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SPECIAL ARTICLE

ESMO Expert Consensus Statements on the management of breast cancer during pregnancy (PrBC)

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The management of breast cancer during pregnancy (PrBC) is a relatively rare indication and an area where no or little evidence is available since randomized controlled trials cannot be conducted. In general, advances related to breast cancer (BC) treatment outside pregnancy cannot always be translated to PrBC, because both the interests of the mother and of the unborn should be considered. Evidence remains limited and/or conflicting in some specific areas where the optimal approach remains controversial. In 2022, the European Society for Medical Oncology (ESMO) held a virtual consensus-building process on this topic to gain insights from a multidisciplinary group of experts and develop statements on controversial topics that cannot be adequately addressed in the current evidence-based ESMO Clinical Practice Guideline. The aim of this consensus-building process was to discuss controversial issues relating to the management of patients with PrBC. The virtual meeting included a multidisciplinary panel of 24 leading experts from 13 countries and was chaired by S. Loibl and F. Amant. All experts were allocated to one of four different working groups. Each working group covered a specific subject area with two chairs appointed:

1. PrBC: incidence, epidemiology, biology and pathology, diagnostic work-up, staging and risk assessment, prognosis (Chairs: Vincent Vandecaveye, Fedro Peccatori).
2. Clinical pharmacology of systemic agents during pregnancy: management of localized disease and (neo) adjuvant therapies, management of systemic disease (Chairs: Giuseppe Curigliano, Peter Schmid).
3. Obstetric care and fetal/newborn follow-up and outcomes: metastases to fetus, management of pregnancy during anticancer therapy, lactation, psychological support (Chairs: Elyce Cardonick, Mathilde van Gerwen).

Planning, preparation and execution of the consensus process was conducted according to the ESMO standard operating procedures.

Key words: (neo) adjuvant therapy, pregnancy management during cancer, pregnancy-related breast cancer

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INTRODUCTION

The management of breast cancer during pregnancy (PrBC) is a relatively rare indication, although incidence of breast cancer (BC) in young women has increased,[1] and an area where no or little evidence is available since randomized controlled trials cannot be conducted. In general, advances related to BC treatment outside pregnancy cannot always be translated to PrBC, because both the interests of the mother and of the unborn should be considered. Evidence remains limited and/or conflicting in some specific areas where the optimal approach remains controversial. In 2022, the European Society for Medical Oncology (ESMO) held a virtual consensus-building process on this topic to gain insights from a multidisciplinary group of experts and develop statements on controversial topics that cannot be adequately addressed in the current evidence-based ESMO Clinical Practice Guideline.

The overall lack of high-level evidence around this topic underscores the expert opinion level of the statements. Therefore, it is even more important to include the patients and their partners' preference in the clinical decision making.

METHODS

The aim of this consensus-building process was to discuss controversial issues relating to the management of patients with PrBC. The virtual meeting included a multidisciplinary panel of 24 leading experts from 13 countries and was chaired by S. Loibl and F. Amant. All experts were allocated to one of three different working groups. Each working group covered a specific subject area with two chairs appointed:

1. PrBC: incidence, epidemiology, biology and pathology, diagnostic work-up, staging and risk assessment, prognosis (Chairs: Vincent Vandecaveye, Fedro Peccatori).
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Planning, preparation and execution of the consensus process was conducted according to the ESMO standard operating procedures (https://www.esmo.org/content/download/729269/17224532/1/ESMO-ECS-Standard-Operating-Procedure.pdf). No systematic literature search was undertaken. All statements compiled by the group were accompanied by a level of evidence, strength of recommendation based on the 'Infectious Diseases Society of America-United States Public Health Service Grading System' (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.08.001) and percentage of expert's consensus based on the number of votes of agreement/disagreement (the abstainers have been considered null).

The final manuscript was reviewed and approved by all panel members.

RESULTS

WP1: PrBC: incidence, epidemiology, biology and pathology, diagnostic work-up, staging and risk assessment, prognosis

QUESTION 1: Is BC diagnosed during pregnancy distinct from that diagnosed during the postpartum period?

STATEMENT 1: BCs diagnosed in the postpartum period are biologically distinct from those diagnosed during pregnancy. Given the biological differences and unique challenges associated with managing PrBC, future studies should aim to study each group independently (III).

DISCUSSION: Pregnancy-related BC is defined as BC diagnosed during pregnancy or within a year postpartum.[2] Indeed, childbirth at any age confers a transiently increased risk for BC soon after delivery with a lower risk within the first few years postpartum.[3] However, epidemiological, clinical and biological data have now shown that PrBC is a distinct entity from the tumors diagnosed in the postpartum period [postpartum breast cancer (PPBC)].[4-6]

The mammary gland is a highly dynamic tissue that reaches its maximal functional differentiation during lactation when, through milk production, it provides nutrition and immunological protection to the mammalian offspring. When lactation ends, and weaning takes place, the excess tissue developed during pregnancy and lactation is no longer needed, and the mammary gland has to regress to a pre-pregnant state in a process coined postpartum involution. PPBC, diagnosed up to 10 years after pregnancy, has been associated with a worse prognosis, suggesting that the mammary gland milieu, characterized by massive apoptosis, wound-healing processes and T-cell suppression during this key developmental stage, allows for and promotes disease progression.[6-8] Further, cancer care in women diagnosed during pregnancy needs to be individualized according to disease stage and tumor biology, as with any other breast tumor diagnosis, but it also needs to account for gestational age and fetal safety. In contrast, treatment decisions for PPBC do not need to consider these fetal concerns. However, the postpartum setting is a poor prognostic factor and standard treatment for high-risk disease is mandatory.

Thus, PrBC and PPBC must be considered distinct entities. Parity and the age at first and last delivery should be accurately registered in the anamnesis of any BC patient to assess prognosis, and further research is needed to better characterize either of these diseases.

24 agree, 0 disagree

100% consensus

QUESTION 2: What is the likely reason for the recent increasing trend in diagnosed BC during pregnancy?

STATEMENT 2: The rising trend of delaying childbearing to later in life appears to be the most likely reason to the increasing diagnosis of PrBC (III).

DISCUSSION: The BC incidence in premenopausal women is increasing over time across many populations. Most, but not all, studies have found an increasing incidence of PrBC.[9-12] The incidence and risk trends of PrBC depend on both the underlying incidence trend of BC, as well as the trends of childbearing. BC risk increases with age. If women postpone childbearing into ages where BC is more common, then the incidence of PrBC will increase regardless of what the underlying incidence trend in BC is. Studies have found that the increasing incidence of PrBC appears to be less strong when age is adjusted for.[9-11]

Other factors that could explain an increasing incidence of PrBC are factors that are associated with both pregnancy and BC rates, the so-called confounding factors. Incidence could increase if there are increasing groups in the population with both higher childbearing rates and higher BC rates.

24 agree, 0 disagree
100% consensus

QUESTION 3: Could genomic assays be used to refine the risk of recurrence and to inform on the type of adjuvant systemic therapy in pregnant patients with estrogen receptor-positive (ER+) disease?

STATEMENT 3: Debate exists on the performance of genomic assays in stratifying the risk of premenopausal women. These assays can be considered to assist decision making in pregnant women with pN0 ER+ BC, but patients should be informed about potential limitations in the risk assessment and the limited level of evidence, especially in the pregnant population (V).

DISCUSSION: No studies have specifically evaluated the prognostic performance of commercially available genomic signatures in patients diagnosed with PrBC. Only one study looked into the gene expression of GENE70[13] and no difference was found between the two groups.

Even outside pregnancy, debate exists on the performance of genomic signatures in young patients with BC and their capacity to inform on the possibility to forego chemotherapy,[14,15] yet critical analyses point out to their clinical utility.[16] Unlike in postmenopausal patients, the majority of ER+ tumors diagnosed in young patients are of the highly proliferative luminal-B genotype[17,18] that benefit more from chemotherapy. Nevertheless, a fraction (estimated around 15%-20%) of BC occurring in young women are of the luminal-A genotype in which endocrine therapy alone would suffice. Even if data are lacking in the specific scenario of pregnant patients with early-stage ER+ BC, genomic testing could be considered in pN0 patients to confirm a low-risk situation. If confirmed, endocrine therapy alone might be appropriate but must be deferred until the postpartum period.

