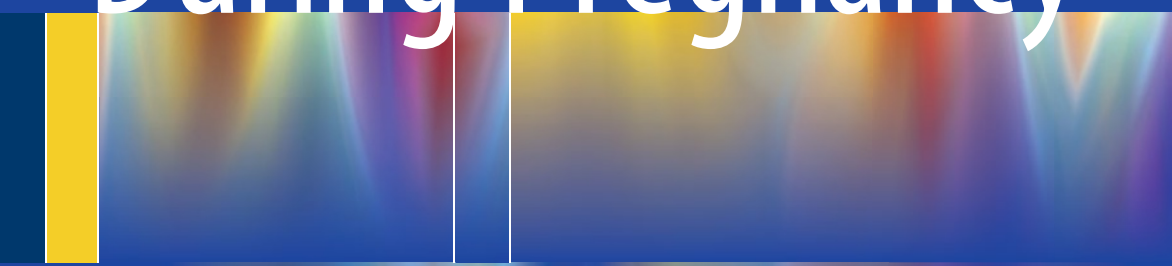
Managing Cancer During Pregnancy



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This book is dedicated to two men. One is a man who served as a role model for me over the years and inspired me to join the oncology field, my father Hamdy A. Azim. The other is the man who introduced me to the field of cancer in pregnancy and mentored me selflessly for a long time, my very good friend, Fedro Peccatori.

Foreword

The issue of cancer in pregnancy is becoming increasingly important as women are delaying the birth of their first child. The trends of first pregnancy have increased from the age of the early twenties to the mid and late twenties depending on the country. Cancer in pregnancy is clearly an extremely important area since two lives are at stake when treating pregnant women with cancer. This book is an immensely valuable and unique addition to the literature because it touches on every aspect of care from diagnosis, surgery, radiation, psychological, to treatment. Since there are no randomized studies possible in pregnant women for treatment of their cancer, recommendations have to be made based on observational data. This can be either retrospective or prospective. With recognition internationally that this is an important topic, physicians have worked together to collect the data available so that clearer conclusions and guidelines can be made. This collection of excellent articles by a diverse and distinguished group of experts synthesizes the data that is published and allows the practitioner to make an informed recommendation to their patients. It is a very emotional topic and difficult decisions have to be made. The information in these chapters will give treating physicians and consequently their patients, the confidence needed to know that they are on the appropriate path. I give Dr. Azim much credit for following his passion and making certain that this information is readily available to all of us.

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Preface

This book describes practical tips in managing patients diagnosed with cancer during pregnancy, which remains one of the most delicate and feared situations facing both oncologists and obstetricians. Given the relative rarity of this disease, treatment decisions are largely individualized and based on anecdotal evidence. However, over the past 5 years, several groups have made important contributions in the field of management of pregnant cancer patients, providing refined evidence on the magnitude of benefit and harm of the different treatment modalities, and their effects not only on the mother but also on the baby. This includes studies investigating the biology and prognosis of these patients, the safety of the different anti-cancer medications, long-term toxicity of chemotherapeutic agents, role of targeted therapy during pregnancy, potential role of radiotherapy and the use of novel staging modalities, and many other hot topics. This book also includes disease-specific chapters, which provide further insights that should be taken into account, in managing each individual cancer, when diagnosed during gestation. Importantly, this book provides clear statements on several controversial issues based on sound evidence, interpreted by authors who are experts in the field with hands-on experience in managing pregnant cancer patients and who have made valuable research contributions in this domain.

Thus, it is thought that this book is arriving at the right moment to provide the oncological and obstetrical communities with a valuable resource to guide busy clinicians in managing these challenging cases in daily practice.

Brussels, Belgium — Hatem A. Azim Jr, MD, PhD

Acknowledgment

I would like to thank all the authors who have contributed in this book, for their efforts in preparing such high quality work in a very timely manner.

Special thanks are extended to Isabel Arnold, the editor behind the idea of publishing a dedicated book on cancer in pregnancy and the project coordinator, Mahalakshmi SathishBabu, who provided extensive support for the editor and the authors in all phases of preparation of this book.

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Part I

Overview

Epidemiology of Cancer in Pregnancy

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Kembra L. Howdeshell and Michael D. Shelby

Introduction

Cancer diagnosed during pregnancy is rare, and the incidence rate of pregnancy-associated cancer is expected to increase as women continue to delay childbearing to their later reproductive years [38]. The definition of pregnancy-associated cancer varies from study to study, but most frequently is defined as a diagnosis during pregnancy or up to 1 year after delivery. The incidence rate of cancer diagnosed during pregnancy is reported to range from 17 to 38 cases/100,000 births [14, 21, 29, 49], while the incidence of rate of cancer diagnosed during pregnancy or up to 1 year after delivery (94–137/100,000 births) approaches the rates observed in all women of reproductive age (15–44 years old; Table 1.1) [47]. Significant increases in incidence rates of pregnancy-associated cancer over time have been reported in studies spanning the years 1977–2008; however, the tendency to delay pregnancy was only partially responsible for the increased incidence rates [14, 29]. Other factors contributing to the increase in rate of pregnancy-associated cancer over time may be improvements in diagnostic techniques and detection and increased interaction with medical services during pregnancy. It has also been hypothesized that the hormones and growth factors necessary for fetal growth may accelerate tumor growth.

This chapter reviews current information regarding the incidence and prognosis of seven of the cancer types frequently diagnosed during pregnancy: breast cancer, cervical cancer, ovarian cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and melanoma (Fig. 1.1). These seven cancers are also among the cancers most frequently diagnosed in women of reproductive age, accounting for about

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Table 1.1 Incidence of malignant cancer among all women of reproductive age (15–44 years) in the USA, reported in the year 2012

Cancer type	All cancer sites	Breast	Cervix	Leukemia	Hodgkin lymphoma	Non-Hodgkin lymphoma	Ovary	Melanoma
Incidence	130.4[a]	41.6	6.9	3.3	3.5	4.5	4.0	11.9

The site-specific cancers included in this table represent seven of the most frequently diagnosed cancers in women during pregnancy

[a]Data are age-adjusted and are rates per 100,000 women as reported by Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute [47]

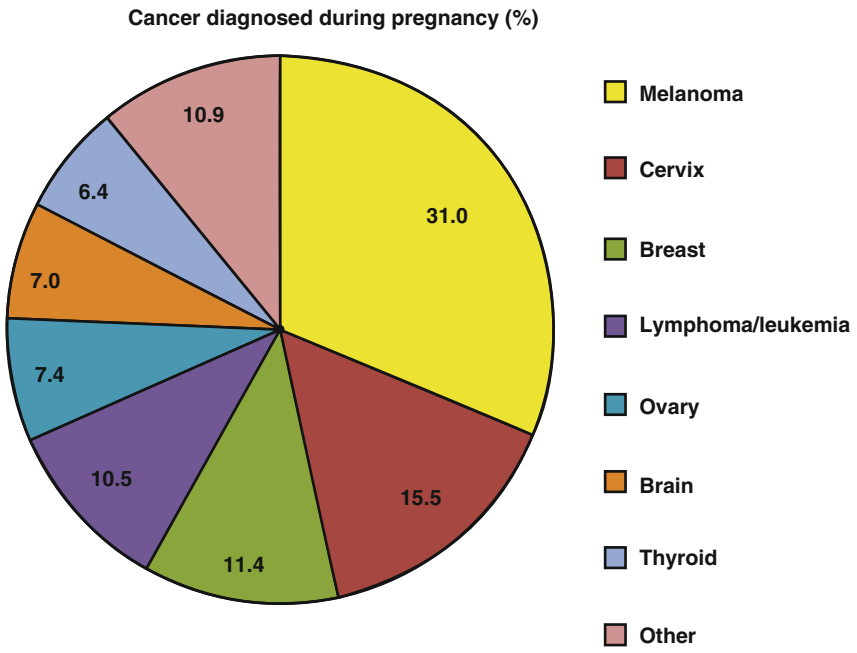

Fig. 1.1 Percentage of cancer types diagnosed during pregnancy in Norway from 1967 to 2002 as reported in Stensheim et al. [51] ($n = 516$ cases). Other types of cancers frequently diagnosed during pregnancy include the thyroid, colorectal, and brain/central nervous system [14, 21, 29, 49, 51]

58 % of all cancers in this age group (Table 1.1) [47]. The incidence data reviewed in this chapter focus on population-based studies, while the prognosis literature focus on studies reporting matched controls and larger sample sizes as well as meta-analyses, when available. Several smaller studies that assess the incidence and prognosis of pregnancy-associated cancer are included in the National Toxicology Program monograph on *Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use During Pregnancy* [42] and other reviews. The majority of studies evaluating the prognosis define pregnancy-associated cancer as a diagnosis of cancer during pregnancy or up to 1 year postpartum, which makes it

difficult to determine the prognosis of patient with cancer diagnosed during pregnancy only. When data are available, this chapter also reviews the prognosis of women diagnosed with cancer specifically during pregnancy (referred to as diagnosed during pregnancy).

Breast Cancer and Pregnancy

Occurrence Rate During Pregnancy

The incidence rate of pregnancy-associated breast cancer was reported in seven population-based studies [1, 5, 14, 21, 23, 29, 49] (Table 1.2). The crude incidence rate of breast cancer diagnosed during pregnancy was 1.3–7.9/100,000 births. The incidence rate of pregnancy-associated breast cancer increased over the time period covered by the four studies (1963–2008), which was partially attributable to a delay in childbearing to an older age [1, 5, 14, 29].

Impact of Pregnancy on Prognosis

Pregnancy and lactation increase the size and density of the breasts, making it more difficult for the patient or the clinician to detect masses in the breasts. This is thought to lead to a delay in diagnosis of some tumors and, hence, to the presence of more advanced-stage tumors at diagnosis in many pregnant breast cancer patients when compared to their nonpregnant counterparts [6, 44]. Petrek and Seltzer [44] reviewed the evidence for pregnancy impacting the prognosis of breast cancer. They reported that women with pregnancy-associated breast cancer are more likely than nonpregnant patients to have positive lymph nodes and less likely to have tumors smaller than 2 cm. They noted that pregnant women had a 2.5-fold higher risk of diagnosis with metastatic breast cancer and a significantly decreased chance of an earlier stage (stage I) diagnosis. These observations are supported by two recent studies reporting that pregnancy-associated breast cancer cases have more advanced disease [24, 52] and larger tumors at diagnosis than nonpregnant breast cancer patients [52].

A majority of studies report that survival is worse in pregnancy-associated breast cancer patients than in their nonpregnant counterparts. In a meta-analysis of 30 retrospective control-matched, population-based, and hospital-based studies published from years 1969 to 2012, Azim et al. [6] observed that pregnancy-associated breast cancer was associated with poor prognosis, even after adjustment for confounding factors (e.g., age, stage of tumor). However, both univariate and multivariate analyses observed significant heterogeneity among the studies assessing the overall survival of pregnancy-associated breast cancer. The authors suggest that part of the poor prognosis may be due to delayed diagnosis and suboptimal systemic therapy [6]. Several recent publications of control-matched studies have reported similar results of shorter disease-free survival and lower overall survival of pregnancy-associated

Table 1.2 Incidence of cancer during pregnancy from population-based studies

			Crude incidence per 100,000 births (number of births)						
Reference	Years of data	Total number of births	Breast	Cervix	Leukemia	Hodgkin lymphoma	Non-Hodgkin lymphoma	Ovary	Melanoma
Haas [21]	1970–1979	2,103,112	1.3 (28)	10.9 (229)	0.4 (8)	0.7 (15)	0.2 (4)	0.9 (19)	0.6 (12)
Dgani et al. [12]	1960–1984	1,083,652	–[a]	–	–	–	–	2.1 (23)	–
Smith et al. [49]	1991–1999	4,846,505	5.1 (246)	3.6 (175)	1.4 (67)	2.2 (107)	0.7 (33)	2.4 (115)	3.1 (12)
Ives et al. [23]	1982–2000	NR[b]	7.9 (NR)[c,d]	–	–	–	–	–	–
Andersson et al. [5]	1963–2002	4,156,190	2.4 (99)	–	–	–	–	–	–
Abenhaim et al. [1]	1999–2008	8,826,137	6.5 (573)	–	–	–	–	–	–
Lee et al. [29]	1994–2008	1,309,501	7.3 (95)	1.8 (24)	–	–	–	1.5 (19)	–
Al-Halal et al. [2]	1999–2008	8,826,137	–	3.3 (294)	–	–	–	–	–
Eibye et al. [14]	1977–2006	2,427,670[c]	3.7 (91)[c]	4.0 (96)[c]	–	–	–	–	5.8 (141)[c]
Bannister-Tyrrell et al. [7][e]	1994–2008	1,309,501	–	–	–	–	–	–	14.9 (195)
El-Messidi et al. [15]	2003–2011	7,916,388	–	–	–	8.1 (638)	–	–	–
El-Messidi et al. [16]	2003–2011	7,917,453	–	–	–	–	5.4 (427)	–	–

[a]No data reported for specific cancer type
[b]Not reported
[c]Total number of pregnancies, including live births and induced abortions; incidence rates based on pregnancies
[d]Incidence rate of cancer diagnosed during pregnancy only was estimated as one-third of the incidence of cancer diagnosed during pregnancy and up to 1 year postpartum
[e]Follow-up study of same population reported in Lee et al. [29]

breast cancer cases compared to a nonpregnant breast cancer cohort [3, 13, 24, 36, 46]. However, limitations of these studies include a lack of adjustment for chemotherapy regime or incomplete data on chemotherapy treatment to do so reliably and a lack of data on time between diagnosis and treatment. Another recent study did not observe a difference in overall survival between these two patient groups [52].

The prognosis of breast cancer diagnosed during pregnancy appears to be largely comparable to the nonpregnant cohort. The meta-analysis of 30 studies by Azim et al. [6] reported a slightly greater risk of death for breast cancer patients diagnosed during pregnancy only compared to nonpregnant controls; however, the pooled hazard ratio of the multivariate analysis was not statistically significant (pooled HR: 1.29; 95 % CI [0.74–2.24]) and had high heterogeneity. Six studies published since the meta-analysis report comparable overall survival rates between breast cancer patients diagnosed during pregnancy and a nonpregnant breast cohort [4, 13, 17, 34, 36, 52]. In particular, two studies controlled or adjusted for systemic treatment in their analysis and observed comparable clinical outcomes for breast cancer patients diagnosed during pregnancy and nonpregnant breast cancer patients [4, 34]. Litton et al. [34] conducted a matched case-control study of breast cancer patients treated during the second and third trimesters with standard 5-fluorouracil-adriamycin-cyclophosphamide (FAC) therapy matched on age and stage of cancer with a nonpregnant cohort. The authors reported comparable, if not improved, disease-free survival, progression-free survival, and overall survival of the breast cancer patients treated during pregnancy compared to the nonpregnant patients [34]. Amant et al. [4] conducted a cohort study using data from an international registry of women diagnosed with breast cancer during pregnancy compared to nonpregnant breast cancer patients and adjusted for age, stage, grade, hormone receptor status, histology, human epidermal growth factor 2 status, type of chemotherapy (administered in the second or third trimester), and any postpartum treatment with trastuzumab, radiotherapy, and hormone therapy. The authors observed similar disease-free and overall survival of women diagnosed with breast cancer during pregnancy compared to the nonpregnant cohort [4].

Cervical Cancer and Pregnancy

Occurrence Rate During Pregnancy

Cervical cancer was among the three cancers most frequently diagnosed during pregnancy in four of the five population-based studies reviewed herein [2, 14, 21, 29, 49] (Table 1.2). The crude incidence rate of cervical cancer diagnosed during pregnancy was 1.8–10.9 cases/100,000 births. Haas [21] reported that the age-adjusted incidence rate of cervical cancer diagnosed during pregnancy increased with increasing maternal age, which she suggests may be due to the introduction of cervical screening programs during the time period of the study (1970–1979). However, the age-adjusted rate of cervical cancer did not appear to rise over time in two other population-based studies that were conducted at either a later date

(1999–2008) [2] or over a broader time period (1977–2006) [14]. Cervical intraepithelial neoplasia, a precursor to cervical cancer, appeared to increase over time and was observed in younger patients (<25–34 years), whereas cervical cancer patients were older (25 to ≥35 years) [2].

Impact of Pregnancy on Prognosis

There is general agreement in the literature that pregnancy does not appear to change the prognosis of cervical cancer. In their review of the literature, Germann et al. [19] stated that the majority of the studies do not report a difference in the prognosis of pregnancy-associated invasive cervical cancer. No differences in survival between pregnancy-associated cervical cancer cases and nonpregnant patients with cervical cancer have been reported by at least three retrospective cohort studies published since 2005 [28, 45, 51], including one study that also evaluated the cause-specific survival by timing of diagnosis (during pregnancy or during lactation) and found no significant differences with nonpregnant cervical cancer patients [51].

Some studies reported unique characteristics of pregnancy-associated cervical cancer. A younger age at diagnosis was reported for women diagnosed with pregnancy-associated cervical cancer versus nonpregnant patients [37, 40]. Women with pregnancy-associated cervical cancer were more likely to be diagnosed at stage I than nonpregnant patients [19, 37]. Lee et al. [28] reported that, unlike nonpregnant cervical cancer patients, the depth of the stromal invasion did not correlate with the involvement of the lymph vascular space or lymph node metastasis in women diagnosed with pregnancy-associated cervical cancer. The authors suggest that pregnancy-induced enlargement of the uterine cervix may reduce the depth of the stromal invasion, which may lead to earlier lymph node metastasis [28].

Lymphomas and Leukemia and Pregnancy

Occurrence Rate During Pregnancy

Five population-based studies that addressed the occurrence rate of pregnancy-associated lymphohematopoietic cancer are reviewed [15, 16, 21, 29, 49] (Table 1.2). Of the three lymphohematopoietic cancer types, Hodgkin lymphoma was the most commonly diagnosed during pregnancy. The crude incidence rate of Hodgkin lymphoma diagnosed during pregnancy ranged from 0.7 to 8.1/100,000 births across the three available studies [15, 21, 49]. The incidence rate of Hodgkin lymphoma appeared to be relatively stable in the USA from 2003 to 2011 when assessing the age-adjusted incidence rates [15], although the rates were greater than those observed in the USA in the 1990s [49] (Table 1.2). Leukemia was the second most common lymphohematopoietic cancer occurring in pregnancy with crude incidence rates for diagnosis during pregnancy of 0.4–1.4/100,000 births [21, 49]. There were no data reported regarding the incidence rate of leukemia over time. Finally, the

crude incidence rate of non-Hodgkin lymphoma diagnosed during pregnancy was 0.2–5.4/100,000 births [16, 21, 49]. The crude incidence rate of non-Hodgkin lymphoma diagnosed during pregnancy was observed to increase significantly from 4.4/100,000 birth in 2003 to 7.7/100,000 births in 2011 in a study conducted in the USA [16]. One study reported the cases of pregnancy-associated lymphoma or leukemia as a combined incidence rate of 4/100,000 births diagnosed during pregnancy from 1994 to 2008 [29], which was similar to the rates of the three cancer types combined from Smith et al. [49].

Impact of Pregnancy on Prognosis

The impact of pregnancy on the prognosis of Hodgkin lymphoma and leukemia appears negligible, while there are limited data available on the prognosis of non-Hodgkin lymphoma so the impact is unclear. However, these conclusions are based primarily on small retrospective series and case reports (see below). The only retrospective, population-based cohort study to evaluate prognosis of the pregnancy-associated lymphohematopoietic cancers (combined) found no difference in the rates of cause-specific death between women diagnosed during pregnancy and nonpregnant cases [51]. The authors did not evaluate the prognosis of Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemia separately.

Hodgkin Lymphoma

Two cohort studies reported no differences in prognosis for pregnancy-associated Hodgkin lymphoma compared to nonpregnant patients. In a retrospective cohort study from one hospital, Barry et al. [8] reported no difference in survival curves or median survival times between 84 pregnancy-associated Hodgkin lymphoma patients and 228 age-matched, nonpregnant Hodgkin patients; pregnancy associated was defined as diagnosed during pregnancy and up to 3 months postpartum in this study. In another retrospective cohort study from a single hospital, Lishner et al. [32] identified 48 women who became pregnant 3 months prior to or up to 9 months after first treatment for Hodgkin lymphoma and 67 age-matched nonpregnant Hodgkin lymphoma cases. They observed no statistical difference in the 20-year survival or the distributions of stages at diagnosis between the pregnancy-associated Hodgkin lymphoma cases and their age-matched, nonpregnant cohort. Finally, a third study compared the prognosis of women diagnosed during pregnancy with Hodgkin lymphoma versus non-Hodgkin lymphoma at one hospital [18]. They noted that the clinical behavior of Hodgkin disease during pregnancy did not appear to differ from that outside of the pregnancy setting; however, the pregnancy-associated cases were not compared to a nonpregnant, age-matched cohort.

Non-Hodgkin Lymphoma

The prognosis of non-Hodgkin lymphoma during pregnancy is unclear due to very little primary data. Lishner et al. [33] reviewed the literature on retrospective series and case reports and concluded, "…there is evidence to suggest that

pregnancy does not affect the course of [non-Hodgkin] lymphoma when properly treated." Rapid clinical progression of pregnancy-associated non-Hodgkin lymphoma was reported in a series of 6 patients and review of 22 cases in the literature [50]; the affected patients were in advanced stage at diagnosis. Finally, significantly poorer prognosis was reported for women diagnosed during pregnancy with non-Hodgkin lymphoma patients compared to women diagnosed during pregnancy with Hodgkin lymphoma patients [18]; however, the cases were not compared to a nonpregnant cohort.

Horowitz et al. [22] conducted a systematic review of the literature published between 1967 and 2011 in order to determine the characteristics and outcomes of pregnancy-associated non-Hodgkin lymphoma. Women with pregnancy-associated non-Hodgkin lymphoma were significantly more likely to have highly aggressive (e.g., Burkitt lymphoma, immunoblastic lymphoma, and unspecified highly aggressive lymphomas) than aggressive lymphoma (e.g., diffuse large B-cell lymphoma and T-cell lymphomas) and an advanced stage of cancer at time of diagnosis. Extranodal involvement was observed in patients with advanced-stage pregnancy-associated non-Hodgkin lymphoma, which could be due to a later diagnosis of the cancer. The reproductive organs were the most common extranodal areas involved and may represent a unique characteristic of pregnancy-associated non-Hodgkin lymphoma as involvement of the reproductive organs is rarely observed in nonpregnant patients with this cancer. Finally, 6-month survival was 53 % for pregnancy-associated non-Hodgkin lymphoma patients. Patients with pregnancy-associated non-Hodgkin lymphoma treated prior to 2000 had significantly poorer 6- and 12-month survival (41.9 % and 36 %, respectively) than patients with pregnancy-associated non-Hodgkin lymphoma treated from 2000 to 2011 (6-month survival = 73 % and 12-month survival = 70 %).

Leukemia

There is general agreement in the literature that pregnancy does not influence the course of leukemia, but few primary data are presented or cited to support this position. Nicholson [41] concluded that there is no good evidence that pregnancy has a deleterious effect on leukemia, based on a review of five cases and the literature from 1959 to 1965. He calculated median survival rates of 5 months for acute leukemia ($n = 98$ cases) and 38 months for chronic myeloid leukemia ($n = 44$ cases); both survival rates were similar to survival rates of nonpregnant adult females. Catanzarite and Ferguson [9] conducted a review of the literature published from 1972 to 1982 of pregnant patients with acute leukemia. They estimated a median survival of 6–12 months postpartum for women diagnosed with acute leukemia during pregnancy, which they stated was consistent with survival for adults treated for acute leukemia. Finally, Chelghoum et al. [10] collected information via mailed questionnaire from 13 French centers that administered care to women diagnosed with acute leukemia during pregnancy. Based on the data from 37 cases from 1988 to 2003, they reported that overall survival rate was 65 % at 3 years and 46 % at

5 years and concluded that pregnancy does not affect the course of acute leukemia. None of the abovementioned studies of pregnancy-associated leukemia included a nonpregnant cohort.

A challenge in assessing the prognosis of leukemia diagnosed during pregnancy is selection bias. Leukemia has a rapid progression course and can be fatal without immediate treatment, and some women diagnosed with leukemia in the first trimester may elect to terminate their pregnancy [20]. Thus, the prognosis of pregnancy-associated leukemia would be based on a smaller sample of pregnant women diagnosed with cancer in the first trimester.

Ovarian Cancer and Pregnancy

Occurrence Rate During Pregnancy

Four population-based studies that addressed the rate of occurrence of pregnancy-associated ovarian cancer are reviewed [12, 21, 29, 49] (Table 1.2). The reported crude incidence rates of pregnancy-associated ovarian cancer were fairly similar across the four studies; however, no study specifically assessed the incidence rate of pregnancy-associated ovarian cancer over time. The crude incidence rate of ovarian cancer diagnosed during pregnancy only ranged from 0.9 to 1.8/100,000, about a twofold range. Differences in the rates of occurrence may occur based on what malignant ovarian cancer types are included in the analysis. For example, in a follow-up study to Smith et al. [49], Leiserowitz et al. [30] assessed the incidence rate of pregnancy-associated ovarian cancer versus the low malignant potential ovarian tumors. They reported an incidence rate for ovarian cancers of 1.8/100,000 births (87 cases). If the 115 cases diagnosed with tumors of low malignant potential are included, the incidence rate is 4.2/100,000 births (202 total cases); the crude incidence of diagnosis of ovarian cancer and tumors of low malignant potential during pregnancy only is 1.9/100,000 births as 90 cases were diagnosed during pregnancy only out of 4,858,505 births [30]. A comparable incidence rate of pregnancy-associated low malignant potential ovarian tumors was reported by Dgani et al. [12].

Impact of Pregnancy on Prognosis

Only one case-control study on the possible impact of pregnancy on the clinical course of ovarian cancer was identified in the medical literature. Stensheim et al. [51], a population-based study from Norway, reported no elevation in risk of cause-specific death (HR: 0.46; 95 % CI [0.17–1.23]) in patients diagnosed while pregnant. The comparable survival of ovarian cancer patients diagnosed during pregnancy and nonpregnant ovarian cancer patients may be due to the frequency of obstetric examinations (e.g., ultrasounds) during pregnancy.

Melanoma and Pregnancy

Occurrence Rate During Pregnancy

Four population-based studies that assessed the incidence of pregnancy-associated melanoma are reviewed [7, 14, 21, 49] (Table 1.2). The crude incidence rate of melanoma diagnosed during pregnancy only ranged from 0.6 to 14.9/100,000 births. A significant increase in the crude and age-adjusted incidence rates of pregnancy-associated melanoma was observed over time for a study from Sweden (1977–2006) [14]. A study in Australia reported a significant increase in the crude incidence rates, but not the age-adjusted rates, of pregnancy-associated melanoma from 1994 to 2007, which was attributed to increasing maternal age [7]. In particular, women aged 40–55 years old were at 7.55 times higher risk of pregnancy-associated melanoma as women aged 15–24 years [7]. The substantial differences in the estimated rates of pregnancy-associated melanoma between studies are not unexpected (Table 1.2), considering the differences in melanoma occurrence rates in different geographic regions, different age groups, and other maternal characteristics (e.g., geographical remoteness [7]). For example, the highest incidence rates of pregnancy-associated melanoma were reported for Australia, which is known to have the highest rates of melanoma in the world [7].

Impact of Pregnancy on Prognosis

Early reports suggested that pregnant patients with melanoma had more advanced lesions and shorter survival times than nonpregnant melanoma patients [26, 43]. However, the majority of case-control studies with longer follow-up evaluations reported no difference in survival between pregnancy-associated melanoma patients and their nonpregnant melanoma cohort [11, 27].

In a review of the literature, pregnancy-associated melanomas were often reported to have thicker tumors compared to nonpregnant patients, although this observation was not always statistically significant [27]. Thickness of the tumor has been identified as a significant predictor of survival in multivariate analyses in two separate studies [31, 48]. There is disagreement in the literature regarding whether pregnancy decreases the disease-free interval in melanoma patients with one case-control study reporting shorter disease-free interval for pregnancy-associated melanoma compared to nonpregnant patients [48], while others reported no significant effect of pregnancy status [35, 39].

The majority of studies report that survival of women diagnosed with melanoma during pregnancy is not different than nonpregnant women with melanoma. Leachman et al. [27] reviewed the available literature on the survival of pregnant versus nonpregnant melanoma patients and noted that stage I–II melanoma does not behave more aggressively in pregnant patients. They further noted that there were fewer reported cases of pregnant patients with stage III–IV melanoma; thus, it is unknown whether pregnancy may or may not influence the more advanced stages of this cancer type [27]. One recent population-based study in Norway reported a

slightly elevated risk of cause-specific death (HR: 1.52; 95 % CI [1.01–2.31]) in patients diagnosed during pregnancy. The authors observed that the localization of the tumors were significantly different between the women diagnosed with melanoma during pregnancy (e.g., larger proportions of tumors on the head, neck, and trunk) compared to nonpregnant patients (e.g., larger proportion of tumors on the leg). Following adjustment for localization of the tumor, the hazard ratio for pregnant women was smaller (HR: 1.45; 95 % CI [0.96–2.21]), and the authors concluded their study was consistent with others that found that melanoma was not likely influenced by pregnancy-related hormones [51]. Pregnancy-associated melanoma patients also had no worse prognosis in cause-specific mortality than age-matched nonpregnant patients in a population-based study in Sweden, which adjusted for age, time period, parity, education, and tumor location [25].

Conclusions

Based on data from population-based studies, the incidence rate of pregnancy-associated cancer appears to have increased over time. This increase has been attributed, at least in part, to a trend for women to become pregnant later in their reproductive years. Of the seven cancer types reviewed, the incidence rates of breast cancer, melanoma, and non-Hodgkin lymphoma diagnosed in association with pregnancy appear to increase over time, while Hodgkin lymphoma has no temporal trend. Data on incidence rates across time are lacking for pregnancy-associated ovarian cancer and leukemia, and the rate of pregnancy-associated cervical cancer appears to increase or decrease depending on the population under study. Pregnancy does not appear to influence the progression of these seven cancers, with the possible exception of breast cancer. The observation of possibly poorer prognoses among pregnancy-associated breast cancer patients may be largely due to breast cancer patients being diagnosed with more advanced stages of cancer or diagnosed postpartum, which was not discussed in this chapter. The definition of pregnancy-associated cancer strongly influenced the resulting incidence rates. For example, the crude incidence rates for all the cancer types are substantially lower for cases diagnosed during pregnancy compared to incidence rates for cases diagnosed during pregnancy and up to 1 year following delivery. Future research on pregnancy-associated cancer should include an analysis of the timing of diagnosis to better understand any differences in incidence or prognosis between women diagnosed with cancer during pregnancy versus women diagnosed postpartum compared to a nonpregnant cancer patient cohort.

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Staging Workup in Pregnant Cancer Patients

2

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Introduction

Imaging and image-guided biopsies play an important role in the diagnosis, staging, and management of cancer, and guidelines exist for the radiologic evaluations of patients diagnosed with a variety of malignancies [1]. Pregnancy-associated cancers are increasing in frequency, and due to possible risks to the developing fetus, practice guidelines may not be applicable to the situation of pregnancy [2]. Therefore, given the need to balance the clinical needs of the mother with any potential adverse effects to the child, clinical imaging paradigms for this patient population may deviate from established guidelines and may be highly individualized. This chapter will provide an overview of specific imaging modalities that can be considered in pregnant cancer patients, as well as imaging strategies for specific anatomic locations.

Radiation Risks from Imaging

When imaging a pregnant patient, especially when considering the use of ionizing radiation, one must carefully weigh the benefits of the modality versus the potential risks to the fetus. Ionizing radiation exposure may occur with common imaging modalities, including X-rays and computed tomography (CT). There

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Table 2.1 ACR summary of suspected in utero-induced deterministic effects [4]

Menstrual or gestational age (days)	Conception age (days)	<50 mGy	50–100 mGy	>100 mGy
0–2 weeks (0–14)	Before conception	None	None	None
3rd and 4th weeks (15–28)	1st and 2nd weeks (1–14)	None	Probably none	Possible spontaneous abortion
5th to 10th week (29–70)	3rd to 8th week (15–56)	None	Potential effects are scientifically uncertain and probably too subtle to detect clinically	Possible malformation increasing in likelihood as dose increases
11th to 17th week (71–119)	9th to 15th week (57–105)	None	Potential effects are scientifically uncertain and probably too subtle to detect clinically	Risk of diminished IQ or of mental retardation increasing in frequency and severity with increasing dose
18th to 27th week (120–189)	16th to 25th week (106–175)	None	None	IQ deficits not detectable at diagnostic doses
>27th week (>189)	>25 week (>175)	None	None	None applicable to diagnostic medicine

are two main categories of risk from ionizing radiation – deterministic and stochastic. Deterministic effects involve damage to multiple cells and do not occur below certain threshold doses; their severity increases with increased radiation dose (Table 2.1). Deterministic effects in a fetus include malformations, growth retardation, mental retardation, and death. The International Committee on Radiological Protection concluded in a 2007 report that no deterministic effects of practical significance would be expected to occur below a dose of 100 mGy (milligray = a measure of the absorbed radiation dose), which is above the normal radiation exposure of a single diagnostic radiology or nuclear medicine study [3]. Deterministic effects, if they occur, are more significant in the earlier stages of pregnancy. During first trimester organogenesis, exposure above threshold values may lead to increased risk of deterministic effects, with less risk of toxicity in subsequent trimesters [4]. Stochastic effects occur due to damage of a single cell and can lead to carcinogenesis. Unlike deterministic effects, there is no threshold dose, though the risk of damage increases with escalating radiation dose. An additional risk of carcinogenesis of 1 in 10,000 is quoted with fetal radiation doses of up to 1 mGy [5]. The American College of Radiologists (ACR) describes the carcinogenesis risk at a dose of 10 mGy as increasing background rates of malignancy from 0.2–0.3 % to about 0.3–0.7 % [4]. Increased awareness of radiation doses, as well as improvements in imaging technology (including automatic exposure control software and iterative reconstruction algorithms), may contribute to reductions in the risk of both maternal and fetal radiation exposure [6].

Specific Imaging Modalities

Radiography involves the use of ionizing radiation with the associated risks as discussed previously. However, if the pelvis is outside the field of view, the fetal radiation dose is minimal. For example, the fetal radiation dose from a chest X-ray is estimated to be 0.002 mGy and from an extremity radiograph <0.001 mGy; these are both far less than the background radiation exposure from a transatlantic flight [7].

CT is associated with higher levels of radiation exposure, but again the dose to the fetus varies, with higher levels of radiation when the field of view is closer to the uterus. CT of the head, neck, and extremities can generally be safely performed during pregnancy regardless of the trimester; however, consideration of imaging modalities without radiation can be considered if appropriate for the specific anatomic location [8]. Shielding of the abdominopelvic region with a lead apron during a CT scan may reduce radiation dose from the minimal amount of external scattered radiation that comes from the exposed tissue or imaging equipment, however will not decrease internal scattered radiation [9].

Ultrasound (US) may be safely used during pregnancy with no adverse events to a fetus documented to date. Ultrasound is useful for a spectrum of focused clinical assessments, including in the evaluation of a palpable breast mass, the evaluation of adnexal lesions, and the assessment of the presence of hepatic metastases. There are limitations with obesity, operator dependence, and the presence of bowel gas, with decreased sensitivity in later pregnancy due to increase in abdominal girth and mass effect from the gravid uterus.

Magnetic resonance imaging (MRI) is an imaging modality that does not use ionizing radiation. No adverse effects to the fetus have been conclusively documented with MRI imaging exposure to date during any stage of pregnancy [10]. The primary safety concerns are the effects of noise on the fetus and the possible heating effects from radiofrequency pulses during an MRI [11]. Similar to the use of CT in pregnancy, the ACR recommends that before a pregnant patient undergoes MRI, the risks versus benefits in performing the examination during pregnancy should be weighed. MRI should be utilized only if (1) the information cannot be acquired by alternate nonionizing methods such as ultrasound, (2) the examination cannot wait until the patient is no longer pregnant, or (3) the imaging could potentially impact care for the patient or fetus during pregnancy [10].

Positron emission tomography–computed tomography (PET-CT) combines functional imaging provided by PET with cross-sectional anatomic information from CT. Due to its radiation dose, PET-CT is not recommended for oncology staging during pregnancy. The most common radiopharmaceutical used in PET imaging is fluoro-2-deoxy-D-glucose (F^{18}-FDG), a radiolabeled glucose analog. PET-CT is commonly used in oncology imaging for staging disease and also for assessing response to therapy. However, PET-CT contributes ionizing radiation from both the injected radionuclide marker and the CT, leading to a potentially high fetal radiation dose; therefore, PET-CT is not recommended during pregnancy. In the ACR parameter guide for performing PET-CT in oncologic imaging, when appropriate, a

pregnancy test to exclude pregnancy is necessary prior to performing a PET-CT [12]. Reducing the amount of radionuclide injected and changing CT parameters to impart less radiation may decrease the dose from PET-CT. There have been a few cases in the literature where PET-CT was used in pregnancy, with reported fetal doses as low as 1.1 mGy and as high as 21.8 mGy [13, 14].

Intravenous Contrast Administration in Pregnancy

Iodinated Contrast

Studies evaluating the safety of low osmolar contrast media (LOCM), which is the current type of iodinated intravenous CT contrast administered, are limited, and the sequelae of contrast exposure on fetal development are largely unknown. Iodinated CT contrast media given as part of a diagnostic CT has been shown to cross the placenta and enter the fetus [15]. There have been historic reports of hypothyroidism in infants, following administration of fat-soluble contrast during pregnancy as part of amniofetography, used to detect congenital malformations. However, fat-soluble contrast is no longer used in diagnostic imaging [16]. No mutagenic or teratogenic effects have been demonstrated during in vivo animal testing with LOCM [17]. No cases of neonatal hypothyroidism or other adverse effects have been reported from maternal administration of water-soluble contrast agents to date [18]. Due to insufficient evidence regarding the safety of LOCM to the fetus, it is recommended that prior to use in a pregnant patient, the potential added risks of contrast media should be considered and the administration of intravenous contrast be deemed essential for the planned study. In addition, informed consent potentially should be obtained from the mother, and consideration should be given to screening newborns for hypothyroidism, a paradigm that is already standard pediatric practice in North America and Europe [19].

Gadolinium Contrast

No adverse effects to the fetus have been reported when the clinically recommended doses of gadolinium-based contrast agents have been given to pregnant women [20]. However, the US Food and Drug Administration has classified gadolinium as category C, indicating that animal studies have revealed adverse effects on the fetus. Although there have been no controlled studies in pregnant women, potential benefits of using gadolinium may warrant its use despite potential risks, depending on the clinical situation. Gadolinium-based agents have been shown to cross the placenta, and the possibility of gadolinium in the amniotic fluid dissociating into toxic-free gadolinium ions cannot be excluded [19]. The ACR recommends using gadolinium only when the potential benefit to the patient or fetus outweighs the possible risks and should be reviewed on a case-by-case basis. Both the patient and the referring physician should be counseled as to the potential risks and benefits of gadolinium contrast prior to its administration [19].

Breast Imaging During Pregnancy

Ultrasound (US) is the primary imaging technique used in a pregnant patient presenting with a palpable breast mass. Ultrasound does not involve ionizing radiation and is highly sensitive and specific in imaging pregnancy-associated breast cancer [21, 22]. In locally advanced pregnancy-associated breast cancers, neoadjuvant chemotherapy may be indicated; in this scenario, ultrasound can be utilized to assess response [23]. Ultrasound can be used to guide core needle biopsy of any suspicious masses and to evaluate for axillary nodal disease.

Mammography is less sensitive during pregnancy due to increased parenchymal density in the breast secondary to hormonal effects. However, mammography can be useful in assessing suspicious microcalcifications that might not be visible sonographically in a patient diagnosed with breast cancer and can help determine the disease extent, as well as evaluate the contralateral breast (Fig. 2.1). Mammography can be performed safely during pregnancy with minimal fetal radiation exposure, with the dose to the uterus estimated as less than 0.03 mGy [24]. Lead apron shielding can be offered, but the majority of radiation to the uterus will be scatter radiation and lead shielding will have limited efficacy. Contrast-enhanced MRI is not recommended during pregnancy due to the unknown effects of gadolinium on the fetus.

Image-guided biopsy is most often performed with US due to lack of ionizing radiation, though stereotactic biopsy and wire localization can be performed safely

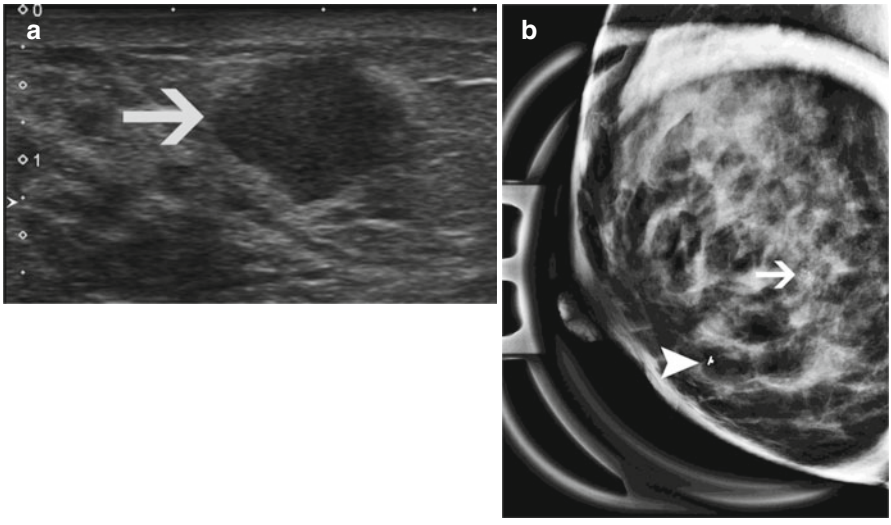

Fig. 2.1 A 32-year-old at 20 weeks gestation palpated a nodule in the right lower breast. (**a**) US of the right breast demonstrates a 30 × 10 mm hypoechoic mass (*arrow*). Biopsy consistent with invasive ductal carcinoma. ER negative and PR and HER2-neu positive. (**b**) Right MLO spot magnification demonstrates clip in the biopsy-proven carcinoma (*arrowhead*) and a 5 mm separate cluster of pleomorphic calcification posteriorly (*arrow*). Biopsy of calcification consistent with DCIS

in pregnancy for lesions not visible sonographically. Core biopsy in pregnancy has a slightly increased risk of bleeding and infection due to increased breast vascularity. There is also a very small risk of a milk fistula, though there is more concern for this complication with open surgical procedures [25–27]. Subcutaneous anesthesia with lidocaine can be safely administered and does not have any adverse effect on the fetus.

Osseous Imaging During Pregnancy

Radiography and CT of the extremities, with the exception of the hip and pelvis, have little to no exposure to the fetus if the beam is properly collimated. Therefore, pregnancy status should not alter the decision to perform these examinations [4]. MRI of an extremity can be performed for assessing a primary bone tumor or a soft tissue tumor. In the evaluation of diffuse osseous metastases, whole body MRI without contrast can be safely performed [28].

Another method of assessing bone metastases is with bone scintigraphy (nuclear medicine bone scan), which is performed using technetium-99m, a short-lived radionuclide with a half-life of 6 h. An average dose in early pregnancy may have a fetal exposure of 4.7 mGy, decreasing to 1.8 mGy by 9 months [29]. Given the potential fetal dose, bone scans are not commonly performed in pregnancy though there are methods to further reduce the radiation dose including decreasing the amount of activity injected and encouraging maternal hydration and frequent voiding, as this radionuclide is excreted by the kidneys and accumulates in the bladder [30].

Head and Neck Imaging During Pregnancy

In a patient with a palpable neck mass, ultrasound is the preferred initial imaging modality and can also be used to guide biopsy. CT or MRI of the neck may also be performed for evaluation of a neck mass or lymphadenopathy, with minimal radiation or no radiation exposure to the fetus, respectively. CT of the neck has fetal radiation doses quoted of $\leq$1.0 mGy [4, 29, 31].

