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The treatment of hematologic malignancies in pregnancy

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1. Introduction

Cancer and especially hematological cancer during pregnancy is infrequent and its management is difficult for patients, their families and their physicians. When termination of pregnancy is unacceptable, decisions regarding the use of chemotherapy and irradiation are complicated by the well-known risks of abortion and fetal malformation.

This article reviews the available data regarding the different aspects of diagnosis and – especially chemotherapeutical – treatment of hematological cancer during pregnancy.

2. Methods

We systematically searched the English literature using MEDLINE and PubMed-database for the years 1990-2009. Combination of Medical Subject Headings (MeSH) terms (cancer, lymphoma, radiation, chemotherapy, leukemia, Hodgkin, non-Hodgkin) combined with pregnancy and gestation were used. All titles and abstracts were evaluated excluding letters and editorials. We selected 15 review-articles, 1 registry-based cohort study and 50 case reports. All together representing 403 cases.

3. Epidemiology of cancer during pregnancy

a) *Epidemiology - general*

The incidence of pregnancy-associated cancer is relatively low, complicating 0.02-0.1% of all pregnancies. This would translate into about 5000 annual new cases of pregnancy-associated cancer in the United States alone. However, cancer is the second most common cause of death in women during their reproductive years (Sadural and Smith, 2007).

The current trend to delay pregnancy, the age-dependent increase in the incidence of several malignancies and the suggested high incidence of AIDS-related non-Hodgkin lymphoma especially in developing countries are expected to raise the occurrence of pregnancy-associated cancer. Table 1 summarizes the incidence of the most common types of pregnancy-associated cancer. Table 2 details the change in frequency of malignant neoplasia in women according to age. The diagnosis of cancer during pregnancy poses challenges to the woman, her family and the medical team. The relative rarity of pregnancy-associated cancer precludes conducting large prospective studies to examine diagnostic, management and outcome issues and the literature is largely composed of small retrospective studies and case reports (Pereg D. *et al*., 2008; Lishner M. *et al*., 2003; Stensheim H. *et al*., 2008).

b) *Outcome of cancer in pregnancy*

In hematological cancers, pregnancy has not been associated with measurable effect on maternal outcome. Most studies on the effect of pregnancy on cancer prognosis have been retrospective and covered long periods of time during which cancer diagnosis and treatment had changed. However, according to various reports and a very recent report of (Stensheim *et al*. 2008), it appears that pregnancy has no significant adverse effect on maternal outcome when matched to non-pregnant patients (Pereg D. *et al*., 2008; Weisz B. *et al*., 2001; Stensheim *et al*. 2008).

In general (excluding the non-Hodgkin-lymphomas), young women – pregnant or not – usually demonstrate biologically more aggressive disease. Histopathological features in pregnancy-associated cancers are similar to age matched non-pregnant women. We can conclude that overall survival in the pregnant group is similar to that in the non-pregnant-cancer-group. With effective chemotherapy, complete remission can be obtained

Table 1. — Distribution of Tumor Types in Pregnancy (Van Calsteren *et al*., 2009).

Breast	46%
Hematologic malignancies	18%
Hodgkin's disease	6%
Non-Hodgkin's lymphoma	4.7%
Acute lymphatic leukemia	1.9%
Acute myelogenous leukemia	3.2%
Dermatologic malignancies	10%
Cervical cancer	8%
Other (ovarian, colorectal, brain...)	18%

in up to 75% of patients with hematological malignancies (Bachanova and Connors, 2008).

Remarkably, in contrast to these findings, it appears that pregnant patient with *non Hodgkin lymphoma* tend to present with a more aggressive histology – most commonly diffuse large B-cell or peripheral T-cell lymphomas – compared to non-pregnant patients (Ali *et al*., 2004; Pereg D. *et al*., 2007).

4. Diagnosis of hematological malignancies in pregnancy

a) *Physical examination and routine blood-tests*

The rare occurrence and subtle presentation of these malignancies in pregnancy often delay their diagnosis, which may adversely impact on prognosis. In addition, the psysiological changes associated with pregnancy (see chapter 5B) can mask certain laboratory abnormalities that are typically present in patients with hematological disorders; (simple anemia of pregnancy, leukocytosis or gestational thrombocytopenia, may temporarily hide a more serious hematological process such as leukemia) (Sadural and Smith, 1995; Doll *et al*., 1988).

b) *Histopathological examination*

The diagnosis of a hematological malignancy requires a lymph node biopsy or bone marrow aspirate and/or biopsy for diagnosis. Biopsies can safely be done under local anesthesia during pregnancy. Overall, it appears that with modern surgical and anesthetic techniques, elective surgery – under general anesthesia - in a pregnant woman is safe even during the first trimester. The risk of spontaneous abortion is comparable with that of normal miscarriage and there is no significant increase in the risk of maternal death, birth defects or late neurodevelopmental delays (Cohen-Kerem *et al*., 2005; Doll *et al*., 1988).

c) *Diagnostic medical imaging*

The possible embryonic or fetal damage from radiation may be classified into two principal types: The first is teratogenic which may occur on exposure to radiation in the first 12 weeks of pregnancy (when the embryo is in the stage of organogenesis and the CNS is especially sensitive to radiation (Table 4)) (Kal and Struikmans, 2005). The second type is carcinogenic. Gilman *et al*. suggested that the risk due to radiation is higher in the first trimester than in the second and third, but this is not fully established. These two effects are manifested in the first decade of life. The available information on radiation-induced embryonic damage is derived from animal studies, follow-up of individuals exposed to atomic bomb explosions in Japan (Jablon and Kato, 1970; Miller and Mulvihill, 1976), and statistical analyses (Fenig *et al*., 2001).

Teratogenicity and carcinogenicity are related to total dose, dose fractionation, field size and gestational age. Stewart et al reported already in 1956 evidence that diagnostic radiography might be carcinogenic for the fetus. Doll *et al*. concluded in 1997 that there is strong evidence that low dose radiation (10 mGy) of the fetus in utero - particularly in the last trimester - causes an increased risk of cancer in childhood (6% per Gy). The major unresolved question is the maximum safe dose. Several studies have shown no increase in abortion, growth retardation or congenital malformation from diagnostic exposures below 10cGy (at any time during gestation) (Doll *et al*., 1988; Nuyttens *et al*., 2002). As *Table 3* demonstrates, the estimated fetal dose from routine radiologic diagnostic procedures is less than 10 cGy. The probability of developmental damage or childhood cancer due to embryonic-fetal irradiation of 1cGy does not exceed one in 1000, and may be only

Table 2. — Frequency of malignancies in women of reproductive age (Koren G. *et al*., 2007).

