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INTEGRATED STUDY MASTER'S FINAL THESIS

Cancer During Pregnancy: a Literature Review of the Five Most Common Tumours and Their Obstetric Implications

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ABBREVIATIONS

AJCC = American Joint Committee on Cancer

AL = Acute leukemia

ALARA = As Low as Reasonably Achievable

ALL = Acute lymphoblastic leukemia

AML = Acute myeloid leukemia

AYA = Adolescents and young adults

CRC = Colorectal carcinoma

DTC = Differentiated thyroid cancer

FIGO = International Federation of Gynecology and Obstetrics

FNA = Fine-needle aspiration

FTC = Follicular carcinoma

HL = Hodgkin lymphoma

HPV = Human papillomavirus

IUGR = Intrauterine growth restriction

LVSI = Lymphovascular space invasion

MPN = Myeloproliferative neoplasms

NACT = Neoadjuvant chemotherapy

NHL = Non-hodgkin lymphoma

PABC = Pregnancy associated breast cancer

PAC = Pregnancy associated cancer

PAM = Pregnancy-associated melanoma

Pap test = Papanicolaou test

PA-HL = Pregnancy-associated Hodgkin lymphoma

PA-NHL = Pregnancy-associated Non-Hodgkin lymphoma

PTC = Papillary thyroid carcinoma

SLNB = Sentinel lymph node biopsy

TBG = Thyroxine-binding globulin

TSH = Thyroid-stimulating hormone

SUMMARY

The occurrence of cancer during pregnancy, estimated at 1 in 1,000 to 1,500 cases, is becoming more significant due to trends toward delayed childbearing and advanced maternal age. This narrative review examines the interaction between pregnancy and the most common malignancies, focusing on epidemiology, diagnostic challenges, treatment options, and obstetric management across breast cancer, cervical cancer, hematologic malignancies, melanoma and thyroid cancer.

Diagnosis is often delayed by around four weeks, as physiological changes of pregnancy can mask cancer symptoms. Some entities profit from routine prenatal screening, which leads to detection in early stages. Management requires balancing maternal oncologic treatment with fetal safety. Surgery and chemotherapy after the first trimester are generally feasible, while radiotherapy and certain systemic agents remain contraindicated. Gestational age is the key determinant of treatment timing and feasibility.

Maternal prognosis is mainly driven by tumor biology and stage, whereas fetal outcomes depend largely on obstetric management, with iatrogenic prematurity representing the main source of neonatal morbidity. Direct tumor effects on the fetus are rare.

The effective management of cancer in pregnancy relies on an individualized and multidisciplinary framework aimed at balancing maternal and fetal outcomes.

SANTRAUKA

Vėžys, komplikuojantis nėštumą, pasitaiko maždaug 1 iš 1 000–1 500 nėštumų ir tampa vis aktualesnis dėl didėjančio motinų amžiaus bei vėlesnio gimdymo. Šioje apžvalgoje nagrinėjama nėštumo ir dažniausių piktybinių navikų sąveika, daugiausia dėmesio skiriant epidemiologijai, diagnostikos sunkumams, gydymo galimybėms ir akušerinei taktikai krūties, gimdos kaklelio, kraujo sistemos piktybinių navikų, melanomos ir skydliaukės vėžio atvejais.

Diagnozė dažnai nustatoma maždaug keturiomis savaitėmis vėliau, nes nėštumo fiziologiniai pokyčiai gali užgožti vėžio simptomus. Kai kurių onkologinių ligų atvejais reguliari nėščiųjų patikra gelbsti, nes leidžia aptikti vėžį ankstyvosiose stadijose. Gydymo taktika turi būti suderinta taip, kad būtų užtikrinta pusiausvyra tarp motinos onkologinės ligos gydymo ir vaisiaus saugumo. Chirurginė operacija ir chemoterapija po pirmojo nėštumo trimestro paprastai yra įmanomos, o spindulinė terapija ir tam tikri sisteminiai vaistai lieka kontraindikuotini. Nėštumo trukmė yra pagrindinis veiksnys, lemiantis gydymo laiką ir jo įgyvendinamumą.

Motinos prognozę daugiausia lemia naviko biologija ir stadija, o vaisiaus baigtis didžiąja dalimi priklauso nuo akušerinės taktikos, visgi iatrogeninis priešlaikinis gimdymas yra pagrindinė naujagimių sergamumo priežastis. Tiesioginis naviko poveikis vaisiui pasitaiko retai.

Apskritai, vėžio atvejais nėštumo metu reikalingas daugiadisciplinis, individualizuotas požiūris, kad būtų galima veiksmingai suderinti motinos ir vaisiaus baigtį.

KEYWORDS

Cancer in pregnancy, pregnancy-associated cancer, obstetric management, maternal cancer treatment, fetal outcomes

1. INTRODUCTION

Cancer during pregnancy is an increasingly significant clinical entity, occurring in approximately 1 in 1,000 to 1,500 pregnancies. While traditionally considered rare, its incidence is rising in high-income countries due to delayed childbearing and increasing maternal age (1). As a result, pregnancy increasingly overlaps with the age range of highest cancer risk (2).

Pregnancy-associated cancer (PAC) presents a unique clinical challenge. The masking of early symptoms due to physiological changes in pregnancy can lead to delayed diagnosis, while the implementation of diagnostic and therapeutic measures requires careful consideration of fetal safety (3).

Management of cancer in pregnancy requires balancing maternal oncologic treatment with fetal well-being, often necessitating individualized, multidisciplinary decision-making (3).

1.1. Aim of the Review

The aim of this narrative literature review is to provide a structured and clinically relevant overview of cancer during pregnancy, with a focus on the five malignancies most commonly encountered in this setting. In particular, this review aims to compare diagnostic challenges, treatment strategies, and obstetric management across these tumor types, and to highlight key factors influencing both maternal and fetal outcomes.

2. METHODOLOGY

This thesis was conducted as a narrative literature review with the aim of providing a comprehensive and clinically oriented overview of cancer during pregnancy, focusing on the most common malignancies and their obstetric implications. A narrative review design was chosen due to the heterogeneity of available evidence, the rarity of pregnancy-associated cancer and the lack of large randomized controlled trials in this field. This approach allows for an integrative synthesis of clinical guidelines, observational studies, systematic reviews, and expert consensus statements.

2.1. Literature Search Strategy

A literature search was carried out using the electronic databases PubMed and Scopus to identify relevant publications addressing cancer during pregnancy. The search was conducted between October 2025 and February 2026.

Search terms included combinations of keywords related to pregnancy and cancer, such as “cancer in pregnancy”, “pregnancy-associated cancer”, “breast cancer in pregnancy”, “cervical cancer in pregnancy”, “hematologic malignancies in pregnancy”, “melanoma in pregnancy”, “thyroid cancer in pregnancy”.

The primary search focused on publications released between 2010 and 2026 in order to reflect current clinical practice and recent developments in oncologic and obstetric care. However, earlier landmark publications were also considered, when they provided essential information or widely cited epidemiological data. After the initial search, titles and abstracts were reviewed for relevance to the topic of cancer during pregnancy, and full texts were subsequently assessed when the abstracts indicated potential relevance.

2.2. Literature Selection

Literature was selected based on its relevance to the clinical management, epidemiology, and obstetric implications of cancer during pregnancy. This process followed a flexible approach, consistent with the narrative design of the review.

2.2.1. Inclusion Criteria

- Focus on cancer during pregnancy, specifically the five most common malignancies: breast cancer, cervical cancer, hematologic malignancies, melanoma and thyroid cancer
- Publication types: Peer-reviewed articles, including:
    - Systematic and narrative reviews
    - Literature reviews
    - Meta-analyses
    - Population-based or observational studies
    - Clinical practice guidelines
- Time frame: Publications from 2010 to 2026, with earlier seminal studies included if relevant.
- Language: English.

2.2.2. Exclusion Criteria

- Studies not related to pregnancy-specific cancer management
- Non-peer-reviewed sources

- Abstracts without accessible full text
- Non-English publications
- Studies lacking information on clinical management, obstetric planning or maternal-fetal outcomes

3. EPIDEMIOLOGY OF CANCER IN PREGNANCY

3.1. Overall Incidence

The incidence of cancer during pregnancy is a rare but growing clinical challenge that requires a complex balance between the health of the mother and the protection of the fetus (3,4). Pregnancy-associated cancers is generally defined as a malignant disease diagnosed either during pregnancy or within one year postpartum (5–7).

The estimated frequency of pregnancy-associated cancers is around 1 case per 1,000 pregnancies in most studies (2,6,7). Other research indicates a wider range of 1 in 1,000 to 1 in 1,500 or even 1 in 2,000 pregnancies (1,8). Systematic reviews show that about 25% of cases are detected directly during pregnancy, while the majority of diagnoses are made in the postpartum period (4).

The incidence rates vary considerably depending on the type of cancer. For example, the global frequency of pregnancy-associated breast cancer (PABC) is estimated approximately 19.2 cases per 100,000 pregnancies (5). For invasive cervical carcinoma in pregnancy, estimates range from 1.4 to 4.6 cases per 100,000 pregnancies (8). Hematological malignancies are less common, such as Hodgkin lymphoma with approximately 8.06 cases per 100,000 births or leukemia with a rate of 1 per 75,000-100,000 pregnancies (10,11).

3.1.1. Global Trends and Geographical Variations

A global upward trend in the diagnosis of PAC can be observed (3–5,8,12). Between 2000 and 2019, the share of deliveries associated with active cancer increased twofold, according to U.S. inpatient data. (12). Similar developments can be seen in Denmark, where the number of cases rose from 572 in the period of 1977-1986 to 1,052 in the years 1997-2006 (13). In Canada, in the province of Alberta, some of the highest incidence rates reported in the literature were observed, with up to 156.2 cases per 100,000 deliveries (6).

Geographical differences often reflect the incidence of cancer in the general population. For example, the risk of pregnancy-associated melanoma is significantly higher in countries with a generally high melanoma rate, such as Australia (4). Interestingly, there are regions where no significant increase has been observed over the decades, such as Lombardy in Italy between 2001 and 2012 (4,14). It is also suspected that incidence rates in developing countries may be higher in some cases than in developed industrialized nations (5).

3.1.2. Increasing Maternal Age, Reproductive Timing, and Other Risk Factors

The primary driver of the increase in PAC is the shift in maternal age at birth (delayed childbearing) (3,7,8,12,15). Between 1970 and 2023, the mean age at which women in the U.S. have their first child increased from 21.4 years to 27.5 years, reflecting a substantial upward trend (8). Since the overall risk of cancer is highly age-dependent, this sociodemographic change increases the likelihood that a woman will develop cancer during her fertile years (3,4,16). Maternal age is now considered the leading risk factor for cancer diagnosis during or shortly after pregnancy (17). The risk analysis illustrates how strongly the incidence correlates with increasing age. While the risk for women under 30 is around 60 per 100,000 pregnancies, it rises sharply to 265 per 100,000 for women over 40 (14). In addition to age, other factors have been identified that can influence the risk of PAC. These include smoking, nulliparity, and a non-migrant background (17). Non-obstetric trends in the population, such as the increase in obesity, lack of exercise, and changes in dietary patterns, are also being discussed as potential factors influencing the incidence of cancer in younger adults, which indirectly affects PAC statistics (6,15).

3.1.3. Improved Diagnostic Detection and Challenges

Improved diagnostic capabilities contribute to the reported rise in incidence (4,12). Modern imaging techniques and increased medical vigilance during pregnancy lead to earlier detection of tumors (4). A significant technological advance is non-invasive prenatal testing (NIPT). Although this test was primarily developed to detect fetal chromosomal abnormalities, it can incidentally identify occult maternal malignancies at an early stage by analyzing cell-free DNA in maternal blood (8,18).

Despite these advances, diagnosis during pregnancy remains difficult. Physiological changes such as nausea, fatigue, anemia, or changes in breast tissue can mask the symptoms of a tumor (3,4,8,15,19). This often leads to delayed diagnosis, which is why a significant proportion of PAC cases are only diagnosed postpartum, once the physiological changes of pregnancy have subsided (4,6). One theory for the “postpartum rebound effect” also suggests that cancers that were overlooked during pregnancy due to diagnostic reluctance become more apparent immediately after birth (4).

3.2. Most common cancers in pregnancy

The distribution of cancer types in pregnant women reflects the spectrum of malignancies that typically occur in women of reproductive age (20). The most diagnosed types of tumors are:

1. Breast cancer
2. Cervical carcinoma
3. Hematological malignancies (Lymphomas and leukemias)
4. Malignant melanoma

5. Thyroid carcinoma (4,9).

Besides these, colorectal carcinoma (CRC) is also considered a rare but increasingly clinically relevant diagnosis during pregnancy. The growing clinical significance of CRC during pregnancy is linked to the rising frequency of early-onset colorectal cancer (diagnosis under the age of 50 years). As childbearing is increasingly postponed to later reproductive ages, when the biological risk of early-onset CRC is higher, the number of cases during gestation is expected to increase (15).

3.2.1. Correlation with Reproductive Age

The accumulation of these specific types of cancer can be explained by the overlap between the typical age of onset of the tumors and the delayed childbearing age of women (3).

In the context of cervical cancer, the peak incidence of underlying HPV infections occurs between the ages of 20 and 30, which correlates with the phase of highest fertility (8). The same applies to Hodgkin lymphoma, which peaks in young adults aged 25 to 34 (10).

3.2.2. Regional Differences

While the overall distribution of PAC appears largely consistent worldwide, international data indicate regional variations in incidence patterns.

- In Australia and Denmark, malignant melanoma often ranks first among PAC diagnoses, reflecting the high rate of skin cancer among the young general population in these regions (4,13).
- In Italy and the United States, breast cancer and thyroid carcinoma often represent the most prevalent malignancies (4).
- In Sweden, breast cancer is the most common, while melanoma and cervical cancer rank second and third (4).
- In Canadian studies, breast cancer was the leading diagnosis during pregnancy (6).

3.2.3. Epidemiological Characteristics

3.2.3.1. Pregnancy-Associated Breast Cancer

Breast cancer is the most commonly diagnosed PAC, reflecting the overall incidence of this malignancy in women of childbearing age (21). The global incidence is reported at approximately 19.2 cases per 100,000 pregnancies (5). Women younger than 40 years account for roughly 10% of all breast cancer cases. Among adolescents and young adults (AYA; 15-39 years of age), the leading cancer diagnosis is breast cancer. Between 0.2% and 2.6% of all breast cancer cases are estimated to be diagnosed during gestation, whereas most cases in women younger than 45 years occur within 5-10 years postpartum (21).

