ANTIBLASTIC TREATMENT, FOR SOLID TUMORS, DURING PREGNANCY: A CRUCIAL DECISION

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Cancer is the second leading cause of death during the reproductive years complicating between 0.02% and 0.1% of pregnancies. The incidence is expected to rise with the increase in age of childbearing. The most common types of pregnancy-associated cancers are: cervical cancer, breast cancer, malignant melanoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma and ovarian cancer. The relatively rare occurrence of pregnancy-associated cancer precludes conducting large, prospective studies to examine diagnostic, management and outcome issues. The treatment of pregnancy-associated cancer is complex since it may be associated with adverse fatal effects. In pregnant patients diagnosed with cancer during the first trimester, treatment with multidrug anti-cancer chemotherapy is associated with an increased risk of congenital malformations, spontaneous abortions or fetal death, and therefore, should follow a strong recommendation for pregnancy termination. Second and third trimester exposure is not associated with teratogenic effect but increases the risk of intrauterine growth retardation and low birth weight. There are no sufficient data regarding the teratogenicity of most cytotoxic drugs. Almost all chemotherapeutic agents were found to be teratogenic in animals and for some drugs only experimental data exist. Moreover, no pharmacokinetic studies have been conducted in pregnant women receiving chemotherapy in order to understand whether pregnant women should be treated with different doses of chemotherapy. This article reviews the available data regarding the different aspects of the treatment of cancer during pregnancy.

Cancer is the second most common cause of death during reproductive years (1). It complicates approximately 0,02 – 0,1% of all pregnancies (2). However, the current trend to delay pregnancy and the age-dependent increase in the incidence of several malignancies (3) are expected to raise the occurrence of pregnancy-associated cancer.

The incidence of specific malignancies in pregnant women is similar to that of non-pregnant women of reproductive age (4). The most frequent malignancies associated with pregnancy are cervical and breast cancer, malignant melanoma and Hodgkin's lymphoma. Less frequent malignant tumors are leukemia, ovarian and colorectal cancer (5).

When cancer occurs during gestation, it poses a very difficult challenge to the pregnant patient, her relatives and the medical staff. The benefit of the diagnostic work-up and the use of antiblastic chemotherapy (AC), radiotherapy (RT) and surgery should be weighed carefully against their risk to the unborn child. This often raises conflicts between optimal maternal therapy and fetal well-being. Generally, systemic therapy for cancer in pregnancy must be individualized and may be different if the patient is diagnosed during the first versus the second or third trimesters. AC during the first trimester may cause more severe fetal effects, and when malignancies requiring AC are diagnosed during the first trimester, termination of

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pregnancy should be considered.

For women who do not request pregnancy termination, the choice of drugs must take into account the fetus and may direct therapy to non-standard regimens (for example, single versus combination therapy). For malignancies diagnosed in the second trimester, consideration for the fetus with respect to drug effects should be given, but in cases of a maternal cancer that responds to AC, it is unwise to delay treatment until after delivery. Termination of pregnancy is also a possibility, but the effects of medications on the fetus will potentially be less than in the first trimester.

The likely adverse effects on the fetus have prompted practitioners to consider delaying AC until the postpartum period for cancer diagnosed in the third trimester (table 1).

The relative rarity of pregnancy-associated cancers precludes conducting large prospective studies to examine diagnostic, management and outcome issues and the literature is largely composed of small retrospective studies and case report.

In this article, we review the available data, regarding the impact of the malignant process during pregnancy and its treatment.

METHODS

We systematically searched the English literature using MEDLINE and Cochrane Controlled Trials Register databases from 1971 to 2012. Combination of Medical Subject Headings terms (cancer, breast, cervical cancer, gastrointestinal, lymphoma, leukemia, lung, melanoma, myeloma, urogenital, and chemotherapy) combined with pregnancy and gestation were used. All titles and abstracts were evaluated excluding letters and editorials. Each article was evaluated according to the inclusion criteria which included studies reporting relevant data regarding the diagnosis and treatment of cancer during pregnancy.

Diagnosis of Cancer during pregnancy:

During pregnancy the women's body undergoes physiological changes that may make the diagnosis of several cancers more challenging. Pregnancy-related increase in hormone levels causes breasts enlargement which makes it more difficult to notice small lumps. Furthermore, women and their physicians may mistakenly relate findings consistent with breast cancer to normal pregnancy-induced changes, leading to an average 5 – 7 months delay in the diagnosis of pregnancy-associated breast cancer (6-12). A pregnant women is at 2,5-fold higher risk of being diagnosed with advanced breast cancer than non-pregnant patients (6).

Evidence also exists suggesting a delay in the diagnosis of malignant melanoma during pregnancy due to misinterpretation of malignant lesions as hyper-pigmentation which is experienced during gestation (13-15).

In contrast, pregnancy provides an opportunity for early diagnosis of invasive cervical cancer since visual inspection, cytological examination and bimanual palpation are part of routine antenatal care. Therefore, earlier stages of invasive cervical cancer are found more frequently during pregnancy than in the general population (16-19), representing a 2-3-fold higher probability of being diagnosed at an operable stage (19).

Cancer diagnosis requires tissue sampling and cytological examination. Most routine modes for tissue sampling, including open biopsies under local anesthesia, can be safely performed during pregnancy without harming the mother or the fetus (3, 20-22).

In most types of cancer, the histopathological features are similar in both pregnant and non-pregnant patients. For example, histopatological evaluation of pregnancy-associated breast cancer specimens exhibits poor histologic and prognostic features like high percentage (about 80%) of estrogen or progesterone receptor negative and increased expression of HER-2/neu, p53, Ki-67 nuclear antigen which are all poor prognostic markers (23, 24). Moreover, also in pregnant patients with non-Hodgkin lymphoma, the disease shows a more aggressive histology (most commonly diffuse large B-cell or peripheral T-cell lymphomas) compared to non-pregnant patients (25).