15 to 24 years	**25 to 34 years**	**35 tot 44 years**
Hogkin lymphoma	Breast carcinoma	Breast carcinoma
Thyroid carcinoma	Cervical carcinoma	Cervical carcinoma
Melanoma	Thyroid carcinoma, melanoma	Melanoma

Table 3. — Estimated average fetal dose (Kal *et al*., 2005.

Procedure	dose to fetus (Gy)
Extremity	0.00001
Cervical spine	0.00002
Chest RX	0.00008
Pelvis	0.00040
Abdomen	0.00290
Hip	0.00300
CT abdomen	0.05000

one in 10 000 or even zero. These figures are negligible when compared to the overall 4-6% rate of birth defects in the general population (Fenig *et al*., 2001). However, abdominal and pelvic CT are associated with exposures of up to 50 cGy (still below the threshold dose – 0.1-0.2 Gy – for organogenesis defects). As ultrasonography or magnetic resonance imaging (MRI), may provide the desired diagnostic information without measurably increasing the risk of fetal malformations; therefore abdominal and pelvic CT should be avoided during pregnancy (Doll *et al*., 1988; Pereg D. *et al*., 2008; Pereg D. *et al*., 2007). Iodinated contrast seems safe to use in pregnancy (Chen *et al*., 2008). In contrast to previous belief, also gadolinium-enhanced magnetic resonance imaging is possible during pregnancy (Webb *et al*., 2005).

PET-CT has been increasingly used for both staging and treatment follow-up in patients with lymphoma. FDG (fluor-2-deoxy-D-glucose) can cross the placenta and reach the fetus. It may involve higher radiation exposure than regular CT and its use cannot be recommended during pregnancy. It should be performed for (re)evaluation after delivery (Doll *et al*., 1988).

5. Treatment of hematological malignancies in Pregnancy

a) *General approach*

Overview by trimester (Peccatori *et al*., 2004; Cardonick and Lacobucci, 2004)

The occurrence of many congenital abnormalities has been ascribed to gene mutations, chromosomal mutations, and exogenic causes. In the large majority of cases, however, the exact cause is unknown. Exogenic causes (7% of congenital developmental abnormalities) can be subdivided into infections, X-rays, metabolic diseases, and drug- or xenobiotic-induced injuries (Ebert *et al*., 1997).

Cancer treatment (chemotherapy and radiotherapy) during the first trimester increases the risk of spontaneous abortion, fetal death, and major malformations. Malformations reflect the gestational age at exposure: the fetus is especially vulnerable when exposed during organogenesis – weeks 2-8 after conception – and the heart, neural tube, and limbs are affected earlier than the palate and ear (Cardonick and Lacobucci, 2004; Peccatori *et al*., 2004, Pereg *et al*., 2007).

After organogenesis, the eyes and genitalia, as well as the haemopoietic system and the CNS, remain vulnerable to continued exposure. Exposure during the second and third trimesters increases the risk of intrauterine growth retardation (IUGR) and low birth weight (Cardonick and Lacobucci, 2004). Maternal nutritional deficiencies, caused by the tumour or by chemotherapy-induced anorexia, can also affect fetal growth and birthweight. However, studies with long-term follow-up of children after chemo exposition have not shown impairments in learning

Table 4. — Effects and risks after exposure to ionizing radiation in utero, and spontaneous frequency (no radiation) (Kal *et al*., 2005)

Time after conception (w)	Effect	Risk per 0.01 Gy	Spontaneous frequency
0 - 2	Prenatal death*	0.01 - 0.001	0.3 - 0.6
8 - 15	Mental reatardation IQ decrease§	0.004	0.005
16 - 25	Mental retardation IQ decrease#	0.001	0.005
0 - 38	Leukemia, solid tumors In childhood	0.003 - 0.004	0.002 - 0.003

Based on experimental data. ¥Above threshold dose of 0.1 - 0.2 Gy. §Reduction of 21 IQ points per 1 Gy above threshold of about 0.05 Gy. Trheshold dose for mental retardation about 0.06 Gy, #Reduction of 13 IQ points per 0.1 Gy above threshold dose of about 0.05 gy, threshold dose for mental retardation about 0.25 Gy.