3.2.3.2. Cervical Cancer

Cervical cancer is the most common gynecological malignancy in pregnancy. The incidence is estimated at approximately 1.4 to 4.6 cases per 100,000 pregnancies (8).

3.2.3.3. Malignant Melanoma

In many Western countries, melanoma is one of the three most common PAC diagnoses (4,13,17). Nearly one-third of all cancers diagnosed during pregnancy are attributable to this cancer type (22). Its occurrence shows marked regional variation, with melanoma often ranking among the leading PAC in high UV-exposure regions (4,13).

3.2.3.4. Thyroid Cancer

Thyroid cancer is particularly common in the postpartum period (6,16). It is one of the most common diagnosed malignancies in women of reproductive age, with an increasing incidence worldwide (16).

3.2.3.5. Hematological Cancers

Within the group of women in reproductive age, Hodgkin lymphoma is the most common, as it mainly affects people in young adulthood. Non-Hodgkin lymphoma (NHL) has been only infrequently reported (11). Most cases of leukemia present as acute, either myeloid - accounting for about two-thirds - or lymphoid. Chronic leukemias and myelodysplastic syndromes are rare in pregnancy (11).

4. GENERAL PRINCIPLES OF CANCER MANAGEMENT DURING PREGNANCY

4.1. Multidisciplinary Approach

To best balance the often competing interests of maternal health and fetal safety, multidisciplinary care is essential (23).

An effective team consists of experts from various medical specialties (24). These primarily include medical oncologists, obstetricians, perinatologists, and neonatologists (15). Depending on the type of cancer, other specialists may be involved, such as radiologists for safe imaging, gynecologic oncologists, or hematologists (3,8). Specialized nurses (cancer care coordinators), dietitians, social workers, and psychologists provide support to help alleviate the patient’s immense emotional burden (15).

4.1.1. Role of Tumor Boards and Individualized Treatment Planning

The tumor board serves as the central decision-making body. Each case is evaluated individually during interdisciplinary case conferences. Each board determines the appropriate treatment strategy, including modality choice as well as the sequencing and timing of interventions (21). In doing so,

epidemiological, pathophysiological, and teratogenic risks (e.g. from ionizing radiation or chemotherapeutic agents) must be weighed against the benefits of treatment (3). The goal is a treatment plan that maximizes the mother's chances of cure while minimizing the child's morbidity (8).

The decision regarding treatment is highly individualized and depends on the tumor stage, weeks of gestation, and the patient's personal preferences. The guiding principle is that the patient should be treated as closely as possible according to standard protocols for non-pregnant patients, while maintaining the pregnancy for as long as possible (21).

4.1.2. Communication About Risks and Options

All communication should take place within a compassionate culture. The entire team is responsible for providing information, although oncologists and obstetricians are often the primary points of contact. Decision-making should be based on informed consent in which maternal and fetal risks are openly discussed. Suboptimal counseling on topics such as fertility preservation or termination of pregnancy should be avoided by involving psychosocial services (2,3). Since medical facts alone are often insufficient, the patients personal preferences, religious beliefs, and values must play a decisive role in the decision-making process (25).

4.2. Decision-Making Patterns

4.2.1. Immediate Treatment vs. Wait-and-See Approach

In the case of aggressive diseases such as acute leukemia (AL), the mother's health takes priority, which may necessitate termination of the pregnancy in the early stages to allow for adequate treatment (11). For other tumors (e.g. early-stage cervical cancer), a wait-and-see approach or delaying treatment until the second trimester may be justifiable (8).

4.2.2. Trimester-Specific Considerations

The guiding principle is that the patient should undergo standard oncological treatment while maintaining the pregnancy as long as possible (21).

4.2.2.1. 1st Trimester (Week 1-12)

During the first 12 weeks, organogenesis takes place, particularly weeks 6-10. During this time the fetus is extremely sensitive to teratogens (8). Exposure to certain chemotherapeutic agents, such as fluorouracil, during the first trimester has been linked to a malformation rate over 30% and is therefore not recommended (15). In cases of aggressive diseases, for example AL, pregnancy termination may be required to initiate immediate treatment (11).

4.2.2.2. 2nd Trimester (Week 13-27)

Surgical procedures are considered to be safest when performed during the second trimester. In this phase of pregnancy, the fetus remains relatively small, allowing improved access to the abdominal cavity, with a lower risk of pregnancy loss or preterm labor than in the first and third trimesters (8). Systemic chemotherapy can often be administered safely only starting from the 12th to 14th week (23).

4.2.2.3. 3rd Trimester (Week 28-Labor)

The primary goal is to reach fetal maturity. Since cancer treatment often leads to iatrogenic preterm birth, close coordination of the timing of delivery, ideally from 37 weeks onward, is crucial. In case of ongoing chemotherapy during pregnancy, the final chemotherapy session scheduled approximately 2-4 weeks before delivery to stabilize bone marrow function (1,2).

4.3. Monitoring of Mother and Fetus

A key factor for success is treatment at specialized tertiary centers that possess the necessary expertise in oncology and neonatology, including access to neonatal intensive care units (8).

4.3.1. Diagnostic Imaging Principles

Diagnostic imaging during pregnancy should always follow the ALARA principle (As Low As Reasonably Achievable) to keep radiation exposure to the fetus as low as possible. Diagnostic procedures should be timed patient-specific, given the need for timely cancer detection, the risks associated with diagnostic delay, and the requirement to balance both the maternal and fetal risks (2). In this setting, preference is given to imaging modalities like ultrasonography and magnetic resonance imaging without contrast agents, as they are considered safe. Diagnostic procedures that rely on ionizing radiation, such as computer tomography or positron emission tomography are, however, used selectively only when there is an urgent medical indication and after careful consideration of the benefits and risks (2).

Several factors influence the risk to the fetus from ionizing radiation, including overall dose, length of exposure, and, when applicable, the radionuclide used. Radiation-related fetal effects are also strongly influenced by gestational timing, ranging from early embryonic loss shortly after conception to congenital anomalies in early pregnancy and subsequent neurodevelopmental impairment, including reduced IQ, in later stages. Threshold-dependent effects are typically observed at exposure levels exceeding 100-200mGy If several imaging studies are necessary, careful monitoring of cumulative fetal radiation dose is essential (21).

4.3.2. Fetal Monitoring

Given the association between chemotherapy administered during the second and third trimesters and adverse fetal growth outcomes, including low birth weight, fetal growth must be monitored regularly via ultrasound. Following chemotherapy, it is often recommended to monitor maximum systolic velocity of the middle cerebral artery in order to detect fetal anemia at an early stage. Finally, extended postnatal monitoring of the offspring is required to assess possible delayed effects related to exposure during pregnancy (8,21).

4.3.3. Maternal Monitoring

In addition to oncological monitoring, close obstetric care is necessary to manage complications such as fetal growth restriction or preterm birth, which occur more frequently in women with PAC receiving chemotherapy (8).

4.4. Fundamental Ethical Questions

Managing cancer requires a highly individualized ethical evaluation that aims to ensure maternal survival while carefully preserving the potential life and development of the fetus.

Iatrogenic preterm birth is the leading complication, as birth is commonly induced or scheduled before spontaneous delivery begins, to intensify the mother's treatment (1). The ethical challenge lies in determining the optimal time for delivery, balancing the risk of the infant's immaturity against the risk of disease progression in the mother. Psychological support is of enormous importance for the mother in coping with anxiety and depression (2). Fortunately, long-term studies show that, with appropriate treatment, the prognosis for mothers is generally no worse than that for non-pregnant patients (1).

4.4.1. Abortion

Termination of pregnancy is typically considered when an aggressive form of cancer, as AL or advanced hematologic malignancies, requires immediate, highly toxic therapy as early as the first trimester. In such cases, delaying treatment can significantly reduce the mother's chances of recovery (11). If the patient decides against continuing the pregnancy, treatment is carried out according to standard protocols for non-pregnant women (8). For diagnoses made later in pregnancy, continuing the pregnancy under close monitoring is often feasible (11).

5. CANCER-SPECIFIC CLINICAL CONSIDERATIONS AND OBSTETRICAL MANAGEMENT

5.1. Breast Cancer in Pregnancy

The definition of pregnancy-associated breast cancer generally refers to breast cancer diagnosed during gestation or within the first year after childbirth (6). In other epidemiological studies, this timeframe is prolonged up to two years postpartum (20). PABC is the most commonly diagnosed type of cancer during pregnancy and affects around 1 in 3.000-10.000 women, corresponding to an estimated 2.000-4.000 affected women in Europe each year (21).

5.1.1. Clinical Presentation & Delayed Diagnosis

The diagnostic challenge with PABC lies in the massive physiological adaptions in the mother's breast tissue in the course of pregnancy. Under the influence of pregnancy hormones, there is marked hypertrophy of the mammary glands, increased vascularity, and a significant increase in tissue density. These normal changes cause general swelling and increased breast tenderness, which makes palpation significantly more difficult. The most common symptoms of PABC are palpable lump or nipple discharge (21). Since pregnancy-related changes of the breast can mask these symptoms, careful assessment is advised for any palpable or suspicious mass that remains present for more than two weeks in pregnancy (19,21).

5.1.2. Diagnostic Evaluation of Breast Cancer

In terms of diagnosis, the clinical examination is the first step; however, imaging techniques are essential for an accurate assessment. Breast ultrasound and mammography are the preferred modalities for initial diagnosis and local staging (21).

5.1.2.1. Local Staging

Mammography is considered safe even during pregnancy, provided the fetus is properly protected. However, ultrasound is often the preferred method, as it does not use ionizing radiation and can effectively distinguish between solid masses and benign lesions, such as cysts. In pregnancy, the identification of malignancy is associated with a sensitivity of 80.1% and a specificity of 88.4% (21). In combination with bilateral mammography (craniocaudal and mediolateral oblique views) it is used to evaluate the extent of the tumor and to detect possible multifocality or involvement of both breasts. Regional lymph node status is evaluated sonographically, with suspicious nodes verified by fine-needle aspiration (FNA) or biopsy. Disease staging is based on the American Joint Committee on Cancer (AJCC) tumor, node and metastasis staging system (21).

5.1.2.2. Distant Staging

For further staging to detect distant metastases, the ALARA principle must be strictly followed. This means that every diagnostic procedure must be planned in such a way that radiation exposure to the embryo or fetus is kept as low as possible (2).

Imaging modalities involving ionizing radiation, such as CT and PET/CT, should only be applied in selected cases during pregnancy when diagnostic uncertainty persist and when the findings are expected to have a relevant impact on clinical decision-making without the possibility of postponement until the postpartum period. Cumulative fetal doses exceeding 100mGy should be avoided (21).

5.1.2.3. Pathological Phenotype

The phenotype of PABC is similar to that commonly found in younger breast cancer populations, with a predominance of high-grade invasive carcinoma not otherwise specified, often accompanied by aggressive features, including larger tumor size, increased lymph node involvement, and lymphovascular space invasion (LVSI) (21).

5.1.3. Treatment during Pregnancy

Treatment decisions in PABC are guided by gestational age and cancer stage and require close collaboration within a multidisciplinary team involving specialists from surgical disciplines, medical and radiation oncology, as well as experts in maternal and fetal medicine alongside additional supportive care teams. Where clinically appropriate, initiation of therapy should be delayed until the first trimester has been completed in order to limit risk of teratogenicity (19).

5.1.3.1. Surgery

Surgical intervention is generally feasible throughout all stages of gestation; however, the first trimester is considered less suitable because of increased vulnerability during early fetal development. Since breast surgery does not involve the abdominal cavity, the likelihood of adverse obstetric and fetal outcomes, including pregnancy loss, early delivery and comprised fetal well-being, is considered relatively low (19). In principle, surgical management should adhere to the same principles as in non-pregnant patients, with breast-preserving approaches being preferred if conditions allow. The selection of mastectomy versus breast-sparing approaches is further determined by the planned use of neoadjuvant systemic therapy (19). The scheduling of surgical intervention should be tailored to individual circumstances, taking into account tumor-related factors, the stage of gestation, and the patient's wishes, whereas non-urgent procedures are generally deferred until the postpartum period (21).

Intraoperative fetal heart rate monitoring using cardiotocography remains controversial but may be considered depending on stage of pregnancy and fetal viability. Uteroplacental circulation largely relies on maternal arterial pressure and does not exhibit effective autoregulatory capacity; consequently, episodes of maternal hypotension, such as caused by hemorrhage or hypovolemia, may reduce placental perfusion and lead to fetal hypoxia. After 20 weeks of gestation, positioning the patient in a left lateral tilt is essential to prevent vena cava compression to maintain adequate maternal circulation (21).

Irrespective of timing, surgical procedures should take place in facilities that provide rapid availability of both obstetric and neonatal support to ensure appropriate management of arising complications (21).

The use of sentinel lymph node staging in pregnant patients is regarded as a safe approach. When indicated, the procedure is typically carried out using technetium-99m as the tracer, as this approach is not associated with increased risk to the mother or the fetus if appropriate protocols are followed. In contrast, the application of blue dye is typically avoided, as it carries a small but relevant chance of maternal anaphylactic reactions, which may lead to fetal compromise (19).

5.1.3.2. Systemic Therapy

Chemotherapy

Chemotherapy represents a central component of breast cancer treatment in young patients and is also the preferred approach in case of metastatic disease (21). In PABC, management is guided by principles comparable to those used in non-pregnant individuals. When planning treatment, both the stage of pregnancy and the broader therapeutic concept need to be considered, particularly with regard to surgical timing, possible administration of HER2-directed therapies, and whether radiotherapy is indicated (21). Chemotherapy can be administered after the first trimester (from approximately 12 weeks of gestation) and may be used in both neoadjuvant and adjuvant settings (21).

Agents feasible during pregnancy include anthracyclines, fluoropyrimidines, taxanes, and platinum compounds (19,21). Methotrexate is contraindicated throughout pregnancy due to its teratogenic potential. Available evidence indicates that chemotherapeutic exposure beyond the first trimester is linked to malformation rates comparable to those in the general population, supporting its relative safety during this period (21).