Antiblastic chemotherapy and fetal risk:

The physiological changes of pregnancy must be considered when prescribing AC. During pregnancy, drugs are easily absorbed, and the serum concentration of albumin for drug binding is lower than in non-pregnant women. Pharmacokinetic changes during pregnancy include a higher volume of distribution, lower maximum plasma concentration, lower steady serum state concentration, lower plasma half-life, higher clearance rate, and faster hepatic oxidation. The small spatial configuration and the high lipid solubility of most AC facilitates an easy transfer of an unbound drug or its metabolite across the placenta or into the breast milk. Virtually all drugs cross the placenta, and therefore, the unbound concentration of the drug is similar or higher in the fetal serum and amniotic fluid than in the maternal serum.

These changes in pregnant women might decrease active drug concentrations compared with non-pregnant women who share the same weight. Most cytotoxic agents in current use reach the fetus in significant concentrations following maternal administration because the placenta acts as an ineffective barrier. Drugs with a molecular weight less than 600 kDa usually cross the placenta

(unless strongly protein bound), whereas those weighing more than 1000 kDa do not cross the placenta. Virtually all cytotoxic agents have a molecular weight between 250 and 400 kDa, allowing an easy passage to the fetus (26).

No pharmacokinetic studies have been conducted in pregnant women receiving AC in order to understand whether pregnant women should be treated with different doses of AC. There are not sufficient data regarding the teratogenicity of most cytotoxic drugs. Almost all chemotherapeutic agents were found to be teratogenic in animals and for some drugs only experimental data exist (27). Furthermore, since cytotoxic drugs are usually not used individually, as mono-therapy, most human reports arise from exposure to multi-drug regimens making it difficult to estimate the exact effects of each drug (27-30). Data regarding the experience with the different anti-cancer drug that are more commonly used during pregnancy are presented in Table 1 (27-46). For more details the reader is referred to the CCOPE database (www.motherisk.org).

To evaluate the risk for the unborn child, fetal exposure may be divided into three periods: (I) ovum, from fertilization to implantation; (II) embryo, from the second through the eighth week; and (III) fetus, from the eighth completed week until term.

AC during the first trimester may increase the risk of spontaneous abortions, fetal death and major malformations (47,48). Malformations reflect the gestational age at exposure and the fetus is extremely vulnerable during weeks 2 – 8 when organogenesis occurs (27). During this period, damage to any developing organ may lead to major malformations. After organogenesis, several organs, including the eyes, genitalia, hematopoietic system and the central nervous system remain vulnerable to AC (27). Overall, the risk of teratogenesis following cancer treatment seems lower than that estimated from data on animals. First trimester exposure to AC has been associated with 10-20% risk of major malformations (22). A study on 139 cases of first trimester exposure to AC has demonstrated a 17% risk for malformations after single-agent exposure and 25% after combination drugs exposure (49). When folate antagonists were excluded, the incidence of fetal malformations with single-agent AC during the first trimester declined to 6% (50). Another study of 210 cases demonstrated 29 fetal abnormalities, including 27 associated with first-trimester exposure (51). However these studies included pregnant women that were treated with different chemotherapeutic regimens and covered long periods of time during which the treatment of cancer has changed. Furthermore, these evaluations were based on a collection of case reports and there may be a reporting bias whereby malformed infants are more likely to be reported after drug exposure than healthy infants.

Second and third trimester AC exposure is not associated with teratogenic effects but increases the risk for intrauterine growth retardation (IURG) and low birth weight (48). A review of 376 cases of fetuses exposed to in-uterus AC, most after organogenesis, has demonstrated 6% of fetal or neonatal death, 7% of IUGR, 5% of premature delivery and 4% of transient myelosuppression (27).

BREAST CANCER DURING PREGNANCY

Epidemiology

Breast cancer is the most common malignancy associated with pregnancy after cervical carcinoma with an estimated incidence of about 1 in 3000 pregnancies. Up to 0.2-3.8% of breast cancers coincide with pregnancy. In the last decades, there has been an increase in the incidence of breast cancer in women of childbearing age due to a delay in initiating pregnancies. In the European register the median age at diagnosis during pregnancy is 33 years (22-43 years) (52).

Biological features/pathology

The invasive ductal carcinoma is the most prevalent type (75-90%), followed by invasive lobular carcinoma. The majority of pregnancy-associated breast cancers (PABC) are high grade and lymph vascular invasion is common (9).

Estrogen and progesterone receptors are often negative in PABC (around 70% of tumors). Approximately 28-58% of PABC express HER2/neu (53). Biological features are similar to those in young non-pregnant women and seem to be related to age rather than to pregnancy itself.