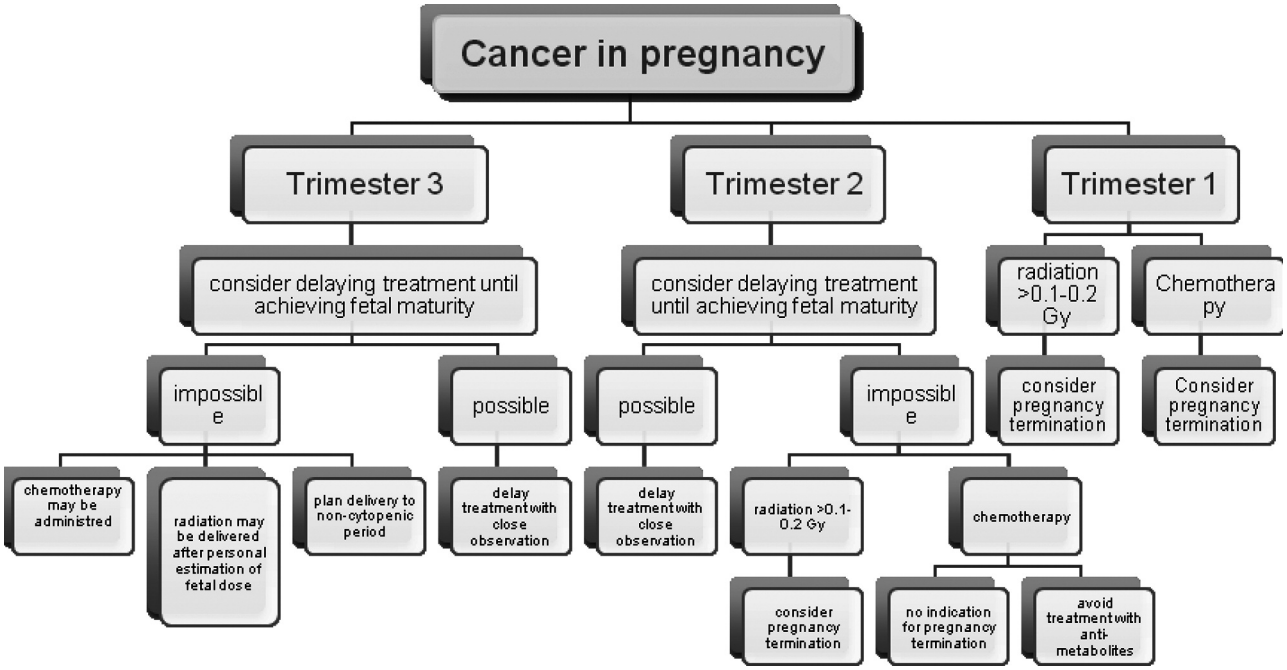


Fig. 1. — Treatment of cancer in pregnancy: possible decision tree

behaviour or haematological or immunological abnormalities (Cardonick and Lacobucci, 2004).

Issues and conflicts concerning "treatment of cancer in pregnancy"

Should the therapy of choice be different in the presence of pregnancy? The presence of pregnancy aggravates the situation for the physician and the patient because the decision made needs to take into account the interests of the mother and the fetus (Oduncu *et al*., 2003).

An important and difficult issue in the treatment of malignancies in pregnancy is the marternal-fetal conflict:

Pregnant women must confront the diametrically opposed facts of a life-giving and a life-threatening process. Omission of tumor therapy for the fetus' sake will increase maternal morbidity and mortality. Chemo- and/or radiotherapy administered during the first trimester will raise the risk of fetal malformations or spontaneous abortion. Most authors suggest that maternal well-being is primordial to fetal well-being when a decision to therapy has to been made.

Different Treatment modalities

Therapeutic approaches of pregnancy-associated cancer include radiotherapy, chemotherapy, supportive treatment and induced delivery (*Figure 2*: possible decision tree, Pereg D. *et al*., 2008).

b) *Chemotherapy*

Patients with pregnancy-associated malignancy, who choose to continue pregnancy, are mostly treated with chemotherapy (Hansen *et al*., 2001). To date there are few prospective clinical studies assessing the short - and long - term effects of chemotherapy during pregnancy. Most available information is reliant upon case reports and small retrospective case-controlled studies (Weisz *et al*., 2001). Recently Van Calsteren *et al*. reported an observational study of 215 patients with cancer diagnosed during pregnancy (Van Calsteren *et al*., 2010).

The teratogenicity of any drug depends on the timing of exposure (which trimester?), dose, frequency and duration of treatment and the characteristics affecting placental transfer: High lipid solubility, low molecular weight, and loose binding to plasma proteins favour transfer of drugs from mother to fetus (Ali *et al*., 2003). Genetic predispositions to teratogenicity *might* explain why people given the same agents have differing susceptibility. Synergistic teratogenic interactions may occur with combination chemotherapy (Doll *et al*., 1988).

Many chemotherapeutic agents are teratogenic in animals. Such data can only suggest that the drugs endanger human fetuses. Therapeutic doses used in humans are often lower than the minimum teratogenic dose applied in animals and animal data will apply clinically only if the teratogenic dose does not

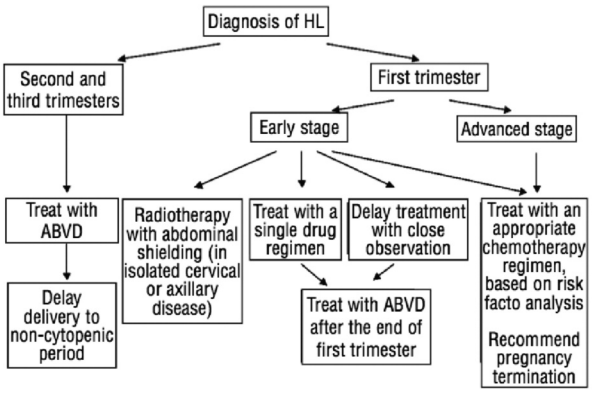


Fig. 2. — Proposes a possible algorithm for the treatment of pregnancy-associated HD (Pereg 2007).

Table 5. — Chemotherapeutic agents in hematological tumours and mechanism of action.

Antracycline antibiotics:
daunurobicine, doxorubicine, adriamycine
– act by interposing between DNA

Alkylating agents:
cyclophosphamide, Thioguanine, dacarbazine, mechlorethamine, Busulfan, procarbazine
– Crosslinking of DNA, which prevents uncoiling of the DNA-double -helix

Antimetabolities:
Cytarabine, mercaptopurine, Methotrexate
– False substrate during DNA or RNA synthesis

Vinca alkaloids:
Vincristine, vinblastine
– prevent cells from undergoing mitosis by disrupting microtubule polymerisation

Others:
ATRA, Hydroxyurea, alfa-Interferon, Imatinib
– check paragraph 6 for mechanisms of action

Published adverse-effects of these products: check www.motherisk.org

cause additional maternal toxic effects (Weisz *et al*., 2001).

Most drugs used for the treatment of neoplasms are classified by the US Food and Drug Administration (FDA) as risk category D. That means there is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risk (Weisz *et al*., 2001). *Table 5* gives an overview of

a) the different anti-cancer drugs used in pregnancy for hematological malignancies, b) their mechanisms of action. Also check www.motherisk.org.

When treating pregnant patients with chemotherapy, it is important to consider the physiological changes during pregnancy. These changes (as summarized in *Table 6*) might decrease or increase active drug concentrations compared with women who are not pregnant and have the same weight. So far, one pharmacokinetic studie has been conducted in pregnant women receiving chemotherapy in order to understand whether pregnant women should be treated with different doses of chemotherapy (Van Calsteren *et al*., in press). During pregnancy the distribution volume (plasma volume expansion by 50%) and clearance were increased and the Area Under the Curve (AUC) and C_{max} decreased. This assumes that physiological changes of pregnancy result in lower plasma levels of chemotherapeutic agents. This appears to be associated with a decreased bone marrow toxicity.

