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Society for Maternal-Fetal Medicine Consult Series #76: Cancer in pregnancy

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Abstract

Approximately one in 1000 pregnancies is complicated by the diagnosis of cancer each year, and the incidence of cancer among reproductive-age individuals is increasing. Management of a pregnant person with cancer can be complex and warrants a multidisciplinary approach to care. Recent data have demonstrated reassuring outcomes for pregnant persons and their offspring after treatment of many types of cancer in pregnancy. Treatment of cancer in pregnancy must be individualized based on the specific type and stage of cancer, gestational age at diagnosis, and the patient's desire to continue the pregnancy. This document aims to aid clinicians by summarizing the principles of diagnosing cancer in pregnancy and counseling patients about their reproductive and treatment options. It provides current, evidence-based recommendations for the medical and obstetrical management of patients with cancer. The following are the Society for Maternal-Fetal Medicine recommendations: (1) we suggest that ultrasonography and non-contrast magnetic resonance imaging (MRI) be used as first-line imaging techniques in the evaluation of a pregnant person with suspected cancer (GRADE 2B); (2) although non-contrast MRI and ultrasonography are first-line diagnostic imaging modalities in pregnancy, we recommend that computed tomography (CT) with or without contrast, gadolinium contrast for MRI, and fluorine-18-fluorodeoxyglucose positron emission tomography plus CT (18-FDG-PET/CT) not be withheld from a pregnant person if clinically indicated (GRADE 1C); (3) we recommend initiating thromboprophylaxis for all patients with active hematological or gynecological cancers during pregnancy and considering thromboprophylaxis for all patients with non-hematological or nongynecological cancers during pregnancy, based on individual risk factors (GRADE 1C); (4) we recommend that surgery for the treatment of cancer not be delayed or withheld from a pregnant patient at any gestational age in pregnancy (GRADE 1C); (5) we recommend that chemotherapy generally be administered after 12 weeks of gestation, provided that the patient desires to continue

the pregnancy and that delaying treatment until after 12 weeks of gestation is not expected to significantly change the pregnant patient's prognosis compared with initiating treatment immediately after diagnosis (GRADE 1C); (6) to improve long-term neurodevelopmental outcomes of children exposed to chemotherapy in utero, we suggest avoiding clinician-initiated preterm delivery when possible (GRADE 2C); (7) we recommend intravenous methylprednisolone, 62.5 mg (corresponding to 10 mg of dexamethasone), or oral prednisolone, 30 mg (corresponding to 6 mg of dexamethasone), as first-line therapy for chemotherapy-induced nausea when corticosteroids are indicated (GRADE 1B); (8) we recommend serial fetal growth surveillance every 3–4 weeks in pregnancies with an active cancer diagnosis, regardless of treatment (GRADE 1C); (9) we recommend initiation of antenatal fetal surveillance starting at 32 weeks of gestation in pregnancies with an active cancer diagnosis, regardless of treatment, unless indicated earlier for maternal or fetal reasons (GRADE 1C); (10) we recommend that planned delivery prior to 37 weeks of gestation in pregnant patients with cancer generally be avoided unless indicated for medical or obstetrical reasons (GRADE 1C); (11) we recommend that chemotherapy treatment generally be stopped by 34 weeks of gestation to allow 3–4 weeks for recovery of myelosuppression before spontaneous labor or planned delivery, except for weekly paclitaxel, which can be administered up to 35 or 36 weeks, as only 1–2 weeks are necessary for recovery before delivery (GRADE 1C); (12) we recommend that the mode of delivery be determined by routine obstetrical indications for most patients with cancer in pregnancy (GRADE 1C); (13) we recommend a placental pathology examination in all cases of cancer during pregnancy, regardless of cancer type or treatment (GRADE 1C); (14) we recommend that cancer be considered as part of the differential diagnosis for pregnant patients with multiple chromosomal aneuploidies or single autosomal monosomy detected by cell-free DNA screening that is discordant with fetal findings (GRADE 1C).

KEYWORDS
cancer, chemotherapy, counseling, delivery, imaging, malignancy, maternal-fetal medicine, pregnancy, thromboprophylaxis

1 | INTRODUCTION

Cancer diagnosed during pregnancy or within 1 year postpartum complicates one in 1000 pregnancies [1]. Breast cancer is one of the most common cancers in pregnancy, affecting up to one in 3000 pregnant people [2]. Three percent of females with Hodgkin lymphoma are pregnant at the time of diagnosis [3], and 10% of thyroid cancers in reproductive-age females are diagnosed during pregnancy or within 1 year postpartum [4]. In recent decades, average maternal age has increased and parity has decreased, yet these changes only partially account for the observed increase in rates of pregnancy-associated cancer [5–8]. Other contributory factors include improved cancer screening and increased exposure to environmental triggers [6–8]. Additionally, the implementation of cell-free DNA (cfDNA) screening has led to an increase in the detection of preclinical or occult malignancies [9–12]. In the United States, the overall incidence of early-onset (i.e., before age 50) cancer has increased since 2010; this increase disproportionately affected female individuals, highlighting the continued relevance of this issue to obstetrical care providers [13].

Management of a pregnant person with cancer requires a multidisciplinary approach to optimize care. Comprehensive person-centered counseling is essential, and each patient should have access to the full range of reproductive options, including abortion care [14]. Historically, a lack of data regarding the potential impact of cancer treatment in pregnancy on the developing fetus led to the

avoidance of oncological therapy during pregnancy [15]. Until recently, postnatal follow-up of the growth and development of children exposed to chemotherapy in utero was limited to case reports, small case series, and retrospective reviews within individual medical systems, which rarely included data beyond 2 years of age [16–20]. The United States Cancer and Pregnancy Registry [21] and the International Network on Cancer, Infertility and Pregnancy [22] prospectively collect diagnostic information and treatment plans as well as newborn developmental follow-up to facilitate large-scale studies and provide comprehensive and standardized guidance for people with cancer and their healthcare providers [23]. The purpose of this Consult is to review general principles in the diagnosis and treatment of cancer in pregnancy, provide evidence-based recommendations for medical and obstetrical management of pregnant individuals with cancer, discuss associated perinatal outcomes, and outline implications for patients with cancer who are considering future pregnancies.

2 | CLINICAL QUESTIONS

2.1 | What are pregnancy-specific considerations for the evaluation and diagnosis of suspected cancer?

In many cases, cancer is more likely to be diagnosed in the postpartum period than antenatally [24]. This occurs as presenting symptoms of cancer (such as palpable breast masses, nipple discharge, fatigue, vaginal or rectal bleeding, anemia, nausea, or bone pain) may be ascribed to common conditions of normal pregnancy, resulting in a delayed diagnosis [25, 26]. However, not all cancer symptoms overlap with pregnancy symptoms. For instance, lymphoma can present with weight loss, cough, and night sweats [27]. During pregnancy, diagnostic studies (e.g., colonoscopy, biopsy) to evaluate a sign or symptom that is concerning for cancer should proceed as if the patient were not pregnant to minimize delays in diagnosis.

Nonionizing imaging studies, such as ultrasonography and non-contrast-enhanced magnetic resonance imaging (MRI), are preferred for the evaluation of suspected cancer or staging cancer during pregnancy [5]. Recent technological innovations have led to the investigation of whole-body diffusion-weighted MRI (WB-DWI/MRI) for the workup and staging of cancer during pregnancy. WB-DWI/MRI evaluates functional tissue properties and tumoral lesions by combining heavy diffusion-weighting and background signal suppression of organs, blood vessels, and body fluids without a contrast agent [28]. A single-center cohort study of 20 pregnant patients with suspected malignancy demonstrated the feasibility of WB-DWI/MRI to identify the primary tumor site and improve the detection of nodal and distant metastases compared with conventional staging (e.g., ultrasonography, radiography, computed tomography [CT], positron emission tomography [PET], or MRI without diffusion-weighting) [28]. **We suggest that ultrasonography and non-contrast MRI be used as first-line imaging techniques in the evaluation of a pregnant person with suspected cancer (GRADE 2B)**.

Although gadolinium-based contrast agents can be useful in evaluating a patient with cancer, gadolinium can cross the placenta [29, 30]. The duration of fetal exposure is unknown, as the fetus can excrete, swallow, and reabsorb gadolinium into the gastrointestinal tract. While there is no direct evidence of toxic effects in humans, there is a theoretical risk. A recent large retrospective cohort study of more than 11 million pregnancies from the United States identified 5991 pregnancies exposed to MRI (including 782 with gadolinium-based contrast agents) and reported no increased risk of fetal or neonatal death associated with gadolinium MRI exposure during pregnancy (adjusted relative risk [RR], 0.73; 95% confidence interval [CI], 0.34–1.55) [31]. Other studies have reported similar reassuring findings of no increased risk of congenital anomalies associated with gadolinium exposure at any time in pregnancy [32]. Although rare, gadolinium exposure has been associated with an increased risk for a broad set of rheumatic, inflammatory, or infiltrative skin conditions in children up to 4 years of age (adjusted hazard ratio [HR], 1.36; 95% CI, 1.09–1.69) [32]. More research is needed to understand the full impact of gadolinium exposure on fetal development.

Fetal harm secondary to radiation exposure during diagnostic studies in pregnancy has not been reported with exposure less than 50 mGy, which is a level above the range of exposure for commonly performed studies, such as a single abdominal and pelvic CT, chest radiograph, or mammogram (Table 1) [33]. Risks of fetal radiation exposure depend on gestational age and dosage (Tables 2 and 3) [34–36]. A small but increased risk for childhood cancers such as leukemia has been associated with in utero exposure to ionizing radiation (a 10–20 mGy exposure increases the risk 1.5–2 times over the background rate of approximately one in 3000 cases) [29]. Although abdominal lead shielding provides reassurance for patients, shielding may increase internal scatter and, thus, the radiation dose to the fetus [37]. Therefore, shielding of the pelvis is no longer recommended [38]. Animal and human studies have not demonstrated any increased risk associated with iodinated contrast despite its ability to cross the placenta and theoretically adversely affect the fetal thyroid [39, 40]. Therefore, iodinated contrast can be used if it improves the diagnostic performance of the imaging study.

TABLE 1 Approximate fetal dose from common diagnostic imaging techniques [35, 41–46].

Conventional radiography	**Mean (mGy[a])**	**Maximum (mGy)**
Abdomen	1.4	4.2
Chest	<0.01	<0.01
Lumbar spine	1.7	10
Pelvis	1.1	4
Skull	<0.01	<0.01
Thoracic spine	<0.01	<0.01
Mammography	Negligible	Negligible
Computed tomography	**Mean (mGy)**	**Maximum (mGy)**
Abdomen/pelvis	10	50[b]
Chest	0.06	0.96
Head	<0.005	0.05
Lumbar spine	2.4	8.6
Nuclear medicine	**Range (mGy)**	
Sentinel node mapping	<0.05-2.2	
Bone scintigraphy	2-3.3	
FDG-PET	1.1-50	

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography.
[a]1 Gy = 1000 mGy = 100 rad.
[b]In contemporary practice, the maximum fetal dose may be lower due to advances in equipment technologies, dose reduction techniques, and radiation awareness initiatives.