Diagnosis and staging

Diagnosis is difficult due to the confounding effect of physiological changes within the breast occurring during pregnancy such as increased glandularity, size and density of the breast tissue. However any new palpable mass persisting beyond 2-4 weeks should be investigated further (54). Mammography with proper fetal shielding is acceptable in terms of radiation exposure to the fetus (the estimated fetal radiation exposure is estimated to be 0.4 mrad which is less than the 5 rad level known to be associated with fetal malformations) but has a lower sensitivity during pregnancy due to the increased density of the breast (55). Ultrasonography (US) is an accurate and safe imaging technique in pregnancy which helps to differentiate solid from cystic structures and to assess their morphology (56). The routine use of magnetic resonance imaging (MRI) during pregnancy is not recommended due to both difficulties in image interpretation and concerns on gadolinium safety which is known to cross the placenta and cause fetal abnormalities in animal

Table 1: *current reports of clinical experience with the anti-cancer drugs during the pregnancy*

Drugs	Study details	Pregnancy outcome	references
Breast Cancer			
Cyclophosphamide Doxorubicin 5-FU	86 cases treated in II and III trimester	2 cases of congenital anomalies one of them with bilateral ureteral reflux, and one with club foot. 1 case of Down Syndrome 1 case of IUGR	Aviles et al 2001[30]
Docetaxel	16 cases treated in II and III trimester	1 case of anhydramnios 1 case of haloprosencephaly	Mir O'Ann et Al 2010[40]
Lapatinib	1 case treated in I and II trimester	No congenital abnormalities were observed	Kelly et Al 2006[41]
Paclitaxel	21 cases treated in II and III trimester	1 case of anhydramnios 1 case of preeclampsia 1 case of IUGR	Mir O'Ann et Al 2010[40]
Taxanes combinations Paclitaxel plus Docetaxel	3 cases, treated in II and III trimester.	1 case Pyloric stenosis	Mir O et Al 2010[40]
Trastuzumab	11/15 cases treated in the first trimester	8/15 cases experienced oligohydramnios or anhydramnios 4 neonatal deaths secondary to premature delivery	Azim et Al 2009[42]
Cervical cancer			
Cisplatinum	10 cases	2 cases with moderate bilateral hearing loss 2 cases of IUGR 1 newborn with idiopathic ventriculomegaly	Kyoung Chou et Al 2010[43]
Ovarian Cancer			
Irinotecan 5-FU	1 case treated at II trimester	No complication and congenital abnormalities were observed.	Taylor et Al 2009[44]
Bleomycin Etoposide	22 cases trested with various protocols,	1 case of newborn with respiratory distress (dead)	Zao et Al 2006[45]

Platinum Taxanes	during II and III trimester, 13 of them lives babies		
Miscellaneous			
Busulfan	14 cases, 8 of the treated in I trimester	2 cases of gastric malformation (pylori stenosis) exposed in II trimester.	Cardonik et Al 2004 [27]
5-Fluorouracil	53 cases, 5 of them treated in I trimester	1 case of fetal death 1 case of neonatal death 6 cases of IUGR	Cardonik et Al 2004 [27]
6-mercaptopurine	49 cases, 29 of them treated in I trimester	2 cases of fetal death 5 cases of IUGR	Cardonik et Al 2004 [27]
Daunarubicin	59 cases treated during all trimester	3 cases of fetal death 1 case of congenital malformation (treated in I trimester in combination with cytarabine) 5 cases of IUGR 2 cases of spontaneous abort 1 case of myocardial necrosis	Cardonik et Al 2004 [27]
Mitoxantrone	3 cases treated in II and III trimester	No congenital anomalies were observed	Aviles et Al 2006 [31]
Platinum derivates	43 cases treated during II and III trimester for melanomas, Lung cancer, Cervical and Ovarian cancer a	2 cases of fetal malformation occurred after In-Utero exposure to cisplatinum	Mir O et Al 2008 [46]
Trofosfamide Idarubicin Etoposide	1 case of Alveolar Rhabdo Myosarcoma treated in III trimester	No congenital anomalies were observed	Sieperman et Al 2012

models (57). Biopsy of a suspicious mass is the gold standard for the diagnosis of breast cancer. A core needle biopsy is the technique of choice. Fine needle aspiration cytology (FNAC) may be misleading and should not be performed during pregnancy (58). The pathologist should be informed about the pregnancy of the patient because pregnancy-associated cytological changes can suggest atypia.

Limited data exist regarding the use of sentinel lymph node biopsies for staging of the regional lymph nodes during pregnancy (59). The use of radioactive colloid is reported to be safe in terms of radiation exposure to the fetus (60), whereas the use of isosulfan blue dye should be avoided due to the possible teratogenic effects and the risk of anaphylaxis for the patient (61). However, the sensitivity of lymphatic mapping is reduced when only radiocolloids are used to guide it.

Usually the staging is limited to chest radiography and abdomino-pelvic US to detect lung and liver metastases, respectively. MRI without contrast is the preferred technique to detect bone metastases (54).

Role of antiblastic chemotherapy

Indications for AC (62) during pregnancy should not be different from those outside pregnancy and should depend upon the patient disease stage and tumor biology. Physicians should consider administration of AC starting from the completion of the 12th week of gestation (i.e. at the end of organogenesis). Although pregnancy alters the pharmacokinetics of drugs, currently there are no studies justifying a change in dosages (63). In the adjuvant setting different anthracycline-based regimens are described. Some authors suggested both escalated-dose epirubicin and anthracycline-taxane regimens as the most effective in terms of disease-free survival and overall survival. Moreover, the regimen based on weekly epirubicin (35 mg/m^2) has been described as safe and effective, whereas outside pregnancy could be suboptimal. In the advanced/ metastatic setting, anthracyclines and anthracycline-based regimens remain the best choice as well. For patients who are not good candidates for anthracycline-based regimens (i.e. previously exposed in the adjuvant setting), single agent taxane (paclitaxel or docetaxel) would be the preferred option (54, 62). Data on other drugs used in the metastatic setting remain scarce. Only case reports are available on the use of vinca-alkaloids (62) (safely used in hematological malignancies during pregnancy) and platinum salts in pregnancy (46). Regarding the treatment of bone metastases data obtained from preclinical studies have shown an increase risk of fetal skeletal anomalies secondary to in-uterus exposure to biphosphonates (64). These drugs also cause hypocalcaemia which could affect uterine contraction and should be better administered following delivery, whenever possible. Trastuzumab, is well known to improve survival, both in the adjuvant and metastatic setting, in HER2 over-expressing tumors, in non-pregnant women. In pregnant women, it is reported to cause a reduction in the amniotic fluid volume (ioligohydramnios or anhydramnios) which is known to significantly increase the risk of premature delivery, fetal morbidity and mortality. However, current clinical evidence relies on 15 published case-reports only (42).