21 agree, 1 disagree, 2 abstain
95.45% consensus

QUESTION 4: What diagnostic imaging modalities should be used for diagnosis and locoregional staging in PrBC?

STATEMENT 4: Breast ultrasound is the first-line imaging modality for primary tumor assessment and staging of regional and supraclavicular lymph nodes and is complemented by mammography (III) or—in selected cases—magnetic resonance imaging (MRI) with diffusion-weighted sequence to aid in the delineation of tumor extent and multifocality (IV).

DISCUSSION: Breast ultrasound is the first-line imaging modality for locoregional staging as it allows immediate differentiation between obviously benign lesions such as cysts and galactocoeles and solid breast lesions that warrant core biopsy. Ultrasound has an overall sensitivity and specificity for detection of malignancy of 80.1% and 88.4%, respectively in a non-pregnant population.[19] An additional mammography is indicated in a single mediolateral oblique view to look for microcalcifications or tissue distortions when the initial assessment suggests malignancy.[20] Ultrasound is also the primary imaging modality for assessment of axillary and periclavicular lymphadenopathies with reported sensitivity between 26.4% and 92% and specificity between 55.6% and 98.1%, respectively, in a non-pregnant population.[21] In the same population, ultrasound-guided core biopsy or fine-needle aspiration cytology (FNAC) of lymph nodes can further improve pre-operative determination of nodal status. The sensitivity of ultrasound-guided FNAC for lymph nodes ranges from 36% to 86.4%, with specificity from 95.7% to 100%. Due to the high positive predictive value of ultrasound-guided FNAC, this is of high value to plan axillary lymph node dissection.[22] Changes in breast tissue during pregnancy will impact the accuracy of these imaging modalities.

Dynamic contrast-enhanced (DCE) breast MRI should be avoided, as exposure of the fetus to gadolinium contrast increases the risk of rheumatological, inflammatory or dermal conditions, as well as stillbirth or neonatal death.[23] The incorporation of diffusion-weighted imaging (DWI) allows the utilization of non-contrast breast MRI in pregnant patients and has sensitivities between 72.4% and 97% and specificities between 54.4% and 91.7% for regional nodal staging and sensitivities between 75.7% and 78.9% to assess multifocality or contralateral breast involvement.[24] Although non-contrast breast MRI can be of complementary value to ultrasound for locoregional staging, it is rarely indicated in this setting.[25,26]

The need for shielding during diagnostic and staging procedures is best discussed with the radiologist. Modern equipment more precisely directs the beam, without fetal harm. In cases where the primary beam is less precise, fetal shielding is advised.

23 agree, 0 disagree, 1 abstain
100% consensus

QUESTION 5: What is the optimal imaging strategy for systemic staging of PrBC?

STATEMENT 5: Locoregional tumor stage determines the staging strategy during pregnancy. Chest X-ray and

abdominal ultrasound are easily accessible for initial screening of metastases. If inconclusive or if there is a high risk of metastases, additional non-contrast MRI with DWI sequence of the full-spine and pelvic bone and liver combined with chest computed tomography (CT) are suggested. When available onsite, whole-body MRI with diffusion-weighted sequence (WB-DWI/MRI) is recommended as a single-step staging modality (III).

DISCUSSION: The initial locoregional tumor stage and the histopathological diagnosis will generally determine the extent of imaging modalities needed.[27,28] Most patients with early BC are unlikely to benefit from extensive staging.[29] In case of risk factors including clinically positive axillary nodes, large tumors (e.g. diameter larger than 5 cm), aggressive biology (e.g. triple-negative tumors, HER2+ tumors, luminal BC with high Ki67) and clinical or laboratory signs of presence of metastases, imaging for distant staging should be considered. Current international guidelines show no consensus on how and when to screen with imaging for metastases over the most frequently affected sites including the skeleton, liver and lungs.[30] Chest x-ray and liver ultrasound provide easily accessible and rapid screening of metastases but their use should be carefully balanced with the risk for metastatic disease due to their relatively low sensitivities for detecting lung and liver metastases and their inability to detect skeletal metastases.[31-33] In case of high clinical suspicion of metastatic disease, staging should be expanded by non-contrast MRI with DWI of the spine and pelvis and the liver combined with low-dose CT of the chest.[28,33] Chest CT offers superior sensitivity with minimal radiation exposure to the fetus. Skeletal MRI with DWI showed high pooled sensitivity and specificity for detecting skeletal metastases, superior to bone scintigraphy in an updated meta-analysis.[34] Liver MRI with DWI provides excellent diagnostic performance for detecting liver metastases equivalent to contrast-enhanced MRI.[35] WB-DWI/MRI is an emerging imaging modality and has been shown to allow accurate identification of the primary tumor and more accurate staging of nodal and distant metastases in a single step compared to conventional staging, particularly in pregnant patients with BC.[26,36] WB-DWI/MRI has shown high accuracy for detecting bone, liver and peritoneal metastases.[37] Moreover, it allows the detection of additional lymph node metastases irrespective of nodal morphology.[38] WB-DWI/MRI should only be complemented by unenhanced chest CT in case of equivocal lung nodules at MRI.[39] When available onsite, WB-DWI/MRI is recommended as a single-step staging modality.

Nuclear imaging tracers induce relatively low fetal radiation exposure. However, the standard use of hybrid imaging with CT increases the final cumulative dose, ranging between 10 and 50 mGy. Therefore, low-dose positron emission tomography/CT and bone scintigraphy are only recommended as second-line imaging modalities, to be selectively carried out in case of unresolved distant findings when the benefit for the mother clearly outweighs the risk to the fetus and/or when MRI is not available.[40] The staging strategy is best discussed with the radiologist and physicist in order to minimize the fetal exposure and taking a cumulative exposure of 100 mGy as a maximum.

22 agree, 0 disagree, 2 abstain

100% consensus

QUESTION 6: Does PrBC have different biological features compared to BC patients of the same age and stage?

STATEMENT 6: Limited biological differences exist in tumors when diagnosed during pregnancy. Yet, to date, this does not appear to have an important impact on patient management (III).

DISCUSSION: Several studies have looked into the differences in classic clinicopathological features between pregnant and young non-pregnant BC patients. Histological grade and subtype were consistently found to be comparable between both groups. However, few studies have pointed out a tendency of a higher proportion of ER-negative (ER−) tumors, although differences hardly reach statistical significance in any of the studies.[41-43] The largest study included 311 pregnant and 865 non-pregnant patients in which the proportion of ER− tumors was almost doubled in pregnant compared to non-pregnant patients (53.4% versus 25.5%).[41]

Tumors diagnosed during pregnancy were shown to have high level of receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL).[44] These findings underscore the potential impact of pregnancy on the breast microenvironment that subsequently alters tumor biology.

At the genomic level, the pattern of common somatic mutations (e.g. *TP53*, *PIK3CA* etc.) appears to be rather comparable between pregnant and age-matched non-pregnant BC patients.[44,45] However, whole-genome sequencing analysis showed higher frequency of non-silent mutations, higher frequency of mutations in the mucin gene family and enrichment in the mismatch repair deficiency mutational signature.[45] The potential clinical implications of such findings are not clear, although it could point out that some pre-existing subclones could have a growth advantage under the pregnancy state.

21 agree, 1 disagree, 2 abstain

95.45% consensus

QUESTION 7: Does PrBC have worse prognosis compared to BC in young patients of the same stage and disease subtype?

STATEMENT 7: Prognosis of BC diagnosed during pregnancy is similar to that in young BC patients with the same stage and disease subtype, provided it is adequately managed (II).