While ultrasonography and MRI are favored as initial imaging methods for the workup of cancer in pregnant patients, there may still be diagnostic uncertainty in some cases. CT, fluorine-18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) plus CT, and bone scintigraphy may be considered on a selective basis, particularly when the potential benefits to the patient appear to outweigh fetal risks of exposure and treatment decisions will be affected by the study results [47]. Indeed, emerging evidence suggests that the results of 18-FDG-PET/CT may change cancer staging and treatment in 60% of pregnant people [48]. Techniques such as Foley catheter placement with intravenous hydration to promote washout, using a smaller dose, and doubling image time can reduce fetal radiation exposure [49]. If multiple radiation studies are required, consultation with a radiology specialist or medical physicist to conduct a priori estimates of fetal dose exposure should be considered. **Although non-contrast MRI and ultrasonography are first-line diagnostic imaging modalities in pregnancy, we recommend that CT with or without contrast, gadolinium contrast for MRI, and 18-FDG-PET/CT not be withheld from a pregnant person if clinically indicated (GRADE 1C)**. If needed, obstetricians and maternal-fetal medicine subspecialists should advocate for the necessary imaging modalities.

Lactating patients exposed to iodinated contrast or gadolinium, which have high water solubility, should not interrupt their breastfeeding practices, as less than 0.01% of such contrast would be absorbed in the infant's gastrointestinal tract [29].

2.2 | What are the general therapeutic principles of cancer treatment in pregnancy?

Cancer treatment during pregnancy employs the same curative intent as cancer treatment for nonpregnant patients. This requires balancing the benefits of cancer therapy for the patient against the known risks to the pregnancy from the proposed treatment. Additionally, the risks of delaying cancer treatment must be considered. Whenever possible, therapy should align with the standard of care offered to nonpregnant individuals with the same cancer, including options of surgery, systemic therapy (i.e., chemotherapy or targeted therapy and immunotherapy), and radiation therapy. To support the patient and family, shared decision-making should occur with multidisciplinary counseling from specialists representing maternal-fetal medicine, oncology, general obstetrics, neonatology, and psychology, among other fields.

2.2.1 | Thromboprophylaxis

Both pregnancy and malignancy (especially gynecological and hematological cancers) are risk factors for venous thromboembolism (VTE). Pregnancy increases hypercoagulation and venous stasis, while cancer alters the expression of hemostatic proteins, production of inflammatory cytokines, and adhesion of tumor cells to the endothelium. International guidelines suggest thromboprophylaxis for nonpregnant cancer patients who are hospitalized or undergoing major surgery for cancer, but not for ambulatory patients [50]. However, cancer in pregnancy is associated with an increased risk of VTE independent of antepartum hospitalization or surgical intervention. A 2024 systematic review and meta-analysis involving 5928 pregnant individuals with active malignancy reported a significantly increased likelihood of VTE compared with pregnant patients without cancer (odds ratio [OR], 6.8; 95% CI, 3.8–12.1). Patients with thyroid cancer (OR, 2.7; 95% CI, 1.3–6.3), cervical cancer (OR, 6.6; 95% CI, 2.4–18.0), other gynecological cancers (OR, 10.6; 95% CI, 4.4–25.8), Hodgkin lymphoma (OR, 8.7; 95% CI, 3.3–23.4), or acute leukemia (OR, 17.1; 95% CI, 10.9–26.8) had increased odds

TABLE 2 Adverse effects on offspring of radiation during pregnancy [29, 34].

Gestational age at exposure	Effects	Estimated threshold dose
0–2 weeks	Pregnancy loss (all or none)	50–100 mGy[a]
2–8 weeks	Congenital malformations (skeleton, eyes, genitalia) Fetal growth restriction	200 mGy 200–250 mGy
8–15 weeks	Severe intellectual disability (high risk) Intellectual deficit Microcephaly	60–310 mGy 25 IQ-point loss per 1000 mGy 200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy

[a]1 Gy = 1000 mGy = 100 rad.

TABLE 3 Fetal risks based on radiation dose and gestational age [36].

Gestational age at exposure	Radiation dose		
	<50 mGy[a] (<5 rad)	50–100 mGy (5–10 rad)	>100 mGy (>10 rad)
0–2 weeks	None	None	None
3–4 weeks	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Possible early pregnancy loss
5–10 weeks	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Possible malformations increasing in likelihood as dose increases
11–17 weeks	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Increased risk of deficits in IQ or intellectual disability that increase in frequency and severity with increasing dose
18–27 weeks	None	None	IQ deficits not detectable at diagnostic doses
>27 weeks	None	None	Not applicable to diagnostic medicine

Note: Adapted from [36].
[a]1 Gy = 1000 mGy = 100 rad.

of VTE. In contrast, those with brain cancer, breast cancer, malignant melanoma, or non-Hodgkin lymphoma did not have statistically significant increased odds of VTE compared with pregnant patients without cancer [51]. A retrospective, population-based cohort study reported statistically increased odds of VTE for the following cancers: cervical (OR, 8.6; 95% CI, 2.2–34.8), ovarian (OR, 10.4; 95% CI, 1.4–74.2), Hodgkin disease (OR, 7.9; 95% CI, 2.9–21.1), and myeloid leukemia (OR, 20.8; 95% CI, 6.6–65.1) [52]. The same study found a nonsignificant increased risk of VTE for patients with breast cancer, while no cases of VTE occurred among pregnant patients with brain cancer, thyroid cancer, or melanoma. The authors' suggestion to give thromboprophylaxis in pregnant patients with hematological malignancies and gynecological cancers is consistent with the systematic review by Folkins et al. [51]. The Royal College of Obstetricians and Gynaecologists has developed a formal VTE risk assessment with numerical scoring for pregnant patients based on a combination of preexisting, obstetrical, and transient risk factors [53]. In this scoring system, the antenatal presence of cancer alone equates to a score of three, and thromboprophylaxis beginning at 28 weeks of gestation can be considered. Incorporating scoring systems to guide thromboprophylaxis in high-risk pregnant patients has been shown to improve consistency in clinical management and mean duration of thromboprophylaxis in those at risk [54]. **We recommend initiating thromboprophylaxis for all patients with active hematological or gynecological cancers during pregnancy and considering thromboprophylaxis for all patients with nonhematological or nongynecological cancers during pregnancy, based on individual risk factors (GRADE 1C)**. Postpartum thromboprophylaxis for patients with cancer is discussed later in the document. (See Section 2.7.)

2.2.2 | Surgery

Clinically indicated surgery for maternal cancer should be performed regardless of gestational age [55, 56]. Recent retrospective cohort studies report a low risk of maternal and

fetal complications and preterm birth associated with nonobstetrical surgery during pregnancy [57, 58]. Miscarriages occur in 10% to 15% of all spontaneously conceived pregnancies, and the risk of spontaneous pregnancy loss in pregnant patients exposed to surgical intervention in the first trimester is approximately the same [55]. A series of more than 12,000 cases described an increased risk of pregnancy loss only after cases complicated by peritonitis [59]. General anesthesia does not increase the risk of fetal malformations [60]. When the risks of maternal hypotension or hypoxia are minimal or can be adequately mitigated, indicated surgery during any trimester does not appear to subject either the patient or fetus to risks significantly beyond those associated with the underlying diagnosis, the clinical condition of the patient, or the complications of surgery in nonpregnant individuals [55, 59, 61]. Strategies to minimize risks associated with surgery in pregnancy include placing the patient in a left-lateral tilt position from 20 weeks of gestation onward to avoid compression of the vena cava, using laparoscopy instead of laparotomy if feasible with relatively low intra-abdominal pressure (10–15 mmHg), and maintaining normal blood pressure and oxygenation levels throughout the case [55]. The decision regarding intraoperative fetal monitoring is complex and should be individualized, considering the patient's desire to continue the pregnancy, gestational age, and feasibility based on the location and type of surgery. If intraoperative fetal heart rate monitoring is planned, counseling before surgery should include obtaining informed consent that permits emergency delivery if it becomes necessary due to fetal indications that are not resolved by resuscitative measures, would not compromise maternal well-being, and is desired by the patient [55, 62]. Similarly, preoperative antenatal corticosteroid administration can be considered, incorporating shared decision-making based on the balance of risks versus benefits for gestational age, individualized preterm birth risk, and desire for intervention. **We recommend that surgery for the treatment of cancer not be delayed or withheld from a pregnant patient at any gestational age in pregnancy (GRADE 1C)**.

2.2.3 | Chemotherapy, targeted therapy, or immunotherapy

Systemic therapy is an integral part of oncological treatment in pregnancy. The most common chemotherapy agents used in pregnancy are alkylating agents, such as cyclophosphamide, anthracyclines, taxanes, and platinum agents. Table 4 presents various properties of these agents, including their mechanisms of action, notable side effects and toxicities, and recommendations for use during pregnancy. Properties that affect the degree of placental transfer include molecular weight, ionization constant, and protein binding [5].

Novel advances in cancer research have led to the development of targeted therapy and immunotherapy over recent years (Table 4). Transplacental transfer of monoclonal antibodies is minimal during the first and early second trimesters of pregnancy and increases during the late second trimester into the third trimester [63]; therefore, fetal exposure during organogenesis appears to have minimal impact on embryo development and pregnancy maintenance. Specific recommendations for the use of these treatments in various types of cancer are discussed later in this document. (See Section 2.3.1.)

In general, chemotherapy is avoided during the first trimester due to a potential impact on fetal organogenesis and subsequent risk of major congenital malformations [5, 25]. However, there may be instances in which, after discussing the risks and benefits of chemotherapy, a patient who desires to continue pregnancy makes an informed decision to initiate chemotherapy during the first trimester (e.g., an aggressive cancer diagnosis). In a large multicenter cohort of 755 patients, chemotherapy exposure prior to 12 weeks of gestation was associated with a 21.7% risk of major congenital malformations (95% CI, 7.5%–43.7%; OR, 9.24 [95% CI, 3.13–27.30]) [64]. Exposure after 12 weeks of gestation was associated with a 3% risk of major congenital malformations (95% CI, 1.9%–4.6%), which is similar to the expected rate in the general population [64]. Similarly, research accounting for more than 1500 exposures to chemotherapy after the first trimester showed that the incidence of congenital malformations was comparable to that of the general population up to 2 years of age [15, 65–69].

Chemotherapy has been associated with other adverse perinatal outcomes, including spontaneous preterm birth and fetal growth restriction. In a cohort of 225 pregnant patients, initiation of chemotherapy prior to 18 weeks of gestation was associated with increased odds of spontaneous preterm birth prior to 37 weeks of gestation (OR, 3.9; 95% CI, 1.4–10.9) [70]. Patients should be counseled about this risk, particularly those with a prior preterm birth. Moreover, chemotherapy started before 15 weeks of gestation was associated with an increased risk for fetal growth restriction (OR, 2.3; 95% CI, 1.0–4.9) [70]. Crucially, any potential fetal benefit of delaying chemotherapy until after the first trimester must be weighed against the potential risk to the pregnant person of delayed treatment.

Chemotherapy regimens should be based on protocols used to treat nonpregnant patients and dosage based on the patient's weight during pregnancy, as opposed to ideal weight or prepregnancy weight [49]. After 34 weeks of gestation, most chemotherapy agents are discontinued to allow approximately 3–4 weeks for resolution of

TABLE 4 Recommendations on the use of chemotherapy, targeted therapy, and immunotherapy agents in pregnancy [5, 15, 24, 25, 49, 63–73].