Ultrasound of both the thyroid gland and cervical lymph nodes is the preferred imaging modality for evaluation of a thyroid nodule. There are no definite features of thyroid malignancy; however, suspicious findings include a solid rather than cystic appearance, calcifications, irregular margins, and the presence of lymphadenopathy [32]. The typical size criterion for fine needle aspiration is usually >10 mm, as diagnosis of subcentimeter thyroid cancers does not improve life expectancy [33].

In imaging suspected central nervous system tumors, MRI of the brain is superior to CT for characterizing tumors, especially when using diffusion weighting and intravenous contrast (contrast allows for added features of perfusion and spectroscopy imaging). As MRI contrast is not recommended during pregnancy,

characterization from a non-contrast MRI may be limited to diffusion weighting as well as T1 and T2 characteristics. CT of the brain is most useful in urgent cases of raised intracranial pressure and in excluding hemorrhage; there is minimal associated radiation exposure to the fetus [4, 7].

Thoracic Imaging During Pregnancy

Thoracic imaging in pregnancy may be performed in the evaluation of mediastinal masses and pulmonary masses or, more commonly, for assessment of metastatic disease. A chest radiograph has a negligible fetal dose, with estimates ranging from 0.0005 to 0.002 mGy [7, 29]. Chest CT is more sensitive in evaluating mediastinal structures, lymphadenopathy, and pulmonary parenchyma. Though fetal doses are slightly higher than with radiography, they remain relatively low, ranging between 0.01 and 0.66 mGy, when performed with pelvic shielding [29]. MRI of the chest has excellent contrast and spatial resolution, without radiation to the fetus or to the maternal breast tissue. While MRI is limited compared to CT for evaluating the pulmonary parenchyma, it has value in assessing lesions involving the mediastinum (Fig. 2.3), chest wall, pleura, lymph nodes, and spine, even without the use of intravenous contrast [34]. CT-guided biopsy of mediastinal and pulmonary pathology can be performed for diagnosis and has been shown to be accurate and technically feasible at low doses [35, 36]. When thoracic biopsies are performed in pregnancy, both tube voltage and tube current may be decreased to reduce the radiation dose, and the number of fluoroscopic images can also be limited to further reduce radiation.

The incidence of pulmonary embolism is higher both in pregnancy and in oncology patients compared to the general population. There is increased risk especially in patients with CNS tumors and pancreatic, upper GI, and lung cancers [37, 38]. For suspected pulmonary embolus, CT pulmonary angiogram (CTPA) or ventilation–perfusion scintigraphy (VQ) can be performed. The fetal radiation dose from both studies is low, with VQ conferring a fetal dose of approximately 0.1–0.5 mGy and CTPA 0.01–0.66 mGy [29]. There are conflicting data in the literature regarding the diagnostic accuracy of one test over the other, though one meta-analysis has shown CTPA to be better than VQ in an oncology population. CTPA also has the advantage of assessing other thoracic pathology, such as pulmonary metastases and thoracic nodal disease [39].

Abdominal and Pelvic Imaging During Pregnancy

Abdominopelvic imaging in pregnancy may be performed for evaluation of a primary malignancy, for assessment of nodal disease, or for evaluation of metastatic disease (including hepatic metastases). The use of CT for evaluation of the abdomen and pelvis during pregnancy is associated with high fetal doses of

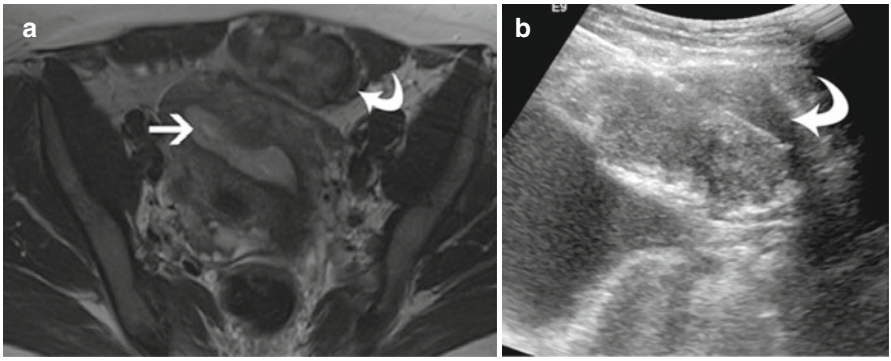

Fig. 2.2 A 35-year-old woman, 5 weeks pregnant with an incidental 7 cm pelvic wall mass at initial obstetric US. (**a**) Axial T2-weighted MRI performed at 5 weeks, demonstrating an early intrauterine pregnancy with a gestational sac (*arrow*). There is a low intensity mass arising from the left rectus abdominis muscles (*curved arrow*). (**b**) There is a 15 G introducer needle present in the abdominal wall mass (*curved arrow*). The biopsy result demonstrated desmoplastic fibroblastoma

radiation. Estimated fetal dose for an abdominal CT ranges between 1.3 and 25 mGy and for a pelvic CT from 10 to 50 mGy [29]. Therefore, CT imaging of the abdomen and pelvis in pregnancy is not commonly utilized. MRI or US is preferred to evaluate the abdomen and pelvis (Fig. 2.2), particularly in evaluation for hepatic metastatic disease. Percutaneous biopsy of hepatic lesions may be performed with US or MRI guidance, if required to definitively stage cancer.

Melanoma staging in pregnancy should initially involve the primary tumor site and local-draining lymph nodes. However, if metastatic, melanoma may spread hematogenously to the lungs, liver, adrenal glands, and small bowel. Less commonly, metastatic melanoma has been reported in the spleen, pancreas, kidneys, and gallbladder [40]. Whole body MRI is useful in the evaluation of melanoma, as well as lymphoma occurring in pregnancy (Fig. 2.3). Whole body MRI has shown higher sensitivity than PET-CT in detecting liver, splenic, and bony metastases, though is less sensitive for lung and nodal metastases [41].

Cervical cancer is the most common malignancy occurring in pregnancy. Cervical cancer diagnosed in pregnancy tends to be detected at earlier stages, possibly due to the more frequent cervical examinations as part of prenatal care [42, 43]. Cervical cancer tends to spread by local extension, and staging of cervical cancer is optimally performed with pelvic MRI. This modality can evaluate the size of the primary tumor in three planes, as well as assess for parametrial or vaginal invasion, lymphadenopathy, and potential secondary complications, such as hydronephrosis, if there is bladder or ureteric invasion [44].

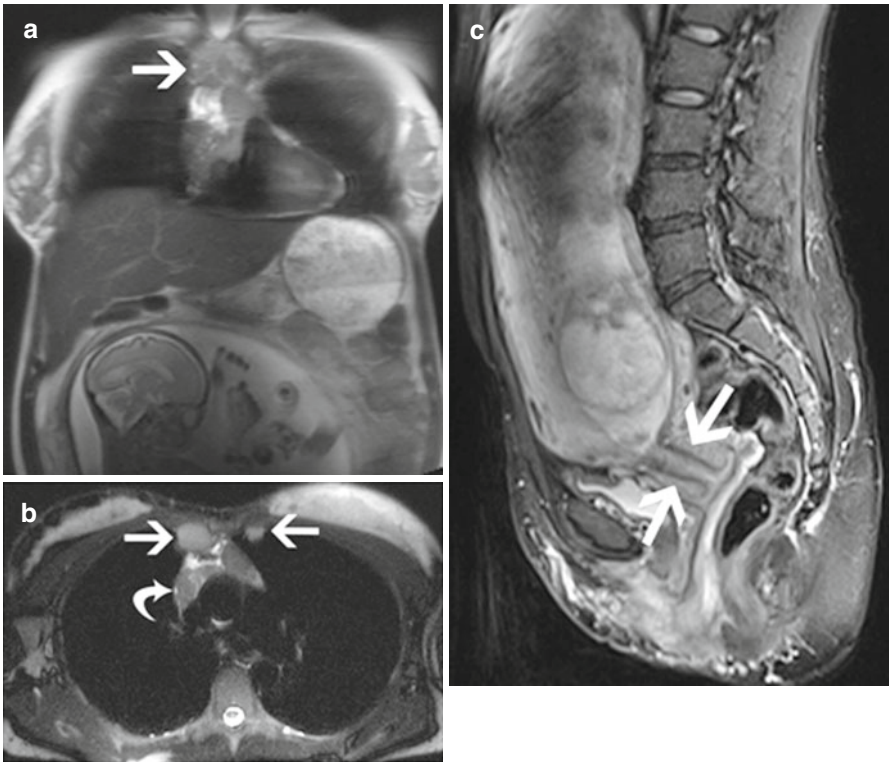

Fig. 2.3 Whole body MRI performed in a 36-year-old patient with Hodgkin's lymphoma at 23 weeks gestation. (**a**) Coronal T2-weighted image shows an anterior mediastinal mass (*arrow*). The fetus is visible in the lower abdomen inferior to the liver and stomach. (**b**) Axial T2-weighted image demonstrates bilateral internal mammary lymphadenopathy measuring 3.3 × 2.5 cm on the right and 1.2 × 1.0 cm on the left (*arrows*). The anterior mediastinal mass is also again demonstrated (*curved arrow*). (**c**) A sagittal STIR image in the same patient does not demonstrate pathology but shows how well delineated the cervical stroma is on MRI (*arrows*)

Conclusions

Radiologic imaging plays a crucial role in the diagnosis, staging, and monitoring of most malignancies. As with much of the clinical management of pregnant patients with cancer, the potential risks of imaging to the fetus, including exposure to ionizing radiation or intravenous contrast, must be balanced against the need for accurate diagnostic evaluation and effective treatment of the mother. Alternative imaging strategies that present fewer risks can be considered, such as MRI and US. A proposed general strategy for radiologic evaluation of the pregnant patient is presented in Fig. 2.4. However, optimal selection of imaging in pregnant patients with cancer may be best achieved through individualized multidisciplinary consultation with radiology colleagues.

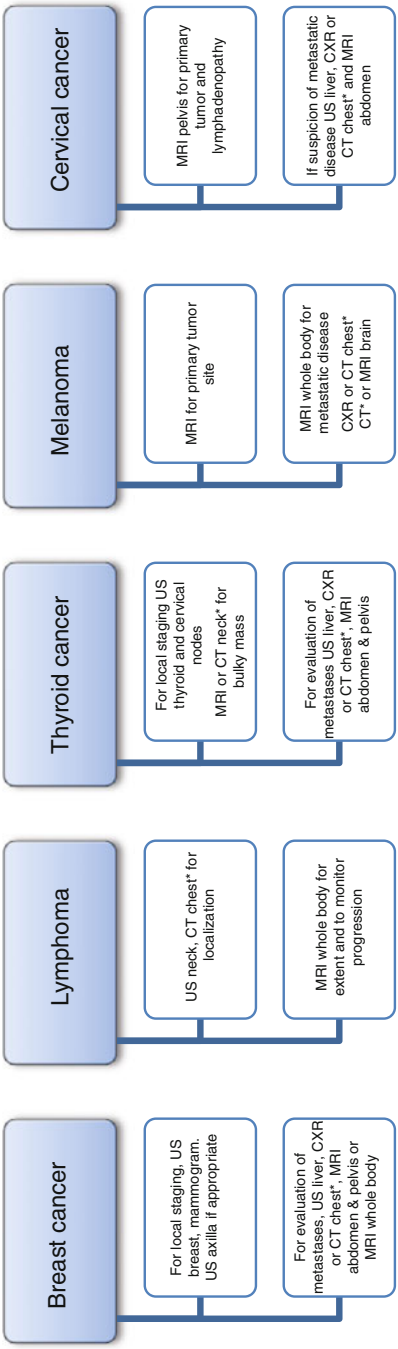

Fig. 2.4 Possible algorithm for assessment of common cancers occurring during pregnancy (*Abdominal shielding can be placed during CT)

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General Concepts on Surgical Management of Cancer During Pregnancy

3

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Introduction

The concurrence of cancer and pregnancy is a relatively rare problem, occurring in about 1 in 1,000 pregnancies.

Whenever a pregnant woman undergoes nonobstetric surgery, consultations among her obstetrical team, surgeon(s), anesthesiologist(s), and neonatologist(s) are important to coordinate management.

The anesthetic plan for a pregnant patient must take into account: type of surgery, underlying medical conditions (including changes of pregnancy), effects of anesthesia and surgery on both the patient and the fetus, preferences of the patient, anesthesiologist, and surgeon. Laparoscopy is not contraindicated during pregnancy, but its advantages compared to standard laparotomy should be evaluated in the specific and individual context.

Anatomic and physiologic changes related to pregnancy and concerns about the fetus may require modifications to anesthetic and surgical management.

According to the American Congress of Obstetricians and Gynecologists, some general recommendations can be pointed out [1]:

- A pregnant woman should never be denied surgery if indicated regardless of trimester.
- Surgery should be done at an institution with neonatal and pediatric services.

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- An obstetrics care provider with cesarean delivery privileges should be readily available.
- A qualified team should be promptly available to interpret the fetal heart rate.

During surgery the fetus is exposed to the transplacental effects of anesthetic agents. However, patients should be made aware that commonly used anesthetics, including enflurane, barbiturates, and narcotics, have been extensively used safely in pregnancy. It is important to highlight that the risks to the fetus during surgery are not just anesthetic-related but also intraoperative complications, such as hypoxia and hypotension. Furthermore, decreased placental perfusion secondary to long-term positioning of the mother in the supine position might represent a mechanical problem during late gestational age. Additionally, postoperative problems, such as fever, infections, gastrointestinal problems, and changes in nutritional intake, thrombosis, and pulmonary embolus, could have serious adverse effects on fetal well-being.

Physiological Changes During Pregnancy and Possible Surgical Implications

Physiological changes related to pregnancy occur in virtually all systems and are caused by both hormonal and mechanical factors.

Pertinent changes in major organ systems are briefly summarized below:

Cardiovascular Cardiac output (CO) increases by 20 % at 8 weeks and continues to rise until 30–32 weeks of gestation, at which time it plateaus at approximately 50 % above baseline. After 32 weeks of gestation and until the beginning of labor, CO remains stable.

During surgical evaluation of the gravid patient, it is important to understand the effects of the gravid uterus on cardiac output. After 20 weeks' gestation, the uterus is at the level of the bifurcation of the great vessels (at the level of the umbilicus). In the supine position, the gravid uterus compresses the inferior vena cava, reducing venous return and thereby reducing preload and cardiac output by as much as 25–30 % [2, 3].

Pulmonary Beginning in the first trimester, increases in tidal volume and respiratory drive (due to the stimulatory effects of progesterone) cause hyperventilation and a chronic respiratory alkalosis. Oxygen consumption increases, and the displacement of the diaphragm leads to a 20 % decrease in functional residual capacity (FRC). The surgical team needs to take into account that decreased functional residual capacity occurs as a result of compression by the gravid uterus. As a result, the mother has a lower threshold for hypoxemia and atelectasis becomes more common [4, 5].

Hematologic Plasma volume increases by 50 % by 32 weeks of gestation; total red blood cell mass increases only by 20–30 %, resulting in hemodilution. Pregnancy is a procoagulant state. The concentration of clotting factors is increased

and there is reduced fibrinolysis. The risk of deep vein thrombosis (DVT) is highest in the 4–6 weeks' postpartum, and this can be considered a challenge for the surgical team for the management of thromboprophylaxis [5]. Pneumatic compression should be considered in every patient, and pharmacologic thromboprophylaxis should be determined on a case-by-case basis, taking into account the expected scope and length of the procedure and whether the woman has risk factors for venous thrombosis in addition to the pregnancy (e.g., thrombophilia, prolonged immobilization, past history of venous thrombosis, malignancy, diabetes mellitus, varicose veins, paralysis, or obesity).

Gastrointestinal Gastroesophageal reflux occurs in 30–50 % of pregnancies, most likely related to increases in intra-abdominal pressure and to decreased lower esophageal sphincter tone during all trimesters [6].

Renal Glomerular filtration rate (GFR) and renal blood flow rise markedly during pregnancy, resulting in a physiologic fall in the serum creatinine concentration. In pregnancy, the kidneys increase by 1 cm in size, and the ureters become physiologically dilated because of the muscle-relaxing effects of progesterone and the pressure effect of the growing uterus.

Preoperative Evaluation

Pregnant patients who require surgery should be evaluated preoperatively in the same manner as nonpregnant patients. Additional testing is not indicated in an uncomplicated pregnancy. A thorough history should document underlying medical and obstetrical conditions, and the physical examination should include detailed assessment of the airway. Laboratory and other testing should be performed as indicated by the patient's medical problems and the proposed surgery.

Timing of Surgery

Urgently needed surgery should be performed regardless of the trimester, whereas completely elective surgery should be postponed until after delivery. There is no strong evidence of increased risk of miscarriage or teratogenesis from anesthetic agents used during early pregnancy. Because common first trimester adverse outcomes (e.g., miscarriage, vaginal bleeding, fetal structural anomalies) may be attributed to surgery and anesthesia in the absence of other obvious causes, it is prudent to minimize exposure of the fetus to surgery and medication during pregnancy, especially during organogenesis. The first trimester background miscarriage rate is approximately 8–16 % of clinically recognized pregnancies under 13 weeks of gestation, and it is 2–4 % of pregnancies between 13 and 20 weeks. Estimates of fetal deaths during surgery in the first trimester suggest that the risks are between 8 and 11 %, but in these few small reports, indications or types of surgery were not specified and the risk of fetal malformation was not increased [7]. Therefore, patients

should be reassured that surgery can be performed with minimal risks which are not demonstrated to be clearly increased compared to pregnancy without surgery in terms of miscarriage and malformation. The recommendation to perform surgery during the second rather than the third trimester, whenever possible, is primarily mechanical: in the early second trimester, the uterus is still small enough to not obliterate an abdominal operative field, and the risk of preterm labor may be lower when surgery is performed during the second trimester as compared with the third trimester [8].

Preoperative Preparation for Surgery

Fasting Guidelines Standard adult fasting guidelines are applicable to nonobstetric surgery in pregnant patients. The American Society of Anesthesiologists (ASA) recommends that patients abstain from solid food for at least 6 h prior to surgery (8 h for fried or fatty foods); clear liquids, which have a more rapid gastric transit time, may be ingested until 2 h prior to surgery.

Aspiration Risk Preoperative medication to minimize risk from aspiration in pregnant women is felt to be a reasonable precaution by most experts, although no specific intervention has been shown to improve clinical outcome. However, this is still an area of some controversy with some authors not endorsing aspiration prophylaxis: as gastric emptying is not affected by pregnancy, it is not clear whether gastric acid secretion is altered in pregnant women or the actual risk of aspiration appears to be small [6, 9].

Thromboprophylaxis During pregnancy, the increasing of vitamin K-dependent coagulation factors and decreasing of protein C and S levels result in a hypercoagulable state. This effect protects against excessive blood loss at delivery, but also increases the risk of a thromboembolic event in the postoperative period. The 2012 American College of Chest Physicians (ACCP) clinical practice guideline on prevention and treatment of thrombosis recommends mechanical or pharmacologic thromboprophylaxis for all pregnant patients undergoing surgery. For laparoscopic procedures (gynecologic or general surgical) predicted to last >45 min, the use of low molecular weight heparin is suggested as well as for patients undergoing surgery for oncological reasons; mechanical thromboprophylaxis is a reasonable alternative for shorter procedures. Oral anticoagulants (warfarin) usually are contraindicated during pregnancy because of possible teratogenic effects. Early mobilization is encouraged to minimize the risk of deep vein thrombosis [10].

Antibiotic Prophylaxis The need for antibiotic prophylaxis depends on the specific procedure. Most drugs are safe to use during pregnancy, including most antibiotics and medications to treat common conditions such as upper respiratory tract and gastrointestinal complaints. Antibiotics that can be administered safely in pregnant women include cephalosporins, penicillins, erythromycin, azithromycin, and

clindamycin. Several studies have shown that prophylactic antibiotics administered preoperatively reduce the risk of surgical site infection (SSI) in patients undergoing surgery [11].

Analgesia The most common indication for acute narcotic analgesic therapy is for postoperative pain relief. Women who require surgery during pregnancy can be safely treated with a variety of analgesic agents for postoperative pain with relative safety for the fetus. Paracetamol is safe in pregnancy and is a first-line analgesic. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally avoided because of premature closure of the ductus arteriosus, and they can also affect the fetal kidney, causing reversible oligohydramnios. Opiates are suitable for more severe pain [12].

Prophylactic Glucocorticoids Administration of a course of antenatal glucocorticoids 24–48 h prior to surgery between 24 and 34 weeks of gestation can reduce perinatal morbidity/mortality if preterm birth occurs. This decision depends upon the urgency of the surgery, and the obstetrician's estimate of whether the patient is at increased risk of preterm birth because of the underlying disease or the planned procedure.

Prophylactic Tocolytics There is no proven benefit to routine administration of prophylactic perioperative tocolytic therapy. Tocolytics are indicated for treatment of preterm labor until resolution of the underlying, self-limited condition that may have caused the contractions.

General principles of nonobstetric surgery in pregnant women
1. Provide mechanical or pharmacologic thromboprophylaxis.
2. Follow standard fasting recommendations; additional aspiration prophylaxis is not necessary in patients not otherwise at risk of aspiration.
3. A variety of analgesic agents can be used with relative safety for the fetus.
4. Minimize disruption of fetal homeostasis by avoiding maternal hypotension, hypoxemia, and hypercarbia or hypocarbia.
5. Left laterally displace the uterus in the second half of pregnancy, to reduce the risk of hypotension.

Anesthesiologic Management

Positioning When the pregnant patient is placed in a supine position, the gravid uterus places pressure on the inferior vena cava resulting in decreased venous return to the heart. This decrease in venous return results in significant reduction in cardiac output with concomitant maternal hypotension and decreased placental perfusion during surgery. Supine patients beyond 18–20 weeks of gestation should be positioned with a 15 % left lateral tilt, to reduce aortocaval compression. Alternatively, a wedge may be placed under her right hip.

Fetal Heart Rate Monitoring The fetal heart rate should be documented pre- and postoperatively at all gestational ages. The American College of Obstetricians and Gynecologists has stated that the decision to use intermittent or continuous intraoperative fetal monitoring should be individualized, based on factors such as gestational age, type of surgery, and available resources. For abdominal operations, some centers use transvaginal ultrasound to monitor fetal heart rate. If adequate maternal oxygenation and uterine perfusion are maintained, the fetus usually well tolerates surgery and anesthesia [1].

The fetal heart rate typically displays reduced variability with induction of general anesthesia, presumably by anesthetizing the brainstem center that modulates intrinsic cardiac automaticity.

Traditional teaching in the setting of fetal bradycardia, tachycardia, or repetitive decelerations, is to optimize uteroplacental oxygen delivery and blood flow (by minimizing aortocaval compression), to maintain maternal hyperoxia and normocarbia (by appropriate ventilation and adjustment of FiO_2), and to correct hypovolemia and hypotension (if present, with fluids, blood, and/or vasopressors). These measures are recommended and may have some benefit [13].

Type of Anesthetic The anesthetic plan for a pregnant patient must take into account:

- Type of surgery
- Underlying medical conditions (including changes of pregnancy)
- Effects of anesthesia and surgery on both the patient and the fetus
- Preferences of the patient, anesthesiologist, and surgeon

There are no studies showing differences in neonatal outcome (teratogenicity or preterm delivery) based on type of anesthetic; however, concerns regarding fetal drug exposure, maternal intubation, and maternal aspiration lead to a preference for regional anesthesia when possible. However, most non-obstetrical surgery in pregnancy is abdominal (laparotomy or laparoscopy), so the majority of cases are performed under general anesthesia.

The most common medications used during monitored anesthesia care) are propofol for sedation, fentanyl as an analgesic, and midazolam as an anxiolytic, administered in small incremental doses.

Sedation is generally minimized due to concerns related to the administration of sedative drugs during pregnancy:

- Sedation-induced hypoventilation may cause respiratory acidosis, with deleterious effects on placental circulation.
- Aspiration may occur during deep sedation, due to decreased gastroesophageal sphincter tone in pregnancy.
- Patients often request that drugs which may affect the fetus be avoided.

Induction of anesthesia through preoxygenation is critical during any stage of pregnancy. Although many clinicians continue the historic practice of rapid sequence intubation (RSI) in all pregnant patients, the incidence of aspiration at induction of anesthesia during pregnancy is low, and there is no evidence that RSI improves clinical outcome. However, it may be reasonable to manage pregnant patients who have not followed fasting guidelines or are felt to be at high risk of aspiration for other reasons, in the same manner as nonpregnant patients are at risk of aspiration. A healthy, fully preoxygenated nonpregnant woman will decrease her saturation level from 100 % to less than 90 % in approximately 9 min of apnea; it takes only 3 min for a term-pregnant patient to reach the same degree of desaturation and approximately 90 s in a morbidly obese pregnant patient [14].

Intubation during pregnancy has the same considerations as intubation at delivery. Most experts recommend rapid sequence intubation with cricoid pressure in all pregnant patients, due to concern that decreased lower esophageal sphincter tone leads to increased risk of regurgitation [15].

In all patients, the goal of hemodynamic and fluid management is to maintain perfusion and oxygenation to critical organs; during pregnancy, this includes fetal homeostasis, which relies on maternal blood pressure and oxygenation. Hypovolemia, drugs, neuraxial blockade, or aortocaval compression can cause hypotension, leading to a decrease in uteroplacental perfusion.

Anesthetic agents have minimal direct effects on uterine blood flow; however, many anesthetic agents have direct cardio-depressant or vasodilatory effects leading to hypotension and thus may indirectly lower uterine blood flow. The lower limit for acceptable maternal blood pressure is not known and is patient dependent; in the experience of one author and colleagues with fetal monitoring during nonobstetric surgery in the second trimester, the fetal heart rate remained in an acceptable range with maternal systolic blood pressure below 90 mmHg, with adequate inhalation anesthesia [16].

Mechanical ventilation should be adjusted to maintain the normal physiological chronic respiratory alkalosis of pregnancy. The $PaCO_2$ to ET CO_2 gradient decreases during pregnancy; thus, the goal for end-tidal carbon dioxide pressure (ET CO_2) is around 30 mmHg. Because CO_2 crosses the placenta relatively easily, higher levels of maternal CO_2 may lead to acidosis and myocardial depression in the fetus; very low maternal CO_2 and severe respiratory alkalosis ($PaCO_2$ less than 23 mmHg and pH higher than 7.5) caused by maternal hyperventilation can compromise uterine blood flow and fetal oxygenation.

Laparoscopy Versus Laparotomy During Pregnancy

When laparoscopic techniques were initially described, pregnancy was considered a contraindication to laparoscopy. Effects of CO_2 pneumoperitoneum on venous return and cardiac output, uterine perfusion, and fetal acid-base status were unknown. Laparoscopy was safely used in several series to evaluate pregnant patients for ectopic pregnancy. Those patients with an intrauterine pregnancy had no increase in fetal loss or observed negative effect on long-term outcome [20].

Major concerns of laparoscopy during pregnancy include injury to the uterus, decreased uterine blood flow, fetal acidosis, and preterm labor from increased intra-abdominal pressure. During the second trimester, the uterus is no longer contained within the pelvis. There has been much debate regarding abdominal access in the pregnant patient with preferences toward either a Hasson technique or Veress needle. The concern for the use of the Veress needle has largely been based on concerns for injury to the uterus or other intra-abdominal organs. Because the intra-abdominal domain is altered during the second and third trimesters, initially accessing the abdomen via a subcostal approach has been recommended [17, 18].

Trocar placement in the pregnant patient does not differ radically from placement in the nonpregnant patient early in pregnancy. Later in pregnancy, the camera port must be placed in a supraumbilical location, and the remaining ports are placed under direct camera visualization. The gravid uterus enlarges superiorly; adjustments in trocar placement must be made to avoid uterine injury and to improve visualization. An angled scope may aid in viewing over or around the uterus. The uterus should be manipulated as little as possible.

Decreased uterine blood flow from pneumoperitoneum remains theoretical because significant changes in intra-abdominal pressure occur normally during pregnancy with maternal Valsalva maneuvers. The risk for pneumoperitoneum may also be less than the risk for direct uterine manipulation that occurs with laparotomy. Fetal respiratory acidosis with subsequent fetal hypertension and tachycardia were observed in a pregnant sheep model but were reversed by maintaining maternal respiratory alkalosis. Additionally, in the small series comparing laparoscopy and open techniques, no significant difference in preterm labor or delivery-related side effects was observed. Some authors have recommended intra-abdominal insufflation pressures be maintained at less than 12 mmHg to avoid worsening pulmonary physiology in gravid women [19].

A laparotomy is more likely to interfere with pregnancy than an extraabdominal surgical procedure. Surgery for abdominal malignancies becomes increasingly difficult as the uterus enlarges. Access is impaired and an oncologically optimum resection is technically more difficult. The uterus might need retraction, but care is essential to avoid impairment of placental flow or placental separation. Major abdominal and pelvic surgery during pregnancy should be undertaken with the close cooperation of a multidisciplinary team involving an obstetrician, a neonatologist, and skilled anesthetists. Fetal monitoring during surgery, if feasible, is invaluable, and expert opinions on pharmacological suppression of a threatened miscarriage or premature labor are crucial. Treatments to improve fetal lung maturity should be administered prophylactically where surgery carries a risk of precipitating premature delivery.

Potentially, laparoscopic surgery in the pregnant patient should result in the proven advantages of laparoscopy seen in the nonpregnant patient: decreased pain, earlier return of gastrointestinal function, earlier ambulation, decreased hospital stay, and faster return to routine activity. In addition, a decreased rate of premature delivery due to decreased uterine manipulation, decreased fetal depression secondary to decreased narcotic usage, and a lower rate of incisional hernias may be seen in the pregnant patient [20].

Table 3.1 Advantages and disadvantages of the use of laparoscopy instead of laparotomy in pregnancy

Advantages
Decreased fetal depression secondary to decreased narcotic requirement
Lower rates of wound infections and incisional hernias
Diminished postoperative maternal hypoventilation
Decreased manipulation of the uterus
Faster recovery with early return-to-normal function
Decreased risk for ileus
Disadvantages
Possible uterine injury during trocar placement
Decreased uterine blood flow
Preterm labor risk secondary to the increased intra-abdominal pressure
Increased risk of fetal acidosis and unknown effects of CO_2 pneumoperitoneum
Decreased visualization with gravid uterus

The following table compares main advantages and disadvantages between laparoscopy and open approach (Table 3.1).

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) drew up recommendations on laparoscopic surgery during pregnancy that are briefly summarized in the following table [20]:

SAGES guidelines for the use of laparoscopy during pregnancy
1. Obstetric consultation is obtained preoperatively.
2. When possible, operative intervention is deferred until the second trimester, when fetal risk is lowest.
3. Pneumoperitoneum enhances lower extremity venous stasis already present in the gravid patient, and pregnancy induces a hypercoagulable state. Therefore, pneumatic compression devices are used whenever possible.
4. Fetal and uterine status, as well as maternal end-tidal CO_2 and arterial blood gases, needs to be monitored.
5. The uterus needs to be protected with a lead shield if intraoperative cholangiography is a possibility. Fluoroscopy is used selectively.
6. Given the enlarged gravid uterus, abdominal access is attained using an open technique.
7. Dependent positioning is used to shift the uterus off the inferior vena cava.
8. Pneumoperitoneum pressures are minimized to 8–12 mmHg and not allowed to exceed 15 m.

Surgical Complications and Pregnancy

Estimates of fetal deaths during surgery in the first trimester suggest that the risks are in the region of 8–11 % on the basis of a few small reports—which do not specify indications or type of surgery—with no increase in the risks of fetal

malformation. Risks to the fetus during surgery are not just anesthetic-related, but also include intraoperative complications, such as hypoxia and hypotension [21].

Furthermore, decreased placental perfusions secondary to long-term positioning of the mother in the supine position is a mechanical problem in late pregnancy.

Additionally, postoperative problems, such as fever, infections, gastrointestinal problems and changes in nutritional intake, thrombosis, and pulmonary embolus, could have serious adverse effects on fetal well-being. Anxieties about anesthesia during pregnancy are probably greater than the actual risks. A background risk of a 15 % spontaneous abortion rate might not be appreciated, and therefore, any miscarriage might be blamed on the surgery or anesthesia.

However, a large analysis by Van Carsten et al. on 215 patients showed that surgery alone has the lowest complication rate compared to radiant therapy and chemotherapy (6.1 % VS 39.4 % VS 33.3 %) suggesting that surgery during pregnancy is preferable than other treatment modality [22].

Conclusions

Management of pregnant women with cancer has changed in the last decades. This change is due to the improvement of knowledge of the pathophysiology of pregnancy and of monitoring systems. Therefore, if before pregnancy was considered a "risk factor" for the well-being of the patient and the termination rate was higher, now pregnant patients can be operated safely.

Obviously the patient should be carefully evaluated in the preoperative setting to avoid any risk, and all the maneuvers for the protection of the fetus must be implemented. A multidisciplinary consultation is mandatory to minimize any kind of complication.

Many studies have been published and report less complication rate compared to chemotherapy or radiotherapy.

The choice regarding the surgical approach (laparotomy vs. laparoscopy) has changed too. In fact, the laparoscopic approach has proven to be feasible and complication rates are comparable to open surgery. In addition, post-op recovery has proven to be more favorable in terms of reduction of hospitalization and better control of postoperative pain. Therefore, in the absence of contraindications, we recommend the use of laparoscopy.

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Contributions and Risks of Radiation Therapy in Managing Cancer During Pregnancy

4

Hanneke J.M. Meijer, Marion Essers, Henk Struikmans, Jack L.M. Venselaar, and Philip Poortmans

Introduction

Radiation therapy plays an important role in the treatment of most malignancies diagnosed during pregnancy, including breast cancer, cervical cancer and Hodgkin's lymphoma [1]. However, physicians are often hesitant to apply radiotherapy in pregnant women because of concerns about foetal safety. The risk for the unborn child after in utero irradiation depends on the radiation dose as well as on the stage of pregnancy. The International Commission on Radiological Protection (ICRP) reports on estimated foetal risks based on results of animal studies, data from survivors of nuclear explosions, data on children who were exposed to radiation in utero as a result of the Chernobyl accident and data from children exposed in utero to diagnostic X-rays [2]. Recently, Amant et al. [3] were the first to perform tests on general health, neuropsychological functioning and cardiac outcome in a group of children who were exposed to radiation therapy antenatally.

This chapter provides an overview of the knowledge on risks for the foetus, and recommendations are given for the administration of radiotherapy in pregnant women.

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Risks Associated with Foetal Exposure to Irradiation

Table 4.1 [1] gives an overview of estimated foetal risks after exposure to irradiation.

Two categories of effects of exposure to radiation can be distinguished: deterministic effects and stochastic effects. Deterministic effects are dose dependent: the severity of the effect depends on the dose given, and the effect occurs only above a certain threshold. The severity of stochastic effects, however, does not depend on the dose given, a threshold does not exist, but the probability of the effect to occur is dependent on the dose [4]. These effects are also referred to as teratogenic and carcinogenic effects, respectively.

Deterministic Effects

First Trimester

The first trimester is the period of organogenesis. During the first two weeks after conception, the number of cells is small and their nature is not yet specialized. Exposure to radiation is likely to result in failure to implant or death, resulting in spontaneous abortion [4]. From the third week after conception, malformations may be induced. The threshold for the occurrence of malformations is 100–200 mGy. This threshold is usually not reached with diagnostic procedures, but can be reached with radiotherapy. At this threshold, the risk of malformations is low, but the risk increases with increasing dose [4]. From 8 weeks after conception, the central nervous system is sensitive to radiation exposure. This is described in more detail below [4].

Table 4.1 Effects and risks after exposure to ionizing radiation in utero and spontaneous frequency (without exposure)

Time after conception (weeks	Effect	Risk per 0.01 Gy	Spontaneous frequency
0–2	Prenatal death[a]	0.01–0.001	0.3–0.6
3–8	Malformation[a]	0.005[b]	0.06
8–15	Mental retardation IQ decrease[c]	0.004	0.005
16–25	Mental retardation IQ decrease[d]	0.001	0.005
0–38	Leukaemia, solid tumours in childhood	0.003–0.004	0.002–0.003

Data taken from [1]

[a]Based on experimental data

[b]Above threshold dose of 0.1–0.2 Gy

[c]Reduction of 21 IQ points per 1 Gy above threshold of about 0.05 Gy; threshold dose for mental retardation about 0.06 Gy

[d]Reduction of 13 IQ points per 0.1 Gy above threshold dose of about 0.05 Gy, threshold dose for mental retardation 0.25 Gy

Second and Third Trimesters

In the last part of the first and in the second and third trimesters, the central nervous system is being developed. It is sensitive to radiation exposure from 8 to 25 weeks after conception, mainly from 8 to 15 weeks post conception. Only above a threshold of 50 [1]–100 [4] mGy, an effect on the central nervous system has been described. The main effect is a decrease of the intelligence quotient (IQ). This effect is dependent on foetal age and increases with increasing dose above 100 mGy. In the most sensitive period of the central nervous system, from 8 to 15 weeks after conception, a foetal dose of 1000 mGy (1 Gy) reduces the IQ by 20–30 points [1, 4]. The probability of mental retardation is about 40 % with this dose in this period of gestation [4]. The threshold for mental retardation is 250 mGy [1]. From 16 to 25 weeks of gestation, the risk of IQ decrease and mental retardation decreases. In this period, the risk of mental retardation is 0.1 % for every 10 mGy, and every 100 mGy above the threshold reduces the IQ with 13 points (Table 4.1) [1]. After 25 weeks of gestation, this effect is not seen. When informing a patient on these risks, it is important to relate the magnitude of radiation effects to the magnitude of spontaneously occurring abnormalities. Severe mental retardation occurs spontaneously in about 0.5 % of births. This incidence increases with a number of environmental factors, such as malnutrition, maternal alcoholism and rubella infections during pregnancy [4]. Figure 4.1 summarizes the effects of prenatal irradiation on the foetus [5].

Stochastic Effects

The main stochastic effect of radiation exposure to a foetus in utero is the induction of childhood cancer and leukaemia. It is assumed that the unborn foetus is at the same risk for potential carcinogenic effects of radiation as are children.

The spontaneous incidence of childhood cancer and leukaemia (ages 0–15 years) is 0.2–0.3 %. At low doses, this incidence does not seem to increase. Following a foetal dose of about 10 mGy, the relative risk is maximum 1.4. This means that the probability of childhood cancer remains low (0.3–0.4 %) [4].

A second stochastic effect is the induction of genetic mutations to the oocytes in case of preconceptional irradiation. In mice, mature oocytes are more radiosensitive than immature oocytes. In humans, no heritable effects that would be linked to parental radiation exposure have been described. However, based on the mice studies, it is often recommended that pregnancy should be delayed several months to 1 year after radiation treatment out of safety concerns [4]. This should be weighed to other considerations such as the age of the women and therefore not be an absolute criterion by itself.

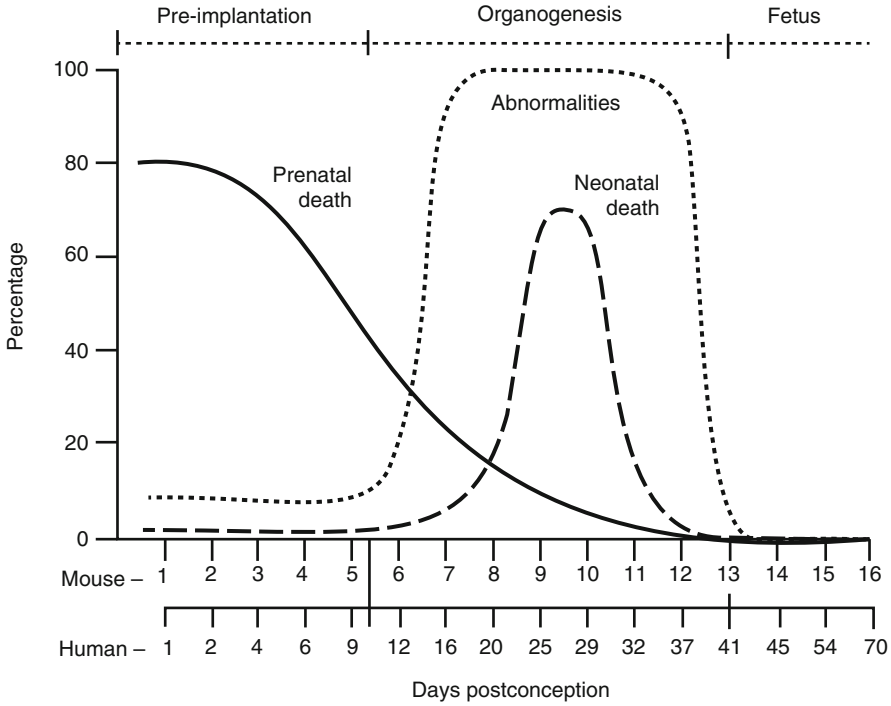

Fig. 4.1 The occurrence of lethality and abnormalities in mice after a prenatal radiation exposure of about 2 Gy, given at various times post conception. The two scales for the abscissa compare developmental stages in days for mice and humans (Redrawn from Hall 1994 [5] with permission of E. Hall and the publisher)

Consequences of Foetal Risks of Radiation Exposure from Radiation Therapy

In pregnant women, as in any other patient, the benefits and disadvantages of a radiation treatment should be weighed carefully. However, this can be much more complicated due to the fact that the foetal risk also has to be considered. The ICRP advises that in case of a pregnant patient, factors that should be considered include [4]:

- The stage and aggressiveness of the tumour
- Other various therapies and their length, efficacy and complications
- Impact of delaying therapy
- Stage of pregnancy
- Expected effects of maternal ill-health on the foetus
- Foetal assessment and monitoring
- How and when the baby could be safely delivered
- Whether the pregnancy should be terminated
- Legal, ethical and moral issues

Besides these issues, the distance from the target volume to the foetus should be considered, as this gives an indication of the expected exposure of the foetus to radiation. If the foetus is either in or very close to the target volume, the effects on the foetus are severe and usually lead to foetal death. Radiotherapy can therefore not be given to the pelvic region during pregnancy.

Radiation therapy can certainly be considered during pregnancy when the target volume lies outside the pelvis. In order to be able to estimate the foetal risk, an estimation of the foetal dose should be made. The fact that the uterus grows during the radiation treatment may decrease the distance of the foetus to the target volume. This should be taken into consideration when estimating the foetal dose. For example, when giving breast or chest wall irradiation during early pregnancy, the embryo will be exposed to 0.1–0.3 % of the dose given (50–150 mGy with a prescription dose of 50 Gy) [1], which carries a very low supplementary risk of malformations (Table 4.1). Whereas, towards the end of the pregnancy, the dose to the foetus can exceed 2 Gy. However, radiation-induced congenital abnormalities are extremely rare in case of exposure after organogenesis [4]. During this period, the main risks for the unborn child are a lower IQ and a risk of radiation-induced malignancies for the child after exposure to radiation in utero [4]. Amant et al. reported on an International Consensus Meeting that was held on treatment of breast cancer during pregnancy. After extensive discussion, the participants agreed that radiation therapy during the first and second trimesters carries relatively low foetal risk, but that radiation therapy should be avoided in the third trimester because of the related significantly higher foetal dose [6].

Attempts should be made to decrease the foetal dose as much as possible, for example, with additional shielding. When the foetal risk is acceptably low, the radiation treatment should be given when this provides a beneficial effect for the patient. This was confirmed by recent findings of the group of Amant [3]. They performed neurological examination, tests to investigate cognitive functioning, questionnaires on general health and echocardiographic evaluation in 16 children (median age 6 years, range 1.5–9) and 10 adults (median age 33 years, range 22–49) who had been exposed to radiation therapy in utero. Median dose to the mother was 48 Gy (range 12–70 Gy) and median foetal dose was 91 mGy (range 0–1690 mGy). They reported that neuropsychological, behavioural and general health outcomes were within normal ranges. There was no linear relationship between foetal dose and cognitive outcome. In one child, there was a severe cognitive delay; however, in this case, foetal dose was relatively low (34 mGy), and there were other complications during pregnancy that may explain this delay, such as preterm delivery.