Cytotoxic drugs are usually not used separately as described in most reports. That's why we emphasise the effects of in utero-exposure to multi-drug regimens.

c) *Radiotherapy*

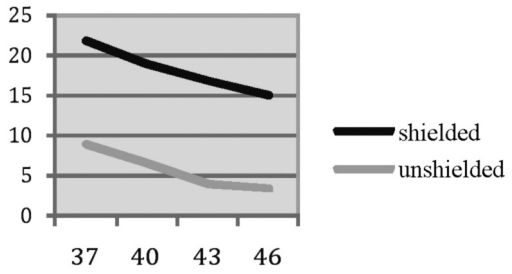
The adverse effects of radiotherapy on embryos and fetuses include lethality, malformations, mental retardation, growth retardation, carcinogenesis and genetic abnormalities (Doll *et al*., 1997; Fenig *et al*., 2001; Kal and Struikmans, 2005; Mazonakis *et al*., 2003; Nakagawa *et al*., 1997; Stovall *et al*., 1995).

Radiation doses used in cancer therapy are usually within the range of 4000-7000 cGy which is more than 1000-fold the level in diagnostic radiology. Fetal exposure depends on several factors including the target dose, size of radiation fields and the distance from the edges of the radiation fields to the fetus. Generally, a distance of over 30 cm from the field edges will yield an exposure of the fetus to only 4-20 cGy and therefore many areas such as the head, neck and extremities can be treated with radiation without significant fetal exposure. Radiation treatment can be safely given during pregnancy when necessary. The use of supplemental fetal-shielding can reduce the fetal exposure by 20% to 60% (*Graph 1*) and should always be taken into consideration. For embryo doses of 10 cGy, the risk of hereditary effects is negligible whereas the probability that a child will not develop cancer from ages zero to 19 years is 99.1%. Thus, embryo dose up to 10 cGy should not be considered a reason for pregnancy termination (Mazonakis *et al*., 2003; Stovall *et al*., 1995).

Lishner and co-workers described 21 women who received radiotherapy during Hodgkin disease in pregnancy, of whom 16 had radiotherapy as single therapy, and five had involved-field radiotherapy combined with chemotherapy. Healthy offspring were born without anomalies (Lishner *et al*., 1992).

Table 6. — Physiologic changes of pregnancy (Doll 1988).

altering drug metabolism:
– Stomach empties more slowly
– Plasma volume increase of 50%
– Albumin decreases, plasma proteins increase
⇒ altered plasma unbound drug concentration
– Enhanced hepatic oxidation
– increased glomerular filtration and renal plasma flow



Graph 1. — Distance from field isocenter to fetus (cm, X-axis) vs embryo dose (% tumor dose, Y-axis) (Doll, 1997).

Patients with Hodgkin's disease stage I and II are treated mainly with polychemotherapy followed by radiotherapy given only to the originally involved sites (involved-field radiotherapy). In stage III-IV disease, radiotherapy seems to be of no benefit if given routinely in patients who show a complete remission after chemotherapy: RT could benefit patients with partial responses after chemotherapy in these cases (Fenig *et al*., 2001; Kal and Struikmans, 2005).

d) *Supportive treatment (Pereg et al., 2008; Amant et al. 2009)*

Up to 70% of cancer patients may suffer from nausea or emesis following chemotherapy. No association was found between treatment with metoclopramide, anti-histamines or ondansetron-based anti-emetics and fetal malformations in both animal models and humans. As pregnant women with malignancy might be treated with antibiotics – especially due to neutropenic fever – their effects on the mother and fetus must be addressed. There is large data regarding fetal safety of penicillins, cephalosporins and erythromycin. Aminoglycosides seem to be safe in first trimester on limited data. A higher rate of cardiovascular malformations was found after treatment with trimethoprim-sulfamethazine in the second-third months of pregnancy. Quinolones that cause arthropathy and tetracyclines that affect bone and teeth should be avoided during pregnancy. Sulfonamides, similar to other folate antagonists have been associated with neural tube defects and cardiac malformations and should be avoided as well (Pereg *et al*., 2008; Werler *et al*. 2005).

Appropriate pain control: Paracetamol has been reported to be used by up to 65% of pregnant women and is number one during pregnancy. It can be administered safely throughout pregnancy. Non steroidal anti-inflammatory drugs (NSAID's) are not considered teratogenic. However, their effect on prostaglandins, in third trimester (> 32 weeks), is associated with premature closure of the ductus arteriosus, oligohydramnion and prolonged gestation and labor (these drugs are effective tocolytic agents).

Limited evidence exists suggesting that the treatment of chemotherapy-induced cytopenias by granulocyte colonystimulating factor and erythropoietin is safe to both mother and fetus (Pereg *et al*., 2008; Cardonick *and Lacobucci*, 2004). Regarding the use of corticoids, methylprednisolone and hydrocortisone are extensively metabolized in the placenta. They are therefore preferred over dexa- or betamethasone (Amant *et al*., 2009).

e) *Induced labour*

If possible, chemotherapeutical treatment should be delayed until after delivery. When possible, the delivery should be delayed until 35 to 37 weeks and beyond and preferably not before 32 weeks. When delivery is planned before 34 weeks, fetal lung maturation must be considered (Amant *et al*., 2009).

If chemotherapy has been given during pregnancy, delivery should be induced or cesarean section performed as near to term as possible when maternal blood cell counts are not compromised due to cancer therapy. Antineoplastic agents – administered systematically – may reach significant levels in milk (little date is known about this); therefore, breast-feeding is contra-indicated if the mother is receiving or has recently received chemotherapy. Long-term follow-up of the infant is lacking in literature. In a small series, Van Calsteren *et al*. suggested that children (median follow-up 35 months; 10 cases) who were exposed in utero to cytotoxic drugs showed a tendency towards a thinner ventricular wall. However, confirmation in lager series with longer duration of follow-up is needed.