Agent	Mechanism of action	Notable side effects/toxicities[a]	Use in pregnancy, by trimester		
			First	Second	Third
Alkylating agents					
Cyclophosphamide	DNA alkylation	Hemorrhagic cystitis	Avoid[b]	Possible	Possible
Anthracyclines					
Doxorubicin	DNA intercalation, topoisomerase inhibitor	Cardiotoxicity for the patient, rare reports of cardiotoxicity in neonates	Avoid[b]	Possible	Possible
Daunorubicin	DNA intercalation, topoisomerase inhibitor	Cardiotoxicity for the patient, rare reports of cardiotoxicity in neonates	Avoid[b]	Possible	Possible
Epirubicin	DNA intercalation, topoisomerasone inhibitor	Cardiotoxicity for the patient, rare reports of cardiotoxicity in neonates	Avoid[b]	Possible	Possible
Idarubicin	DNA intercalation, topoisomerase inhibitor	Transient neonatal cardiomyopathy	Avoid	Avoid	Avoid
Taxanes					
Paclitaxel	Microtubule stabilization	Peripheral neuropathy, acral erythema	Avoid	Possible	Possible
Docetaxel	Microtubule stabilization	Peripheral neuropathy, acral erythema	Avoid	Possible	Possible
Platinum agents					
Carboplatin	Covalent binding with DNA	Nephrotoxicity Maternal and neonatal ototoxicity, but less than cisplatin	Avoid	Possible	Possible
Cisplatin	Covalent binding with DNA	Maternal and neonatal ototoxicity	Avoid	Possible	Possible
Oxaliplatin	Covalent binding with DNA	No reports of ototoxicity in adults	Avoid	Possible	Possible
Antimetabolites					
5-fluorouracil	Thymidylate synthase inhibitor	Diarrhea	Avoid	Possible	Possible
6-mercaptopurine	DNA synthesis inhibitor	Hepatotoxicity	Avoid[b]	Possible	Possible
Methotrexate	Dihydrofolate reductase inhibitor	Hepatotoxicity	Avoid[b]	Possible[c]	Possible
Cytarabine	DNA replication inhibitor	Corneal toxicity	Avoid	Possible	Possible
Vinca alkaloid					
Vincristine	Microtubule formation inhibitor	Neurotoxicity	Possible[d]	Possible	Possible
Vinblastine	Microtubule formation inhibitor	Neurotoxicity	Possible[d]	Possible	Possible
Bleomycin	DNA oxidative damage	Pulmonary toxicity	Avoid	Possible	Possible
Targeted therapy and immunotherapy					
Trastuzumab	Human epidermal growth factor receptor-2/neu receptor	Cardiotoxicity Fetal oligohydramnios and neonatal renal failure	Avoid	Avoid	Avoid
Rituximab	CD20 on B cells	Transient absence of neonatal B cells	Possible	Possible	Possible

(Continues)

TABLE 4 (Continued)

Agent	Mechanism of action	Notable side effects/toxicities[a]	Use in pregnancy, by trimester		
			First	Second	Third
Nivolumab	PD-1 receptor on T cells	Immune-related adverse events, hypersensitivity	Possible[d]	Possible[d]	Possible until 32 weeks[d]
Ipilimumab	CTLA-4 on T cells	Immune-related adverse events	Possible[d]	Possible[d]	Possible until 32 weeks[d]
Tamoxifen	Selective estrogen receptor modulator	Venous thromboembolism Fetal skeletal abnormalities, uterine epithelial dysplasia, ambiguous genitalia	Avoid	Avoid	Avoid
Imatinib	Tyrosine kinase inhibitor	Fetal exencephaly, encephalocele, calvarial hypoplasia in first-trimester exposure only	Avoid	Possible	Possible
Nilotinib	Tyrosine kinase inhibitor		Avoid	Possible[d]	Possible[d]
Dasatinib	Tyrosine kinase inhibitor	Cardiotoxicity Fetal leukopenia, thrombocytopenia	Avoid	Avoid	Avoid
Vemurafenib	*BRAF* inhibitor	Skin toxicity (toxic epidermal necrolysis), hepatotoxicity	Avoid	Possible[d,e]	Possible[d,e]

[a]Maternal toxicities listed unless otherwise specified for fetus or newborn.
[b]Consider for use as induction therapy in patients with acute leukemia.
[c]Avoid intrathecal methotrexate use before 20 weeks of gestation.
[d]Based on limited data.
[e]Caution in patients with sulfa allergy.

maternal and neonatal myelosuppression before delivery [49]. Treatment plans should be a product of a multidisciplinary team, including the patient's obstetrical and oncology providers. Before each cycle of chemotherapy during pregnancy, an obstetrician should assess maternal and fetal health and the risk of premature labor [74]. **We recommend that chemotherapy generally be administered after 12 weeks of gestation, provided that the patient desires to continue the pregnancy and that delaying treatment until after 12 weeks of gestation is not expected to significantly change the pregnant patient's prognosis compared with initiating treatment immediately after diagnosis (GRADE 1C)**.

2.2.4 | Radiation therapy

Radiation therapy is usually postponed until postpartum, as surgery and chemotherapy can be given during pregnancy for most cancers, and limited information was previously available on long-term neurological outcomes after exposure to radiotherapy in utero. As radiation dose is inversely proportional to distance, the use of radiotherapy for nonpelvic cancers, such as central nervous system (brain) cancers or respiratory-compromising large mediastinal lymphomas, can be considered in pregnancy [75, 76]. Fetal exposure is calculated based on a combination of internal and external scatter, as well as leakage radiation [5]. Careful planning with a multidisciplinary team, including a radiology specialist or medical physicist, should be considered whenever proceeding with radiation therapy in pregnancy.

A neurocognitive analysis of 43 children exposed to extra-abdominopelvic radiotherapy in utero for maternal cancer documented neurocognitive outcomes within normal ranges for all participants [77]. Median age was 3 years at the first assessment and 12 years at the last assessment. The median number of assessments was two, and no associations were found with fetal radiation dose or timing of radiotherapy during pregnancy.

2.3 | What are the management considerations when cancer is diagnosed during pregnancy?

Multiple factors contribute to shared decision-making between the patient and their multidisciplinary team, including the cancer diagnosis, stage, and prognosis;

gestational duration; whether the pregnancy is desired; the recommended cancer treatment plan; and the patient's values and beliefs. All pregnant individuals with cancer should receive comprehensive pregnancy options counseling, including information about abortion care [14, 78, 79]. Clinicians should familiarize themselves with the laws and regulations governing abortion care in their particular practice setting. Pregnancy options counseling should allow for the patient's decision to evolve. Discussions about pregnancy options and cancer treatment while continuing pregnancy are complex and should incorporate the basic ethical principles of autonomy, beneficence, and non-maleficence and input from a multidisciplinary team, including oncologists, neonatologists, and maternal-fetal medicine subspecialists. Access to cancer treatment should not be denied to a patient who desires to continue pregnancy [79].

2.3.1 | Management of specific cancer types

Breast cancer

Oncologists often refer to "pregnancy-associated" breast cancer as including breast cancer diagnosed during pregnancy and up to 1 year postpartum. As the prognosis for postpartum breast cancer differs from breast cancer diagnosed during pregnancy, some argue that "pregnancy-associated" breast cancer should only include cases diagnosed between conception and spontaneous pregnancy loss, induced abortion, or delivery [80, 81]. This Consult does not address the treatment of breast cancer diagnosed postpartum.

The histopathological features of breast cancer diagnosed during pregnancy are similar to those of nonpregnancy-associated breast cancer, with invasive ductal carcinoma representing the most common subtype [82]. Reassuring data from multiple cohort studies have demonstrated that patients diagnosed with and treated for breast cancer during pregnancy have overall survival rates comparable to age- and stage-matched nonpregnant patients when surgery and chemotherapy are given according to standard guidelines with gestational age-related treatment adaptations in the timing of chemotherapy (i.e., avoiding the first 12 weeks and including a pause after 34 weeks to allow for delivery) and delay of radiation and hormone therapy until postpartum [83–85]. Mammography entails negligible (0.001–0.01 mGy) fetal radiation exposure [41], but its sensitivity in evaluating breast masses during pregnancy is decreased due to the associated change in water and fat content of breast tissue [86]. Therefore, ultrasonography is recommended as the first-line imaging modality for breast masses detected in pregnancy, followed by mammography once cancer is diagnosed to detect multiple cancers in the same breast or bilateral disease [87].

Surgical treatment with either modified radical mastectomy or breast-conserving surgery with sentinel lymph node biopsy can be performed in any trimester [88, 89]. Sentinel lymph node biopsy mapping using technetium-99 or isocyanine green dye may be performed in pregnancy and has similar accuracy as in nonpregnant patients, reducing the risk of lymphedema associated with complete axillary lymphadenectomy [90, 91]. Surgical management with mastectomy for patients diagnosed in early pregnancy is no longer the only preferred management option. The decision regarding mastectomy versus breast-conserving surgery in pregnancy should be based on personal choice after informed consent, not the gestational age at diagnosis. The use of chemotherapy between lumpectomy and delivery often allows for ongoing treatment in pregnancy without significant delays in the initiation of radiation postpartum. A small case series reported reassuring findings regarding local recurrences after breast-conserving surgery during pregnancy with chemotherapy at a median follow-up of 44 months [92]. Breast reconstruction, aside from placement of expanders [93], is delayed until postpartum for best cosmetic results to match the unaffected breast after pregnancy and lactation. For the reasons already described, radiation therapy is generally delayed until postpartum.

Chemotherapy regimens for breast cancer treatment in the second and third trimesters are based on tumor biology and prognostic factors and can be given in neoadjuvant or adjuvant settings. The most commonly used agents described in the literature are cyclophosphamide and doxorubicin or epirubicin, with or without 5-fluorouracil [49, 87, 94]. Due to limited evidence supporting a survival benefit with 5-fluorouracil use, the current preferred regimen is doxorubicin and cyclophosphamide administered every 2–3 weeks [94–97]. Taxanes, including paclitaxel and docetaxel, can be given weekly or biweekly and should be offered to pregnant people with high-risk early-stage and advanced breast cancer, given their established efficacy for such cases in nonpregnant patients, minimal transplacental passage, and reassuring long-term neonatal data [98–108]. Among a cohort of 130 pregnancies with breast cancer from the Cancer and Pregnancy Registry, chemotherapy was given in 104 cases at a mean gestational age of 20 weeks, of which 69% received doxorubicin and cyclophosphamide [97]. The majority of subjects were diagnosed with stage II or III disease, and survival at a mean follow-up of 3 years from primary diagnosis was 86%, which is comparable to nonpregnant patients at 5 years [97]. Similarly, a large cohort of 2743 breast cancer patients reported comparable prognoses between pregnant patients treated with chemotherapy at a median gestational age of

23 weeks and nonpregnant patients [84]. Approximately 70% of patients received an anthracycline (either doxorubicin or epirubicin) with cyclophosphamide and a taxane [84].

