diagnosis or by altered tumour biology during pregnancy and lactation.[5]

Laboratory testing

Specific tumour markers can be measured at diagnosis, treatment evaluation or the detection of recurrence during follow-up. These markers are not only produced by tumour cells, but also as a response to (para)neoplastic conditions (e.g. inflammation). Sensitivity and specificity is therefore low and increased levels of tumour markers are also associated with other benign situations like pregnancy.[6] In pregnancies complicated by obstetrical problems, the variation of these markers is even greater.[7] The use of tumour markers during pregnancy or in pregnancy following a previous cancer is therefore limited. Carbohydrate antigen 15-3 (CA 15-3) is used in breast cancer patients and is significantly increased during pregnancy, especially in the third trimester, with 3.3% to 20.0% above cut-off levels.[6] Squamous cell carcinoma antigen (SCC) is used in the management of squamous cell carcinomas (e.g. cervix, head and neck, oesophagus and lung). While mean concentrations stayed below cut-off value 3.1 to 10.5% raised above this value, especially in the third trimester.[6,8] Cancer antigen 125 (CA 125) is used in monitoring non-mucinous epithelial ovarian cancer and is also elevated during pregnancy, with the highest concentration reported of 550 U/ml in the first trimester.[6,8] Alpha-fetoprotein (AFP) is a marker for hepatocellular carcinoma and is largely increased during pregnancy by fetal production. In the presence of pregnancy complications like preeclampsia, this is even higher, up to 13 times above tumour cut-off point and is therefor not reliable as a tumour marker during pregnancy.[8] Levels of Inhibin B and Anti-Müllarian hormone (AMH), Human epididymis protein 4 (HE4), lactate dehydrogenase (LDH), carbohydrate antigen 19-9 (CA 19-9) and carcino-embryonic antigen (CEA) were not elevated by pregnancy and can be used like in the non-pregnant population.[6,8,9]

Imaging in diagnosis and staging

Diagnostic examinations and staging should preferably be performed as in non-pregnant women, although a potential conflict between maternal benefit and fetal risk should be balanced. Ionizing imaging techniques should not be withheld if beneficial for the further oncologic management and treatment of the pregnant patient but should, as in the general population, always follow the rule that radiation doses should be kept as low as reasonably achievable (ALARA). Generally the following issues need to be taken into account when choosing appropriate imaging techniques in the pregnant population: (1) safety of the imaging technique towards the fetus, (2) risk of metastatic disease, and (3) the aim to achieve similar accuracy for diagnosis and staging as in the non-pregnant patient. Physiological alterations secondary to the pregnancy may influence image quality and lesion detectability. If non-ionizing imaging alternatives with equal accuracy as standard imaging tools are available, they should preferably be used over ionizing techniques. When using ionizing imaging techniques, the cumulative fetal radiation exposure should be monitored in detail with a preferred maximum of 100 mGy to prevent adverse fetal outcome due to radiation. At this threshold the increased change of malformation and childhood cancer is approximately 1% higher compared to the non-exposed pregnant population.[10] Higher exposure doses can cause adverse effects including congenital malformation, growth retardation, fetal death and neurologic detriment. The effect of radiation to the fetus however depends on multiple variables including the gestational age (GA) and fetal cellular repair mechanisms. Importantly, when the diagnosis of cancer has been confirmed, it is advised to have a multidisciplinary tumour board meeting to discuss further diagnostic imaging management and potential radiotherapy in order to avoid suboptimal imaging strategies and accumulation of fetal radiation exposure above the preferred 100 mGy threshold further along in pregnancy.[11,12]

Ionizing imaging techniques

Rontgen radiation (X-radiation)

Non-abdominal x-rays, including mammography, with proper abdominal shielding carry a

negligible fetal radiation exposure of less than 0,1 mGy (see Table 2). Abdominal x-rays have

a higher fetal exposure but have no clear indication for cancer diagnosis or staging and

should not be considered relevant to the discussion in pregnant patients.[11]

An issue of particular importance concerns mammography. In pregnant women with breast

cancer, mammography is more challenging since physiological hypervascularisation and

increased breast density make it more difficult to interpret.[13,14] Mammography for a

suspicious mass in pregnancy must be accompanied by ultrasound evaluation, both to

combine the optimal detection of lesions in the dense breast tissue and microcalcifications.