To reduce the risk of impaired maternal and fetal bone marrow recovery, chemotherapy should be discontinued prior to delivery and is generally avoided beyond 35-37 weeks of gestation, depending on the regimen (21).

Ultimately, any delay in treatment to reduce fetal risk must be carefully weighed against the potential for maternal harm (19,21).

Targeted Therapy

Data on targeted therapies during pregnancy remain limited. It should be noted that these agents act on tumor-specific pathways that also play essential roles in fetal growth and development.

Although HER2-targeted therapy is a cornerstone in the treatment of HER2- positive breast cancer, monoclonal antibodies such as trastuzumab and pertuzumab are contraindicated during pregnancy (19).

Trastazumab contact during the early fetal development pahse appears to carry a lower risk, as the active placental transport mechanisms required to reach the fetus are not yet functional. After approximately 14 weeks of gestation, this transplacental transport becomes active, increasing fetal exposure and the risk of adverse effects; therefore, trastazumab should be avoided beyond the first trimester (21).

Endocrine Therapy

The use of hormonal therapy is generally contraindicated throughout pregnancy and is typically deferred to the postnatal period. Exposure to tamoxifen during gestation has been linked to a higher likelihood of congenital malformations and pregnancy loss; however, the existing evidence remains limited (21). Importantly, fetal abnormalities have been described even when pregnancy is initiated shortly after stopping tamoxifen, particularly within a timeframe of approximately two months following cessation. As tamoxifen may impair milk secretion, its use is not advised in the postnatal period (19).

5.1.3.3. Radiation Therapy

Due to the potential of fetal toxicity, including growth restriction, congenital abnormalities, and pregnancy loss, radiotherapy is contraindicated during pregnancy and is commonly deferred until after childbirth. Although postponement of therapy for several weeks – up to roughly three months – may be acceptable in selected cases, such delays have been linked to a gradual rise in the risk of local disease recurrence, estimated at around 1% per month. These considerations should be integrated into surgical decision-making, particularly since in early gestation a mastectomy may be chosen more often to avoid the need for prompt subsequent adjuvant treatment (19).

5.1.4. Clinical Indications for Pregnancy Interruption

Pregnancy-associated breast cancer presents healthcare providers with the challenge of balancing the mother's oncological safety with the protection of the unborn child. In modern oncology, the principle holds that induced abortion generally does not improve the mother's outcome and is therefore not

routinely recommended. Nevertheless, there are specific clinical situations in which termination of pregnancy must be considered (1,21).

5.1.4.1. Therapeutic Urgency in the First Trimester

The most significant clinical indication arises during the first trimester, when immediate systemic therapy is absolutely necessary. Since chemotherapy is strictly contraindicated during organogenesis to prevent severe malformations, treatment must be postponed until the second trimester. In cases of extremely aggressive, rapidly progressing tumors, this delay can significantly worsen the mother's chances of recovery, which may constitute a medical indication for termination (2,21).

5.1.4.2. Necessity of Contraindicated Treatments

Certain systemic therapies are contraindicated throughout pregnancy, including HER2-targeted agents and endocrine therapies (19). If maternal survival critically depends on the use of such contraindicated treatments and no safe alternative is available, this may constitute an indication for termination of pregnancy (2,21).

5.1.4.3. Advanced Metastasis and Palliative Care

For patients who already have advanced metastatic disease at the time of diagnosis, the primary focus is on preserving the mother's health and quality of life. If the necessary palliative treatment carries a high risk of fetal toxicity or if the mother's life expectancy is so low that the fetus is unlikely to reach viability, termination of pregnancy may be clinically indicated (21).

5.1.4.4. Patient Preference and Ethical Considerations

A key factor is the value-based, informed consensus process. An indication for termination exists if, after receiving comprehensive information about the risks of treatment during pregnancy (e.g. iatrogenic preterm birth), the patient refuses to continue the pregnancy in order to receive standard treatment in accordance with protocols for non-pregnant women (1,2).

5.1.5. Obstetrical Management

Multidisciplinary collaboration is central to the management of any pregnancy-associated malignancy, in order to ensure the mother's oncological safety and the well-being of the child. The planning of delivery, the mode of delivery, and subsequent postpartum management must be tailored individually to the stage of cancer, the treatment plan and the gestational age (2).

5.1.5.1. Delivery Planning

The primary goal of birth planning at PABC is to maintain the pregnancy for as long as possible to minimize the risks associated with preterm birth (21). According to current guidelines, delivery should ideally be scheduled at or after 37 weeks of gestation (21). A key factor in determining the timing is coordination with systemic therapy. If the patient is receiving chemotherapy, the last dose must be scheduled to ensure a safety margin of 2-4 weeks prior to the expected delivery date. This period is essential to allow for recovery of the maternal and fetal bone marrow. Delivery during the nadir phase (the lowest point in blood counts following chemotherapy) must be avoided, as this would significantly increase the risk of serious infections and hemorrhagic complications in both the mother and the newborn (2,19).

5.1.5.2. Birth Mode

With regard to the mode of delivery, there is a consensus in the medical literature that cancer alone does not constitute a mandatory indication for a caesarean section. The determination of the delivery strategy should be based primarily on obstetric criteria (21).

In the absence of clear medical contraindications, vaginal delivery is usually favored. A cesarean section is usually considered only when there are urgent obstetric reasons or when very precise timing is required for the immediate initiation of aggressive postpartum therapies (such as radiation therapy) that cannot wait until spontaneous delivery (2,21).

5.1.5.3. Postpartum Management

In the absence of contraindications, administration of low-molecular-weight heparin for thromboprophylaxis should be evaluated in the postpartum period. Provided that no systemic or radiation therapy is scheduled, breastfeeding is generally considered acceptable for a period of 1-2 weeks after childbirth, with the option of continuation thereafter. This changes once treatment such as chemotherapy, targeted therapy, or endocrine therapy is initiated, at which point breastfeeding should be avoided (19).

5.2. Cervical Cancer in Pregnancy

Cervical cancer is the most prevalent gynecological malignancy during pregnancy. According to estimates, about 0.05% of all pregnancies are affected by cervical cancer (9). Reported rates range from 0.44 to 5.08 cases per 100,000 pregnancies (25). The occurrence of invasive cervical cancer during gestation is uncommon; with reported incidence rates ranging from 1.4 to 4.6 cases per 100,000 pregnancies (8).

5.2.1. Clinical Presentation

The clinical presentation of cervical cancer during pregnancy is characterized by a complex interplay of physiological adaptations, nonspecific symptoms, and diagnostic challenges.

5.2.1.1. Physiological Changes in the Cervix and Their Consequences

During pregnancy, the cervix undergoes significant physiological changes that are regulated by hormonal influences, particularly estrogen and progesterone. These changes serve to maintain the pregnancy but significantly complicate the clinical and diagnostic assessment of cervical cancer (25).

- **Hypertrophy and hyperplasia:** There is marked hypertrophy of the cervical glands and hyperplasia of the stroma, which causes the cervix to enlarge and become softer overall.
- **Eversion:** The columnar epithelium of the endocervical canal turns outward onto the cervical os. While this makes the transformation zone clearly visible on colposcopy in 90-100% of cases, it can also mimic inflammatory reactions or dysplastic changes.
- **Hyperemia and vascularization:** Blood flow to the cervix increases significantly. Consequently, diagnostic procedures such as biopsies or conization, there is significantly increased risk of severe bleeding.
- **Decidual changes:** Decidua may form in the cervical stroma (Arias-Stella reaction). Macroscopically and colposcopically, these changes may mimic the appearance of preinvasive disease.
- **Excessive mucus production:** Increased activity of the endocervical glands lead to increased mucus production, which can impair visibility during diagnostic procedures (25).

5.2.1.2. Most Common Clinical Symptoms

The clinical presentation of cervical cancer during pregnancy is insidious, as the disease is often completely asymptomatic, particularly in its early stages, or exhibits only very subtle clinical signs (26). In many cases, therefore, the malignancy is first detected during routine gynecological checkups at the beginning of pregnancy through cytology or speculum examinations (25).

When symptoms occur, vaginal bleeding is the most commonly observed clinical manifestation. This bleeding may present as contact bleeding after sexual intercourse, irregular spotting, or heavy, profuse vaginal bleeding (8).

Another key symptom is abnormal vaginal discharge which affected patients often describe as watery. Depending on the stage and extent of tissue breakdown, this discharge may also be mucous-like or purulent and have a distinct foul odor. As the disease progresses and the tumor grows, pelvic or back pain, as well as dyspareunia often occur (8,25).

In locally advanced stages, the carcinoma can also lead to urological dysfunction or cause chronic anemia as a result or persistent unnoticed blood loss (25).

5.2.3. Diagnostic Evaluation of Cervical Cancer

The diagnosis of cervical cancer follows a structured process that ranges from early detection and tissue sampling to the precise determination of the extent of the disease.

5.2.3.1. The Role of Pap Smears and HPV Testing

Screening forms the basis of diagnosis, with the Papanicolaou (Pap) test traditionally serving as the standard method for early detection. Sustained infection with high-risk human papillomavirus (HPV) types, notably HPV 16 and 18, represents the primary underlying factor in the development of cervical cancer. Since 2021 the World Health Organization has advised the use of HPV DNA testing as the preferred primary screening approach (25,26). During pregnancy, routine prenatal care provides a useful chance to assess women of younger age groups who would otherwise be less likely to take part in screening programs. However, interpreting cytology results during pregnancy can be complicated by hormonal influences, which can lead to both over- and underdiagnosis (25).

5.2.3.2. Diagnostic Workflow

If suspicious symptoms or abnormal screening results are present, the diagnostic workflow begins with a medical history and physical examination. The most common symptoms are postcoital bleeding, intermittent spotting, or watery vaginal discharge; however, these are often absent in the early stages or not recognized by the patient (26).

The rest of the process is as follows:

1. **Colposcopy:** If a Pap smear is abnormal, a colposcopic evaluation of the transformation zone is indicated. This procedure is safe during pregnancy, but can be challenging due to physiological changes of the tissue (25).
2. **Biopsy:** A histopathological examination is essential to confirm the diagnosis (8). A punch biopsy is considered safe and reliable even during pregnancy. Fine-needle aspiration is not recommended as a primary method because it makes it more difficult to assess tissue architecture compared to core-needle or excisional biopsies (2,25).
3. **Conization (loop or cold knife biopsy):** This procedure is necessary if the biopsy is insufficient to definitively determine whether invasion has occurred, or if a microinvasive lesion needs to be accurately assessed. The extent and shape of the cone biopsy can be adjusted based on the size, type and anatomical location of the lesion. A cold knife cone with a

minimum length of 10mm is generally recommended, with the option to extend it to 18-20mm in patients who have completed childbearing (26).

5.2.3.3. Imaging

Imaging is used to assess the degree of the local disease and to rule out metastases. In particular for pregnant women, the ALARA principle is applied to minimize radiation exposure (2).

Ultrasound is the primary diagnostic tool for the initial evaluation and assessment of adnexal masses (2).

The method of choice for evaluating local tumor extent and parametrial invasion is Pelvic MRI. The use of gadolinium-based contrast agents is not recommended, as they are able to pass the placental barrier and accumulate in the amniotic fluid. Furthermore, in patients with PAC, whole-body diffusion-weighted MRI (WB-DWI/MRI) has been assessed as a single-step staging tool, showing an accuracy of detection rates of around 90% for the primary tumor, 98.5-99.5% for nodal involvement, and 90-100% for distant metastatic disease (25,26).

As previously discussed, CT and PET/CT scans use ionizing radiation and are therefore generally avoided during gestation unless the maternal benefit clearly exceeds potential fetal risk (25).

5.2.3.4. Staging and FIGO-Classification

The staging of cervical cancer is based on the system of the International Federation of Gynecology and Obstetrics (FIGO), which was last comprehensively updated in 2018/2019. The current FIGO system allows for integration of imaging (radiology “r”) and pathological findings (“p”) to determine the stage (8). The most recent FIGO classification is reflected in figure 1.

- **Stage I:** Carcinoma strictly confined to the cervix. Subdivided into IA (detectable only microscopically) and IB (clinically visible lesions).
- **Stage II:** Spread beyond the uterus, but not extending to the lower third of the vagina or the pelvic wall.
- **Stage III:** Involvement of the lower third of the vagina or pelvic wall, with/without presence of hydronephrosis (IIIB), and/or involvement of regional lymph nodes (IIIC).
- **Stage IV:** Extend outside of the true pelvis or involvement of the bladder/rectal mucosa (IVA) or distant metastases (IVB) (8).

LVSI leaves the FIGO stage unchanged but is considered an important prognostic factor (26). In patients with localized disease (IA2 to IB1), surgical lymph node staging via laparoscopic pelvic lymphadenectomy is also indicated to rule out high-risk disease; this is technically feasible during pregnancy up to approximately the 22nd week (25).