DISCUSSION: In the past, several studies have shown that PrBC has a worse prognosis compared to non-gestational BC. In a nationwide registry-based study on 234 patients diagnosed with PrBC from 1970 to 2018, the hazard ratio (HR) of death was 1.80 [95% confidence interval (CI) 1.43-2.28].[46] In a recent large meta-analysis of 76 studies, the

HR of death was 1.46 (95% CI 1.12-1.90) for patients with PrBC.[47] However, a key observation of these studies is that patients were not necessarily adequately treated during pregnancy and some analyses included BC diagnosed within 1 year of delivery. This is supported by the result of the largest case control study to date that included 311 patients diagnosed with PrBC and 865 non-pregnant controls; the HR for overall survival was 1.06 (95% CI 0.66-1.68), with patients receiving similar treatments, regardless of their pregnancy status.[41] Similar results were reported in a series of 58 triple-negative PrBCs, where no differences in survival were observed when a propensity score-matched analysis with 92 non-pregnant patients was carried out.[48] A recent study in more than 600 patients with PrBC who were treated with chemotherapy during pregnancy supports earlier findings.[49] Thus, it appears that—if adequately treated—pregnant BC patients would have highly comparable prognoses to patients of the same age and stage.

On the other hand, this is not the case with PPBC, where the involuting breast with its peculiar immunological milieu is responsible of a high rate of recurrences, thus accounting for worse prognosis.[7]

23 agree, 1 disagree
95.83% consensus

QUESTION 8: Is noninvasive prenatal testing (NIPT) as reliable in patients with PrBC?

STATEMENT 8: Positive NIPT is less reliable when carried out in pregnant BC patients. An abnormal NIPT must be confirmed by a diagnostic test before a final decision is made (III).

DISCUSSION: In pregnancies occurring in women without cancer, NIPT allows the detection of aneuploidies through the analysis of fetal cell-free DNA (cfDNA) in maternal blood.

However, blood from pregnant BC patients may also contain tumor cfDNA. Thus, positive NIPT results could simply reflect the maternal cancer and not necessarily a fetal genetic disease. The first case was published in 2013[50] followed by others that demonstrated cancer detection after NIPT in the range of 20%-30%.[51-53] Mainly, hematological and solid cancers other than BC were revealed during pregnancy in asymptomatic women.[53] Thus, the possibility that NIPT in cancer patients might have a higher rate of false positive and false negative should be considered and patients should be informed during the prenatal test counseling.[54]

21 agree, 0 disagree, 3 abstain
100% consensus

WP2: Clinical pharmacology of systemic agents during pregnancy: management of localized disease and (neo) adjuvant therapies, management of systemic disease

QUESTION 9: When can chemotherapy be safely administered during pregnancy?

STATEMENT 9: Chemotherapy is contraindicated in the first trimester of gestation to avoid interference with organogenesis; fetal benefit of treatment delay until the second trimester should be balanced against maternal risk (V). Although fetal growth impairment is associated with earlier start of chemotherapy, children reach their developmental milestones. Therefore, chemotherapy can be administered during the second and third trimester.

DISCUSSION: Chemotherapy is contraindicated in the first trimester of gestation to avoid interference with organogenesis, as early exposure has been associated with up to 20% risk of major malformations. Fetal benefit of treatment delay until the second trimester should be balanced against maternal risk. Chemotherapy is associated with an increased risk of congenital malformations only in the first 12 weeks of pregnancy.[55] After 12-14 weeks of gestation, administration of a number of chemotherapy drugs is safe and feasible. Standard (neo) adjuvant anthracycline-taxanes-based regimens could be administered as in the non-pregnancy setting.[56] After 35 weeks of gestation, chemotherapy in a 3-weekly schedule is usually discouraged to allow a certain window with regard to the administration scheme for maternal and fetal bone marrow recovery between the last cycle of chemotherapy and delivery.[57] Weekly chemotherapy schedules can be continued until closer to delivery.

22 agree, 0 disagree, 2 abstain
100% consensus

QUESTION 10: Are chemotherapy dose adjustments required when treating pregnant BC patients?

STATEMENT 10: Chemotherapy standard doses should be used during pregnancy without adjustments. Actual weight should be used to calculate the chemotherapy dose (V).

DISCUSSION: Pregnant patients have larger distribution volume than non-pregnant patients. As chemotherapy is partly metabolized by the placenta as well, this results in lower peak plasma concentration of chemotherapy and faster clearance, compared to non-pregnant patients.[58]

Available studies have shown that chemotherapy pharmacokinetics are altered during pregnancy, with relatively lower exposure reported in women treated during pregnancy.[59] The decrease in exposure is more apparent for taxanes rather than anthracyclines. It is unknown whether this has any effect on treatment benefit, although it is unlikely to be considerable, if any. This is supported from the neoadjuvant setting in which pathological complete response (pCR) rates were shown to be rather comparable between pregnant and non-pregnant BC patients.[60,61] In a large series of PrBC patients that received chemotherapy during pregnancy, the oncological outcome was unaffected by the pregnancy.[49]

Thus, a priori dose modifications due to pregnancy should not be adopted and all women should be treated with standard doses as in the non-pregnancy setting using their actual and not adjusted weight.

21 agree, 0 disagree, 3 abstain
100% consensus

QUESTION 11: Can we safely deliver radiation therapy to women during pregnancy?

11.a) STATEMENT: The delivery of radiation therapy is not contraindicated *per se*. The radiation dose to the fetus depends on the distance from the radiation target volumes and on radiation therapy parameters including prescribed dose, size and site of the target volumes combined with technical parameters. Importantly, the radiation sensitivity of the fetal tissues and thereby the radiation-related toxicity risks depend on the gestational age. Therefore, stage of pregnancy combined with radiation therapy-related parameters determine the risks, and early involvement of the radiation team might be beneficial.

DISCUSSION: The influence of radiation on pregnancy in general may include fetal death in the first 2 weeks after conception, malformations up to 2 months and intelligence quotient (IQ) decrease between the third and sixth month. Moreover, growth disturbances and carcinogenic effects are reported. Most risks are dose related, depend on gestational stage and can be expressed in risk per dose unit as well as in risks ratios compared to the spontaneous frequency. We discriminate deterministic effects, occurring above a threshold dose with a severity related to the dose (e.g. teratogenesis), from stochastic effects, without a threshold, dose-related frequency and dose-independent severity (e.g. carcinogenesis). The cumulative fetal exposure of ionizing radiological examinations (and radiotherapy) determines the fetal risk.

In BC, the most common indications for radiation therapy consist of post-operative breast/chest wall with or without draining lymphatics, after breast-conserving therapy and after mastectomy in the presence of risk factors, and for palliative indications for sign- or symptom-relief of metastatic disease. More recently, the concept of radical metastases-directed radiation therapy in oligometastatic disease became more commonly used. Biological features of disease guide selection and sequence of treatments. In the post-operative setting, if the patient has a high-risk tumor, often chemotherapy can be given until shortly before delivery, postponing radiation therapy. In case of a low-risk cancer, generally ER+, without an indication for chemotherapy, timing of radiation therapy depends on gestational stage, balancing the risks of postponement in the presence of high serum estrogen levels and estimated doses to the fetus, with radiation therapy delivery generally preferable up to 20-24 weeks and postponement thereafter.

22 agree, 0 disagree, 2 abstain
100% consensus

11.b) STATEMENT: During the first and most of the second trimester, irradiation to the supradiaphragmatic region should not be associated with high fetal exposure, if appropriate after supplementary pelvic shielding (using mobile lead shield to be positioned between the source of the radiation and at sufficient distance from the patient). Thus, it could be considered, specifically if postponing until delivery could have a detrimental impact on prognosis (III).

DISCUSSION: Local and locoregional radiation therapy: An accurate estimation of the dose to the fetus can be made based on radiation therapy parameters combined with the distance between the irradiation volume and the fetus, which depends on especially the gestational stage, with a contribution of the physical parameters of the patient (e.g. the dose will be lowest in tall and lean patients, while being highest in short and obese patients). In general, the dose to the fetus will not exceed 100 mSv, which is considered as having acceptably low risks, during at least the first half of the pregnancy. Depending on the aforementioned parameters, the dose can be further reduced by supplementary shielding around the pelvic region. Finally, the recently introduced ultra-hypofractionated radiation therapy regimen of 26 Gy in five fractions over 1 week[62] assessed in non-pregnant patients should be favored as the total dose is considerably lower than that with moderate hypofractionation (and even more compared to 'historical' fractionation). Another advantage of this 1-week schedule is that more time is available to safely deliver radiation therapy, compared to 3 or even 5 weeks, again resulting in a lower dose to the fetus, without compromising on quality of treatment (for breast/chest wall only as the 26 Gy in five fractions over 1 week is not yet validated for lymph node irradiation).