The sensitivity of mammography during pregnancy is 78-90% in women with clinical

abnormalities and evaluation of both breasts is recommended.[13,14]

Computed tomography (CT)

With the exception of a CT-scan of the pelvis, all ionizing diagnostic techniques stay far

below the 100 mGy threshold and should therefore be considered safe during pregnancy,

particularly when MRI is not able to answer the clinical question or is contra-indicated (e.g.

pacemaker, claustrophobia). However, care should be taken to minimize fetal radiation

exposure where possible.[11] No clear consensus currently exists concerning the use of

iodinated contrast-agents during pregnancy due to insufficient literature on possible risk for

the fetus. However, in clinical practice the American College of Radiology (ACR) Manual on

Contrast Media recommends the use of intravenous iodinated contrast-agent only in

pregnant patients when necessary.[12,15] The largely increased use of CT in pregnant

patients due to its value as a rapid diagnostic tool in acute or critical disease may avoid delay

and therefor improve maternal and fetal morbidity and mortality. [16,17] However, as pregnant patients undergo treatment, response assessment by additional (contrast-enhanced) CT-scans and may lead to inacceptable cumulative radiation and contrast doses. Reducing radiation dose can be done by decreasing voltage and current, increasing the pitch, widening the beam collimation and limiting the scanned areas.[12] Moreover, the application of iterative reconstruction enables the application of ultralow dose CT.[18] Current studies on contrast-enhanced CT only investigated fetal exposure towards a single contrast-dose.[19] In characterization and local staging of pelvic tumours, nodal staging and detection of liver and peritoneal metastases the accuracy of (contrast-enhanced) CT is lower compared to MRI respectively PET and is therefore not the first choice in pregnant patients with oncologic disease.[20,21] On the contrary, a CT-chest should be strongly considered when lung metastases are suspected since it only exposes limited radiation to the fetus, requires no iodinated contrast and has highest sensitivity to assess small lung metastases accurately.[22]

Stand-alone nuclear medicine imaging

Over the last years the use of positron emission tomography (PET) imaging in the management of cancer patients for accurate diagnosis, staging and evaluation has grown.[23] In pregnant patients with cancer, the use of PET imaging has been debated since it uses radioactive labelled tracers and therefore cause fetal exposure to radiation. For PET imaging in most cancer patients, 2-deoxy-2-[fluorine-18]fluoro- D-glucose (^{18}F-FDG) is the used radiotracer, due to its high sensitivity and specificity.[16]

Physiological pregnancy changes during different periods of pregnancy can alter the effective dose of different radiotracers, which should be taken into account when dose calculation is made to avoid potential harmful effects for both mother and fetus. For

radiotracers like ^{11}C, [11]C-4DST, ^{18}F-FBPA and ^{68}Ga-EDTA, the effective dose can get up to 55% lower in the ninth month of pregnancy compared to early pregnancy.[23]

The amount of fetal radiation exposure depends on the weight of the fetus, the type of radiotracer and the administered dose.[23] See Table 3 for an overview of the different studies that have addressed the fetal radiation exposure of ^{18}F-FDG in pregnancy. A non-equal distribution of the absorbed dose in the fetal body is observed for all radiotracers, with the brain receiving the highest dose.[23] Therefore a lower IQ or mental retardation after birth is theoretically possible.[24] It is important to calculate maternal and fetal risks from a PET-scan and if necessary, alter administered tracer dose. Literature on the effect of different radiotracers on the fetal brain development has not yet been published. Even though the absorbed dose from a single PET-scan does not seem to exceed the 100 mGy threshold, the administration of nuclear labelled tracers should only be done if maternal outcome can be improved.[25] The use of bone scintigraphy in evaluation of bone metastases is possible during pregnancy when MRI is inconclusive, although literature on this subject is scars.[26,27] For both PET-scan and bone scintigraphy, where tracers are administered intravenously, it is advised to reduce fetal radiation exposure by placing a bladder catheter and simultaneous provide intravenous hydration to avoid accumulation of tracer.[27]