Trastuzumab, a commonly used monoclonal antibody that targets human epidermal growth factor receptor 2 (HER-2) in patients with HER-2-expressing breast cancer, can be nephrotoxic to the fetus and has been associated with oligohydramnios and subsequent neonatal respiratory and renal failure [109–113]. Therefore, trastuzumab administration should be delayed until after delivery. Similarly, hormone treatment with agents such as tamoxifen should be postponed until after delivery [114].

Cervical cancer

Management of cervical cancer in pregnancy depends on the cancer stage and gestational age at diagnosis. Diagnostic cervical conization for suspected microscopic invasive cancer in pregnancy should be performed in the first or early second trimester (up to 22 weeks of gestation). Simple trachelectomy for stage IB1 cervical cancer can be performed in pregnancy in highly selected cases, while abdominal trachelectomy is not recommended during pregnancy. Lymph node staging should be performed if technically feasible until 24 weeks of gestation [74].

While the association between cervical surgery and spontaneous preterm birth is well known [115], obstetrical management for preterm birth prevention after fertility-sparing surgery in cases of cervical cancer in pregnancy remains a subject of debate. There is no evidence that prophylactic cerclage placement for the sole indication of previous cone biopsy reduces the risk for preterm birth, and cerclage placement may independently increase preterm birth risk in these individuals [116–119]. Cerclage in patients undergoing trachelectomy has typically been performed despite inconsistent data and a lack of randomized trials evaluating its efficacy in this rare clinical scenario [120]. In patients with a history of trachelectomy, transabdominal cerclage may be considered if not already placed. The decision to place a prophylactic cerclage should be individualized and account for preterm birth risk factors, including obstetrical history and cervical shortening [121].

Sentinel lymph node biopsy in these cases should be performed with isocyanine green. Favorable outcomes have been reported using a laparoscopic approach to pelvic lymphadenectomy in an international cohort of 32 patients during the first and second trimesters with stage IA to IIA cancer [122]. After this gestational age, MRI is recommended to assess lymph node status. For patients with advanced disease (i.e., stage IB1 >2 cm, IB2, or higher), neoadjuvant platinum-based chemotherapy during the second and third trimesters should be given [123]. An elective delay of chemotherapy up to 14 weeks without compromise of survival has been reported for small invasive carcinomas without lymph node involvement, which may be relevant for patients diagnosed early in pregnancy or those in the third trimester [123–127]. Patients should be counseled regarding the associated risk of neonatal ototoxicity for cisplatin-containing regimens. If cisplatin and carboplatin are determined to be equally efficacious for the pregnant patient's particular cancer, carboplatin is preferred, as it carries a lower risk for fetal ototoxicity. Although pediatricians should be encouraged to avoid gentamicin or other ototoxic antibiotics for exposed neonates, obstetricians should continue to treat chorioamnionitis in pregnant patients as clinically indicated [128, 129]. Radiation therapy is delayed until postpartum.

Hodgkin lymphoma

The prognosis for Hodgkin lymphoma diagnosed in pregnancy is comparable to that of nonpregnant patients [3]. Treatment for Hodgkin lymphoma most commonly includes chemotherapy with or without radiation. Some pregnant patients with asymptomatic, stage IA, IB, or IIA non-mediastinal disease may defer treatment until after delivery, particularly if diagnosed in the third trimester [3]. The most commonly used chemotherapy regimen includes doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD), which has demonstrated safety when administered in the second and third trimesters [130–133]. Data from a recent multicenter retrospective cohort of 134 pregnant patients with Hodgkin lymphoma reported no difference in 5-year progression-free and overall survival between pregnant and nonpregnant matched controls in early-stage and advanced-stage disease [134]. In this cohort study, preterm contractions and preterm rupture of membranes occurred more frequently in patients receiving antenatal chemotherapy compared with those who did not initiate treatment during pregnancy [134].

Patients with advanced-stage Hodgkin lymphoma have better survival with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine than ABVD [135]. However, brentuximab vedotin is not recommended in pregnancy due to concerns that the CD30 immunoconjugate will cross the placenta and target fetal lymphocytes. Checkpoint inhibitors are also used in combination with doxorubicin, vinblastine, and dacarbazine in nonpregnant patients with Hodgkin lymphoma, but they have only been used during pregnancy in limited refractory cases [136].

Radiation treatment for Hodgkin lymphoma is usually given after delivery. On an individualized basis, radiation during pregnancy can be considered for patients with disease progression despite chemotherapy, for those with mediastinal masses causing respiratory distress, or if chemotherapy is not an option [3]. A radiology specialist or

medical physicist should be consulted to estimate the fetal exposure risk prior to treatment [137]. (See Section 2.2.4.)

Non-Hodgkin lymphoma

The diagnosis of non-Hodgkin lymphoma should be considered in patients who present with bilateral breast or ovarian masses during pregnancy. Breast or ovarian masses should not be surgically removed after a biopsy confirming non-Hodgkin disease, as they typically respond to systemic chemotherapy. The prognosis for non-Hodgkin lymphoma diagnosed in pregnancy is comparable to that of nonpregnant patients [138]. Treatment for non-Hodgkin lymphoma often includes a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) initiated after the first trimester [139]. In a cohort of 76 patients with ongoing pregnancies, there was one stillbirth (1.3%) [140]. Overall, there was a high incidence of small-for-gestational-age neonates (39%), preterm delivery (52%), and obstetrical (41%) and neonatal complications (12.5%); receipt of antenatal chemotherapy could not fully explain these outcomes [140].

For diffuse large B-cell lymphoma, immunotherapy with rituximab has commonly been added to chemotherapy regimens such as CHOP, as in nonpregnant patients [141]. Rituximab is a chimeric immunoglobulin G1 antibody that can cross the placenta (after 14 weeks) and affect fetal B-cell development with minimal impact on early B-cell precursors, allowing for rapid B-cell recovery post-treatment. Although newborns may have absent mature B lymphocytes after exposure to rituximab, spontaneous recovery of mature B lymphocytes in exposed newborns occurs within 4–6 months when immunoglobulin G production typically begins. Data from a cohort of 231 exposed pregnancies reported no mutagenic potential and minimal risk regarding infectious complications in neonates [142]. Other case series have also reported normalization of B lymphocyte levels and vaccination titers within 6–10 months after birth with no infection-related complications following antenatal exposure [143]. Rituximab should be added to chemotherapy treatment regimens in pregnancy if it is expected to improve prognosis and overall survival. There are also two case reports using nivolumab immunotherapy for relapsed lymphoma in pregnancy with reassuring maternal and newborn outcomes [136, 144]. The infant's pediatrician should be informed about in utero rituximab exposure to determine whether the live vaccine schedule should be altered.

Ovarian cancer

In contrast to nonpregnant patients, ovarian cancer during pregnancy is more commonly diagnosed at early stages due to the routine use of ultrasonography [145]. Surgical management for staging in the setting of a suspicious mass via laparoscopy is preferred [123]. Animal studies have suggested that early pregnancy loss is associated with bilateral oophorectomy in pregnancy due to loss of progesterone maintenance [146]. Thus, for ovarian cancer requiring a bilateral salpingo-oophorectomy prior to 12 weeks of gestation, progesterone supplementation (at a daily dose of 60–120 mg) can be considered in the first trimester [147]. Staging procedures, including omentectomy and lymph node dissection, can be performed in pregnancy; however, because of technical challenges caused by the gravid uterus, patients may require restaging in the postpartum period [123]. Ovarian cancer in the second and third trimesters is most commonly treated with platinum-based chemotherapy. The specific agent is determined based on histological subtype [106, 123]. International consensus management algorithms for epithelial and nonepithelial ovarian tumors in pregnancy have been published [123].

Acute leukemia

Leukemia is often diagnosed after abnormal routine prenatal laboratory studies showing leukocytosis or leukopenia, anemia, or thrombocytopenia, or when a patient presents with bruising or mucosal bleeding. Given the aggressive nature of this disease, administration of chemotherapy must not be delayed [67, 148]. Acute leukemia can present as a life-threatening illness and represents a particular challenge when encountered in the first trimester [148]. Chemotherapy treatment for acute leukemia depends on histological type and includes anthracyclines, vinca alkaloids, steroids, cyclophosphamide, and/or cytarabine. In cases with significant leukocytosis, leukapheresis can be performed at any gestational age [149]. Treatment delay to avoid fetal exposure to chemotherapy worsens the prognosis for the patient and fetus [150]. Procedural abortion in patients with acute leukemia may carry significant morbidity and mortality risk (i.e., sepsis, uterine perforation with hemorrhage, disseminated intravascular coagulation). Thus, induction chemotherapy may be considered to facilitate safe abortion care [150]. Some patients may choose to continue pregnancy after first-trimester chemotherapy. Although limited by biases that preclude generalizability, a small case series reported reassuring fetal outcomes in patients with acute leukemia who received chemotherapy in the first trimester [151]. Of the 14 cases included, 13 pregnancies resulted in live births at a median gestational age of 35 weeks. Median birthweight was 3010 g, and there were no congenital malformations [151]. Follow-up cardiac and neurological evaluations at a median age of 20 years were within normal limits and comparable to a control group of untreated individuals [151].

Patients with acute promyelocytic leukemia (APL) may present with bruising and disseminated intravascular

coagulation. APL in the first trimester is associated with increased obstetrical and fetal complications and a high rate of early pregnancy loss, regardless of all-trans-retinoic acid (ATRA) use [152–154]. Safe use of ATRA has been reported in 40 cases during pregnancy [152–155]. While reports of fetal arrhythmias have occurred, concurrent use of anthracyclines makes it challenging to determine whether they were caused by ATRA exposure. In a systematic review of new-onset APL in pregnancy ($n = 71$ patients), inclusion of ATRA in the chemotherapy regimen was not associated with increased risk of obstetrical complications (30.8% in the ATRA group vs. 38.5% in the non-ATRA group, $p = 0.74$) or fetal complications (50.0% in the ATRA group vs. 40.0% in the non-ATRA group, $p = 0.56$) [156]. There are limited data regarding the use of arsenic in pregnancy for APL [157, 158].

Chronic leukemia

In patients who are asymptomatic and without splenomegaly, observation without treatment can be considered for chronic leukemia in pregnancy. If treatment is indicated, tyrosine kinase inhibitors, such as imatinib, have become the mainstay of therapy in nonpregnant patients with chronic myeloid leukemia [159]. Imatinib has demonstrated teratogenic potential in animal studies during the first trimester [160]. Data regarding human exposure in the second and third trimesters have been reassuring; thus, imatinib after completion of the first trimester can be considered [161–164]. Nilotinib is the current second-line therapy that can be considered during pregnancy [165, 166]. In patients who prefer to avoid tyrosine kinase inhibitors, leukapheresis and/or interferon alpha may be used during pregnancy, although evidence of long-term benefit is lacking. Hydrops fetalis has been reported after the use of dasatinib in pregnancy for chronic myeloid leukemia [167].

Colorectal cancer

Presenting symptoms of colorectal cancer may overlap with common symptoms in pregnancy, such as a change in bowel habits and rectal bleeding [168] presumed to be secondary to hemorrhoids, resulting in a delayed diagnosis [25]. The incidence of colorectal cancer is increasing in younger individuals, which has prompted recent recommendations to begin screening endoscopy at younger ages [169]. Endoscopy during pregnancy to evaluate for colorectal cancer should be performed at any gestational age when clinically indicated [170]. Pregnant patients should receive the same regimens as nonpregnant patients for the treatment of colorectal cancer [171, 172]. Neonatal outcomes have been reassuring after exposure to folinic acid, 5-fluorouracil, and oxaliplatin during pregnancy [173, 174].