Tamoxifen is not recommended in pregnancy due to several studies reporting malformations, mainly craniofacial anomalies, ambiguous genitalia and Goldenhar's syndrome (65).

Aromatase inhibitors are contraindicated as a single-agent endocrine therapy in premenopausal women. Gonadotropin-releasing hormone (GnRH) analogues are not recommended during pregnancy, though no malformations are reported in a series of 5 patients (66).

GYNECOLOGIC CANCERS DURING PREGNANCY

General considerations:

Among the cancers diagnosed during pregnancy, gynecological malignancies are the most common (67). When managing these tumors, physicians need to consider both fetal preservation and the potential loss of the patient's reproductive capacity as a result of cancer therapy. The most common gynecological cancers diagnosed during pregnancy are of cervical and ovarian origin (67).

CERVICAL CARCINOMA

Introduction

One third of all cervical carcinomas occur during the reproductive period (68). This type of malignancy is the second greatest cause of death due to cancer, only preceded by breast cancer (68).

Due to routine prenatal care pregnant women are usually diagnosed with cervical cancer in its initial stage (69).

Diagnosis

In most cases, patients with stage I, cervical carcinoma are asymptomatic. When symptomatic, the most prevalent symptom is vaginal bleeding, occurring in 50% of the cases (70).

Direct inspection of the uterine cervix during pregnancy may generate errors of diagnosis with neoplastic lesions as cervix may increase double or almost triple in size and transformation zone become exuberant with emersion of squamocellular junction (70).

Table II. *Selected cases of successfully treated pregnant by reduced-dose chemotherapy*

Reference	Drugs	Dosage	Cycles and schedules	Pathology (Staging)	GA (week)	Follow up (months)	DR/DS
Doi et al 2009	Paclitaxel	120mg/m^2	5 cycles every 2 weeks	Mucinous Cyst adenocarcinoma (FIGO Ic)	24	40	69%
Seamon et al 2009	Cisplatin	40mg/m^2		Glassy cell cervical carcinoma (FIGO IIIb)	25	49	80%
Sood et Al 2001	Paclitaxel	135mg/m^2/24h	3 cycles every 3 weeks	Papillary serous adenocarcinoma (FIGO III)	28	29 (died of the mather)	77%
	Cisplatin	75mg/m^2					Full dose
Li et Al 2011 #two cases	Cisplatin	50mg/m^2	2 cycles every 2 weeks	Cervical cancer (FIGO IB2) in both cases	29 case#1; 27 case#2	13 case#1; 21 case#2	67%
	Paclitaxel	175mg/m^2					Full dose
Sieperman et Al 2012	Trofosfamide	2x75mg/m^2 day 1-10	4 cycles without interruption (40 consecutive days). Oral delivery	Alveolar Rhabdo Myosarcoma (stage T1b N0 M0)	28	24	Induction therapy (trial CWS-96-IV)
	Idarubicin	1x5mg/m^2 day 1-4-7-10					
	Etoposide	2x25mg/m^2 day1-10					

GA: Gestation time to start Chemotherapy; DR/DS: (Dose reduction/ standard dosage)x100

Any pregnant woman with abnormal cytological test results should be referred for colposcopy (71, 72) in order to identify suspected neoplastic lesions and to identify the most appropriate site for biopsy.

Among pregnant women, the sensitivity and specificity of biopsies, in relation to the final diagnosis of the lesion, are 83.7% and 95.9%, respectively (70). Conization is reserved for pregnant women with suspected invasion, though the time of execution is frequently postponed to the postpartum period, due to possible complications such as hemorrhage, abortion, preterm labor or infection (70).

Among imaging examinations, abdominal and pelvic US and MRI are considered the methods of choice for staging pregnant women (70).

TREATMENT

Pre-invasive cervical cancer

Data from literature suggest that only about 0-10% of biopsy proven CIN II and CIN III progress towards invasive cancer, whereas regression has been observed in 47-70% of cases (73, 74). Therefore, a conservative approach during pregnancy is advocated when CIN is diagnosed. However, cervical cancer precursor lesions should be monitored during pregnancy using cytology and colposcopy performed at three months interval. Treatment can be postponed until the postpartum period.

Invasive cervical cancer

The management of pregnancy and invasive cervical carcinoma occurring concomitantly will depend on the gestational age at the time of diagnosis, disease staging, size of the lesion and the patient's wish to maintain pregnancy and fertility.

Although there is no consensus regarding treatment of micro invasive carcinoma (stage IA1), some authors recommend conization only if the initial biopsy shows micro invasion. Subsequently, they propose a two-month interval colposcopy during the prenatal period and cytology plus colposcopy six weeks after delivery. However, other investigators suggest that the best approach should be observation without conization, with similar time schedule for observation measures (70).

As concerns treatment of invasive carcinoma (stages IA2, IB and IIA), there is a wide divergence regarding the gestational age that should be the limit for taking an observational approach instead of administering immediate treatment, ranging from the end of the first trimester to the 20th week (75, 76). However, it's of note, that all studies regarding postponement of treatment after the 16th week of pregnancy, in order to obtain fetal maturity, have shown that maternal prognosis was not affected.