Palliative indications: If other treatments do not alleviate the symptoms sufficiently, radiation therapy can be considered depending on the target volume and the required dose. Metastases in the pelvic region and part of the abdomen will often be in very close proximity to the fetus. However, effective palliation can be obtained with radiation doses as low as 8 Gy, so even lumbar vertebral metastases might be considered for palliative radiation therapy early in the pregnancy. The same might be valid for stereotactic radiation therapy of liver metastases in oligometastatic disease. Dose estimations should, therefore, always be considered in these cases. In the cases of larger distances between the target lesion and the fetus, radiation therapy might be possible up to the end of pregnancy (like in brain metastases).

Finally, treatment technique and treat of infracture-related parameters influence the dose outside of the target volume. For this, close collaboration with the medical physics and radioprotection teams is of utmost importance. The accurate estimation of the dose to the fetus, comparing various set-ups with/without additional shielding, should always precede the final decision on the administration of radiation therapy.

19 agree, 0 disagree, 5 abstain
100% consensus

QUESTION 12: Could sentinel lymph node (SLN) biopsy be carried out as in the non-pregnancy setting?

STATEMENT 12: SLN biopsy can be carried out during pregnancy using low-dose technetium (Tc)-labelled albumin nanocolloid. Allergic reaction has been reported with blue dye and thus should be avoided during pregnancy (V).

DISCUSSION: Several studies are currently available pointing out to the safety of sentinel node procedures during pregnancy.[63,64] The largest series included 145 pregnant BC patients who underwent SLN biopsy during gestation. No neonatal adverse events related to SLN were reported. Patient outcome was comparable to what is expected in the non-pregnancy setting.

Low dose of Tc-labelled albumin nanocolloid (average 10 Mbq) can be injected locally 2 h before the procedure. Almost 90% of this dose will be collected in the sentinel node, resulting in low systemic exposure and minimal fetal risk.[57] The use of blue dye for the detection of a sentinel node should be avoided given the risk of anaphylactic reaction.

22 agree, 0 disagree, 2 abstain
100% consensus

QUESTION 13: In patients diagnosed with early triple-negative breast cancer (TNBC) who are candidates for neoadjuvant therapy, can we deliver platinum salts and/or immunotherapy during pregnancy?

STATEMENT 13: Immunotherapy, namely immune checkpoint inhibitors (ICIs) such as anti-programmed cell death protein 1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) should be avoided during pregnancy and deferred until delivery. Carboplatin instead of cisplatin should be preferred as it has a more favorable fetal toxicity profile (V).

DISCUSSION: PD-1/PD-L1 interactions have been shown to play a key role in immunotolerance of the mother towards the paternal alloantigens of the fetus.[65] In addition, PD-L1 is a negative regulator of the maternal alloimmune responses and blockade of this pathway could result in enhanced fetal rejection. ICIs pass the placenta after the 14th week of gestation.[66] Hence ICIs could potentially result in an immune response against the fetus. Very few reports exist on the administration of anti-PD-1/PD-L1 during pregnancy, mostly in malignant melanoma.[67] Several fetal adverse events were reported, albeit many of them could be also related to preterm delivery which occurred in most of the patients. However, intrauterine growth restriction and placental insufficiency were described in 4/7 patients treated with ICI underscoring the potential interference of these drugs with placental and fetal development. Of note, immune-related adverse events were reported in at least two patients,[68,69] including a neonatal hypothyroiditis.[70] Therefore, maternal benefit should be carefully balanced against the potential fetal side-effects.

Several reports have been published on the safety of platinum salts administration during pregnancy, mostly in an ovarian cancer setting. Short-term fetal outcomes appear to be reassuring, mostly with carboplatin.[71,72] However, it is worth noting that data from baboon models have pointed out to a high transplacental passage of carboplatin to the fetus, with exposure up to 50% of that of the mother.[58,73] Ototoxicity has been described in children antenatally exposed to cisplatin.[74]

In patients diagnosed with early TNBC eligible to neoadjuvant therapy, recent data have shown that the addition of anti-PD-1 therapy to carboplatin and paclitaxel followed by standard anthracycline-based regimens considerably improve pCR and event-free survival.[75,76] At this time until more pregnancy data are available, immunotherapy should be deferred until after delivery. A preclinical study found that immune checkpoint inhibition increases immune cell infiltration and tumor necrosis factor-α expression within the ovary, diminishes the ovarian follicular reserve and impairs the ability of oocytes to mature and ovulate.[70] These data demonstrate that ICIs have the potential to impair both immediate and future fertility, and studies in women should be prioritized. Additionally, fertility preservation should be strongly considered for women receiving these immunotherapies, and preventative strategies should be investigated in future studies.[77] If diagnosed during pregnancy, the preference is to start with anthracycline-based regimens first for a total of four cycles. Thereafter, should the patient still require treatment pre-partum, carboplatin in combination with weekly paclitaxel can be administered subsequently until delivery. Anti-PD-1 could be added to the neoadjuvant therapy following delivery.

21 agree, 0 disagree, 3 abstain
100% consensus

QUESTION 14: In patients diagnosed with metastatic disease during pregnancy not candidates for treatment with anthracyclines, what are the treatment options that could be considered?

STATEMENT 14: Treatment decision making in metastatic disease should be based on the biology and extent of the disease (i.e. imminent organ failure). Single-agent paclitaxel, carboplatin and to a lesser extent vinorelbine could be considered starting in the second trimester. Tamoxifen, poly ADP-ribose polymerase (PARP) inhibitors or CDK4/6 inhibitors, HER2-targeted therapy (including antibody—drug conjugates) and ICIs such as anti-PD-1/PD-L1 and anti-cytotoxic T lymphocyte-associated antigen-4 should be avoided during pregnancy (V).

DISCUSSION: Weekly paclitaxel remains the first-choice option in patients not candidates for treatment with anthracyclines.[78] Unlike 3-weekly docetaxel, this regimen is better tolerated, not associated with high risk of neutropenia, has a short nadir period and does not require steroid premedication. Other options could include carboplatin and vinorelbine, albeit data are more limited particularly for the latter.

On the contrary, targeted agents have different structures (small molecules versus monoclonal antibodies) and different considerations apply. The fetal effect will depend on the

presence or absence of the respective target. Generalization of fetal effects is therefore not possible, instead each targeted agent needs a separate assessment. Hormonal therapies, namely tamoxifen, are contraindicated during pregnancy. It was shown to induce abnormalities in the development and function of the reproductive tracts of female offspring.[79] Human reports were mostly in patients who became accidentally pregnant while being on tamoxifen. Several congenital malformations were reported, including ambiguous genitalia in girls exposed to tamoxifen *in utero*.[80] The risk of fetal malformations and complications is estimated to be high, more than 20% with tamoxifen exposure.[81]

No data exist on the use of PARP or CDK4/6 inhibitors during pregnancy. In mouse models, PARP1 up-regulation is vital for embryo implantation.[82] In addition, PARP inhibition might result in decidualization failure and pregnancy loss.[83] CDK4/6 inhibitors, on the other hand, were shown to cross the placental barrier in different animal species.[84] This does not constitute a strong argument to opt against its use during pregnancy, given that most chemotherapeutic agents cross the placenta as well. However, the lack of data in humans, and the usual combination with teratogenic hormonal therapies, argue against their use in this setting.

