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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 and their families, but also for their physicians since two lives with different priorities have to be considered. Treatment should adhere the standard treatment for the specific type and stage of cancer. Small adaptations can be considered in order to avoid adverse effects on fetal development. This chapter reviews the available data regarding the different aspects of diagnosis and – especially chemotherapeutical – treatment of hematological cancer during pregnancy.

First we will discuss the general approach of a woman diagnosed with cancer during pregnancy. Second we will give a quick overview of chronic leukemia, Hodgkin and non-Hodgkin disease during pregnancy and a more extended overview of acute leukemia during pregnancy.

2. Diagnosis

2.1 Physical examination and routine blood tests

The rare occurrence and subtle presentation of these malignancies in pregnancy often results in a delay in diagnosis, which may worsen the prognosis. In addition, the physiological changes associated with pregnancy 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).

2.2 Histopathological examination

The diagnosis of an hematological malignancy requires a lymph node biopsy or bone marrow aspirate and/or biopsy for diagnosis. Biopsies can safely be performed 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).

2.3 Diagnostic medical imaging

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).

The possible embryonic or fetal damage from radiation may be classified into two principal types. Firstly, the deterministic radiation effects, such as mental retardation and organ malformations, which arise above a threshold dose of 0.1 – 0.2 Gy (Kal and Struikmans, 2005). Teratogenic effects mainly occur after 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 (Kal and Struikmans, 2005).

Secondly, there are stochastic effects. They generally manifest many years later (so-called "late" effects) and cannot definitively be associated to the radiation exposure. Examples of these effects include cancer induction and genetic effects (in the offspring of irradiated individuals). These effects do not occur in relation to a certain threshold, but it is the probability of the effect that increases with administered 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). 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 one in 10 000 or even less. These figures are very low 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 high exposures and should therefore be avoided during pregnancy (Doll et al., 1988; Pereg D. et al., 2008; Pereg D. et al., 2007). The more because ultrasonography or magnetic resonance imaging (MRI) may provide the desired diagnostic information without increasing the risk of fetal malformations. Iodinated contrast seems safe to use in pregnancy (Chen et al., 2008). Gadolinium adds to sensitivity and specificity but crosses the placenta resulting in high fetal concentrations. Gadolinium is associated with nephrogenic systemic fibrosis in adults with an impaired kidney function. Children under 1 year are considered at low-risk to develop nephrogenic systemic fibrosis, because of their immature renal function. If needed, preference should be given to Gadobenate dimeglumine (Multihance®) and Gadoterate meglumine (Dotarem®) contrast media since no unconfounded cases of nephrogenic systemic fibrosis have been reported with these agents (Bellin et al., 2005). In contrast to previous belief, gadolinium-enhanced magnetic resonance imaging is thus 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). Positron emission tomography scan (¹⁸F-PET) is a highly sensitive technique for the detection of tumoral lesions. Since PET-technology is based on positron-electron annihilation and the detection of rather high energy photons, the biological effect of the

used radiopharmaceuticals is more significant. Optimization of the scanning protocol is therefore even more crucial, which should also include an evaluation of the protocol and necessity of the concurrent CT-scan in case of a combined PET/CT examination. A standard ^{18}F -FDG-PET examination results in a dose exposure of a 6-month old fetus of 5-6 mSv, which is still acceptable in many indications in view of the important information PET can add to the staging of e.g. lymphoma. In any case, consultation of the nuclear medicine physician and medical physicist before the pregnant patient presents herself to the nuclear department, allows to take some simple measures which can significantly limit the fetal exposure by limiting the dose of the radiopharmaceutical, supplementary maternal hydration and the use of a bladder catheter.

3. Obstetrical and placental issues

3.1 General follow-up

Prenatal care in women diagnosed with cancer during pregnancy should be performed in a high-risk obstetric unit. As treatment options will be dependent on the gestational age, it is very important to have a correct dating of the pregnancy. Before oncological treatment is started, we advise to perform a careful fetal examination by ultrasonographic screening, to ensure there are no pre-existing fetal anomalies. Further ultrasound scans should be performed every 2-3 weeks to evaluate the fetal growth, development and well-being. In case of abnormal findings, more stringent monitoring of the fetus or even preterm delivery might be necessary. Pregnancy-related complications should be treated according to the standard obstetrical care.