Recent advances (77) in neonatal intensive care have set in 34 weeks of gestation a reasonable period for delivery, through caesarean section. An immediate and

definitive approach during pregnancy of less than 20 weeks should mean radical hysterectomy (78) with the fetus *in situ* and lymph adenectomy, or external RT (79) with the fetus in situ, which in most cases will lead to spontaneous abortion. In young women, radical surgery is the treatment of choice with the possibility of sparing functioning ovaries. For pregnancy of more than 20 weeks most studies suggest emptying of the uterine cavity by caesarean section followed by radical hysterectomy with lymph adenectomy. Neoadjuvant AC based on cisplatin (80, 81) should be used during the second trimester of pregnancy in order to make it possible to wait for fetal pulmonary maturity, with definitive treatment applied after delivery. This approach seems feasible and relatively safe for the fetus.

By chance, stages IIB, III and IV cervical carcinoma, rarely occur during pregnancy (69). However an immediate treatment with cisplatin-based AC followed by RT is the treatment of choice. For diagnoses made during the second trimester of pregnancy or better when the fetus is at term a *caesarean* section is the first option followed by AC-RT (70).

OVARIAN CANCER

Epidemiology

The risk for ovarian cancer is rare in pregnancy, with a reported incidence between one in 12,000 and 47,000 (82). Nevertheless it is the second most common gynecological malignancy in pregnancy.

Based on data obtained from retrospective studies, benign tumors accounted for 92-98% of surgically managed ovarian masses. Among them, dermoid cysts and cyst adenomas are the most frequent. Moreover, low malignant borderline tumors are almost as common as frank malignancies. Among invasive malignancies epithelial ovarian cancer is more common than germ cell tumors. The majority of these cancers are detected at an early stage (80% are stage I at diagnosis) (83).

Diagnosis

Most ovarian masses in early pregnancy are physiological and resolve spontaneously. Masses persisting after the first trimester or found during the second trimester may represent malignancies.

The advent of US use in early pregnancy resulted in increased detection of ovarian masses. Moreover, certain features on US such as thick-walled cysts, septations, large amount of free fluid in the pelvis or abdomen, solid areas and papillary projections, increase suspicion for malignancy. When in doubt, further evaluation by MRI scan can help distinguish benign from malignant, with an overall accuracy of 93% for malignancy (84).

Tumor markers like CA-125 (85) have a limited role in the differentiation between benign and malignant tumors as levels increase during pregnancy.

Role of antiblastic chemotherapy

As concerns AC (86), non-epithelial ovarian neoplasms may benefit of combinations such as cispltain-vinblastin-bleomycin or paclitaxel-carboplatin, whereas there are no favorable reports on bleomycin-cisplatin-etoposide (BEP) combination. For epithelial ovarian malignancies during pregnancy standard paclitaxel-carboplatin can be given. The administration of AC, during the first trimester, which is the period of organogenesis, should be avoided whereas the use of AC during second and third trimester has been reported with safety and as a mean to prevent prematurity.

For invasive epithelial ovarian carcinoma (87) the treatment depends on disease stage and grade. For stage IA, grade 1, surgical staging is similar to borderline tumors. For stage IA grade II-III, IB, IC and IIA, lymph adenectomy and adjuvant platinum-based chemotherapy are mandatory.

In advanced-stage ovarian cancer during pregnancy, several treatment strategies have been described, including primary de bulking with termination of pregnancy or delivery, expectant management, surgery during pregnancy followed by post pregnancy AC, surgery followed by AC during pregnancy with final surgery during/after delivery.

Urologic cancers during pregnancy:
General considerations:

Urologic cancers occur extremely rarely during gestation. The exact incidence is not known. According to some estimations approximately 13 pregnancies in 1,000,000 are complicated by urological cancers (74). Among urological cancers during pregnancy, renal cell carcinoma (RCC) is the most common, followed by bladder cancers and adrenal tumors, especially pheochromocytoma whereas urethral and urethral malignancies are even more rare during pregnancy (75).

As a consequence, due to their rarity, clinicians often do not consider urological cancers in the differential diagnosis in the presence of signs and symptoms occurring during pregnancy such as microscopic hematuria, loin pain or hypertension. It's true that these signs and symptoms are usually secondary to more common conditions (such as urinary infection, renal calculus disease, pyelonephritis, threatened abortion or preeclampsia) but also may hide a cancer.

Renal cancer:
Epidemiology

According to two reviews (90, 91) of the published

cases of renal neoplasm during pregnancy, RCCs account for the majority of cases, followed by renal angiomyolipoma, nephroblastoma and sarcoma.

Among mechanisms involved in the increased risk of renal cancer in pregnancy, the increase in body mass index, hypertension and diabetes are often mentioned, as in the general population. Moreover, the increased angiogenesis (90) in pregnancy might have a role in the genesis of RCC. In addition, some authors suggest a definite role of female hormones (92) on the development of RCC, but some others fail to confirm these date (90).

Clinical presentation

The most common presenting symptoms of RCC in pregnancy are a palpable mass, flank or abdominal pain and hematuria (90, 91).

Diagnosis

US and urine cytology should be obtained initially. If not sufficient for diagnosis, MRI is a good option (89). In cases of indeterminate masses, a US-guided biopsy should be performed.

Role of antiblastic chemotherapy

No systemic effective AC can be offered to pregnant patients affected by advanced or metastatic RCC. Interferon a has a poor response rate (below 10%) but can be safely used in pregnancy (93). Interleukin 2 with a response rate of around 20% has been found to cause placental detachment in pregnant rats (94) and is characterized by a substantial systemic toxicity. No data are available on tyrosine kinase inhibitors use in pregnant women with RCC.

Bladder cancer:

Bladder cancer during pregnancy is rare and can consist of transitional cell carcinoma, adenocarcinoma or squamous cell carcinoma (89).