When the estimated foetal risk seems high, other treatment options, or reversing the sequence of treatment modalities, should be considered (e.g. administration of chemotherapy first, in order to delay radiation treatment until after delivery). Ultimately, termination of the pregnancy or early delivery can be considered. It is of utmost importance that the pregnant patient and her partner are involved in this decision-making process. They should be carefully informed about the benefits and disadvantages of all options for the patient as well as of the unborn child. Shared decision making should be pursued in all cases [1, 4].

Calculation and Measurement of the Dose to the Foetus

During external beam radiation therapy, the patient receives dose outside of the primary radiation field. We use the term peripheral dose in this chapter, although sometimes it is also referred to as the out-of-field dose.

Contributions to the Peripheral Dose

Contributions to the peripheral dose originate from several causes, as illustrated in Fig. 4.2 [7, 9]:

1. Leakage radiation through the treatment head of the accelerator
2. Radiation scattered from the collimator and beam modifiers
3. Radiation scattered from the floor, walls or ceiling
4. Radiation scattered in the patient or internal patient scatter

Leakage Radiation

According to standards set by the International Electrotechnical Commission for medical electrical equipment (IEC 601–2–1 1981), the leakage dose outside the radiation field at 1 m from the beam axis should be less than 0.1 % of the dose inside the beam. Measurements have shown that in reality, the leakage dose is well below this 0.1 % value and that the variation between linear accelerator brands and energies is small [8]. During acceptance of a new accelerator, the physicist should always measure the radiation leakage. The measurement will contain some scattered radiation as well, so the true leakage value will be smaller than the actual measured value. According to Stovall et al. [9] in their report of the American Association of Physicists in Medicine (AAPM) Task Group 36, leakage becomes the main contributor at greater distances from the field edge.

Radiation Scatter from the Collimator and Beam Modifiers

Radiation scattered from the collimator and beam modifiers depends on the collimator design: the collimator jaws and flattening filter. Measurements in large water phantoms for older accelerators show average collimator-scattered radiation values of about 0.35 % of the central axis dose maximum for a 20×20 cm^2 field at 30 cm distance [6, 8]. In addition, the collimator-scattered radiation dose is lowest for 6 MV photon beams, about 10 % lower than for 10 MV beams and 30 % lower than for 23 MV beams. For photon energies larger than 15 MV, neutrons are a significant contributor to the out-of-field dose [10]. Just outside the beam, the collimator scatter contributes 20–40 % of the total peripheral dose [7]. Older literature (e.g. [9, 11]) also mentions the peripheral dose increase through the use of wedges, by a factor of 2–4. The use of physical wedges should thereby be avoided for pregnant patients. The use of dynamic (Varian) or universal wedges (Elekta) or the use of a secondary multileaf collimator (MLC) does not increase the peripheral dose [12, 13]. Field-in-field techniques, where small extra beams are used to obtain a homogeneous dose distribution, can also be used.

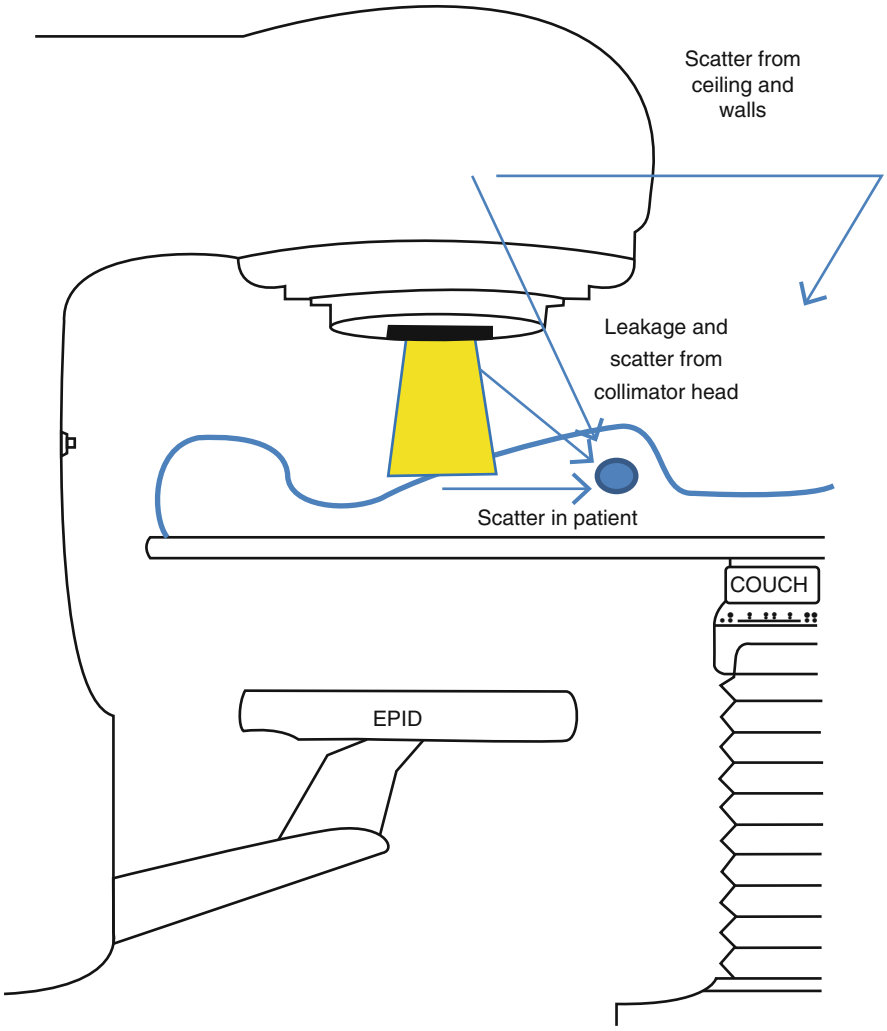

Fig. 4.2 Pathways of radiation contributing to the peripheral dose

The above described leakage and collimator-scattered dose can be reduced by placing a lead shield over the critical area. Measurements have shown that shielding can reduce the dose to the foetus by 50 % [9]. It is, therefore, advised to use proper and safe (mechanical) shielding, and if necessary refer the patient to a hospital with dedicated equipment and experience. Examples of shielding designs are given in the literature, e.g., [9].

It should be noted that shielding can only intercept the radiation from the head of the machine. Due to the high energy, shielding requires strong constructions carrying the heavy shielding material such as lead sheets. Four to five half-value layers of lead correspond to approximately 5–7 cm of lead or 6–8.5 cm of Cerrobend [9].

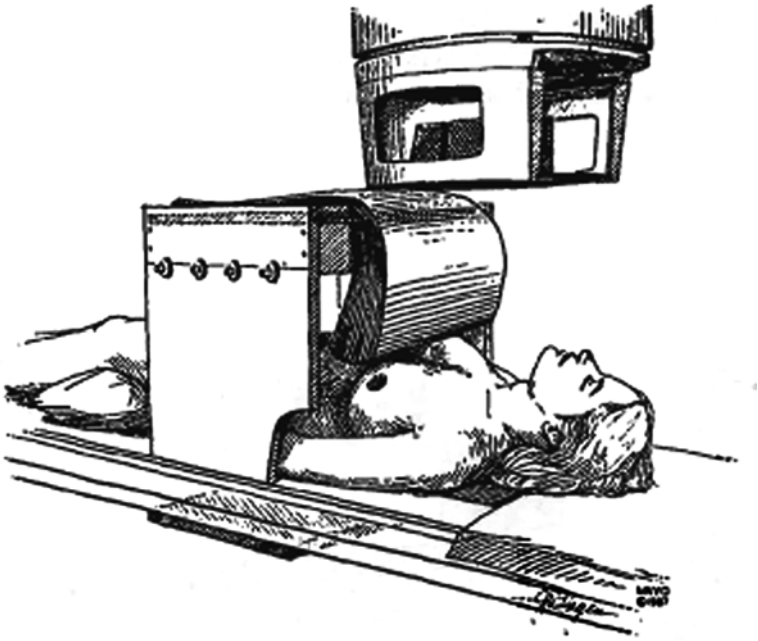

Fig. 4.3 Example of a shielding bridge with the patient in treatment position (Taken from: AAPM Report No. 50. AAPM Task Group 36, 1995 [9] with permission of AAPM)

Both constructions with a bridge placed over the patient on the treatment table, as well as mobile shields, are described in the AAPM TG-36 report. An example is shown in Fig. 4.3. For tangential field set-ups, the shielding design should allow protection for both the medio-lateral and the latero-medial beam directions.

Radiation Scattered from the Floor and Walls

The third origin of peripheral dose is the dose scattered from the floor, walls or ceiling, which is only described in very few papers (e.g. [14]) and which is one or two orders of magnitude lower (about 0.01 % for 6 MV) than the collimator leakage and scatter.

Radiation Scattered in the Patient

The final source of peripheral dose is the radiation scattered in the patient. The dose scattered in the patient increases with increasing irradiated volume, so both are with field size and patient thickness in the primary beam. Patient scatter rapidly decreases, approximately exponentially, with increasing distance from the field edge, from a few per cent of the primary beam dose very close to the field edge to about 0.01 %, at 30–80 cm from the beam axis, depending on the field size [14].

Patient scatter is the main contributor to the peripheral dose near the field edge (more than 80 % at distances up to 10 cm from the field edge), while leakage

radiation is the major contributor at large distances from the field edge (more than 80 % at distances from 50 cm from the field edge). At about 10 cm from the field edge, the dose is about 1 % of the central axis beam dose, more or less independent of energy and depth, but increasing from 0.5 % for a 5×5 cm^2 field to 2 % for a 25×25 cm^2 field [9].

Calculation of Peripheral Dose

Dose calculation algorithms and treatment planning systems (TPS) are designed to ensure a high-accuracy dose delivery at the target volume in the patient. Therefore, the dose calculation is generally very accurate inside the treatment field, even in the presence of inhomogeneities, but outside the field, where the delivered dose is very low, still large uncertainties in dose calculations may be present.

Calculation of Peripheral Dose for Conventional Radiotherapy Techniques

Due to the lack of accurate data and the observed inaccuracies in treatment planning beam modelling in out-of-field regions, Van der Giessen in the 1990s [8, 14] collected and published many data sets of various beam energies and accelerator models in dependence on distance, field size and depth in large water phantoms. An example of these data is shown in Fig. 4.4 with the peripheral dose for a number of field sizes expressed as a percentage of the maximum central axis dose vs. distance from the beam axis. The data were modelled in a freeware software programme called Peridose for the radiotherapy techniques at that time. However, this programme was written for conventional radiotherapy techniques with linear accelerators and cobalt-60 equipment only.

Calculation of Peripheral Dose in Modern Radiotherapy Techniques

These data and other literature concerning peripheral dose were published before the introduction of the present state-of-the-art treatment techniques, using virtual wedges, intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT, Elekta) or RapidArc (Varian). For these treatment techniques, the number of monitor units (MUs) required to obtain an adequate dose distribution might be increased significantly, resulting in an increased peripheral dose as a result of collimator leakage and collimator-scattered dose.

In 2013 Huang et al. compared dose measurements and calculations outside the treatment field for several IMRT plans, calculated using the Pinnacle v9.0 treatment planning software [15]. With increasing distances from the field edge, the dose decreases, but the underestimation of the measured dose by the treatment planning system (TPS) becomes larger, with an average underestimation of the dose by the TPS of 50 % at 15 cm and of 80 % at 30 cm. More or less the same underestimation of the dose by the TPS was found by Howell et al. for a simple mantle field calculated with Eclipse (Varian) [16]. It is clear that the medical physicist should model the beam in the TPS with great care during the commissioning phase, not only

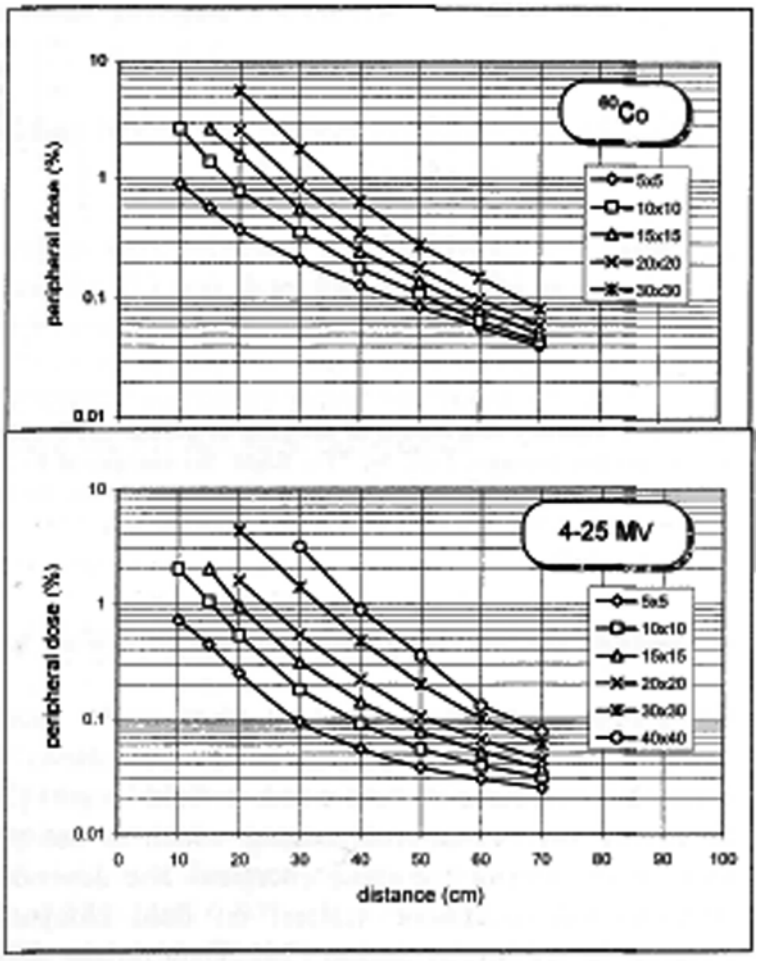

Fig. 4.4 Total peripheral dose in percentage of the central axis maximum dose as a function of distance for a number of field sizes (Taken from P.H. Van der Giessen, Thesis Leiden University 1997, with permission of the author)

paying attention to the beam profiles in the central area and penumbra but also to a sufficient large distance outside the penumbra. If the TPS is modelled well and if the distances to given points or structures (e.g. representing the foetus) are reasonably near to the target volume, dose volume histograms can be used for a good estimate to those points or structures. With increasing distance, the uncertainties in those outcomes will increase.

Proper shielding might reduce leakage and collimator-related contributions to the peripheral dose, but the amount of shielding that has to be applied is considerable. Therefore, when the patient is pregnant, the advantages of IMRT or modern arc therapies should be weighed against the increased dose to the foetus.

Image-guided radiotherapy, where the patient positioning is checked and corrected for during each treatment session, has become very common in modern radiotherapy departments. The treatment position is checked on-line (images taken every day) or off-line (e.g. imaging during the first few fractions and repeat images every week) using orthogonal MV images, orthogonal kV images, or cone-beam CT (CBCT). ICRP Publication 129 [17] estimates typical absorbed doses between 1 and 40 mGy when obtained with kV CBCT. MV CBCT with beam energies up to 6 MV shows typical absorbed doses between 20 and 100 mGy. It is noted that the imaging volumes can be significantly larger than the target volume of the radiotherapy course. Such repeated exposures are not included in the calculated peripheral dose estimates by the TPS, but they do add up to the total absorbed foetal dose. For pregnant patients, it is therefore recommended to limit the image fields and to apply orthogonal kV images to obtain the lowest possible addition to the total peripheral dose as a result of imaging.

Measurement of Peripheral Dose

The total dose outside a field can be measured in a phantom, either in a water tank, a solid polystyrene phantom or an anthropomorphic phantom. Ionization chambers, diodes or thermoluminescent dosimeters (TLDs) are suitable instruments. If specific shielding for the pregnant patient is available, the measurement can be performed with and without the shielding thus showing the dose reduction. Points of measurement should be sufficient to determine the range of dose to the foetus. The AAPM report [9] recommends to compare measurements at representative points outside the beam in a phantom with specific points at the surface of the phantom, to be able to correlate these data to foetal dose when monitoring at points on the patient, e.g. the fundus, symphysis pubis and umbilicus.

For in vivo measurements, the daily doses may be relatively small. Therefore, the medical physicist should ensure that the dosimeters measure accurately at these low dose levels.

Peripheral Dose with CyberKnife and Helical Tomotherapy

Chuang et al. [18] investigated the peripheral dose for a brain and thorax treatment to an anthropomorphic phantom with a CyberKnife unit after upgrading of the accelerator shielding. The results demonstrated that the additional shielding decreased the peripheral dose on this unit by a maximum of 59 % at 30 cm from the field edge to a value comparable to that measured for other treatment modalities. For distances between 30 and 70 cm from the field edge, the CyberKnife peripheral dose remained higher than doses measured in a previous study of the authors on IMRT.

Ramsay et al. [19] measured peripheral doses in-phantom using a helical tomotherapy system which is designed to deliver highly conformal intensity-modulated radiation therapy (IMRT). The concern of the authors was a possible increase of whole body dose due to increased leakage radiation as a consequence of the

relatively long treatment times of the equipment. The investigation showed that the delivery system was designed to maximize shielding for radiation leakage. As such, the peripheral doses are equal to or less than the published peripheral doses for IMRT delivery on other linear accelerators. This study, as does the one from Chuang et al. [18], indicates that peripheral dose values of higher or at best similar magnitude are obtained with these specific treatment delivery units compared to conventional linear accelerators. As such, at least similar shielding requirements should be considered compared to linear accelerators.

Radiotherapy with Heavy Particles during Pregnancy

There is much less experience with heavy ion radiotherapy during pregnancy. We can only cite from a few case studies. Tachibana et al. report a case of heavy ion radiotherapy to a lung metastasis of a sarcoma to a dose of 57 Gy. Foetal dose (equivalent) was 35 mSv, and a healthy baby was delivered [20]. Another group reports on a successful radiation treatment with carbon ions to a skull-base chordoma. Dose to the uterus was <0.2 mSv. Also in this case, a healthy baby was delivered [21].

Step-By-Step Delivery of a Treatment Plan in a Pregnant Patient

The AAPM provided a series of recommendations [9] which have been taken over by the ICRP in their report on radiotherapy during pregnancy [4]. These are listed here in a modernized form for present-day equipment (e.g. radiographic films for position checks are rarely used nowadays):

- Complete all planning as usual. If the foetus is situated near the treatment beam, avoid using large-field imaging or CBCT.
- Consider modifications to the treatment plan that would reduce the radiation dose to the foetus by changing field size, angle, radiation energy and beam modifiers such as blocks and wedges. Photon energies above 10 MV should be avoided.
- Estimate dose to the foetus without special shielding, using out-of-beam phantom measurements at the symphysis pubis, fundus and a midpoint.
- The AAPM recommends using shielding if foetal dose is above 50–100 mGy, with 4–5 half-value layers of lead. Measure dose to foetus in a phantom or simulated treatment with the shielding in place, adjusting radiation amount and location.
- Document the treatment plan and discuss it with the staff involved in patient set-up. Document the shielding.
- Check weight- and load-bearing specifications of the treatment couch or other aspects of shielding support.
- Be present during the initial treatment to assure that shielding is correctly placed.
- Monitor foetal size and growth throughout the course of treatment and reassess foetal dose if necessary.

- At completion of treatment, document total dose including range of dose to the foetus during therapy.
- Consider referring patient to another institution if equipment and personnel are not available for estimating and reducing the foetal dose.

We suggest adding the following recommendations:

- During commissioning of the TPS, take special care in accurately measuring the peripheral dose to a distance of at least 10 cm from the field edge and also compare measurements (preferably also with TLD) and calculations at distances of 5, 10, 15 and 20 cm from the field edge.
- If possible, use the lowest beam energy (often: 6 MV), since the peripheral dose is lowest for this energy and no neutrons are generated [6].
- Use optimized treatment plans with as little MUs as possible.
- Use kV imaging for image guidance, and limit the field size as much as possible instead of using MV imaging or CBCT.

Pregnancy Termination

In some cases, termination of the pregnancy might be considered. This, of course, is an individual decision. For foetal doses under 0.1 Gy, termination of the pregnancy does not seem medically justified. From studies in animals and from data on survivors of the nuclear explosions in Japan, it can be derived that at foetal doses, this low, foetal risk is negligible. In these studies, this dose was delivered in a single fraction. Therefore, with multiple fractions as delivered in clinical circumstances, the foetal risk at foetal doses of under 0.2 Gy seems to be so low that termination of pregnancy might also not be justified with foetal doses of 0.1–0.2 Gy. As was shown in the previous sections, foetal dose does generally not exceed this threshold when a tumour site at a distance from the uterus is being irradiated.

With higher doses, the foetal risk increases. Depending on the gestational stage, the foetus is at risk of developing malformations or IQ reduction (Table 4.1). In the case of substantial foetal risk, termination of the pregnancy can be considered, after carefully informing the parents on the significance and extent of this risk [3].

Conclusion

In pregnant patients, malignancies that are outside the pelvis and abdomen can generally safely be treated with radiotherapy. However, every case needs to be individualized depending on the type of cancer, stage of the disease and gestational stage. Other treatment options or a different order of treatment modalities should be considered. Doctor-patient shared decision-making after carefully informing the patient and her partner should be pursued. When the best option seems to irradiate during pregnancy, precautions need to be taken to reduce the foetal dose as much as possible, in order to minimize the foetal risk.

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Pharmacokinetics of Systemic Anticancer Therapies During Pregnancy

5

Paul Berveiller and Olivier Mir

Introduction

Systemic treatment with chemotherapy has a crucial role in pregnancy-associated cancers since it appeared to improve the overall survival, for instance, in breast cancer patients [1, 2]. Moreover, delaying anticancer agent administration as a result of pregnancy may adversely affect maternal survival [2]. In this complex medical and ethical situation, clinicians need to balance embryo-fetal well-being with maternal prognosis. Recent clinical data indicate that systemic treatment in cancer patients during the second and third trimesters of pregnancy is feasible and should be as close as possible to that used in nonpregnant patients [3–6]. Conversely, some other anticancer agents such as trastuzumab should be avoided given their potential fetal toxicity [3, 7].

Despite these general findings, the optimal use of cytotoxic drugs in pregnant patients remains undefined, particularly regarding molecule selection, dosing, dose intensity (standard or dose-dense regimens), and their potential repercussions of transplacental transfer. Indeed, both physiological changes in pharmacokinetics and pharmacodynamics play a critical role in drug safety (differential transplacental

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transfer) in one hand and in drug efficacy in the other hand. We herein focus on the pharmacokinetic data, the pharmacological changes occurring during pregnancy, and the subsequent potential changes in drug dosing and transplacental transfer that may be considered for selected drugs considered for the treatment of solid tumors during pregnancy.

Firstly, plasma concentrations should be in the optimal therapeutic window in order to display a favorable efficacy profile (to be above the minimum effective concentration) and must be below the maximum tolerated concentration. However, anticancer drugs are characterized by a narrow therapeutic index, i.e., their therapeutic concentration is very close to their concentration leading to significant toxicity. Hence, for these types of drugs, even minor changes in drug concentrations may lead to significant consequence represented by toxicity if concentration exceeds toxicity threshold and of inefficacy if concentration is below efficacy concentration level.

Conversely, regarding drugs that display a wide therapeutic index, moderate changes in drug concentration will not lead to significant clinical effects.

Finally, given the crucial physiological changes occurring during pregnancy and potentially leading to significant alterations of anticancer drug pharmacokinetics, physicians have to treat their patients carefully taking into account updated data that are listed below:

Physiological Changes During Pregnancy

Pregnant patients exhibit significant variations of pharmacokinetic parameters potentially altering drug metabolism in comparison with nonpregnant patients [8]. Physicians have to take into account that during pregnancy, these parameters may add their effects or cancel it and lead to no change in drug concentration.

Clearance

Drug clearance represents how the administered drug is metabolized and subsequently eliminated by the body. Thus, clearance affects directly total drug exposure and is used in order to determine maintenance dosing. Clearance is dependent on hepatic/renal blood flow, protein binding of studied drugs, and the activity of hepatic drug-metabolizing enzymes.

Hence, an increased blood flow may lead to an increase hepatic/renal clearance. Conversely, some factors inducing decreased hepatic/renal blood flows may subsequently decrease hepatic/renal clearances and lead to a drug overexposure. For example, during pregnancy, renal clearance is increased by 45 % at the beginning of gestation and reached 150 % at mid-gestation versus nonpregnant patients. Thus, physicians have to take into account these elements by making dosing adjustments (by increasing drug dosage or decreasing in some cases).

Drug Metabolism

Drug metabolism represents the fact that a xenobiotic is biotransformed in another one or many (one or many metabolites). Drug metabolism enzymes allow one molecule to be transformed in active or inactive metabolites. Many drug-metabolizing enzymes are involved in either phase I (often precedes phase II) or phase II metabolism, or in both phases. Thus, isoforms of cytochrome P450 (CYP1A2, CYP3A4, CYP3A5, CYP2D6) and alcohol dehydrogenase are involved in phase I reactions. UD-glucuronyltransferase (UGT), sulfotransferase, glutathione S-transferase (GST), etc. are involved in phase II [8].

Notably, the activity of cytochrome P450 isoform CYP3A4 increases by 50–100 % during the third trimester of pregnancy [9], potentially leading to a lower maternal exposure to drugs metabolized by this isoenzyme. Conversely, CYP1A2 activity appears to decrease during pregnancy, subsequently resulting in greater maternal plasma concentrations [9].

Finally, in case of cancer diagnosed during pregnancy, some other therapeutics such as ondansetron or codeine may be used, and these ones are also metabolized by cytochromes and potentially altered by the pregnancy setting (CYP1A2 and CYP2D6, respectively).

To conclude, many anticancer drugs are metabolized by metabolism enzymes; some of them are listed in Table 5.1 [10].

Table 5.1 Metabolism enzymes involved in anticancer drugs and supportive drug pharmacokinetics

Anticancer drugs	P450 cytochrome	Effect
Cyclophosphamide	CYP2B6, CYP3A4	Activation
Ifosfamide	CYP2B6, CYP3A4	Activation
Doxorubicin	CYP3A4	Inactivation
Docetaxel	CYP3A4	Inactivation
Paclitaxel	CYP2C8, CYP3A4	Inactivation
Etoposide	CYP3A4	Inactivation
Erlotinib	CYP1A2, CYP3A4	Inactivation
Gefitinib	CYP3A4	Inactivation
Vinorelbine	CYP3A4	Inactivation

Supportive treatment	P450 cytochrome	Effect
Codeine	CYP1A2	Inactivation
Morphine		Activation?
Paracetamol		Activation?
Metoclopramide	CYP2D6	
Ondansetron	CYP1A1, 1A2, CYP2D6	Activation?

Adapted from Scripture et al. [10]

The Area Under the Concentration-Time Curve

AUC represents the overall systemic drug exposure and is dependent on the dose, clearance, and bioavailability of the considered anticancer drug. For many drugs, AUC is well correlated with outcomes whereas for others drugs, minimum/maximum concentrations are better correlated.

Protein Binding

Protein-binding levels are dramatically involved in targeted concentration of various treatments such as anticancer agents. As an example, serum albumin levels significantly decrease during the second and third trimesters of pregnancy (approximately 13 % at 32 weeks), potentially resulting in elevated unbound drug levels and subsequent potential fetal toxicity [11, 12]. In pathologic conditions, these albumin levels may even be lower. Interestingly, albumin is not the only drug-binding protein; other plasma proteins such as alpha, beta, or gamma globulins and orosomucoid also play a significant role in protein binding (Table 5.2). Of note, physicians have to be extremely precautious in using, for example, drugs highly bound to plasma protein and displaying a narrow therapeutic range.

Table 5.2 Protein binding and unbound fraction of frequently used anticancer drugs

Anticancer drugs	Unbound fraction (%)	Binding protein
Bleomycin	>99	Plasma
Carboplatin	1	Albumin
Cisplatin	<5	Albumin, transferrin, gamma globulins
Cyclophosphamide	87	Plasma
Docetaxel	<2	Albumin, orosomucoid, HDL
Doxorubicin	15–25	Albumin
Etoposide	4	Albumin
5-fluorouracil	>95	Albumin, alpha, beta, and gamma globulins
Ifosfamide	45	Plasma
Irinotecan (CPT-11)	65	Albumin
Methotrexate	54	Albumin
Oxaliplatin	13–21	Albumin, gamma globulins
Paclitaxel	2–8	Albumin, orosomucoid, HDL
SN38 (active metabolite of CPT-11)	2	Albumin, orosomucoid
Tamoxifen	<2	Albumin, beta globulins
Topotecan	79	Albumin
Vinorelbine	12	Orosomucoid

Volume of Distribution

Volume of distribution (V_d) is not a physical space but a pharmacological theoretical volume that the total amount of administered drug would have to occupy (if it were uniformly distributed), to provide the same concentration as it currently is in the blood plasma.

Some drugs display a small V_d (0.1–1 L/kg) whereas some other drugs display larger V_d (1–10 L/kg). The volume of distribution is used to determine the loading dose needed to achieve the targeted concentration. Many physiological changes will occur during pregnancy and that may subsequently lead to an altered V_d.

Hence, plasmatic volume significantly increases during pregnancy (30–45 %) and peaks between 28 and 34 weeks of gestation, and the total body water will increase up to 8 l at term. These crucial physiological changes will lead to a decreased concentration peak and a higher trough concentration and subsequently to an increased distribution volume [13, 14].

Half-Life

Half-life corresponds to the period necessary for the drug concentration to be divided by two. This parameter is helpful to determine the administration frequency. Half-life directly depends on distribution volume and clearance. If the distribution volume of a drug is increased during pregnancy (or if clearance is decreased), its half-life will subsequently be longer and the interval between two administrations will have to be extended. Conversely, when the distribution volume is decreased and/or if the clearance is increased, the interval between two administrations will have to be shortened. In some cases, changes in distribution volume and in clearance do not lead to substantial changes in interval dosing.

Placental Metabolism and Placental Transfer

Although the placenta acts as a biologic barrier, the placenta also plays major role such as an endocrine organ and a metabolizing organ. Even if placental metabolizing activities have been described as relatively moderated, in some cases, their role may lead to potential consequences. This placental metabolism has to be taken into account when prescribing anticancer drugs.

The impact of pregnancy setting of the expression/activity of placental cytochromes is listed in Table 5.3 [15]. Interestingly, placental metabolizing activities may not only be altered in the pregnancy setting but also in patients who abuse tobacco, alcohol, or drugs or are exposed to polluted air.

Besides, all anticancer drugs can cross the placental barrier, but placental transfer may considerably vary [16]. Historically, three major mechanisms of placental transfer have been described: passive diffusion, facilitated diffusion, and active transport [16]. Chemical properties of drugs that influence their placental transfer

Table 5.3 Cytochrome P450 (CYP) expression and activity in the first trimester and term human placentas

CYP isoenzyme	CYP subtype	First trimester	Term
CYP1	CYP1A1	$+^{1,2,3}$	$+^{1,2,3}$
	CYP1A2	$+^{1}$	$-^{1,2}$
	CYP2B1	$+^{1}$	$+^{1}$
CYP2	2A6	$-^{1}$	$-^{1}$
	2A7	$-^{1}$	$-^{1}$
	2A13	$-^{1}$	$-^{1}$
	2B6	$-^{1}$	$-^{1}$
	2B7	$-^{1}$	$-^{1}$
	2C	$+^{1}$	$-^{1}$
	2D6	? ($+^{1}$, $-^{3}$)	$-^{1,3}$
	2E1	? ($+^{1,2}$, $-/+^{3}$)	? ($+^{1}$, $-/+^{2,3}$)
	2 F1	$+^{1}$	$+^{1}$
CYP3	3A3	?	? ($+^{1}$, $-^{2}$)
	3A4	$+^{1,2}$	? ($+^{1}$, $+/-^{2}$, $-^{3}$)
	3A5	$+^{1,2}$	? ($+^{1}$, $+/-^{2}$)
	3A6	$+^{1,2}$	? ($+^{1}$, $-^{2}$)
	3A7	$+^{1,2}$	? ($+/-^{1,2}$)
CYP4	4B1	$+^{1}$	$+^{1,2}$

Adapted from Syme et al. [15]
1: mRNA expression +: detectable
2: protein expression –: undetectable
3: enzyme activity ?: unknown or controversial results

are molecular weight, lipophilia, ionization at physiological pH, and plasma protein binding (see above). Grossly, low molecular weight drugs, weakly bound to plasma proteins, highly lipophilic, and nonionized at physiologic pH, may theoretically cross the placenta more easily [16].

Nevertheless, these concepts remain highly theoretical and many other factors may contribute to make the placental transfer varying. Thus, some drugs sharing these characteristics may be substrates of maternal-faced placenta proteins (efflux transporters) such as the P-glycoprotein (P-gp, MDR1, ABCB1) or the breast cancer resistance protein (BCRP, ABCG2) [15, 17]. These transporters are expressed in human placenta all along pregnancy and therefore may protect the fetus from various xenobiotics such as paclitaxel [18, 19] and may thereby counterbalance the unfavorable chemical properties of the drugs. Hence, physiological changes of pharmacology during pregnancy, placental metabolism, and the differential expression of placental transporters may subsequently alter transplacental transfer. Thus, we will provide below available data regarding the resulting transplacental transfer of various systemic anticancer therapies.

Placental Transfer of Selected Drugs: Preclinical and Clinical Data

Cyclophosphamide

Regarding in vivo data, no study documenting maternal pharmacokinetic parameters or amniotic fluid/neonatal blood cord dosage after cyclophosphamide administration was found. Regarding human ex vivo studies, only one study documented maternofetal passage of cyclophosphamide [20]. The authors described the case of a 33-year-old woman diagnosed with stage IVB Hodgkin's lymphoma treated with a combination therapy with cyclophosphamide (400 mg/m^2) started at 29th gestational week. At 34th gestational week, an amniocentesis was performed 1 h after the last dose of cyclophosphamide concomitantly with maternal blood sample analyses (second course). Interestingly, the level of cyclophosphamide in amniotic fluid was 25 % of the plasma level at the first hour post-administration of cyclophosphamide.

Interestingly, in animals such as baboons, transplacental transfer was obviously evidenced using ex vivo studies, with 25 and 63 % of maternal concentration of 4-hydroxy-cyclophosphamide found in fetal plasma and cerebrospinal fluid [21].

Cisplatin and Carboplatin

To our knowledge, only two ex vivo studies investigated the cisplatin transport from the maternal to the fetal circulation in human perfused placental cotyledon. In the first one [22], the authors found a transport fraction of cisplatin roughly reaching 13 % of reference marker value (antipyrine). Thus, the authors assumed that cisplatin transport remains negligible in the human placenta at term and may be used with minimal risk in pregnant patients [22]. In the second one, the authors found that carboplatin does cross the placental barrier, especially at higher concentrations in a placental perfusion model [23]. The placental transfer of carboplatin was concentration dependent. The concentration of carboplatin in fetal compartment ranged from 2.2 % up to 23.7 % of the total drug concentration crossing the placenta across all experiments. The authors concluded that doses of carboplatin up to an area under the curve of 7.5 were not associated with significant placental transfer, fetal exposure, or fetal toxic effects.

An animal ex vivo study described transplacental transfer of labeled cisplatin used as a tracer in pregnant mice at different times of gestation [24]. Interestingly, very small amounts of radioactivity were detected in the embryos during the first days of gestation, whereas increasing amounts of radioactivity were evidenced during the late days of gestation. These data suggest that placental transfer may be gestational age dependent, and progressive transporters expression may influence drug transfer along with placental maturation. Another animal study confirmed the transplacental transfer of carboplatin in baboons with fetal concentrations reaching up to 57.5 % of maternal concentration [25].

Two human in vivo reports highlighted a significant cisplatin transplacental transfer with detection of cisplatin in umbilical cord blood of two neonates exposed

to cisplatin during pregnancy [26, 27]. These neonatal cisplatin levels were 40 µg/ml at the third day post-chemotherapy (first day of life) [27] and 0.82 µm/L versus 1.10 µm/L for the mother [26].

Another in vivo report described the case of a 40-year-old pregnant woman with ovarian cancer, in whom cisplatin 100 mg/m^2 was initiated at 20 weeks of gestation, followed by carboplatin 300 mg/m^2 [28]. Platinum-DNA adducts were detected in amniotic fluid (after amniocentesis), placental tissues, blood cord, and maternal blood (at delivery). Platinum-DNA adducts were not detected any more 3 months after delivery.

Koc et al. reported the detection of platinum-DNA adducts after carboplatin 400 mg/m^2 administration at 22 weeks of gestation [29]. Platinum-DNA adducts were detected in blood cord lymphocytes 9 weeks after the last administration of carboplatin.

Interestingly, Marnitz et al. studied cisplatin concentration in amniotic fluid after a second cycle of cisplatin (20 mg/m^2) dose for cervical cancer in a 35-year-old patient with twin pregnancy [30]. Cisplatin maternal serum concentrations were 293.8 mg/L before and 1148.8 mg/L 30 min after cisplatin administration. At the same time, cisplatin amniotic fluid concentration was 106.7 mg/L. Hence, cisplatin amniotic fluid concentration reached approximately 10 % of maternal concentration. At delivery, cisplatin concentrations were studied in the twin neonate blood cords and in amniotic fluid. The blood cord concentrations were 57.1 mg/L for the first neonate and 61.2 mg/l for the second. Amniotic fluid concentration was roughly one third of blood cord concentrations. Moreover, maternal pharmacokinetic parameters were studied after the third cycle of cisplatin-based chemotherapy and were comparable to nonpregnant patients.

In very recent study, Köhler et al. investigated the transplacental transfer of platinum [31]. Twenty-one patients with cervical cancer diagnosed in the second trimester were treated with neoadjuvant cisplatin chemotherapy, started between the 17th and the 25th week at the dose of 20 mg/m2 on days 1–3 every 3 weeks. At the time of delivery by cesarean delivery, synchronous samples from maternal blood, umbilical cord blood, and amniotic fluid were taken and analyzed for cisplatin concentrations. Cisplatin concentrations in umbilical cord blood and amniotic fluid were 23–65 % and 11–42 % of the maternal blood, respectively.

All these data confirm an obvious transplacental transfer of platinum salts through the placental barrier.

Doxorubicin

Only one ex vivo study using human perfused placental cotyledon model documenting transplacental transfer of doxorubicin was found [32]. The authors investigated passage of maternal doxorubicin concentrations of 3, 30 and 150 mg/l through the cotyledon. The global transfer value was 2.96 % and did not seem to be dose dependent.

Regarding in vivo data, several reports documented the transplacental transfer of doxorubicin in humans. In a pregnant patient receiving 60 mg/m^2 [33]. 3 weeks after the last infusion of doxorubicin, no doxorubicin was detectable, neither in neonate blood nor in the placental tissues.

In another case report, the authors investigated the transplacental transfer of doxorubicin 20 mg/ m^2 started at 32 weeks of gestational age [34]. After four courses of chemotherapy, an amniocentesis was performed (96 h after the last doxorubicin administration). Accordingly with the previous case report, doxorubicin and its metabolite were not detectable in amniotic fluid.

Karp et al. [35] reported two cases of transplacental transfer of doxorubicin. The first patient received 45 mg/m^2 of doxorubicin-based treatment. At delivery (2 days after the last administration), doxorubicin levels in the placental-maternal side, placental-fetal side, and umbilical cord were at 1.186, 0.786, and 0.083 nmol/g of tissues, respectively. Interestingly, doxorubicin was not detectable in blood cord. The second patient received 45 mg/m^2 doxorubicin-based treatment. Sixty hours after the last administration, the mother delivered a stillborn baby. Noteworthy, no doxorubicin could be detected in any fetal tissue; however metabolite was highly detected in fetal spleen and was also present in lower concentrations in fetal liver, lung, kidney, muscle, heart, and duodenum.

Another case report available documented the use of 30 mg/m^2 doxorubicin for myeloblastoma diagnosed at 20 weeks of gestational age [36]. Four and 16 h after doxorubicin administration, amniocentesis were performed. Interestingly, no doxorubicin could be detected in amniotic fluid.

Conversely, D'Incalci et al. investigated 15 h after a 40 mg doxorubicin infusion (therapeutic abortion) transplacental passage in fetal tissues [37]. Doxorubicin reached high concentrations in the lung, liver, and fetal kidneys (ten times the maternal concentration), whereas no doxorubicin was detected in the amniotic fluid, brain, intestine, and gastrocnemius muscle. The authors explained the undetectable doxorubicin in the amniotic fluid by important distribution volume during pregnancy.

To our knowledge, no in vivo data were available in the literature regarding transplacental transfer of pegylated liposomal doxorubicin. However, a very recent article studied its transfer in human placental cotyledon [38]. Interestingly, the pegylated doxorubicin did not cross the placenta whereas liposomal doxorubicin crossed the placental barrier (12 % of the maternal concentration maximum).

Paclitaxel

Three human ex vivo studies documented transplacental transfer of paclitaxel [17].

Firstly, the authors investigated placental transfer of paclitaxel 85 ng/ml using perfused placental cotyledon model (seven placentas). The final fetal concentration of paclitaxel was 3.7 ng/ml, which represented roughly 4.3 % of initial maternal concentration.

Noteworthy, as paclitaxel is known to be a substrate of the P-glycoprotein (P-gp, MDR1, ABCB1) [39], the authors investigated the role of P-gp administration on transplacental transfer rate of paclitaxel with six placentas. Fetal concentrations with P-gp inhibitors were found to be two times higher than without P-gp inhibitors (7.5 ng/ml), representing 8.8 % of initial maternal concentration. Thus, transfer of paclitaxel through the placenta was significantly higher with P-gp inhibitors, reinforcing the role of protecting fetus against drugs such as paclitaxel.

Secondly, using the same model with the same concentrations of paclitaxel (12 placentas), Nanovskaya et al. found similar results [40]. Fetal concentrations of paclitaxel with and without P-gp inhibitor were 3.97 and 6.56 % of initial maternal concentration, respectively.

Finally, we have recently documented a low transplacental transfer rate of paclitaxel (close to 5 %) with however an important inter-patient variability [41].

An ex vivo study investigated with another model (cellular culture of Caco-2 cells) the efflux permeability of paclitaxel with and without P-gp inhibitor [42]. Using a P-gp inhibitor, the authors confirmed the fact that paclitaxel is a P-gp substrate by documenting a significant increase in influx permeability (roughly three times higher).

Docetaxel

We have recently studied the transplacental transfer rate of docetaxel (close to 5 %) in an ex vivo cotyledon perfusion model [41]. Similarly to what was found with paclitaxel, inter-patient variability was important.

No other ex vivo nor in vivo data documenting the transplacental transfer of docetaxel in humans was found in the literature, neither in summary of pharmaceutical product.

However, in baboons, Van Calsteren et al. investigated the transplacental transfer of docetaxel [21]. Interestingly, although they did not find significant level of docetaxel in fetal blood samples after administration of 100 mg/m^2 of docetaxel, they detected 5–50 % in fetal tissues of maternal tissue concentration after 3 h. Interestingly, fetal and maternal tissue concentrations were similar after 26–76 h.

To conclude, physicians have to pay attention to the physical properties of the administered drugs, the term of pregnancy, and the available data in the literature to better handle these drugs during pregnancy and potentially change drug dosing.

Recent Clinical Pharmacokinetic Data

Although clinical data indicate a good tolerability of anthracyclines and taxanes during the late trimesters of pregnancy [43–46], the existence of physiological variations in drug pharmacokinetics during pregnancy raises important concerns regarding the optimal drug dosing in pregnant patients [8, 47]. Indeed, the favorable toxicity profile of these agents during the late trimesters of pregnancy questions whether pregnant patients could achieve suboptimal plasma concentrations (underdosing) compared to that observed in nonpregnant patients, potentially leading to a decreased antitumor efficacy [47]. Recent data summarized as follows provide some information that may help clinicians to better handle anticancer agents during pregnancy:

- Most anticancer agents are empirically prescribed according to the body surface area (BSA), resulting in large inter-patient variability (even outside the pregnancy

setting). To date, when a pregnant patient is diagnosed with a cancer, no data are available to support the use of alternative dosing methods [4]. Thus, dosing based on the BSA, using the current patient's weight (prior to every course), remains a standard [48]. Conversely, the use of target-AUC-based dosing, used, for example, for carboplatin (in platinum-sensitive diseases such as triple negative breast cancer), cannot be currently recommended in pregnant patients [48]. Indeed, the formula (Calvert or Chatelut) used to calculate carboplatin dose according to the target AUC was obtained from population pharmacokinetic models that did not include pregnant patients, and the impact of physiological changes associated with pregnancy on these models is unknown.