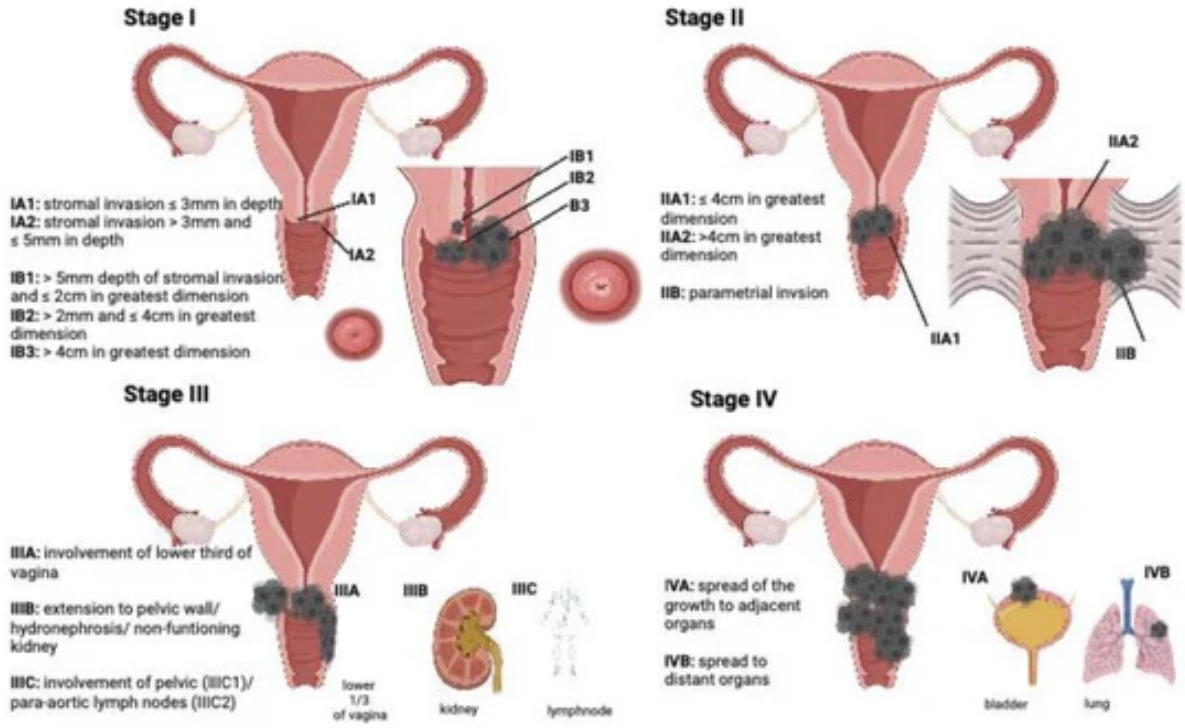

Figure 1: FIGO staging of cervical cancer. Reproduced from Schubert M, Bauerschlag DO, Muallem MZ, Maass N, Alkatout I. Challenges in the diagnoses and individualized treatment of cervical cancer. Medicina (Kaunas). 2023;59(5):925. Available from: https://doi.org/10.3390/medicina59050925.

5.2.4. Delayed Diagnosis and Diagnostic Challenges

The diagnosis of cervical cancer during pregnancy presents healthcare providers with a number of complex diagnostic dilemmas, as the physiological changes in the mother's body often mask the classic warning signs of a malignancy. One of the biggest challenges is symptom masking: Common signs like vaginal bleeding or discharge are often misinterpreted by both patients and doctors as normal symptoms of pregnancy, signs of a threatened miscarriage, or harmless cervical erosion (25). The misinterpretation leads to a significant delay in diagnosis – by an average of about four weeks – compared to non-pregnant patients, which increases the likelihood that the tumor has already reached a more advanced stage by the time it is first detected (2,8).

In addition, the diagnostic value of laboratory tests and tumor markers is severely limited. Markers such as squamous cell carcinoma antigen are nonspecifically elevated during pregnancy and therefore unreliable for initial diagnosis (1,25). The CA-125 tumor marker also fluctuates significantly due to pregnancy – it rises during the first trimester and immediately after childbirth – which undermines its diagnostic specificity for cervical adenocarcinoma (1). Even cytological assessment using a Pap smear is complicated by hormonal influences, as the altered morphology of the epithelium can lead to both over- and underestimation of lesions (25).

As previously described, colposcopic assessment of the cervix is significantly impaired by pregnancy-related hyperemia, increased vascularization, and the formation of decidua in the cervical stroma (25). These physiological changes can mimic the appearance of malignant invasion macroscopically and colposcopically, or mask true preinvasive lesions. The reliability of colposcopy therefore decreases significantly, particularly after the 20th week of pregnancy (2,25). Another obstacle is the prohibition of endocervical curettage, which is absolutely contraindicated during pregnancy because it significantly increases the risk of premature rupture of membranes or miscarriage (25).

Finally, invasive diagnostic procedures carry specific risks. A biopsy to confirm diagnosis is considered safe, but a necessary conization to investigate microinvasion carries a risk of up to 25% of fetal loss, particularly in the first trimester (9).

5.2.5. Treatment During Pregnancy

The treatment of cervical cancer during pregnancy requires highly personalized considering the FIGO stage, the stage of pregnancy and the patients explicit wishes regarding the pregnancy, as illustrated in Figure 2 (25).

5.2.5.1. Basic Principle Based on the Patient's Wishes

Management is primarily guided by the patient's wishes regarding pregnancy continuation (see Figure 2). If the patient desires to end the pregnancy (non-pregnancy sustaining management): Treatment largely follows standard protocols for non-pregnant patients.

- **Early stages (IA2 to IB2):** A radical hysterectomy with lymph node staging is the standard of care in the first or early second trimester, this is done without prior delivery of the fetus. From the late second trimester onward, the uterus is usually emptied via hysterotomy prior to hysterectomy (9,25).
- **Locally advanced stages (IB3 to IVA):** Definitive chemoradiotherapy is initiated. If this occurs before the 12th week, the radiation will cause fetal death and spontaneous abortion. After the 12th week, surgical evacuation is indicated before treatment begins (25).

If the patient desires to continue the pregnancy (pregnancy-sustaining management): The goal is to ensure the mother's oncological safety while simultaneously achieving fetal maturity without serious complications (25). Radiation therapy is absolutely contraindicated in this context because of the risk of fetal mortality (9). During early pregnancy, it is often recommended to defer interventions until the start of the second trimester, as surgical procedures carry fewer risks at that point and the organogenesis phase has been completed (8).

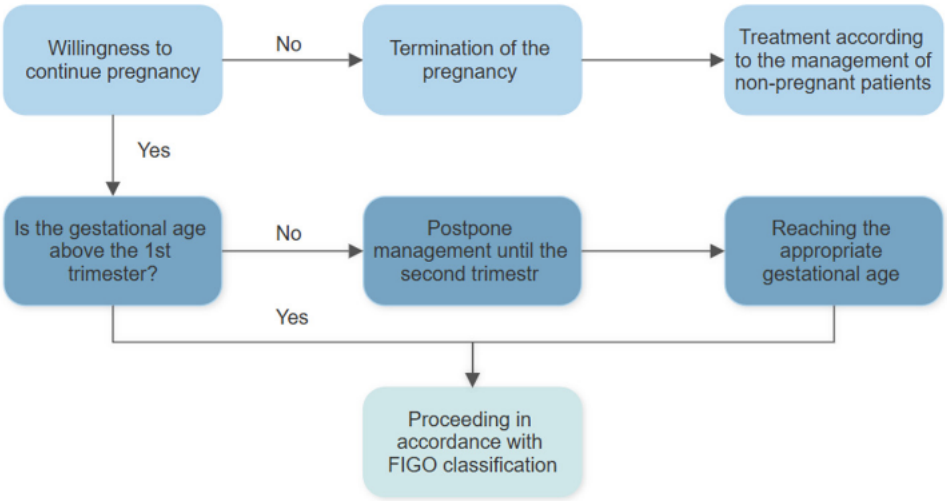

Figure 2: Management guided by the patient's wish to maintain the pregnancy. Adapted from (8).

5.2.5.1. Treatment According to FIGO Stages

In cases where the pregnancy is continued, the management strategy varies considerably depending on tumor burden and extent of the disease.

5.2.5.1.1. Stage IA1 (Microinvasive)

- **Without LVSI:** A conization with clear margins is often sufficient. This is ideally performed during the second trimester (weeks 14-20), as surgical procedures are safest at this stage. Alternatively, with close monitoring, therapy may be delayed to the postnatal period (1,25).
- **With LVSI:** The recommended approach is the same as for stage IA2, including lymph node assessment (8).

5.2.5.1.2. Stage IA2 to IB1 (Tumor size 2cm ≥)

Here, the extent of lymph node involvement is the key marker of prognosis (8). A laparoscopic pelvic lymphadenectomy should be performed by the 22nd to 25th week of pregnancy (8). After that, the procedure is technically almost impossible due to the size of the uterus (25).

If the lymph nodes are tumor-free, definitive treatment (conization or simple trachelectomy) can be postponed until fetal maturity is reached. A radical trachelectomy is generally avoided in pregnancy, as it is associated with unfavorable obstetric outcomes (8).

If lymph node results are positive, the option of terminating the pregnancy must be discussed to allow for immediate standard treatment (9).

5.2.5.1.3. Stage IB2 to IVA (Tumor size > 2cm or locally advanced)

Treatment at these stages poses a particular challenge, as simply waiting until delivery is usually not a viable option due to the high risk of disease progression. If the patient wishes to continue the pregnancy, neoadjuvant chemotherapy (NACT) is the cornerstone of treatment. Before starting NACT, laparoscopic pelvic lymphadenectomy is often recommended at these stages (25). If lymph nodes are negative, NACT may be continued until delivery. In case of positive results, induced abortion should be urgently discussed due to the poor prognosis and the need for immediate chemoradiotherapy (8).

Chemotherapy in this context is not intended to achieve definitive cure but rather serves as a bridge to fetal maturity. Its primary aims are to control tumor growth and prevent further disease progression, to reduce tumor volume and enhance radiosensitivity for subsequent treatment, and to prolong the pregnancy to a gestational age at which neonatal survival without severe morbidity is possible, ideally beyond 34-37 weeks (8,25). NACT should only be initiated after the first trimester, once organogenesis is complete. The standard regimen consists of a platinum-based combination, most commonly cisplatin and paclitaxel. However, many experts favor the use of carboplatin instead of cisplatin to reduce the risk of fetal ototoxicity (8,25).

5.2.5.2 Monitoring During Treatment

Given the risk of tumor progression during chemotherapy, close monitoring is essential. Response rates range from 66% to 85%. Maternal monitoring includes clinical assessments every three weeks, with radiological response evaluated by MRI at six-week intervals. Fetal monitoring involves ultrasound examinations every 2 to 4 weeks to assess growth, given the risk of Intrauterine growth restriction (IUGR) and risk for small gestational age, as well as to evaluate amniotic fluid volume (25).

5.2.6. Clinical Indications for Pregnancy Interruption

The decision to end a pregnancy after a diagnosis of cervical cancer is a highly complex and emotionally taxing process that may be medically indicated in several clinical situations. As previously discussed, lymph node status is a key factor. If lymph node metastases are detected, an urgent recommendation to terminate the pregnancy is generally made, as immediate chemoradiotherapy is necessary to ensure the mother’s survival and is incompatible with continuing the pregnancy (25).

The FIGO stage and the extent of local or systemic tumor spread also play a decisive role, as locally advanced stages (FIGO IIB-IVA), metastatic disease (FIGO IVB), or inoperable tumors in particular

often require primary radiation therapy or systemic therapy, which precludes pregnancy continuation due to their fetal lethality (9,25).

Furthermore, the timing of the diagnosis and the resulting therapeutic incompatibility are critical, particularly in the case of an early diagnosis during the first trimester, when continuing the pregnancy is not possible due to the intensity of the required treatment – such as immediate pelvic radiation therapy (2).

Finally, medical urgency – in the interest of the mother's safety – is also a high priority: in emergency situations, in cases of impending organ dysfunction, or in the event of tumor progression during neoadjuvant chemotherapy, termination may be necessary to ensure the patient's survival and prevent irreversible health damage (2,8).

5.2.7. Obstetrical Management

Because cervical cancer during pregnancy is uncommon, affected patients should ideally be managed in centers with expertise in high-risk obstetrics, where close collaboration is possible and adequate neonatal intensive care is available for cases of extremely preterm delivery (25).

5.2.7.1. Delivery Planning

As previously discussed, the primary aim of birth planning in patients with PAC is to prolong pregnancy whenever possible to reduce the risks of prematurity, with delivery ideally planned at or beyond 37 weeks of gestation (21). Timing should be carefully coordinated with ongoing chemotherapy, ensuring a 2-4 week interval prior to delivery to allow for adequate maternal and fetal bone marrow recovery (8). Should maternal health decline or the tumor fail to respond to treatment and continue to progress, early delivery may need to be considered (25).

5.2.7.2. Birth Mode

The choice of delivery method depends heavily on the stage and location of the tumor. Vaginal delivery is generally considered acceptable in early-stage disease (IA1 and IA2), provided that no obstetric contraindications are present (9). However, there is a specific risk of tumor cell dissemination into episiotomy sites or vaginal tears, and episiotomy should therefore be strictly avoided (9). Cesarean section is regarded as the favored delivery approach in more advanced stages (from IB onward) or in the presence of large, fragile, or highly vascular tumors. It is also indicated when the tumor obstructs the birth canal or when there is a high risk of bleeding during labor (9,25). In many cases, cesarean delivery is combined with definitive surgical cancer treatment, such as radical hysterectomy (1,25).

5.2.7.3. Postpartum Management

After childbirth, the focus is on ongoing cancer treatment and the safety of both mother and child.

Thromboprophylaxis is indicated because both malignancy and pregnancy increase the risk of venous thromboembolism; therefore, prophylactic anticoagulation is warranted for at least six weeks postpartum (25).

Placental assessment should routinely include histopathological examination after delivery to detect potential metastases. Although placental involvement in cervical cancer is rare, this information is important for guiding subsequent monitoring of the newborn (25).

Breastfeeding is contraindicated if the mother requires immediate postpartum treatment with chemotherapy, hormonal therapy, or targeted agents, as many of these drugs can be transferred into breast milk (9). If a temporary interruption is feasible, a safety interval of at least three weeks after the last chemotherapy dose should be observed before initiating breastfeeding (2).

Oncologic treatment can typically be resumed shortly after delivery, usually within a few days following vaginal birth or after 1-2 weeks in the case of cesarean delivery, once adequate wound healing has occurred (2).

Neonatal follow-up should include hearing assessment in infants exposed to platinum-based agents in utero, preferably using brainstem evoked response audiometry rather than otoacoustic emissions, to allow early detection of potential ototoxicity. In addition, blood counts as well as liver and renal function parameters should be monitored (2).

5.3. Hematologic Malignancies in Pregnancy

Hematologic malignancies during pregnancy can be divided into the following main groups:

1. **Lymphomas**: This is the most common group of hematological cancers during pregnancy. They are divided into Hodgkin Lymphoma (HL), which is the most common subtype, and non-Hodgkin Lymphoma (NHL). While Pregnancy-associated HL (PA-HL) often exhibits characteristics similar to those seen in non-pregnant patients, PA-NHL is characterized by an overall more aggressive behavior and shows a tendency to affect reproductive organs, including the breast, ovaries, or uterus, more frequently than other sites (18,27).
2. **Leukemias**: Acute leukemias account for about 90% of all leukemia diagnoses during pregnancy (1). Acute myeloid leukemia (AML) accounts for the largest proportion, representing about two-thirds of cases, followed by acute lymphoblastic leukemia (ALL). Chronic forms such as chronic myeloid leukemia are less common in this patient group (11).
3. **Myeloproliferative neoplasms (MPN)**: These include conditions such as essential thrombocythemia and polycythemia vera, which are associated with an increased risk of thrombotic complications in the mother and placenta (11).