6. Literature review: Treatment of most frequent hematological malignancies in Pregnancy

Hodgkin disease (Jacobs et al., 1981)

Hodgkin's disease (HD) is a unique malignant disorder, usually arising in lymph nodes and defined by the presence of the pathognomonic Reed-Sternberg

ABVD-regimen: Adriamycine + Bleomycine + Vinblastine + Dacarbazine (Standard therapy)					
Diagn.	**Mean age**	**# cases**	**Start trim.**	**Additional Drugs**	**Complication child (#w)**
HL	NA	32 6 4	I II All Trim.	No No No	- Nihil - 1 death due to prematuritas, Nihil - 1 death in utero (32w), Nihil
M-/COPP-regimen: Mechlorethamine / Cyclophosphamide + Vincristine + Procarbazine + Prednisone					
HL	25	22 5 3	I II All Trim.	+ cyclophosphamide + ABVD No No	- IUGR, floating thumb, hypoplasie 2 phalanges (?w), other not specified malformations (?w), hydrocephalie, others: nihil - Nihil - 1 Gastroenteritis (12w) + death, others were healty
Radiotherapy: mantleradiation, size and dose restricted, with shielding					
HL	NA	17 26 5	I II III	- abdominal shield - measured fetal dose	- Nihil - Nihil - Nihil

Hodgkin Disease – (Bachanova and Connors, 2008; Dilek *et al*., 2006; Ebert *et al*., 1997; Garcia *et al*., 1999; Wiebe and Sipila, 1994; Jones *and Weinerman,* 1975; Jacobs *et al*., 1981; Kal and Struikmans, 2005; Nuyttens *et al*. 2002).

giant cell (Sadural and Smith, 1995). HD is a neoplasia with a peak incidence between the ages of 20-30 and another peak incidence after the age of 55. The illness affects male patients more than female patients. Due to the peak incidence among young people it is not rare to diagnose HD in pregnant women. In these cases the incidence varies between 1:1,000 and 1:6,000 deliveries (Anselmo *et al*., 1999).

The current trend in the treatment of HD is to administer chemotherapy for all stages. Radiotherapy can still be considered as mentioned above.

Literature review (1990-2009) reveals 120 cases of treated HD in pregnancy:

- 71 patients were treated during the first trimester of pregnancy; 32 of them were treated with the ABVD-regimen and all of these mothers gave birth to a healthy child. 17 patients were treated by size/dose restricted mantleradiation and abdominal shielding, without complications to any of the children. 22 patients were treated with the M-/COPP-regimen during first trimester of pregnancy: 1 child died because of hydrocephalus 4h after birth, 1 child developed multiple anomalies (not specified) and 1 child - whose mother was treated with COPP before pregnancy + ABVD in the first trimester developed IUGR and a floating thumb malformation on the left hand, as a result of partial agenesis of a metacarpal bone and hypoplasia of two phalanges (Dilek *et al*., 1999). This is the only case of a COPP-ABVD exposed fetus.

Possible mechanisms for growth retardation (Weisz *et al*., 2001) include: diminished oxygen transfer to the fetus caused by decreased maternal hemoglobin concentration, aggregation of leukemic cells in the utero-placental circulation and possible intravascular coagulation. Decrease of the postdelivery growth rate has also been reported as an effect of daunorubicin in mice.

- 37 patients were treated starting from the second trimester of pregnancy. 1 child died due to prematurity (29 weeks), 36 children were healthy (Lishner *et al*., 1992).
- 5 patient received RT in third trimester without fetal anomalies. 7 patients were treated during the entire pregnancy (trim I, II and III). One fetus died in utero at 32 weeks (ABVD-regimen).

114 of 120 (95%) children out of our review, exposed to chemotherapy in utero, were born healthy and free of congenital malformations. (compared with random risk of fetal congenital malfomation in random population not treated with chemo: 3-4%) (Doll *et al*., 1988; Pereg *et al*., 2008).

In summary, this literature review suggests that patients diagnosed with HD in pregnancy should be treated with the ABVD-regimen rather than with a M-/COPP-regimen; especially during the first trimester. Patients with early stage HL diagnosed in the first trimester should be followed-up at short intervals for signs of disease progression without any treatment until the second trimester (Fisher *et al*., 1996; Pereg *et al*., 2007).

CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone (Standard therapy)					
Diagn.	**Mean age**	**# cases**	**Start trim.**	**Additional drugs**	**Compl child (#w)**
NHL	31,5	1 3 4	I II III	No + Rituximab No	- Nihil - Nihil, Necrotizing enterocolitis, leucopenia (33w) - Nihil, 1 spontaneous abortion (30w)
M-/VACOP-B: methotrexate / etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone - Bleomycine					
NHL	27,5	8 22	II All trim.		- Nihil (1 twin) - Nihil
6-MP: 6-Mercaptopurine					
NHL	NA	1	I	No	- Spontaneous abortion

Non-Hodgkin Disease – (Dilek *et al*., 2006; Ebert *et al*., 1997; Garcia *et al*., 1999; Lees *et al*., 1994; Toki *et al*., 1990; Soliman *et al*., 2007; Wiebe and Sipila, 1994; Lambert *et al*., 1991; Nantel *et al*., 1990; Rey *et al*., 2009).
DNR: daunurobicin, CYT: cytarabine, TH: thioguanine, VCR: vincristine, MP: mercaptopurine, HU: hydroxyurea, MTX: methotrexate.

Non-Hodgkin disease

Non-Hodgkin-lymphoma (NHL) forms an heterogeneous group of hematological malignancies. According to the WHO-classification, we can divide them in three groups (indolent, aggressive and very aggressive). This disease is extremely rare in pregnancy: NHL has an age dependent incidence pattern with a sharp increase in frequency starting in middle life (in contrast to HD). These differences in age distributions together with the higher incidence of NHL in young males compared to women, probably explains the scarcity of reports of NHL associated with pregnancy (Lishner *et al*., 1994). However, NHL in pregnancy is most commonly associated with more aggressive histology and disseminated disease! (Mavrommatis *et al*., 1998)

The CHOP-regimen, (often associated with Rituximab: R-CHOP) has been commonly used for patients with NHL, especially large B-cell lymphoma.