- In addition, an increased activity of major enzymes involved in the metabolism of taxanes and anthracyclines (such as cytochrome P450 isoforms CYP3A4 or CYP2C8) is observed during the late trimesters of pregnancy [49], potentially resulting in decreased drug exposure. Moreover, given the fact that albumin concentrations significantly vary during pregnancy and taxanes being highly protein bound, these may lead to significant changes in taxane pharmacokinetics [47].
- Furthermore, very recent pharmacokinetic data comparing the use of anthracyclines and taxanes in pregnant versus nonpregnant patients highlighted the fact that exposure to taxanes was significantly decreased during pregnancy, especially for paclitaxel [47]. Conversely, exposure to anthracyclines such as doxorubicin and epirubicin was not significantly modified [47], confirming recent additional data [50].

Thus, anthracycline dosing method should probably be remained unchanged during pregnancy, whereas physicians should be aware of potential suboptimal exposure while using taxanes (paclitaxel and docetaxel) in this particular setting. However, whether doses should be increased in this population is uncertain because such increases could result in severe thrombocytopenia, neutropenia, and infection, with potentially serious consequences for both mother and neonate [4]. Although granulocyte-colony stimulating factor (G-CSF) support can reduce the occurrence of febrile neutropenia in nonpregnant patients, its effectiveness and safety profile during pregnancy are not clearly established [8, 46, 51].

- Finally, platinum salts may have a role in gynecologic, lung, and triple negative breast cancer, especially carboplatin. Although the use of platinum salts may be considered during the late trimesters of pregnancy, significant transplacental transfer was demonstrated and long-term effects remain unknown [52]. Little is known regarding the platinum salt displaying the best toxicity profile, but carboplatin might have a less global toxicity compared to cisplatin [6].
- Otherwise, although maternal drug exposure is a concern in terms of treatment efficacy, the transplacental transfer of anticancer agents is critical for fetal safety. Data on transplacental transfer rates indicate similar and reassuring data on doxorubicin, epirubicin, and taxanes [32, 41, 53], still with major inter-patient variability, particularly marked with docetaxel [41]. As a consequence, from the fetal safety point of view, paclitaxel should probably be preferred to docetaxel in the setting of pregnancy [54].

- Some other therapies such as targeted anticancer agents may be indicated in specific cases, notably in breast cancer, for instance, trastuzumab. Initiating trastuzumab therapy as early as possible is associated with a better long-term outcome in non-pregnant patients with HER-2-positive breast cancer [55]. Regarding the use of trastuzumab during pregnancy, in a recent review, some authors retrospectively collected data from numerous reports [56]. Thus, oligo-/anhydramnios was described as the most frequent adverse outcome. Interestingly, this adverse outcome was in general limited when trastuzumab therapy was discontinued [56]. However, the rate of prematurity was found to be high, sometimes leading to neonatal deaths mainly caused by respiratory failures. Indeed, trastuzumab is an IgG1, the subclass of antibodies that is the most actively transferred across the placenta during the second and third trimesters of pregnancy, and HER-2-signaling pathway is critical for fetal renal development [57].

Although trastuzumab use is currently not recommended during pregnancy [8], short inadvertent fetal exposure to trastuzumab therapy should not systematically lead to termination of pregnancy.

Regarding other targeted agents such as bevacizumab, pertuzumab, or trastuzumab emtansine, to our knowledge, no data is available on their use during pregnancy [8].

- Moreover, physicians have to deal with the timing of systemic therapy, taking into account anticancer molecule, drug dosing, and potential fetal consequences according with gestational age. In order to summarize, systemic therapy should be avoided during the first trimester due to the embryologic organogenesis period [3]. During the late trimesters (second and third), taking into account parameters such as disease stage and gestational age, various anticancer agents may be used with a favorable safety profile as abovementioned [6].

During the end of the third trimester, to allow the bone marrow to recover and minimize the hematological consequences (risk of maternal and fetal neutropenia), delivery should be postponed at least 3 weeks after the last course of chemotherapy [3, 58].

- Finally, some authors introduced the potential use of dose-dense chemotherapy during pregnancy [59]. Among ten patients who received dose-dense chemotherapy, there was no significant difference regarding neonatal outcomes (birth weight, congenital anomalies, neutropenia, and preterm births) and maternal outcomes (neutropenia, recurrence, time to recurrence, survival) [59]. Although a very small sample of patients was treated, these data suggest that dose-dense chemotherapy might be used in some particular cases. Nevertheless, further studies on dose-dense chemotherapy are mandatory in order to encourage or not the use of dose-dense chemotherapy regimen during pregnancy.

Conclusion

To conclude, various systemic anticancer agents such as anthracyclines and taxanes using standard protocols are feasible during the last trimesters, whereas monoclonal antibodies such as trastuzumab should be avoided along the preg-

nancy. Given the major pharmacokinetic changes during pregnancy and given recent published data, a potential dose increase could be useful especially for taxanes, but further studies remain necessary to confirm these preliminary results and to confirm that transplacental transfer is not subsequently increased.

Anthracycline-based chemotherapy might be preferred in the first intention due to concerns regarding paclitaxel and docetaxel exposure and efficacy during pregnancy. Platinum salts might be used (using the BSA-based dosing method) in particular settings, even though their transplacental transfer has been established as significant, and potential long-term outcomes remain unknown.

As a consequence, although very recent studies provided highly interesting data, further pharmacokinetic studies are warranted before changing our chemotherapy protocols during pregnancy.

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Obstetrical Care of a Pregnant Woman with Cancer

6

Kristel Van Calsteren

Introduction

Cancer is the second leading cause of death in women during the reproductive years and complicates between 1 in 1000 to 2000 pregnancies. In Europe, this number translates yearly into 3000–5000 new patients with cancer diagnosed during pregnancy. As women in developed societies defer childbearing to the third or fourth decade of life, and the incidence of most malignancies rises with increasing age, the rare coincidence of cancer and pregnancy is likely to become even more common. The most frequently encountered tumour types are identical to the group of nonpregnant women between 25 and 45 years old: breast cancer, haematological malignancies, dermatological malignancies and cervical cancer [1].

It is evident that in situations of life-threatening maternal diseases, priority is given to maternal health management. Nevertheless, cancer treatment during pregnancy includes risks for the fetus. Therefore, the pregnancy makes decisions on treatment and the treatment itself more complicated. On the other hand, terminating the pregnancy early to enable 'standard oncological treatment' includes pregnancy loss and iatrogenic prematurity of which the consequences are often underestimated in the oncological world.

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Diagnosis of Cancer During Pregnancy

Pregnancy is a period in which women regularly consult a doctor and have physical exams, blood analysis and ultrasound examinations. This gives the opportunity for early diagnosis of major diseases like cancer. Hereby it is important to perform further technical examinations in case of a suspicious history and physical examination. A missed diagnosis or delayed treatment often poses a greater risk to the patient and her pregnancy than the hazard associated with ionizing radiation.

The International Commission on Radiological Protection (ICRP) recommends to keep the fetal radiation dose 'as low as reasonably achievable (ALARA) principle', with an absolute maximum dose of 100 mGy. At this dose threshold, no deterministic effects are expected, like fetal death, malformations or mental retardations, and the risk of stochastic effects, like cancer induction, is below 1 % [2].

To obtain an accurate diagnosis and staging, various diagnostic modalities are required that may have an impact on the developing fetus. In order to obtain all the required information on the stage of the disease, with the lowest achievable fetal radiation exposure, the optimal staging strategy should be discussed in a multidisciplinary setting with a maternal-fetal medicine specialist, medical and surgical oncologist, radiologist and nuclear medicine specialist.

Following diagnosis and staging, the stage of disease, gestational age and patient's wishes will define the therapeutic options. The complex medical, ethical, psychological and religious issues arising in pregnant women with cancer demand care from a multidisciplinary team with maternal-fetal medicine specialists, oncologists, radiation oncologists, surgeons, paediatricians, geneticists and psychologists. On the other hand also the patient and her family should be actively involved in the decision-making process following adequate information and counselling [3, 4]. The relative rarity of pregnancy-associated cancer makes it hard to conduct large prospective studies to examine diagnostic, management and outcome issues. However, it is evident that curing the mother is the priority, but also the fetal health should be taken into consideration.

When Should We Deliver/Terminate the Pregnancy?

To determine the best timing for ending the pregnancy, the risks and benefits for the mother and the fetus should be balanced.

In order to obtain an optimal prognosis for the *mother*, unnecessary delay in treatment should be avoided and standard cancer treatment, defined as the treatment with the best outcome results in RCT in nonpregnant patients, should be applied. Standard cancer treatment includes surgery, systemic treatment (chemotherapy, targeted treatment) and radiotherapy or a combination of these. Hereby, slight modifications can be acceptable as long as these adaptations will not worsen the maternal outcome, e.g. some weeks delay in adjuvant radiotherapy to defer it till postpartum.

Pregnancy was shown not to have a negative impact on the maternal oncological outcome, except for melanoma [5]. Termination of pregnancy after a diagnosis of cancer does not seem to improve survival [6].

Therefore, the only medical indications for terminating the pregnancy are unacceptable high risks of the cancer treatment for the fetus and a very poor maternal medical condition and prognosis.

The risks for the *fetus* are defined in teratogenicity of cancer treatment and comedication, in prematurity after preterm delivery and extremely rarely in fetal metastasis.

Teratogenicity of Cancer Treatment

Standard cancer treatment consists of surgery, systemic treatment (chemotherapy, targeted treatment) and radiotherapy.

Surgery is considered to be safe. The potential risk of fetal damage induced by cytotoxic treatment will largely depend on the exposure period in pregnancy. During the first 10 days post-conception (fertilization/implantation), a fetotoxic event will have an 'all or nothing' effect. When sufficient cells survive, the embryo will develop normally; otherwise, a miscarriage occurs. Between 10 days and 8 weeks after conception, cytotoxic therapy may interfere with organogenesis and result in congenital malformations. The potential for fetal damage varies depending on the type of treatment and dosages used. After single-agent chemotherapeutic treatment, 7–17 % malformations are seen; after combination schemes, the risk rises till 25 %. Excluding the folic acid antagonists, a risk of 6 % is reported [7]. After radiotherapy, fetal malformations are expected to occur from a threshold dose of 100 mGy [8]. The type of malformation depends on the timing of exposure in the embryological development. The most frequently described malformations are skeletal problems (face, limbs).

During the second and third trimesters of pregnancy, organogenesis is completed with the exception of the eyes, gonads and central nervous system. Consequently no major malformations are expected to be caused by cytotoxic treatment. Nevertheless, growth restriction, prematurity, intrauterine and neonatal death and haematopoietic suppression have been reported after exposure to chemotherapy or a fetal radiation dose exceeding the threshold of 100 mGy. Moreover, potential problems of neurodevelopmental delay, subfertility, carcinogenesis and genetic defects have to be considered on the long term [9–11].

In order to avoid problems associated with haematopoietic in the patient and neonate (bleeding, sepsis, anaemia) and to avoid drug accumulation in the fetus, an interval of 3 weeks should be respected between the last cycle of chemotherapy and the anticipated delivery [3, 12].

Studies evaluating the long-term outcome of children exposed to chemotherapeutics during the second and third trimesters of intrauterine life are hampered by small numbers and reduced follow-up time. Most recent studies do not show significant increase of congenital malformations or developmental impairment in these

children [13–17]. However, it is accepted that the risks associated with fetal exposure to chemotherapeutics in utero are not limited to pre- and perinatal risks. Careful examination at birth but also systematic long-term follow-up of neurologic and psychomotor development is advisable for all children that underwent in utero exposition to chemotherapeutic agents or radiotherapy.

Experience with targeted therapy agents during pregnancy is limited. Nevertheless, their use in pregnancy has been associated with fetal complications. The use of hormonal agents such as selective oestrogen receptor modulators (SERMs) or the aromatase inhibitors in the treatment of breast cancer interfere with the hormonal situation of a normal pregnancy and should be avoided. They have been associated with vaginal bleeding, spontaneous abortion, birth defects including craniofacial malformations and ambiguous genitalia and fetal death [18]. Monoclonal antibodies are large molecules that require active transport via the placenta to reach the fetus. Exposure to these agents after the first gestational trimester has been linked to specific 'on target' effects, e.g. oligohydramnios with respiratory and renal failure after trastuzumab exposure and B-cell depletion after rituximab exposure [19].

On the other hand, small molecules like tyrosine kinase inhibitors (TKIs) can cross the placenta throughout the pregnancy period and therefore also can cause major congenital malformations [19].

Apart from the cytotoxic treatment, these women are exposed to supportive treatment agents, like painkillers, antiemetics, corticosteroids and GSF. For each group of supportive agents, drugs which are shown to be safe during pregnancy should be selected [20, 21]. The use of steroids deserves attention, since repeated antenatal exposure is associated with increased incidences of attention problems and higher rates of cerebral palsy [22]. In contrast to dexamethasone and betamethasone, methylprednisolone and hydrocortisone are extensively metabolized in the placenta and are therefore the preferred steroids to use during pregnancy, except to achieve fetal lung maturation.

Prematurity

In rare cases, the condition of the mother is deteriorating so rapidly that delivery needs to be expedited for maternal reasons. More often, a dilemma between the risks related to iatrogenic preterm birth and exposure to chemotherapy and radiotherapy arises at some point during pregnancy. As a result, a lot of these babies are delivered preterm.

Perinatal mortality and morbidity are known to decrease dramatically from 24 weeks onwards with every week that is gained in utero in good condition. For individual countries and regions, these figures can vary substantially. It therefore seems advisable that parents are informed based on the local or national statistics and include not only survival figures but also data on neonatal and long-term morbidity.

Preferably, delivery should not be performed before 35–37 weeks [21]. Prematurity, including late prematurity (34–37 weeks), is associated with general

health problems and cognitive and emotional development disorders, on the short and on the long term [23, 24]. Therefore, maximal efforts should be made to avoid unnecessary prematurity in patients where cancer treatment can be given during pregnancy.

Fetal Metastasis

Documented reports of maternal malignancy metastases in the placenta are rare. Since the first description in 1866, less than 100 cases have been described. Most frequently reported tumour types are malignant melanoma, leukaemia and lymphoma, breast cancer and lung cancer. Proven maternal metastasis to the fetus is exceptional, with only 17 cases reported so far [25]. Despite this, each placenta should be thoroughly examined for metastasis, which, if present, should alert the clinician to monitor the infant for development of malignant disease.

How Should We Follow Up the Pregnancy?

In most cases, routine obstetrical follow-up is sufficient. However, one should be aware that the average age of these patients is increased compared to the normal obstetric population. Special attention is therefore required not only for the oncological condition of the patient but also for age-related pregnancy risks like hypertension, gestational diabetes and increased risk for fetal aneuploidy.

Before staging examinations or oncological treatment is started, fetal structural development and growth should be evaluated to exclude pre-existing anomalies [12]. Monthly a detailed fetal assessment should be performed by a maternal-fetal medicine specialist in order to follow up fetal growth and detect possible teratogenic effects.

Furthermore, special attention is required for preterm labour and fetal growth restriction [1]. Apart from the obstetrical follow-up for these complications, it is important to consider adequate painkilling, prompt treatment of complications as infections and anaemia and sufficient nutrient intake.

How Should We Deliver?

Like in the general population, there are several important advantages to opt for a vaginal birth in most of these patients including reduced blood loss, reduced operative risk, reduced infection risk, shorter duration of hospitalization and better preservation of reproductive future. This is especially important for patients with myelosuppression after cancer therapy. Moreover, the faster recovery after a vaginal delivery in comparison to caesarean section is important for women in need to start chemotherapy shortly after the delivery.

Despite this, a large number of patients are reported to deliver preterm by caesarean section. In some rare cases, like cancer metastasis to the long bones which

increases the risk for fractures during labour precipitated by lithotomy position during labour and expulsion, a caesarean section has to be preferred. Active pushing can also be contraindicated in central nervous system tumours that cause increased intracranial pressure. Assisted vaginal delivery can then be safely offered in most cases. Although cervical intraepithelial neoplasia is not an indication for operative delivery, vaginal birth in women with cervical cancer can lead to fatal recurrences in the episiotomy scar. Operative delivery avoiding surgical trauma of the lower uterine part in order to prevent wound metastasis is therefore recommended in cervical cancer patients [21]. In patients operated for vulvar cancer during pregnancy, vulvar scarring and the risk for vulvar trauma can be an indication for caesarean section [21].

What Is Important in the Postpartum Period?

Oncological treatment can be started again within a week after an uncomplicated delivery.

As the postpartum period and malignancy are both risk factors for venous thromboembolism, prophylaxis should be considered after an operative delivery.

Advice on breastfeeding should be individualized since its safety depends on the type, site and timing of the treatment. Contraindications for breastfeeding are, e.g. the administration of chemotherapy within the peripartum period, radiotherapy of the breast and status after mastectomy.

In the postpartum period, special attention is required for the psychological condition of the patient. Often they keep very well during the pregnancy; 'they fight for their child'. Once the baby is born, it seems much more difficult to deal with the cancer diagnosis and treatment for many women. The combination of normal postpartum difficulties like sleep deprivation and baby blues makes these patients extremely vulnerable in the postpartum period. It is important to talk about this before the delivery and make sure enough 'helping hands' are available.

Summary

Cancer during pregnancy is uncommon though not rare. Perinatologists play a crucial role when cancer staging and treatment is planned during pregnancy. A summary of the key obstetrical care measures is given in Table 6.1. A missed diagnosis or delayed treatment often poses a greater risk to the patient and her pregnancy than the hazard associated with ionizing radiation. The diagnosis and treatment of cancer in a pregnant woman is a clinical and ethical challenge for all medical care workers. The benefits and risks of the different diagnostic and therapeutic modalities should be carefully balanced for both the mother and the fetus in a multidisciplinary setting.

Table 6.1 Key obstetrical care measures that need to be performed for pregnant cancer patients

Gestational phase	Obstetrical points of attention
Preconception	Perform a general and gynaecological history and physical exam with PAP smear. In case of clinical suspicions, delay the pregnancy until further technical examinations for diagnosis are performed
	Patients treated for cancer should be actively informed and prescribed anticonception
Pregnancy follow-up	Cancer diagnosis and treatment
	Consider the possibility of maternal cancer in case of suspicious history or findings at physical exam or prenatal ultrasound
	Do not delay technical exams and required treatment, but consider fetal safety:
	Maximum fetal radiation dose is 50–100 mGy
	Avoid chemotherapy in the first trimester
	Avoid targeted therapy
	Termination of pregnancy can be discussed for patients with a poor maternal prognosis and cancer diagnosis early in pregnancy
	Offer psychological support
	High-risk obstetrical follow-up
	Subgroups are at risk for preterm delivery and fetal growth restriction
	Fetal metastasis are extremely rare, but possible
	During chemotherapy treatment periods of haematopoietic suppression make the pregnant woman more vulnerable for complications of infections, anaemia and bleeding. Delivery should be avoided in these periods. These complications should be treated promptly
	Multiple (co-)medications are prescribed, consider optimal dose and fetal safety
Delivery	Timing
	Aim for delivery after 37 weeks (exception: deterioration of maternal or fetal condition)
	Keep a 3-week interval between the last chemotherapy cycle and delivery
	Mode:
	Preferably vaginal delivery (exception: cervical or vulvar cancer)
	Placenta:
	Should be examined for metastatic disease
Postpartum	Low molecular weight heparin should be considered
	Advice on breastfeeding should be individualized
	Offer psychological support

We stress the need for large international collaborative studies on the outcome of the mother and children after cancer during pregnancy, to be able to control the outcomes for confounding factors, like prematurity and stage of disease at diagnosis. Ongoing studies on this subject are performed by, e.g. the International Network on Cancer, Infertility and Pregnancy (INCIP) and the German Breast Group (GBG).

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Psychological and Psychosocial Care of a Pregnant Woman with Cancer

7

Angela Ives, Toni Musiello, and Christobel Saunders

Introduction

A pregnant woman attends your clinic and tests have confirmed a diagnosis of cancer. Your role today is to break this news to her. How you interact (verbally and non-verbally) with her over the next few minutes and coming weeks will have a lasting impact on her adjustment to cancer and motherhood. As a clinician, you want to do your utmost to ensure this woman has the best chance of long-term survival, but this has to be balanced against the viability and safe delivery of the child/foetus. Your views on the woman's immediate treatment may differ from that of her and her family. The information you provide about the best treatment for her cancer and care for her unborn child needs to be conveyed in an unbiased and supportive manner, so that she can make an informed decision that is right for her and her family.

In this chapter, we describe some of the psychological and social issues for younger women diagnosed with cancer. In particular, we highlight the issues raised by women who have experienced a cancer diagnosis during pregnancy. The information provided is to assist you to communicate effectively with your patient and raise your awareness of the impact that your interaction and behaviour can have on these women. Given that breast cancer is the most common malignancy associated with pregnancy, much of the information presented is based on the experiences of women diagnosed with breast cancer whilst pregnant. Whilst treatment between cancers will differ, the psychosocial issues can be similar. However, where evidence from other malignancies exists, it will be highlighted.

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Common Issues for Younger Women Diagnosed with Cancer

All women diagnosed with cancer will have some psychological and social issues. For many these will resolve naturally, but some women may experience long-term distress. A woman's psychological response to her diagnosis and treatment changes over time as she reaches disease-free milestones or if her disease recurs [1, 2]. With women of all ages diagnosed with cancer surviving longer, these psychological highs and lows are accentuated in younger women, who may have greater amounts of anxiety and stress and a much longer potential lifespan [2, 3]. This can potentially lead to sustained psychosocial problems for women who are diagnosed with cancer when aged less than 50 years, who are single, live alone, have poor social support, have a pre-existing mental health condition and/or have children aged less than 21 years [4]. We also know that younger women diagnosed with cancer are psychologically more vulnerable than older women diagnosed with cancer [5]. Those diagnosed with cancer when pregnant are no exception. Briefly below we discuss the common issues reported for younger women diagnosed with cancer.

Younger women diagnosed with cancer will experience greater levels of stress and anxiety than their older counterparts [4–6]. Unique issues and stressors for younger women include the untimeliness of the disease and feelings of uncertainty about the future, the impact of the disease on their self-esteem and relationship/future relationship with a partner, sex and body image, fertility, the risk of treatment-related permanent or temporary early menopause and managing the practical realities of diagnosis and treatment of cancer alongside caring for young children, continuing a career and financial burdens [2, 7–9]. Practical issues can cause additional stress and concerns for younger women diagnosed with cancer. Looking after a household, particularly when you have young children, is challenging for a woman who is also coping with cancer treatment [4, 10]. The stress will be increased if the woman is socially isolated. For example, women living long distances from family and friends, or who have a limited social support network, may experience greater stress and more difficulties in adjusting to their illness and treatment.

Women diagnosed with cancer who have children report they fear not seeing their children grow up and will miss out on being around when their children have families of their own [10]. They also worry about how their partner will cope with the children and the additional caregiving responsibilities and maternal duties if they are not around. Women may also be fearful that they may pass on their cancer genes to their children [11]. These fears may be accentuated when women are diagnosed with, and treated for, cancer during pregnancy.

There are many avenues of psychological and practical support for women diagnosed with cancer. Specialist cancer nurses, however, are reported to be the best initial source of support for women diagnosed with breast cancer, and these specialist cancer nurses are becoming more common for other cancers (e.g. gynaecological and colorectal); therefore, this invaluable support should become more widespread [4]. A woman diagnosed with cancer during pregnancy is likely to need more psychological and social support than other women dealing with a diagnosis of cancer, but there is little research in this area [12, 13].

Issues Specific to Women Diagnosed with Cancer During Pregnancy

> …How could life be so cruel…here am I expecting my beautiful, beautiful baby. It should have been like the most exciting, the happiest time of my life how cruel that I couldn't enjoy it. And even though I would look at this beautiful baby…I'm thinking I should be so happy and yet the joy – there was something – there was like a grey cloud over all the joy…

One of the most important things that you can say to a woman newly diagnosed with cancer during pregnancy is 'you are not alone'. The overwhelming feeling these women report is that they felt they were the only woman who had experienced pregnancy and a diagnosis of cancer concurrently [12, 14]. As a result, these women felt incredibly isolated, which negatively impacted on their emotional well-being and their cancer and pregnancy experiences. These feelings of isolation can be reduced during your consultations by reassuring woman that other women have been through a similar experience. Additionally, effective communication between the oncology and obstetric health professionals is vital to support and reassure these women. A multidisciplinary approach to care should be provided, linking women with other health professionals such as a specialist cancer nurse, social worker or psychologist to ensure that they and their family are well supported during this difficult time [12, 15, 16].

Motherhood is an important influence on what women diagnosed with cancer during pregnancy decide about their cancer treatment. The stage of motherhood (no children, pregnant, with children) that a woman is at when diagnosed with cancer in turn influences any feelings of isolation they experience, the support and information they require, the decisions they make and their perception of how people judge them [12]. Whilst these issues are not unique to women diagnosed with cancer during pregnancy, they are more relevant to these women as they balance protecting their unborn child and ensuring optimal treatment for their own health and well-being. These issues and, in particular, how they influence decision-making at the time of diagnosis are discussed below, with particular reference to women who have been diagnosed with breast cancer.

Motherhood

Women diagnosed with cancer during or just after completing a pregnancy are forced to deal with two conflicting life events simultaneously. Thus, a woman who is pregnant will need to make decisions that affect both her and her unborn child's morbidity and mortality. A decision to protect the health of her unborn child at the expense of her own health after a diagnosis of cancer or vice versa is not taken lightly [7, 17]. Every one of us is different and these women are no exception. Therefore, the decisions a woman makes at this time will be unique to her and will be based not only on the information provided to her about treatment options, but on her life experiences, beliefs, values and needs. The views women have on

motherhood, including their desire for (more) children, play a major role in the decisions they make about their cancer treatment. Women who have children and/or want to have children in the future make decisions based on their children's needs and/ or their maternal needs [14].

Women who feel their family is complete are more likely to choose the best treatment possible to improve their chances of survival. This decision is in part based on the fear of not seeing their children grow up; this is a well-documented stressor for women diagnosed with cancer [4, 9, 10, 18].

Women who are pregnant and believe their family is incomplete are often prepared to delay or forego optimum cancer treatment and risk their own lives, so that their unborn child is protected from the effects of treatment, or so they could conceive again in the future. Other women may choose to terminate their pregnancy for their own health, particularly if they already have children or because they fear that their child will grow up without a mother. Some women who believe at the time of their diagnosis that they want to protect their fertility may reassess their lives and relationships after cancer treatment and decide they are not prepared to have a child in such circumstances [14].

The cancer treatments chosen by the mother may have a psychological impact on her relationship with her child. This is not only the case when a woman is diagnosed with cancer when she is pregnant but also for women who are diagnosed when they have young babies. For example, a woman diagnosed with cancer who undergoes surgery may find it difficult to lift or carry her baby in the short term, and recovery from the operation and these physical limitations may impact on mother-child bonding. In addition, a woman cannot breastfeed whilst she is receiving chemotherapy or radiotherapy for breast cancer, and if this was her chosen method of feeding, this disruption can negatively impact on her emotional well-being [4].

If chemotherapy commences or continues after the birth of the child, women report feeling robbed of bonding with their child at that time [14]. However, later they saw this as positive and felt their child grew up to be easy going and independent. Mothers of primary school children at the time of their diagnosis identified few long-term psychological effects in their children. However, some mothers of older children were concerned that their children suffered psychological consequences as they understood more about the diagnosis and therefore worried about their mother. Previous studies have highlighted the importance of family-centred support as a useful service for women diagnosed with cancer who have school-aged children [19].

Isolation

> They were all so caring…Everybody used to pop their heads in… It was beautiful. But it wasn't that we were a celebrity for the good reasons. It was because they had all heard of my situation.

Young women diagnosed with cancer often feel 'different' [20]. When a woman is diagnosed whilst she is pregnant, this feeling of being 'different' is exacerbated.

Dealing with two conflicting events concurrently causes enormous stress, to the woman and her family. Many issues arise for these women, including a fear of not being able to cope with the demands of motherhood and cancer treatment; the implications of others taking on the maternal role when they are unable to do so during treatment; having to bottle-feed, particularly if they have previously breastfed or if their maternity unit has a breastfeeding policy; and perceived pitying responses from others in their community. These factors compound the feelings of isolation these women experience [12, 14].

Whilst it can be stressful for those caring for a woman diagnosed with cancer whilst pregnant, it is important that health professionals think about the woman's psychological and social needs as well as her physical care. Thought and discussion needs to be given to which hospital (maternity or general) ward or room a woman is admitted. Being aware that a woman may be particularly vulnerable to other peoples' reactions to her situation is important. For example, other patients and health professionals may want to show their support for these women at such a difficult time, but their kindness can be misconstrued, and the woman may feel like she is on show or an 'unusual specimen' to be observed [12, 14].

The woman may fear that she will not be able to cope at home with a new baby and cancer treatment; therefore, linking her to appropriate emotional and practical supports is essential. Not all families have the support of an extended family or a network of friends, so working collaboratively across disciplines and offering links to services or information which can make life easier are vital for these women. Husbands or partners who have to or want to take time off work to support their partner are often financially disadvantaged with limited government support, particularly if they are self-employed. Private health cover does not cover all associated medical costs, and the support needed by new mothers undergoing treatment for cancer and caring for a newborn may be practical in nature. For example, help with cleaning, washing, ironing and cooking. Such services can be costly and are not always readily available, but specialist cancer nurses, midwives, social workers and psychologists are well placed to ensure that appropriate emotional, financial and physical support are available and provided when necessary [12, 14]. Such support helps women bond effectively with their new baby and reduces their feelings of isolation [21, 22].

Support and Information

> They were all like sixty and seventy year old people. There was one other lady there that had a couple of young kids. But she was the only one there. Yeh, everybody was. They were all older. I didn't really find anywhere that was really for younger people….I didn't really find it helpful because all they wanted to do was look at the baby.

Young women diagnosed with cancer will all want access to differing levels of information and support relating to their cancer, contraception, fertility and/or pregnancy at different times during their cancer journey. Many young women report that

they found it difficult at times to access the relevant information and support that they needed [9, 10, 23]. This is possibly because cancer diagnosed during or prior to pregnancy is uncommon, and information and support needs to be provided on a case-by-case basis.

The women often report that their treating clinician is not necessarily the best source of information or support [9]. This in part is due to a lack of time and knowledge of services and limited information available for this group of women. Gestational cancers are uncommon, and the clinician often does not have experience of treating pregnant women diagnosed with cancer. Whilst the primary focus of the oncology clinicians is the cancer treatment and cure, the woman and her family may feel that other issues such as future fertility and contraceptive are important to them, and it is essential that the women's views are listened to, discussed and acknowledged [2, 10]. Women who have access to specialist cancer nurses see these health professionals as the best primary source of support and information. Whilst they do not always have the information to hand, they are perceived as empathic and play a central role in the woman's care and support [4, 15].

Women diagnosed with cancer during pregnancy have emphasised the importance of peer support from other women who have been through a similar experience but are some way down the survival pathway. This is not in itself unusual as young women want hope that they will get through the experience, but it is an issue that can easily be overlooked by those around them [9]. For women diagnosed with cancer during pregnancy, the task of finding someone with similar experiences is even more difficult because the event is uncommon and the willingness of women who have been through such experiences to support others may decline over time as they do not want to be reminded of when they were ill [12].

Due to the limited number of women who are diagnosed with cancer when pregnant, there is often a lack of information or support locally. Often women need to access relevant resources from international groups such as the Young Survival Coalition (YSC) website (www.youngsurvival.org), aimed specifically at young women diagnosed with breast cancer. Other young adult cancer websites may also be able to provide additional information for pregnant women diagnosed with other cancers. In addition, Hope for Two, the pregnant with cancer network (http://www.hopefortwo.org/), has been set up to specifically assist and support women diagnosed with cancer during pregnancy. A telephone or online support network such as those provided by YSC and Hope for Two is ideal as women can access these from home at a time convenient to them and with minimal cost.

Support Groups

In general, cancer support groups are not necessarily perceived as a good mechanism for support by younger women [9, 10]. As many cancer types are more commonly diagnosed in older people, the majority of people who attend support groups have different support needs from those women diagnosed with cancer during pregnancy, or women who have young children. Support groups set up specifically for younger women, however, may be beneficial.

Decisions, Respect of Choice and Judgement

> …I don't believe she understood at an emotional level what it meant to have a child. I just mean in relation to me she didn't understand on that level…It got to a point where she said to me…Well you've got two children. You've been lucky enough to have two children. You should be grateful for that and your life is far more important than worrying about what might be. And that was really upsetting and quite devastating…I realised at that point that she really was not listening to what I was saying. I don't mean that she was wrong medically but she hadn't acknowledged that it was a really big concern for me.

The decisions women diagnosed with cancer make about their cancer treatment and pregnancy are difficult. For many women, the ability to keep their options open and have some control over their lives is of great importance to them. Women want their views acknowledged, they want to feel heard, and they want their decisions respected. Unfortunately, this does not always happen, and it can have devastating consequences for the woman and her family. For example, a woman who feels she has not been listened to, respected or heard may refuse to undergo the recommended treatment resulting in neither the woman nor her unborn child surviving.

The psychological impact of medical decisions that can lead to loss of a pregnancy, or fertility leading to menopause, is not well known or fully understood. Currently, there is limited knowledge of the short- and long-term psychological effects for women who undergo termination of a pregnancy due to cancer diagnosis or treatment, particularly if the cancer treatment results in infertility [13]. Research suggests that fertility is important to women of child-bearing age diagnosed with cancer, and the impact of potential fertility loss should not be underestimated in how it impacts the cancer treatment decision-making process [10, 24]. Women who have had at least one child before their diagnosis of cancer may have a different perspective on this to women who are childless but want children [13]. Importantly, already having children does not imply that women do not want more children. Women may therefore need emotional support to work through issues surrounding a potential loss of fertility. In addition, women dealing with an enforced loss of a pregnancy or fertility will often worry about what effect such a loss could have on current or future relationships [2].

A clinician's aim is to treat their patient to the best of their ability and without doing harm. It is important, however, that a holistic approach to care be taken which includes consideration of the woman's values and concerns, even if these do not mesh with conventional/optimal treatment, or the perspective of the clinician. It is important that health professionals give women all the information they can in a rational and balanced way so that the woman is supported to make an informed decision that is right for her. Quite often if the woman and her family feel that they are listened to and reassured, they will undergo the optimal treatment. For some cancers with extremely poor outcomes particularly when diagnosed in early pregnancy, or cancers diagnosed at an advanced stage, then optimal treatment can include the termination of the pregnancy and palliative care [25]. Whatever choice

a woman makes, it is important that health professionals support the woman and her family in their decisions even if they do not agree with them. This will reduce the chance of a woman disengaging with health professionals which could potentially lead to poor outcomes for the woman and her child.

Conclusions

Overall the main aim in supporting women who have been diagnosed with cancer whilst pregnant should be to provide holistic, individualised, supportive care. This will assist women and their families with decision-making throughout the pregnancy and cancer journey. To support these women, it is important that health professionals remember to:

- Listen, respect and acknowledge the woman's views even if they differ from your own
- Utilise a multidisciplinary and multiagency approach to care
- Link individuals to services and information that assist with both emotional and practical support
- Offer support to women that will reduce isolation, yet does not make the woman feel unique or different
- Provide open communication and collaboration with the woman, her family and the obstetrics and oncological teams to ensure the best possible outcome for both the woman and her baby

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Supportive Care During Pregnancy

8

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The definition of supportive care treatment is the use of agents to counteract the side effects of cancer treatment. It is well known that the most common adverse events of chemotherapy are nausea, vomiting, and hematologic toxicities. An oncologist may prescribe a variety of supportive medications in order to overcome the adverse events of chemotherapy; this is quite challenging and not well established as the main concern is the effect of the drugs on the developing fetus and long-term complications after in utero exposure. The most commonly used agents as supportive care in patients receiving chemotherapy are antiemetics, dexamethasone, bisphosphonates, granulocyte colony-stimulating factor, erythropoietin, antibiotics, etc. Unfortunately, there are limited data regarding supportive treatment in pregnant women receiving chemotherapy. Table 8.1 summarizes the categories of drugs for use during pregnancy, while Table 8.2 summarizes the safety of the most commonly used agents during pregnancy and lactation.

5-HT3 Antagonists

This category of agents is often used in conjunction with glucocorticoid steroids such as dexamethasone for the treatment of acute emesis occurring in the first 24 h after chemotherapy administration. There are three major classes of the chemical structures of the first-generation 5-HT3 receptor antagonists: (I) carbazole derivatives (ondansetron), (II) indazoles (granisetron), and (III) indoles (dolasetron) [1].

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Table 8.1 Categories of drugs for use in pregnancy

FDA pregnancy category	Recommendation
Category A	Controlled studies do not demonstrate a risk to the fetus
Category B	Animal studies have shown adverse effect but human studies show no risk
Category C	Animal studies have shown an adverse effect on the fetus and there are no controlled studies in humans
Category D	There is positive evidence of human fetal risk from investigational studies
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience. The drug is contraindicated

Palonosetron is a highly selective second-generation 5-HT3 receptor antagonist that has two stereogenic centers and may exist as four stereoisomers. Palonosetron has a longer half-life (40 h) and greater receptor binding affinity versus first-generation 5-HT3RAs [1]. Some studies advocate for intravenously administered 5-HT3 antagonists; others argue for oral administration. The concomitant use of aprepitant, an NK1 receptor antagonist, significantly increases the efficacy of the 5-HT3 antagonist in acute or delayed chemotherapy-induced nausea and vomiting.

Nausea and vomiting are really often symptoms during pregnancy; hence, there are a lot of data published in the literature regarding administration of antiemetics during pregnancy. On the other hand, there are no data regarding chemotherapy-induced vomiting during pregnancy; however, we normally extrapolate the data for pregnant women receiving chemotherapy from pregnant women not receiving chemotherapy.

As far as antiemetics is concerned, Einarson et al. [2] reported that there was no increased risk for a major malformation after exposure to ondansetron comparing with other antiemetics among 176 pregnant women. In line with the aforementioned findings, Anderka et al. [3], using data from the National Birth Defects Prevention Study, reported that there is no increased risk with the use of 5-HT3 antagonists as antiemetics. Of note, metoclopramide is considered the first choice of treatment for nausea and/or vomiting and is also recommended during lactation, whereas ondansetron is more effective in controlling vomiting and may safely be used during pregnancy (Table 8.2).

Corticosteroids During Pregnancy

Corticosteroids are used during pregnancy as supportive treatment mainly for controlling vomiting and nausea. However, systematic, inhaled, and topical use of corticosteroids is frequently used as a treatment of a plethora of diseases. According to the study of Janssen et al. [4], there are two categories of corticosteroids: those that are needed to treat fetal conditions (i.e., immature lungs) such as dexamethasone and betamethasone because they are less metabolized by the placenta and greater doses are available to the fetus and those that are needed to treat maternal conditions

Table 8.2 Safety of the most commonly used agents during pregnancy and lactation

Agent	Trimester			Lactation	Category (FDA)
	First	Second	Third		
Antiemetic					
Granisetron	Y	Y	Y	Y	B
Ondansetron	Y	Y	Y	Y	B
Tropisetron	N	N	N	Y	C
Scopolamine	Y	Y	Y	Y	C
Metoclopramide	Y	Y	Y	Y	B
Antidiarrheal					
Loperamide (Imodium)	Y	Y	Y	Y	B
Antibiotics					
Tetracycline	N	N	N	N	D
Phenicols					
Broad-spectrum penicillin	Y	Y	Y	Y	B
Beta-lactamase-sensitive penicillins	Y	Y	Y	Y	B
Beta-lactamase-resistant penicillins	Y	Y	Y	Y	B
Beta-lactamase inhibitor (Tazobactam)	Y	Y	Y	Y	B
Cephalosporins	Y	Y	Y	Y	B
Carbapenems (imipeneme/meropeneme)	Y	Y	Y	Y	B/C
Trimethoprim	N	Y	Y	Y	C
Sulfonamides	Y/N	Y	Y	Y	
Macrolides					
Azithromycin	Y	Y	Y	Y	B
Clarithromycin	N	N	N	Y	C
Erythromycin	Y	Y	Y	Y	B
Josamycin	Y/N	Y/N	Y/N	Y	B
Roxithromycin	Y/N	Y/N	Y/N	Y/N	C
Spiramycin	Y	Y	Y	Y	B
Lincosamides (clindamycin/lincomycin)	Y	Y	Y	Y	B
Streptomycin	N	N	N	Y	D
Fluoroquinolone	N	N	N	N	C
Amphotericin B	Y/N	Y/N	Y/N	Y/N	B
Corticosteroids					
Betamethasone	Y/N	Y/N	Y/N	Y	B
Dexamethasone	Y/N	Y/N	Y/N	Y	B
Hydrocortisone	Y/N	Y/N	Y/N	Y	B
Methylprednisolone	Y/N	Y/N	Y/N	Y	B
Prednisolone	Y	Y	Y	Y	B
Prednisone	Y	Y	Y	Y	B
G-CSF (filgrastim)	Y	Y	Y	Y	B
Epoetin	Y	Y	Y	Y	B

Y yes, *N* no, *Y/N* could be used if highly indicated

such as prednisone which is metabolized by the placenta and only a small percentage of the maternal dose can cross human placenta.

As far as the complications of the use of corticosteroids on the fetus is concerned, there are case reports of women treated with prednisone without any evidence of embryopathy [5, 6]. The increased incidence of low birth weight reported in fetuses exposed to corticosteroids may be linked with the underlying maternal conditions for which the agents were given. Several studies have mentioned a slightly increased risk of oral clefts using systematic corticosteroids but cohort studies have not [7, 8]. Regarding the complications of the use of corticosteroids on pregnant woman, there are the pregnancy-specific complications such as premature rupture of the membranes, exacerbation of gestational diabetes, and hypertension and the nonspecific complications that may occur in nonpregnant patients (such as immunosuppression, avascular necrosis of bone, osteopenia, hypertension, hyperglycemia, etc.) [4]. Hence, it seems that corticosteroids may be given relatively safe during pregnancy (Table 8.2).

During lactation, the breast milk of women taking prednisone can contain small amount of these drugs; however, according to the American Academy of Pediatrics, women who take high doses of glucocorticoids are encouraged to breastfeed. They should wait 4 h after ingesting a dose to resume breastfeeding; this is a strategy that decreases the amount of glucocorticoid in the milk [9].

Granulocyte Colony-Stimulating Factor

The granulocyte colony-stimulating factor (G-CSF) is commonly used in cancer patients receiving myelosuppressive chemotherapy associated with febrile neutropenia in order to decrease the incidence of infection. Although filgrastim has a very high molecular weight, it has the possibility to cross the human placenta at least in the second and third trimester [10]. Medlock et al. [11] reported that maternally administered rhG-CSF crosses the placenta of rats and specifically induces bone marrow and spleen myelopoiesis in the fetus and neonate. The significant myelopoietic effects of rhG-CSF at low concentrations in the fetus suggest an exquisite degree of developmental sensitivity to this cytokine and may provide enhanced defense mechanisms to the neonate [12]. Moreover, it seems that maternal administration of rhG-CSF increases neonatal defenses against a lethal bacterial challenge.

However, data on human beings are limited. According to Calhoun et al. [13], rhG-CSF administration to women before preterm delivery does not appear to have any significant immediate adverse effects on either the mother or the neonate; moreover, it could increase fetal neutrophil production and improve neonatal outcome. In line with the above, Cardonick et al. [14] reported that there is no significant difference in gestational age at birth, congenital abnormalities, birth weight, incidence of long-term medical issues, mean WBC, or neutropenia at birth between the newborns exposed to G-CSF added to chemotherapy and newborns exposed to chemotherapy alone before the delivery.