3.2 Monitoring around treatment

Before every cycle of cytotoxic treatment, an evaluation of fetal morphology, growth and well-being must be carried out by ultrasound screening. After treatment, it is important to consider fetal well-being and counsel patients to be alert when contractions occur, since an increased incidence in preterm contractions was reported after cytotoxic treatment during pregnancy (Van Calsteren et al., 2010). Furthermore, since cases have been described of neonatal pancytopenia, the possibility of fetal anemia has to be considered and checked before and after chemotherapy in pregnancy (Doppler measurement of peak systolic velocity of the middle cerebral artery).

3.3 The delivery

Delivery should take place in a hospital with a neonatal care unit. The timing of delivery needs to be determined according to the oncological treatment schedule and the maturation of the fetus. As in non cancer patients, a (near-) term delivery (> 35-37 weeks) should be aimed for (Van Calsteren et al., 2010). Prematurity and low birth weight associated with preterm delivery have been identified as negative contributing factors in the neurological and emotional development of children (Wood et al., 2000; Doyle, 2004; Mikkola et al., 1997; Ancel et al., 2006). When delivery before 34 weeks is inevitable, fetal lung maturation by corticosteroids should be considered and managed according to local policy (Crowley et al., 1990). The mode of delivery is determined based on obstetrical indications. To allow the bone marrow to recover and to minimize the risk of maternal and fetal neutropenia/thrombocytopenia/anemia, delivery should be planned 3 weeks after the last

dose of anthracycline-based chemotherapy (Loibl et al. 2006). Chemotherapy should not be administered after 35 weeks since spontaneous labor becomes more likely. Furthermore, neonates - especially preterm babies - have limited capacity to metabolize and eliminate drugs due to liver and renal immaturity. The delay of delivery after chemotherapy will allow fetal drug excretion via the placenta (Sorosky et al., 1997). Chemotherapy can be restarted when needed after delivery. An interval of one week after an uncomplicated caesarean section is required.

3.4 Postpartum

Although placental metastases are rare, the placenta should be analysed histopathologically after delivery (Alexander et al., 2003). In the absence of safety data, breastfeeding during or shortly after chemotherapy is contraindicated. Primary inhibition of milk production is needed because especially lipophylic agents can accumulate in the milk.

Cancer type	Cases placental M+	Cases fetal M+	Cases fetal and placental M+	Total
Melanoma	21	3	3	27
Breast cancer	15	0	0	15
Lung cancer	8	1	1	10
Leukemia	6	3	0	9
Lymphoma	3	2	1	6

Table 1. Case reports of placental/fetal metastasis (Alexander et al., 2003)

3.5 Transplacental transfer of chemotherapy during pregnancy

Chemotherapy during pregnancy has been associated with congenital malformations and neonatal bone marrow suppression, suggesting that at least a fraction of these drugs is passing the placenta (Cardonick E and Iacobucci A, 2004.). Transfer mainly occurs by passive diffusion, but also active transporters like P-glycoprotein, Multidrug Resistance Proteins and Breast Cancer Resistance Protein have an important role in the regulation of the placental drug transfer (Syme et al., 2004.). In humans only a few case reports are available, however results are not conclusive (Gaillard et al., 1995; Grohard et al., 1989; Roboz et al., 1979, D'Incalci et al., 1983; Karp et al., 1983; Koc et al., 1994). Results in a baboon model showed that transplacental transfer of chemotherapeutics varies substantially among different drugs. Significant levels of platinum (57.5+14.2% of maternal plasma levels (n=7)) after intravenous carboplatinum administration were detected in fetal plasma samples, but lower levels of doxorubicin (7.5+3.2%, (n=6)), epirubicin (4.0+1.6%, (n=8)), docetaxel (not detectable in fetal samples, (n=9)), paclitaxel (1.4+0.8%, (n=7)), vinblastine (18.5+15.5%, (n=9)) and 4-OH-cyclophosphamide (25.1+6.3%, (n=3)) were measured (Van Calsteren et al., 2010a, 2010b, 2011)