Hybrid nuclear medicine imaging

Nowadays, the use of hybrid imaging (PET/CT and PET/MRI) possesses great potential for cancer patients since morphological, functional and molecular information is gathered in one exam. PET/CT is already a widespread used method, but extracting it to the pregnant population holds potential risks for the fetus due to the ionizing properties of both techniques. The use of PET/MRI would therefore be a good alternative since the ionizing

radiation dose is much lower especially when the abdomen and uterus is positioned in the radiation field.[20,23]

Non-ionizing imaging techniques

Ultrasound

The main advantages of ultrasound include its widespread availability, non-invasiveness, and ability to immediately guided biopsy or fine needle aspiration cytology (FNA). Therefore, ultrasound is the preferred technique for initial evaluation when an abdominopelvic mass or a lump in the breast, head and neck region or subcutaneous soft tissues is found. For characterization of suspected masses in the breast, ultrasound shows high sensitivity (77-100%) and specificity (86-97%).[14,28] In adnexal masses grey-scale and Doppler ultrasound have a high sensitivity and specificity, especially when applying the 'IOTA simple rules'.[29] It is also the primary modality for nodal staging in thyroid cancer and breast cancer and has complementary value in head and neck cancer and melanoma. Accuracy for nodal staging has been reported to be up to 89% in papillary thyroid cancer and in breast cancer it has a sensitivity up to 79.5% and specificity up to 98.1%. Adding FNAC increases sensitivity to 87.2%.[30]. In head and neck cancer, ultrasound, combined with FNAC, can reach specificity of 100% and sensitivity to 73%.[31] A major disadvantage of ultrasound is the difficulty to assess deeper abdominal structures related to superimposing bowel gasses or obesity. This is aggravated by the pregnant uterus and reduces the value of ultrasound for comprehensive cancer staging. This is reflected by only moderate sensitivity of 63% for detecting liver metastases and low sensitivity of ultrasound for detecting abdominal lymphadenopathies, as described for lymphomas.[32] Therefore, ultrasound often requires additional and more conclusive imaging tests.

Magnetic Resonance Imaging (MRI)

As a non-ionizing technique, MRI has the advantage over ultrasound in allowing more comprehensive evaluation of entire organ systems and, more recently, even whole body (WB) evaluation. Additionally, the technique allows evaluation of functional tissue properties through the use of diffusion-weighted imaging (DWI) for lesion characterization and detection as well as treatment follow-up.[33,34]

The safety profile of MRI towards the fetus has been subject to debate and relates mainly to assumed invalidated risks concerning potential heating effects from radiofrequency pulses, biological damage from the static magnetic field and acoustic noise that may relate to risk of fetal growth restriction, premature birth and respectively hearing impairment. As such, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) has recommended that elective MRI should be postponed beyond the first trimester.[12,35] However, a recent retrospective case-control study in 751 neonates failed to show any cases of impaired hearing or low birth weight percentiles secondary to MRI exposure.[35] Also, there are to date no studies that have indicated that any pulse sequences cause significant increases in temperature.[21,36] It is important to note that currently available MRI-systems operate within well-defined safety margins inhibiting scanners to expose subjects beyond the FDA safety limits of 4 W/kg specific absorption rate (SAR) while routinely implemented technical developments such as multichannel phased-array and parallel transmission further decrease SAR.[10,12,36] Data in a phantom fetus showed no sequences exceeding the FDA SAR-threshold at 1.5 and 3 Tesla.[36]. The 2007 ACR guidelines indicate that MRI can be used in pregnant patients, regardless of gestational age when the benefit outweighs potential risks to the fetus.[37]