Concerning breastfeeding, there is no data available. Filgrastim may be excreted in breast milk, but there is no risk to a nursing infant, as filgrastim is a glycoprotein and probably is digested in his stomach [15].

Erythropoietin

Erythropoietin is a glycoprotein hormone that is produced by the interstitial fibroblasts of the kidney and stimulates red blood cell production (erythropoiesis). Recombinant human erythropoietin is often used to treat anemia caused by chemotherapy and by chronic renal failure. Unfortunately, there are no data concerning the treatment of chemotherapy-induced anemia with recombinant human erythropoietin in cancer pregnant patients. However, there are some data concerning the use of recombinant human erythropoietin in women with renal failure [16, 17]. More specifically, it has been reported that the recombinant human erythropoietin does not cross the placental barrier according to data on pregnant women with renal failure; hence, it seems to be safe for the fetus and the mother [18, 19]. However, more data on pregnant women with cancer diagnosis are more than warranted in order to draw definitive conclusions.

Antibiotics

It is widely known that there is an increased risk of infection in patients receiving chemotherapy. This is mainly due to neutropenia caused by the toxic effect of chemotherapy on the bone marrow. This complication adds complexity to treatment especially if the patient is a pregnant woman. Antibiotics, such as penicillins (beta-lactamase-sensitive and beta-lactamase-resistant penicillins, beta-lactamase inhibitor), cephalosporins, carbapenems, and the most of macrolides (azithromycin, erythromycin, and spiramycin), are approved by FDA as category B, and their use is recommended during pregnancy. Table 8.2 summarizes the safety of the most commonly used antibiotics [20].

Bisphosphonates During Pregnancy

Bone metastases, commonly seen in many solid tumors, may cause major morbidity including fractures, severe pain, hypercalcemia, and nerve compression [20]. It is widely known that bone-targeted agents, i.e., bisphosphonates, have changed the natural history of patients suffering from bone metastases. The bisphosphonates are analogues of pyrophosphate, and their structure allows them to bind to the bone matrix and promote the skeletal retention [20]. Hence, it is obvious that treatment with bisphosphonates represents a cornerstone in the supportive therapy of cancer patients [21]; however, their data on pregnant women are limited.

Bisphosphonates cross the placenta, and animal studies, done mostly at doses much higher than those commonly used in humans, have shown adverse effects on both the fetus and the mother (protected parturition, maternal mortality, embryolethality, several general underdevelopment, and marked skeletal retardation of the fetuses) [22]. However, human reports regarding women exposed to bisphosphonates before conception or during pregnancy did not demonstrate complications except for low neonatal birth weight and transient hypercalcemia [23].

In line with the above, in a recently published review on 78 pregnant women exposed to bisphosphonates before conception or during pregnancy, no serious secondary effects were noted in the vast majority of mothers and infants [22]; hence, it seems that in cases of absolute or relative indications of bisphosphonates prior to pregnancy, close observation of the mother and the infant, especially during the first 2 weeks of life, is mandatory. Furthermore, no increased risk of major birth defects from intrauterine exposure to bisphosphonates was recorded in a multicenter prospective study including 21 women who used bisphosphonates during or within 12 months before pregnancy [24]. In this study, the indications of bisphosphonate administration were primary osteoporosis, osteoporosis associated with cancer, and osteoporosis secondary to corticosteroid use.

However, given that bisphosphonates remain in mineralized bone for several years and that data on pregnant patients are limited, it should be clearly stated that bisphosphonates should be used on personalized basis and with caution; if used, hypocalcaemia affecting the contractility of the uterus should be avoided.

Conclusion

In conclusion, it seems that physicians should pay special attention apart from the treatment per se to supportive therapy given to prevent or treat adverse events correlated with chemotherapy administration. The optimal supportive treatment of pregnant women with cancer diagnosis is not well established; the main concern is the effect of the agents on the developing fetus and long-term implications in offspring born after in utero exposure. A multidisciplinary approach involving medical oncologists, high-risk obstetric care, pharmacists, and neonatologists is mandatory for the successful management of women with cancer during pregnancy.

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Neonatal and Long-Term Consequences of In Utero Exposure to Systemic Anticancer Therapy

9

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Introduction

Many physicians remain reluctant to use drugs during pregnancy. It is very challenging to demonstrate the safety of drugs during pregnancy, because it can take many years to prove an association between the drug and potential adverse effects for the child that may arise on the short or long term. The absence of an association is even more difficult to prove, because it requires a long-term study in a large group of patients. Cancer during pregnancy is a rare but increasing phenomenon due to delay of childbearing age, with an estimated incidence of 1 out of 1000–2000 pregnancies. Definitive evidence on the safety of cytotoxic treatment during pregnancy will require long-term follow-up with a thorough assessment of the children.

When a pregnant woman has been diagnosed with cancer and treatment is indicated, two lives need to be considered. Although the maternal benefit may outweigh the potential fetal risks in this life-threatening situation, the primordial concerns on the potential teratogenic risks for the fetus caused by chemotherapeutic agents remain. Chemotherapy is cytotoxic and interferes with cell growth. The consequences for the fetus may depend on the timing of exposure during pregnancy and the chemotherapeutic agents, the number of cycles and the dose. When cell damage occurs during the third or fourth week of gestation at the moment that conception and cell division take place, this will result in an all-or-nothing phenomenon: either a miscarriage or a

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normal developing embryo. During week 5 until 10 of pregnancy, when cell growth takes place and organs are formed, damage will result in structural anomalies. Therefore, chemotherapy administration during the first trimester of pregnancy is contraindicated. Vital organs including the heart and the central nervous system deserve our special attention. The heart is formed between the fourth and the tenth week of gestation, while the central nervous system starts to develop in the fifth week of pregnancy and its development continues throughout pregnancy and even after birth. The third trimester of pregnancy is characterized by fetal growth. Therefore, even when chemotherapy is administered during the second or third trimester of pregnancy, the potential impact on fetal development needs to be well considered.

In the following paragraphs, we review current knowledge on fetal, neonatal, and long-term outcome of children prenatally exposed to chemotherapy.

Intrauterine Growth Restriction and Postnatal Growth

Several studies have investigated the effect of in utero exposure to chemotherapy on fetal growth and weight. While some studies found normal birth weight and height according to gestational age [1–3], others reported an increased incidence of intrauterine growth restriction (IUGR). IUGR is generally defined as a birth weight below the 10th percentile of gender- and age-matched controls. In the study of Amant et al., 21 % of the children prenatally exposed to chemotherapy ($N=70$) were born with IUGR [4]. Cardonick and Iacobucci found incidences of IUGR ranging from 7 to 17 %, depending on cancer disease and treatment [5]. IUGR places an infant at significant risk of perinatal morbidity and mortality and may have fetal, maternal, or placental causes. Several factors may be related to this increased risk. Placental causes, resulting in a mismatch between nutritional or respiratory demands and supply, and maternal factors including medical conditions with impact on the uteroplacental blood flow are the most frequent and present factors in pregnancies complicated by cancer and/or cancer treatment.

Although lower birth weights may be present in chemotherapy-exposed children, this growth restriction is in most cases caught up in the first months of childhood. Amant et al. found normal values for weight, height, and head circumference in 70 chemotherapy-exposed children aged 16.8 months to 17.6 years [4].

Neonatal Outcome (Table 9.1)

Congenital Malformations

In the first trimester of pregnancy, chemotherapy induces an elevated risk of congenital malformations, ranging from 7.5 to 25 %, compared to 4.1 % in general population. On the contrary, Aviles et al. reported on the outcome of 54 children born after chemotherapy exposure during the first trimester of pregnancy. Clinical examination at birth revealed no congenital malformations [6]. Although they concluded that chemotherapy may also be given during the first trimester, no reasons for this low risk of

Table 9.1 Neonatal outcome of children in utero exposed to chemotherapy

First author	Sample	Malignancy	Main results
Van Calsteren [7]	*N* = 185 (cancer in pregnancy) of which *N* = 62 (exposed to chemotherapy)	Diverse	Mean gestational age (GA) (*N* = 185), 36.3 weeks ± 2.9 weeks Prematurity in 54.2 % (of *N* = 185) of cases with an increase of 12.9 % (of *N* = 62) for children prenatally exposed to chemotherapy 24.2 % (of *N* = 62) were born small for GA 51.2 % (of *N* = 185) were admitted to a neonatal intensive care unit, mainly because of prematurity 2.9 % major and 4.6 % minor congenital malformations were reported, comparable to the general population
Abdel-Hady [2]	Study: *N* = 61 Controls: *N* = 60 matched for GA	Diverse	Incidence of neonatal survival, preterm birth, and small for gestational age was not significantly different between study and control group. No congenital malformations were reported
Avilés [6]	*N* = 54	Hematological malignancies	No congenital malformations after first trimester chemotherapy exposure
Murthy [8]	*N* = 81	Breast cancer	35.6 % of the children were born preterm after prenatal exposure to fluorouracil, Adriamycin, and cyclophosphamide
Cardonick [9]	Study: *N* = 35 exposed to chemotherapy Controls: *N* = 22 nonexposed	Diverse	51.4 % of the children prenatally exposed to chemotherapy were born preterm, compared to 38.1 % of the control children. The difference was not statistically significant

N sample size, *GA* gestational age, *Med* median, *IUGR* intrauterine growth restriction

chemotherapy exposure during the most vulnerable period of life were specified. However, information that allows to estimate the teratogenic risks is lacking, for instance, the developmental stage at exposure, the dose, the duration, and the frequency of drug administration. As described in our introduction, the outcome may depend on the timing of exposure during the first trimester. The use of chemotherapy during the first trimester remains potentially dangerous, and therefore caution remains primordial. Chemotherapy given beyond the first trimester has been considered safe, with no increased risk of congenital malformations as reported in different retrospective studies (3 % major malformations, 7.5 % minor) [7].

Preterm Labor and Premature Birth

An increased incidence of preterm labor and prematurity was reported. Van Calsteren et al. observed an incidence of preterm labor of 12.9 %, compared to 4 % in the general population. This was mainly due to induction of labor and elective cesarean section to start (part of) treatment after delivery (76.7 %). The incidence of preterm premature rupture of the membranes (PPROM) was not increased (4.8 % compared to 3 %) [7]. In the study of Amant et al., 67.1 % of 70 children prenatally exposed to chemotherapy was born preterm, compared to a normal ratio of 4 % [4]. Murthy et al. and Cardonick et al. also found an increased preterm birth rate of 35.6 % in 81 children prenatally exposed to fluorouracil, Adriamycin, and cyclophosphamide (FAC) for breast cancer and in 51.4 % of 35 children prenatally exposed to chemotherapy, respectively [8, 9]. Till today no clear pathophysiologic pathway of cancer disease and treatment leading to preterm labor is known. Because chemotherapeutic agents may cause an increase of preterm contractions, a dedicated follow-up is indicated.

Hematologic Toxicity

A common side effect of chemotherapeutic agents is myelosuppression. When given during pregnancy, suppressed hematopoiesis may not only occur in the mother, but also in the unborn fetus. Hoopmann et al. described a case of maternal acute myelocytic leukemia (AML) for which she received one cycle of induction chemotherapy with cytarabine, thioguanine, and daunorubicin at 20w6d GA. At 25w4d GA, the fetal anemia was diagnosed and an intrauterine transfusion was performed [10]. Cardonick et al. discussed the use of chemotherapy during pregnancy and described the use of cytarabine and thioguanine in literature, with an increased risk of fetal malformations, fetal cytopenia, intrauterine death, neonatal infections, and mortality [5]. Therefore, these agents should be avoided during pregnancy. Other agents (e.g., anthracyclines, alkylating agents, taxanes, platinum-based agents, etc.) are nowadays more investigated and administered for cancer in young (pregnant) women and can be considered safe when given in the second and third trimester of pregnancy.

When delivery takes place in the first 2 weeks after chemotherapy administration, neonatal hematopoiesis may be suppressed [5, 7]. A 3-week interval between administration of chemotherapy and delivery is recommended to avoid a delivery at the nadir, which is related to increased maternal and fetal hemorrhage and infections. As the hepatic and renal clearance in the newborn are still immature, especially in preterm newborns, the 3-week interval allows the fetus to clear the drugs via the placenta [5].

General Health (Table 9.2)

Poorer health outcomes have been described in premature born children, with a gradient effect correlated to a decreasing gestational age. Not only the general health status (chronic medical, neurological, or mental health conditions) but also

Table 9.2 General health, neurocognitive development, and behavior problems of children in utero exposed to chemotherapy

First author	Sample	Malignancy	Duration of follow-up	Measures	Main results
Avilés [1]	*N* = 84 *N* = 12 second-generation children	Hematological malignancies	*Med* = 18.7 years (range, 6–29)	General health and neurological, psychological, and educational outcome	No congenital, psychological, or neurological abnormalities Normal weight and height at birth Educational and learning performance were normal No observations of secondary malignancies during follow-up period
Hahn [11]	*N* = 40	Breast cancer	Range 2–157 months	Parent or guardian report on general health and development	No registration of stillbirths, miscarriages, or perinatal deaths after exposure in second or third trimester Congenital anomalies were reported in two children: club foot and congenital bilateral ureteral reflux. All children had normal development, except for one child with Down syndrome Special educational needs for one child with attention deficit disorder and for the child with Down syndrome
Amant [4]	*N* = 70	Diverse	*Med* = 22.3 months (range, 16.8–211)	Mental development, intelligence, attention, and memory assessment. Behavior and general health questionnaires	Median gestational age (GA), 35.7 weeks (range, 28.3–41.0) Normal incidence of central nervous system, heart, and hearing problems. General health and growth curves were normal Overall neurocognitive results were within normal ranges. However, a severe cognitive delay was observed in a twin A positive correlation was found between gestational age and cognitive outcome

(continued)

Table 9.2 (continued)

First author	Sample	Malignancy	Duration of follow-up	Measures	Main results
Murthy [8]	*N*=50	Breast cancer	*Med*=7 years (range, 1–21)	Parent or guardian report on general health	All children were in good health An increased incidence of allergy and/or eczema was reported (36 %)
Cardonick [9]	Study: *N*=35 exposed to chemotherapy Controls: *N*=22 nonexposed	Diverse	*M*=4.5 years	Cognitive, school performance, and behavioral assessment	No significant differences were found for cognitive outcome, school performance, and behavioral problems between the chemotherapy-exposed and the unexposed group Older children had higher rates of internalizing problems than younger children. Behavior problems could not be predicted by maternal survival, mother's health status at time of evaluation, or child sex For the exposed group, prematurity was associated with lower cognitive outcome

N sample size, *GA* gestational age, *M* mean, *Med* median

the parental reception of ill health is higher in very preterm children (born < 32 weeks GA). Considering children exposed to chemotherapy in utero, questions arise on the general health status and the risks of a diminished general health. Hahn et al. and Murthy et al. reported on the results of a parent or guardian survey of 40 and 50 children in utero exposed to chemotherapy, respectively [8, 11]. All parents and guardians indicated that their child was in good health. In the study of Murthy et al., allergies and/or eczema were more commonly found in the study group (36 %) than in the general population (11–25 %) [8]. Amant et al. investigated general health in 70 children prenatally exposed to chemotherapy by a pediatric examination and a general health questionnaire. The incidence and type of medical problems were comparable to the general population [4]. Considering these results, prematurity seems to induce more general health problems than the use of chemotherapy during pregnancy.

Neurocognitive Development and School Performance (Table 9.2)

Studies in adult cancer patients who have received chemotherapy have described an array of potentially long-lasting disturbances in cognitive functions such as attention, concentration, memory, language, reaction time, information processing, judgment, and planning, referred to as the "chemo brain." Similarly, survivors of childhood acute lymphoblastic leukemia have been reported to exhibit variations in cognitive functions such as information processing speed, verbal, performance and total intelligence, attention, and verbal and visual memory. Imaging studies, such as a recent MRI study on a series of breast cancer survivors, have revealed an association between changes in cognitive functioning and changes in cerebral white matter integrity, indicating an anatomical substrate for chemotherapy-induced cognitive dysfunction [12, 13]. The pathophysiological basis for the relationship between chemotherapy and changes in brain functions, however, is largely unknown. Chemotherapy-induced excess of cytokines in the brain is thought to play a role; excess of TNF-α has been postulated to lead to oxidative stress and mitochondrial dysfunction, leading to impaired working memory.

As the development of the central nervous system continues throughout pregnancy and even after birth, there is a possible impact of prenatal exposure to chemotherapy on neurocognitive functioning that has to be investigated. Aviles and Neri reported on the normal neurological and psychological examinations of 84 children aged 6–29 years born to mothers treated with chemotherapy during pregnancy for hematological malignancies [1]. According to school informants, learning and academic performances were normal. Hahn et al. reported on the data of 40 children, aged between 2 months and 13 years, exposed to fluorouracil-Adriamycin-cyclophosphamide (FAC) chemotherapy for maternal breast cancer [11]. Except for one child with Down syndrome and one child with attention deficit disorder, all children were thought to develop normally, according to a parent

or guardian survey. In 2012, Amant et al. published the first prospective multicenter evaluation of children with antenatal exposure to cancer treatment [4]. Seventy children aged 1.5–18 years (median 22 months) were tested at predefined time intervals using standardized age-appropriate assessment. Mental development, intelligence, attention, and memory results were compared to the norms of the respective tests and were considered normal. However, both children of a twin pregnancy were found to have a severe cognitive delay. Moreover, an increased incidence of disharmonic intelligence profiles was noticed (39 % compared to 15 % in general population). Results on the mental development and intelligence tests were found to be lower in preterm-born children and to be positively correlated to the gestational age at birth. Recently, Cardonick et al. compared 35 chemotherapy-exposed children to a control group of 22 nonexposed children born to mothers with cancer during pregnancy [9]. Assessment of mental development, intelligence, and school performance was executed at a mean age of 4.5 years for the study group and 4.9 years for the control group (range 18 months to 10.4 years for the whole group of 57 children). One child in the chemotherapy-exposed group and two children in the nonexposed group had cognitive results below the normal range. There was no statistical significant difference in the number of abnormal results on cognitive development between the two groups. No differences in school performance were found between the study and control group. On the tests of academic achievement, 75 % of the chemotherapy-exposed group and 67 % of the nonexposed group had normal results for mathematics, while 75 % of the study group and 83 % of the control group scored in the normal range for reading abilities.

Behavior Problems (Table 9.2)

Amant et al. reported on the results of 21 children aged 5.0–15.9 years prenatally exposed to chemotherapy, assessed with the Child Behavior Checklist (CBCL), a questionnaire to be filled in by the parents measuring behavior problems [4]. An increased score for internalizing, externalizing, or total problem behaviors ($z > 1$) was found in 29 % of cases. Cardonick et al. found no differences in internalizing, externalizing, or total problem behaviors on the CBCL between a group of 35 chemotherapy-exposed children and a group of 22 nonexposed children from mothers with cancer during pregnancy [9]. Behavior problems could not be predicted by maternal survival, mother's health status at time of evaluation, child sex, or child age at evaluation. Scores in the clinical range were found for 23 % of the study group and 18 % of the control group. Although the scores between the two groups were not significantly different, it is not clear whether these scores are elevated compared to the general population and, if so, are related to prenatal or postnatal stress due to maternal cancer disease and treatment. Increased maternal stress hormone levels may cross the

placenta and thereby increase fetal stress hormone levels, causing hypothalamic-pituitary-adrenal axis regulation and thereby increasing the incidence of behavior problems later in life.

Alterations in Brain Morphology and Functioning

The (minor) differences in neurocognitive functioning described above are preliminary indications that antenatal exposure to cancer treatment may cause subtle frontal lobe dysfunctions, responsible for attention and behavior that either appear or persist on the long term. This raises the hypothesis that there could be structural or functional differences in the brain such as microstructural differences in the white matter or differences in brain connectivity between different regions. A neural substrate for cognitive impairment after prenatal exposure to chemotherapy is so far not available.

However, recent studies in adults and children with cancer have shown that chemotherapeutic drugs can have an impact on cognitive functioning and brain regions responsible for attention, memory, and executive functions. Advanced neuroimaging techniques have detected structural and functional changes in the brain after cytotoxic treatment. Schuitema et al. studied the long-term effects of chemotherapy 25 years after treatment for pediatric lymphoid malignancies [14]. Compared to controls, they found a decreased fractional anisotropy (FA), a measure reflecting the degree of organization of the white matter (WM), which correlated with the observed neuropsychological dysfunction. Deprez et al. studied the WM integrity before and after treatment of women with breast cancer [13]. They found a decreased FA in frontal, parietal, and occipital regions. Moreover, a correlation could be found between the mean regional FA changes and the performance changes in attention and verbal memory. Supposed some chemotherapeutic agents pass the placenta (in part) and reach the fetus, this raises the assumption that similar effects could arise in the child.

Furthermore, there is a possible influence of the indirect effects of maternal cancer on the fetal neural development. As mentioned above, (late) preterm delivery is common in cancer in pregnancy cases, and prematurity has been shown to be related to cognitive impairment. The brain damage underlying these effects is thoroughly studied using magnetic resonance imaging. Although most studies report on the effects of very preterm birth (<33 weeks of gestation), Degnan et al. found that prefrontal connectivity in late preterm-born children (gestational age of 34–36 weeks) is altered [15].

In addition, children in utero exposed to high maternal anxiety are known to have increased risk of impaired cognitive development, mainly due to the impact of maternal stress hormones. It has been confirmed in imaging studies that antenatal stress can cause changes in brain microstructure. Buss et al. found an association between high pregnancy anxiety at 19 weeks gestation and decreased gray matter

(GM) density in school-aged children [16]. Also changes in WM microstructure, more specific in the limbic prefrontal region which underlies child social behavior, have been related to prenatal stress [17].

Cardiac Functions (Table 9.3)

Anthracyclines are commonly used in combination with other agents in the treatment of breast and hematological cancers. The relationship with acute and chronic cardiotoxicity in children and adults has been repeatedly demonstrated [18]. However, several factors influence the risk of cardiotoxicity: the cumulative dose (>250 mg/m^2), gender, age, association with radiotherapy, stem cell transplantation, or a combination with other cardiotoxic chemotherapeutic agents (Herceptin, cyclophosphamide, amsacrine). Children as well as adults may develop cardiac toxicities; however, this seems to appear after longer time intervals and to have a different pattern of development. Despite low transplacental passage of anthracyclines, adverse cardiac fetal outcomes have been described. Cardiomyopathy has been reported after idarubicin exposure,

Table 9.3 Cardiac functioning of children in utero exposed to chemotherapy

First author	Sample	Malignancy	Duration of follow-up	Measures	Main results
Avilés [20]	*N* = 81	Diverse	*M* = 17.1 years (range, 9.3–29.5)	Echocardiogram	Normal echocardiogram and fractional shortenings
Gziri [22]	Study: *N* = 10 fetuses Controls: *N* = 10 fetuses matched for gender and age	Diverse		Biometry, amniotic fluid index, fetal two-dimensional echocardiography	Normal fetal Doppler flow parameters but mild changes in the myocardial performance index and in the tricuspid inflow pattern were found
Amant [4]	*N* = 70	Diverse	*Med* = 22.3 months (range, 16.8–211)	Electro- and echocardiography	Lower but clinically normal values were reported for ejection fraction, fractional shortening (FS), and interventricular septum thickness

N sample size, *M* mean, *Med* median, *IUGR* intrauterine growth restriction, *FS* fractional shortening, *TDI* tissue Doppler imaging, *LV* left ventricle

a highly liposoluble anthracycline derivate [19]. Aviles et al. were the first to report on cardiac outcome after prenatal exposure to anthracyclines in 81 children aged 9.3–29.5 years [20]. Echocardiogram and fractional shortenings were normal for all children. Besides these limited data and different monitoring strategies, suggestions have been presented how to monitor cardiotoxicity in children and perform research on preventive measures [21]. A first pilot study to evaluate maternal and fetal cardiac functions by two-dimensional (2D) echocardiography, reporting on ten pregnant women and their fetuses compared to controls, showed no significant effect of maternal anthracycline exposure on both maternal and fetal cardiac functions during the acute phase [22]. Amant et al. reported on the results of a European multicenter long-term prospective follow-up of cardiovascular outcome of 65 children prenatally exposed to chemotherapy [4]. Global heart function was compared to controls and appeared to be normal. However, small differences in the ejection fraction (EF), fractional shortening (FS), and some of the diastolic parameters (isovolumic relaxation time (IVRT), mitral A-duration) were noticed. A long-term follow-up is necessary, given these small differences as well as the knowledge that anthracycline cardiotoxicity may only become apparent after many years. The assessment of global strain analysis and tissue Doppler imaging as early parameters of cardiotoxicity may also improve our knowledge on anthracycline-induced cardiac dysfunctions that may arise on the long term.

Hearing Loss

Ototoxicity, especially hearing loss, has been reported in children and adults with cancer treated with platinum-based antineoplastics (e.g., cisplatin, carboplatin). This ototoxicity is dose dependent and irreversible. Amant et al. reported on auditory functioning of 21 children with a median age of 6.5 years (range 5.0–17.4) [4]. Eighteen of these children had a normal hearing function, of which three were prenatally exposed to cisplatin. One child in utero exposed to cisplatin was diagnosed with hearing loss in the high regions. However, a perforated eardrum was observed on a computed tomography scan, possibly a consequence of middle ear infections, which may be a confounding factor. A twin in utero exposed to idarubicin and arabinoside cytosine was found to have minor hearing loss at the right side in the low regions. In these cases, neurodevelopmental problems may confound the results. Geijteman et al. also reported a single case of prenatal cisplatin exposure (5 cycles of 70mg/m^2) with severe bilateral perceptive hearing loss [23]. Given the observation that platin derivatives cross the placenta in a substantial percentage and given the anecdotal hearing loss, cisplatin should only be administered after careful consideration.

Secondary Malignancies

Second malignant neoplasms have been associated with certain types of chemotherapeutic agents administered to adults and children with cancer. Mostly these malignancies are myeloid neoplasms. Leukemia has been reported to occur after the administration of platin-based chemotherapeutic agents, topoisomerase II

inhibitors, and antimetabolites. The risk to develop secondary solid tumors is more limited, but has been reported. Side-specific risks have been reported for sarcoma and cancer of the lung, stomach, intestines, bladder, and thyroid after the administration of alkylating agents. Sasshi et al. reported on the occurrence of secondary malignancies after treatment for indolent Hodgkin lymphoma in a 16-year follow-up study. Thirty-nine of 563 patients developed a secondary malignancy, concluding on a cumulative incidence of cancer at 12 years of 10.5 % [24]. The risk of developing secondary malignancies in children prenatally exposed to chemotherapy still needs further investigation at long-term follow-up. One case has been reported by Reynoso et al. of a twin pregnancy exposed to cyclophosphamide in utero. The boy, also born with anomalies, developed thyroid cancer and a neuroblastoma at, respectively, 11 and 14 years of age. His twin sister had no abnormalities and did not develop any tumors [25]. Two long-term follow-up studies published up till now have reported on 70 and 84 children with a maximum follow-up duration of 18 and 29 years of age, respectively. In these cases, no secondary malignancies were found [1, 4].

Fertility

Chemotherapy induces infertility in young women with cancer. The type and dose of chemotherapy and the age of the patient are the most important prognostic factors. However, little is known about the impact of prenatal exposure to chemotherapy on fertility. Aviles and Neri reported on 12 second-generation children of 84 adults prenatally exposed to chemotherapy for hematological malignancies [1]. Although this may be an indication of normal fertility for these few patients, nothing is known about the nature of conception (spontaneous conception or assisted reproduction).

Conclusion

Chemotherapy is more commonly used during pregnancy for maternal cancer treatment. The available evidence is still based on small numbers and a short follow-up period. However, in general, results on neonatal outcome, postnatal growth, general health, neurocognitive development, and cardiac functions are comparable to the general population. Intrauterine growth may be affected and needs close monitoring. Term delivery is important in order to avoid long-term consequences. Insufficient data are available to draw conclusions for each type of chemotherapy. In particular, cisplatin in high dosage should be avoided given the concerns on ototoxicity. More children and a longer follow-up are necessary in order to have more solid data. In particular, more children are needed to investigate outcomes for each cytotoxic drug or combination of drugs. Such a studies are currently ongoing in the framework of the International Network on Cancer, Infertility and Pregnancy (INCIP) (www.cancerinpregnancy.org), the Pregnant with Cancer Network (United States, www.pregnantwithcancer.org), and the Motherisk Program (Canada, www.motherisk.org) that aim for a thorough follow-up of these children.

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Part II

Disease-Specific Chapters

Managing Breast Cancer During Pregnancy

10

Sibylle Loibl and Bianca Lederer

Introduction

Breast cancer during pregnancy (BCP) accounts for approximately 2 % of primary breast cancer patients. The term pregnancy-associated breast cancer (PABC) refers to all cancers diagnosed during pregnancy and up to 1 year after delivery. This article will focus on breast cancer diagnosed and treated during pregnancy because treatment might need adaptation. An increase in breast cancer incidence and a rise in maternal age in the past decades have led to more cases of breast cancer diagnosed during pregnancy. This upward trend in the occurrence of BCP in recent years has prompted an increased awareness for management strategies of this rare and delicate disease. While BCP has shown to generally present in more advanced stages compared to breast cancer in non-pregnant women, all available evidence suggests that it has a similar prognosis provided that standard treatment is administered. In 2006, the first recommendations for diagnosis and treatment of BCP were published [1] with the consensus that treatment during pregnancy should adhere as closely as possible to the general recommendations for young non-pregnant women. With recent advances in breast cancer therapy, including the use of carboplatin, dose-dense chemotherapy, trastuzumab, neoadjuvant therapy and sentinel lymph node biopsy as sole treatment, options for breast cancer patients have increased. Therefore, a panel of experts has recently reviewed latest treatment strategies and adaptations for BCP and published a consensus paper on BCP management recommendations [2]. In general, all management strategies need to weigh maternal treatment efficacy against foetal safety. The main aspects will be highlighted in this chapter.

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Management Strategies in Breast Cancer During Pregnancy

Diagnosis: Imaging - Pathology - BRCA Testing

Routine examination of the breast is not part of the general examinations for pregnant women in contrast to the Pap smear for early detection of cervical cancer. There are no typical signs or symptoms for BCP, and tumours will not be screen detected, because general screening is not indicated in this age group. Signs and symptoms should not be neglected, and a lump should be biopsied for histology if it is not disappearing within 4 weeks to avoid unnecessary delays in the right diagnosis and treatment, even if 80 % of breast biopsies performed in pregnant women will prove to be benign. A 1-month delay in diagnosis can increase the risk of nodal involvement by 0.9–1.8 %. Core biopsy is the standard procedure to obtain tissue, whereas fine needle biopsy or aspiration cytology is not recommended. For any woman with a confirmed or particularly suspicious malignant lesion in the breast, bilateral mammography is recommended. However, especially during pregnancy, many patients and physicians are concerned about radiation safety. A prospective study on exposure during a standard bilateral mammogram, however, has shown that radiation doses to all organs other than the breast are extremely low (less than 3 mGy) and that the dose to the uterus or foetus, especially in the early phase of pregnancy, is minimal [3]. Although many factors, like gestational age, anatomic site, modality and technique, can influence maternal and foetal radiation exposure and dose, breast ultrasound and mammography can generally be considered safe during pregnancy. In general, imaging and staging procedures should only be conducted in advanced stages, i.e. where they might alter the treatment, and, like in non-pregnant breast cancer patients, unnecessary or less accurate procedures should be avoided.

The diagnosis of BCP based on histopathologic evaluation of core biopsies from suspicious lesions is considered the gold standard. In this context, it is crucial that the pathologist is informed about the pregnancy of the patient when examining the tumour. Generally, the histological features of tumours from BCP patients are not different from those in young non-pregnant women with breast cancer. The vast majority are ductal invasive, mainly hormone-receptor negative and undifferentiated [4]. Moreover, tumour mutations do not differ between pregnant and non-pregnant young women. Small series on biological features at the genomic level showed significant differences in gene expression. In particular, tumours diagnosed during pregnancy showed higher expression of the IGF1 (insulin-like growth factor 1) gene and an activation of the GPCR (G protein-coupled receptor) and the serotonin receptor pathway. Moreover during pregnancy, the PD1 (programmed cell death 1)-PDL-1 (programmed cell death ligand 1) interaction is activated to allow foetomaternal tolerance. A high expression of PD1 during pregnancy is an appealing topic due to the recent efficacy data on anti-PD1 and anti-PDL-1 inhibitors [5]. However, no definite conclusions for general practice can be drawn from these analyses. The selection of appropriate control cohorts, matched by treatment and/or histology, as well as by age, will be required in future research in this challenging field.

At diagnosis, assessment of the family history of the patient is important, and genetic counselling should be provided according to national guidelines. Based on personal and family history, germline *BRCA* testing can be offered to patients who are likely to have an inherited mutation. The results of the germline *BRCA* determination will be of treatment relevance. The majority of patients with BCP have triple-negative breast cancer (TNBC), and it has been shown that in young TNBC patients under the age of 40, the probability of detecting a germline *BRCA* mutation is around 40 % [6].

Local Treatment: Surgery - SLNB - Radiotherapy

In terms of surgery, patients with BCP should be treated with the same approach as non-pregnant patients. Mastectomy used to be the standard treatment for patients developing BCP. However, nowadays, the pregnancy alone is no indication for mastectomy because of the resulting delay of the radiotherapy. Breast conservation has been shown to be an option, and, especially when performed in the second or third trimester, it is possible to delay subsequent radiotherapy until after delivery. In this case, chemotherapy would generally be given during pregnancy followed by radiotherapy after delivery. For patients requiring or opting for a mastectomy, immediate breast reconstruction is an essential component in the patient management and particularly important for patients diagnosed at a young age. Tissue expander insertion has been discussed for women diagnosed with BCP as it ensures a short operation time and does not seem to be associated with considerable morbidity to the patient or the foetus [7]. However, it needs to be well considered if this is the ideal time point to start breast reconstruction.

According to ASCO guidelines 2014, patients with BCP should not undergo sentinel lymph node biopsy (SLNB) based on cohort studies and/or informal consensus. However, it has been shown that this procedure can be safely performed during pregnancy [8]. Radioactivity doses injected loco-regionally during SLNB are relatively low and show a rapid clearance as well as substantial and stable uptake at the injection site, which is shortly thereafter removed by surgery. In optimised protocols for radiopharmaceuticals and the amounts of activity typically used for SLNB, the doses absorbed by the foetus are mostly below 20 μGy for 10–20 MBq (about 1 μGy/MBq) [9]. Also, for the BCP patient herself SLNB appears to be safe having shown a low recurrence rate [10]. Therefore, pregnant breast cancer patients should be offered SLNB rather than axillary clearance whenever it is indicated according to general practice in non-pregnant patients. In terms of recommended protocols, an advised option to minimise radiation exposure is to inject colloid in the morning (1-day protocol). Using blue dye as a sole procedure is not recommended outside pregnancy. Due to a low (1 %) but potentially harmful underlying risk of an anaphylactic maternal reaction, this method should not be used in BCP, although a small series of 25 women receiving SLNB during pregnancy did not show any SLNB-associated complications for the seven women who received blue dye for mapping [11].

Radiation therapy (RT) during pregnancy is not generally recommended since the available information on long-term consequences of in utero exposure is limited. Generally, it is therefore recommended to delay RT until after delivery whenever possible.

Gestational age plays an important role in the consequences that RT may have during pregnancy. The radiation dose received by the foetus is dependent on the distance between the RT field and the position of the foetus, which is dependent on gestational age but also on the amount of leakage of irradiation outside the radiation field. The use of effective shielding can reduce the dose to the foetus by up to 75 %. RT administered during BCP with low foetal doses has been reported for several cases to result in the delivery of healthy babies [12]. Therefore, in case it is absolutely indicated, RT can be considered in the first or early second trimester, if the risk of postponing or omitting RT for the mother might outweigh the harm to the foetus.

Systemic Therapy: Chemotherapy - Endocrine Therapy - Targeted Therapy - Special Considerations

Systemic treatments such as chemotherapy, hormonal therapy, and targeted therapies are key in modern breast cancer treatment regimen, but due to their harmful side effects, administration in pregnancy needs to be considered carefully.

Chemotherapy is contraindicated during the first trimester of pregnancy due to a higher risk of inducing foetal malformations as well as abortions. A recent report shows that the prevalence of malformations following chemotherapy in the first trimester is 14 %, but decreases to 3 % if given later in pregnancy [13], which is comparable to rates reported for the general population in the USA (3 %) and data from a German registry (6.7 %). Completely postponing chemotherapy treatment in pregnant patients until after delivery might seem to be an option. However, in non-pregnant young women, postponing of chemotherapy has been shown to be associated with an increased risk of relapse. Therefore, it is recommended to treat women with BCP during the second and third trimester following guidelines for non-pregnant young patients as closely as possible [1]. Other anticancer agents used as systemic treatment, such as trastuzumab, tamoxifen and endocrine agents, should in general be avoided during pregnancy, given their potential foetal toxicity [1]. The standard adjuvant or neoadjuvant combination of anthracyclines, cyclophosphamide and taxanes for non-pregnant patients is also recommended for the treatment of BCP after the first trimester [14]. Epirubicin/cyclophosphamide (EC) followed by weekly paclitaxel (EC-Pw) or the reverse sequence, starting with a taxane, can be used during pregnancy. Regimen that are not standard or no longer indicated for breast cancer therapy in non-pregnant women, such as anthracycline- or taxane-free regimen or 5-fluorouracil, should be avoided in pregnant as well as in non-pregnant patients. Platinum derivatives may have a role in the treatment of triple-negative tumours of breast cancer patients. The addition of carboplatin in neoadjuvant trials has led to significantly higher pathological complete response rates in two phase II

prospectively randomised trials, but data are still immature for survival analyses [15, 16]. Carboplatin can thus also be considered during the second and third trimesters of pregnancy. Whether or not carboplatin is more effective than cisplatinum remains unclear; however, it may have less overall toxicity and seems therefore the preferred platinum agent during pregnancy.

Dose-dense (same dose administered over a shorter interval) or intensified dose-dense (IDD, higher dose over a shorter interval) chemotherapy regimen have been shown to lead to better survival compared with conventionally dosed chemotherapy regimen, especially in high-risk patients [17]. While dose-dense chemotherapy (e.g. EC every 2 instead of every 3 weeks) seems to be an acceptable option during pregnancy, there are no systematic studies and only a small number of reports on IDD chemotherapy [18]. Due to a high rate of grade 2–4 anaemia (59 %), with a need for transfusion in 20 % of patients, and a high risk of febrile neutropenia (7 % despite primary G-CSF prophylaxis) [17], the administration of IDD chemotherapy in BCP patients demands for a very strict risk/benefit analysis. Therefore, to date, IDD cannot generally be recommended in BCP.

In addition to the choice of therapy for BCP patients, there are some special considerations based on the physiological aspects during pregnancy. The variations in drug pharmacokinetics during pregnancy raise important concerns regarding optimal drug dosing in pregnant patients. Thus, physiologic alterations associated with pregnancy may result in lower maximal concentrations of chemotherapy and a lower area under the concentration-time curve. Since most anticancer agents are empirically prescribed according to body surface area (BSA), a large inter-patient variability for dosage exists, even outside the pregnancy setting. Another aspect of changed pharmacokinetics in pregnancy is the increased activity of major enzymes involved in the metabolism of taxanes and anthracyclines (including cytochrome p450 isoforms such as CYP3A4 or CYP2C8) during the late trimesters of pregnancy, which may result in decreased drug exposure. Additionally, albumin concentrations vary significantly during pregnancy, and, since taxanes are highly protein bound, this may lead to significant changes in taxane pharmacokinetics [19].

A comparison of pregnant versus non-pregnant patients in terms of pharmacokinetics of anthracyclines and taxanes showed that taxane serum levels significantly decreased during pregnancy, especially for paclitaxel, whereas the exposure to anthracyclines was not significantly modified by pregnancy in a very limited number of investigated patients [19]. Whether or not doses should be increased in pregnancy remains uncertain, given that such increases could result in severe toxicities, with potentially serious consequences for both mother and child. In overweight women, who also have altered pharmacokinetics, the dose is not increased. Furthermore, it was shown that the chemotherapy is as active in pregnant as in non-pregnant women [20]. Women who were treated with neoadjuvant chemotherapy for breast cancer during pregnancy achieved the same pathological complete response rate as non-pregnant women treated with neoadjuvant chemotherapy and women with BCP receiving neoadjuvant therapy after delivery. Thus, dosing based on BSA, using the current patient weight (prior to every course), should be the standard, as well as using the same dose for pregnant as non-pregnant women.

While maternal drug exposure is necessary to achieve optimal treatment efficacy, the transplacental transfer of active agents is a concern in terms of foetal safety. In addition to its functions in protecting the foetus and preparing the women for pregnancy and lactation, the placenta is also the central organ for foetal-maternal exchange. Transplacental transfer of drugs can be studied using the perfused human ex vivo placenta; however, toxic effects of cancer therapy on the human placenta are poorly understood. Data are limited, mainly because most animal models are devoid of central common features with the human placenta and even closely related species such as rhesus monkeys show diverging invasion patterns.

A preclinical study on transplacental transfer rates indicates similar and reassuring data on different anthracyclines and taxanes, although with marked inter-patient variability, particularly with docetaxel [21]. Consequently, paclitaxel might be preferred to docetaxel in the pregnancy setting regarding foetal safety. Carboplatin was also analysed and demonstrated significant transplacental transfer but long-term data remain limited [13].

Giving chemotherapy during pregnancy has been associated with a significantly higher incidence of small-for-gestational-age babies [4]. A potentially toxic influence on placental development leading to placental malfunction, e.g. via incomplete trophoblast invasion into the uterus, has been suggested, which could result in a decreased supply of nutrients for the foetus [4]. The start of chemotherapy is often considered after week 10 of gestation, since organogenesis is completed around that time. However, trophoblast invasion of the placenta is not completed until around week 20. Therefore, even starting chemotherapy at week 14 might interfere with late stages of placental development (Fig. 10.1), which is highly hypothetical and remains to be proven. Chemotherapy should not be started before the end of the first trimester and should be stopped around the 36th week of gestation to allow for a 2-week chemo-free interval prior to delivery and to allow for a term delivery (>37 weeks). Children exposed to chemotherapy in utero seem to have no adverse outcome when compared to age-matched children, on the short and the long run. However, close monitoring of the pregnancy, as well as an exact determination of the gestational age prior to start of the therapy, is indicated.