Administration of anti-HER2-targeted agents should be delayed until delivery. Data are mainly available for trastuzumab, but the recommendation is probably applicable to all anti-HER2-targeting agents. Trastuzumab administration during the second and third trimesters is associated with high risk of oligohydramnios, which predisposes to preterm delivery, fetal asphyxia and mortality.[85] The risk is considered high and related to the number of trastuzumab infusions. Neonatal respiratory problems are attributed to transplacental transfer of trastuzumab starting from the week 14 of gestation and its inhibitory effect on the fetal kidney—the organ responsible for amniotic fluid production—as it expresses HER2.[86]

Considering the major safety concern associated with the administration of several agents that have been shown to improve survival in the metastatic setting, each patient should be properly counseled regarding the risk associated with not administering these agents on her prognosis, versus the risk of fetal complications if they were administered during gestation. Pregnancy termination remains a possibility that should be discussed as well in such cases. Pregnancy termination does not improve the prognosis. Another option is starting (neo)adjuvant therapy with chemotherapy alone and adding anti-HER2 therapy after delivery as in the HERA study.[87] Latrogenic preterm delivery in this context in order to start anti-HER2 therapy early might be discussed and the risks of this must be weighed against the potential minimal benefit of an earlier start of anti-HER2 therapy. Nevertheless, multiple factors could influence patient decision (social, cultural, religious belief, etc.). Thus, it is of utmost importance that she understands every consequence of the different options to make a fully informed decision.

19 agree, 1 disagree, 4 abstain
95% consensus

QUESTION 15: Could granulocyte colony-stimulating growth factors (G-CSF) safely be used during pregnancy?

STATEMENT 15: G-CSF could be used during pregnancy, if clinically indicated (V).

DISCUSSION: Transplacental passage of G-CSF has been demonstrated in several studies.[88,89] In cancer patients, case reports and case series were reported,[90-92] showing pregnancy outcomes comparable to what is expected without the administration of G-CSF. Importantly, in one study, no major neurological or functional cardiological abnormalities were found in children almost 2 years after delivery.[90] Other non-oncology studies have also evaluated the use of G-CSF to treat chronic neutropenia.[93-95] None of these studies found an increased incidence of fetal death or congenital malformation, which is reassuring. Of note, a study showed that neonates born to mothers who received G-CSF shortly before delivery had increased neutrophil count compared to the control group.[88] Thus, if clinically indicated, short- or long-acting G-CSF could be administered during pregnancy as it does not appear to be associated with considerable fetal risk.

20 agree, 0 disagree, 4 abstain
100% consensus

QUESTION 16: How to counsel women who become accidentally pregnant on adjuvant anti-HER2-targeted therapy?

16.a) STATEMENT: Once pregnancy is confirmed, it could be allowed to continue if the decision to stop anti-HER2 treatment is taken following discussion of recurrence risks. Brief exposure to HER2-targeted therapy early in the first trimester does not appear to be associated with risk of congenital malformations. It is mandatory to discuss adequate contraception with patients on adjuvant anti-HER2-targeted therapy (V).

DISCUSSION: Transplacental models in different species have shown no transplacental passage of immunoglobulins early in pregnancy.[66] As monoclonal antibodies are large molecules exceeding 100 kDa, they cannot be transported across the placenta by simple diffusion, but require active transport via a specific receptor-mediated mechanism that is activated starting week 14 of gestation.[86] Thus, accidental exposure to anti-HER2 therapy early in pregnancy is unlikely to impact the fetus.

These data have been further confirmed in the HERA, ALTTO and NeoALTTO trials which investigated trastuzumab or its combination with lapatinib.[86,96] No congenital malformation was observed in any of the pregnancies. Short-term neonatal outcomes were favorable. No data about safety of pertuzumab in this setting are available.

Thus, in women who become accidentally pregnant on adjuvant anti-HER2 therapy, it is reasonable to consider continuing pregnancy, provided stopping anti-HER2 treatment is decided after a thorough discussion of recurrence

risks. Patients should be aware that the data supporting this approach are limited albeit reassuring and in line with transplacental models. It is vital that physicians adopt a proactive approach and promote for adequate contraception in women on adjuvant anti-HER2 therapy to avoid facing such a situation.

19 agree, 1 disagree, 4 abstain
95% consensus

16.b) STATEMENT: Once pregnancy is confirmed, when women with high-risk HER2-positive BC declines to stop anti-HER2 (neo)adjuvant therapy, we need to establish a support process based on shared decision making. In the shared decision-making process, we need to integrate multifaceted information, including cancer stage and relapse risk, weeks of pregnancy and the patient's desire to bear children, and use it to examine viable treatment options (V).

DISCUSSION: Health care professionals may face dilemmas such as limiting or delaying cancer treatment in order to preserve the pregnancy and the choice of cancer treatment versus teratogenic risk. Decision-making support is provided to both the patient and her family. Anti-HER2 treatment without firm evidence that it does not harm cannot be continued. Azim et al.[97] explored the effect of previous or concurrent trastuzumab administration on pregnancy outcome based on data emerging from the HERA trial, one of the largest phase III trials evaluating trastuzumab treatment in the adjuvant setting, and reported that 25% of pregnancies that occurred on or within the first 3 months of stopping trastuzumab treatment resulted in spontaneous abortions.

19 agree, 1 disagree, 4 abstain
95% consensus

QUESTION 17: Could antiemetics and/or steroids be used to manage or prevent chemotherapy-induced nausea and vomiting (CINV) during pregnancy?

STATEMENT 17: Ondansetron, metoclopramide and steroids commonly used for prevention and treatment of CINV could be used to treat nausea and vomiting during pregnancy and are considered to be safe. Steroid of choice in pregnancy is methylprednisolone or prednisolone (V).[78]

DISCUSSION: Metoclopramide 5-10 mg orally, every 6-8 h is commonly used by pregnant women to treat nausea and vomiting of pregnancy. In a meta-analysis of six cohort studies including 33,000 first-trimester women who used metoclopramide and over 37,000 controls, the risk of major congenital defects was not significantly increased (odds ratio 1.14, 99% CI 0.93-1.38).[98]

The use of ondansetron in early pregnancy has not been linked to a high risk of congenital defects, but a marginal relative increase in cleft palate and cardiovascular malformations (septum defects in particular) has been described. This risk has been shown to be small (0.03% absolute increase in orofacial and 0.3% in ventricular septal defects).[99] Data on the safety of 5-hydroxytryptamine receptor subtype 3 (5-HT3) antagonist other than ondansetron are limited.

Glucocorticosteroids have been shown to cause an increase in oral clefts incidence when used before 10 weeks of gestation.[100] If administered after 10 weeks, there are no concerns since the palate has been formed.[101] Use of betamethasone or dexamethasone as premedication is discouraged due to an almost 100% placental passage to the fetus, and these are better replaced by steroids that are metabolized in the placenta including methylprednisolone, prednisolone or hydrocortisone.

There are no human data regarding the safety of neurokinin-1 (NK-1) antagonists during pregnancy, but the first-generation agent aprepitant has been classified by the Food and Drug Administration as pregnancy class B under the prior system of pregnancy risk category classification. The injection formulation, however, contains ethanol and its use should be avoided.[102] Finally, exposure to second-generation antipsychotics like olanzapine has been linked to increased risk for ventricular and septal defects.[103] Both aprepitant and olanzapine should be used when absolutely necessary and after discussion of expected benefit and potential risks.[78]

20 agree, 1 disagree, 3 abstain
95.24% consensus

WP3: Obstetric care and fetal/newborn follow-up and outcomes: metastases to fetus, management of pregnancy during anticancer therapy, lactation, psychological support

QUESTION 18: As a pregnant patient with BC, what additional procedures or testing is suggested in addition to routine prenatal care?

STATEMENT 18: Pregnant patients with cancer, especially those receiving chemotherapy, need additional ultrasounds (q3-4 weeks) to document adequate-interval fetal growth. Fetal umbilical artery Doppler exams should be added in case of growth restriction and considered to evaluate fetal anemia via measurements of the peak systolic velocity (PSV) of the fetal middle cerebral artery when chemotherapy is administered (V).

DISCUSSION: Patients with (metastatic) BC need intensified obstetric surveillance and oncology care. Complications during or after chemotherapy during pregnancy might include fetal growth restriction, fetal anemia and preterm birth. Close monitoring of the fetus should be carried out to document adequate-interval fetal growth and the PSV measurement should be used for detection of fetal anemia.[104] In addition, many pregnant women with BC have no family history of BC and are the index case for their families. Due to the young age of the patients in this group, genetic counseling is suggested to discuss the role of testing for *BRCA1/2* germline mutations.