Diagnosis

Hematuria, in the absence of a benefit from antibiotic therapy and of proteinuria, is a common symptom of bladder cancer. Some experts (95) recommend urinalysis and urine culture obtained by catheterization to distinguish between urinary and vaginal bleeding. If bladder cancer suspect persists further investigations the patient should undergo are US, urine cytology and flexible cystoscopy (95). US is used to diagnose calculi or renal tumors, but it was diagnostic in approximately a half of bladder cancer reported cases (95). Urine cytology may be helpful to evaluate cancer but negative results are frequent also in presence of low-grade carcinomas and it cannot postpone or replace cystoscopy. Cystoscopy under local anesthesia is safe in pregnancy and can confirm the diagnosis (96).

Management

Superficial tumors can be resected cistoscopically with safety during pregnancy. In non pregnant patients, the standard procedures include intravescical therapy to avoid recurrence. However, Bacillus Calmette-Guerin (BCG) immunotherapy has not been thoroughly studied in pregnant patients (97). Radical cistectomy with pelvic lymph node dissection is the standard therapy for patients with muscle invasive bladder cancer localized to the pelvis. Some investigators suggest termination of pregnancy if invasive cancer is diagnosed during the first or early second trimester, followed by definitive treatment.

Adjuvant pelvic RT or systemic AC may improve loco regional tumor control and survival of patients with node- positive or perivisceral fat-extending malignancies, but in view of the toxicity and their marginal benefit, they should be administered post-partum.

Malignant melanoma during pregnancy

General considerations

Malignant melanoma is one of the most common types of cancer occurring among women during their childbearing years. However, reports from 2 population-based studies (98, 99) showed that the risk of developing melanoma is not greater for pregnant women that for women who are not pregnant. These data have been recently confirmed by two large cohort studies (100,101).

Moreover, pregnancy does not adversely influence maternal survival from melanoma, as few reports (101-103) failed to show a significant difference in overall and disease-free survival between women who developed melanoma during pregnancy and age-matched control group of women who were not pregnant when diagnosed with melanoma.

Fortunately, placental and fetal metastasis from maternal malignant disease is an exceptionally rare event. However, melanoma is the most common type of malignancy to metastasize to the placenta and fetus, representing 30% of placental metastases and 58% of fetal metastases (104). A careful microscopic examination of the placenta with known metastatic melanoma should be recommended as well as close observation and follow-up of the infant.

Diagnosis

The prognosis of pregnant women with melanoma is dependent primarily on tumor thickness and ulceration status (105). Early detection is critical and prompt biopsy of suspicious lesions is important. The earliest sign of a melanoma is a change in the size, shape or color of a lesion, whereas the earliest symptom is persistent itching

of a lesion (106).

Management

Treatment of malignant melanoma is based on wide surgical excision with appropriate margins. Biopsies and wide local excisions can be performed safely during pregnancy (104).

The use of adjuvant immune therapy with a-interferon is an accepted treatment option and available data suggest that its use does not significantly increase the incidence of fetal malformations or abortion when used during pregnancy (107).

The use of AC in a pregnant woman affected by metastatic melanoma is a challenging situation (108, 109). This is due mainly to its palliative value with the absence of significant increase in survival and the potential adverse events on the fetus. AC agents with activity in patients with metastatic melanoma include single-agent dacarbazine and combinations such as tamoxifen, carmustine, dacarbazine and cisplatin or tamoxifen, nimustine, cisplatin and dacarbazine. Generally, AC should be offered in the presence of symptomatic metastatic disease and with the intent to carry the pregnancy to delivery. Moreover, risk of toxic effects on the fetus are lower in the second and third trimester of pregnancy.

Lung cancer during pregnancy:
Epidemiology

The association between lung cancer and pregnancy has been rarely described, but is expected to rise due to current trends in delaying pregnancy to later in life and the increasing rates of cigarette smoking among young women (110).

Diagnosis

The clinical picture of lung cancer during pregnancy is similar to that of non-pregnant lung cancer patients. Signs and symptoms may be secondary to either the primary tumor in the chest or distant metastasis.

MRI without gadolinium (111) is the most safe and adequate imaging technique. Tissue biopsy can be performed safely for any palpable lesion (e.g. cervical lymph node) or by an US guided biopsy, or broncoscopy (112).

Role of antiblastic chemotherapy

AC, outside pregnancy, is the standard approach for managing patients with advanced stage (IIIB/IV) non-small lung cancer or extended small cell lung cancer. The administration of AC during the first trimester of pregnancy is associated with high risk of miscarriage and malformation reaching 20%. This risk is reduced to 1% when AC is administered during the second and third trimester (113).

A platinum-based doublet is a reasonable option. Cisplatin seem to be associated with more fetal adverse events compared with carboplatin (46). Vinorelbine and taxanes have been used with safety in breast cancer patients during pregnancy (114) and may be coupled to platinum-based chemotherapy. On the contrary, gemcitabine and premetrex, antimetabolite drugs, with a structure resembling that of metotrexate, a drug with a high teratogenic potential effect, should be discouraged (113). Not enough data support the use of target agents, even if there is a report of good tolerance with erlotinib therapy (115) during the first trimester of pregnancy.

Gastrointestinal cancers during pregnancy:
Colorectal cancer:
Epidemiology

Colorectal cancer (CRC) is the second most common cause of mortality from cancer in women, though it is uncommon in women aged less than 40 years (116). The cumulative risk of developing CRC in women before their forties is about 1 in 2,000. The incidence of CRC during gestation appears to be 1 in 13,000 pregnancies (117), with a median patient age of 31 (118). Overall, 300 cases of CRC during pregnancy have been reported (119).