Anti-HER2 Treatment

Treatment with targeted agents such as trastuzumab has become an essential part of primary treatment in breast cancer patients with HER2+ tumours. An early introduction of trastuzumab and combined rather than sequential administration of cytotoxic agents has been associated with a better survival in non-pregnant patients. During pregnancy, it is generally recommended to avoid trastuzumab, since several case reports have demonstrated development of oligo-anhydramnios and reported foetal deaths [22]. However, inadvertent foetal exposure of 1–2 cycles of trastuzumab is no reason for termination of pregnancy [23]. In special high-risk situations, trastuzumab during pregnancy might even be considered, though not without carefully weighing foetal and maternal risks and benefits during an informed

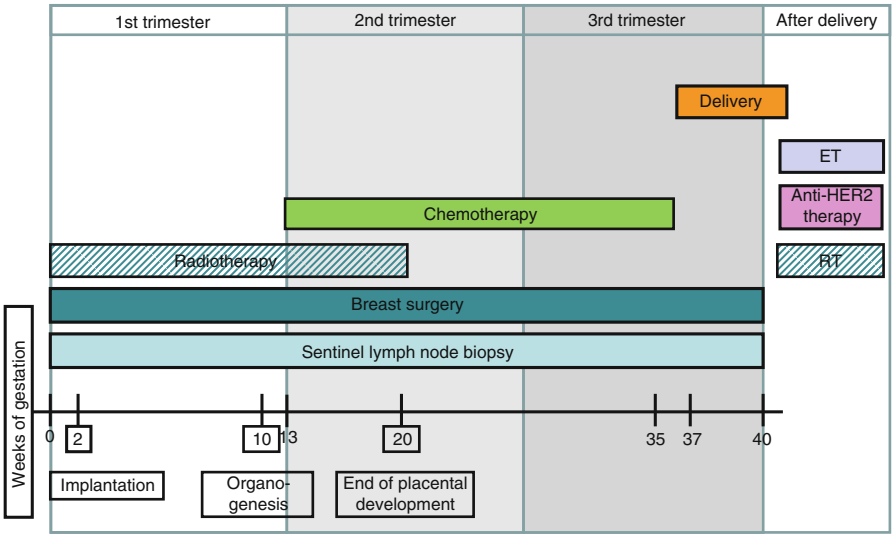

Fig. 10.1 Therapeutic options during pregnancy. Crucial phases: implantation (0–2w), organogenesis (2–10w) and foetal phase (>10w). Starting chemotherapy from week 13–14 instead of week 10 allows a 'safety period'. If radiotherapy is indicated and decided (against preferred option) to not postpone until after delivery, it can be applied during the first and until early second trimester. Endocrine therapy and anti-HER2 treatment should be delayed until after delivery. *RT* radiotherapy, *ET* endocrine therapy

decision-making process. The double HER2 blockade with pertuzumab in addition to trastuzumab and chemotherapy has shown to increase pathological complete response rate in patients with HER2+ breast cancer, but data on the use of pertuzumab during pregnancy are currently lacking. Therefore, although the dual blockade with trastuzumab and pertuzumab is recommended as neoadjuvant treatment in breast cancer, this does not seem to be an option in women with BCP.

Obstetrical/Perinatal Care

A further major concern in prenatal care of pregnant women treated with cancer therapy is preterm delivery and subsequent development of the children.

Antenatal chemotherapy exposure has been associated with an increased risk of preterm rupture of membranes (3 % vs. 0 %) and preterm labour (6 % vs. 2 %) [4]. Recent studies have reported a mean gestational age at delivery of 36–37 weeks, indicating that a significant proportion of patients deliver (iatrogenically) preterm. A long-term study of children exposed to chemotherapy in utero showed no impairment of cognitive, cardiac or general development of the children [24]. However, prematurity was correlated with worse cognitive outcome, independent of cancer treatment. Therefore, prematurity should be avoided whenever possible, and treatment during pregnancy may help to achieve a full-term pregnancy. The complex

medical situation of BCP renders a primordial multidisciplinary discussion. A close collaboration of the obstetrician and perinatologist and frequent (at least once in 3 weeks) in addition to standard prenatal care are warranted. Moreover, a 2–3-week interval between last chemotherapy and delivery is recommended in order to allow the bone marrow to recover and prevent haematologic toxicity to the mother and child.

Conclusion

The management strategies in breast cancer during pregnancy should follow the general guidelines for young non-pregnant patients as closely as possible. Breast cancer during pregnancy is not per se a reason for abortion, but it is important to discuss and treat this complex medical situation within a multidisciplinary team. A careful risk/benefit analysis is crucial to avoid both over- and undertreatment in order to minimise foetal toxicity and not compromise on maternal treatment efficacy. Delivery should be as close as possible to term to reduce the risk for developmental shortfalls.

To improve treatment strategies for breast cancer during pregnancy, large prospective cohort studies are needed. Long-standing international collaborations have already provided the basis of current knowledge on management strategies of BCP and will continue to do so. Patients can be registered online through the German Breast Group (www.gbg.de).

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Managing Melanoma During Pregnancy

11

Stergios Boussios and George Pentheroudakis

Introduction

Malignant melanoma is on the second place in terms of the incidence among the population between 20 and 39 years of age. Although the disease is more frequent in men, its incidence during the reproductive period is higher among women. The impact of pregnancy to the course of melanoma does not appear to be related to the patients' survival.

In this chapter, data are reviewed, and key aspects of the immunohistochemical expression of hormone receptors, use of SLNB, therapeutic management, and transplacental metastasis are presented.

The treatment of melanoma in pregnant women is similar to that in the general population, and the therapy is based upon stage. Surgical excision remains the only effective treatment. With modern surgical and anesthesia techniques, the maternal death rate is negligible and surgery during the first trimester does not appear to increase the incidence of major birth defects. When indicated, an SLNB can be performed. Interferon alpha 2b (IFNα2b) has been implemented safely in pregnancy in terms of treatment of hepatitis, myeloproliferative disorders, and multiple myeloma. The toxicity of high-dose regimen, indicated for the treatment of metastatic disease, was not estimated throughout the course of pregnancy. The knowledge concerning the use of dacarbazine in pregnant women is sparse, based on isolated clinical cases or small series, and in the majority of cases, dacarbazine was administered as part of poly-chemotherapy. The recent development of novel agents has revolutionized the field of melanoma treatment, but given the lack of experience

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on treating women during pregnancy, treatment should be avoided and postponed until postpartum when possible.

Melanoma is the most common malignancy to metastasize to the placenta. Very rarely, fetal metastasis is seen. Following delivery, the placenta should be examined both grossly and histologically for signs of metastatic melanoma including appropriate immunohistochemical staining.

Hormonal Regulation of Melanoma

The consideration of dismal prognosis for maternal melanoma in the 1970s and 1980s was based on the aggressive phenotype of this hormonally stimulated malignancy in women with high levels of hormones, which is the case in pregnancy.

Increased systemic estrogen levels have been related to hyperpigmentation and nevus enlargement found during pregnancy. Estrogen receptor-β (ERβ) protein is frequently expressed in melanoma. Immunohistochemical and real-time polymerase chain reaction analyses showed that expression of ERβ is reversely proportional to Breslow's thickness. Progesterone has been shown to inhibit the proliferation of human melanocytes and has been either detected in the cytoplasm and nucleus of melanocytes by immunohistochemistry.

Hormone replacement therapy does not seem to be a risk factor for melanoma. The use of oral contraceptives does also not affect the incidence of the disease. High-dose hormones, such as in the case of protocols for in vitro fertilization or intrauterine insemination, have not yet been evaluated in this context.

Sentinel Lymph Node Procedure and Pregnancy

The approach for the treatment of melanoma begins with the identification of a suspicious lesion followed by biopsy and should not be deferred due to the pregnancy. The currently known factors determining outcome are mostly the Breslow thickness, ulceration status, dermal mitotic rate, and deep and peripheral margins [1]. Invasive lesions with Breslow's thickness ≤1.0 mm are overall associated with a favorable prognosis [1], and wide surgical excision is the treatment of choice even during pregnancy. If the primary cutaneous melanoma has Breslow's depth greater than 1.0 mm and there are no clinically palpable lymph nodes, an SLNB should be considered [2].

In general, this is a staging process of melanoma, developed to identify patients with subclinical nodal involvement who could be candidates for complete lymph node dissection and adjuvant therapy. Overall, it is a minimally invasive, low-morbidity procedure performed with the use of blue dye and radiolabeled colloids. Nevertheless, some studies conclude that the use of blue dye can be avoided if SLNB is imaged on lymphoscintigraphy due to the possibility of anaphylactic allergic reactions [2]. Apart from the primary arguments, SLNB appears feasible in pregnant women, exposing the fetus under the 50 mGy threshold and hence to minimum risk. Most of the data concerning SLNB and pregnancy is retrieved by patients with breast cancer. In terms of the experience in this population, the procedure

appears to be safe and accurate using either methylene blue or technetium 99-Tc. Gropper et al. reported recently that in pregnant women with breast cancer who underwent SLNB, 25 infants were born alive, of whom only 1 had cleft palate in the maternal risk factors [3]. Nevertheless, given the anatomical distance, the radioactive exposure of the fetus from the 99-Tc should be lower in patients undergoing axillary SLNB as compared to groin SLNB; this difference should be minimal since all radioactivity is cleared by the kidney and excreted through the bladder. Although safe during pregnancy, there is still controversy in terms of the appropriate timing of the procedure. Interestingly enough, Broer et al. [4] proposed the option of resecting the primary tumor under local anesthesia and postponing the SLNB postpartum in pregnant melanoma patients. On the other hand, Gziri et al. [5] argue against deferring SLNB basing their position on the fetal outcome of 12,000 cases of non-obstetric surgical interventions [6].

Treatment of Melanoma During Pregnancy

The management of melanoma during pregnancy involves careful consideration of the disease stage, treatment options, and fetal risks such as treatment-related teratogenicity, all of which are dependent upon the gestational age of the pregnancy. We will expose below the feasibility of the different therapeutic approaches usually used which include surgery, immunotherapy, chemotherapy, and radiotherapy.

Surgery

Multiple studies have evaluated the risk of general anesthesia for both mother and child during pregnancy. A literature review by Cohen-Kerem et al. [6], with consideration of more than 12,000 patients, evaluated that the complication rates following surgery with general anesthesia during pregnancy resulted in a miscarriage rate of 5.8 %, induction of premature labor in 3.5 %, fetal loss in 2.5 %, prematurity rate of 8.2 %, and major birth defects in 3.9 %. Nevertheless, these adverse events were not statistically higher as compared to the control population; they designate the clear risk of the fetus. Overall, in cases that the delay of surgery would put at a higher risk the mother and the fetus, then the potential risk of general anesthesia does not outweigh the risk of surgical delay.

The primary treatment for melanoma today remains to be wide surgical excision including the full thickness of the skin and subcutaneous fat tissue around the tumor site with 1–3 cm margins, according to the thickness of the primary lesion. Lateral or posterolateral neck dissection and axillary dissection including level III can easily be performed during pregnancy. Although inguinal lymphadenectomy has historically been the standard treatment for metastatic melanoma in the inguinal lymph node basin, multiple studies have reported significant morbidity following the procedure. At that regard, the deep part of the groin dissection could be delayed until after delivery; nevertheless with SLNB techniques, it could be feasible at the time of the primary tumor wide excision. The patients with melanoma at low risk for

nodal involvement (T1b to T2b) can undergo resection of the primary lesion under local anesthesia and delay the SLNB to the postpartum period. If the relevant risk is higher, such as in Breslow's depth greater than 2.0 mm, resection of the primary melanoma can be performed under local anesthesia, and either delaying the SLNB until after the delivery or proceeding to SLNB under local anesthesia is reasonable. Patients with metastatic melanoma identified in their SLNB should undergo completion lymphadenectomy under general anesthesia. If a positive SLNB is detected under local anesthesia during the gestation, postponement of completion lymphadenectomy until postpartum could be an option.

In the select group of patients with isolated single or a limited number of metastases, surgical resection should be strongly considered and performed without deferment as it is safe in pregnant patients. However, there are no studies comparing surgical with conservative treatment of single metastasis. Cryosurgery or laser ablation for small lesions is also an option for the treatment of locoregional metastases. Certain studies demonstrated successful treatment with isolated extremity perfusion by melphalan and tumor necrosis factor-α. However, there is no experience in this procedure during pregnancy. The termination of pregnancy will not alter the maternal prognosis in this cohort of patients.

Adjuvant Therapy

The use of adjuvant IFNα2b in patients with high-risk melanoma is controversial. The results of various studies are conflicting. An updated meta-analysis published by the Cochrane group of a total of 10,499 participants found that adjuvant IFNα2b was associated with a significant improvement in disease-free survival but improved overall survival only in a subset of patients with ulcerated primary melanoma and microscopic SLNB involvement [7]. Nevertheless, there are insufficient data on IFNα2b safety in pregnant patients with melanoma; some reports regarding its use in some other indications are available. Among 41 pregnant patients, IFNα2b was administered to treat 33 diagnosed with chronic myeloid leukemia (CML), 2 with hairy cell leukemia, 4 with melanoma, and 1 patient with Hodgkin lymphoma and multiple myeloma respectively [8]. A total of 43 infants were born, including 2 sets of twins. From the available data, 19 patients commenced treatment during the first trimester and 20 in the second and third trimester. Only 2 patients received the agent as polytherapy. Major malformations attributable to in utero exposure to IFNα2b were observed in only 1 out of the 43 live-born infants (2 %) who was yet exposed to imatinib in the first trimester. As a point of reference, the prevalence of major malformations in the general population of the USA is 3 %. Similarly, Azim et al. [9] described 26 CML patients exposed to IFNα2b during the course of pregnancy without reported congenital abnormalities. Nevertheless, IFNα2b can be safely administered throughout the course of pregnancy; this is a subject of controversy due to the absence of a clear benefit in survival. Careful consideration should be made in each patient in order to balance potential maternal benefits with possible fetal risks. The adjuvant treatment in metastatic setting requires higher doses of IFNα2b which is not evaluated in pregnant patients and such therapy should be implemented postpartum.

Systemic Therapy for Metastatic Disease

The use of chemotherapy in a pregnant woman affected with metastatic melanoma is a much more challenging situation, widely considered as palliative and not associated with increase in overall survival. The use of the alkylating agents fotemustine and dacarbazine in pregnant women has been the subject of only a few publications in the literature. Since the 1960s, 36 cases of administration of dacarbazine to pregnant women have been reported [10]. Congenital abnormalities were observed during the first trimester exposure in two cases. Among the infants exposed in utero to dacarbazine in the second and third trimesters of pregnancy, one fetus died and nearly 50 % were born prematurely. In all these cases, dacarbazine had been applied in association with other cytotoxic agents. However, the follow-up of children exposed in utero to chemotherapy is often too short, and therefore, the risk of secondary malignant disease is likely to be underestimated. In conclusion, the use of dacarbazine in pregnant women is sparse, based on isolated clinical cases or small series, and in the majority of cases, dacarbazine was administered as part of poly-chemotherapy.

Intensive research in metastatic melanoma treatment achieved significant results in the past few years. Several new drugs proved to be more effective than standard dacarbazine therapy, and it is required to properly understand whether these compounds are safe in the subset of pregnant patients without jeopardizing fetal outcome. Approximately 50 % of malignant melanoma carries an activating mutation of the proto-oncogene BRAF. The BRAF inhibitor vemurafenib demonstrated improved progression-free and overall survival over dacarbazine in patients with previously untreated advanced melanoma with BRAF V600E mutation. In terms of safety, vemurafenib has not been associated with teratogenesis in animal studies [11]. In 2013, Maleka et al. [11] described a 37-year-old woman diagnosed with metastatic melanoma and treated with vemurafenib during gestation. The patient had a 3-month progression-free survival, which enabled the delivery of a healthy baby at week 30 with low birth weight but no evidence of metastatic disease. Interestingly enough, the pharmacological study indicated placental transfer of the drug, 10.9 μg/mL in the umbilical cord as compared to 24.3 μg/mL in the mother [11]. Given the lack of experience on treating pregnant patients, this type of therapy should be avoided and postponed until postpartum when possible.

Ipilimumab, a monoclonal antibody which binds to cytotoxic T-lymphocyte-associated antigen (CTLA4), causes autoimmunity which may be expressed through a syndrome, similar to lupus or antiphospholipid syndrome. This may be fatal both for the fetus and the mother. Finally, although the experience is limited in the subset of pregnant patients with CML, a disturbing cluster of rare teratogenic effect has prevented imatinib, a tyrosine-kinase inhibitor, from being recommended safely during the pregnancy.

Radiation Therapy

Nevertheless, the efficacy of radiotherapy is poor in melanoma; the palliation of the relevant symptoms in the setting of recurrent or metastatic disease could be an indication for this approach. Furthermore, for a few brain metastases, patients can be

treated by neurosurgical resection or stereotactic radiosurgery (SRS). In most of cases, brain melanoma metastases are multifocal, and in this context, the correct risk/benefit balance for the use of radiotherapy would be steroid-resistant symptomatic metastasis. Irradiation of brain lesions to high dose during pregnancy may result in fetal exposure < 0.10 Gy, without other harmful effects to the fetus after the fourth week of gestation. Phantom thermoluminescent dosimeter measurements estimate fetal dose with precision for energies < 10 MV and should be adopted for each pregnant patient considered for treatment to confirm and record acceptable dosage. There are two reported cases of radiotherapy during pregnancy for cerebral metastases of melanoma [10]. In the first case, whole-brain radiotherapy (WBRT) was associated with the administration of fotemustine during the second and third trimesters; in the second case, brain gamma knife SRS was performed as a single treatment at 23 weeks of gestation for cerebral metastases. The fetal dose was estimated in the second case to be between 0.02 and 0.04 Gy for a maximum tumor dose of 20 Gy which was below the deterministic threshold value of 0.10 Gy. No morphological abnormalities were observed in the two infants.

There is no clear consensus on the effect that gamma knife treatment for melanoma cerebral metastases may have on the outcome of the newborns and its implementation would not be recommended during gestation. Given that SRS is associated with a higher risk of distant brain failure resulting in a higher likelihood of retreatment during the pregnancy, WBRT alone is presented as the safest and most conservative management. Some reported cases in the literature of healthy neonates following WBRT emphasize the importance of discussing the risk/benefit ratio of therapy with respect to the patients' desires regarding their pregnancies.

In addition, a possible irradiation of some distant regions postoperatively, due to positive margins, could be considered. Sinusal melanoma irradiation was proven useful and it is safe for the fetus. On the other hand, adjuvant radiotherapy after lymphadenectomy demonstrated no benefit and should be avoided during pregnancy.

Transplacental Melanoma Metastasis

Vertical transmission of malignant cells to the placenta or fetus is uncommon. Placentofetal malignant seeding takes place via hematogenous spread and less often via lymphatic spread or contiguous invasion. Melanoma is known as the malignancy with the propensity to metastasize to the products of conception (Fig. 11.1).

A literature review from 1866 to 2002 by Alexander et al. [12] identified 87 cases of placental or fetal metastases with melanoma accounting for 27 cases (31 %). Eighteen out of the 27 patient cases (67 %) resulted in healthy, unaffected infants, nevertheless the median follow-up was only 14.2 months. The involvement of the fetus was identified in 6 of the 27 patients with placental metastases from melanoma (22 %). Five out of the six infants died. The mean age at the time of metastatic presentation was 4.6 months (range, 0–8 months). In terms of the factors indicating unfavorable fetal or infant outcome, male gender seems to be at higher risk for development of metastasis of maternal melanoma and composed 80 % of all infants with

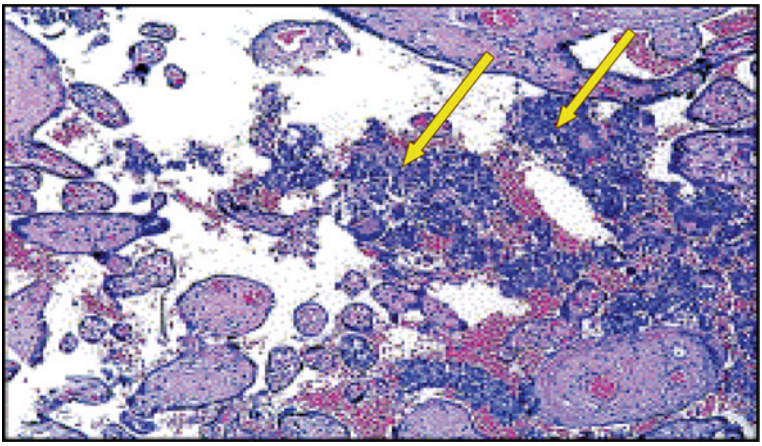

Fig. 11.1 Sections of placenta show multiple aggregates of atypical epithelioid cells in the intervillous space (With permission of Boussios S. from the 20th Congress of the Hellenic Society of Medical Oncology [HeSMO], 2014). The *yellow arrows* indicate areas with atypical epithelioid cells in the intervillous space.

metastasis of melanoma. At that regard, male fetuses are probably more immunotolerant than female. On the other hand, it is unlikely for tumor burden to be a prognostic indicator, taking into consideration that only three placentas of the six patients with fetal melanoma metastasis demonstrated evidence of the disease. In addition, gross placental involvement was identified in six patients without fetal melanoma metastasis. The placenta is a site of production for many growth factors including placental growth factor, hepatocyte growth factor, and vascular endothelial growth factor. It is highly possible that these factors promote adhesion, survival, and invasion of melanoma cells. This relative tendency of melanoma for placental metastasis, growth, and invasion may increase the risk of fetal metastasis. There is no difference in the timing of maternal metastasis of melanoma between placental and fetal metastasis. Fetal metastasis may arise before the immune system is well developed, whereby the fetus develops tolerance toward the tumor and is subsequently unable to eliminate it. Morbidity for the fetus in patients with placental disease is unclear. Prematurity was a common complication in infants born with placental disease, with a mean gestational age of 34 weeks, but the mortality rate secondary to prematurity was low. Maternally derived metastases consisted mostly of subcutaneous nodules, abdominal masses, and liver metastases. These infants have poor outcome, with death typically occurring within 3 months of diagnosis. Neonates delivered with concomitant placental involvement without clinical evidence of the disease should be considered at high risk. They should be periodically evaluated for development of melanoma for at least 24 months postpartum. Evaluation should include a baseline chest X-ray and liver enzymes, including lactate dehydrogenase, abdominal ultrasound, skin inspection, and screening for melanocytic proteins in urine which may be repeated every 6 months. Adjuvant treatment of infants born to women with placental metastasis of melanoma has not been reported.

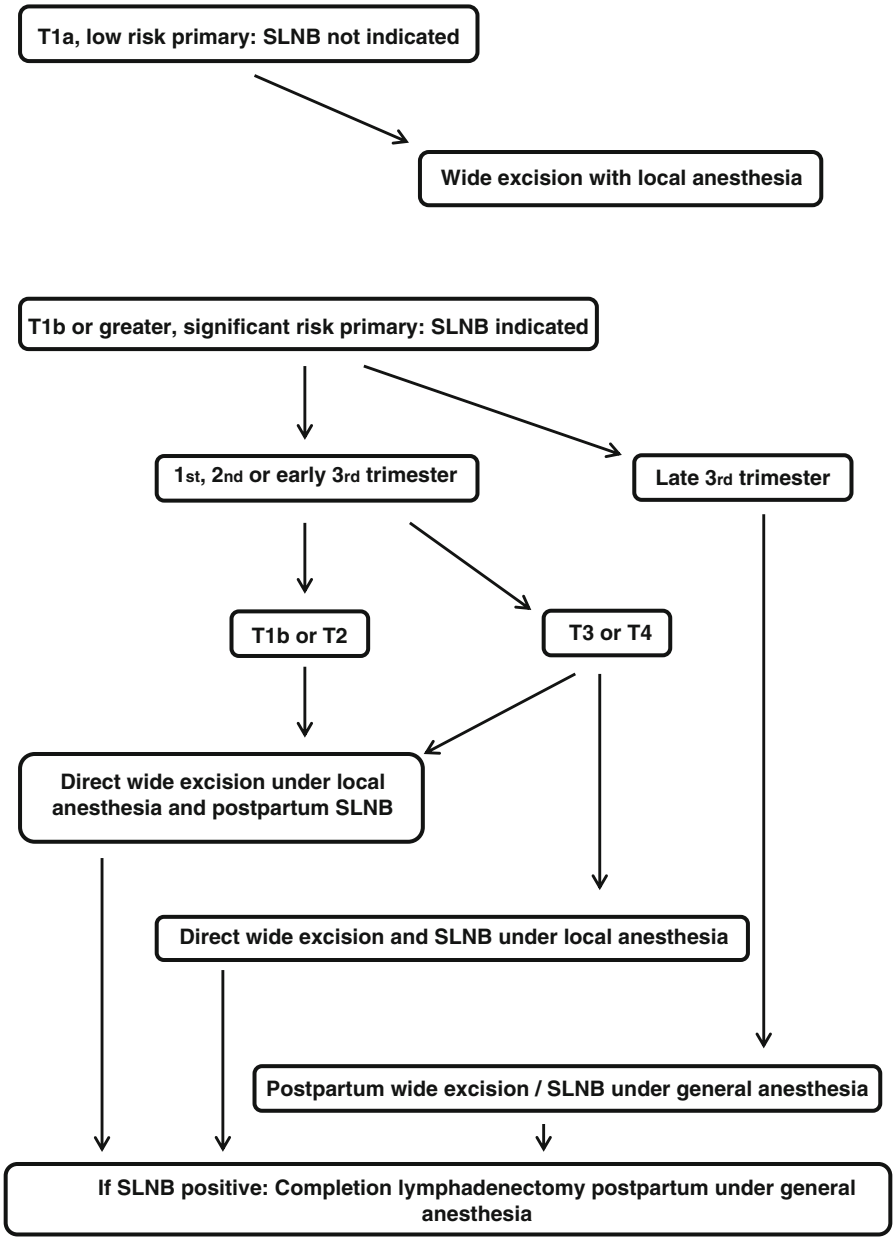

Fig. 11.2 Proposed algorithm for surgery in maternal melanoma

The placenta should be closely evaluated by gross and microscopic examination for evidence of metastases in any patients with a history of melanoma. Immunohistochemical staining for melanoma antigens should be performed on histologic sections, using S-100, HMB-45, or other appropriate markers. Research

Table 11.1 Controlled studies evaluating the maternal survival rates since 1989

Author and year of publication	Number of patients diagnosed with maternal melanoma (group 1)	Number of patients within nonpregnant group (group 2)	Breslow's thickness (mm) group 1/group 2	Survival rates between groups	Follow-up time (months)
Broer et al. (2012) [4]	5	3657	1.52/NA	NS	8–120
Lens et al. (2004) [13]	185	5348	1.28/1.07	NS	139.2 (median)
Wong et al. (1989) [14]	66	619	1.24/1.28	NS	NR
MacKie et al. (1991) [15]	92	143	2.38/1.96	NS	NA
O'Meara et al. (2005) [16]	149	2451	0.77/0.81	NS	24–120
Stensheim et al. (2009) [17]	160	4460	NA	NS	142.8 (median)
McManamny et al. (1989) [18]	23	243	1.62/1.72	NS	2–240
Slingluff et al. (1990) [19]	100	86	2.17/1.52	NS	72 (median)
Travers et al. (1995) [20]	45	420	2.28/1.22	NS	NA
Daryanani et al. (2003) [21]	46	368	2/1.70	NS	106 (median)
Silipo et al. (2006) [22]	10	30	NA	NS	60 (median)
Miller et al. (2009) [23]	11	65	4.28/1.69	NS	NA
Khosrotehrani et al. (2011) [24]	14	26	1.4/1.3	NA	NA
Zhou et al. (2014) [25]	18	18	1.63/2	NS	15.8 (median)

Abbreviations: *NA* not available, *NS* statistically nonsignificant difference in survival rates between groups

Table 11.2 Reviewed information summary about maternal malignant melanoma

Frequency in pregnancy	1:1000–10,000 gestations
Diagnosis	The same index of suspicion for melanoma as compared to the general population. A, B, C, D danger signs of melanoma: Asymmetry (A) Borderline irregularity (B) Color variations from one area to another (C) Diameter larger than 6 mm (D)
Staging	Assessment of Breslow's thickness, ulceration status, dermal mitotic rate, deep and peripheral margins Ultrasound Fine-needle aspiration biopsy SLNB (eventually postpartum for stage T1 and T2 disease) MRI (gadolinium should only be used if absolutely necessary)
Histology	Superficial spreading melanomas most common (41 %)
Treatment	Similar to that for nonpregnant women, but with specific considerations associated to pregnancy Stage T1b to T2b Resection of the primary lesion under local anesthesia Stage T3 to T4 Resection of the primary lesion under local anesthesia and either Delay of SLNB until after the delivery Proceeding to SLNB under local anesthesia Metastatic disease Completion of lymphadenectomy under general anesthesia Adjuvant treatment IFNα2b in high dose should be implemented postpartum Systemic treatment Dacarbazine (lack of evidence of in utero exposure) BRAF inhibitors (lack of experience) Anti-CTLA-4 antibody (to be avoided during gestation) Oral contraceptives and melanoma No increased risk of melanoma Hormone replacement therapy No increased risk of melanoma
Metastases to products of conception	It is the most frequent cancer that metastasizes to the placenta or fetus, accounting for 31 % of reported cases The placenta and the fetus of women with suspected metastatic melanoma during pregnancy should be closely evaluated by gross and microscopic examination
Prognosis	When matched for age, anatomic site, and stage, most studies have not demonstrated a difference in survival between pregnant and nonpregnant women
Pregnancy after treatment of melanoma	Pregnancy after melanoma diagnosis and treatment is safe Decreased risk of cause-specific deaths for women who had subsequent pregnancies in a study

tests that may be of value include examination of cord blood buffy coat for the presence of tumor cells using immunohistochemical staining or reverse transcriptase polymerase chain reaction (Fig. 11.2, Tables 11.1 and 11.2).

Conclusion

The ability to diagnose and treat melanoma with local surgery allows for prompt diagnosis and treatment despite the pregnant state, maximizing patients' survival. The arrival of innovatory therapies in the area of advanced melanoma, such as immunotherapy with anti-CTLA4 antibodies or targeted therapies, constitutes a breakthrough in the care of these patients and raises hopes in terms of prognosis. Dealing with these drugs during pregnancy will be a challenge.

Pregnancy was not identified as an independent prognostic factor for recurrence or survival. Fetal morbidity or mortality does not significantly increase either, in comparison to the general population. Large cohort studies with long-term follow-up are needed to evaluate the entire spectrum of adverse effects of melanoma or melanoma treatment on offspring of the patients.

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Managing Cervical Cancer During Pregnancy

12

Michael J. Halaska and Lukas Rob

Introduction

Cervical cancer is one of the most common malignancies diagnosed in the pregnant population. Because of the anatomical proximity to the developing foetus, it is also one of the most challenging tasks facing the surgical oncologist. More detailed epidemiology can be found in Chap. 1.

During the past few decades, a large body of findings related to the prognosis of cervical cancer diagnosed during pregnancy has been described. Majority of the studies show that prognosis is not negatively influenced when the disease is diagnosed during pregnancy. During counselling, a patient's gestational age at diagnosis, stage of the disease and the patient's wishes regarding continuation of pregnancy are important factors that need to be taken into account when choosing an optimal treatment. Most probably we can consider pregnancy-preserving management in early-stage disease (FIGO stage IA–IB2) tumours without compromising the prognosis. Indeed, preservation of pregnancy in a patient with advanced disease would not be a reasonable treatment option. Further, if a patient wishes to have her fertility preserved despite the risks, her physician must contend with prognostic uncertainty.

Diagnostics and Staging

Most women diagnosed with cervical cancer during pregnancy have early-stage disease [1] which might be explained by regular gynaecological examinations offered during pregnancy, making early detection more likely. Symptoms are

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usually absent in stage IA disease, whereas postcoital bleeding or spotting occurs in 20 % of the cases and abnormal oncological cytology in 63 % with stage I cancer during pregnancy [2].

Colposcopic and cytologic examinations are more difficult to interpret during pregnancy because of the occurrence of physiological pregnancy changes of the tissue (e.g. increased cervical volume, increased vascularisation, stromal oedema and glandular hyperplasia), even though eversion of the cervix facilitates inspection. An experienced oncogynaecologist should always be involved in managing any suspicious cases. In case of colposcopic suspicion of microinvasion, a flat cone biopsy is recommended, preferably between the 13th and 20th week of pregnancy. The risks of bleeding and abortion are the lowest during this period of pregnancy [3]. In larger tumours, a biopsy without significant risks can be performed [4]. For imaging methods, ultrasound is preferred in that it poses minimal risks to the foetus but is more operator dependent than magnetic resonance imaging (MRI). Increased perfusion during pregnancy can make diagnostics more difficult. Use of MRI in pregnant women with cervical cancer has been described [5]. MRI imaging in six pregnant patients was not different from non-pregnant patients, although some pregnancy changes have been reported, including movement of the foetus and physiological hyperintensity of the cervix in pregnancy. The teratogenic effects of gadolinium have been found only in extremely high or repetitive doses though when necessary it could be used after the 1st trimester of pregnancy [6].

The most important prognostic factor in cervical cancer, in addition to the size of the tumour, is lymph node involvement. Several publications have described lymphadenectomy performed during pregnancy as either staging surgery alone or combined with cone biopsy or trachelectomy. Table 12.1 summarises published studies of such lymph node dissection procedures performed in pregnancy. Lymphadenectomy can be carried out through abdominal incision or, more frequently, using a less invasive laparoscopic (transperitoneal or retroperitoneal) approach. The lymphadenectomy can be safely performed during pregnancy between the 13th and 22nd week of gestation. From 56 published cases, the majority of patients underwent surgery before the 22nd week of gestation. A median of 17 (range 6–71) harvested lymph nodes were detected in these 56 cases. With increasing gestational age, the probability of retrieving a sufficient number of lymph nodes decreases. Thus, at higher gestational stages, this staging procedure cannot be oncologically reliable and should not be performed.

The issue of detection of sentinel lymph nodes is disputable. No case report has been published on a patient with foetus in utero as technetium is injected into the cervix, which is in the near proximity of the foetus. Patent blue is contraindicated because of the risk of an anaphylactic reaction. Use of indocyanine green could be a safe option. Concerning the above-mentioned facts, we distinguish between different management algorithms of cervical cancer in pregnancy based on the feasibility of lymphadenectomy, with 22nd–25th week of gestation (preferably the 22nd week) being determinative. Deciding which surgical

Table 12.1 Staging lymphadenectomy during pregnancy

Author	Number	Stage	Surgery	Gestational age	Number of LNs	Positive LNs	Follow-up	Follow-up
				Week		%		Month
Stan (2005) [8]	1	IB2	LS-TP	16	72	0	NED	48
Alouini (2008) [9]	8	IB1-IIIA	3× LS-TP, 5× LS-RP	12–32	11–28	37.5	5× NED, 3× DOD	8–103
Sioutas (2011) [10]	1	IB1	Abdominal	13	18	0	NED	30
Sioutas (2011) [10]	1	IA2	LS-TP	12	28	0	NED	27
Ferriaoli (2012) [11]	1	IA2	LS-TP	7	13	0	NED	120
Ferriaoli (2012) [11]	1	IA2	LS-TP	13	30	0	NED	240
Carillon (2011) [12]	1	IB1	LS-TP	13	NA	0	NED	12
Vercellino (2014) [7]	32	IA1-IIA	32× LS-TP	6–25	6–57	16.7	NED	17–164

LS-TP laparoscopic transperitoneal lymphadenectomy, *LS-RP* laparoscopic retroperitoneal lymphadenectomy, *LNs* lymph nodes, *NED* no evidence of disease, *DOD* died of disease

technique to employ depends largely on the experience and preference of the surgeon. When laparotomy is used, a lower midline incision is preferred. Laparoscopy was found to have a comparable complication rate under certain conditions (e.g. operating time less than 90 min, a maximal pneumoperitoneum of 13 mmHg, open laparoscopic technique, skilled surgical team). Some authors have described the placement of laparoscopic ports based on gestation week at surgical procedure in order to avoid an injury of the uterus and to enable sufficient access to the retroperitoneal space [7].

Management of a Patient with Cervical Cancer Diagnosed During Pregnancy

After fully informed counselling, which should be made up of an obstetric evaluation of the patient, the presentation should include vaginal findings, pregnancy risk assessment, ultrasonographic datation of the gravidity and exclusion of foetal malformations or other disorders. It should also include a decision, and an exact treatment plan should be prepared by a team that should comprise an oncogynaecologist, perinatologist, neonatologist and oncologist (and eventually an anaesthesiologist, pathologist, radiodiagnostician), as well as the patient herself and her partner. Figure 12.1 provides an overview of the management of a pregnant patient with cervical cancer.

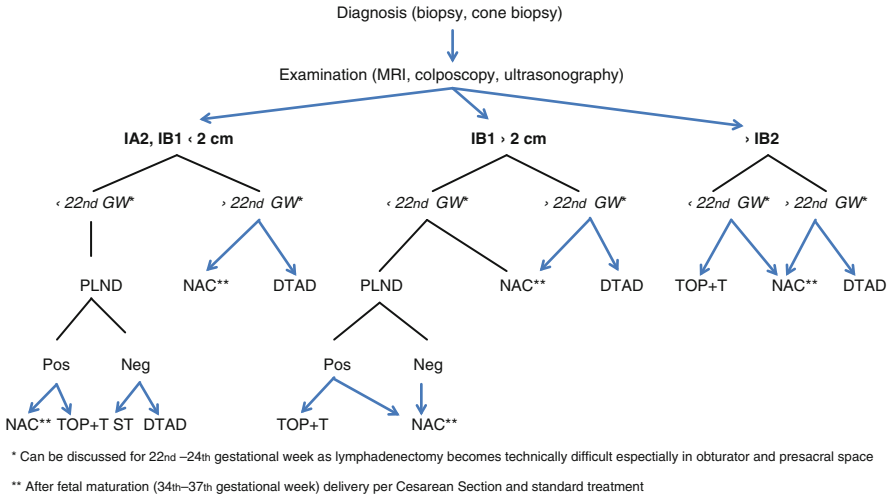

Fig. 12.1 Management of a cervical cancer patient diagnosed during pregnancy. *PLND* pelvic lymph node dissection, *NAC* neoadjuvant chemotherapy, *TOP+T* termination of pregnancy and standard treatment, *ST* simple trachelectomy, *DTAD* delayed treatment after delivery, *GW* gestational week of pregnancy, *MRI* magnetic resonance imaging

Non-preserving Management in Pregnancy

Some patients have an explicit wish not to preserve the pregnancy. Usually, they are represented by women who were diagnosed while planning an artificial abortion, advanced-stage disease patients or multiparous women who have concerns about their previous children. Because cervical cancer represents an obstacle to the surgical abortive procedure, the situation becomes immediately more complicated. In an operable disease, radical hysterectomy can be performed with the foetus in utero (during the 1st trimester) or after Caesarean section surgery to reduce the uterine volume (during the 2nd trimester). In advanced-stage disease when chemoradiotherapy is indicated, two alternative options are available. One is to start chemoradiotherapy with the foetus in utero, which usually leads to foetal demise within one month after exposure to radiotherapy. The option that is more frequently used today involves first performing an ureterotomy with evacuation of the foetus and then starting chemoradiotherapy within one week after termination. The advantages and disadvantages of performing Caesarean section prior to the initiation of radiotherapy need to be carefully weighed for each patient. Benefits include no need to recalculate the radiation field, no interruption of radiotherapy once started, lower number of obstetric complications (bleeding, disseminated intravascular coagulation) and reduced psychological distress for the patient. On the other hand, surgery involves several risks: formation of adhesions, which might increase the toxicity of radiotherapy; surgical site infection, possibly delaying the radiotherapy; and the risk of implantation metastasis.

Pregnancy-Preserving Management

The treatment of cervical cancer in pregnancy is still considered experimental, particularly in an advanced disease. Continuation of pregnancy should be offered to only highly motivated, carefully selected patients after informing them about the most current state of knowledge on the clinical issues under consideration. Based on the possibility to perform a staging lymphadenectomy (in early-stage tumours), the patients can be divided into groups diagnosed during the 22nd week and after the 22nd week of pregnancy.

Tumours Diagnosed Before the 22nd Gestational Week

For *IA1* tumours, cone biopsy is a surgical procedure offering sufficient and relatively safe treatment in pregnancy. For more progressive tumours, staging lymphadenectomy should be performed first to identify high-risk tumours (i.e. tumours with positive lymph nodes). In node-positive cases, termination of pregnancy followed by standard treatment should be advocated.

For stage *IA2 and IB1 tumours smaller than 2 cm* in lymph node-negative patients and in younger women with early cervical cancer, a trachelectomy could be suitable. The standard procedures for fertility sparing in non-pregnant women in such cases are vaginal or abdominal radical trachelectomy. An overview of published cases in pregnancy (see Table 12.2) describes not only the technical

Table 12.2 Cases of abdominal and vaginal radical trachelectomy performed during pregnancy

Author	Stage	Size	Histologic type	Surgery	Surgery	Delivery	Outcome	Patient outcome	Follow-up
		mm			Week				Week
Ungar (2006) [17]	IB1	NA	Squamous cell	ART + PLND	7	AB	Abortion at the 1st post-op day	NED	NA
Ungar (2006) [17]	IB1	NA	Squamous cell	ART + PLND	8	AB	Abortion at the 1st post-op day	NED	NA
Ungar (2006) [17]	IB1	NA	Squamous cell	ART + PLND	9	38	0	NED	20
Ungar (2006) [17]	IB1	NA	Squamous cell	ART + PLND	13	AB	Abortion at the 16th post-op day	NED	NA
Ungar (2006) [17]	IA2	NA	Squamous cell	ART + PLND	18	39	0	NED	72
Mandic (2009) [18]	IB1	4	Squamous cell	ART + PLND	19	36	5 h, blood loss 450 ml	NED	12
Abu-Rustum (2009) [19]	IB1	12	Lympho-epithelial	ART + PLND	15	39	3.5 h, blood loss 1600 ml, left ureter lesion	NA	NA
Enomoto (2011) [20]	IB1	NA	Squamous cell	ART + PLND	15	37	7.5 h, blood loss 960 ml	NED	6
Aoki (2014) [21]	IB1	20	Squamous cell	ART + PLND	17	38	6.5 h, blood loss 2510 ml	NED	40
Karateke (2010) [22]	IB2	50	Squamous cell	ART + PLND	22	AB	4 h, abortion 4 h post-op	NA	NA
Ferriaoli (2012) [11]	IA2	4	Adenocarcinoma	VRT + PLND	5	35	0	NED	120
Ferriaoli (2012) [11]	IA2	10	Squamous cell	VRT + PLND	11	AB	Abortion on the 7th post-op day	NED	240
Bravo (2012) [23]	IB1	35	Squamous cell	VRT + PLND	11	36	0	NED	160
Alouini (2008) [9]	IB1	20	Squamous cell	VRT + PLND	12	AB	Abortion on the 2nd post-op day	NED	132

Alouini (2008) [9]	IB1	25	Adenocarcinoma	VRT + PLND	12	30	0	DOD	18
Sioutas (2012) [10]	IA2	3.6	Squamous cell	VRT + PLND	12	37	0	NED	26
Sioutas (2010) [10]	IB1	NA	Adenocarcinoma	VRT + PLND	13	37	0	NED	47
Sioutas (2011) [10]	IB1	NA	Adenocarcinoma	VRT + PLND	13	29	0	NED	33
Iwami (2011) [24]	IB1	NA	Adenocarcinoma	VRT + PLND	16	37	0	NED	14
Kolomainen (2013) [25]	IB2	42	Adenocarcinoma	VRT	16	26	PROM 8 weeks after surgery, NEC	NED	184
van de Nieuwenhof (2008) [26]	IB1	8	Squamous cell	VRT + PLND	18	36	6.5 h, blood loss 1550 ml	NED	9
Saso (2015) [27]	IB1	4	Squamous cell	VRT	19	36	0	NED	64
Ferriaoli (2012) [11]	IB1	27	Adenocarcinoma	VRT + PLND	22	31	IVH on the 2nd post-op day	DOD	48

ART abdominal radical trachelectomy, *VRT* vaginal radical trachelectomy, *PLND* pelvic lymph node dissection, *PALND* para-aortic lymph node dissection, *PROM* premature rupture of membranes, *AB* abortion, *NEC* necrotising enterocolitis, *IVH* intraventricular haemorrhage, *NED* no evidence of disease, *DOD* died of disease, *NA* not available, *POSTOP* post-operative

difficulties (e.g. prolonged operative time associated with significant blood loss and an increase in infection rates) but also the loss of pregnancy in 6 out of 23 cases (26 %). Therefore, radical trachelectomy should not be recommended during pregnancy. Meanwhile, a number of recent studies in non-pregnant women have demonstrated that the risk of parametrial involvement in node-negative patients is less than 1 % for these stages (IA2 and IB1 ˂ 2 cm tumours), which justifies using simple trachelectomy (an oncologically safe procedure) and omitting radical parametrectomy [13]. The feasibility and safety of this technique have been reported elsewhere [14, 15].

Patients diagnosed with tumours in stage *IB1 larger than 2 cm* with negative lymph nodes are indicated for neoadjuvant chemotherapy (NACT) until reaching foetal maturity. Another option is to administer NACT without performing a lymphadenectomy, but which is then performed after delivery. With negative lymph nodes, some authors propose the delay of treatment until after delivery. A literature review included 76 stage IB1 cases of delayed treatment with a 95 % survival rate at a mean follow-up of 37.5 months [16]. The median delay was 16 weeks and no recurrences were reported for node-negative patients. If progression of disease were suspected through either clinical examination or MRI, termination of pregnancy or NACT should follow.