Melanoma

Because physiological skin changes are common during pregnancy and clinicians are hesitant to perform skin biopsies in pregnant patients, the diagnosis of melanoma in pregnant patients is often made at a more advanced stage than in age-matched nonpregnant patients [49, 175–177]. For suspicious skin lesions that would prompt concern in nonpregnant individuals (as determined by the asymmetry, border, color, diameter, and short-term change in appearance [size, shape, or color]), wide local incision with or without sentinel lymph node biopsy can be performed at any gestational age [178]. Immunotherapy agents should be used with caution and after thorough counseling on the risks and benefits for pregnant patients with metastatic melanoma [179, 180]. For advanced disease, immunotherapy has recently demonstrated improvements in progression-free and overall survival for nonpregnant individuals; it has been used in 10 reported cases in pregnancy with reassuring neonatal outcomes [181–186]. Data regarding targeted therapy using *BRAF* inhibitors such as vemurafenib are limited to case reports [179, 187, 188]. Vemurafenib should be used with caution in patients with sulfa allergies, as there can be cross-reactivity to sulfonamide compounds that carry a risk of adverse skin reactions [180]. Vemurafenib may cause toxic epidermal necrolysis alone or in relation to concomitantly or previously used checkpoint inhibitor drugs [189].

Thyroid cancer

Although thyromegaly is a common physical examination finding during pregnancy and does not require specific follow-up, prominent nodules should be further investigated. Surgery is considered the mainstay of treatment for thyroid cancer in pregnancy and can be performed at any gestational age when indicated by cancer subtype or lymph node status [190, 191]. Depending on the cancer subtype, surgery for slow-growing tumors such as well-differentiated types (e.g., follicular) can be delayed until after delivery. In contrast, surgery should not be delayed for medullary or anaplastic tumors or biopsy-proven nodal disease [192]. Endocrinologists may consider tumor-based genetics to aid in the timing of surgery, such as the *BRAF* V600E mutation in papillary thyroid cancer. Radioactive iodine I-131 for the treatment of thyroid cancer is contraindicated during pregnancy due to potential effects on the fetal thyroid [29, 193]. Thyroid supplementation is initiated after total thyroidectomy, and, if performed before or during pregnancy, monitoring of serum calcium levels during pregnancy should be considered in the event of unintentional parathyroid tissue excision. This approach is especially indicated when magnesium therapy is used or

when the patient experiences labor with muscle exertion, both of which can decrease serum calcium levels [49].

2.4 | How should patients be counseled regarding fetal exposure to chemotherapy, targeted therapy, and immunotherapy in pregnancy?

Before beginning chemotherapy during pregnancy, the patient should be counseled regarding fetal risks, including congenital malformations with first-trimester exposure, fetal growth abnormalities, potential immunosuppression, and long-term developmental outcomes. Analyses of large international cohorts have reported an association between chemotherapy and small-for-gestational-age birthweights, prompting the recommendation for serial fetal growth surveillance in these settings [61, 70, 194].

Chemotherapy, particularly with the use of platinum and nonplatinum alkylating agents, has been associated with short-term effects, including preterm uterine contractions and spontaneous preterm birth, possibly related to hypothalamic-pituitary-adrenal axis activation or chemotherapy-induced apoptosis in fetal membranes [194]. Patients are advised to be well hydrated before, during, and after chemotherapy sessions. Delivery within a short time interval after chemotherapy administration has also been associated with neonatal leukopenia and neutropenia, which may increase the risk of infectious morbidity [195, 196]. The recommended timing of delivery after chemotherapy is discussed later in this document. (See Section 2.6.)

If chemotherapy is avoided during organogenesis, malformations due to exposure are not anticipated, but as the central nervous system continues to develop throughout pregnancy, the patient should also be counseled on any anticipated long-term neurocognitive effects for the offspring. Long-term data evaluating neurodevelopmental outcomes in children exposed to chemotherapy have been reassuring. In a study prospectively examining 84 children with in utero exposure to chemotherapy for hematological malignancies (38 during the first trimester), all had normal birthweights, educational performance, and neurocognitive development [197]. Long-term follow-up (median of 19 years) also demonstrated no incidence of cancer in this cohort [197]. Subsequent multicenter cohort studies that included other types of cancers demonstrated similar long-term neurocognitive outcomes among children exposed to maternal cancer with or without chemotherapy exposure [198–202]. Results of neurocognitive evaluations at 3, 6, 9, and 12–15 years of age have been comparable to those of age-matched controls from uncomplicated pregnancies or pregnancies of individuals with cancer who did not receive chemotherapy before delivery [198–203]. Although within normal ranges, statistically significant differences have been found in mean verbal IQ and visuospatial long-term memory, with lower scores in the exposed group at 6 years of age [198]. Based on parental evaluation, children at age 6 who had been exposed to chemotherapy had poorer emotional regulation [203]. In some cases, the death of the child's mother before age 2 may have been a contributing factor to language development [203, 204]. Young children who had been exposed to chemotherapy in utero also had a significant increase in the need for glasses [204]. In a multicenter cohort of 151 nine-year-old children, subgroup analysis of those exposed to chemotherapy prenatally (n = 109, 72.2%) revealed normal cognitive and behavioral outcomes and no associations between Full-Scale IQ scores and chemotherapy agent, exposure level, or timing of exposure during pregnancy [205]. Recently, a cohort of 166 adolescent children from 12 to 15 years of age born after a pregnancy complicated by maternal cancer and treatment underwent developmental testing. Neurocognitive outcomes, including intelligence, memory, and attention, were within normal limits. Maternal education, gestational age at birth, and maternal death were key predictors of adolescent health and neurodevelopment. Of note, pubertal development was within standard ranges, with no significant associations found between chemotherapy exposure and puberty onset [206]. Multicenter cohort studies consistently find that newborn IQ improves with each week of pregnancy prolongation, and prematurity has a more significant impact on newborn neurodevelopment than chemotherapy exposure [200, 205]. **To improve long-term neurodevelopmental outcomes of children exposed to chemotherapy in utero, we suggest avoiding clinician-initiated preterm delivery when possible (GRADE 2C)** [206]. Future research in this population should include long-term follow-up into adulthood.

Long-term effects of chemotherapy include cardiotoxicity [207–209]. Before beginning treatment with anthracyclines, the pregnant patient should undergo a baseline evaluation of cardiac function with an echocardiogram rather than the nuclear multigated acquisition scan typically ordered for nonpregnant individuals. Studies evaluating newborn cardiac function after chemotherapy exposure have been reassuring [198, 199]. Postnatal echocardiography for newborns exposed to anthracycline chemotherapy is not required.

Limited data exist on the use of targeted therapy and immunotherapy agents in pregnancy, and they should be used with caution, as they may interfere with fetal development. Commonly used medications for hematological malignancies, such as imatinib (tyrosine kinase inhibitor), have been linked to abnormal pregnancy outcomes when

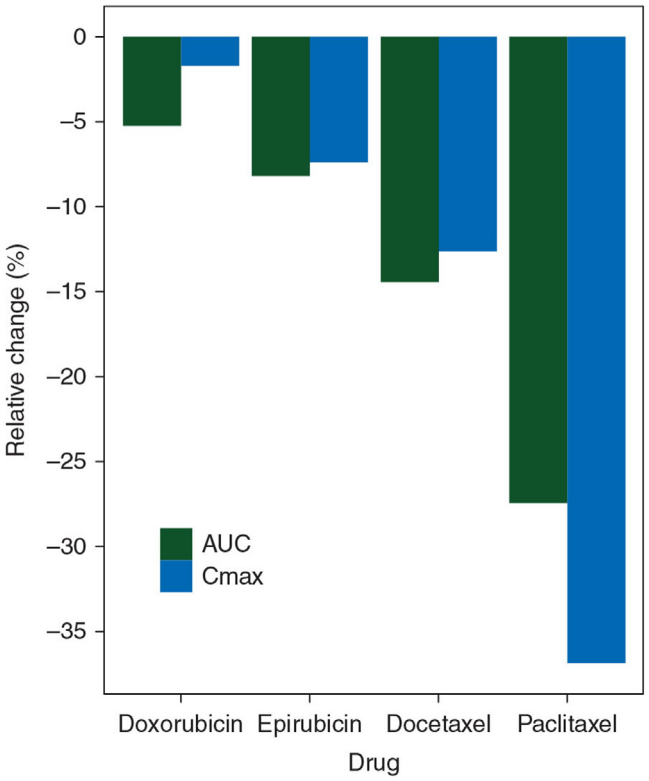

FIGURE 1 Typical predicted relative changes in chemotherapy exposure during pregnancy compared with nonpregnant patients [210]. AUC, area under the curve; Cmax, maximum serum concentration. Reprinted with permission from [210].

administered during the first trimester but appear to be safe when used during the second and third trimesters [160–163]. Other targeted therapies, including antivascular endothelial growth factor and antiangiogenic medications, should be avoided in pregnancy due to their mechanism of action, limited available evidence, and risks of pregnancy loss and skeletal malformations associated with their use [5].

2.4.1 | Supportive medications for chemotherapy side effects during pregnancy

Pregnant patients often report less severe symptoms with chemotherapy than nonpregnant patients, likely because the physiological changes of pregnancy affect free drug levels (Figure 1) [210]. This decreased exposure does not appear to result in decreased efficacy, as shown by comparable outcomes in pregnant and nonpregnant individuals with breast cancer [84]. Side effects of chemotherapy during pregnancy are similar to those experienced in nonpregnant patients, including nausea, vomiting, alopecia, poor weight gain, stomatitis, and infection from transient immunosuppression [49]. Antiemetic medications, including ondansetron, can be given during pregnancy, although the use of aprepitant is discouraged due to a lack of data. Corticosteroids are an integral part of the treatment and prevention of chemotherapy-induced nausea [211]; dexamethasone is most commonly prescribed to nonpregnant patients. Because of the placental transfer of dexamethasone and betamethasone [212], their use for reducing prematurity-related complications in patients at high risk of preterm birth [213], the negative impact associated with repeated dosing [214, 215], and concerns about adverse long-term effects on children exposed in utero [216], nonfluorinated corticosteroids such as prednisone or methylprednisolone are preferred for pregnant patients. These corticosteroids, in addition to prednisolone, are actively metabolized by 11β-hydroxysteroid dehydrogenase in the placenta, limiting fetal exposure. **We recommend intravenous methylprednisolone, 62.5 mg (corresponding to 10 mg of dexamethasone), or oral prednisolone, 30 mg (corresponding to 6 mg of dexamethasone), as first-line therapy for chemotherapy-induced nausea when corticosteroids are indicated (GRADE 1B)**. Growth factors such as filgrastim or pegfilgrastim in the setting of neutropenia after chemotherapy treatment have been shown to be safe in pregnancy [217].

2.5 | What type of fetal ultrasound surveillance is indicated in patients with cancer during pregnancy?