Though, young patients with CRC, are believed to have a higher proportion of risk factors or hereditary syndromes (i.e. adenomatous polyposis coli, hereditary non-polyposis colorectal cancer, longstanding inflammatory bowel disease) than older patients. These high-risk groups account for a minority of CRC during pregnancy (119).

Biological features/Pathology

An intriguing finding is the high incidence of rectal cancer in pregnant women. According to Bernstein et al. (118), 80% of malignancies, in 205 pregnant patients, are located in the rectum, whereas only 20-25% of CRC occur in the rectum in the general population. This phenomenon may not reflect a real different incidence in pregnant women compared to general population but a consequence of an easier diagnosis of rectal tumors because of exacerbation of rectal symptoms from uterine pressure or frequent pelvic and rectal examination during pregnancy.

Another important feature of pregnancy-associated CRC is the reported high frequency of ovarian deposits (25% of cases) in contrast to their rarity (3-8%) in women older than 40 years (120). Metastases to the embryo and to the placenta are very rare (121).

Adenocarcinoma is by far the most frequent histologic type of CRC. Several case reports and patient series describe a predominance in pregnant women of poorly

differentiated mucinous tumors. However, many published studies omit histologic findings and the relative proportion of poorly differentiated mucinous tumors cannot be safely estimated (122, 123).

Data on lymphatic/vascular invasion, perineural invasion, aneuploidy, microsatellite instability, thymidilate synthase levels, APC gene, ras gene, p53 gene, the presence of estrogen and progesterone receptors in CRC women during pregnancy are largely lacking (119).

Diagnosis and staging

Symptoms and signs such as abdominal cramps, rectal bleeding, diarrhea, constipation, weight loss, nausea and vomiting, abdominal mass and anemia make up a clinical picture common both to the general population and pregnant CRC patients. However, a majority of these symptom may be attributed to gestation rather than to cancer (119). Laboratory investigations reveal microcytic anemia, hypo albuminemia and altered liver function tests in the presence of hepatic metastases. Also these features may be related to pregnancy as iron/folate deficiency, increase of plasma volume, and enhanced placental synthesis of alkaline phosphates are common in pregnancy. For these reasons, pregnant women are diagnosed with locally advanced or metastatic CRC more often than their non-pregnant counterpart (124).

US of the abdomen is cheap and safe for the fetus and can detect hepatic metastases larger than 1 cm with 75% sensitivity. Tran rectal US may help the study of intestinal wall infiltration and regional lymph adenopathy with a sensitivity of 75-85% (125). Non contrast-enhanced MRI is equally effective to computerized tomography (CT) in depicting pelvic and hepatic lesions, with a reported sensitivity of 80% (126). Colonscopy is a diagnostic modality that picks up the 5% of patients with a synchronous second tumor of the large intestine and provides biopsy material. The hypothetical risks of uterine pressure and placental detachment, intestinal perforation, fetal injury from maternal hypotension/hypoxia or diazepam/midazolam administration have never been reported (127). Serum carcinoembryonic antigen (CEA) levels are not elevated by pregnancy and may be used for follow-up of pregnant CRC women or for evaluation of response to therapy (128).

Role of antiblastic chemotherapy

AC is the standard treatment for Dukes C, high-risk Dukes B (in the adjuvant setting) and Dukes D (in the metastatic setting) CRC, in general population. In pregnancy, AC should not be used in the first trimester because of potential teratogenicity but in the presence of a symptomatic, high-volume or rapidly progressing malignancy pregnancy termination should be pursued and immediate institution of AC is warranted (129). Conversely, AC administration during the second and third trimester is relatively safe.

The most commonly used AC agent for the treatment of CRC is 5-fluorouracil (5-FU). 5-FU could potentially cause fetal abnormalities by affecting fetal DNA synthesis and cell development through inhibition of embryonic thymidylate synthetase (130). Moreover, 5-FU crosses the placenta and enters fetal circulation in the rat and causes fetal toxicity in several laboratory animals (i.e. rats, monkeys) (119). Limited data have been published on fetal safety in humans and 5-FU seems to be safe for the fetus particularly during second and third trimester (119).

Studies in mice have found that capecitabine (131), a 5-FU pro-drug, during organogenesis, causes malformations and embryo death. However there are no adequate and well-controlled studies of capecitabine in pregnant women.

Oxaliplatin (131) has not been studied in pregnant women. However, studies in animals have shown that oxaliplatin causes miscarriages, decreased weight or death to the fetus, and problems with bone formation. Irinotecan (131) may cause harm to the fetus when given during pregnancy. No human data are available. Bevacizumab (131) has not been studied in pregnant women. Studies of the effect of cetuximab (131) in pregnancy has not been performed in humans or animals.

Gastric cancer:
Epidemiology

Only 1% of gastric cancers are diagnosed in patients aged less than 30 years, and 3.5%-6.5% in those aged less than 40 years (132). Only 131 cases of gestational gastric cancer have been reported in the literature.

Pathology/biologic features

In contrast with the general population the majority of gastric cancer associated with pregnancy are high-grade malignancies, diffuse-type according to Lauren classification. Tumor growth follows a diffuse scirrhous pattern (Borrmann type III or IV). These pathological features, along with metastatic behavior, have to be related more to young age than to pregnancy. In fact, young women (<35-40 years of age) usually have diffuse-type gastric carcinomas and develop ovarian, mesenteric-para-aortic nodal and peritoneal deposits in 20%-40% of cases (133).

Diagnosis

Presenting symptoms (such as nausea, vomiting, anorexia, weight loss, epigastric pain) and signs (chronic iron-deficiency anemia, hematemesis and melena) are not specific of cancer and do not help distinguish between

gastric cancer, peptic ulcer or pregnancy itself. We know from two large reviews of reported cases (134,135) that a majority (65%-80%) of gastric cancers are diagnosed after the 30th gestational week. As a result, most patients are diagnosed with locally advanced or metastatic gastric cancer. Esophagogastroscopy, the definitive diagnostic modality for gastric cancer, is reported safe in pregnancy (135).