3.6 Short and long term effect of prenatal exposure to chemotherapy on children

The potential fetal effects depend on the gestational age at exposure. During the implantation period (first 10 days after conception) the number of surviving omnipotent

stem cells will determine whether a miscarriage occurs, or a normal embryo will develop. Between 10 days and 8 weeks after the conception organogenesis occurs and therefore, this period is at risk for congenital malformations. For foetal protection, the administration of chemotherapy is considered contraindicated until a gestational age of 10 weeks. If a 'safety period' of 4 weeks is respected, chemotherapy may start from a gestational age of 14 weeks (Amant et al., 2009). During the second and third trimester of pregnancy, no major malformations are expected to be caused by cytotoxic treatment. However, cases of growth restriction, prematurity, intra-uterine and neonatal death, and hematopoietic suppression have been reported (Cardonick and Iacobucci, 2004).

Data on the long term of children after prenatal exposure to chemotherapy are scarce. Based on theoretical assumptions, potential problems of neurodevelopmental delay, sterility, carcinogenesis and genetic defects have to be considered, but up till now available data do not suggest these problems. A study that includes 84 children who were born to mothers who received chemotherapy during pregnancy for haematological malignancies and with a median follow-up of 19 years, did not show any congenital, neurological, immunological and psychological abnormalities including normal learning and educational behaviour (Aviles et al., 2001). Hahn et al. surveyed 57 parents/guardians regarding outcomes of children exposed to chemotherapy in utero for breast cancer treatment. At ages ranging from 2 to 157 months, most children had a normal development. Only 2 children required special attention in school: 1 had attention deficit disorder, whereas the other was the child with Down syndrome (Hahn et al., 2006). In a small study, 10 children were between 2 months and 66 months of age when a full neurologic and cardiologic examination was performed. Whether the occurrence of a cortical malformation in a twin whose fraternal twin was normal, was related to cytotoxic drugs remains unclear. Otherwise, we encountered no development problems (Van Calsteren et al., 2006).

The few studies that looked at the cardiac effect of chemotherapy in the foetus showed that acute myocardial dysfunction can appear during pregnancy with anthracyclines. (Cardonick and Iacobucci, 2004; Germann et al., 2004). However, follow-up with cardiac ultrasound in 81 children who received anthracycline treatment in utero (age 9 - 29 years, mean 17 year) was reassuring (Aviles et al., 2006).

4. Supportive treatment

4.1 Antiemetics

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 (Tincello and Johnstone, 1996; Siu et al., 2002; Guikontes et al., 1992; World, 1993).

4.2 Antibiotics

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).

4.3 Pain control

Paracetamol has been reported to be used by up to 65% of pregnant women. It can be administered safely throughout pregnancy. NSAID's are preferably not used during pregnancy, but if needed can be considered during the first and second trimester of pregnancy. In the third trimester (> 32 weeks) NSAID's are contraindicated because they are associated with premature closure of the ductus arteriosus, oligohydramnion and prolonged gestation and labor (Pereg et al., 2008; Cardonick and Lacobucci, 2004).

4.4 Growth factors

Erythropoietin does not cross the placenta and its use is felt to be safe in pregnancy (Briggs and Yaffee, 2005). Granulocyte colony-stimulating factor use in pregnancy has been reported in a registry series of 20 patients with severe chronic neutropenia with a median dose of 2.7 mcg/kg/day administered daily or every other day during all three trimesters with an average duration of three trimesters. These data, although limited, did not reveal an increase in adverse congenital abnormalities or fetal death compared to pregnant patients that did not receive the drug (Dale et al., 2003).

4.5 Bisphosphonates

Animal studies with bisphosphonates have displayed maternal toxicity, foetal underdevelopment, embryoletality, hypocalcaemia and skeletal retardation during pregnancy. Bisphosphonates are therefore contra-indicated in pregnancy and have a FDA category C pregnancy risk. A recent literature search including 51 patients exposed to bisphosphonates shortly prior to conception or during pregnancy did not find evidence of skeletal abnormalities or malformations in the foetuses of the exposed mothers (Djokanovic et al., 2008). If bisphosphonates are indicated in a pregnant patient hypocalcemia affecting the contractility of the uterus must be avoided.