All patients with cancer who continue pregnancy should undergo a detailed fetal anatomy survey. A large international cohort study of 1170 patients evaluated the associations between cancer type and treatment modality on obstetrical and neonatal outcomes [194]. Of the 779 patients (67%) who received treatment during pregnancy, chemotherapy was administered in 429 patients (55%), and the incidence of small-for-gestational-age live births was 21% [194]. An increased risk for small-for-gestational-age births was found with systemic disease (OR, 1.9; 95% CI, 1.0–3.3) and platinum-based chemotherapy (OR, 3.1; 95% CI, 1.5–6.7) [194]. Although cancer type was not associated with an increased risk for small-for-gestational-age births in this cohort, other reports have suggested that hematological cancer types have the highest associated risk for fetal growth restriction and pregnancy loss [61, 218]. **We recommend serial fetal growth surveillance every 3–4 weeks in pregnancies with an active cancer diagnosis, regardless of treatment (GRADE 1C)**. More frequent ultrasound surveillance may be needed based on obstetrical indications. A small number of stillbirths (n = 14; 1% of the 1089 singleton pregnancies with

a known obstetrical outcome) were reported in the international cohort study, making it challenging to evaluate the association of cancer in pregnancy with stillbirth and whether initiation of antenatal fetal surveillance would reduce such risk [194]. However, this rate is similar to that reported in pregnancies complicated by other conditions, such as hypertensive disorders of pregnancy, diabetes, and fetal growth restriction, in which antenatal testing is recommended [219]. **We recommend initiation of antenatal fetal surveillance starting at 32 weeks of gestation in pregnancies with an active cancer diagnosis, regardless of treatment, unless indicated earlier for maternal or fetal reasons (GRADE 1C)**.

2.6 | How does a cancer diagnosis during pregnancy guide the timing and mode of delivery?

Delivery timing and mode depend on cancer type, treatment regimen, obstetrical factors, and patient goals. A multidisciplinary approach with specialists in maternal-fetal medicine, oncology, anesthesia, and neonatology at a tertiary care center is strongly encouraged. Delivery is commonly planned to optimize the timing of any treatment-free interval, with the goal being a term birth. Planned deliveries prior to 37 weeks of gestation should be avoided to reduce the associated prematurity-related complications when the cancer type allows safe treatment during pregnancy. If delaying treatment would significantly impact maternal prognosis—or the cancer type requires a treatment modality not studied in pregnancy—delivery timing should be determined on an individualized basis with a multidisciplinary team. **We recommend that planned delivery prior to 37 weeks of gestation in pregnant patients with cancer generally be avoided unless indicated for medical or obstetrical reasons (GRADE 1C)**. For patients who do not require any further cancer therapy postpartum, pregnancies should be allowed to progress beyond 37 weeks of gestation.

For patients undergoing chemotherapy during pregnancy, delivery at least 3–4 weeks after the last treatment is encouraged to allow for resolution of maternal and neonatal myelosuppression [195, 196]. Complete blood count evaluations from 135 infants exposed to chemotherapy revealed that the highest incidence of neutropenia (absolute neutrophil count <1000 m^3) occurred in those delivered 22–28 days after chemotherapy [195]. Most chemotherapy agents should not be given after 34 weeks of gestation. Paclitaxel represents an exception; it can be given up to 35 or 36 weeks. **We recommend that chemotherapy treatment generally be stopped by 34 weeks of gestation to allow 3–4 weeks for recovery of myelosuppression before spontaneous labor or planned delivery, except for weekly paclitaxel, which can be administered up to 35 or 36 weeks, as only 1–2 weeks are necessary for recovery before delivery (GRADE 1C)**. Given the high incidence of preterm contractions in patients undergoing taxane therapy [194], intravenous fluid hydration during treatment and oral hydration after treatment are encouraged, and preterm labor precautions should be emphasized.

For most cancers diagnosed during pregnancy, cesarean delivery should be reserved for the usual obstetrical indications. For patients with cervical cancer, vaginal delivery may result in tumor laceration, hemorrhage, or implantation of malignant cells at the site of perineal laceration or may not be possible due to obstruction [220–222]. Patients with microinvasion can safely undergo a trial of labor, but patients with invasive cervical cancer should undergo a cesarean delivery, with or without a plan for simultaneous hysterectomy and lymph node evaluation with gynecological oncology specialists. A classical incision may be needed to avoid the lower uterine segment where invasive cervical cancer is located. Similar risks may occur in patients with vulvar cancer as well [123]. Cesarean delivery is recommended to prevent vulvar wound dehiscence after vulvectomy, but vaginal delivery may be an option in cases of healed wounds without reconstructive surgery [123]. **We recommend that the mode of delivery be determined by routine obstetrical indications for most patients with cancer in pregnancy (GRADE 1C)**.

Although rare, placental metastases have been reported in pregnancies, most commonly in those complicated by melanoma and hematological malignancy [223–226]. Furthermore, villous involvement has been linked to fetal and neonatal metastases [224]. **We recommend a placental pathology examination in all cases of cancer during pregnancy, regardless of cancer type or treatment (GRADE 1C)**.

2.7 | How should a patient with cancer be managed in the postpartum period?

Postpartum management of a patient diagnosed with cancer during pregnancy includes determining the optimal time for initiation or reinitiation of any indicated treatment (i.e., surgery, systemic therapy, radiation therapy) in collaboration with oncology specialists. Such treatments can occur as soon as within 1 week of an uncomplicated vaginal birth or 1–2 weeks after an uncomplicated cesarean birth without signs of wound infection [227]. As malignancy and the postpartum period are both significant risk factors for VTE [228], prophylactic anticoagulation, particularly in the setting of additional risk factors (e.g., obesity,

cesarean delivery [229], immobility), should be considered during the postpartum period [53]. The optimal postpartum anticoagulation dose and duration in patients with active cancer is unknown, but prophylactic dosing for 6–8 weeks postpartum is a common regimen for individuals at high risk for VTE [230, 231].

The benefits of breastfeeding for maternal and neonatal well-being are well known in the general population. A patient undergoing imaging evaluation with 18-FDG-PET/CT should wait 2–4 h after injection to hold the infant close or breastfeed [232]. For patients receiving chemotherapy postpartum for cancer treatment, breastfeeding is currently discouraged due to case reports of children developing neutropenia [233]. If sufficient time has elapsed between chemotherapy treatment during pregnancy and delivery, giving the infant colostrum and breastmilk until chemotherapy is resumed is possible in most cases. A recent publication detailed the elimination of five chemotherapeutic drugs (cyclophosphamide, doxorubicin, paclitaxel, carboplatin, and cisplatin) from human milk samples and calculated the relative infant dose according to the time from treatment. For cyclophosphamide, paclitaxel, and carboplatin, cumulative relative infant doses below 1% or 0.1% were reached if breast milk was discarded for 1–3 days after treatment [234]. This finding might suggest that breastfeeding in between cycles is an option. However, other pharmacological parameters (such as oral bioavailability, safety, and drug metabolism in infants) must be considered to enable recommendations on washout periods that minimize infant exposure. Doxorubicin and the active metabolite doxorubicinol require more quantification. Similarly, breastfeeding during treatment with cisplatin might cause substantial exposure, and caution is advised. Further research is necessary to better counsel patients about the risks of breastfeeding during chemotherapy. Breast milk donor banks may be an option for patients receiving postpartum chemotherapy.

For patients who are considering breastfeeding and do not require postpartum chemotherapy, an interval of at least seven half-lives is recommended, which for most agents falls within the recommended 3- to 4-week interval between the last course in pregnancy and delivery [235]. For agents such as carboplatin, levels can be detectable in milk more than 3 weeks after treatment [236], which emphasizes the importance of detailed counseling for each agent used during pregnancy.

Patients who express interest in breastfeeding after completing chemotherapy should be counseled that breastfeeding difficulties are more common in such patients [237]. A prospective cohort study of 96 patients reported that those who underwent chemotherapy during pregnancy more commonly reported a lack of or a perceived decrease in breast milk supply and the need to provide supplemental feeding to their infants compared with patients who did not undergo chemotherapy during pregnancy (63.5% vs. 9%) [238]. Given the wide availability of nutritionally appropriate and safe feeding alternatives, including donor milk, it is suggested that patients and their multidisciplinary team engage in shared decision-making regarding breastfeeding. Patients with estrogen receptor- or HER-2-positive breast cancer who are interested in breastfeeding should discuss with their oncologists an agreed-upon duration of breastfeeding before starting hormonal or immunotherapy, at which time breastfeeding would be discouraged [239].

For breast cancer patients undergoing radiation therapy, feeding from the contralateral breast is safe. Patients are encouraged to empty the affected breast immediately before the scheduled radiotherapy session. Feeding from the affected side may pose challenges for treatment if mastitis develops and is not recommended [240, 241].

2.8 | What is the psychological impact of cancer in pregnancy?

The impact of cancer on mental health is well known and has been associated with anxiety and depression, especially in young individuals [242, 243]. Moreover, initiating cancer treatment may be associated with psychological distress [244]. Although data evaluating the psychological impact of cancer in pregnancy are limited, studies have suggested early screening and referral to appropriate consultants for psychological support should be considered [245, 246]. Patients diagnosed with cancer have reported high rates of intrusive thoughts and anxiety; in one survey, these symptoms were more common in patients who had not received fertility assistance, had been advised to terminate the pregnancy, had a preterm or cesarean delivery, had not produced sufficient milk, had been experiencing a recurrence, or had undergone surgery postpregnancy [237]. Furthermore, psychological distress from a cancer diagnosis has negative impacts on the patient's child(ren) and partner [246, 247]. Additional research exploring the association between cancer diagnosis in pregnancy and psychological distress and its impact on parenting and parent-infant bonding is needed. Hope for Two, the Pregnant with Cancer Network (https://www.hopefortwo.org) [248], offers free support for patients diagnosed with cancer during pregnancy by connecting them with others who have experienced a similar cancer diagnosis during pregnancy and postpartum.

2.9 | How does prenatal aneuploidy screening with cfDNA affect the detection of occult malignancies?

With the increased use of cfDNA screening for fetal aneuploidy in pregnancy, occult malignancies have been identified in pregnant patients [9–11, 249]. The most common types of cancer identified by cfDNA aneuploidy screening include lymphoma and breast cancer, while leukemia and colon cancers have also been diagnosed [9, 11, 12, 249]. Detection of multiple chromosomal aneuploidies or single autosomal monosomy via cfDNA screening appears to be associated with the highest likelihood of a maternal malignancy detection, with variation in predictive value. Data from a large US cohort of 113,415 patient samples demonstrated maternal malignancy incidences of 19% (five out of 26) in those with multiple aneuploidies and 4% (one out of 27) in those with single autosomal monosomy where fetal or neonatal karyotypes were available and discordant with aneuploidy screening results [250]. Forty-one cancer cases were detected in a recent cohort of 639 patients with multiple chromosomal aneuploidies on cfDNA screening from China (total of 1,930,000 genome-wide samples), yielding a positive predictive value of 7.6% [249]. The predictive value was further improved by incorporating a novel bioinformatics algorithm and plasma tumor markers. Variations in patient populations and technical analysis likely contributed to the differences in reported rates between the studies from the United States and China. Another US cohort study evaluating cfDNA screening results suspicious for malignancy using a single-nucleotide polymorphism-based technology reported 38 abnormal results out of 2,004,428 samples (0.002%) [9]. Of the 30 patients with clinical follow-up, cancer was identified in 20 patients (66.7%; 95% CI, 47.2%–82.7%) [9].