In patients with tumour stage *IB2 and higher*, the only option to preserve a current pregnancy would be to administer NACT. The therapeutic value of staging lymphadenectomy before the initiation of chemotherapy is unclear, but such information might be useful in further management of pregnancy preservation.

There is growing knowledge on the oncological safety of NACT administered during pregnancy. The major purpose of NACT is to stabilise the tumour and prevent its spread.

Tables 12.3 and 12.4 summarise data of 42 stage IB patients who received NACT in pregnancy. The chemotherapy regimens were based on platinum alone or in combination with paclitaxel, vincristine, 5-FU, cyclophosphamide or bleomycin. Chemotherapy was administered at a 3-week interval. Overall survival rate was 81.6 % (31/38) at a median follow-up of 24 (range 1–153) months. The survival rate was 88.9 % (16/18) in stage IB1 at a median follow-up of 14.5 months (one patient diagnosed with small cell cancer died). In stage IB2, the overall survival rate was 73.7 % (14/19) at a median follow-up of 27 months. These results need to be interpreted with caution because of the short follow-up time and because different chemotherapy regimens were included. Recently published guidelines on gynaecologic cancer treatment in pregnancy recommend a platinum-based chemotherapy (cisplatin 75 mg/m^2), preferably with paclitaxel (175 mg/m^2) at a 3-week interval [48]. An alternative to cisplatin is carboplatin (AUC 5-6), which has been shown to have a more favourable maternal toxicity profile. Data on the use of gemcitabine, vinorelbine and topotecan during pregnancy are very limited, and these agents should be avoided in pregnant patients. Alternative chemotherapeutic protocols are cisplatin 75 mg/m^2 with ifosfamide 2 mg/m^2 in patients with spinocellular carcinoma and cisplatin 75 mg/m^2 with Adriamycin 35 mg/m^2 in patients with adenocarcinoma given in a10-day regimen.

Table 12.3 Cases of neoadjuvant chemotherapy in stage IB1 tumours

Author	Age	GW	Stage	Histological type	Grade	Size	Chemotherapy	GW at delivery	Patient outcome	Follow-up
						mm				Month
Cardonick (2010) [28]	NA	NA	IB1	NA	NA	NA	P	NA	NA	NA
Cardonick (2010) [28]	NA	NA	IB1	NA	NA	NA	PV	NA	NA	NA
Favero (2010) [29]	31	14	IB1	Squamous cell	2	NA	P	32	NA	NA
Favero (2010) [29]	29	18	IB1	Adenocarcinoma	3	NA	P	34	NA	NA
Favero (2010) [29]	31	18	IB1	Squamous cell	3	NA	P	34	NED	10
Favero (2010) [29]	34	22	IB1	Squamous cell	2	NA	P	36	NED	5
Marnitz (2010) [30]	35	15	IB1	Adenocarcinoma	2	NA	3× PT	32	NED	17
Marnitz (2010) [30]	31	20	IB1	Squamous cell	3	NA	3× PT	32	NED	12
Marnitz (2010) [30]	35	22	IB1	Squamous cell	2	NA	3× PT	35	NED	7
Marnitz (2010) [30]	36	15	IB1	Squamous cell	2	NA	3× PT	36	NED	3
Marnitz (2010) [30]	29	19	IB1	Adenocarcinoma	3	NA	3× PT	33	NED	3
Marnitz (2010) [30]	35	19	IB1	Adenocarcinoma	2	NA	3× PT	34	NED	1
Giacalone (1996) [31]	34	19	IB1	Squamous cell	2	20	3× P	32	NED	12
Fruscio (2012) [32]	34	26	IB1	Adenocarcinoma	3	20	P	36	NED	43
Fruscio (2012) [32]	37	8	IB1	Squamous cell	3	20	P	36	NED	23
Ayhan (2012) [33]	26	18	IB1	Clear cell	NA	20	3× P	32	NED	36
Caluwaerts (2006) [34]	28	15	IB1	Squamous cell	2	30	6×P	32	NED	10
Chun (2010) [35]	27	25	IB1	Small cell	NA	30	3× PT	35	DOD	49
Fruscio (2012) [32]	34	22	IB1	Squamous cell	2	30	P	36	NED	65
Fruscio (2012) [32]	39	20	IB1	Adenocarcinoma	1	30	P	36	NED	41
de Lima (2013) [36]	24	23	IB1	Adenocarcinoma	NA	32	2× P + Vin	34	NED	24
Kong (2014) [37]	31	19	IB1	Adenocarcinoma	2	32	3× PT	33	NED	96

P cisplatin, *V* vinblastine, *Vin* vincristine, *T* paclitaxel, *DOD* died of disease, *NED* no evidence of disease, *AWD* alive with disease, *NA* not available, *GW* gestational week

Table 12.4 Cases of neoadjuvant chemotherapy in stage IB2 tumours

Author	Age	GW	Stage	Histological type	Grade	Size	Chemotherapy	GW at delivery	Patient outcome	Follow-up
						mm				Month
Karam (2007) [38]	28	23	IB2	Squamous cell	3	40	7× P	33	NED	16
Li (2011) [39]	36	27	IB2	Squamous cell	3	42	2× PT	33	NED	21
Peculis (2014) [40]	27	17	IB2	Squamous cell	NA	42	6× PA	34	NED	20
Rabaiotti (2010) [41]	27	15	IB2	Squamous cell	3	50	3× P	32	DOD	24
Chun (2010) [35]	27	28	IB2	Squamous cell	NA	50	2× TC	36	NED	60
Li (2011) [39]	39	29	IB2	Squamous cell	NA	50	2× PT	33	NED	13
Kong (2014) [37]	38	18	IB2	Squamous cell	NA	50	3× PT	35	NED	36
Islam (2012) [42]	37	10	IB2	Adenocarcinoma	2	53	1× P	34	NED	36
Fruscio (2012) [32]	37	18	IB2	Squamous cell	3	60	P	32	NED	153
Fruscio (2012) [32]	28	16	IB2	Squamous cell	3	60	PT	33	NED	113
Fruscio (2012) [32]	36	16	IB2	Squamous cell	3	60	PT	34	NED	115
Fruscio (2012) [32]	32	20	IB2	Squamous cell	3	70	P	35	DOD	27
Fruscio (2012) [32]	29	13	IB2	Squamous cell	3	70	PV	30	DOD	27
Tewari (1997) [43]	36	21	IB2	Squamous cell	2	70	4× PV	32	NED	24
Smyth (2010) [44]	26	23	IB2	Small cell	NA	94	3× A +CFA	35	OT	NA
Lai (1997) [45]	NA	NA	IB2	NA	NA	NA	PVB	NA	DOD	52
Lai (1997) [45]	NA	12	IB2	NA	NA	NA	PVB	NA	DOD	59
Lanowska (2011) [46]	41	14	IB2	Squamous cell	2	NA	4× P	31	NED	1
Gambino (2011) [47]	28	20	IB2	Squamous cell	NA	NA	1× P	22	NED	24
Gambino (2011) [47]	42	24	IB2	Squamous cell	NA	NA	3× P	36	NED	36

P cisplatin, *V* vinblastine, *B* bleomycin, *T* paclitaxel, *A* doxorubicin, *CFA* cyclophosphamide, *C* carboplatin, *DOD* died of disease, *NED* no evidence of disease, *OT* ongoing treatment, *NA* not available

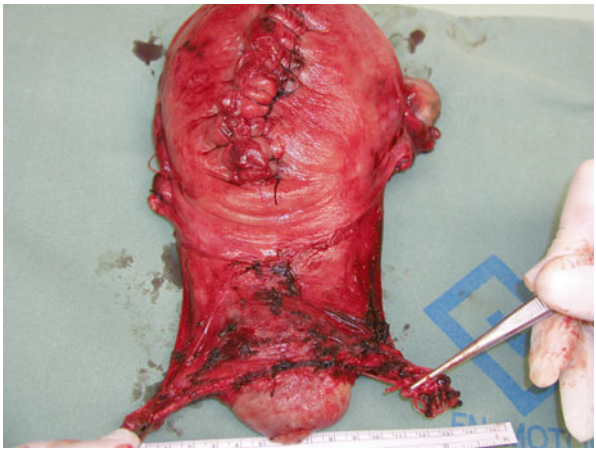

Fig. 12.2 Specimen of the uterus after Caesarean section combined with radical hysterectomy

Tumours Diagnosed After the 22nd Gestational Week

As mentioned above, complete pelvic lymphadenectomy is difficult to perform beyond 22 weeks gestation; therefore, nodal status cannot be taken into account in the decision-making process. In stage IA2 and IB1 tumours smaller than 2 cm, one option is to delay treatment until foetal maturity is achieved and then discuss timing of delivery with a neonatologist. Another option is administration of NACT. For higher stages, NACT is the only means to preserve pregnancy and reach foetal maturity.

Mode of Delivery

Vaginal delivery is possible in patients with no evidence of residual tumours, especially after cone biopsy or trachelectomy. However, most patients should deliver via Caesarean section. Ripening of the cervix during spontaneous delivery that underwent surgery during pregnancy could be abnormal. Both episiotomy and laparotomy recurrences have been documented [43, 49]. Caesarean section allows the surgical team to combine surgery with radical hysterectomy. We recommend performing midline uterotomy to avoid getting too close to the cervix during surgery. The procedure, however, poses an increased risk of higher blood loss. If carried out by an experienced team, it could be performed as standard procedure. Figure 12.2 depicts a specimen of the uterus after Caesarean section combined with radical hysterectomy.

Conclusion

Cervical cancer belongs to one of the most challenging cancer diseases when diagnosed during pregnancy. Pregnancy-preserving management should be considered as it seems that pregnancy does not negatively influence the prognosis of the patients, and moreover, majority of cases are diagnosed at the early stage of

disease. Combination of conservative surgery and neoadjuvant chemotherapy offers interesting therapeutic options in the management of patients diagnosed with cervical cancer during pregnancy.

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Managing Ovarian Tumors During Pregnancy

13

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Introduction

Ovarian masses may complicate 2.3–4.1 % [1] of all pregnancies. Due to the extensive use of transvaginal ultrasound (US) in the first trimester for the assessment of fetal viability, growth, and anomalies, the diagnosis of ovarian masses during pregnancy has increased in the last decades. Most of these are asymptomatic and undergo spontaneous resolution without treatment [2]. Pain related to mass torsion, enlargement, or rupture occurs in 3–28 % of cases. Most persistent ovarian masses diagnosed during pregnancy are benign tumors, with only 1–3 % [3] being malignant. After cervical cancer, ovarian cancer (OC) is the second most frequent gynecologic cancer complicating pregnancy, with an incidence rate of 1:12.000–47.000 pregnancies. Updated INCIP (International Network on Cancer, Infertility and Pregnancy) registration study described the frequency of cancer in pregnancy in European countries [4]: among more than 1000 cases of diagnosed cancer during pregnancy, ovarian cancer accounts for 5 % of all cases.

Histological subtypes are similar to those reported for young nonpregnant women. Most common benign tumors are teratomas and serous cystadenomas, whereas most common malignant histology is epithelial invasive and borderline cancer. Eighty percent of malignancies are diagnosed at early stage. Germ cell tumors are less frequent, with few cases reported in several series [5]. Table 13.1 describes a summary of ovarian cancer cases reported in literature so far.

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Table 13.1 Epithelial and non-epithelial ovarian cancer in pregnancy published reports

Authors	Year	Total	Epithelial						Non-epithelial		
			BL	BL	BL	Malignant	Malignant	Malignant			
			Total	ES	AS	Total	ES	AS	Total	ES	AS
Whitecar M	1999	8	**4**	4		**1**	1		**3**	2	1
Sood AK	2001	1				**1**		1			
Sayedur M	2002	9				**7**	6	1	**2**	2	
Sherard GB	2003	8	**5**	N/A	N/A				**3**	N/A	N/A
Mendez LE	2003	1				**1**		1			
Zanetta G	2003	2	**2**	2							
Picone O	2004	1				**1**		1			
Ferrandina G	2005	1				**1**		1			
Zhao XY	2006	22	**6**			**5**			**11**		
Machado F	2007	13	**4**	2	2	**6**	6		**3**	3	
Modares M	2007	1				**1**		1			
Hubalek M	2007	1							**1**		
Mantovani G	2007	1				**1**		1			
Behtash N	2008	23	**5**	5		**4**	1	3	**14**	12	2
Rouzi AA	2009	1				**1**		1			
Doi D	2009	1				**1**	1				
Palmer J	2009	1				**1**		1			
Gezginc K	2011	11	**4**	4		**4**	3	1	**3**	2	1
Li X	2011	13	**8**	8		**3**	3		**2**	2	

Serkies K	2011	1				**1**		1			
Dobashi M	2012	10	**2**	2		**6**	6		**2**	2	
Fauvet R	2012	40	**40**	38	2						
He S	2012	1				**1**	1				
Smith E	2013	1				**1**	1				
Gottheil S	2013	1				**1**	1				
Akhter N	2013	1				**1**	1				
Morikawa A	2014	41	**25**	24	1	**8**	7	1	**8**	8	
Total		**215**	**105**	**89**	**5**	**58**	**38**	**15**	**52**	**33**	**4**

BL borderline, *ES* early stage, *AS* advanced stage, *N/A* not available

Diagnosis

The radiological evaluation of ovarian masses during pregnancy is hampered by uterine growth and limited by the potential detrimental effects on the fetus due to radiation exposure. In the first trimester, the most reliable diagnostic tool is vaginal ultrasound, while magnetic resonance imaging (MRI) may be used at higher gestational age (GA) [6].

Sonographic malignancy criteria are the same as for nonpregnant patients, and IOTA group risk prediction scores demonstrated sensitivity and specificity of 95 % and 98 %, respectively [7]. Ultrasound (US) is more accurate when performed by a specialized gynecologic oncologist.

Aggarwal et al. reviewed ten studies describing US assessment and treatment of pregnancy-associated ovarian masses [3]. The diagnosis was made in the first or second trimester in almost half of the 940 women studied. The diagnosis was occasional in most patients, whereas it was due to pain or other symptoms (bleeding/obstruction/rupture) in 25 % of cases. Successful conservative treatment was reported in 69.4 % of prospectively followed cases, with spontaneous mass resolution or surgical removal during cesarean section or in the postpartum period. Taking into account the low rate of malignancy and the high rate of spontaneous resolution, an expectant management is deemed reasonable [8], unless malignancy is suspected or symptoms mandate surgical intervention. A specific challenge of pregnancy-related ovarian mass is the decidualization of ovarian endometriomas due to the hormonal changes of pregnancy. In this case, sonographic features can be erroneously interpreted as malignant, and a close follow-up is needed.

MRI can be used after the first trimester to better evaluate a persistent ovarian mass and differentiate degenerating leiomyoma from ovarian neoplasm. The European Society of Urogenital Radiology states that when there is a strong indication for contrast-enhanced MRI, the smallest possible dose of one of the stable gadolinium contrast agents should be used. No neonatal tests are necessary after delivery [9].

CT scan is not recommended [10] during pregnancy due to possible fetal harm. The fetal radiation exposure is reported between 20 and 40 mGy. This diagnostic method should be considered only when the life of the woman is at risk.

18F-FDG PET has little application in pregnancy. Radioactive nuclides could affect the fetal health depending on the tracer pharmacokinetics, proximity of the fetus to maternal bladder, and gestational age. Few experiences described a radiopharmaceutical dose reduction in pregnant patients [11].

Serum tumor markers, including AFP, CA125, and beta-HCG, are not reliable tools to assess ovarian masses during pregnancy. Studies demonstrated that CA125 has a lower positive predictive value during pregnancy, with variations based on gestational age [12]. CA125 rises in the first trimester, with normalization during the second and third trimester, and remains elevated at the time of delivery and 48 h thereafter [13]. On the other hand, AFP and beta-HCG increase rapidly during the first and second trimester, but are mainly secreted by the trophoblast and thus may not be used as tumor markers. Accordingly, biomarker assessment should only be performed at least 2–10 weeks postpartum in order to obtain reliable information.

Surgical Treatment

Preoperative Considerations

To successfully treat ovarian cancer during pregnancy, a multidisciplinary evaluation should take place. The multidisciplinary team should include a gynecological oncologist, an obstetrician, a pathologist, a neonatologist, a psychologist, and an anesthesiologist. The patient and her family should be informed of the different options and the possible fetal risks. It is highly recommended to refer these cases to specialized centers where specific competences are present and care of pregnant patients with cancer is common practice.

So far, no evidences have demonstrated the benefit of medically induced abortion followed by standard treatment of pregnancy-associated ovarian cancer. This decision should be carefully discussed with the parents as a potential option, especially in the first trimester.

Pregnant women can perceive abdominal surgery as a violation of their maternal status. When a surgical approach is indicated, appropriate information and supportive care considerations are critical in the preoperative assessment.

Timing of Surgery

Surgery during the first trimester may be associated with a higher incidence of miscarriage [14], due to corpus luteum disruption or direct uterine manipulation. Whenever possible, delaying surgery between 14 and 20 weeks of gestation is a safer option. In the third trimester, the risk of preterm delivery should be taken into account.

If surgery is planned in the first trimester, intramuscular (IM) daily injection of progesterone is suggested. For surgery occurring between 24 and 34 weeks, corticosteroid for fetal lung maturation should be administered 48 h prior to operation. Prophylactic tocolysis might be administered for the same reason in the third trimester, even if this indication remains controversial. In a series of 28 patients undergoing surgery in the third trimester [15], tocolytic agents (indomethacin or terbutaline) were administered, and no obvious uterine contractions were reported in 86 % of cases, even if a control arm without tocolysis was not present.

Intraoperative Care

During anesthesia, the patient should be placed in left lateral oblique position to prevent inferior vena cava compression and supine hypotension syndrome as well as to improve uterine perfusion. The placenta is not able to self-regulate the blood flow; thus, particular care should be taken to control maternal vital parameters in order to keep constant blood pressure and avoid life-threatening fetal hypoxia (maternal hypotension, hemorrhage, and hypovolemia).

Fetal assessment by cardiotocography is indicated before and after the surgical procedure, but continuous monitoring is not considered necessary. Immunoprophylaxis with anti-Rh serum is recommended for Rh-negative mothers after surgery [16]. Thromboprophylaxis is mandatory for an adequate period in order to cover the risk of thromboembolic events related to pregnancy and cancer diagnosis.

Access Technique: Laparoscopy or Laparotomy Two retrospective studies compared maternal and fetal outcome after laparoscopy or laparotomy performed during pregnancy for different indications [17, 18]. Sixty-eight laparoscopies and 78 laparotomies were compared, without any significant difference in terms of fetal and maternal outcomes. A population registry-based Swedish study [19] compared patients undergoing abdominal surgery in pregnancy. Fetal outcomes were compared in 2181 laparoscopies and 1522 laparotomies. An increased risk of birth weight <2500 g, preterm delivery, and intrauterine growth restriction was described in both groups compared to the general population. No difference in fetal outcome was reported.

Considering the low incidence of ovarian cancer in pregnant patients with an adnexal mass, a laparoscopic starting approach is advisable to minimize perioperative complications. Intra-abdominal pressure should be kept between 10 and 12 mmHg, to preserve maternal cardiac output and to avoid the hypoxic effect of CO_2 on the fetus. Laparoscopic procedure should be adjusted to overcome uterus size and to avoid fetal and genital tract accidental injuries. An open technique is preferred [17], and the first trocar should be placed in a supraumbilical position. The operative trocars should be placed in cranial positions to allow a more comfortable movement in the abdomen. Nonetheless, systematic reviews highlight the risk of intraoperative cyst rupture, tumor tissue spread, and port site metastases when laparoscopy is used in early-stage malignant ovarian cancer [20]. Thus, a laparotomic conversion should be considered in any case of malignancy, taking into consideration gestational age and the necessity of accurate tumor staging. In these situations, a midline incision can offer wide exposure of the pelvis and should be considered.

Staging Procedures

Pelvic surgery during pregnancy may be hampered by several technical limitations, including the increased uterine volume due to pregnancy and the limited manipulations needed to preserve the pregnancy. Frozen section should be available to guide the surgical management. Definitive pathologic diagnosis should be performed by well-trained pathologist in the field of gynecologic malignancy since it is necessary to interpret histological aspects in the context of the physiologic changes that may appear in hormone-sensitive tissues.

Recent data demonstrate that *borderline ovarian tumors* occurring during pregnancy have a more aggressive behavior [21]. Intraepithelial carcinoma, microinvasion, micropapillary features, and invasive implants were described in a higher proportion of cases, compared to the nonpregnant patients. Restaging surgery was necessary in 52 %, with upstaging in 24 % of patients [21]. The recurrence rate among this small group was

7.5 %, not different from other series of nonpregnant cases. In order to avoid spillage and to perform staging procedures, a midline laparotomy with unilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, and appendectomy should be performed. A laparoscopic approach can be preferred in selected cases with limited disease.

Early-stage epithelial ovarian cancer should be accurately staged with open surgery, including intraperitoneal and retroperitoneal staging. For stages IA to IIA, pelvic and para-aortic lymph node dissection is recommended. Large series showed the feasibility to offer a comprehensive staging procedure with fertility-sparing surgery [22] outside pregnancy.

Forty-four cases were reported in the literature with a diagnosis of early-stage ovarian cancer in pregnancy (Table 13.1). Most of these cases underwent a conservative surgery in pregnancy with secondary radical surgery after delivery. If a complete staging primary surgery is not feasible during pregnancy, postpartum restaging should be considered.

The diagnosis of *advanced-stage epithelial ovarian cancer* in pregnancy is a rare situation, with only 16 cases reported in the literature (Table 13.1). If the patient is willing to preserve the pregnancy, radical debulking surgery is not feasible during pregnancy. Alternative approaches include primary debulking surgery with pregnancy termination or delivery, expectant management until delivery, or surgery during pregnancy followed by chemotherapy. To allow the fetus to reach a viability condition, a reasonable treatment plan could be a comprehensive surgical diagnostic procedure, as a diagnostic laparoscopy, adjuvant chemotherapy, and radical surgery after delivery.

A fertility-sparing surgical approach is recommended in *non-epithelial ovarian cancers patients*: almost 90 % of cases published during pregnancy cases were at an early stage. Usually a peritoneal staging is sufficient and lymph node dissection is not recommended.

A summary of proposed management is reported in Table 13.2.

Table 13.2 Proposed management of OC in pregnancy

	First trimester	Second trimester	Third trimester
Borderline ovarian cancer	Close observation until second trimester	Surgery, frozen section diagnosis and intraperitoneal sampling	Close observation and postpartum treatment
Early-stage epithelial ovarian cancer	Close observation until second trimester	Surgery, frozen section diagnosis and chemotherapy (according to grade of nuclear differentiation and stage)	Close observation and postpartum treatment *or* surgery and postpartum chemotherapy
Advanced-stage epithelial ovarian cancer	Close observation until second trimester	Debulking surgery and postoperative chemotherapy *or* diagnostic surgery and neoadjuvant chemotherapy (carboplatin and paclitaxel)	Neoadjuvant chemotherapy *or* preterm delivery and debulking surgery
Non-epithelial ovarian cancer	Close observation until second trimester	Surgery and chemotherapy (according to disease stage)	Close observation and postpartum treatment

Carboplatin AUC 6, Paclitaxel 175 mg/sqm q 21 days

Systemic Chemotherapy

Epithelial Ovarian Cancers

Platinum derivatives and taxanes represent the backbone of first-line chemotherapy of epithelial ovarian cancer. Platinum derivates are known to be teratogenic in rodents during the first trimester, and historic series [23] reported the same effect in humans. When fetuses were exposed to platinum compounds in the second and third trimester, platinum-DNA adducts were detected, but no detrimental effects were reported. The largest revision of ovarian cancer patients treated with platinum derivates was made by Mir et al. [24]. These Authors identified 2/43 newborns with major malformations including ventriculomegaly and microphthalmos after platinum exposure. Both mothers had been treated with cisplatin during the first trimester. When cisplatin is administered in the third trimester, newborn renal function should be thoroughly assessed. As carboplatin is less nephrotoxic than cisplatin and animal data report a fetal plasma concentration of 50 % compared to maternal plasma concentration, this drug should be preferentially used during pregnancy [25]. Consistent experience now also exists concerning the use of paclitaxel use during pregnancy [26, 27].

Bevacizumab, a humanized anti-vascular endothelial growth factor (VEGF) antibody, prolonged progression-free survival in advanced-stage ovarian cancer when administered with standard chemotherapy and as maintenance treatment. VEGF plays a crucial role in pregnancy, stimulating trophoblastic vessel invasion and fetal growth, as well as enhancing amniotic fluid production [28]. Anti-VEGF agents inhibit organogenesis and fetal development in mice models, and their use during pregnancy is not recommended. The standard doublet with carboplatin and paclitaxel seems to give the best results in terms of fetal safety and maternal outcome [29].

Non-epithelial Ovarian Cancers

The standard chemotherapy for non-epithelial ovarian cancer is the association of bleomycin, etoposide, and cisplatin. A recent consensus suggested replacing etoposide during pregnancy: reasonable alternatives would be paclitaxel-carboplatin or cisplatin-vinblastine-bleomycin [30].

Delivery Considerations

Delivery should be planned according to the obstetrical situation aiming at term vaginal delivery. If the patient has received chemotherapy, white blood cell nadir should be avoided possibly waiting 3–4 weeks after last cycle to allow blood values to rise.

Conclusions

The occurrence of ovarian malignancies during pregnancy is rare, and most of the ovarian masses diagnosed in the first trimester are benign. Nonetheless, when ovarian cancer is diagnosed during pregnancy, the clinical management should

take into consideration maternal and fetal well-being with careful evaluation of the best surgical management and the most appropriate systemic treatment. Surgery is best performed during the second trimester, and either a laparoscopic or laparotomic approach can be considered, according to the clinical characteristic of the tumor. Carboplatin- and paclitaxel-based chemotherapy may be used after the first trimester, when indicated. Patients should be referred to specialized centers where surgical, oncological, obstetrical, and neonatological competences are present, and each case should be reported within international registries to better understand the biology and outcome of this rare situation.

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Managing Lymphoma During Pregnancy

14

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Introduction

Lymphoma is one of the most common cancers that occur during pregnancy. Primarily due to its typical peak onset in the reproductive years, Hodgkin lymphoma (HL) occurs more often than non-Hodgkin lymphoma (NHL) during pregnancy. Several recently published series on lymphoma during pregnancy indicate that the majority of patients present with advanced-stage disease and that the occurrence of extranodal disease is relatively common and that it may occur in unique sites (e.g., reproductive organs), especially in NHL.

The evaluation and treatment of lymphoma in pregnant patients is highly individualized based in part on the clinical scenario as well as patient and family wishes. Furthermore, overarching objectives for the diagnosis and treatment of pregnant mothers are to optimize maternal survival and minimize treatment-related fetal toxicity and prematurity. This is maximized by involvement of high-risk maternal–fetal medicine as part of the multidisciplinary team and also promoting the goal of continuing the pregnancy to full term. This review details available information on staging of lymphoma, disease characteristics, gestational data, treatment (including targeted therapeutics), maternal and fetal complications, and additional special considerations of patients diagnosed with NHL and HL during pregnancy.

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Staging, Disease Characteristics, and Gestational Data

Staging

The diagnosis of lymphoma in the pregnant patient is no different than the typical patient requiring a lymph node biopsy, which can usually be safely done, including in the first trimester, utilizing either local or general anesthesia. Staging of a pregnant patient with lymphoma includes a detailed history and physical, laboratory testing, bone marrow biopsy, and shielded chest X-ray. For further imaging, the use of nonionizing ultrasound and MRI are preferred to abdominal/pelvic CT imaging (0.02 Gy). There is no evidence of harmful fetal effects with MRI; however, some regulatory bodies discourage the use of gadolinium during pregnancy in part due to potential acoustic damage and systemic fibrosis [1, 2]. Gadoterate meglumine and gadobenate dimeglumine may be safer than gadolinium and can be considered for use antepartum. PET scan should be avoided during pregnancy as it results in pelvic irradiation and ^{18}F-FDG crosses the placenta, which is considered fetotoxic [3].

Disease Characteristics

There are several important considerations regarding the presentation of lymphoma occurring during pregnancy. Lymphomas often occur later in gestation (i.e., second and third trimester), are typically an aggressive subtype, involve the reproductive organs, and the majority are diagnosed at a more advanced stage. Delay in diagnosis may occur as symptoms related to lymphoma may mimic pregnancy-related symptoms (e.g., fatigue, nausea, anemia, etc.). A systematic review of 121 published NHL cases [4] occurring during pregnancy described 48 % of NHLs as aggressive, DLBCL and T-cell lymphoma, and 47 % as highly aggressive, Burkitt lymphoma; 76 % of all patients had stage IV disease and 49 % had reproductive organ involvement. In addition, a recent multicenter retrospective analysis studied 90 patients with lymphoma (NHL and HL) that occurred during pregnancy [5]. Fifty patients in that series had NHL; the most common subtype was DLBCL, which constituted 56 % of all NHLs and 73 % of B-cell NHLs. The vast majority of patients had newly diagnosed disease. NHL patients more likely had advanced-stage disease compared with HL, and extranodal involvement was common in NHL patients with one-quarter of patients having >1 extranodal site (e.g., breast, gastrointestinal tract, gynecologic (i.e., uterine, cervical, placental), bone marrow, and central nervous system (CNS)) [6]. For patients in this series, HL patients more commonly had bulky disease compared with NHL (30 % vs. 17 %, respectively) [5].

Gestational Data

In the aforementioned series, the diagnosis of lymphoma occurred at a median of 24 weeks gestation (range, 5–38 weeks) with no difference based on lymphoma

subtype [5]. Pregnancy was terminated in only 7 % of patients in order to enable immediate multi-agent chemotherapy (5 in first trimester and 1 patient early second trimester who required high-dose methotrexate). Among other patients, 33 % had therapy deferred until postpartum; these patients had lymphoma diagnosed at a median of 30 weeks gestation compared with all other patients who received treatment during pregnancy, the latter group diagnosed at a median gestation of 22 weeks ($P < 0.0001$).

Treatment

Goals in the treatment of lymphoma during pregnancy can be divided into maternal outcomes, fetal outcomes, and obstetric outcomes. Maternal outcomes of interest include overall survival and progression-free survival. Fetal outcomes of interest include fetal demise, NICU admission, malformations, and low gestational age (defined as below tenth percentile for age and sex). Obstetric outcomes impact both the mother and the fetus and include preterm delivery (defined as delivery prior to 37 weeks gestation), spontaneous preterm delivery (such as premature rupture of membranes (PROM) or preterm labor), postpartum hemorrhage (>500 mL for vaginal delivery, >1000 mL for cesarean), preeclampsia, gestational diabetes, endometritis, and route of delivery.

The decision on whether to administer therapy antepartum and moreover when, which, and how much treatment to recommend is highly individualized and based on the clinical scenario and patients' wishes. General precautions in administering chemotherapy in pregnant patients include renal clearance and third spacing (from amniotic fluid) that may decrease active drug concentrations (including chemotherapy) in the first trimester [3, 7]. Given their low molecular weight, chemotherapeutic drugs have the potential to cross the placenta (Table 14.1). During the organogenesis of the first trimester, especially weeks 2–8, there is a significant increased risk of drug-related teratogenicity, including fetal death [3].

This risk is highly reduced during the second and third trimesters (i.e., beginning week 12), but there remains risk of palate and ear anomalies after 10 weeks gestation [8]. In the second trimester, the risk shifts from that of malformations to low birth weight or intrauterine growth retardation (IUGR) and impact on delivery such as stillbirth and preterm births. Overall, however, most therapeutics are safer for the mother and fetus during the second and third trimesters [8]. There are a handful of chemotherapy agents that are proven human teratogens and contraindicated throughout pregnancy (e.g., older-generation alkylators (i.e., procarbazine and busulfan), thalidomide and lenalidomide, and the antimetabolite, aminopterin) [9].

The decision to administer radiotherapy antepartum is controversial as fetal exposure may cause malformations, growth retardation, and death. Further, long-term side effects such as mental retardation, sterility, and cataracts may occur resulting from cell death due to irreparable DNA damage. The occurrence and severity of these effects depend strongly on fetal dose and gestational stage, with the highest risk during the embryonic, organogenesis, and early fetal phases. Thus,

Table 14.1 Chemotherapy in NHL and its effects on pregnancy

Chemotherapy	Distribution	Maternal Patient	Fetus (first trimester)	Fetus (second and third trimester)
Cytoxan	Liver cytochrome P450; found in the brain, cerebrospinal fluid, milk, saliva, and amniotic fluid	Myelosuppression	First trimester: Malformations: oculofacial malformations, missing digits and nail abnormalities, coronary artery defects, umbilical hernia, hemangioma, imperforate anus, rectovaginal fistula, cleft palate, microcephaly, growth restriction, and developmental delays	Second and third trimester: Growth restriction, microcephaly (rare), and possibly, neonatal pancytopenia
Chlorambucil		Myelosuppression	First trimester: Malformations: renal and ureter agenesis, cardiac defects	
Cisplatin	Highest in the liver and kidneys	Myelosuppression; nephrotoxicity and neurotoxicity	No congenital defects reported; unknown late-term effects	
Bleomycin	Intra-/extracellular fluid	Pneumonitis (caution with supplemental oxygen)	No congenital defects reported	
Methotrexate	Fluid spaces; amniotic fluid	Myelosuppression; acute renal failure	Malformations: cephalic and skull, widened nasal bridge, mandible, cardiac defects (less prominent after 20 weeks)	
Etoposide	All body fluids and tissue	Myelosuppression; prolonged PT/INR	Intrauterine growth restriction and pancytopenia	
Doxorubicin	Wide distribution	Myelosuppression; cardiotoxicity	Anal malformation; rectovaginal fistula, microcephaly	
Vincristine	Wide distribution; poor penetration of blood–brain barrier	Neurotoxicity (peripheral neuropathy, CN palsies; CNS dysfunction, seizures, coma)	ASD; renal hypoplasia, pancytopenia; absent radii	
Vinblastine	Wide distribution; poor penetration of blood–brain barrier	Myelosuppression; neurotoxicity (less than vincristine)	Unclear teratogenicity	

radiotherapy is usually contraindicated prior to week 16, except for rare clinical scenarios [10]. If radiotherapy is administered, a medical physicist should be closely involved in the patient care. Exposure to doses ≥100 mSv (especially ≥500 mSv) is associated with increased risks of malformation and mental retardation, while after 25 weeks, 1 Sv (1000 mSv) or less is considered relatively safe depending on the radiation site. Altogether, if used, radiotherapy should be involved-field or involved-site and used primarily for locations distant from the fetus with additional protection against leakage and room scatter [11].

Collectively, there should be strong consideration to have all treatment delayed until after the first trimester and in select scenarios (e.g., indolent lymphomas, diagnoses in late third trimester, etc.) held until after delivery. It is important to highlight that labor should not be induced to expedite therapy. An overarching goal in the care of all pregnant patients diagnosed with lymphoma is to have delivery at full term (i.e., beyond 37 weeks). A therapeutic abortion should primarily be considered if urgent multi-agent chemotherapy is warranted during the first trimester (especially before week 8), owing to the heightened risk of teratogenicity. Intermediate-to-high-dose corticosteroids may be used as "bridging" therapy, providing symptom management for lymphoma, especially in the first trimester. Steroids that cross the placenta in the smallest amounts, such as prednisolone and methylprednisolone, should be considered.

Treatment of NHL

For asymptomatic patients with indolent NHL (e.g., follicular) and low tumor burden, clinical observation without therapy is an option. Additionally, patients diagnosed later in the third trimester (i.e., beyond 35 weeks) without life-threatening disease, including ones with aggressive histology (e.g., diffuse large B-cell lymphoma (DLBCL)), may have therapy delayed until postpartum. Furthermore, steroids may be used as a "bridge" to allow maturation from the first to second trimester or from late third trimester to delivery.

If antenatal chemotherapy is warranted, therapeutic choices are guided in part by NHL subtype and extent of disease (Fig. 14.1). For patients with DLBCL, rituximab, cyclophosphamide, doxorubicin, Oncovin, and prednisone (R-CHOP) may be considered during the second and third trimesters. Patients treated with 3–6 cycles of R-CHOP prior to delivery have been shown to have overall good outcomes, although with increased incidence of preterm births [5, 8, 12].

The use of anthracyclines is somewhat controversial [9]; transient and permanent cardiomyopathy has been diagnosed in neonates, while other studies have found no link to myocardial damage [13–15]. Despite the known effects in adults, the use of bleomycin or vinca alkaloids has not been associated with pulmonary or neurologic complications of the fetus (Table 14.1) [7, 9]. There remains risk of these drug-specific toxicities, however, in the mother. This includes caution with the use of supplemental oxygen in patients exposed to bleomycin. Antimetabolites are the most teratogenic agents and should be used with caution, especially before 20 weeks. Methotrexate interferes with organogenesis and should be prohibited before 20 weeks; cytarabine has overall lower fetotoxic potential.

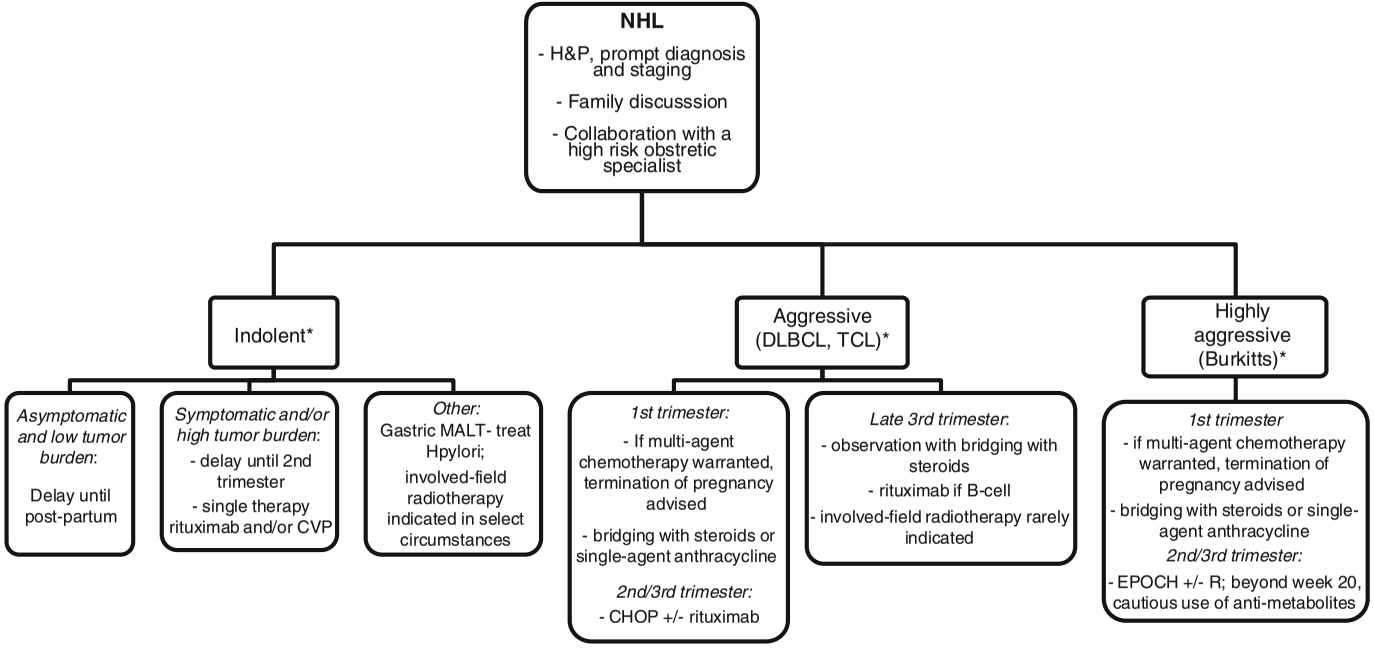

Fig. 14.1 Algorithm for treatment of NHL in pregnancy. *Recommendations given are listed vertically in order of overall preference. Abbreviations: *NHL* non-Hodgkin lymphoma; *DLBCL* diffuse large B-cell lymphoma; *TCL* T-cell lymphoma; *CVP* cyclophosphamide, vincristine, prednisone; *CHOP* cyclophosphamide, Adriamycin, Oncovin, prednisone; *EPOCH* etoposide, prednisone, Oncovin, cyclophosphamide, Adriamycin

Highly aggressive NHLs (e.g., Burkitt's lymphoma) and/or ones that warrant antimetabolite therapy (e.g., primary CNS lymphoma) are challenging to treat. There are reports in the literature utilizing antimetabolites during pregnancy [16, 17]; however, caution is advised regarding fetal teratogenicity (e.g., methotrexate syndrome and myelosuppression). Thus, as noted before, antimetabolites are not recommended before 20 weeks gestation and should also be used thereafter with caution. Additionally, use of etoposide, prednisone, Oncovin, cyclophosphamide, and doxorubicin (EPOCH) infusional therapy may be considered beyond the 1st trimester similar as to recommendations for CHOP. There are no published data of EPOCH during pregnancy, however, lymphoma experts have advocated this approach in select cases (personal communication, Dr. Wyndham Wilson, NCI) interestingly.

Treatment of HL

Treatment decisions in the pregnant patient with HL should be guided by both the stage of the disease and the gestation of pregnancy. Almost all chemotherapeutic agents have documented teratogenic effects either in animal models or in humans [3, 9]. The use of combination chemotherapy is associated with a higher risk of major malformations in the first trimester compared with the risk of single-agent chemotherapy [3, 18, 19]. Although this data is based largely on older chemotherapy regimens that are not commonly in use today, combination chemotherapy should be avoided during the first trimester when the risk of teratogenicity and miscarriage is highest [3].

For early-stage disease diagnosed in the first trimester, the patient may be followed closely, and treatment can be delayed until the second trimester when the risk of congenital malformation is significantly reduced. Another option is to initiate single-agent chemotherapy with a vinca alkaloid or anthracycline [3, 9, 20] during the first trimester. Although this is considered safe for the fetus, the efficacy of single-agent chemotherapy in early-stage HL is reduced compared with combination chemotherapy, and the patient may require combination chemotherapy during the second trimester. In select cases, radiotherapy can be considered for the treatment of early-stage HL. This should be considered primarily for patients with isolated and symptomatic supradiaphragmatic disease involvement [3]. Anthropomorphic phantoms can safely achieve 25 Gy tumor dose while keeping the fetal exposure below 0.1 Gy during first trimester [21].

For patients with advanced HL in the first trimester, the risk to the mother must be weighed against the risk to the fetus. As delaying therapy may adversely affect patient survival, combination chemotherapy with ABVD is recommended. The risk of major malformation with chemotherapy during the first trimester is 10–20 % [22]. Due to the high risk of congenital abnormalities associated with combination chemotherapy, it is appropriate to discuss termination of the pregnancy. There may also be consideration for use of vinblastine and/or steroid therapy in order to bridge patients to the 2nd trimester. During the second and third trimesters, the risk of teratogenicity associated with chemotherapy is significantly reduced, and there is data supporting the safety for both the mother and the fetus of combination chemotherapy [3, 9, 22–29]. Patients with symptomatic HL in the second and third trimesters may be treated with combination chemotherapy as they would if they were not

pregnant (e.g., ABVD). More intensive combination chemotherapy regimens are not recommended (e.g., BEACOPP) due in part to higher doses of anthracycline and the inclusion of alkylating agents in this regimen. For patients with nonaggressive clinical disease, the use of antenatal single-agent vinblastine, reserving combination chemotherapy until after delivery, is an alternative option [20]. During the third trimester, delivery should be planned during a non-cytopenic period of the treatment cycle to minimize the risks of maternal infection and bleeding and the risks of drug accumulation and hematologic suppression in the neonate [30]. As noted before, a critical overarching goal of all therapy should be for full-term delivery (i.e., 37 weeks and beyond). Additionally, chemotherapy should not be administered after weeks 35–36 of pregnancy as the spontaneous delivery becomes more likely.