Role of antiblastic chemotherapy

Adjuvant AC-RT may have a role in pregnant women with gastric cancer during the third trimester and can only be administered post-partum. On the contrary, the role of neoadjuvant or adjuvant AC after the first trimester is marginal due to a narrow risk/benefit ratio. Metastatic gastric cancer is an incurable disease and AC has only a palliative intent. Administration of the most active compounds (i.e. 5-FU, cisplatin) is relatively safe for the mother and the embryo, provided it starts after the first trimester (129).

Hepatocellular carcinoma:
Epidemiology

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and the fourth most common cause of death (136). Although the worldwide incidence of HCC in women is 5.5/10,000 (137), HCC during pregnancy is so rare that only 47 such cases have been reported so far.

Pathology/biologic features

One must consider both the mother and the fetus when treating pregnant patients with HCC. In addition, pregnancy presents an obstacle for diagnosing and treating HCC. These factors add to the complexity of diagnostic and therapeutic plans. There is controversy over whether the HCC during pregnancy is different from the HCC seen in non-pregnant women. Many authors have reported more aggressive behavior of HCC during pregnancy and some have suggested that this is due to the elevated levels of sex hormones (4). To our knowledge, the largest review of HCC during pregnancy was reported by Lau et al. (138) in 1995. That report suggested pregnancy was an adverse factor for the prognosis of HCC, because the median survival of the 28 pregnant women in that report was significantly shorter than that of non-pregnant patients with inoperable HCC (138). Most authors who have described such cases have concluded that pregnancy has a negative impact on the outcome of HCC (137-141). A minority of authors have presented opposing opinions, but supporting evidence is scarce because the disease is uncommon.

Diagnosis

Remarkable advances have been achieved recently in the diagnosis and treatment of HCC. Various laboratory tests, such as that for alpha-fetoprotein (AFP) (142), have been developed for HCC screening. Radiologic techniques such as abdominal US, dynamic computed tomography, and MRI have also contributed to greater diagnostic sensitivity. The surveillance for HCC, as recommended by the European Association for Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), uses these laboratory and radiologic tests (143, 144).

Role of antiblastic chemotherapy

The use and the efficacy of AC in the treatment of HCC is controversial. To date the treatments with proven efficacy are surgery and loco regional approach. In the series reported by Choi K.K et al. (137), the patients treated with trans arterial chemo embolization (TACE) obtained a long term (3,5 year) survival despite advanced disease. Considering that it's difficult to do further considerations due to scant data available.

CONCLUSIONS

The decision to use AC during pregnancy must be weighed against the effects of treatment delay on maternal survival. If possible, AC should be avoided during the first trimester, as should low-molecular-weight and highly diffusible drugs. If multidrug treatment in the first trimester is required, anthracycline antibiotics, vinca alkaloids, or single-agent treatment followed by multi-agent therapy after 12 weeks should be considered. Requena and colleagues (145) suggested using lower doses of AC during pregnancy to induce remission, followed by consolidative therapy at standard doses postpartum. To date, there are no ongoing studies that justify changes in standard dosage of AC. Only few authors reports cases of AC reduced-dosage during a pregnancy (Table 2). However, even therapeutic doses might theoretically not be adequate for pregnant women, in view of the pharmacokinetic changes during pregnancy. Use of AC in the second and third trimesters seems to be safe. The background incidence of IUGR varies according to the population, geographic location, and standard growth curves used as a reference. In general, 4–8% of all infants born in developed countries are classified as growth restricted (146). The mother's underlying illness might also affect perinatal complications.

Children and adults given AC for lymphoma are at risk of secondary leukemia within 10 years (147). The risk of secondary malignant disease after in uterus exposure to chemotherapy is unknown. No cases have been reported of secondary leukemia in exposed fetuses. Delivery should be delayed by 2–3 weeks after AC to allow the bone marrow

to recover, and iatrogenic preterm deliveries should be avoided. When more than one regimen is available and effective for a particular cancer, agents should be chosen on the basis of the most extensive investigation. Placental pathology is suggested in all cases.

Moreover, studies on the teratogenicity of cancer AC are usually based on animal models. However, the AC doses used in humans are often lower than the minimum teratogenic doses applied in animals. Therefore, it is difficult to extrapolate data from animal models to humans. Recently, there has been a growing interest in studying the effect of different drugs, including AC agents, on the placenta (148-150). For example, the adverse effect of 6-mercaptopurine on the placenta has been documented with inhibition of both migration and proliferation of trophoblast cells in first-trimester human placental explants culture (150). Placental perfusion studies can provide additional valuable information regarding both transfer and biotransformation of different drugs in the human placenta (151-153). To date, most of these studies were held using drugs not usually administered for cancer treatment. However, they can serve as a model for the assessment of cancer AC transfer and thus add important information regarding its safety during pregnancy.

Due to the relative rarity of pregnancy-associated cancer, only few medical centers or physicians have gained an expertise in this field. Therefore, there is a critical need for multi-center cooperation and a central registry that will collect and follow a large number of cases of pregnancy-associated cancer. This will facilitate conducting better epidemiologic studies and improved long-term follow-up that will enable physicians to more accurately predict patients that can continue the course of their pregnancy and those with a worse prognosis in whom cancer therapy cannot be delayed.

A multidisciplinary team including specialists in oncology, perinatology, and neonatology is needed to coordinate care, improve the chance of cure in the mother, and decrease neonatal harm.

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