4.6 Leukapheresis

Leukapheresis has been used in both acute and chronic leukemia to rapidly reduce high whiteblood cell counts in patients with impending vascular occlusion. Experience with leukapheresis during pregnancy is limited to only a handful of cases used to treat both chronic and acute leukemias (Ali et al., 2004a, 2004b; Bazarbashi et al, 1991; Broccia et al., 1984; Fitzgerald et al., 1993, 1986; Nolan et al., 1988). In general, the therapy was tolerated well by the mother and the fetus. Although experience is limited, leukapheresis may be used as a short-term temporizing measure when no other options exist or in patients refusing other therapies during pregnancy.

4.7 Corticoids

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).

5. Leukemia in pregnancy

The diagnosis of leukemia in a pregnant woman is a dramatic event that generates complex ethical and therapeutic dilemmas. Leukemia often presents as a medical emergency and induction of appropriate therapy must be initiated promptly. The therapeutic decisions should involve a multidisciplinary team including at least an haematologist, an obstetrician, a neonatologist, a psychologist and a social worker. Hypothetically the treatment decision must be based on data from prospective clinical trials but unfortunately the available data in the literature derives from retrospective case reports and case series.

Leukemia occurring during pregnancy is very rare with an estimated incidence of one per 100.000 pregnancies annually (Pavlidis, 2002). This frequency is 3.5 times lower than the incidence of leukemia in the general population in Western world. This is explained by the fact that acute lymphoblastic leukemia occurs mainly in childhood, while acute myeloid leukemia occurs usually in late adulthood, thus relatively sparing the childbearing ages.

The majority of cases of leukemia during pregnancy are acute leukemias, of which two-thirds are acute myeloid leukemias and one-third acute lymphoblastic leukemias (Pentheroudakis and Pavlidis, 2006). The main chronic leukemia during pregnancy is chronic myeloid leukemia and accounts for about 10% of all pregnancy-associated leukemias, since chronic lymphocytic leukemia is extremely rare (Caligiuri and Mayer, 1989).

5.1 Acute leukemia in pregnancy

Since Virchow's first description in 1856 of leukemia in pregnant woman, more than 500 cases have been reported (Sadural and Smith, 1995). Acute leukemias are diagnosed more frequently during the later stages of pregnancy. It is estimated that 23% of acute leukemias diagnosed during pregnancy were detected in the first trimester, 37% in the second and 40% in the third trimester respectively (Caligiuri, 1992).

The initial diagnosis of acute leukemia is often challenging and sometimes can be delayed because pregnant women frequently describe various non-specific symptoms like fatigue. Anemia, as already mentioned, is accompanied by marked thrombocytopenia and neutropenia. Recurrent infections and bleeding reflect bone marrow failure. The diagnostic approach is the same as in the general population. Bone marrow aspiration for morphologic examination and biopsy, detailed immunophenotyping, cytogenetics and molecular studies are essentials.

No prospective studies comparing outcome in nonpregnant and pregnant women with acute leukemia are available. Case control series and historical control comparisons offer no evidence to suggest that pregnancy has an impact on the course and prognosis of acute leukemia provided that therapy is not delayed (Fey and Surbek, 2008).

Vertical transmission of leukemia in the fetus is exceptionally rare due to placental barrier and fetal immune system. Nevertheless the placenta is not an absolute barrier and single maternal leukemic cells can pass from mother to fetus and few cases of leukemic placenta infiltration and leukemia dissemination to the fetus have been described (Dildy et al., 1989; Osada et al., 1990; Van der Velden et al., 2001).

Cytotoxic agents have a relatively low molecular weight; most of them can cross the placenta and reach the fetus. When treating a pregnant woman with chemotherapy it is crucial to

consider that many physiologic changes occur in gestation, which can potentially alter the effectiveness of antineoplastic agents by changing their metabolism or clearance (Redmond, 1985). Plasma volume is increased up to 50%, the amniotic fluid creates a pharmacologic third space and renal clearance and hepatic oxidation of drugs are enhanced (Williams and Schilsky, 2000; Muchlow, 1986). For different drugs, among which chemotherapy, changes in pharmacokinetic characteristics have been shown. Recently we described a lower plasma drug exposure for doxorubicin, epirubicin, paclitaxel and carboplatin during pregnancy (Van Calsteren et al., 2010)). However these findings could not be related to different outcomes, and therefore it is currently advised to administer the same drug regimens/dosages to pregnant and nonpregnant women (Cardonick and Iacobucci, 2004).