39 cases reporting treatment of NHL during pregnancy were selected:

Patients were treated following the CHOP-regimen, M-/VACOP-B-regimen or following the administration of 6-mercaptopurine.

36/39 (92%) reported cases resulted in healthy, normal babies.

One child developed necrotizing enterocolitis and leucopenia (preterm delivery at 33 weeks. The risk of necrotizing entercolitis in preterm infants is 5-10%: probably this manifestation is not due to chemotherapy-treatment, but rather caused by prematurity) (Thompson and Bizarro, 2008). 2 spontaneous abortions occured: 1 abortion during CHOP-regimen in third trimester (abortion at 30 weeks) and 1 abortion during treatment with antimetabolite-treatment in first trimester.

We reviewed one case of CHOP-administration during first trimester (Dilek *et al*., 2006); Evidence regarding the fetal safety of CHOP during the first trimester is extremely limited. CHOP is considered to be safe in second and third trimester, however only seven case reports have been published. No reviewed data is available about the safety of M-/VACOP-exposition during pregnancy.

The spontaneous abortion after exposition to 6-MP in first trimester, suggests that antimetabolites in first trimester should be avoided (as mentioned by several previous review-rapports, although large data is lacking). Rituximab seems safe and without significant consequences for the foetus (Decker *et al*., 2006; Friedrichs *et al*., 2006; Rey *et al*., 2008).

Acute leukemia

Acute leukemias (derived from primitive hematopoietic progenitor cells): are subdivised into acute myeloid leukemia (AML, cells derived from myeloid

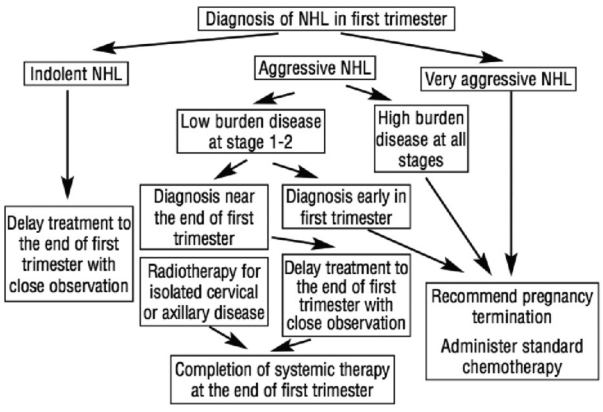


Fig. 3. — Proposes a possible algorithm for the treatment of First-trimester-associated NHL (Pereg *et al*., 2007).

precursors) and acute lymphoblastic leukemia (ALL, arising from lymphoid stem cells). Although they are rare cancers, accounting for less than 3% of all malignancies, they are the leading cause of death in young persons younger than 35 years of age. The incidice of acute leukemia in pregnancy is about 1 per 100.000 pregnancies. Eight different types of AML (M0-M7) and three types of ALL (L1-L3) can be distinguished. AML-M3 (promyelocytic leukemia) is a frequent form of leukemia in pregnancy: it's important to distinguish this form because ATRA-therapy has proven therapeutic benefits and because of high incidence of potentially lethal coagulopathy in this subtype. Although most adults with acute leukemia initially respond to chemotherapy, relapse is the rule rather than exception. Prompt treatment is absolutely necessary as delaying leads to a poor prognosis both for mother and fetus (Carradice *et al*., 2002; Pejovic and Schwartz, 2002; Sadural and Smith, 1995; Weisz *et al*., 2001). The earlier the diagnosis of leukaemia in pregnancy, the higher the perinatal mortality (Cardonick and Lacobucci, 2004).

81 cases reporting treatment of acute leukemia (1990-2009) during pregnancy were selected:

The initial course of chemotherapy is induction and is followed by consolidation and maintenance chemotherapy. Specific induction chemotherapeutic regimens include Ara-C and daunorubicin/6-thioguanine for AML and vincristine, prednisone, 6-MP, MTX, asparaginase, cyclophosphamide for ALL (Sadural and Smith, 1995; Weisz *et al*., 2001).

– 23 Mothers have been treated with ATRA (AML-M3). (3 cases during first trimester). Literature reports fetal malformations in 20% of children if ATRA is given during first trimester. The approach to a pregnant woman with APL must take into account the high bleeding complication in case of induced abortion (if preferred instead of treatment during pregnancy) before achieving complete remission due to the disseminated intravascular coagulation (DIC) typical of this disease. ATRA appears to be reasonable safe if given outside first trimester. Complete remission duration induced by ATRA alone is usually short (2-30 months) if not consoli-

ATRA: all-trans-retinoic acid					
Diagn.	**Mean age**	**# cases**	**Start trim.**	**Additional Drugs**	**Complication child (#w)**
AML-M_3	26,4	3	I	No	- 2× small for date (32w, 32w)
		8	II	No	- arrythmia, thrombopenia
		10	III	No	- resp. distress (32w), IUGR (33w), death (29w), pulm hypoplasia and IUGD (28w)
		2	II	+ DNR and CYT	- RDS + death (28w), nihil
Cytarabine (Ara-C) + anthracycline antibiotic (daunorubicin, doxorubicin, adriamycine) (Standard therapy)					
AML M_2, M_4, M_5	27	2	I	+ TG, VCR, 6-MP, mitoxantrone, HU	- 2 fetal death (17w, 25w), 1 marrow aplasia and FailureToThrive (birth 29w), 2 spontaneous abortions
	13	II			
	NA	22	All trimesters	+ 6-MP, MTX, cycloph, VCR, 6-TG	- 1child: choanal stenosis, hypotelorism, hypoplasia oropharynx (chemo at conception)
ALL	19	1	II	+ VCR	- death: ARDS + death mother
Cytarabine (Ara-C) + 6-thioguanine					
AML	NA	3	I	No	- four finger hand with hypoplastic thumbs, iris adhered to cornea, multiple skeletal anomalies, bilateral radius and digit 5 absent, fetal death: (no normal children).
		2	II	No	
Cyclophosphamide + daunurobicin + Asparaginase + vincristine + methotrexate + 6-mercaptopurine + prednisone					
ALL	NA	3	I	+ Radiotherapy	- Chromosomal gaps (1), sever bone marrow hypoplasia (1), pancytopenia (1), 3 normal children
		3	II		
Multiple modified chemotherapeutic combinations for ALL-treatment in literature					

