CHAPTER 3

Difficulties with diagnosis of malignancies in pregnancy


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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 such as computed tomography (CT) or positron emission tomography (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 development of non-ionizing techniques such as magnetic resonance imaging (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.
DIFFICULTIES WITH DIAGNOSIS

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 easy to detect when compared to more internally localized cancers. The physiologic gestational changes may contribute to this masking of cancer symptoms. As cancer during pregnancy is relatively rare with an estimated incidence of one in 1000 pregnancies, it might not be high on the list of different potential diagnoses. It has been reported that due to pregnancy, delay in diagnosis occurs, leading to a higher stage of disease at diagnosis. Pregnant women with cancer enface an even more complex problem as standard interventions in diagnosing, staging and treatment of cancer may be harmful for the unborn child. However, as these interventions are standard patient management, alternatives should be applied with caution in order to accurately assess the maternal condition. In this review, we 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 these complaints as pregnancy-related. A malignancy may not be the most obvious cause, but it has the greatest impact on the mother and the unborn child. Table 1 shows the most common overlapping symptoms. This large overlap makes it more understandable that both patient's delay and doctor's delay may occur.

Table 1. Overview of common overlapping symptoms of pregnancy and malignant disease.

<table>
<thead>
<tr>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Appetite changes</td>
</tr>
<tr>
<td>Constipation/haemorrhoids</td>
</tr>
<tr>
<td>Abdominal discomfort/pain</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Increased volume &amp; consistency of breast tissue/palpable mass in the breast</td>
</tr>
<tr>
<td>Hyperpigmentation/changed nevi</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
</tbody>
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Andersson et al.\(^5\) found fewer new cancer diagnoses during pregnancy than expected based on population-based numbers with a ratio of 0.46 (95% confidence interval [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 in the detection of recurrence during follow-up. These markers are produced not only by tumour cells but also as a response to (para)neoplastic conditions (e.g. inflammation). Sensitivity and specificity are therefore low, and increased levels of tumour markers are also associated with other benign situations such as 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 it is significantly increased during pregnancy, especially in the third trimester, with 3.3 to 20.0% above cut-off levels.\(^8\) 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 it 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 it is largely increased during pregnancy by fetal production. In the presence of pregnancy complications such as preeclampsia this is even higher, up to 13 times above tumour cut-off point, and it is therefore 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), CA 19-9 and carcino-embryonic antigen (CEA) were not elevated by pregnancy, and they can be used as 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 further oncological management and treatment of the pregnant patient, but they 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. 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.

**Ionizing imaging techniques**

**Rontgen radiation (X-radiation)**

Non-abdominal X-rays, including mammography, with proper abdominal shielding carry a negligible fetal radiation exposure of <0.1 mGy (see Table 2). Abdominal X-rays have a higher fetal exposure, but they have no clear indication for cancer diagnosis or staging, and they should not be considered relevant to the discussion in pregnant patients.

An issue of particular importance concerns mammography. In pregnant women with breast cancer, mammography is more challenging as physiological hypervascularization and increased breast density make it more difficult to interpret. Mammography for a suspicious mass in pregnancy must be accompanied by ultrasound evaluation, to both 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.
Table 2. Fetal radiation exposure for X-ray and CT scan for each body region.\textsuperscript{11,23,38}

<table>
<thead>
<tr>
<th>Body region</th>
<th>mGy</th>
<th>Body region</th>
<th>mGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>X – chest</td>
<td>0.0001 – 0.43</td>
<td>CT – head</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>X – mammography</td>
<td>&lt;0.1</td>
<td>CT – chest</td>
<td>0.02 – 0.2</td>
</tr>
<tr>
<td>X – abdomen</td>
<td>1.4 – 4.2</td>
<td>CT – pulmonary embolism</td>
<td>0.2 – 0.7</td>
</tr>
<tr>
<td>X – pelvis</td>
<td>0.16 – 22</td>
<td>CT – abdomen (routine)</td>
<td>4 – 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT – pelvis</td>
<td>6.7 – 114</td>
</tr>
</tbody>
</table>

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

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 they should therefore be considered safe during pregnancy, particularly when MRI is not able to answer the clinical question or is contraindicated (e.g., pacemaker, claustrophobia). However, care should be taken to minimize fetal radiation exposure where possible.\textsuperscript{11} No clear consensus currently exists concerning the use of iodinated contrast agents during pregnancy due to insufficient literature on the possible risk of 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.\textsuperscript{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 therefore it may improve maternal and fetal morbidity and mortality.\textsuperscript{16,17} However, as pregnant patients undergo treatment, response assessment by additional (contrast-enhanced) CT scans may lead to unacceptable 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.\textsuperscript{12} Moreover, the application of iterative reconstruction enables the application of ultralow-dose CT.\textsuperscript{18} Current studies on contrast-enhanced CT only investigated fetal exposure towards a single contrast dose.\textsuperscript{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 it is therefore not the first choice in pregnant patients with oncologic disease.\textsuperscript{20,21} On the contrary, a CT chest should be strongly considered when lung metastases are suspected as it only exposes limited radiation to the fetus, requires no iodinated contrast and has highest sensitivity to assess small lung metastases accurately.\textsuperscript{22}
Stand-alone nuclear medicine imaging