Concerning the use of gadolinium, the ACR paper on safe MRI practices advises for extreme caution in use and only if the maternal benefit overwhelmingly outweighs the theoretical fetal risks.[15] Although no fetal toxic effects have been reported, gadolinium does cross the placenta and after excretion by the fetal kidney in the amniotic fluid, it is unknown how long

it remains here. Although no fetal toxic effects have been reported, the gadolinium ion can dissociate from its chelate molecule and is proven teratogenic in animal studies.[12,38] The use of DWI can potentially obviate the need for gadolinium contrast in imaging. Also, DWI has potential value for pre-operative planning and may reduce invasive staging in pregnant patients with suspected peritoneal metastases due to the close correlation between DWI and surgical based staging of peritoneal disease spread.[39] Recent studies have demonstrated a good diagnostic performance of WB-MRI with DWI for detecting both hepatic as peritoneal metastases in digestive and ovarian cancer compared to contrast-enhanced MRI, contrast-enhanced CT or FDG-PET/CT, irrespective of lesion size. It also appears to have a higher accuracy than bone scintigraphy for detecting skeletal metastases. [33,39–42] Also, DWI increases the sensitivity for detecting nodal metastases in gynaecological malignancies, lung, head and neck cancer and lymphoma compared to conventional MRI and comparative studies have shown that DWI can be a reasonable non-ionizing alternative to PET/CT for nodal staging in lymphoma and lung cancer.[43–47] Even though these results are promising, MRI for locoregional staging should be carefully balanced to its potential added clinical value. For breast cancer in pregnancy, no sensitivity or specificity for MRI have been reported but the value of MRI for screening women with dense breasts remains controversial due to paucity of data and possible overdiagnosis.[48] For adnexal masses, MRI is only advised in cases were ultrasound is inconclusive, with masses too big to fully assess by ultrasound or when there is a high probability of malignancy requiring assessment of peritoneal disease spread.[49] In patients with other pelvic cancers, including rectal and uterine cervical cancer, locoregional MRI is pivotal for staging and treatment planning and should be performed as for the non-pregnant population, without the need for gadolinium.[50,51].

The most important diagnostic difficulties, besides earlier mentioned safety issues, include artefacts in abdominal MRI that may aggravate during pregnancy, physiological alterations

that may impair lesion detection and level of standardization of sequences and imaging interpretation. The most challenging image artefact, which is more pronounced at 3 Tesla compared to 1.5 Tesla, is the inhomogeneity of the magnetic caused by amniotic fluid, particularly in echo-planar (DWI) and spin-echo (standard anatomical T2 sequences). This results in areas of black-out or complete loss of signal and harbours the risk that lesions may be missed.[36] The most optimal solution to avoid this artefact is the use of multichannel transmission coupled with parallel imaging (Figure 1).[52,53] However, this technology is not widely available on all MRI-systems. Alternatively, dielectric pads filled with saline solution placed on the anterior abdominal wall should allow sufficiently reducing this artefact.[54] One should take into account that despite the high lesion conspicuity of DWI, the sequence has relatively poor anatomical properties. This is easily overcome by combining DWI with anatomical T2- and T1-weighted sequences to optimize diagnostic capability. In general clinical practice, DWI is never used as a standalone sequence. Combining DWI with anatomical sequences also allows overcoming pitfalls related to physiological movement. The assessment of small mediastinal and hilar lymphadenopathies and small lung metastases can be impaired at DWI secondary to cardiac pulsations, or by interference with intrapulmonary air.[55] However, the impact on false negative rate in mediastinal nodal staging appears limited, in part due to the addition of dedicated anatomical sequences such as conventional high resolution 3-D anatomical sequences that aid in the detection of small lung metastases.[56] A non-contrast CT of the chest can be added in case of doubt or when the radiologist feels that lung metastases cannot be definitely excluded. While (WB-)DWI has high accuracy for detecting skeletal metastases, increased red bone marrow activation, typically seen in young (pregnant) women, can lead to falsely increased signal at DWI and either lead to the false assumption of metastatic skeletal spread or hide underlying focal skeletal metastases by showing equal signal intensity (Figure 2). Similar as for the T2-shine through effect in liver and skeletal haemangiomas that may cause falsely increased signal in

these benign entities, careful correlation with anatomical sequences overcome misinterpretation in the vast majority of cases.[55] Last, as DWI and WB-DWI are relatively new techniques in oncological imaging, further and rapid standardization of imaging sequence protocols and interpretation criteria and continuing radiologist training is warranted, especially in the management of pregnant patients. Contrary to focal DWI- and MRI-examinations of, for instance, liver or spine, WB-DWI is not yet widespread utilized or available and its use should be carefully balanced towards local radiological expertise. Nevertheless, continuing technical developments, diagnostic performance studies and efforts towards standardization should enable the use of WB-DWI in pregnant patients holding a big future opportunity for adequate staging without potential radiation risks for the fetus.[55]

Pathology

The pathologist should always be informed of the patient's gravid status in order to avoid incorrect diagnosis due to pregnancy-associated tissue changes.[28] Apart from changes in the uterine corpus and the ovaries, pregnancy has various effects on benign conditions that may mimic malignancy.