Different cancers may be characterized by different cfDNA copy number aberration (CNA) profiles, in which one or multiple chromosomes can be affected. While cfDNA profiles with genome-wide CNAs are typical for maternal cancer, benign tumors, such as uterine leiomyomas, or systemic maternal diseases can also cause aberrant CNA profiles. Hence, a cfDNA screening result suggesting an occult maternal malignancy is not diagnostic for maternal cancer. Comprehensive evaluation strategies for patients with a positive cfDNA screening result suggesting maternal cancer have been developed by expert opinion (Figure 2). Whole-body MRI is the imaging modality of choice to evaluate for an occult malignancy when cfDNA screening suggests one may be present [12]. In health systems where WB-DWI/MRI is not accessible, depending on symptoms, initial or follow-up evaluations may also include breast ultrasonography, chest radiography, and targeted ultrasound examinations or CT scans if necessary. A study aimed at determining the best approach for evaluating pregnant people who receive cfDNA screening results that suggest cancer is currently underway (Incidental Detection of Maternal Neoplasia Through Non-invasive Cell-Free DNA Analysis [IDENTIFY]) [251]. In the initial cohort of 107 IDENTIFY participants, a standardized cancer screening protocol including whole-body MRI detected cancer in 48.6% of those who initially received nonreportable or unusual cfDNA sequencing results [252]. The most common finding was multiple chromosomal gains and losses across several chromosomes. **We recommend that cancer be considered as part of the differential diagnosis for pregnant patients with multiple chromosomal aneuploidies or single autosomal monosomy detected by cfDNA screening that is discordant with fetal findings (GRADE 1C)** [253].

In patients with a known active cancer diagnosis, cfDNA screening for aneuploidies is technically feasible, but the presence of tumor-derived cfDNA in the patient's circulation can compromise accuracy [10]. In a cohort of 26 pregnant patients with a known malignancy who underwent cfDNA screening, false-positive rates for trisomies 21, 18, and 13 were 15.4%, 15.4%, and 19.2%, respectively [10]. Theoretical risks of false-negatives for these trisomies were 7.7%, 7.7%, and 15.4%, respectively [10]. Genetic counseling should be considered to review options for prenatal genetic screening and diagnostic testing in these cases [123].

2.10 | How should unplanned pregnancies conceived during cancer treatment be managed?

Patients who become pregnant while undergoing cancer treatment should receive thorough counseling tailored to their circumstances, including assessment of their desire to be pregnant. Due to the complex nature of these decisions, it is crucial that pregnant patients with cancer be counseled on the option of abortion and that they have access to abortion services if desired. Clinicians should familiarize themselves with the laws and regulations governing abortion care in their particular practice setting. In general, the risks versus benefits of continuing treatment, pausing treatment until a later gestational age, delaying treatment until postpartum, and abortion care should be discussed. If applicable, counseling should include the risks of congenital malformations from any treatment administered during organogenesis. For patients who desire to continue pregnancy, early fetal anatomy evaluations may be considered. Conceiving while taking immunotherapy, including monoclonal antibodies or trastuzumab, before 14 weeks of gestation is not associated with an increased risk for

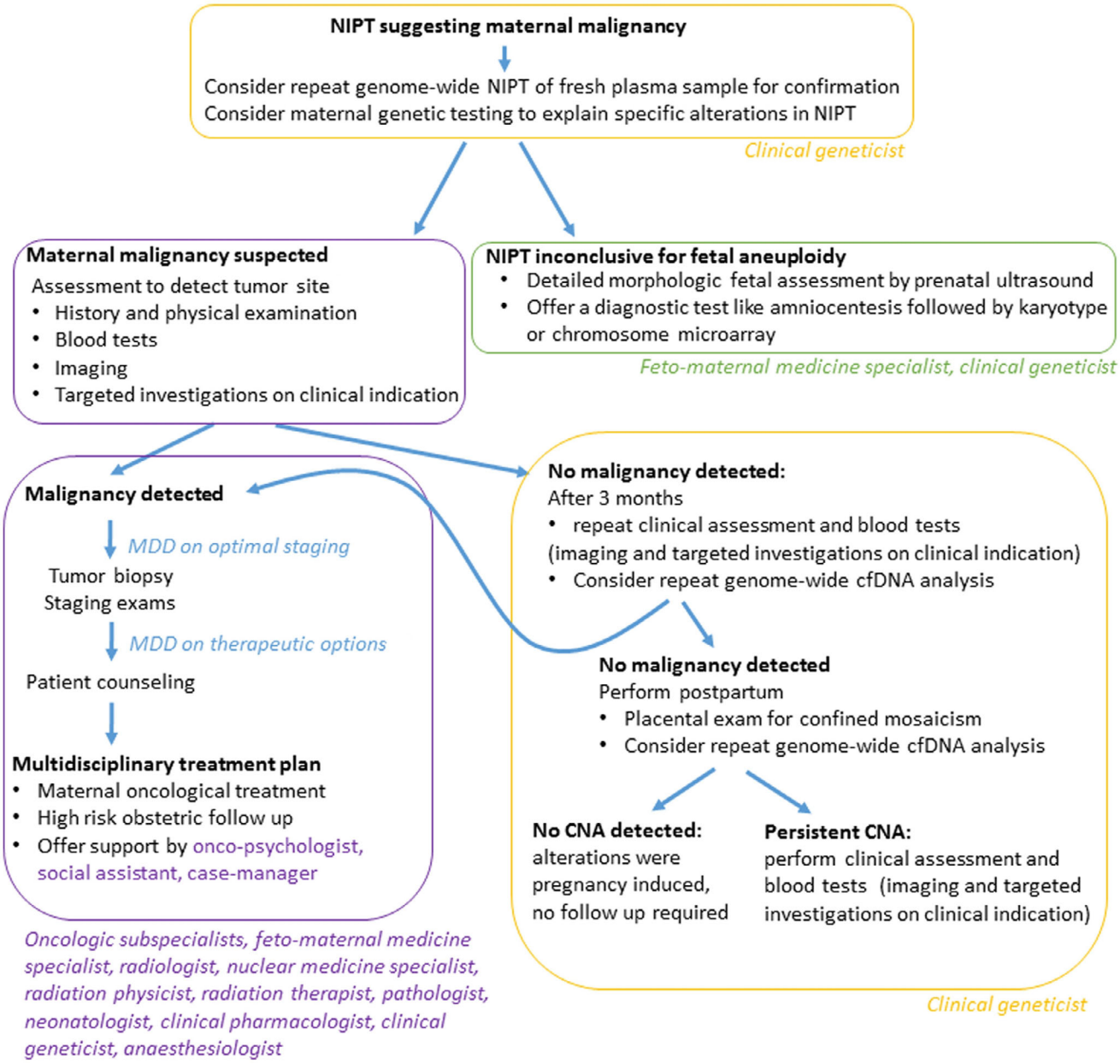

FIGURE 2 Diagnostic workup when noninvasive prenatal testing suggests maternal cancer [253]. cfDNA, cell-free DNA; CNA, copy number alterations; MDD, multidisciplinary discussion; NIPT, noninvasive prenatal testing. Note that the terminology "prenatal screening with cell-free DNA (cfDNA)" is preferred over "noninvasive prenatal testing (NIPT)." Reprinted with permission from [253].

congenital anomalies. However, the pregnancy remains at high risk of maternal and fetal complications [61, 194, 218].

2.11 | How should clinicians address future fertility and subsequent pregnancy for patients with newly diagnosed cancer?

Ideally, fertility preservation counseling should occur at the time of diagnosis before beginning treatment [254–256]. Gonadotoxicity depends on patients' age at treatment and specific chemotherapy agents, with alkylating agents being the most gonadotoxic [257]. Cancer survivors desiring pregnancy who previously received cardiotoxic chemotherapy, such as anthracyclines, should undergo echocardiography, as should those exposed to trastuzumab or left-sided radiation for breast cancer. Patients exposed to chest radiotherapy for Hodgkin lymphoma should be screened for thyroid dysfunction.

To evaluate pregnancy outcomes in survivors of childhood cancer treated with chemotherapy and radiation therapy, Green et al. reported data from more than 4000

pregnancies in young adult cancer survivors in the landmark Childhood Cancer Survivor Study [258]. Eligible patients were 5-year cancer survivors younger than 21 years old at diagnosis between 1970 and 1986 [258]. The live birth rate was 63%, and there were no significant differences in pregnancy outcome by treatment [258]. Reports from case-control studies have also demonstrated no increased risk of adverse pregnancy outcomes, including miscarriage or congenital malformations in pregnancies, after preconception chemotherapy exposure [259–262]. However, analysis of a subgroup of patients from the Childhood Cancer Survivor Study who were previously treated with radiation therapy demonstrated an increased risk for preterm birth (50.0% vs. 19.6%) and low birthweight (36.2% vs. 7.6%) compared with those who were not treated with radiation therapy, especially with exposure before puberty [263]. Other pregnancy-related complications, such as miscarriage, placenta accreta spectrum, and stillbirth, have also been associated with prior pelvic radiation therapy [264–267]. Several mechanisms have been hypothesized to contribute to these findings, such as changes in uterine vasculature, radiation-induced myometrial fibrosis, and endometrial dysfunction leading to altered implantation. Increased risks of gestational diabetes and hypertensive disorders have also been reported in patients after abdominal radiation [268].

Recent data from US-linked cancer and live birth certificate registries have also suggested that specific cancer types may influence pregnancy outcomes after treatment, with higher risks of preterm birth associated with cervical cancer (RR, 2.8; 95% CI, 2.1–3.7), invasive breast cancer (RR, 1.3; 95% CI, 1.1–1.7), and leukemia (RR, 2.1; 95% CI, 1.3–3.5). There was also an increased risk of small-for-gestational-age births associated with brain cancer (RR, 1.7; 95% CI, 1.1–2.8) and advanced non-Hodgkin lymphoma (RR, 2.3; 95% CI, 1.5–3.6) [269].

Counseling regarding the impact of pregnancy on cancer recurrence is an integral part of preconception counseling. Pregnancy after treatment of all malignancies (aside from choriocarcinoma) has not been shown to increase a patient's risk of cancer recurrence or death [270, 271]. Although the risk of melanoma recurrence is highest within 2 years of adequate excision [272], pregnancy does not increase the risk of recurrence [270]. Nevertheless, delaying pregnancy during those 2 years is typically suggested to facilitate appropriate treatment if there is a recurrence. All cancer survivors considering pregnancy should have surveillance for relapsed or recurrent cancer before conceiving.

Evidence suggests that breast cancer survivors who have a subsequent pregnancy have reduced mortality compared with matched controls without a subsequent pregnancy [273]. The risk of cancer recurrence after subsequent pregnancy is more affected by the nodal status and stage of the cancer rather than the receptor status. A subsequent pregnancy in patients with estrogen receptor-positive disease does not appear to decrease disease-free survival compared with estrogen receptor-positive breast cancer patients who do not have subsequent pregnancies (HR, 0.9; 95% CI, 0.7–1.2) [274]. Tamoxifen and trastuzumab are often recommended as maintenance therapy for patients with a history of breast cancer and have been associated with fetal developmental abnormalities [109–113]. Pregnancy prevention is strongly encouraged in this population, and clinicians should engage in person-centered counseling to determine the patient's preferences regarding contraception.