4. **Multiple Myeloma**: Because of the age distribution of this condition, it is diagnosed extremely rarely during pregnancy (11).

5.3.1. Clinical Presentation

As previously discussed in other PAC, the clinical presentation of hematological malignancies is often difficult because its symptoms resemble typical physiological changes during pregnancy.

5.3.1.1. Lymphomas

The symptoms of lymphoma during pregnancy are comparable to those in non-pregnant patients, but can easily be mistaken for pregnancy-related symptoms (11).

Painless lymphadenopathy is the most common presenting sign, typically manifesting as a non-tender swelling of the lymph nodes (1). Dyspnea may occur, particularly in cases with mediastinal involvement, leading to shortness of breath or respiratory discomfort. Fatigue and exhaustion are also frequent but are often misinterpreted as normal symptoms of pregnancy. In addition, aa hypermetabolic state may be observed (11).

In the case of NHL, involvement of the reproductive organs is more frequently observed during pregnancy, including the breasts, ovaries, cervix, or uterus, and may present with corresponding local swelling or symptoms. This tendency may be explained by hormone-driven growth or a pregnancy-relate state of increased cellular proliferation in these tissues (11,27).

5.3.1.2. Leukemias

In acute leukemias (AML and ALL), the primary symptoms are those caused by bone marrow failure (pancytopenia) (1).

General symptoms commonly include pronounced weakness, rapid fatigue and an overall feeling of illness. In addition, patients may present with a bleeding tendency, such as gingival bleeding, epistaxis, or cutaneous manifestations like ecchymoses. Due to a deficiency of functional white blood cells, there is also an increased susceptibility to infections (1). In cases of markedly elevated leukocyte counts, leukostasis may occur, leading to impaired microcirculation with respiratory or neurological symptoms. Furthermore, disseminated intravascular coagulation, a severe coagulation disorder particularly associated with acute promyelocytic leukemia, may develop and result in life-threatening bleeding or thrombotic events (11).

5.3.1.3. Myeloproliferative Neoplasia

This group is clinically characterized primarily by an increased risk of vascular complications. The primary symptom is maternal or placental thrombosis. These can lead to deep vein thrombosis,

pulmonary embolism, or impaired placental blood flow. Pregnancy complications may include IUGR and recurrent miscarriages, frequently associated with the presence of a JAK2 mutation (11).

5.3.2. Diagnostic Evaluation of Hematological Cancers

The diagnosis of hematologic cancers such as lymphomas, leukemias and MPN during pregnancy or in young adulthood is complex due to physiological changes in the body and risks to the fetus (11). A multidisciplinary team is, once again, essential for coordinating the diagnostic steps (9).

5.3.2.1. Lymphomas

Lymphomas usually present as painless lymphadenopathy (1). Doctors must be highly vigilant for symptoms such as anemia, leukocytosis, or exertional dyspnea, as these are often mistakenly attributed solely to pregnancy (27).

Laboratory evaluation includes parameters such as erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH), which must be interpreted carefully, as they may be physiologically altered during gestation (27).

The gold standard for diagnosing lymphoma is through biopsy. The diagnosis is confirmed by histological examination of a removed lymph node (27). To ensure sufficient histopathological evaluation and minimize postponement of diagnosis, core-needle or excisional biopsy is recommended instead of fine-needle aspiration. This procedure can be carried out without significant risk in all trimesters under local anesthesia (2).

5.3.2.2. Leukemias

Because of the aggressive nature of AL, it is important that the diagnosis is made immediately and without delay (1). The first indications come from changes in blood counts, such as marked leukocytosis, anemia, or thrombocytopenia. When interpreting these results it must be considered that, for example, white blood cell counts are naturally slightly elevated during pregnancy (1,11).

A bone marrow biopsy is the key tool for confirming the diagnosis. If there is reasonable suspicion, it should be performed regardless of gestational age. Available data show similar incidence of adverse outcomes compared to non-pregnant patients, therefore have been reported as safe throughout all trimesters (1,2).

5.3.2.3. Myeloproliferative Neoplasm

The rate of MPN among pregnant individuals is increasing, partly due to improved diagnostic techniques. A key diagnostic step is testing for the JAK2 Val617Phe mutation. Detection of this mutation is clinically highly relevant, as it can increase the risk of pregnancy loss (11). Because MPNs

significantly increase the risk of maternal and placental vascular complications, assessing the risk of thrombosis is an integral part of the diagnostic process (11).

5.3.3. Imaging and Staging of Hematological Cancers

As previously discussed, the ALARA principle is strictly applied in imaging and staging. The choice of imaging modality largely depends on the cancer type and the urgency of treatment (27).

5.3.3.1. Lymphomas

Staging is crucial in lymphoma to determine the severity of the condition and plan treatment accordingly. The imaging techniques differ little from other PAC.

- **Ultrasound:** Considered the method of choice for evaluating the abdomen and palpable masses (11).
- **MRI (without contrast agent):** Is the preferred method for detailed staging and visualization of soft tissues. Whole-body MRI with diffusion-weighted imaging is considered highly sensitive and specific for diagnosis and staging during pregnancy (2).
- **Chest X-Ray:** If clinically necessary, this can be performed with lead shielding of the abdomen, as the fetal radiation exposure is minimal in this case (11).

In addition to imaging, histological examination of a lymph node biopsy is the gold standard for determining the type and stage (27).

5.3.3.2. Leukemias

The diagnosis and staging of leukemias during pregnancy require a rapid and precise approach, as acute leukemias are considered medical emergencies and require immediate treatment. Unlike solid tumors, in leukemias, bone marrow biopsy is the most important tool for confirming the diagnosis and serves as the basis for classification and staging, in the sense of risk stratification, through cytogenetic and molecular analyses (1,11).

5.3.4. Treatment During Pregnancy

The treatment of hematologic cancers during pregnancy demands an individualized approach that accounts for both maternal and fetal outcomes. As a general rule, the mother’s health takes priority, as her survival is essential for the survival of the fetus (2).

5.3.4.1. Treatment of HL

Although the treatment generally adheres to the same general principles as in non-pregnant women, it must be adapted to the stage of gestation. In cases of asymptomatic, slowly progressing disease

during the first trimester, treatment can often be rescheduled until the second trimester, allowing the pregnancy to continue without the need for immediate intervention or termination (1,11). During the second and third trimesters, the ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) is considered the standard of care and is generally safe during these stages (1). It is generally recommended to postpone radiation therapy until after childbirth. In urgent cases, radiation above the diaphragm with strict shielding of the abdomen may be considered (2).

5.3.4.2. Treatment of NHL

Treatment depends heavily on the histological subtype. In asymptomatic indolent lymphomas, a watch-and-wait approach is often adopted. Diffuse large B-cell lymphoma and Burkitt lymphoma, as aggressive entities, necessitate urgent therapeutic intervention. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone), often combined with rituximab (R-CHOP), is typically administered from the second trimester onward (11). Available evidence, mainly from case reports, suggests no increased risk of major fetal malformations with CHOP exposure in early pregnancy. When rituximab is administered in the second and third trimesters, it is associated with higher rates of preterm delivery but not with an elevated risk of birth defects (1,27).

5.3.4.3. Treatment of Acute Leukemias (AML and ALL)

These conditions are medical emergencies and require immediate treatment. Generally, standard induction therapy should be initiated without delay. In AML anthracyclines and cytarabine is used. Therapeutic strategies for acute lymphoblastic leukemia typically involve multi-agent chemotherapeutic regimens, which may be combined with tyrosine kinase inhibitors according to cytogenetic and molecular subtype (1,27). Stem cell transplantation is absolutely contraindicated during pregnancy (11).

5.3.4.4. Treatment of Myeloproliferative Neoplasia

The primary risk is thrombotic events; therefore, management includes low-dose aspirin for the prevention of arterial thrombosis, the use of interferon-alpha when needed to reduce cell counts, and low-molecular-weight heparin in cases of high thrombotic risk (11).

5.3.4.5. Monitoring During Treatment

As in any other setting involving chemotherapy, the last dose should is generally recommended to take place 2-4 weeks, or one full cycle, before the expected delivery to reduce the risk of maternal and newborn myelosuppression at birth (2). Monitoring requirements vary depending on the specific therapy. With rituximab, attention should be paid to potential neonatal B-cell depletion and

cytopenias, which typically resolve within the first six months of life (27). In the case of anthracyclines, particularly idarubicin, fetal or neonatal cardiac function should be monitored due to the risk of cardiotoxicity (2). For tyrosine kinase inhibitors, especially in patients with CML receiving imatinib, there is an increased risk of malformations during the first trimester; although imatinib is considered relatively safe thereafter, careful monitoring remains essential (27).

5.3.5. Clinical Indications for Pregnancy Interruption

The clinical indications for pregnancy interruption in the context of hematological malignancies are primarily driven by the urgency of initiating intensive maternal therapy during the first trimester, wellbeing the risk of fetal harm is highest. Because the primary goal of management is to ensure maternal health, termination is often advised at early gestational stages to allow for optimal treatment (11).

Acute leukemias constitute oncologic emergencies requiring immediate full-intensity treatment irrespective of gestational age (11). When diagnosed in the first trimester, pregnancy termination is generally recommended, as delaying or modifying induction therapy significantly worsens maternal prognosis (2). Similarly, if hematopoietic cell transplantation is urgently indicated, termination is necessary, as this procedure is contraindicated during pregnancy (11).

Aggressive non-Hodgkin lymphomas also require prompt initiation of intensive multidrug therapy. In cases diagnosed during early pregnancy, termination is often suggested to allow administration of standard treatment regimens without fetal risk (1,11).

Another key indication for pregnancy interruption is the necessity to use highly teratogenic or abortifacient agents. Drugs such as methotrexate or immunomodulatory agents used in multiple myeloma are contraindicated in pregnancy, particularly during the first trimester (11,28).

More broadly, pregnancy interruption may be considered in situations where delaying therapy poses a substantial risk to maternal life or could result in severe and irreversible morbidity. Clinical guidelines highlight that both patient autonomy and the severity of the clinical condition are central factors in decision making (2).

An overview of the main clinical indications according to disease type and gestational timing is provided in Table 1.

Table 1: Clinical indications for pregnancy interruption in hematological malignancies

Disease Type	Gestational Timing	Indication for Interruption
Acute Leukemia (AML/ALL)	1st Trimester (<12-20 weeks)	Recommended to allow immediate intensive induction therapy (1)

Table 1: Clinical indications for pregnancy interruption in hematological malignancies (Continued)

Disease Type	Gestational Timing	Indication for Interruption
Aggressive NHL	1st Trimester	Suggested to allow immediate standard/intensified multidrug therapy (1,11)
Symptomatic Myeloma	1st Trimester	Suggested approach to allow use of immunomodulatory drugs (11)
Any hematologic malignancy	1st Trimester	If Methotrexate is an essential part of the life-saving regimen (2)
Any hematologic malignancy	Any Trimester	If a stem cell transplant is urgently required (11)

The table shows clinical indications for pregnancy interruption in hematological malignancies according to disease type and gestational timing.

5.3.6. Obstetrical Management

Pregnancy planning is tailored to each individual and is based on the type of cancer, the stage of the disease, the response to treatment, and the gestational age of the fetus. Regardless of cancer type, several general recommendations apply, as for other PAC. Delivery should ideally be planned at or beyond 37 weeks of gestation to minimize the risks associated with prematurity (27). The last chemotherapy cycle should be administered 2-4 weeks prior to expected delivery date. Vaginal delivery is preferred unless standard obstetric indications necessitate cesarean section, as the presence of active malignancy alone does not constitute an indication for cesarean delivery (2,18).

Nevertheless, management may vary depending on the underlying malignancy. In patients with NHL, higher rates of cesarean delivery have been reported, often to allow for a more controlled timing of delivery, although vaginal delivery is frequently feasible and delivery at term remains the goal (27,29).

In cases of acute leukemia (AML/ALL) diagnosed in the third trimester, early delivery may be considered to enable prompt initiation of intensive maternal therapy, such as stem cell transplantation (1,11). Delivery approach should be adapted to the individual clinical situation and is largely determined by the maternal clinical condition, particularly platelet counts and the presence of infection (1).

5.3.6.1. Postpartum Management

The primary goal following childbirth is to safely continue or intensify the mother's cancer treatment while ensuring the newborn's health and the family's psychosocial stability. Concerning resumption of treatment, systemic chemotherapy can generally be reinitiated a few days after a vaginal delivery or one to two weeks after a cesarean section, once adequate wound healing has been confirmed (2). Because certain diagnostic procedures were contraindicated or restricted during pregnancy, comprehensive restaging is often performed after delivery. This includes CT or PET-CT scans to determine the exact extent of the disease and optimize further treatment planning (e.g. radiation therapy or stem cell transplantation) (11).

As with other PACs, breastfeeding is contraindicated during ongoing chemotherapy, hormone therapy, or treatment with targeted therapies, as these medications enter breast milk and may cause toxic effects in the infant. ASCO guidelines recommend a break of at least three weeks after the last dose of chemotherapy (2). Breastfeeding must also be paused following examinations using radioisotopes (e.g. FDG-PET), as these substances accumulate in the breast tissue (11).

5.4. Melanoma in Pregnancy

Cutaneous melanoma is a melanocyte-derived malignancy that mainly affects the skin but may also present in ocular or mucosal tissues. It is one of the most aggressive forms of cancer in young adults and is the most commonly diagnosed malignant disease in women of childbearing age (7,22). Definition of pregnancy-associated melanoma (PAM) refers to melanoma diagnosed during pregnancy or up to one year after delivery (7).

5.4.1. Clinical Presentation

The clinical presentation of PAM is characterized by the diagnostic challenge of distinguishing gestational skin changes of physiological origin from malignant processes.