Mammary glands enlarge rapidly, vascularity increases and the fibro-adipous tissue diminishes. Secretory changes and hyperplasia of the luminal epithelium, with distension of the lobular units and accumulation of secretion occurs frequently. On fine needle aspiration (FNA) these features result in cellular smears with small glandular clusters or abundant dyscohesive cells with abundant vacuolated cytoplasm, hyperchromatic nuclei containing irregular nucleoli (Figure 3).[57,58] As pathologists should be aware of these potential pitfalls leading to a false-positive diagnosis of breast cancer, FNA stays useful in evaluating breast masses to minimize delays in the diagnosis of carcinoma associated with pregnancy.[57] Inflammation and infarction of mammary tissue presenting as a firm nodular

tumour may occur, mostly in the late third trimester.[59] Their cause is uncertain, but might be associated with physiologic pregnancy-related vascular changes. Rarely, breast abscesses may mask lymphomas or other hematologic diseases.[60,61] The predominant type of pregnancy-associated breast cancer is invasive ductal carcinoma and is as in the non-pregnant population of young women more often poorly differentiated, estrogen and progesterone receptor negative and HER-2/*neu* positive.[28,62]

The incidence of cervical cancer and precancerous lesions is the highest in younger women and also in pregnant women cervical intraepithelial neoplasia (CIN) can routinely be detected by PAP smear.[63] Specific physiological changes can occur in the cervix. Pseudodecidual reaction of the stromal cells is usually not mistaken for malignancy, but it may resemble a (glycogen-rich) squamous cell carcinoma. Arias-Stella reaction of the endocervical glands may present as enlarged irregular cells with hyperchromatic nuclei, mimicking cervical adenocarcinoma in situ or even clear cell carcinoma (Figure 4).[64] The latter conditions usually show high mitotic activity, which is absent in Arias-Stella reaction.

Increased mortality for pregnancy-associated melanoma has been described.[65] Classic nevi and dysplastic nevi often become more atypical and show more melanocytic proliferation during pregnancy, mimicking a malignant melanoma (Figure 5). Of note, although nevi and melanoma cells do not harbour hormone receptors, they seem to be estrogen-responsive.[66,67]

The pregnancy tumour of the gums or gingival pyogenic granuloma is a benign tumour-like proliferation of endothelial cells, probably to a non-specific infection.[68] Caution should be exercised as atypia due to ulceration and reactive changes may be more pronounced, but on the other hand, several cases of metastatic choriocarcinoma to the oral cavity have been described.

Surgical staging

As stated before, staging procedures are performed as in non-pregnant patients as far as possible and should only be conducted to alter and determine therapeutic procedures that improve maternal outcome and remain safe for the fetus.

Sentinel node procedure

A sentinel node procedure (SNP) to asses lymph node involvement is performed in patients with breast cancer, melanoma, vulvar cancer and Merkel cell carcinoma. Performing a SNP during pregnancy has been debated due to the possible radiation exposure from the radionuclide, which is used in this procedure. For breast cancer and melanoma, small cases have described SNP in pregnancy and reported no adverse events.[69,70] It has been calculated that when using a nanocolloid with a short half-life and large particle size, like 99-Techneticum, and due to accumulation of the nanocolloid in the lymph node itself the fetal radiation exposure is less than 5 mGy, even in the inguinal lymph nodes.[11,70,71] It is also recommended in pregnancy to use the single day protocol since the administered dose is lower, time between admission and surgery is shorter and detection rate does not differ from the two day protocol.[69,72] Fetal radiation exposure is far below the threshold so when maternal outcome may be by a SNP, it should not be withheld because of fear for fetal radiation exposure. Using blue dye is not recommended in pregnancy as anaphylactic reactions have been described.[28]