Over the last years, the use of PET imaging in the management of cancer patients for accurate diagnosis, staging and evaluation has grown. In pregnant patients with cancer, the use of PET imaging has been debated as it uses radioactive-labelled tracers, and therefore it causes fetal exposure to radiation. For PET imaging in most cancer patients, 2-deoxy-2-[fluorine-18]fluoro-D-glucose (18F-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 the mother and the fetus. For radiotracers such as 11C, 11C-4DST, (18)F-fluoro-L-phenylalanine-fructose (18F-FBPA) and (68)Ga-ethylene diamine tetra acetic acid (68Ga-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 18F-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 intelligence quotient (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 the evaluation of bone metastases is possible during pregnancy when MRI is inconclusive, although literature on this subject is scarce.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 to simultaneously provide intravenous hydration to avoid the accumulation of tracer.27

Hybrid nuclear medicine imaging

Currently, the use of hybrid imaging (PET/CT and PET/MRI) possesses great potential for cancer patients as morphological, functional and molecular information is gathered in one examination. 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 as the ionizing...
radiation dose is much lower especially when the abdomen and the uterus are positioned in the radiation field.\textsuperscript{20,23}

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Gestational age</th>
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<tbody>
<tr>
<td>Russell et al.\textsuperscript{74}</td>
<td>1997</td>
<td>2.7 x 10-2, 1.7 x 10-2, 9.4 x 10-3, 8.1 x 10-3</td>
</tr>
<tr>
<td>Stabin\textsuperscript{76}</td>
<td>2004</td>
<td>2.2 x 10-2, 2.2 x 10-2, 1.7 x 10-2, 1.7 x 10-2</td>
</tr>
<tr>
<td>Zanotti-Fregonara et al.\textsuperscript{75}</td>
<td>2009</td>
<td>3.65 x 10-2, - , - , -</td>
</tr>
<tr>
<td>Zanotti-Fregonara et al.\textsuperscript{76}</td>
<td>2010</td>
<td>4.0 x 10-2, - , - , -</td>
</tr>
<tr>
<td>Takalkar et al.\textsuperscript{77}</td>
<td>2011</td>
<td>1.55 x 10-2, 7.16 x 10-3, 6.16 x 10-3, -</td>
</tr>
<tr>
<td>Xie and Zaidi\textsuperscript{23}</td>
<td>2014</td>
<td>3.05 x 10-2, 2.27 x 10-2, 1.5 x 10-2, 1.33 x 10-2</td>
</tr>
</tbody>
</table>

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

**Non-ionizing imaging techniques**

**Ultrasound**

The main advantages of ultrasound include its widespread availability, non-invasiveness and the ability to immediately guided biopsy or fine-needle aspiration cytology (FNAC). 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%).\textsuperscript{14,28} In adnexal masses, grey scale and Doppler ultrasound have a high sensitivity and specificity, especially when applying the ‘International Ovarian Tumor Analysis (IOTA) simple rules’.\textsuperscript{29} It is also the primary modality for nodal staging in thyroid cancer and breast cancer, and it 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 of up to 80% and specificity up to 98%. Adding FNAC increases sensitivity to 87%.\textsuperscript{20} In head and neck
cancer, ultrasound, combined with FNAC, can reach a specificity of 100% and sensitivity to 73%.\textsuperscript{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 it reduces the value of ultrasound for a comprehensive cancer staging. This is reflected by only moderate sensitivity of 63% for detecting liver metastases and low sensitivity for detecting abdominal lymphadenopathies, as described for lymphomas.\textsuperscript{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. In addition, the technique allows the evaluation of functional tissue properties through the use of diffusion-weighted imaging (DWI) for lesion characterization and detection as well as treatment follow-up.\textsuperscript{33,34}

The safety profile of MRI towards the fetus has been subject to debate, and it 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 the 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.\textsuperscript{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.\textsuperscript{36} Furthermore, there are to date no studies that have indicated that any pulse sequences cause significant increases in temperature.\textsuperscript{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 Food and Drug Administration (FDA) safety limits of 4 W/kg specific absorption rate (SAR), whereas routinely implemented technical developments such as multichannel phased-array and parallel transmission further decrease SAR.\textsuperscript{10,12,36} Data in a phantom fetus showed no sequences exceeding the FDA SAR threshold at 1.5 and 3 Tesla.\textsuperscript{36} The 2007 ACR guidelines indicate that MRI can be used in pregnant patients, regardless of GA, when the benefit outweighs potential risks to the fetus.\textsuperscript{37}