22 agree, 0 disagree, 2 abstain
100% consensus

QUESTION 19: Is the timing or mode of delivery affected by having PrBC?

STATEMENT 19: The mode or timing of delivery is not affected by a diagnosis of PrBC, provided myelosuppression from cytotoxic chemotherapy is avoided by stopping the latter at week 35 for weekly schedules. The need for postpartum treatment may affect a decision to induce at 37 weeks rather than await spontaneous birth up to 41 weeks (II).

DISCUSSION: Decision making about the obstetric management and oncological treatment in pregnancy should be carried out in a specialized center and balance maternal and fetal risks by a multidisciplinary team with patient input. The current view for BC patients is that the treatment stays as close as possible to standard treatment. From the second trimester onwards, chemotherapy is considered as relatively safe.[105] In the management of this, patient evaluation and monitoring of maternal and fetal well-being is important, especially after chemotherapy exposure. Spontaneous contractions may occur during or after chemotherapy, but do not lead to labor in most cases. However, the most commonly reported neonatal outcome is still the high incidence of iatrogenic preterm delivery in pregnancies complicated by cancer because delivery is mostly planned to optimize the timing of treatment.[71] Ideally, in an otherwise uncomplicated pregnancy, iatrogenic delivery should be avoided before 37 weeks of gestation to reduce compromised neonatal outcome.[105] It is recommended to pause chemotherapy with (3-weekly) doxorubicin/epirubicin/cyclophosphamide by around 35 weeks, and with (weekly) paclitaxel by 35-36 weeks and wait 2-3 weeks, respectively, before delivery, to avoid myelosuppression. Three weeks after the last cycle, paclitaxel was not detectable in the fetal blood.[106]

As there is no absolute obstetric or oncological contraindication for a vaginal delivery, this should be aimed for. The reported higher caesarean (C)-section rate for pregnant women with cancer is for non-obstetrical indications, physician and patient preference, not a higher risk for non-reassuring fetal status, higher breech or other indications for C-section.

After delivery, the placenta should be sent for histopathological examination. Chemotherapy can resume within a few days after a vaginal birth and 7 days after C-section if no evidence of infection and the patient's incision is healing well.

23 agree, 1 disagree
95.83% consensus

QUESTION 20: What are the anesthetic goals for BC surgery in pregnancy?

STATEMENT 20: Pregnant women after 20 weeks should be positioned with left uterine displacement and adequate maternal oxygenation and optimal uteroplacental perfusion should be ensured during the entire case (II).

DISCUSSION: A surgery can be carried out safely during pregnancy, as long as some anesthetic adjustments are made.[107-109] The goal during surgery is adequate maternal oxygenation and optimization of uteroplacental perfusion, and strategies to avoid hypoxemia, hyperoxia, hypotension, acidosis (hypercarbia), intraoperative awareness and hyperventilation (respiratory alkalosis) are the most critical elements of anesthetic management.[110] Multimodal analgesia including regional analgesia techniques, infiltration with local anesthetics and opioid use on an as-needed basis are safe in pregnancy.[111,112] Between the third and fifth week after conception when gastrulation occurs, surgery can best be avoided because of the possible association with neural tube defects, otherwise anesthesia and surgery are safe if indicated, during the first trimester.[113]

Postoperatively adequate pain relief is essential to prevent reactive preterm contractions. Paracetamol is the analgesic of choice for the treatment of mild to moderate pain during any stage of pregnancy. If not adequate, short-term narcotic use is also safe. Nonsteroidal anti-inflammatory drugs can inhibit uterine contraction, but should be avoided, particularly after 28 weeks of gestation because they may cause premature closure of the fetal ductus arteriosus and oligohydramnios as they reduce fetal renal function mainly if administered for >48 h.

Pregnant patients with cancer having surgery should undergo risk assessment for thromboembolism because they are at very high risk for venous thromboembolism. After C-section they should receive low-molecular-weight heparin and in case of bedrest whenever possible pneumatic compression of the lower legs. In addition, discussion of possible fetal adverse effects of surgery and after viability of fetus obtaining consent for emergency C-section in case of exceptional severe complications should be carried out.

17 agree, 0 disagree, 7 abstain
100% consensus

QUESTION 21: Is there a prerequisite monitoring for fetal safety in pregnant BC surgery?

STATEMENT 21: In BC surgery during pregnancy if the fetus is considered to be previable, fetal heart tones should be auscultated before and after surgery; if the fetus is viable, simultaneous electronic fetal heart rate and contraction monitoring can be carried out during the procedure to assess fetal well-being and the absence of contractions (V).

Discussion: Patients should be monitored in the perioperative period for signs or symptoms of preterm labor.[109] If previable, auscultation of cardiac activity should be carried out before and after the procedure. No monitoring would otherwise be necessary during the procedure. If the fetus is viable, simultaneous electronic fetal heart rate and contraction monitoring should be carried out before and after or even during the procedure to assess fetal well-being and the absence of contractions. When surgery is carried out at around 24-26 weeks of gestation, it should be discussed whether the future parents desire an active fetal management with intervention in case of maternal or fetal emergencies. On the other hand, there are no data on the

Table 1. Cytotoxic agents in relation to breast-feeding

Agent	Protein binding (%)	Half-life	Waiting period suggested between the last chemo in pregnancy and breast-feeding	Comment	References
Doxorubicin	75	20-48 h	14 days	—	Codacci-Pisanelli et al.[115]
Epirubicin	55	40 h	14 days	—	—
Cyclophosphamide	13	~7.5 h	5 days	Bone marrow suppression reported in 2 neonates while simultaneously receiving chemotherapy	—
Docetaxel	95	11 h	3 days 1 week	—	Manufacturer
Paclitaxel	~89-98	13-52h	15 days	—	—
Carboplatin	85-89	6 h	N/A	—	Manufacturer

incidence of perioperative fetal distress during cancer surgery and the general feeling is that this is a very rare event.

Depending on the risk of prematurity and gestational age, the obstetrician will decide on the need for steroids for fetal lung ripening. Up until 24 weeks, pre-operative cervical length screening can be considered before the procedure to decide about risk of prematurity if the patient has a history of preterm birth.

20 agree, 0 disagree, 4 abstain

100% consensus

QUESTION 22: In pregnancies complicated by BC and treatment with chemotherapy before birth, how is lactation affected?

STATEMENT 22: Surgery involving the areola or nipple complex will affect breast-feeding. If a patient has a mastectomy, the infant can receive adequate milk from a single breast. Patients receiving chemotherapy are currently advised not to breast-feed because of the possible presence of chemotherapy in breast milk and the cytotoxic effects to the infant. During postpartum radiation therapy, it is 'not' recommended to breast-feed or stimulate milk production from the treated breast. Depending on the gestational age when chemotherapy started, and the number of cycles, chemotherapy during pregnancy may affect the amount of milk produced (V).

Discussion: Data on infant safety on oncological treatment during breast-feeding are scarce.[114] Patients receiving chemotherapy are currently advised not to breast-feed because of the possible presence of chemotherapy in breast milk and the cytotoxic effects to the infant. In addition, after chemotherapy during pregnancy, many women report a decreased milk supply. The earlier gestational age at treatment and the increasing number of cycles are significantly related to decreased breast milk production. During postpartum radiation therapy, it is 'not' recommended to breast-feed or stimulate milk production in any way from the treated breast. Radiation does not affect the safety of the milk, but in the radiated breast mastitis is difficult to treat and breast-feeding from the radiated breast is not recommended.

If a patient is discouraged from breast-feeding due to the need to receive chemotherapy, there is a benefit to the infant (and to the mother's birth experience) to provide the infant with colostrum.

Table 1 gives an overview of the different agents and their half-lives for women to decide if enough time has passed between chemotherapy during pregnancy and delivery.