5.4.1.1. Physiological and Hormone-Related Skin Changes

During pregnancy, changes in skin pigmentation are a normal physiological phenomenon driven by an increase in various hormones, such as estrogen, progesterone, melanocyte-stimulating hormone, and beta-endorphins (22,30). These hormonal influences stimulate melanocytes via the enzyme tyrosinase (22). Classic physiological changes include:

- **Hyperpigmentation:** Particularly pronounced in areas with naturally higher pigmentation, such as the secondary areola and the genital area.
- **Linea nigra:** A dark line running vertically across the abdomen.
- **Melasma:** The so-called "pregnancy mask" on the face (22).

- **Changes in nevi:** While nevi in the general population usually remain stable during pregnancy, they may enlarge in areas where the skin is stretched significantly (breasts, abdomen). However, in patients with dysplastic nevus syndrome, the rate of clinical changes in moles during pregnancy is nearly four times higher than in non-pregnant women (7,22).

5.4.1.2. Most Common Clinical Symptoms

The clinical diagnosis of melanoma during pregnancy does not differ significantly from that in non-pregnant patients, but is often delayed due to the physiological changes mentioned above (30). Since about two-thirds of melanomas can develop from existing moles, any change in a mole during pregnancy should be taken seriously (30). New moles, or those that are darkening or changing in any other way, should not be dismissed as a normal part of pregnancy, but require a dermatological evaluation using dermatoscopy (22).

5.4.2. Diagnostic Evaluation of Melanoma

The diagnostic evaluation of PAM largely follows standard protocols for non-pregnant patients; however, due to the potential risks to the fetus, it requires careful selection of diagnostic tools and timing (30).

5.4.2.1. Diagnostic Workflow

The diagnostic process begins with a thorough clinical examination, with the identification of atypical lesions aided by established tools:

Dermatoscopy is a non-invasive procedure that significantly improves diagnostic accuracy and is completely safe during pregnancy (7). Clinical assessment relies on established diagnostic criteria, including ABCDE rule (asymmetry, border irregularity, color variation, diameter $\geq$ 6mm, and evolution), the Glasgow seven-point checklist, and the “ugly duckling” sign (22). If a lesion is suspected, an excisional biopsy with a safety margin of 1 to 3mm is the method of choice. It is essential to avoid any delay in diagnosis. The diagnosis of melanoma ultimately relies on histopathological confirmation as the gold standard (22). Biopsies performed under local anesthesia (preferably lidocaine) are considered safe at all stages of pregnancy (7). Sentinel lymph node biopsy (SLNB) is recommended for tumors with a Breslow thickness > 0.8mm or in thinner melanomas with ulceration. The use of technetium-99m is considered safe due to minimal fetal radiation exposure, whereas blue dyes are generally avoided because of potential maternal and fetal risks. The timing of SLNB remains controversial, and in selected cases, it may be deferred until the postpartum period if it does not impact immediate therapeutic decisions (22,30).

5.4.2.2. Imaging

Ultrasound represents the method of choice for evaluation and follow-up of regional lymph node basins, particularly during the first trimester. For systemic staging, whole-body MRI without contrast is preferred from the second trimester onward, as it is considered safe in pregnancy. Gadolinium-based contrast agents is typically avoided unless a clear benefit-risk advantage is present. Imaging modalities involving ionizing radiation, such as CT or PET-CT, should be avoided whenever possible due to potential fetal risks. However, radiation exposure below 5mGy is generally considered unlikely to result in significant fetal harm (22,30).

5.4.2.3. Staging and Classification

Staging is performed according to the AJCC system (8th edition), based on the TNM classification (22). The T category, reflecting primary tumor classification, is based on histopathological assessment of the excised melanoma. The most important parameter is the Breslow thickness, which represents the maximum vertical depth of tumor invasion in millimeters and serves as the most robust prognostic indicator. In addition, the presence or absence of ulceration significantly influences staging, as ulcerated tumors are associated with a higher risk of metastasis (22). The N category reflects regional lymph node status and is essential for distinguishing between localized melanoma (stage I/II) and regionally metastatic disease (stage III). The M category reflects the presence of distant metastases and is determined through imaging studies as well as assessment of serum lactate dehydrogenase levels (22,30).

5.4.3. Treatment During Pregnancy

The treatment of melanoma during pregnancy presents a complex medical and ethical challenge that requires a multidisciplinary team of oncologists, dermatologists, obstetricians and neonatologists (18).

Surgical excision is the cornerstone of treatment and should not be delayed upon diagnosis of melanoma, regardless of gestational age. As already mentioned, an excisional biopsy performed under local anesthesia is considered safe at all stages of pregnancy. The required safety margins for definitive excision (wide local excision) depend on the Breslow thickness of the tumor: 5mm to 1cm for melanoma in situ, 1cm for tumors <1mm thick, 1-2cm for tumors 1-2mm thick, and 2cm for melanomas thicker than 2mm (22). Starting in the 20th week of pregnancy, the patient should be positioned on her left side (at an angle of approximately 30°) during the procedure to prevent compression of the vena cava and the resulting fetal oxygen deprivation (22).

5.4.3.1. Systemic Therapy for Advanced Melanoma

In cases of unresectable stage III or stage IV melanoma, the decision regarding treatment is particularly difficult. Conventional chemotherapy, such as dacarbazine, is now rarely used due to low response rates (30). Immune checkpoint inhibitors, including nivolumab, pembrolizumab have revolutionized melanoma treatment but pose potential risks to fetal immune tolerance (22). The PD-1 pathway plays a crucial role in protecting the fetus from the maternal immune system, and its inhibition may be associated with adverse outcomes such as miscarriage, stillbirth, or neonatal autoimmune conditions (7). Therefore, their use during pregnancy should be restricted to life-threatening situations (2).

Targeted therapy may be considered in patients with a BRAF V600 mutation. Among BRAF inhibitors, vemurafenib is the best studied in pregnancy and appears to have limited placental transfer, although its use has been associated with preterm delivery (2,22).

Radiotherapy involving the abdominal or pelvic regions is contraindicated due to significant fetal risks, including malformations and growth restriction (18). However, in cases of distant metastases it may be considered with strict uterine shielding and the application of advanced methods such as intensity-modulated radiotherapy or proton therapy (18,30).

5.4.4. Clinical Indications for Pregnancy Interruption

Termination of pregnancy is not routinely medically indicated for PAM, particularly not in the early stages (stage I and II) (7). In line with other pregnancy-associated cancers, induced abortion can be warranted in emergency situations where prompt initiation of systemic therapy is essential to prevent maternal mortality (2). This applies in particular to situations in which delaying treatment until the fetus is viable would significantly reduce the mother's chances of survival or there is a risk of serious impairment of vital organs due to metastases (2).

5.4.4.1. Advanced and Metastatic Melanoma

In cases of metastatic melanoma, adequate disease management during pregnancy is often nearly impossible (22,30). In these cases, termination of pregnancy or early delivery should be considered in order to enable full staging, using ionizing radiation such as PET-CT or CT (30). And to ensure optimal treatment, using aggressive systemic therapies (2).

The diagnosis of high-risk melanoma (pT4b or stage III) in the first trimester represents a particular challenge due to the prolonged interval until delivery. In cases where a SLNB is positive and the patient wishes to proceed with immediate adjuvant therapy, pregnancy termination may be discussed, as these treatments are generally not recommended during pregnancy (30).

5.4.4.2. Risk to the Fetus

Although rare, melanoma is the malignancy most commonly associated with transplacental metastasis. It accounts for a substantial proportion of transplacental metastases, with involvement of the placenta in about 30% of cases and fetal dissemination occurring in approximately 58% with placental disease (7). If the mother is known to have widespread metastasis, this risk must be taken into account during the consultation regarding whether to continue the pregnancy (30).

5.4.5. Obstetrical Management

The obstetric and perinatal management of PAM requires ongoing interdisciplinary collaboration to balance the mother's oncological treatment with the safety of the fetus (2). Monitoring focuses on the early detection of complications that may arise from the disease itself or from systemic therapy.

5.4.5.1. Delivery Planning

As in other pregnancy-associated malignancies, management requires careful coordination of therapy and delivery timing, aiming for term birth. If applicable, chemotherapy should be paused 2-4 weeks prior to delivery (2).

5.4.5.2. Birth Mode

The choice of delivery method is primarily based on obstetric criteria. Vaginal delivery should be prioritized whenever possible. Melanoma alone is not an indication for a cesarean section, unless there are metastases in the birth canal (vagina/vulva) that pose mechanical obstacles or a high risk of bleeding (2). An episiotomy should be avoided in cases of known local tumor spread to reduce the risk of tumor cell implantation in the scar (1). Cesarean section is reserved for routine obstetric indications or is recommended for patients with brain metastases to prevent a dangerous increase in intracranial pressure during the expulsion stage (Valsalva maneuver) (18).

5.4.5.3. Postpartum Management

Following every pregnancy complicated by melanoma, the placenta must undergo both macroscopic and microscopic histopathological examination. Melanoma is the tumor most commonly metastasizing to the placenta (18). If placental metastases are detected, there is a high risk of fetal transmission. Such newborns, require close monitoring by pediatric oncologists, as metastases can develop even months after birth (7,22). As previously outlined, breastfeeding is contraindicated during systemic therapy, and treatment can usually be resumed within days after vaginal delivery or after 1-2 weeks post-cesarean section (2,18). Patients with an elevated risk of recurrence (stage II or

higher) are advised to postpone another pregnancy for 2 to 3 years, as most recurrences occur during this period (1).

5.5. Thyroid Cancer in Pregnancy

Thyroid cancer, often occurring in young women of childbearing age, is the most prevalent endocrine malignancy and is frequently diagnosed in this specific population (31). A cancer diagnosis during pregnancy presents a challenge for both patients and clinicians, where maternal treatment must be balanced against fetal safety considerations (32). Despite this, the prognosis for the most common types of thyroid cancer in pregnancy is generally excellent (31).

5.5.1. Incidence and Classification

The prevalence of thyroid cancer during pregnancy is estimated to be approximately 14 to 27 cases per 100,000 pregnancies (33). About 10% of all thyroid carcinomas in women of childbearing age are detected during pregnancy or in the first year postpartum (31).

Most thyroid cancers diagnosed during pregnancy are differentiated. Follicular carcinoma (FTC) and papillary thyroid carcinoma (PTC) are both classified under differentiated thyroid cancer (DTC). PTC is by far the most frequent form; it typically shows slow growth and primarily spreads via lymphatic pathways to cervical lymph nodes. In contrast, FTC is less common in pregnancy and tends to metastasize hematogenous, for example to the lungs or bones (31,34).

Medullary thyroid carcinoma accounts for approximately 5-10% of cases and is of particular relevance in pregnancy due to its more aggressive clinical behavior (31,34).

5.5.2. Clinical Presentation

The clinical presentation of thyroid cancer during pregnancy is significantly influenced by the major physiological changes occurring in the mother’s body. These changes can complicate the diagnostic process and affect the growth of thyroid tissue.

5.5.2.1. Physiological Changes of the Thyroid Gland and Their Consequences

Pregnancy places a significant physiological strain on the endocrine system and has a strong influence on the thyroid hormonal function (32). It is associated with a substantial upregulation of thyroid hormone production, including an approximately 50% increase in Thyroxine (T4) and Triiodothyronine (T3) levels, accompanied by an equally significant increase in daily iodine requirements (34). In areas with adequate iodine intake, thyroid volume increases by about 10%, whereas in iodine-deficient areas, an increase of 20% to 40% is observed (32). This physiological hypertrophy is driven by several factors:

- **hCG stimulation:** Human chorionic gonadotropin shares a structural similarity with thyroid-stimulating hormone and directly stimulates the thyroid stimulating hormone (TSH) receptor. This leads, particularly in the first trimester, to an increase in free hormone concentrations and a resulting transient suppression of maternal TSH levels (32,34).
- **Increase in TBG:** Elevated estrogen levels lead to an approximate doubling of thyroxine-binding globulin (TBG), which increases total hormone concentrations, while the free fraction initially decreases (31).
- **Increased renal iodine excretion:** During pregnancy, the kidneys excrete more iodine which places additional strain on the mother's iodine reserves (32).

This hormonal stimulation (hCG, estrogen and TSH) can stimulate the formation of new nodules and accelerate the growth of existing ones (34). In addition, the general enlargement of the gland makes it more difficult to palpate smaller malignancies, as pathological findings can be masked by the physiological enlargement (31)

5.5.2.2. Most Common Clinical Symptoms

Thyroid nodules in younger women are often first identified during pregnancy, most commonly through palpation of the neck (35). Compressive symptoms may occur and should be assessed, including dysphagia, dyspnea, as well as throat discomfort (34). Features suggestive of more aggressive disease should be promptly recognized, including lymphadenopathy, a fixed nodule indicating local invasion, or hoarseness due to involvement of the recurrent laryngeal nerve (33).

5.5.3. Diagnostic Evaluation of Thyroid Cancer

The workflow largely follows the procedure used for non-pregnant patients but has specific contraindications. The clinical workflow begins with the detection of a nodule and follows a step-by-step process. First, medical history should include assessment of risk factors such as a family history and prior radiation exposure during childhood (32). The physical examination pays particular attention to the consistency of the lump (e.g. "rock-hard"), fixation to surrounding structures, hoarseness, or the presence of lymphadenopathy (35).

After that, measuring serum TSH levels is the first mandatory laboratory step. A low TSH level could indicate an autonomously functioning nodule, but is difficult to interpret in early pregnancy due to physiological hCG stimulation (32,35).

Ultrasound is the imaging modality of choice and is used for risk stratification based on features such as hypoechogenicity, microcalcifications, or irregular margins (35). Solid nodules with sonographic features that are moderately to highly suspicious for malignancy should undergo fine-needle aspiration when larger than 1cm. FNA cytology is the gold standard in this setting and is considered

safe and reliable in all trimesters of pregnancy (35). Cytological evaluation is performed according to the Bethesda system (33).

A special consideration during pregnancy concerns thyroid scintigraphy, which is absolutely contraindicated during this time because radioactive iodine passes through the placenta and can damage the fetal thyroid gland starting in the 12th to 13th week of pregnancy (34).

5.5.4. Treatment During Pregnancy

For the majority of women with DTC, postponing surgery until after childbirth is the preferred strategy. If this approach is adopted, serial thyroid ultrasound examinations should be conducted in each trimester to monitor for ongoing stability (1). If surgery is postponed until after delivery, medical management with levothyroxine is essential. The goal is to suppress TSH in order to minimize the growth stimulus on the tumor cells. For low-risk carcinomas, the target TSH level is often between 0.5 and 2.0 mU/L, while for advanced stages, levels below 0.1 mU/L are targeted (34).