Acute leukemia – (Ali *et al*., 2003; Camera *et al*., 1996; Carradice *et al*., 2002; Dilek *et al*., 2006; Ebert *et al*., 1997; Fadilah *et al*., 2001; Garcia *et al*., 1999; Giagounidis *et al*., 2000; Greenlund *et al*., 2001; Harrison *et al*., 1994; Hoffman *et al*., 1995; Molkenboer *et al*., 2005; Wiebe and Sipila, 1994)

dated by intensive anthracycline-based chemo. Only two reports were published combining ATRA + DNR/CYT, during pregnancy, resulting in a) fetal death due to pulmonary hemorrhage after 1 day (extensive ventilation because of respiratory distress syndrome (RDS)) and b) normal development. Despite the presence of isotretinoin in umbilical cord blood, no fetal abnormalities have yet been observed from ATRA-treatment in late stage of pregnancy. Several reports conclude that ATRA can be used relatively safe outside the first trimester and that aggressive chemotherapy in combination with ATRA is a possible mode of therapy in pregnant patients with APL (Carradice *et al*., 2002; Garcia *et al*., 1999; Giagounidis *et al*., 2000; Greenlund *et al*., 2001; Harrison *et al*., 1994; Lipovsky *et al*., 1996).

– 38 Mothers were treated with the Ara-C + anthracycline - regimen. 7/38 (18%) of the exposed fetuses, presented with serious congenital anomalies or fetal death. This suggest that Ara-C should be avoided in first and early second trimester.

– 5 mothers have been treated with Ara-C + 6-thioguanine during pregnancy. None of their children developed normal (all had congenital anomalies, most probably due to these chemotherapeutic agents).

These findings confirm that Cytarabine (Ara-C) and thioguanine should be avoided in the first trimester as mentioned in literature (Cardonick and Lacobucci, 2004).

– 6 mothers were treated with Cyclophosphamide + daunurobicin + Asparaginase + vincristine + methotrexate + 6mercaptopurine + prednisone (full conventional regimen for ALL). 50% of these children were healthy, all treated out of first trimester of pregnancy: this regimen seems to be safe if givenout of first trimester of pregnancy (Cardonick and Lacobucci, 2004).

NOTE: anthracyclines represent common chemotherapeutic agents in treatment of acute leukemia and other hematological malignancies. Doxorubicin and daunorubicin have been the most commonly used agents of this class during pregnancy. Idarubicin, a (derivative of daunorubicin and much more liposoluble) is 4 to 5 times more cytotoxic and is reported to be more cardiotoxic (Stroble *et al*., 1999). Five cases have been published using idarubicin in pregnancy: One fetus died after administration; two other cases, both developed cardiac failure (Matsuo *et al*., 2004). Idarubicine should be avoided in pregnancy (Cardonick and Lacobucci, 2004; Goldwasser *et al*., 1995; Weisz *et al*., 2001).

Chronic leukemia:

Chronic leukemias rarely are noted in women of reproductive age. Chronic myeloid leukemia (CML) – a myeloproliferative disorder characterized by overproduction of myeloid cells – represents 90% of chronic leukemias complicating pregnancy.

CML can be subdivided into three clinical phases: chronic, accelerated and acute blastic phase. Hyperleucocytosis/pancytopenia upon the course of the pregnancy and upon fetal development generally mandates therapeutic intervention. Conventional chemotherapy for CML (hydroxyurea (HU) and busalfan) has been joined recently by Imatinib (Pejovic and Schwartz, 2002; Sadural and Smith, 1995; Weisz *et al*., 2001). Bone Marrow Transplantation (BMT) is not an appropriate treatment in pregnancy. Literature reports about 96% of women with CML surviving to delivery. Fetal survival during gestation is 84%. Eventually, patients die of their disease, most from an acute blastic crises with a median survival of 2 months after onset of this crisis (Sadural and Smith, 1995; Weisz *et al*., 2001).

In our literature review, 157 cases of CML during pregnancy were reported between 1990 and 2009:

13/157 (8.3%) cases had congenital abnormalities and 18/157 (11.5%) had spontaneous abortion (resulting in 80.2% of normal development).

– Both HU and busulfan inhibit DNA-synthesis and therefore have potential to cause abortion, IUGR and congenital malformations. HU is thought to have lower mutagenic potential than alkylating agents. Limited cases have been reported treated with HU during pregnancy: One baby was born healthy after HU administration in III trimester, the mother of the other case received hydroxyurea treatment throughout whole pregnancy; an emergency cesarean section was performed because of solutio placentae in the 28th week of gestation. This premature male baby was born with no hematological abnormality, but had RDS following intracranial bleeding, with fatal outcome (Dilet *et al*., 2006; Fadilah *et al*., 2002).

– 48 cases reported in literature, demonstrate the safe use of alfa-interferon during pregnancy.

– 13 cases reported of busulfan exposure (an alkylating agent) plus radiotherapy during all trimesters of pregnancy. One case had mild thrombocytopenia. All other cases showed no congenital anomalies or complications. Busulfan seems to be safe during pregnancy (Cardonick and Lacobucci, 2004).

– Pregnancy seems to be no contra-indication for leukapheresis in CML-treatment (Ali *et al*., 2004; Strobl *et al*., 1999).