Lymphadenectomy

Lymphadenectomy during pregnancy should be performed identically as in the non-pregnant population, except for the pelvic area. Performing a pelvic lymphadenectomy in pregnancy is possible and safe between 13 and 22 weeks of gestation. The procedure can be done by either laparoscopy of laparotomy, based on the preferences and skills of the surgeon. Due to the complex procedure it is highly recommended to have this only

performed by surgeons with experience in this procedure. However, increasing gestational age creates a problem towards the ability to retain the diagnostic minimum of ten lymph nodes following guidelines. Therefore, pelvic lymphadenectomy does not always allow reliable clinical decision making and additional information of clinical examination and imaging should be considered.[73] In pregnant patients with cervical cancer, staging by pelvic lymphadenectomy is advised to identify high-risk disease so a termination of pregnancy can be considered and standard treatment can be continued.[73] In patients with negative pelvic lymph nodes it has been suggested that delay of therapy until after delivery is feasible without worsening maternal outcome. Maternal survival of 95% with a mean follow-up of 37,5 months in 76 pregnant patients with stage IBI cervical cancer was observed. Median delay was 16 weeks and no recurrent disease was reported.[73] Also in ovarian cancer during pregnancy it may be not possible to complete the standard surgical staging procedure since the pelvic peritoneum and pouch of Douglas cannot be reached properly. When staging is not completed during the first surgery, surgical restaging after delivery can be considered.[73]

Summary

Delay in diagnosis is a problem in the pregnant population with cancer due to overlap between symptoms and physiological pregnancy changes. Symptomatic masses and persisting symptoms should be evaluated according to protocol similar to the non-pregnant population. Where possible, non-ionizing imaging techniques should be used. With increasing standardization, WB-MRI and DWI are potentially powerful imaging techniques for pregnant women. If necessary, ionizing imaging can be performed after calculation of fetal radiation exposure, which should in total not exceed 100 mGy. Interpretation of imaging and pathology can be more difficult in pregnant patients. Nuclear medicine and surgery for staging is possible without risk for the fetus, except for lymphadenectomy in the

pelvis, which can only be done safely between 13 and 22 weeks of pregnancy. A

multidisciplinary approach is essential in management for this specific group of pregnant

women.

Acknowledgements

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Table 1. Overview of common overlapping symptoms of pregnancy and malignant disease.[2–4]

Symptoms
Nausea & vomiting
Appetite changes
Constipation/haemorrhoids
Abdominal discomfort/pain
Anaemia
Increased volume & consistency of breast tissue/palpable mass in the breast
Hyperpigmentation/changed nevi
Fatigue

Table 2. Fetal radiation exposure for X-ray and CT-scan per body region.[11,23,38]

Body region	mGy	Body region	mGy
X – chest	0.0001 – 0.43	CT – head	<0.005
X – mammography	<0.1	CT – chest	0.02 – 0.2
X – abdomen	1.4 – 4.2	CT – pulmonary embolism	0.2 – 0.7
X – pelvis	0.16 – 22	CT – abdomen (routine)	4 – 60
		CT – pelvis	6,7 – 114

mGy: milligrays, X: Rontgen radiation, CT: computed tomography

Table 3. Studies on fetal radiation exposure for ^{18}F-FDG during different periods of gestation.

Study	Year	Gestational age			
		1st trimester	Early 2nd trimester	Late 2nd trimester/ early 3rd trimester	Late 3rd trimester
Russell et al.[74]	1997	2.7×10^{-2}	1.7×10^{-2}	9.4×10^{-3}	8.1×10^{-3}
Stabin[25]	2004	2.2×10^{-2}	2.2×10^{-2}	1.7×10^{-2}	1.7×10^{-2}
Zanotti-Fregonara et al.[75]	2009	3.65×10^{-2} (8-wk)	-	-	-
Zanotti-Fregonara et al.[76]	2010	4.0×10^{-2} (10 wk)	-	-	-
Takalkar et al.[77]	2011	1.55×10^{-2} (6 wk)	7.16×10^{-3} (18 wk)	6.16×10^{-3} (23-25 wk) $8,2 \times 10^{-3}$ (28-30 wk)	-
Xie and Zaidi[23]	2014	3.05×10^{-2}	2.27×10^{-2}	1.5×10^{-2}	1.33×10^{-2}

All values are in milligrays/megabecquerels (mGy/MBq).