Surgical intervention during the second trimester is generally reserved for selected cases, including significant tumor progression (e.g. a >50% increase in volume or > 20% increase in diameter up to 24-26 weeks of gestation), confirmed malignant cervical lymph node metastases, the presence of aggressive histological subtypes such as medullary or anaplastic thyroid carcinoma, or the occurrence of clinically relevant compressive symptoms (32–34).

5.5.4.1. Contraindicated Treatment During Pregnancy

The use of radioactive iodine is strictly contraindicated throughout the entire pregnancy. Starting from the 12th to 13th week, the isotope would cause irreversible damage to the fetal thyroid gland (36). A planned pregnancy should not occur until at least 6 months after radioactive iodine therapy (32).

5.5.4.2. Monitoring

Monitoring maternal hormone levels through laboratory tests is crucial for preventing maternal hypothyroidism and controlling tumor growth. For this reason, it is important to measure serum TSH immediately after pregnancy is confirmed, then every 4 weeks until the middle of the pregnancy (approximately weeks 16-20), and at least once between weeks 26 and 32 (32).

For oncological monitoring, regular ultrasound examinations are recommended in each trimester to monitor tumor growth and potential lymph node metastases (32).

5.5.5. Clinical Indications for Pregnancy Interruption

Termination of pregnancy is medically indicated only in extremely rare cases following a diagnosis of thyroid cancer (31). Since most carcinomas are DTC and grow slowly, delaying treatment generally

does not negatively affect the mother's prognosis (31). In cases of diagnoses such as an anaplastic thyroid carcinoma or advanced medullary thyroid carcinoma during early pregnancy, termination of the pregnancy may be necessary in order to initiate immediate treatment, such as radiation therapy (34). In cases of extremely rare conditions, such as primary thyroid lymphoma in the early stages of pregnancy, termination is often a prerequisite for initiating standard chemotherapy (34).

5.5.6. Obstetrical Management

Management requires close interdisciplinary collaboration between endocrinologists, oncologists, and obstetricians. Obstetrical management generally does not differ substantially from that of other pregnancy-associated cancers. In most cases, delivery should be planned at term (from 37 weeks of gestation). Vaginal delivery remains the favored mode, and thyroid cancer itself does not constitute a contraindication (2).

5.5.6.1. Postpartum Management

Immediately after delivery, the levothyroxine dose should be reduced to the pre-pregnancy level. It is recommended to check the TSH level approximately 6 weeks after childbirth (32).
All newborns should undergo routine screening for congenital hypothyroidism (32).

6. COMPARATIVE ANALYSIS

6.1. Clinical Presentation and Diagnostic Challenges Across Cancer Types

The diagnosis of cancer during pregnancy, which affects approximately 1 in 1,000 to 2,000 pregnancies, poses a significant clinical challenge, as physiological changes often mask the early signs of malignant tumors (2). This overlap contributes to an average diagnostic delay of 4 weeks, often leading to more advanced disease at the time of discovery (2).

6.1.1. Physiological Overlap and Symptom Profiles

The degree and nature of symptom masking vary across the five most common cancers in pregnancy:

1. **Breast Cancer**
    - Overlap: Pregnancy causes breast engorgement, hypertrophy and increased tissue density. These changes physically mask the primary symptom of a breast cancer; a palpable lump or mass (21).
    - Pronouncement: The overlap is highly pronounced because the physiological growth of the breast tissue creates a physical barrier to detection during examination (5).

2. **Hematologic Malignancies (Leukemia and Lymphoma)**
    - Overlap: Symptoms such as extreme fatigue, exertional dyspnea and anemia are systemic signs of these cancers. However, these are also considered nearly universal and normal experiences in pregnancy (11,27).
    - Pronouncement: The overlap is most pronounced in this category because the symptoms are systemic and easily misattributed (11).
3. **Cervical Cancer**
    - Overlap: Vaginal bleeding and discharge are symptoms of cervical malignancy that are frequently misattributed to various obstetric complications or normal gestational changes (8).
    - Pronouncement: Moderate; while bleeding is a major red flag, it is common enough in pregnancy to lower a provider's index of suspicion (25).
4. **Melanoma**
    - Overlap: Hormonal shifts during pregnancy lead to generalized hyperpigmentation, including the darkening of existing moles or the appearance of melasma. This can distract from or mask the changes in color, symmetry or borders that characterize melanoma (22,30).
    - Pronouncement: Pronounced; natural pigment changes may lead to either false reassurance regarding malignant lesions or unnecessary attention to benign ones (7,30).
5. **Thyroid Cancer**
    - Overlap: The thyroid gland often increases in size during pregnancy. This can cause thyroid nodules to be misdiagnosed as simple physiological growth (31).
    - Pronouncement: Low to moderate; while the gland grows, ultrasound remains highly effective in distinguishing malignant features (2,31).

The overlap is most pronounced in breast cancer and hematologic malignancies. In breast cancer, the delay is primarily related to physical changes, which can obscure clinical and radiological findings (21). In contrast, in hematologic malignancies, delays are more likely due to the nonspecific nature of systemic symptoms, which frequently overlap with normal pregnancy symptoms and therefore reduce clinical suspicion (11).

6.1.2. Comparison of Stage at Diagnosis

The stage at diagnosis varies dramatically between these cancer types, influenced by screening protocols and symptom presentation. Cancers most likely to be diagnosed at an advanced stage are breast cancer and melanoma (5,7). An overview is provided in table 2 below.

Table 2: Comparison of Stage at Diagnosis

Cancer Type	Common Stage at Diagnosis	Reasons for Stage Profile
Cervical Cancer	Stage I (25)	Routine cytology (Pap tests) and speculum exams at the first prenatal visit lead to early detection (9)
Thyroid Cancer	Stage I (90-95%) (31)	Most cases are identified during the initial antenatal visit (31)
Breast Cancer	Advanced (Stage II or III) (1,5)	Physical masking by breast tissue leads to a 2.5-fold higher risk of advanced diagnosis (9)
Melanoma	Later Stages (7)	Diagnostic delay caused by pregnancy-associated hyperpigmentation often results in ticker lesions at diagnosis (1,7)
Hematologic Malignancies	Variable (1)	HL is often caught at similar stages to non-pregnant patients because it is slow-growing (11). NHL and Leukemia are more likely to be advanced due to aggressive subtypes and systemic symptom overlap (1)

The table shows that the stage at diagnosis varies between cancer types in pregnancy due to various reasons.

6.2. Diagnostic Strategies Across Cancer Types

The diagnosis of cancer during pregnancy is grounded in the ALARA principle, which dictates that ionizing radiation exposure should be minimized while ensuring that maternal health is prioritized for fetal survival (2). Ultrasound is the primary first-line diagnostic tool across nearly all suspected malignancies because it lacks ionizing radiation (28). When further staging is required, MRI without contrast is the preferred advanced imaging modality (28). Ionizing radiation procedures like CT scans and PET-CT are generally avoided unless essential for treatment planning, in which case abdominal shielding and dose-reduction techniques are employed (28). Histological confirmation is essential

and should not be postponed because of pregnancy; core needle or excisional biopsies are generally prioritized over FNA to preserve tissue architecture (2).

6.2.1. Comparison of Diagnostic Workflow

While ultrasound and MRI are used across the board, thyroid cancer diagnosis strictly forbids the use of radioactive isotopes common in non-pregnant patients (32). Conversely, Technetium-99m is considered safe for SLNB in breast cancer and melanoma staging when blue dyes are avoided (2). Cervical cancer is unique because its primary detection method is integrated into routine prenatal care, leading to frequent early diagnosis (25). In contrast, breast and thyroid cancers rely more on incidental palpation during gestation-related physical exams (9,35). Cervical cancer also utilizes laparoscopic pelvic lymphadenectomy as a standard staging procedure during pregnancy, typically feasible until 22-25 weeks of gestation (2). For most other solid tumors, advanced staging is deferred until postpartum or relies on non-invasive MRI (3).

For thyroid nodules, FNA remains the standard, whereas in PABC, core needle biopsy is critical because gestational hormonal shifts cause proliferative breast tissue changes that can lead to false results in cytology (1,9).

Table 3: Comparison of Tumor-Specific Diagnostic Workflows

Cancer Type	Primary Screening & Detection	Imaging Strategy	Biopsy, Histological Confirmation
Breast Cancer	Clinical breast exam at first prenatal visit (1)	First line: Breast Ultrasound (24) Adjunct: Mammography with abdominal shielding (21)5/7/26 12:46:00 PM	Core needle biopsy is preferred over FNA (2)
Cervical Cancer	Routine cytology (Pap test) and speculum exams at initial visit (25)	Pelvic MRI without contrast for local staging (26)	Colposcopy with targeted biopsy is safe (8)
Hematologic Malignancies	Laboratory testing, complete blood count (1,11)	Chest X-Ray (shielded) and MRI (1)	Bone marrow biopsy for leukemia (11) Lymph node biopsy for lymphoma (11)

Table 3: Comparison of Tumor-Specific Diagnostic Workflows (Continued)

Cancer Type	Primary Screening & Detection	Imaging Strategy	Biopsy, Histological Confirmation
Melanoma	Skin examination for ABCDE criteria; dermatoscopy (22)	Ultrasound of regional lymph nodes Whole-body MRI from 2nd trimester (30)	Excisional biopsy with 1-3mm margins under local anesthesia (30)
Thyroid Cancer	Palpation of the neck (33)	Neck ultrasound (32)	Ultrasound guided FNA (1)

The table shows a comparison of tumor-specific diagnostic workflows

6.3. Treatment Strategies Across Cancer Types

The core principles of cancer treatment during pregnancy focus on achieving an optimal oncological outcome for the mother while minimizing hazardous exposures to the developing fetus (2). Standard-of-care protocols for non-pregnant patients should be followed as closely as possible, as maternal survival is essential to fetal survival (2). A multidisciplinary team – including oncologists, obstetricians, neonatologists, and physicians of specific medical specialties – is critical for individualized decision-making (28).

6.3.1. Role of Chemotherapy Across Cancer Types

Often considered the safest window for both surgery and the initiation of chemotherapy is the second trimester (after 12-14 weeks) (2). The necessity and safety of chemotherapy vary significantly across different malignancies. For hematologic malignancies, chemotherapy is the central, and often curative, treatment modality (27). Acute leukemias require immediate treatment regardless of gestational age (24). In breast cancer, chemotherapy also represents a key component of treatment and is commonly used in both neoadjuvant and adjuvant settings (21). Standard regimens, typically including anthracyclines, cyclophosphamide, and taxanes, can generally be administered with relative safety after the first trimester (21). For advanced stages (Stage IB2 and above) in cervical cancer, neoadjuvant chemotherapy is used to stabilize the disease and reduce tumor size, acting as a "pregnancy-sparing" strategy to extend gestation until fetal maturity is reached (8). In melanoma and thyroid cancer, chemotherapy has minimal to no role during pregnancy (30,33).

6.4. Indications for Pregnancy Interruption Across Cancer Types

Oncological care involves carefully weighing the need for effective cancer therapy in the mother against the necessity of protecting fetal well-being, with pregnancy termination remaining a

medically and ethically complex option (2). Indications for termination are not standardized because they depend on a unique convergence of gestational age, tumor biology, and maternal prognosis, and are further complicated by the rarity of these cases (1).

6.4.1. Comparison

Rarely require termination

- Thyroid cancer: Detecting thyroid cancer during pregnancy is almost never an indication for termination (31). Most cases are well-differentiated, meaning surgery can be safely deferred until second trimester or postpartum without impacting maternal survival (33).
- Breast cancer: Termination is not expected to improve the oncological prognosis for the mother (21).

Situation-dependent

- Cervical cancer: Indications depend heavily on the stage and nodal status (25). If lymph node metastases are detected or the disease is locally advanced (Stage IIB or higher), non-preserving management (radical surgery, pelvic radiation, or systemic therapy) is recommended, which results in fetal loss (1,8).
- Melanoma: While localized melanoma rarely requires termination, advanced disease (Stage III/IV) frequently mandates its consideration (22). Adequate management of stage IV melanoma is often impossible while pregnant because life-saving treatments like immunotherapy and BRAF-targeted therapies are contraindicated due to fetal risks (7,22).

Frequently lead to consideration

- Acute Leukemias: These are aggressive medical emergencies that require immediate intensive treatment (1).
- Aggressive NHL: Similar to leukemia, aggressive subtypes (e.g. Burkitt's) diagnosed early in gestation often lead to termination discussions to facilitate immediate multiagent chemotherapy (11).

6.5. Obstetrical Management Across Cancer Types

The obstetrical management of pregnant patients with cancer is a complex process that prioritizes optimizing maternal oncological outcomes while minimizing neonatal morbidity (1). Whenever possible, the intention is to achieve a delivery at full-term (> 37 weeks) to mitigate the risks of prematurity, such as respiratory distress and neurodevelopmental delays (2). Medically induced preterm delivery should be avoided unless maternal health deteriorates or treatment that is

incompatible with pregnancy must be expedited (1). Chemotherapy is typically discontinued 2-4 weeks before the anticipated delivery to prevent neonatal neutropenia, thrombocytopenia and sepsis (2,18).

6.5.1. Mode of Delivery Across Cancer Types

Vaginal delivery is generally the preferred mode according to standard obstetric practice, provided there are no specific oncological or obstetrical contraindications (18).

The specific type and location of the cancer significantly influence both the mode and the urgency of delivery. Cancers involving the pelvic region, such as cervical, vaginal and vulvar cancers frequently mandate cesarean delivery to optimize maternal outcomes and avoid complications related to tumor friability and the risk of spreading malignant cells through perineal trauma (2).