Recently, a study was carried out testing actual breast milk for evidence of chemotherapy in three patients providing milk for analysis while undergoing chemotherapy. Damoiseaux et al.[59] just recently in 2022 suggest that breast-feeding in between cycles is an option as well. Three patients collected 24-h samples of breast milk every day for 1, 2 or 3 weeks after chemotherapy, with a total of 210. After determination of drug concentrations, the infant daily dose, relative daily infant dose (RID%) and cumulative RID were calculated. Cumulative RIDs in patients varied from 10% to values lower than 1%. Rich data allowed us to design a table which gives predictions on the number of days that breast milk has to be discarded to reach cumulative RIDs below 5%, 1% and 0.1% for each compound. For cyclophosphamide, paclitaxel and carboplatin, cumulative RIDs below 1% or 0.1% are reached if breast milk is discarded for 1-3 days after administration. However, still safety data are very limited.

On an individual basis, the patient may be able to provide colostrum to her infant before starting chemotherapy postpartum.

22 agree, 1 disagree, 1 abstain

95.65% consensus

QUESTION 23: How do we address the additional psychological support that may be required for pregnant women with cancer and their families?

STATEMENT 23: Psychological support is required for the families that are confronted with cancer during pregnancy. The need is higher in case of lower coping strategy. Not all women/families need this support; it is suggested to individualize according to the patient's and partner's needs (V).

DISCUSSION: Since cancer or cancer treatment represents a physical and psychological burden for pregnant women, this can lead to stress during pregnancy and postpartum. Even before the diagnosis of cancer, pregnant women are dealing with increased stress in a major life transition involving emotional and physical changes.[116-121]

Table 2. Overview of working packages and main statements

Questions		Statements
WP1: BC during pregnancy: incidence, epidemiology, biology and pathology. Diagnostic work-up, staging and risk assessment, prognosis		
1	Is BC diagnosed during pregnancy distinct from that diagnosed during the postpartum period?	BCs diagnosed in the postpartum period are biologically distinct from those diagnosed during pregnancy. Given the biological differences and unique challenges associated with managing BC during pregnancy, future studies should aim to study each group independently (III).
2	What is the likely reason for the recent increasing trend in diagnosed BC during pregnancy?	The rising trend of delaying childbearing to later in life appears to be the most likely reason to the increasing diagnosis of BC during pregnancy (III).
3	Could genomic assays be used to refine the risk of recurrence and to inform on the type of adjuvant systemic therapy in pregnant patients with ER+ disease?	Debate exists on the performance of genomic assays in stratifying risk of premenopausal women. They can be considered to assist in decision making in pregnant women with ER+ BC, but patients should be informed about potential limitations in the risk assessment and the limited level of evidence, especially in the pregnant population (V).
4	What diagnostic imaging modalities should be used for diagnosis and locoregional staging in BC during pregnancy?	Breast ultrasound is the first-line imaging modality for primary tumor assessment and staging of regional and supraclavicular lymph nodes and is complemented by mammography (III) or—in selected cases—MRI with diffusion-weighted sequence to aid in delineation of tumor extent and multifocality (IV).
5	What is the optimal imaging strategy for systemic staging of BC during pregnancy?	Locoregional tumor stage determines the staging strategy during pregnancy. Chest X-ray and abdominal ultrasound are easily accessible for initial screening of metastases. If inconclusive or if there is a high risk of metastases, additional non-contrast MRI with DWI sequence of the full-spine and pelvic bone and liver combined with chest CT are suggested. When available onsite, whole-body MRI with diffusion-weighted sequence (WB-DWI/MRI) is recommended as a single-step staging modality (III).
6	Does BC during pregnancy have different biological features compared to BC in patients of the same age and stage?	Limited biological differences exist in tumors when diagnosed during pregnancy. Yet, to date, this does not appear to have an important impact on patient management (III).
7	Does BC during pregnancy have worse prognosis compared to BC in young patients of the same stage and disease subtype?	Prognosis of BC diagnosed during pregnancy is similar to that of young BC patients with the same stage and disease subtype provided it is adequately managed (II).
8	Is NIPT as reliable in patients with BC during pregnancy?	Positive NIPT is less reliable when carried out in pregnant BC patients. An abnormal NIPT must be confirmed by a diagnostic test before a final decision is made (III).
WP2: Clinical pharmacology of systemic agents during pregnancy. Management of localized disease and (neo) adjuvant therapies. Management of systemic disease		
9	When can chemotherapy be safely administered during pregnancy?	Chemotherapy is contraindicated in the first trimester of gestation to avoid interference with organogenesis; fetal benefit of treatment delay until the second trimester should be balanced against maternal risk (V).
10	Are chemotherapy dose adjustments required when treating pregnant BC patients?	Chemotherapy standard doses should be used during pregnancy without adjustments. Actual weight should be used to calculate the chemotherapy dose (V).
11.a	Can we safely deliver radiation therapy to women during pregnancy?	The delivery of radiation therapy is not contraindicated *per se*. The radiation dose to the fetus depends on the distance from the radiation target volumes and on radiation therapy parameters including prescribed dose, size and site of the target volumes combined with technical parameters. Importantly, the radiation sensitivity of the fetal tissues and thereby the radiation-related toxicity risks depend on the gestational age.[132] Therefore, stage of pregnancy combined with radiation therapy-related parameters determine the risks.[133]
11.b		During the first and most of the second trimester, irradiation to the supradiaphragmatic region should not be associated with high fetal exposure, if appropriate after supplementary pelvic shielding (using mobile lead shield to be positioned between the source of the radiation and at sufficient distance from the patient).[134-137] Thus, it could be considered, specifically if postponing until delivery could have a detrimental impact on prognosis (III).
12	Could SLN biopsy be carried out as in the non-pregnancy setting?	SLN biopsy can be carried out during pregnancy using low-dose technetium (Tc)-labelled albumin nanocolloid. Allergic reaction has been reported with blue dye and thus should be avoided during pregnancy (V).
13	In patients diagnosed with early TNBC who are candidates for neoadjuvant therapy, can we deliver platinum salts and/or immunotherapy during pregnancy?	Immunotherapy, namely ICIs such as anti-PD-1 and anti-PD-L1, should be avoided during pregnancy and deferred until delivery. Carboplatin instead of cisplatin should be preferred as it has a more favorable fetal toxicity profile (V).
14	In patients diagnosed with metastatic disease during pregnancy not candidates for treatment with anthracyclines, what are the treatment options that could be considered?	Treatment decision making in metastatic disease should be based on the biology and extent of the disease (i.e. imminent organ failure). Single-agent paclitaxel, carboplatin and, to a lesser extent, vinorelbine could be considered starting in the second trimester. Tamoxifen, PARP inhibitors or CDK4/6 inhibitors, HER2-targeted therapy (including antibody—drug conjugates) and ICIs such as anti-PD-1/PD-L1 and anti-CTLA-4 should be avoided during pregnancy (V).
15	Could G-CSF safely be used during pregnancy?	G-CSF could be used during pregnancy, if clinically indicated (V).