Concerning the use of gadolinium, the ACR paper on safe MRI practices advises for extreme caution and only if the maternal benefit overwhelmingly outweighs the theoretical fetal risks.\textsuperscript{16} Gadolinium does cross the placenta, and after excretion by the fetal kidney in the amniotic fluid, it is unknown how long it remains there. Although no fetal toxic
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effects have been reported, the gadolinium ion can dissociate from its chelate molecule, and it has been proven to be teratogenic in animal studies. The use of DWI can potentially obviate the need for gadolinium contrast in imaging. Moreover, DWI has the potential value for preoperative planning, and it 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. 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 with 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. Furthermore, DWI increases the sensitivity for detecting nodal metastases in gynaecological malignancies, lung, head and neck cancer and lymphoma compared with 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. 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 has been reported, but the value of MRI for screening women with dense breasts remains controversial due to the paucity of data and possible overdiagnosis. For adnexal masses, MRI is only advised in cases where ultrasound is inconclusive, with masses too large to fully assess by ultrasound or when there is a high probability of malignancy requiring the assessment of peritoneal disease spread. In patients with other pelvic cancers, including rectal, uterine and cervical cancer, locoregional MRI is pivotal for staging and treatment planning, and it should be performed as for the non-pregnant population, without the need for gadolinium.

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 with 1.5 Tesla, is the inhomogeneity of the magnetic sequence caused by amniotic fluid, particularly in echo planar (DWI) and spin echo (standard anatomical T2 sequences). This results in areas of blackout or complete loss of signal, and it harbours the risk that lesions may be missed. The most optimal solution to avoid this artefact is the use of multichannel transmission coupled with parallel imaging (Figure 1). 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 stand-alone sequence. Combining DWI with anatomical sequences also allows overcoming pitfalls related to physiological movement.

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

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 three-dimensional (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. Although (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 the effect in liver and skeletal haemangiomas that may cause falsely increased signal in these benign entities, careful correlation with anatomical sequences overcomes 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.

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

Mammary glands enlarge rapidly, vascularity increases and the fibro-adipose tissue diminishes. Secretory changes and hyperplasia of the luminal epithelium with distension of the lobular units and accumulation of secretion occur frequently. On FNAC, these features result in cellular smears with small glandular clusters or abundant discohesive cells with abundant vacuolated cytoplasm and hyperchromatic nuclei containing irregular nucleoli (Figure 3A).57,58 As pathologists should be aware of these potential pitfalls leading to a false-positive diagnosis of breast cancer, FNAC stays useful in evaluating breast masses to minimize delays in the diagnosis of carcinoma associated with pregnancy.57 Inflammation
and infarction of the mammary tissue presenting as a firm nodular tumour may occur, mostly in the late third trimester.\textsuperscript{59} Their cause is uncertain, but they might be associated with physiologic pregnancy-related vascular changes. Rarely, breast abscesses may mask lymphomas or other haematologic diseases.\textsuperscript{60,61} The predominant type of pregnancy-associated breast cancer is invasive ductal carcinoma, and it is as in the non-pregnant population of young women more often poorly differentiated, oestrogen and progesterone receptor-negative and HER-2/neu-positive.\textsuperscript{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.\textsuperscript{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 3B).\textsuperscript{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.\textsuperscript{65} Classic nevi and dysplastic nevi often become more atypical, and they show more melanocytic proliferation during pregnancy, mimicking a malignant melanoma (Figure 3C). Of note, although nevi and melanoma cells do not harbour hormone receptors, they seem to be oestrogen-responsive.\textsuperscript{66,67}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3.png}
\caption{(A) Lobular hyperplasia of the breast in pregnancy: the cells have abundant cytoplasm with hyperchromatic nuclei, focally containing punctate nuclei. (B) Endocervical curetting with Arias-Stella phenomenon, mimicking clear cell adenocarcinoma. (C) "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.}
\end{figure}
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. 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 earlier, staging procedures are performed as in non-pregnant patients as far as possible, and they 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 assess lymph node involvement is performed in patients with breast cancer, melanoma, vulvar cancer and Merkel cell carcinoma. Performing an 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 case series have described SNP in pregnancy, and they reported no adverse events. It has been calculated that when using a nanocolloid with a short half-life and large particle size, such as 99-Technetium, and due to the accumulation of the nanocolloid in the lymph node itself, the fetal radiation exposure is <5 mGy, even in the inguinal lymph nodes. It is also recommended in pregnancy to use the single-day protocol as the administered dose is lower, time between admission and surgery is shorter and detection rate does not differ from the 2-day protocol. Therefore, when maternal outcome may benefit from an 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.

**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 GA creates a problem towards the ability to retain the diagnostic minimum of 10 lymph nodes following...
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REFERENCES

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