For highly select cases, radiotherapy may be considered in the second and third trimesters, although the risk of fetal exposure is increased compared to the first trimester. During the second and third trimesters, the progression of the pregnancy results in an increased total fetal dose of 0.12–0.19 Gy even with abdominal shielding due to increased fetal size and close proximity of the fetus to the treatment volume [21]. However, these simulations were done using mantle field radiation, which is no longer recommended for the treatment of HL. Radiotherapy at distant sites from the abdominopelvic region such as for the nasopharynx was shown to result in exposures of less than 0.1 Gy no matter what is the stage of pregnancy [21]. If risks of chemotherapy are deemed prohibitive and treatment is warranted, patients can be considered for treatment with involved field radiotherapy of isolated cervical or axillary disease (primarily for control of local symptoms) with appropriate abdominal shielding during the second and third trimesters [3, 31].

Overall, data on outcomes of pregnant women with HL have shown 3-year progression-free survival of 82 % and overall survival of 97 % at a median follow-up of 41 months among pregnant women with HL [24]. These data also showed acceptable fetal outcomes with no cases of fetal demise, NICU admission, or malformation [24]. For further information on complications related to treatment, please see the section on "Complications" (Fig. 14.2).

Targeted Therapy

There are limited data on the use of biologic agents in pregnancy. Of available data in the literature, rituximab has been the best studied in the treatment of both indolent and aggressive lymphoma pregnancy. An obstetric complication seen in rituximab-treated patients is preterm birth; of 153 reported pregnancies exposed to rituximab globally, there were a total of 90 live births; 27 % were mothers with NHL; 76 % resulted in full-term deliveries and 19 % in preterm deliveries. This rate of preterm delivery is above that seen in the general population (10–12 %) [32]. However, it is unclear if this is rituximab related or an independent risk from malignant disease.

As rituximab may deplete CD20+ B cells for up to 6 months, there is also a potential risk of B-cell suppression in the neonate regardless of rituximab dose. This

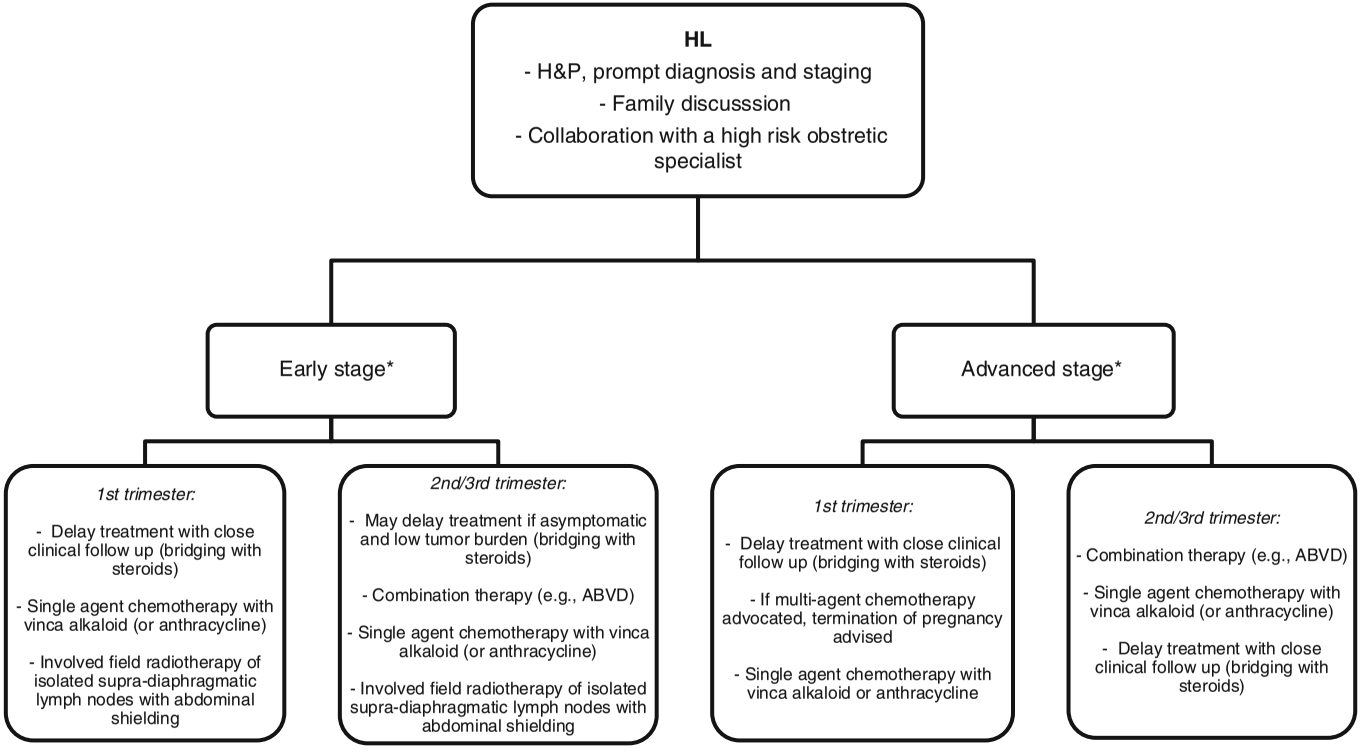

Fig. 14.2 Algorithm for treatment of HL in pregnancy. *Recommendations given are listed vertically in the order of overall preference. Abbreviations: *HL* Hodgkin lymphoma, *H&P* history and physical, *ABVD* Adriamycin, bleomycin, vinblastine, and dacarbazine

was seen in a pregnant 32-year-old female treated with R-CHOP for DLBCL in which cord blood had no CD20+ B cells, IgM, IgA, and low IgG levels [33]. In spite of this, the child had no serious infectious complications and B-cell counts normalized following birth; this was also noted by Klink et al. likely owing to the neonate's dependence on maternal IgG while B cells developed [34]. Overall, with caution given toward B-cell depletion, which is typically reversible, rituximab appears to be generally safe in pregnancy [35]. Other than generic manufacturer drug warnings, there are no additional data regarding the use of other cellularly targeted therapeutic agents such as obinutuzumab, ibrutinib, or brentuximab vedotin during pregnancy. As recently reviewed [35], small molecules like tyrosine kinase inhibitors (TKIs), like chemotherapy, are known to cross the placenta during pregnancy; due in part to this as well as the potential effect of TKIs on physiologic function, their use are currently not advocated.

Supportive Therapy

Supportive care recommendations for the treatment of cancer during pregnancy can be found in a separate chapter dedicated to this topic.

Maternal and Fetal Complications

Data on maternal and obstetric complications of lymphoma in pregnant women are somewhat limited, and the vast majority of available information stems from retrospective analyses. Consideration must be given to physiologic changes in pregnancy as they may relate to chemotherapy including increased plasma volume, increased renal clearance of drugs, and the third space created by amniotic fluid [3].

In a retrospective study by Evens et al., patients diagnosed with NHL and HL during pregnancy were reported to have a slightly higher incidence of postpartum hemorrhage (defined as >500 mL for vaginal delivery or greater than 1,000 mL for cesarean) with 10 % in the group receiving antenatal therapy vs. 0 patients in the groups who received no antenatal therapy. An equal number of patients with NHL in the treatment and nontreatment groups had postpartum hemorrhage (4 % patients in treatment group vs. 8 % patients in nontreatment group) [24]. These same data showed that 44 % of all patients had preterm labor. In the HL group, 39 % of patients who received antenatal treatment had preterm labor as compared with 38 % of patients who had no antenatal therapy. In the NHL group, 32 % of the antenatal treatment group compared with 40 % of the nontreatment group had preterm deliveries [24]. There was a nonsignificant trend toward increased spontaneous preterm delivery (premature rupture of membranes or preterm labor).

In the NHL group, 18 % of the antenatal therapy group versus 23 % of the nontreatment group had premature rupture of membranes. Of the HL group, only one patient experienced premature rupture of membranes, and she was in the no therapy arm [24]. There was also a trend toward increased incidence of preeclampsia that

did not reach statistical significance. These data suggest similar or slightly higher rates of cesarean section compared to the general population. Notably, there was no significant increase of endometritis or gestational diabetes seen.

For fetal outcomes, the effect of chemotherapy and radiation has been studied in lymphoma as well as other malignancies. As elucidated before, the teratogenicity of a drug depends on the timing of exposure, drug dose, and drug characteristics affecting placental transfer. High lipid solubility, low molecular weight, and loose binding to plasma proteins increase transfer of drugs from the mother to fetus [9]. There is an increased risk of spontaneous abortion in the first trimester. Prior to the second week of pregnancy, spontaneous abortion is the most likely result of an insult. As discussed, the highest risk for malformation occurs during organogenesis in the 2nd to 8th weeks of gestation. After organogenesis, the eyes, genitals, hematopoietic systemic, and CNS remain susceptible to chemotherapy. The risk of severe malformation and mental retardation is significantly reduced after the 13–15th week of gestation [3, 9]. These risks are reduced with single-agent chemotherapeutic regimens versus combination regimens [18, 19]. They are also reduced when antimetabolites are excluded [3, 18, 19]. Second and third trimester exposure is not associated with malformations [3, 9, 23].

In data specific to lymphoma, Evens et al. showed a nonstatistically significant trend for neonates to be small for gestation age if the mother received antenatal versus deferred therapy, but no increase in ICU admissions [24]. There has been controversy in the past regarding the effect of anthracyclines on fetal cardiac outcomes; however, more contemporary data support the general safety during pregnancy. This includes an analysis of 81 children with fetal exposure to anthracyclines without evidence of myocardial damage on echocardiogram or functional assessment [3, 15, 36]. In addition, a recent prospective study among 47 children exposed to antenatal therapy (including sub-analysis of 26 children exposed to anthracyclines during pregnancy) showed normal cardiac structure and function by electrocardiography and echocardiography at 36 months [37]. In terms of the effect of radiation on fetal outcomes, this may be found in a separate chapter dedicated to this topic.

More data regarding long-term neurodevelopment of children exposed to chemotherapy is needed, but existing data are reassuring. Aviles et al. found no cognitive, neurological, or psychological abnormalities in 84 children exposed prenatally to chemotherapy, including 18.7 years of follow-up [25]. Formal fertility and cognitive abilities were documented in 12 second-generation children. A combined retrospective and prospective multicenter study involving children who had prenatal exposure to chemotherapy identified a 2.5-point decrease in IQ associated with each week of prematurity in children exposed to chemotherapy [38]. The prospective component of this study was enlarged and prolonged; among 115 children exposed to varied antenatal treatments who had prospective assessment of neurologic function through 36 months, there was no impairment in cognitive or general development [37]. Furthermore, similar to the prior analysis, the cognitive score of children exposed to antenatal therapy was closely linked to gestational age. The average cognitive score increased by 2.9 points for each additional week in gestational age at birth. These data underscore the critical importance of avoiding iatrogenic

prematurity so that impairment in neurodevelopment may be prevented. The safety of breastfeeding during chemotherapy should be evaluated based on maternal health and medications used, although breastfeeding generally is not advised [39].

Special Considerations

Data regarding diabetic pregnant patients with lymphoma are limited. These patients should be treated as per best consensus recommendations on diabetic control with pregnancy. HIV increases the risk of lymphoma, although there is no data on change in incidence during pregnancy. NHL is an AIDS-defining illness, while HL is not [40, 41]. Outcomes of AIDS-related lymphoma have been greatly improved with the use of antiretroviral medications. Data on this population are limited mainly to case reports suggesting that HIV-positive pregnant women with lymphoma should be treated as other women with the addition of double or triple antiretroviral therapy throughout pregnancy [41–43]. Additional prophylaxis for pneumocystis and mycobacterium avium complex should also be considered [41].

Venous thromboembolism during pregnancy is a concern with pulmonary embolism (PE) being a leading cause of maternal death. This is compounded by the fact that cancer is considered to be the second leading cause of maternal mortality behind pregnancy-associated vascular complications. Pregnancy itself is a risk factor for deep vein thrombosis (DVT) (i.e., 4–50 times higher than nonpregnant individual) and can present as DVT in the leg and unusual sites (i.e., cerebral and splanchnic veins) and pulmonary embolism [44]. Preferred treatment includes low molecular weight heparin (LMWH) for short- and long-term anticoagulation [45] as it does not freely cross the placenta and is relatively safe for the woman and fetus. There is also improved efficacy of LMWH compared with coumadin in patients with cancer [46]; aspirin is not indicated. The optimal duration is unknown, but one should keep in mind the increased risk of DVT in the postpartum period. Anticoagulant therapy should be continued for at least the initial 6 weeks following birth. Fondaparinux and the novel anticoagulants including oral factor XA and direct thrombin inhibitors have not been evaluated in pregnant patients and should be avoided.

Conclusions

Lymphoma is one of the most common cancers diagnosed during pregnancy. HL is slightly more common than NHL with NHL patients often presenting with aggressive histology and extranodal disease. Staging studies should include judicious use of radiation with US ± MRI being the recommended imaging modalities. The decision to administer chemotherapy and/or other therapeutic agents during gestation is individualized with the risks of antenatal therapy weighed against the potential adverse effect of delaying curative therapy. Collectively, there should be a strong consideration to have all (nonsteroid) treatment delayed until after the first trimester, and in select scenarios (e.g., indolent lymphomas, diagnoses in late third trimester, etc.), until after delivery.

A therapeutic abortion should be considered if combination chemotherapy is warranted during the first trimester (especially before week 8), owing to the heightened risk of teratogenicity. Intermediate-to-high-dose corticosteroids may be used as "bridging" therapy, providing symptom management for lymphoma, especially in the first trimester. Recent data have shown that standard chemotherapy regimens for NHL and HL (without antimetabolites) administered during the second and third trimester, including as early as 13 weeks gestation, are associated with minimal maternal complications or fetal detriment. The most commonly identified perinatal events that occur in pregnant patients with lymphoma include induction of labor, PROM, and cesarean delivery, with no obvious differences seen among patients who receive antenatal versus deferred therapy. It is also important to highlight that labor should not be induced to expedite therapy. An overarching goal in the care of all pregnant patients with NHL or HL is to have delivery at full term (i.e., beyond 37 weeks). In addition, all patients should be managed concurrently with high-risk maternal–fetal medical expertise and in centers with experience in managing cancer during pregnancy.

Altogether, recent data have helped define optimal timing of therapy, maternal complications, perinatal events, and fetal and maternal outcomes. However, the assessment and management of patients diagnosed with lymphoma during pregnancy remains complex and highly individualized. Continued studies and additional prospective data are needed to continue to help guide clinicians in order to optimize maternal survival and fetal and childhood outcomes.

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Survivorship: Support Group Resources

http://www.cancercare.org/diagnosis/lymphoma.
http://www.cancer.org/treatment/supportprogramsservices/index
http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6298225

Managing Leukemia During Pregnancy

15

Eilon Krashin and Michael Lishner

Introduction

The incidence of leukemia during pregnancy is relatively low, estimated to be about 1 in every 75,000–100,000 pregnancies [9]. This incidence may increase concomitant with the trend to postpone pregnancy until later years. It is estimated that the majority of cases diagnosed in pregnancy are acute, with acute myeloid leukemia (AML) accounting for two-thirds of cases and acute lymphocytic leukemia (ALL) accounting for one-third. Chronic leukemia, generally considered a disease of old age, is uncommon during pregnancy. Chronic myeloid leukemia (CML) occurs in up to 10 % of pregnancy-associated leukemias, and chronic lymphocytic leukemia (CLL) is extremely rare [24]. Due to the relative rarity of pregnancy-associated leukemia, most of the relevant literature is based on small, retrospective studies and case reports rather than on large, prospective studies.

The physiological changes a woman's body undergoes during pregnancy may obscure the diagnosis of leukemia. The nonspecific symptoms and signs of leukemia such as weakness, fatigue, and pallor and laboratory findings such as anemia and leukocytosis may be erroneously attributed to gestation. Nonetheless, there is no evidence suggesting a delay in the diagnosis of leukemia in pregnant patients compared to nonpregnant controls. Most cases of CML and CLL presenting during pregnancy are diagnosed due to abnormal routine blood counts.

The diagnosis of leukemia requires a morphologic, immunophenotypic, and cytogenetic examination of bone marrow. A bone marrow biopsy can be performed safely during pregnancy without harming the fetus [28].

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Table 15.1 Treatment approaches for acute leukemia in pregnancy

Acute myeloid leukemia	
First trimester	Pregnancy termination, then conventional chemotherapy
Second/third trimester	Treat as nonpregnant women, early delivery if allogeneic stem cell transplantation is recommended
Acute promyelocytic leukemia	
First trimester	Pregnancy termination, then conventional therapy (ATRA with anthracycline)
Second/third trimester	Treat as nonpregnant women including ATRA
Acute lymphoblastic leukemia	
First trimester	Pregnancy termination, then conventional chemotherapy
Second trimester	Consider protocols excluding methotrexate until third trimester
Third trimester	Treat as nonpregnant women, early delivery if allogeneic stem cell transplantation is recommended

ATRA all-trans retinoic acid

Management of Acute Leukemia During Pregnancy

Acute leukemia is an extremely aggressive disease and fatal unless treated promptly. It is associated with complications affecting both the pregnancy and the fetus, including cytopenia associated with infection and bleeding, leukostasis, decreased placental blood flow and oxygen exchange, and disseminated intravascular coagulopathy (DIC). Acute leukemia may increase the risk of miscarriage, fetal growth restriction, and perinatal mortality [2]. Some studies suggest that postponing treatment until the postpartum period is associated with increased maternal mortality [14]. Therefore, a diagnosis of acute leukemia mandates immediate, full treatment regardless of gestational stage.

In light of the toxic effects of therapy on the fetus and the mother, it is recommended that women diagnosed with acute leukemia during the first trimester terminate the pregnancy. However, if leukemia presents during the second or third trimester, the application of standard chemotherapy protocols will usually allow both disease remission and delivery of a normal infant. Whenever chemotherapy is required, delivery should be timed for 2–3 weeks after treatment to coincide with recovery of the maternal blood count. Overall, the outcomes for pregnant patients with AML are similar to those of nonpregnant women [9].

Treatment approaches for acute leukemia in pregnancy are summarized in Table 15.1.

Acute Myeloid Leukemia

The standard protocol for the treatment of acute myeloid leukemia (AML) consists of a combination of cytosine arabinoside (cytarabine) with an anthracycline for induction, followed by various intensive combinations for consolidation therapy. Experience with administration of cytarabine during pregnancy is relatively limited. A review of 93 cases of pregnant women exposed to cytarabine alone or in combination with one

or more therapeutic agents (thioguanine, doxorubicin, vincristine, or prednisone) for the management of acute leukemia reported four cases of limb malformations associated with first trimester exposure. Among 89 cases where cytarabine was used during all trimesters, there were 6 cases of intrauterine fetal death (IUFD), 12 cases of intrauterine growth retardation (IUGR), 5 cases of transient neonatal cytopenias, and 2 cases of neonatal death secondary to severe infections [11].

The experience with anthracycline treatment during pregnancy is limited mostly to doxorubicin and daunorubicin. Idarubicin, which is more lipophilic, has increased placental transfer and an affinity to DNA and may be associated with higher rates of adverse fetal outcomes. Therefore, it should be avoided during pregnancy. Daunorubicin and doxorubicin are not associated with an increased risk for severe congenital malformations beyond the first trimester [18], although daunorubicin is more commonly used for the treatment of AML. A major concern is whether anthracyclines are cardiotoxic to the developing fetus. A long-term follow-up study of 81 children whose mothers were treated with chemotherapeutic regimens including anthracyclines found no myocardial damage in both gestational and postnatal echocardiograms [5]. While in utero exposure to anthracyclines does not produce significant changes in cardiac systolic function based on conventional echocardiographic parameters, children exposed to anthracyclines during gestation have a lower normal fractional shortening and mildly decreased left ventricular wall thickness [15], findings of yet undetermined clinical significance.

Given the risk of significant fetal malformations, the need for prompt administration of induction chemotherapy during the first trimester should follow a strong recommendation for pregnancy termination. The available data suggest that a combination regimen consisting of cytarabine with daunorubicin or doxorubicin may be administered safely after the first trimester. Close fetal follow-up is recommended, especially cardiac function monitoring and assessment of limb development. Since aggressive chemotherapy may cause severe complications such as infections, nausea, and cytopenias, adequate maternal supportive treatment is essential.

Consolidation therapy protocols in AML may include lower doses of cytarabine and an anthracycline or other drugs, such as etoposide. Consolidation with cytarabine and anthracyclines is preferred over etoposide, where experience is extremely limited. Treatment of AML in relapse consists of high-dose chemotherapy, bone marrow transplantation (BMT), or experimental drugs. None of these therapeutic options can be administered safely during pregnancy.

Acute Promyelocytic Leukemia

Induction therapy for patients with acute promyelocytic leukemia (APL) includes all-trans retinoic acid (ATRA) and chemotherapy, most commonly an anthracycline. As with all other vitamin A derivatives, ATRA should be avoided during the first trimester owing to extremely high teratogenicity associated with retinoid use (up to 85 %), including severe neurological and cardiovascular malformations. It is commonly accepted that pregnancy termination should precede administration of ATRA during the first trimester.

Normal pregnancy outcomes without congenital malformations were reported after administration of ATRA in combination with an anthracycline during the

second and third trimesters [18]. Due to the risk of fetal cardiac toxicity, stringent fetal monitoring is recommended, with specific emphasis on cardiac function.

Arsenic trioxide is an established teratogen. Thus, it is contraindicated throughout pregnancy [24].

APL is of special importance to the obstetrician because of its association with disseminated intravascular coagulopathy (DIC), which may severely complicate management of pregnancy, labor, and delivery. Patients should be closely monitored for clinical and laboratory manifestations of DIC.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is rare among adults, and less than 30 cases during pregnancy have been reported [26]. Since ALL is a highly aggressive disease, adequate chemotherapy must be administered immediately after diagnosis.

Methotrexate, a crucial component of most ALL chemotherapeutic protocols, is highly teratogenic. First trimester methotrexate exposure is associated with an increased risk of miscarriage. Exposure to high-dose methotrexate (>10 mg/week) during the first trimester was associated with the fetal aminopterin syndrome—cranial dysostosis, delayed ossification, hypertelorism, wide nasal bridge, micrognathia, and ear anomalies [8]. The most sensitive period for malformations appears to be from 6 to 8 weeks of gestation, with risk diminishing as pregnancy advances [19]. Previously, termination of pregnancy was recommended when ALL was diagnosed prior to the twentieth week of gestation due to concern for methotrexate-induced malformations [24]. However, reports from recent years have not shown a significant risk of developmental side effects associated with second trimester methotrexate exposure [18]. Evidence however is relatively scarce. When ALL is diagnosed during the first trimester, termination of pregnancy should be strongly recommended, followed by immediate administration of an adequate treatment regimen. In the second trimester, treatment protocols excluding methotrexate should be considered. Chemotherapeutic regimens including L-asparaginase, vincristine, anthracyclines, cyclophosphamide, and cytarabine have previously been used in the second trimester [26]. During the third trimester, protocols similar to those employed with nonpregnant patients are applied, with close observation of mother and fetus and delivery planned for a non-cytopenic period.

The Philadelphia chromosome (chromosome 9:22 translocation) is found in 15–30 % of all cases of adult ALL. Current treatment for Philadelphia chromosome-positive ALL consists of chemotherapy and a tyrosine kinase inhibitor (TKI). The potential teratogenicity of TKIs as well as chemotherapy must be considered. There are few reports of treatment of Philadelphia chromosome-positive ALL in pregnancy. In two cases, chemotherapy was administered during pregnancy, with TKIs initiated after delivery [26]. Given the available data on the effects of TKIs on the fetus, use during pregnancy in Philadelphia-positive ALL should be based on risk–benefit analysis for both mother and fetus. However, some authors recommend avoidance of TKIs throughout pregnancy [21].

Chronic Myeloid Leukemia

The incidence of chronic myeloid leukemia (CML) is about 1–2 cases per 100,000 per year, yet only 10 % of cases occur in women in childbearing age. The disease is characterized by abnormal myeloid cell proliferation caused by activation of an abnormal fusion gene, BCR-ABL. Overall, pregnancy does not appear to effect on disease outcomes.

Traditional therapeutic options have included interferon alpha, chemotherapy, and bone marrow transplantation. Imatinib mesylate (STI571, Gleevec, Glivec) is a TKI that has been shown to induce dramatic hematological and cytogenetic responses in CML patients. Today, more potent second-generation (dasatinib, nilotinib, bosutinib) and third-generation (ponatinib) TKIs are available for imatinib-resistant patients.

Interferon alpha (IFN-α) is a large (19 kDa) protein that does not cross the placental barrier to a great extent. Neither mutagenicity in vitro nor teratogenicity has been observed in animal studies. Two major case reports [17, 27] reported the outcomes of 40 pregnant patients, 8 of whom with CML, who were treated with IFN-α in various trimesters. There were no reports of congenital malformations when IFN-α was given as monotherapy. It is therefore considered safe throughout pregnancy [20].

Hydroxyurea is a cytotoxic drug which may induce clinical and hematological remission in CML patients. Hydroxyurea exposure is known to produce congenital anomalies in animals. A review of 31 pregnant women treated with hydroxyurea (22 in the first trimester) reported 3 minor congenital abnormalities, 2 cases of intrauterine fetal death, and 9 premature deliveries. Second and third trimester exposure was associated with increased risk of preeclampsia [25]. Based on the available information, hydroxyurea administration should be avoided during the first trimester.

Imatinib Several studies reported significant complications when imatinib was administered during the first trimester. A series of 125 patients who conceived while on imatinib reported a 14.4 % rate of spontaneous abortions and a 9.6 % rate of fetal abnormalities, including a 100-fold greater-than-expected incidence of exomphalos (three cases), as well as renal, bony, and pulmonary abnormalities [22]. A recent series of 167 patients exposed to imatinib during organogenesis displayed similar results [1]. It is hypothesized that these malformations may be due to the inhibition of "off-target" tyrosine kinases such as PDGFR-α. Little information is available on imatinib use in later trimesters. In a report of two patients exposed to imatinib during the third trimester, the concentrations of imatinib and its active metabolite, CGP74588, were found to be higher in the placenta than in maternal blood but low or undetectable in the umbilical cord, suggesting limited placental transfer in late pregnancy, with no observed fetal complications [23].

Dasatinib There have been 17 case reports on dasatinib exposure during pregnancy [7, 10, 12]. In one series of 8 women who conceived while on dasatinib

treatment, 3 underwent termination of pregnancy, 2 had spontaneous abortions, and 3 delivered healthy babies. In one reported case of dasatinib treatment during pregnancy, termination was required in the second trimester due to fetal hydrops [10]. Other reports showed normal pregnancy outcomes when dasatinib was discontinued during the first trimester following pregnancy confirmation.

Nilotinib Of the two published reports of nilotinib exposure in early pregnancy, one resulted in a normal delivery, while the other required pregnancy termination at 3 months due to a large exomphalos [1].

All TKIs are assigned pregnancy category D (evidence of human fetal risk, yet potential benefits may warrant use despite potential risk). The present recommendation for women treated with imatinib and other TKIs is to use appropriate methods of contraception. Women wishing to conceive should remain off TKI therapy prior to conception and preferably throughout pregnancy.

Leukapheresis may be used in the management of acute and chronic leukemia for rapid reduction of elevated white blood cell counts in patients with impending vascular occlusion. The treatment can be performed safely in pregnancy [24], and there have been no reports of adverse events to mother or fetus associated with this procedure. However, leukapheresis is not readily available in all centers, is costly and time consuming, and may be limited by the need for good venous access.

Allogeneic stem cell transplantation remains a treatment option for CML patients who have failed treatment with imatinib and have an HLA-identical donor. Given the aggressiveness of this treatment and lack of reports on stem cell transplantation during pregnancy, it is absolutely contraindicated.

CML Diagnosed During Pregnancy

CML is usually diagnosed incidentally during pregnancy by observation of abnormal blood counts. For many patients, the "watch-and-wait" approach is adequate, with treatment reserved for those with elevated white blood cell counts ($>100\times10^9$/l) or platelet counts ($>500\times10^9$/l). Leukapheresis can be particularly useful during the first trimester and may avoid drug therapy. Low-dose aspirin or low molecular weight heparin, both safe during pregnancy, may also be required to prevent thrombotic events. If leukapheresis is not well tolerated or if counts are poorly controlled despite treatment, IFN-α is the drug of choice.

In cases where there is poor response or intolerance to IFN-α, one approach is to initiate treatment with hydroxyurea. Another approach is the introduction of a TKI. Although there are isolated reports on imatinib safety during late pregnancy [23], there is limited evidence to support this approach. Therefore, most experts recommend avoiding use of imatinib and other TKIs throughout pregnancy [21], aside from patients who present with accelerated disease who reject pregnancy termination. Treatment options per trimester in CML are displayed in Table 15.2.

Table 15.2 Treatment options in CML per trimester

First trimester	Leukapheresis for WBC $>100\times10^9$ IFN-α
Second trimester	Leukapheresis for WBC $>100\times10^9$ IFN-α Consider hydroxyurea if IFN-α cannot be tolerated
Third trimester	

IFN-α Interferon alpha

Pregnancy in Established CML

Given the association of congenital abnormalities with first trimester exposure to imatinib, it is recommended that patients with established CML discontinue imatinib before attempting to conceive. The advisability of discontinuing treatment prior to planned pregnancy depends on the molecular response to imatinib. The ideal scenario for stopping a TKI is in a patient with sustained complete molecular response, defined as undetectable BCR-ABL transcripts (using sensitive RT-PCR test) or a 4.5 log reduction in transcript load for at least 2 years. About 40 % of patients who have achieved sustained complete molecular response can remain off TKI therapy for at least two more years, and those who relapse usually regain their previous excellent disease response upon reintroduction of TKIs [13]. However, if there is less than a major molecular response to TKI, cessation of treatment may lead to cytogenetic or hematological relapse. Even among patients who have achieved sustained molecular negativity, approximately 60 % will experience an increase in BCR-ABL transcript level. Therefore, all patients who stop their TKI in order to become pregnant should be cautioned that their tumor load may rise off treatment. When therapy is stopped, it is recommended that the period from imatinib cessation to pregnancy not exceed 6 months in order to prevent very prolonged periods off treatment. A few days are required between cessation of treatment and unprotected intercourse to permit imatinib washout from the body. BCR-ABL transcripts should be monitored at baseline and at 6–8-week intervals, with more frequent monitoring if transcript levels increase. Imatinib should be resumed as soon as possible after delivery. Because of the potential for adverse reactions from imatinib in nursing infants, breastfeeding is strongly discouraged [23].

Among women who have discontinued treatment after achieving a complete molecular response, no treatment may be required throughout pregnancy. IFN-α therapy can be introduced when loss of cytogenetic response has occurred. Introduction of IFN-α should be considered sooner in women who have stopped a TKI without achieving a major molecular response [21].

Accelerated Disease

Only one case of accelerated phase CML during pregnancy has been reported [3]. The treatment of choice for accelerated phase is imatinib and allogeneic stem cell transplantation. In cases of an unresponsive disease or blast crisis, patients should be treated as in acute leukemia. Due to the need for prompt initiation of aggressive treatment, pregnancy termination should be strongly considered.

Hairy Cell Leukemia

Hairy cell leukemia accounts for approximately 2–3 % of all adult leukemias in the Western world and is very rare during pregnancy. The disease is characterized by an indolent course; therefore, treatment should preferably be delayed until after delivery. When indicated, IFN-α is the treatment of choice. Due to scant data regarding its use during pregnancy, cladribine is not recommended. Splenectomy is reserved for those who fail medical therapy.

Chronic Lymphocytic Leukemia

There are seven case reports of chronic lymphocytic leukemia (CLL) in pregnancy, and only one patient required treatment (leukapheresis) due to advanced disease with severe cytopenias. In all reported cases, patients gave birth to healthy infants with no congenital malformations. There are no data regarding the spread of CLL cells to the fetus. Two cases of placental invasion have been described, but the clinical significance of this is unclear [16].

Since CLL is an incurable disease with an indolent clinical course, treatment should be delayed unless the patient is symptomatic. Most patients can be monitored closely without treatment until delivery or disease progression.

There are several options for treating CLL. The most common drugs are chlorambucil, corticosteroids, and fludarabine. First trimester exposure to chlorambucil has been associated with congenital abnormalities including renal agenesis, ureteral malformations, and cardiovascular anomalies. The few cases of second and third trimester chlorambucil exposure have not been associated with congenital malformations. Corticosteroids may be indicated for treating the autoimmune complications of CLL. There are no reports on the administration of fludarabine during pregnancy. However, since antimetabolites seem to be more teratogenic than other chemotherapeutic agents, their use during pregnancy should be avoided, if possible [16]. Leukapheresis should be offered in case of placental insufficiency associated with severe leukocytosis ($>100\times10^9$/l). There is no chemotherapeutic protocol for CLL which has been shown to be safe during the first trimester. However, CVP (cyclophosphamide, vincristine, prednisone) is an acceptable option from the second trimester onward. As rituximab treatment from the second trimester onward has been reported for other conditions [18], its apparent safety makes it a potential treatment for CLL in pregnant patients.

Outcomes

Several small studies suggest that outcomes for infants born to leukemic mothers may not differ significantly from those of infants born to healthy mothers. One study retrospectively followed the clinical outcomes of 54 infants born to pregnant women who received chemotherapy for hematological malignancies during

the first trimester of pregnancy, 14 of whom had acute leukemia. Low birth weight was the most frequent finding (18.5 %), yet all children recovered normal weight within 10 weeks. Physical, psychological, and neurological development were normal [6].

The available literature on late outcomes of antileukemia chemotherapy is limited and is mainly based on retrospective data. A long-term follow-up study (average 18.7 years) of 84 children born to mothers with hematological malignancies, of whom 29 had acute leukemia, reported normal physical, neurological, and psychological development [4]. The malignancy rate was similar to that of the general population, and 12 of these children became parents.

Ethical Considerations

The maternal–fetal ethical conflict, inherent in any case of cancer during pregnancy, is especially relevant in acute leukemia due to the need for prompt administration of high-dose chemotherapy. It is further complicated by limited clinical experience in the face of the dramatic decisions that need to be made. Treatment of pregnancy-associated leukemia must be case specific. Every decision should be made together with the patient and her significant other after careful consideration of the risks and benefits. However, when there is a clear risk to the mother, her safety must supersede fetal risk.

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Managing Thoracic Tumors During Pregnancy

16

Nicholas Pavlidis and George Zarkavelis

Lung Cancer

Introduction

The purpose of this chapter is to review the therapeutic management and outcome of thoracic tumors during pregnancy. Solid gestational malignant tumors of the lower respiratory tract are rarely documented. Among the chest malignancies diagnosed during pregnancy, lung cancer is the most common cancer followed by thymomas and very rarely by pleural mesothelioma.

Cancer diagnosed during pregnancy is a rare phenomenon complicating one out of 1000 pregnancies. The most frequent diagnosed cancers are obviously those with a peak incidence during woman's reproductive years such as breast and cervical cancer, melanoma, and lymphoma. Lung, gastrointestinal, and urological epithelial malignancies are very rarely diagnosed during gestation [1–3].

Lung cancer is one of the most common killers in developed societies with high cancer-related mortality [4]. Although the incidence of lung cancer is still low during pregnancy, it will be probably increased due to both cigarette smoking in young women and to delaying childbearing to later in life [1].

Non-small cell lung cancer (NSCLC) is the most frequent histological type accounting for 80 % of all cases, followed by small cell lung cancer (SCLC) which constitutes the rest 20 % of patients. Usually, both types of lung cancer are diagnosed in advanced stages where treatment is mainly palliative. Overall survival remains poor. It is generally characterized as a clinically aggressive disease with high predilection to involve placenta and/or fetus.

During the last 15 years, 66 cases of lung cancer, mostly NSCLC, have been reported in the literature [5, 7–12].

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Reported Cases

We searched the Medline and the International Cancer in Pregnancy registration study (CIP study; www.cancerinpregnancy.org) registered with clinical/trials. Gov, number NCT00330447).

Demographics

Since 1998, 66 pathologically confirmed gestational lung cancer cases have been published. The median patients' age was 36 years old, ranging from 17 to 45 years, and the median maternal gestational age was 27.3 months [5–12].

Histopathologically, the most common type was NSCLC. Eighty-two percent of patients were diagnosed with NSCLC, while only 18 % with SCLC.

Smoking history was present in 35 % of pregnant mothers and absent in 27 %, and no information was available for the rest of the patients.

Ninety-seven percent of patients were diagnosed in advanced clinical stages (III–IV) indicating that lung cancer during pregnancy doesn't behave as a slowly growing tumor (Table 16.1) [5, 7–12].

Treatment and Outcome

Thirty-four patients (51.5 %) were treated postpartum and 16 (24 %) during gestational period. Platinum-based chemotherapy was administered in 40 patients (60.5 %), whereas five patients (7.5 %) received targeted treatment, four with erlotinib or gefitinib and two with crizotinib. All of these patients were positive for EGFR or EML4-ALK mutations. Only three patients were treated with palliative radiotherapy. No major responses to chemotherapy have been observed, while targeted treatment offered disease stability for several months. Nevertheless, not adequate data are available to support the use of targeted treatment during pregnancy.

Table 16.1 Demographics of patients with gestational lung cancers: literature review

	Total number of cases (%)
Number of patients (total)	66
Median age (years)	36 (17–45)
Gestational week at diagnosis	27.3 (8–38)
Histopathology	
NSCLC	5.4 (8 %)
SCLC	12 (18 %)
Smoking history	
Absent	18 (27 %)
Present	23 (35 %)
Unknown	25 (38 %)
Stage	
Early (I–II)	1 (1.5 %)
Advanced (III–IV)	64 (97 %)
Unknown	1 (1.5 %)

Table 16.2 Treatment and outcome of patients with gestational lung cancer: literature review

	Number of patients
Treatment	
During gestation	16 (24 %)
Postpartum	34 (51.5 %)
No treatment	9 (13.5 %)
Unknown	7 (11 %)
Chemotherapy	40 (60.5 %)
Erlotinib/gefitinib	4 (6 %)
Crizotinib	2 (3 %)
Radiotherapy	3 (4.5 %)
Maternal outcome (from diagnosis)	
Death 1 month postpartum	8 (12 %)
Alive in 3–5 months	26 (39.5 %)
Alive in 6–11 months	20 (30.5 %)
Alive in 12 months or more	12 (18 %)
Products of conception (outcome)	
Abortion (induced/spontaneous)	6/1
Healthy baby	54 (82 %)
Fetal metastases	3 (4.5 %)
Placental metastases	11 (17 %)
Unknown	1

Maternal survival was very poor. Twelve percent died within 1 month during postpartum period, and 70 % had an overall survival of a few months. Only 12 patients, mainly those diagnosed with early-stage disease, experienced longer survival.

Eighty-two percent of the newborns were born healthy. Metastatic disease to the products of conception was detected in 14 cases, 11 on the placenta and three on the fetuses [5, 7–12] (Table 16.2).

Thymic Tumors

Thymic tumors are rare neoplasms with a peak incidence from 55 to 65 years accounting for less than 1 % of adult cancers. According to the World Health Organization (WHO), thymic tumors are classified as thymomas (types A, AB, B1, B2, B3) or as thymic carcinomas (type C). Presenting symptoms include local pain, dyspnea, or superior vena cava syndrome and occur more commonly in association with autoimmune or other immunological diseases.

These tumors are rarely diagnosed during pregnancy. In the literature, there are only 13 cases reported, all of which are thymomas of various WHO types (Table 16.3) [13, 14].

Table 16.3 Thymic tumors in pregnancy

Total number	13
Median age (years)	25.5 (19–34)
Median size (at diagnosis)	7.6 cm (4–17.3)
WHO type	
A	1/13
AB	2/13
B1	1/13
B2	1/13
B3	3/13
C	0/13
Unknown	5/13
Stage (Masaoka)	
Early (I–II)	2 (15 %)
Advanced (>II–Iva)	9 (70 %)
Unknown	2 (15 %)
Treatment	
Resection	6/13 (46 %)
Radiation	6/13 (46 %)
Chemotherapy	1/13 (8 %)
Pregnancy termination	2/13 (15 %)
No treatment	1/13 (8 %)
Survival	4 months–4 years

Pleural Mesothelioma

Malignant pleural mesothelioma in pregnancy is an extremely rare neoplasm. There is only one report published in 2000 with a 37-year-old pregnant woman presented at 18 weeks with thoracic and shoulder pain, massive pleural effusion, and a large thoracic mass. Biopsy was compatible with an undifferentiated sarcomatoid pleural mesothelioma [15].

Discussion

Female lung cancer mortality is still rising in Europe, whereas there is evidence that smoking women have a double risk of developing lung cancer compared to male population [16, 17]. However, the analysis of the present data revealed that less than half of pregnant women with lung cancer had a positive smoking history. Therefore, it becomes obvious that cigarette smoking is not the only etiological factor in these young women. In addition, there are scarce available data showing that the EGFR and ALK activation mutations are present in these patients [12].

NSCLC of adenocarcinoma type was the most frequent histology accounting for almost 80 % of the cases. More than 90 % of the reported patients presented with

locally or disseminated advanced disease, indicating that lung cancer during pregnancy seems to have an aggressive behavior.

Systemic treatment was provided in almost 50 % of the patients during the postpartum period of gestation. Most patients received combination chemotherapy mainly with platinum-based regimens. Both response rates and survival were poor. Overall survival ranges between 3 and 9 months, whereas 12 % of women died within the first month postpartum. Patients with early-stage disease experienced longer survival of 12 or more months [5, 6].

In general, chemotherapy administration during the first trimester is not recommended due to harmful or lethal effects on the fetus. However, selected chemotherapeutic agents such as carboplatin and paclitaxel can be safely provided during the second and third trimesters [18–20].

Targeting anticancer treatment, especially tyrosine kinase inhibitors (TKIs), is not recommended during pregnancy. Nevertheless, there are already six cases published, two with erlotinib, one with gefitinib, one with erlotinib followed by gefitinib, and two with crizotinib [2, 12]. In half of the cases, small molecules were given during an unrecognized pregnancy and in the rest after delivery. No major responses were seen. In addition, no fetuses' abnormalities or congenital malformations have been observed. Since adequate data on the use of EGFR–TKIs are not available, these agents should be avoided during pregnancy [21].

Usually, pregnant women with cancer are delivering babies without anomalies, although newborn prematurity including complications such as respiratory distress, seizures, or ventricular hemorrhage has been previously reported [1, 2]. Eighty-two percent of babies born in our cohort were found to be completely healthy infants.

Melanoma, cancer of unknown primary, and breast cancer are well-known tumors being most commonly associated with involvement of the products of conception [22, 23]. During the last 20 years, lung cancer has been recognized as an additional tumor with a high predilection to vertical transmission of cancer cells to both placenta and fetus. Up to now, 11 pregnant mothers with lung cancer were found to have placental metastases (17 %), while three fetuses were born with metastatic sites (4.5 %). Due to the relatively high incidence of placental or fetal involvement in gestational lung cancer, it is recommended that placentas should be submitted for histopathological examination along with umbilical cord cytology and neonates should be clinically examined for palpable skin deposits or organomegaly. A close follow-up of all babies every 6 months for 2 years with physical examination, chest X-ray, and liver function tests including serum lactate dehydrogenase is mandatory [5, 23, 24].

In conclusion, gestational lung cancer is becoming an emerging issue, and therefore, both oncologists and gynecologists should be aware of the following related to lung cancer in pregnant women: (a) lung cancer is diagnosed in advanced stages with an aggressive behavior, (b) systemic treatment offers poor results, (c) overall survival is dismal, and (d) placenta and fetus are often involved by transmitted cancer cells, requiring thorough examination of the products of conception. A retrospective as well as a prospective testing for EGFR- and ALK-activating mutations is desperately needed in order to more effectively treat gestational lung cancer.

Thymic tumors and pleural mesotheliomas are extremely rare tumors during pregnancy, and by all means, they are not becoming an emerging issue in daily oncologic practice [13–15].

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