Continued

Table 2. Continued

Questions		Statements
16.a	How to counsel women who become accidentally pregnant on adjuvant HER2-targeted therapy?	Once pregnancy is confirmed, it could be allowed to continue if a decision to stop anti-HER2 treatment is taken following discussion of recurrence risks. Brief exposure to HER2-targeted therapy early in the first trimester does not appear to be associated with risk of congenital malformations. It is mandatory to discuss adequate contraception with patients on adjuvant HER2-targeted therapy (V).
16.b		Once pregnancy is confirmed, when a woman with high-risk HER2-positive BC declines to stop anti-HER2 (neo)adjuvant therapy, we need to establish a support process based on shared decision making. In the shared decision-making process, we need to integrate multifaceted information, including cancer stage and risk, weeks of pregnancy, and the patient's desire to bear children, and use it to examine viable treatment options (V).
17	Could antiemetics and/or steroids be used to manage or prevent chemotherapy-induced nausea/vomiting during pregnancy?	Ondansetron, metoclopramide and steroids commonly used for prevention and treatment of CINV could be used to treat nausea and vomiting during pregnancy and are considered to be safe. Steroid of choice in pregnancy is methylprednisolone or prednisolone (V).[78]
WP3: Obstetric care and fetal/newborn follow-up and outcomes, metastases to fetus. Management of pregnancy during anticancer therapy. Lactation. Psychological support		
18	As a pregnant patient with BC, what additional procedures or testing is suggested in addition to routine prenatal care?	Pregnant patients with cancer, especially those receiving chemotherapy, need additional ultrasounds (q3-4 weeks) to document adequate-interval fetal growth. Fetal umbilical artery Doppler exams should be added in case of growth restriction and considered to evaluate fetal anemia via measurements of the PSV of the fetal middle cerebral artery when chemotherapy is administered (V).
19	Is the timing or mode of delivery affected by having BC during pregnancy?	The mode or timing of delivery is not affected by a diagnosis of BC during pregnancy, provided myelosuppression from cytotoxic chemotherapy is avoided by stopping the latter at week 35 for weekly schedules. The need for postpartum treatment may affect a decision to induce at 37 weeks rather than await spontaneous birth up to 41 weeks (II).
20	What are the anesthetic goals for BC surgery in pregnancy?	Pregnant women after 20 weeks should be positioned with left uterine displacement and adequate maternal oxygenation, and optimal uteroplacental perfusion should be ensured during the entire case (II).
21	Is there a prerequisite monitoring for fetal safety in pregnant BC surgery?	In BC surgery during pregnancy if the fetus is considered to be previable, fetal heart tones should be auscultated before and after surgery; if the fetus is viable, simultaneous electronic fetal heart rate and contraction monitoring should be carried out during the procedure to assess fetal well-being and the absence of contractions (V).
22	In pregnancies complicated by BC and treatment with chemotherapy before birth, how is lactation affected?	Surgery involving the areola or nipple complex will affect breast-feeding. If a patient has a mastectomy, the infant can receive adequate milk from a single breast. Patients receiving chemotherapy are currently advised not to breast-feed because of the possible presence of chemotherapy in breast milk and the cytotoxic effects to the infant. During postpartum radiation therapy, it is not recommended to breast-feed or stimulate milk production from the treated breast. Depending on the gestational age when chemotherapy started, and the number of cycles, chemotherapy during pregnancy may affect the amount of milk produced (V).
23	How do we address the additional psychological support that may be required for pregnant women with cancer and their families?	Psychological support is required for the families that are confronted with cancer during pregnancy. The need is higher in case of lower coping strategy. Not all women/families need this support; it is suggested to individualize according to patient's and partner's needs (V).
24	What additional surveillance is required for the newborns after a pregnancy complicated by BC and/or therapy?	Careful pediatric examination should take place after birth, especially after chemotherapy during pregnancy, for major and minor anomalies, birthweight percentile by gestational age at birth. Long-term surveillance of children prenatally exposed to BC and therapy is also important to document normal neurocognitive and emotional development (V).
25	Is there evidence that exposure of fetus to anesthetic drugs in BC surgery has any effect in the developing brain or teratogenic effects?	Clinical experience does not suggest teratogenicity or adverse effects on the developing brain after uncomplicated surgery and exposure to anesthetic drugs (V).

BC, breast cancer; CINV, chemotherapy-induced nausea and vomiting; CT, computed tomography; CTLA, cytotoxic T lymphocyte-associated antigen; DWI, diffusion-weighted imaging; ER, estrogen receptor; G-CSF, granulocyte colony-stimulating growth factors; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; NIPT, noninvasive prenatal testing; SLN, sentinel lymph node; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PSV, peak systolic velocity; TNBC, triple-negative breast cancer.

Henry et al.[117] compared the stress experienced by pregnant women with cancer to non-pregnant women as well as pregnant women without cancer. Women diagnosed with cancer during pregnancy reported greater distress compared to the other two groups. Clinical distress was significantly related to being advised to terminate their pregnancy after the cancer diagnosis, intrusive thoughts and anxiety, the need for C-section or insufficient breast milk production.

Vandenbroucke et al.[122] reported about coping strategies for couples dealing with a cancer diagnosis during pregnancy. Both women and their partners were concerned about the

child's health; however, couples using internalizing strategies deal with the highest levels of distress and therefore they may benefit from additional psychosocial support.

In general, surveillance of offspring from mothers born after exposure to breast cancer and its treatment is strongly advised for early identification of general as well as specific organ toxicities, general health issues and neurocognitive, behavioral and neuromotor sequelae, as standard of care in dedicated critical illness polyneuropathy-offspring expert centers.

23 agree, 1 disagree
95.83% consensus

QUESTION 24: What additional surveillance is required for the newborns after a pregnancy complicated by BC and or its therapy?

STATEMENT 24: Careful pediatric examination by a neonatologist should take place after birth, especially after chemotherapy during pregnancy, for major and minor anomalies, and birthweight percentile by gestational age at birth. Long-term surveillance of children prenatally exposed to BC and therapy is also important to document normal neurocognitive and emotional development (V).

DISCUSSION: In these high-risk pregnancies, a consultation by a neonatologist or pediatrician shortly after birth is ideally to confirm that the newborn is healthy, to inform the families regarding follow-up, and to support them by giving information and access to specialized medical surveillance and psychosocial family care. After chemotherapy exposure *in utero*, it is recommended that a complete blood count with differential is collected. Preterm and small-for-gestational-age infants require specific neonatal follow-up care. Depending on the anticancer drugs used in pregnancy, specific evaluation for side-effects of chemotherapy in the newborn might be recommended. In case of treatment with anthracyclines during pregnancy, an echocardiogram in the first weeks is advised. After platinum compounds and postnatal aminoglycosides exposure screening for ototoxic effects is advised throughout infancy.[74]

Although the results of the follow-up studies are currently reassuring for the development of the children prenatally exposed to maternal cancer, the associated stress, diagnostic imaging as well as treatments showed that chemotherapy during is possible and safe after the first trimester. Subtle differences in the development of these children emphasize the recommendation for long-term follow-up.[123-126]

Vandenbroucke et al.[127] compared the values of electrocardiogram and echocardiographic assessments between children aged 6 prenatally exposed to chemotherapy and a control group. They found higher diastolic blood pressure in 78 chemotherapy-exposed children versus control children and in a subgroup of 59 anthracycline-exposed versus control children. In this study also the cognitive values were compared. Although no significant differences were identified in most cognitive functions and behavior, children from the cancer in pregnancy group had lower values in verbal IQ and in visuospatial long-term memory outcomes. The differences in verbal IQ were larger in children whose mothers died.

In addition, in a study by van Gerwen et al.[128] parents of children prenatally exposed to chemotherapy reported more difficulties related to emotional control of their children than parents of children in the control group. Children exposed to antenatal maternal anxiety reported more overall problems in behavior, emotional symptoms, peer relationship problems, conduct problems and less prosocial behavior at age 5 years.

To conclude, in children prenatally exposed to hematological malignancies, the needs for supportive care in the child were associated with the loss of the mother.[129] Together, these studies showed that longitudinal follow-up of the offspring is recommended and surveillance of emotional development is important. Early screening of emotional development may prevent difficulties in emotion regulation.

23 agree, 1 disagree
95.83% consensus

QUESTION 25: Is there evidence that exposure of fetus to anesthetic drugs in BC surgery has any effect in the developing brain or teratogenic effects?

STATEMENT 25: Clinical experience does not suggest teratogenicity or adverse effects on the developing brain after uncomplicated surgery and exposure to anesthetic drugs (V).

DISCUSSION: Clinical experience does not suggest teratogenicity or adverse effects on the developing brain after uncomplicated surgery and exposure to anesthetic drugs.[109] However, there are no human studies of miscarriage or teratogenicity for sugammadex; therefore, at the present time it should be avoided.[130] Incorporating paravertebral block into the anesthetic technique could provide significant results concerning acute, chronic and chronic neuropathic pain.[131]

21 agree, 0 disagree, 3 abstain
100% consensus

CONCLUSION

This consensus statement paper aims to update recommendations on PrBC previously published in the medical literature with critical updates and reflections of recently emerged data.[78] A summary of working packages and main statements is listed in Table 2.

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