– Preclinical studies of fetal organogenesis in pregnant rats showed that Imatinib is teratogenic,

HU 4 gr/D					
Diagn.	**Mean age**	**# cases**	**Start trim.**	**Additional Drugs**	**Compl child (#w)**
CML Chronic phase	27	2	All trimesters III	None	All: bleeding, ARDS, Death III: nihil
Alfa-INF					
CML Chronic phase		17 26 5	I II III	abdominal shield measured fetal dose	- Nihil - Nihil - Nihil
Imatinib 400 mg/D (Standard therapy)					
CML Chronic Phase	32,8 NA	3 1 90	I II All trimesters	None None	- Twins: a) nihil b) IUGD+death Pyloorstenosis - Nihil - 63 healthy children (50%) - 18 spontaneous abortions - 8 live births, 1 stillbirth with: cleft palate, polydactyly, meningocoele, premature closure skull sutures, scoliosis, exomphalos (3 ×), hydrocephalus, hypospadias (2 ×), pyloric stenosis, hypoplastic lungs, hemivertebrae, right shoulder anomaly, right renal agenesis (2 ×)
Busulfan + Radiotherapy					
CML Acute/ blastic Phase	NA	13	All trimesters	6-mercaptopurine, alfa-INF, hydroxyurea	- 1 child with thrombocytopenia - Others: nihil

Chronic leukemia – (Ali *et al*., 2005; Baer *et al*., 1992; Buykbayrak *et al*., 2008; Celiloglu *et al*., 2000; Dilet *et al*., 2006; Fadilah *et al*., 2002; Heartin *et al*., 2004; Meera *et al*., 2008; Mesquita *et al*., 2005; Pye *et al*., 2008).

causing defects such as exencephaly, encephaloceles and deformities of skull bones. We found 94 reports on mothers treated with Imatinib during pregnancy. 64/94 (68%) of these fetuses developed normal. 5 infants developed congenital bone-deformities and 3 of them developed exomphalos. The expected incidence of exomphalos in the general population is approximately 1 in 3000 to 4000 births, and the finding of 3 infants out of 94 is far higher than would be predicted. It is of note that the infants with exomphalos all had a combination of very similar, quite complex defects which would be unlikely to occur by chance and make an imatinib-induced effect more probable! In conclusion, imatinib exposure during pregnancy might result in an increased risk of serious fetal abnormalities or spontaneous abortion. Pregnancy should be closely monitored and termination should be considered if any significant abnormalities are identified (Meera *et al*., 2008; Pye *et al*.; 2008).

Burkitt's lymphoma

Burkitt's lymphoma (NHL), is derived from B-lymphocytes and is characterized by rapid progression, early hematogenous dissemination and a propensity to spread to the bone marrow and central nervous system. The endemic form is commonly associated with the Ebstein-Barr virus. The primary treatment of Burkitt's lymphoma is aggressive multiagent chemotherapy with intrathecal chemotherapy for central nervous system prophylaxis (Weisz *et al*., 2001).

CHOP-regimen: cyclophosphamide, vincristine, doxorubicin, prednisone (therapy outside pregnancy: more aggressive)						
Diagn.		**#**	**#w**	**Additional Chemo**	**Outcome moth**	**Compl child (#w)**
Burkitt	20	2 1	II I	Rituximab, etoposide, ifosfamide, cytarabine (intrathecal) None	CR (7, 12 months) CR	Nihil Nihil

Burkitt's lymphoma – (Lam *et al*., 2006; Magloire *et al*., 2006).

Burkitt's lymphoma is a rare event in pregnancy but potentially fatal for mother and fetus if not *promptly* treated with *multiagent* chemotherapy. Our literature review reports 3 cases of multi-agent treated Burkitt-lymphomas in pregnancy. Drugs commonly used in non-pregnant state include R-CHOP-regimen, methotrexate, and cytosine arabinoside. High-dose methotrexate is an integral component of most effective regimens. Most frequent reported fetal effects from methotrexate include cranial dysostosis, hypertelorism, limb deformities, micrognathia, and cerebral anomalies (Cardonick and Lacobucci, 2004; Magloire *et al*., 2006).

All of our reviewed cases where treated with the CHOP-regimen (some of them with additional agents, no reported cases with methotrexate treatment). All of them had a complete remission after treatment, with birth of a healthy child.

Burkitt's lymphoma has been associated with a 60-85% 5-year survival in advanced-stage disease. Given the poor prognosis, immediate multiagent chemotherapy should be considered whenever possible, including those who wish to continue the pregnancy (Magloire *et al*., 2006).

Patients diagnosed during the first trimester, however, may be offered the option of termination, given that methotrexate is a mainstay of optimal treatment and is a known teratogen and abortifacient (Cardonick and Lacobucci, 2004).

7. Discussion

Recent reports agree that - for lymphoma and leukemia, diagnosed during pregnancy - there seems to be no difference in survival compared with a non-pregnant group. Delay in treatment and even diagnostic delay may influence the prognosis for chronic leukemia and indolent non-Hodgkin lymphomas, while in Hodgkin's disease, treatment may be safely postponed until after delivery in selected cases with limited disease.

The decision to use chemotherapy during pregnancy must be carefully weighed against the effect of treatment delay - until after delivery - on maternal survival. If possible, chemotherapy should be avoided during the first trimester or abortion should be taken in consideration. If the mother decides to continue the pregnancy and multidrug treatment in first trimester is required, anthracycline antibiotics, vinca alkaloids or single-agent treatment followed by multi-agent therapy after first trimester should be considered. Use of chemotherapy in the second and third trimesters seems to be safe. Patients requiring an anthracycline should be given doxorubicin rather than idarubicin or epirubicin. Cytarabine, methotrexate (and other antimetabolites), thioguanine and ATRA should be avoided in first trimester of pregnancy. CHOP is safe in second and third trimester. ABVD, Rituximab, busulfan and alfa-Interferon seem to be rather safe in all trimesters of pregnancy. Imatinib should be avoided in all trimesters.

In this review we selected 403 cases of treated hematological malignancies in pregnancy. 342/403 (84.86%) mothers gave birth to a normal, healthy child without congenital abnormalities or IUGR. 108/403 cases were treated during the first trimester. 86/108 (79.6%) children were alive and presented with a normal phenotype at birth. 61/403 (15.14%) of the developing fetuses presented with congenital abnormalities, IUGD, early spontaneous abortion or fetal death short after birth.

The dose to the fetus resulting from most conventional radiographic and nuclear medicine examinations is less than 10 cGy. In patients who are pregnant, most cancers that are remote from the pelvis can be safely treated with radiotherapy.

Decisions about treatment of pregnancy-associated cancer should be approached interdisciplinary and should be made individually for each patient. Every decision should be made together with the patient, after careful consideration of both the risks and benefits.

More women than those identified in this review have probably received chemotherapy during pregnancy, but are not included in the published case reports. Most likely there is an existence of a negative-publication-bias: successful cases have been reported and failed treatments of cancer in pregnancy have been concealed. Therefore we encourage publication of **all** exposed cases and the organisation of (inter)national registries.

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