Table 4: Comparison of How Cancer Types Influence Obstetric Management

Cancer Type	**Influence on Mode of Delivery**	**Key Obstetrical Considerations**
Cervical Cancer	Cesarean section is often preferred, especially for advanced macroscopic disease (18).	Vaginal delivery carries risks of severe hemorrhage, birth canal obstruction, and cancer cell implantation in vaginal tears or episiotomy sites. Episiotomy should be avoided if vaginal delivery is pursued (1,9,25).
Breast Cancer	Mode is determined by routine obstetric indications (21)	Delivery timing is primarily coordinated with chemotherapy cycles (21)
Hematologic Malignancies	Generally based on routine obstetric indications (1)	If delivery coincides with induction therapy, maternal transfusion support for anemia and thrombocytopenia may be necessary (27)

Table 4: Comparison of How Cancer Types Influence Obstetric Management (Continued)

Cancer Type	Influence on Mode of Delivery	Key Obstetrical Considerations
Melanoma	Mode is based on obstetric indications (7)	Melanoma has the highest rate of placental metastasis; therefore macro- and microscopic histological evaluation of the placenta is mandatory (22)
Thyroid Cancer	Mode is based on obstetric indications (34)	Delivery before term is almost never indicated (34)

The table shows a comparison on how cancer types influence obstetric management

6.6. Maternal and Fetal Outcomes

Maternal and fetal outcomes in pregnancies associated with cancer are influenced by a complex interplay of tumor biology, the timing of diagnosis, and the limitations placed on treatment by the need to safeguard the developing fetus.

6.6.1. Maternal Outcomes and Prognostic Categorization

Maternal survival generally depends on the stage at diagnosis and the ability to initiate standard-of-care treatment without significant delay (2). Factors contributing to prognostic differences include diagnostic delay, more aggressive tumor biology and the contraindication of key therapies during pregnancy. Outcomes can be categorized into three prognostic groups:

1. **Generally favorable prognosis**
   - Thyroid Cancer: Survival and disease-free intervals do not vary between pregnant and non-pregnant women, and surgery can often be safely deferred until postpartum (32).
   - Cervical Cancer: Due to routine prenatal screening approximately 75% of cases are diagnosed in early stages (1). Long-term survival is comparable to non-pregnant patients (9).
2. **Intermediate prognosis**
   - Breast Cancer: While some studies show similar survival when adjusted for stage and treatment (2), others report higher mortality (5). PABC is often diagnosed at advanced stages because physiological changes mask tumors and it frequently involves aggressive phenotypes like triple-negative breast cancer (5,19).
   - Hodgkin Lymphoma: Outcomes are generally favorable and caught at similar stages to non-pregnant patients (11).

3. **Poorer prognosis**
   - Acute Leukemias (AML and ALL): These conditions are considered medical emergencies with a highly aggressive course and maternal mortality rates reaching 20% in certain populations (27).
   - Advanced Melanoma: While localized melanoma has a good prognosis, stage III and IV disease carry poor outcomes for both mother and child (1).

6.6.2. Fetal Outcomes and Impact of Cancer

Fetal outcomes in pregnancies complicated by cancer are primarily determined by indirect factors – specifically the timing of treatment and the frequent necessity for iatrogenic prematurity – rather than the direct biological effects of the malignancy itself (1). Direct effects of cancer are rare and limited to specific malignancies, while the consequences of iatrogenic prematurity and the timing of therapy are systemic challenges faced by nearly all patients (2,18).

Table 5: Comparison of Relative Impacts of Cancer on the Fetus

Factor	Relative Impact on Fetal Outcome	Frequency
Indirect: Prematurity	High; primary driver of nearly all common neonatal morbidities (24)	Very high (up to 47-65% of cases) (3,24)
Indirect: Specific toxicities	High; certain agents carry unique risks regardless of timing (28)	Universal
Indirect: Treatment timing	High; determines the risk of malformations and fetal loss (2)	Universal
Direct: Cancer metastasis	Very high; leads to high neonatal mortality (18)	Extremely rare (2)
Direct: Systemic effects of cancer itself	Moderate to high; increases risks of IUGR and fetal demise in specific cancer types (11)	Low (limited primarily to hematologic malignancies) (1)
Direct: Cancer biology	Very high; aggressive biology of certain cancers create a medical emergency, often necessitating pregnancy termination (11)	Low (limited mostly to hematologic malignancies) (24)

The table shows a comparison on relative impacts of cancer on the fetus

7. DISCUSSION

7.1. Principal Findings of the Review

The review highlights that cancer during pregnancy represents a complex clinical scenario requiring continuous balancing between maternal oncologic safety and fetal well-being. Across tumor entities, several consistent patterns emerged regarding diagnostic delay, treatment feasibility, and perinatal outcomes.

A key finding is the presence of a clinically relevant diagnostic delay, primarily driven by the similarity in presentation between cancer symptoms and pregnancy-related physiological adaptions (3). This masking effect appears to be particularly pronounced in PABC, whereas cervical cancer benefits from routine prenatal screening, resulting in higher rates of early-stage detection (1,19).

With regard to treatment, the data consistently support the feasibility of standard oncologic therapies with appropriate modifications (2). Surgery can be safely performed throughout pregnancy, while chemotherapy is considered relatively safe after the first trimester. In contrast, certain treatments – including pelvic radiotheraoy, radioiodine therapy, methotrexate and selected targeted therapies – remain strictly contraindicated due to significant fetal toxicity (2).

Another central finding concerns the importance of treatment timing and obstetric management. Iatrogenic preterm delivery emerged as a major determinant of neonatal morbidity, outweighing the direct effects of in-utero chemotherapy exposure (2). Consequently, current evidence supports aiming for delivery at term whenever oncologically feasible, while maintaining a chemotherapy-free interval prior to birth (1,8).

7.2. Interpretation of Findings

In the scientific debate on cancer during pregnancy, it has become clear that maternal and fetal outcomes depend on a complex hierarchy of interrelated factors. The interaction ultimately determines the prognosis for both patients:

1. **Cancer type and tumor biology:** Tumor aggressiveness is the strongest predictor of maternal survival (2).
2. **Gestational age:** Gestational age acts as a “gatekeeper” for treatment options and thus has the greatest influence on the treatment window. During the first trimester, there is a high risk of teratogenicity during organogenesis (up to 20% rate of malformations with chemotherapy) (27).
3. **Treatment decisions:** The decision regarding the timing of delivery is the most critical factor for neonatal outcomes. Iatrogenic preterm birth (often induced to intensify maternal treatment) is the leading cause of neonatal morbidity and impaired neurological development (24).

A further key dimension influencing these outcomes is the variability in clinical presentation and the resulting diagnostic delay, which differs substantially between tumor entities. These differences are primarily driven by the interaction of symptom overlap with physiological pregnancy changes and the availability of screening strategies. As a result, cancers that benefit from routine prenatal screening are more likely to be detected at earlier stages, whereas tumors with non-specific or pregnancy-mimicking symptoms are frequently diagnosed later, often at more advanced stages (9).

7.3. Clinical Implications

Cancer during pregnancy represents one of the most challenging clinical conditions in onco-obstetrics, requiring a continuous balance between the mother's chances of recovery and fetal safety. The rarity of these cases – approximately 1 in 1,000 pregnancies – and the ongoing updates to evidence-based guidelines make centralization in specialized centers essential for health services research and clinical practice (1,2).

Optimal management relies on a multidisciplinary approach involving gynecologic oncologists, obstetricians, surgeons, neonatologists, and specialized pathologists to enable individualized risk-benefit assessment and coordinated treatment planning. Within this context, patient counseling is an essential component of clinical care and should be conducted in a value-sensitive and non-directive manner (2).

Current evidence indicates that no improvement in maternal diagnosis in case of most solid tumors is achieved through termination of pregnancy. However, in selected cases pregnancy termination may be considered to enable the immediate initiation of potentially life-saving therapy (9).

Ultimately, clinical decision-making should be guided by the best available evidence while maintaining a compassionate, patient-centered approach. Respect for maternal autonomy must remain paramount, ensuring that patients are fully informed and supported in making decisions that align with their individual values and preferences. Access to psychosocial support services is a key component of care, helping to mitigate emotional burden, address practical needs and support patients in complex decision-making processes (2,28).

7.4. Persistent Challenges

The analysis of the current evidence demonstrates that the management of PAC remains characterized by diagnostic, therapeutic, pharmacological, ethical and systemic challenges. Despite advanced in oncologic care, the balance between maternal treatment and fetal safety continues to represent a highly complex dilemma.

A central challenge lies in delayed or difficult diagnosis. Physiological changes during pregnancy frequently mask early cancer symptoms (3). This is further complicated by the limited reliability of

tumor markers many of which are physiologically elevated during pregnancy, as well as restrictions in imaging modalities due to radiation exposure (1).

Beyond diagnosis, treatment planning is inherently complex due to the need to continuously balance maternal benefit against potential fetal harm. While standard oncologic therapies can often be adapted, their timing remains a critical challenge (2). Aligning treatment schedules with gestational age requires careful coordination to avoid both undertreatment of the mother and unnecessary fetal exposure. The need to optimize maternal therapy may lead to iatrogenic preterm birth, which remains the most important contributor to neonatal morbidity (1). Avoiding premature delivery while maintaining adequate oncologic treatment therefore represents a key challenge in clinical decision-making.

In addition, ethical complexity is inherent to the management of cancer during pregnancy. Clinicians and patients are frequently confronted with difficult decisions involving competing priorities, particularly in situations requiring urgent treatment initiation. These scenarios place a significant emotional burden on patients and require careful, individualized counseling (2).

7.5. Limitations of Available Evidence & Areas for Future Research

The current evidence base guiding the management of cancer during pregnancy is characterized by substantial methodological limitations across all investigated tumor entities. A central issue is the systemic exclusion of pregnant patients from clinical trials due to ethical concerns and potential fetal risks (3). As a result, most clinical recommendations are concluded from studies conducted in non-pregnant populations, limiting their direct applicability (2).

Consequently, the available data are largely originated from case reports, small case series, and retrospective observational studies (2). This predominance of retrospective evidence introduces significant risks of selection bias – such as the overrepresentation of complex cases treated in tertiary centers, as well as publication bias favoring favorable outcomes (2,32). In addition, considerable heterogeneity exists across studies, particularly regarding definitions of pregnancy-associated cancers. For example, the diagnostic timeframes for pregnancy-associated breast cancer or melanoma vary widely, ranging from diagnosis during pregnancy to several years postpartum (5,22). This inconsistency substantially limits the comparability of survival outcomes and recurrence rates.

Another critical limitation is the lack of statistical power in many studies, as small cohort sizes hinder the reliable detection of rare events and long-term effects. These general limitations are further compounded by tumor-specific challenges. In breast cancer, inconsistent differentiation between pregnancy-associated and postpartum disease contributes to conflicting conclusions regarding tumor aggressiveness and prognosis (21). In cervical cancer, the absence of prospective data results in management strategies largely based on retrospective analyses and estimation from non-pregnant

populations (25). Hematological malignancies are marked by a pronounced lack of pharmacokinetic data, complicating dose optimization in a physiologically altered maternal system (11,24). In melanoma, the long-standing debate on the prognostic impact of pregnancy remains unresolved due to methodological weakness in earlier studies and insufficient control for confounding variables (7). For thyroid cancer, much of the existing evidence is derived from older studies (36).

These limitations translate into several critical areas for future research. Most notably, there is a lack of long-term follow-up data on children exposed to cancer or its treatment in-utero. Existing studies predominantly focus on neonatal outcomes, while data on long-term development – including fertility, risk of secondary malignancies, and subtle neurocognitive effects – remain scarce (2). Furthermore, there is a profound evidence gap regarding the safety of modern oncologic therapies, including targeted agents and immune checkpoint inhibitors (28). As these treatments increasingly represent standard of care, uncertainty regarding their teratogenic and immunological effects constitutes a major barrier to evidence-based clinical decision-making.

These gaps define key priorities for future research. The expansion and international harmonization of prospective registries, such as the INCIP initiative, are essential to generate high-quality, multicenter data beyond retrospective analyses (2). Given the rarity and complexity of these cases, further strengthening of multidisciplinary care in specialized tertiary centers remains crucial (28). At the same time, in the absence of robust evidence, clinical decision-making must rely on transparent, value-based counseling that acknowledges uncertainty and places patient autonomy at the forefront (2).

In summary, while current evidence supports the relative safety of conventional chemotherapy after the first trimester, substantial uncertainties remain – particularly regarding modern therapeutic approaches and long-term outcomes. Addressing these gaps will require coordinated international efforts and prospective research strategies to improve both maternal and fetal outcomes in this complex clinical setting.

8. CONCLUSION

Pregnancy-associated cancer represents an increasing challenge in modern perinatal and oncological care, driven by demographic changes such as rising maternal age and the resulting overlap between reproductive years and peak cancer incidence. This creates a clinically complex scenario in which maternal oncologic outcomes and fetal safety must be continuously balanced.

Cancer in pregnancy is not defined by a single disease course but by the interaction between tumor biology, gestational physiology, and treatment timing. This interaction leads to cancer-specific patterns, while key clinical challenges are shared across entities: Pregnancy-related physiological changes contribute to diagnostic masking, but the extent and clinical consequences vary by entity.

Breast cancer and hematologic malignancies are particularly affected due to symptom overlap with normal pregnancy, whereas cervical and thyroid cancers are more frequently detected at early stages through routine screening. These differences largely determine stage at diagnosis and subsequent therapeutic pathways.

Treatment feasibility is primarily governed by gestational age, which acts as the central determinant of clinical decision-making. While surgery and chemotherapy after the first trimester are generally feasible across most cancer types, therapeutic intent and applicability vary substantially depending on tumor biology.

Importantly, maternal prognosis is mainly influenced by tumor aggressiveness and stage rather than pregnancy itself. In contrast, fetal outcomes are predominantly driven by treatment timing and obstetric management, particularly iatrogenic prematurity, rather than direct effects of malignancy or chemotherapy exposure. Direct tumor-related fetal involvement remains rare and is largely restricted to specific entities such as melanoma, in which placental metastases may occur. Overall, fetal risk is therefore predominantly indirect.

Taken together, these findings highlight that cancer in pregnancy should be approached as a time-sensitive, multidimensional condition rather than a series of isolated tumor entities. Optimal outcomes rely on individualized, multidisciplinary management that integrates oncologic necessity with gestational physiology. Central priorities include minimizing avoidable preterm delivery, ensuring appropriate timing of therapy, and maintaining maternal oncologic standards of care, as maternal health remains the fundamental prerequisite for fetal survival.

Ultimately, optimizing outcomes in cancer during pregnancy depends less on cancer-specific pathways than on coordinated timing of diagnosis, treatment and delivery within a gestational framework.

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