Figures

Figure 1. T2-weighted pelvic MRI sequence in non-pregant patient before (A) and after (B) the application of multichannel transmission.
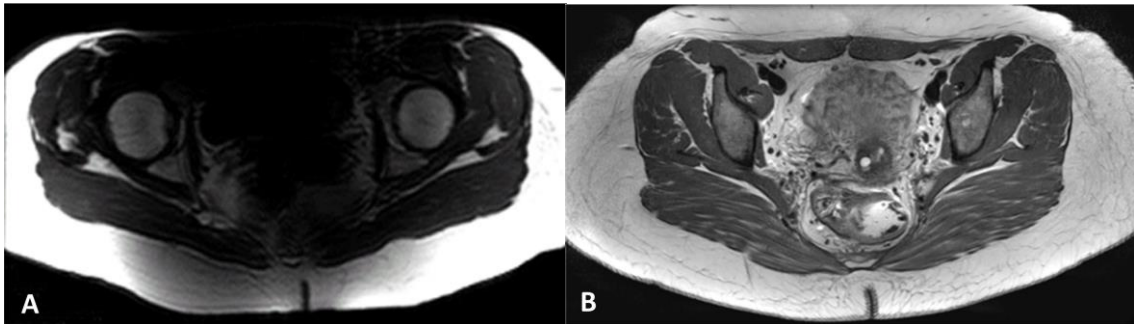

Figure 2. Whole body diffusion MRI in pregnant patient with breast cancer: (A) Moderately hyper intense lesion is difficult to discern from the physiological signal of bone marrow in the right pubic bone (arrow). (B) Co-registered T1-weighted sequence show hypo-intense lesion and allows confident diagnosis of bone metastasis
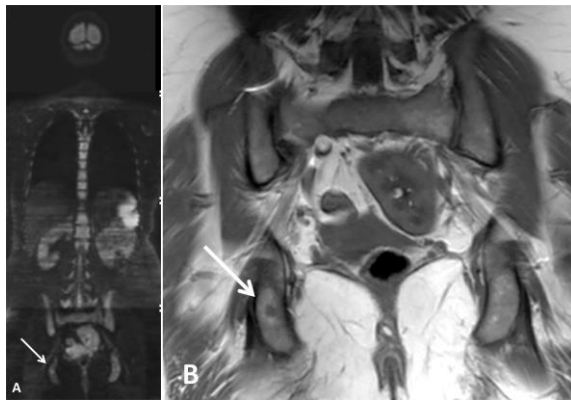

Figure 3. Lobular hyperplasia of the breast in pregnancy: the cells have abundant cytoplasm with hyperchromatic nuclei, focally containing punctate nuclei.
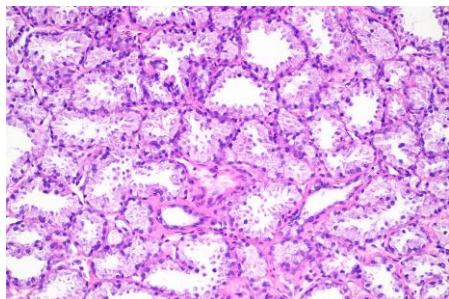
Figure 4. Endocervical curetting with Arias-Stella phenomenon, mimicking clear cell adenocarcinoma.
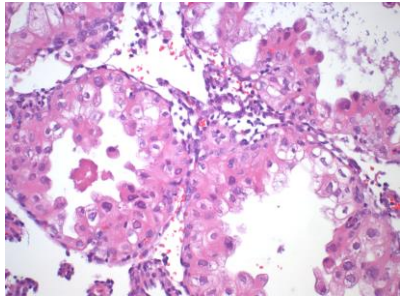

Figure 5. "Activated" nevus in a melanoma patient during pregnancy: this compound nevus darkened and

became larger, with some architectural irregularity, slightly increased nuclear atypia and an intradermal mitosis.