The ideal interval from breast cancer diagnosis to subsequent pregnancy is a commonly encountered question. In a large retrospective US cohort study, becoming pregnant within 10 months of diagnosis was associated with increased mortality in patients over 35 years of age who had positive lymph nodes and local recurrence before pregnancy [273]. Thus, a minimum of 10 months has generally been recommended as an optimal interval. For patients under 35 years of age with lymph node-negative and localized disease, pregnancy did not increase mortality risk if conception occurred within 10 months of diagnosis [273]. A recent systematic review and meta-analysis by Lambertini et al. reported that, compared with patients with breast cancer who did not pursue any subsequent pregnancy, those with pregnancy after treatment for breast cancer had better disease-free survival (HR, 0.66; 95% CI, 0.49–0.89) and overall survival (HR, 0.56; 95% CI, 0.45–0.68). Similar results were observed after correcting for potential confounders and irrespective of patient, tumor, and treatment characteristics; pregnancy outcome; and timing of pregnancy [275]. Still, recurrence risk is highest during the first 2 years after diagnosis.

Whether discontinuing tamoxifen before the recommended 5- to 10-year duration of therapy has any impact on subsequent pregnancy or disease recurrence was recently investigated in the Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) trial [276]. Patients who had taken tamoxifen for at least 18 months and no more than 30 months and wished to temporarily discontinue therapy to attempt pregnancy were advised to have a 3-month washout period before attempting to conceive. Among 516 patients with previous hormone receptor-positive, early-stage disease, temporary interruption of endocrine therapy to attempt pregnancy did not confer an increased short-term risk of breast cancer events compared with controls (44 events during 1638 patient-years of follow-up, with a

safety threshold of 46 events during 1600 patient-years of follow-up) [276]. The 3-year incidence of breast cancer events was comparable between the two groups (treatment interruption: 8.9%; 95% CI, 6.3%–11.6%; control group: 9.2%; 95% CI, 7.6%–10.8%) [276]. Endocrine therapy was resumed after pregnancy.

For patients with a history of fertility-sparing treatment for early-stage ovarian cancer, reports from subsequent pregnancies have been reassuring, with no associated increased risk of cancer recurrence [277]. After chemotherapy, patients may encounter challenges with fertility due to diminished ovarian reserve, prompting the need for collaboration with reproductive endocrinology and infertility specialists.

Contraceptive counseling for patients desiring to postpone pregnancy is essential to prevent unintended pregnancies during cancer treatment and support future reproductive planning [278]. The US Medical Eligibility Criteria for Contraceptive Use provides evidence-based guidance on the safety of various contraceptive methods for individuals with cancer [279]. Healthcare practitioners should refer to this guidance to determine the most appropriate contraceptive options based on the patient's specific cancer type, treatment regimen, and overall health status. Detailed contraceptive counseling considerations for individuals with cancer are described in clinical guidance from the Society of Family Planning and the Society of Gynecologic Oncology [278, 280, 281].

2.12 | What fertility preservation options are available for someone diagnosed with cancer?

For patients who would like to delay conception, fertility preservation options, such as oocyte, embryo, or ovarian tissue cryopreservation and ovarian suppression with hormonal analogs, are available and should be discussed in collaboration with reproductive endocrinology and infertility specialists before beginning cancer treatment [254]. Patients of reproductive age with a cancer diagnosis should be referred to genetic counseling for evaluation of cancer susceptibility variants. Those with hereditary cancer can be referred to genetic counseling to discuss the possibility of in vitro fertilization with preimplantation genetic testing to exclude embryos carrying a confirmed cancer risk genetic variant.

3 | CONCLUSION

Cancer in pregnancy is complex, has several unique considerations, and requires close multidisciplinary management with oncology and maternal-fetal medicine subspecialists to optimize outcomes. Cancer-related symptoms and physical examination findings may initially be attributed to pregnancy-related changes, resulting in delayed diagnoses. Patients with abnormal cfDNA screening results suggesting multiple chromosomal abnormalities should undergo detailed evaluations to exclude malignancy.

Continued collection of cancer in pregnancy cases in registries such as the International Network on Cancer, Infertility and Pregnancy (https://cancerinpregnancy.org) [22] and Cancer and Pregnancy (https://cancerandpregnancy.com) [282] is encouraged, as the incidence of such cancer within any individual institution is low. Patients with cancer should be encouraged to contact the international Hope for Two network to be matched for support from a patient with a similar cancer type who has already undergone diagnosis and treatment during pregnancy [248].

Summary of recommendations.[a]

	Recommendation	Grade
1	We suggest that ultrasonography and non-contrast magnetic resonance imaging (MRI) be used as first-line imaging techniques in the evaluation of a pregnant person with suspected cancer.	2B
2	Although non-contrast MRI and ultrasonography are first-line diagnostic imaging modalities in pregnancy, we recommend that computed tomography (CT) with or without contrast, gadolinium contrast for MRI, and fluorine-18-fluorodeoxyglucose positron emission tomography plus CT (18-FDG-PET/CT) not be withheld from a pregnant person if clinically indicated.	1C
3	We recommend initiating thromboprophylaxis for all patients with active hematological or gynecological cancers during pregnancy and considering thromboprophylaxis for all patients with nonhematological or nongynecological cancers during pregnancy, based on individual risk factors.	1C
4	We recommend that surgery for the treatment of cancer not be delayed or withheld from a pregnant patient at any gestational age in pregnancy.	1C
5	We recommend that chemotherapy generally be administered after 12 weeks of gestation, provided that the patient desires to continue the pregnancy and that delaying treatment until after 12 weeks of gestation is not expected to significantly change the pregnant patient's prognosis compared with initiating treatment immediately after diagnosis.	1C
6	To improve long-term neurodevelopmental outcomes of children exposed to chemotherapy in utero, we suggest avoiding clinician-initiated preterm delivery when possible.	2C
7	We recommend intravenous methylprednisolone, 62.5 mg (corresponding to 10 mg of dexamethasone), or oral prednisolone, 30 mg (corresponding to 6 mg of dexamethasone), as first-line therapy for chemotherapy-induced nausea when corticosteroids are indicated.	1B
8	We recommend serial fetal growth surveillance every 3–4 weeks in pregnancies with an active cancer diagnosis, regardless of treatment.	1C
9	We recommend initiation of antenatal fetal surveillance starting at 32 weeks of gestation in pregnancies with an active cancer diagnosis, regardless of treatment, unless indicated earlier for maternal or fetal reasons.	1C
10	We recommend that planned delivery prior to 37 weeks of gestation in pregnant patients with cancer generally be avoided unless indicated for medical or obstetrical reasons.	1C
11	We recommend that chemotherapy treatment generally be stopped by 34 weeks of gestation to allow 3–4 weeks for recovery of myelosuppression before spontaneous labor or planned delivery, except for weekly paclitaxel, which can be administered up to 35 or 36 weeks, as only 1–2 weeks are necessary for recovery before delivery.	1C
12	We recommend that the mode of delivery be determined by routine obstetrical indications for most patients with cancer in pregnancy.	1C
13	We recommend a placental pathology examination in all cases of cancer during pregnancy, regardless of cancer type or treatment.	1C
14	We recommend that cancer be considered as part of the differential diagnosis for pregnant patients with multiple chromosomal aneuploidies or single autosomal monosomy detected by cell-free DNA screening that is discordant with fetal findings.	1C

[a]See the Supporting Information for the evidence summary table.

Society for Maternal-Fetal Medicine grading system: grading of recommendations assessment, development, and evaluation (GRADE) recommendations [283, 284].

GRADE of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Consistent evidence from well-performed, randomized controlled trials, or overwhelming evidence of some other form Further research is unlikely to change confidence in the estimate of benefit and risk	Strong recommendation that can apply to most patients in most circumstances without reservation Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate	Strong recommendation that applies to most patients Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present
1C. Strong recommendation, low-quality evidence	Benefits appear to outweigh risks and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws Any estimate of effect is uncertain	Strong recommendation that applies to most patients Some of the evidence base supporting the recommendation is, however, of low quality
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form Further research is unlikely to change confidence in the estimate of benefit and risk	Weak recommendation; best action may differ depending on circumstances or patients or societal values
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws Any estimate of effect is uncertain	Very weak recommendation; other alternatives may be equally reasonable
Best practice	Recommendation in which either (i) there is an enormous amount of indirect evidence that clearly justifies a strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize) or (ii) recommendation to the contrary would be unethical		

Source: Adapted from [284].

Guidelines.

The content of this document reflects the national and international guidelines related to cancer in pregnancy.

Organization	Title	Year of publication
Academy of Breastfeeding Medicine	ABM Clinical Protocol #34: Breast Cancer and Breastfeeding [235]	2020
American College of Obstetricians and Gynecologists	Committee Opinion No. 723: Guidelines for Diagnostic Imaging during Pregnancy and Lactation [29]	2017
American College of Obstetricians and Gynecologists	ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy [230]	2018
American College of Obstetricians and Gynecologists	Indications for Outpatient Antenatal Fetal Surveillance: ACOG Committee Opinion, Number 828 [211]	2021
American College of Obstetricians and Gynecologists	Infertility: Disparities and Access to Services: Committee Statement No. 14 [248]	2025
American Society of Clinical Oncology	Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update [255]	2018
American Society of Clinical Oncology	ASCO Ethical Guidance for the US Oncology Community Where Reproductive Health Care Is Limited by Law [79]	2023
American Society for Reproductive Medicine	Fertility Preservation in Patients Undergoing Gonadotoxic Therapy or Gonadectomy: A Committee Opinion [254]	2019
European Society of Gynecological Oncology, International Network on Cancer, Infertility and Pregnancy	Guidelines for the Management of Patients with Gynecological Cancers during Pregnancy [74]	2025
Royal College of Obstetricians and Gynaecologists	Green-Top Guideline No. 37a: Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium [53]	2015
Society of Family Planning	Society of Family Planning Committee Statement: Contraceptive Considerations for Individuals with Cancer and Cancer Survivors Part 1—Key Considerations for Clinical Care; Joint with the Society of Gynecologic Oncology [278]	2025
Society of Family Planning	Society of Family Planning Clinical Recommendation: Contraceptive Considerations for Individuals with Cancer and Cancer Survivors Part 2—Breast, Ovarian, Uterine, and Cervical Cancer [280]	2025
Society of Family Planning	Society of Family Planning Clinical Recommendation: Contraceptive Considerations for Individuals with Cancer and Cancer Survivors Part 3—Skin, Blood, Gastrointestinal, Liver, Lung, Central Nervous System, and Other Cancers [281]	2025

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SMFM recognizes that obstetrical patients have diverse gender identities and strives to use gender-inclusive language in all publications. SMFM uses terms such as "pregnant person" and "pregnant individual" and the singular pronoun "they." When describing study populations

used in research, SMFM uses the terminology reported by the study investigators.

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