5.1.1 Acute Myeloid Leukemia (AML)

Treatment protocols for AML consist of a combination of cytarabine with an anthracycline as an induction course in order to achieve complete remission. Afterwards various intensive chemotherapy combinations are administered as consolidation therapy.

Cytarabine as an antimetabolite carries a significant risk to the fetus. A review of 93 cases of pregnant women exposed to cytarabine alone or in combination with other chemotherapeutic agents reported 4 cases of limb malformations associated with first trimester exposure. The administration in the second and third trimester was associated with transient neonatal cytopenias in 5 cases, intrauterine fetal death in 6 cases, intrauterine growth retardation in 12 cases and 2 cases of neonatal deaths from severe infections (Cardonick and Iacobucci, 2004). Cytarabine use in the first trimester is not advocated and termination of pregnancy is strongly preferred.

Idarubicin and daunorubicin are the anthracyclines in the treatment regimens for AML. Idarubicin is more lipophilic compared to other anthracyclines and so placenta transfer is more likely to occur. Therefore it may be associated with higher rates of fetal complications and should be avoided during pregnancy (Cardonick and Iacobucci, 2004).

The experience with the administration of anthracyclines during pregnancy is limited mostly to doxorubicin and daunorubicin. Of 28 pregnancies after the first trimester, exposed to doxorubicin and daunorubicin for the treatment of various hematologic malignancies, 21 pregnancies were delivered without any complications (Turchi and Villasis, 1988). The results of daunorubicin are worrying especially the combination with cytarabine which is associated with serious fetal morbidity and mortality (Azim et al., 2010). A stillborn fetus was reported in one case after exposure to daunorubicin. Congenital anomalies including limb deformities, ventral septal defect and cardiomyopathy were also reported (Azim et al., 2010).

Doxorubicin has been extensively studied in gestational breast cancer and results are rather reassuring (Hahn et al., 2006). 162 Pregnancies with malignancies, including 25 in the first trimester, were exposed to doxorubicin and reported complications were pre-eclampsia, midtrimester miscarriage, transient neonatal neutropenia with sepsis, intrauterine growth retardation and intrauterine fetal death in 18 cases (Cardonick and Iacobucci, 2004). Since doxorubicin seems to be as effective as the other anthracyclines for the treatment of leukemia, it is the preferred anthracycline during pregnancy (Shapira et al., 2008). Six pregnant patients with AML were treated with a doxorubicin-based regimen with normal outcomes except from one premature delivery (Greenlund et al., 2001; Fassas et al., 1984). Doxorubicin is considered relatively safe throughout pregnancy and is not associated with an increased risk for severe congenital malformations (Azim et al., 2010). Whether in utero

exposure to anthracyclines is cardiotoxic to the developing fetus is unknown (Cardonick and Iacobucci, 2004; Avilés et al., 2006).

In relapsed AML termination of pregnancy is recommended, because therapy requires high-dose chemotherapy, stem cell transplantation or experimental drugs, which cannot be delivered during pregnancy (Shapira et al., 2008).

In summary when a pregnant woman is diagnosed with AML during the 1st trimester a strong recommendation for pregnancy termination must be given. In 2nd and 3rd trimesters treatment with cytarabine and doxorubicin should be instituted promptly. Delivery should be planned after the 32nd week of gestation and 2-3 weeks following treatment to allow bone marrow recovery.

5.1.2 Acute Promyelocytic Leukemia (APL)

APL is a unique type of AML characterized by the reciprocal chromosomal translocation t(15;17) (q22;q21) and its molecular equivalent the PML/RAR α fusion gene. APL has been reported in approximately 10% of cases of leukemia in pregnancy, similar to the percentage in non-pregnant women (Carradice et al., 2002). It is frequently associated with disseminated intravascular coagulation, which may severely complicate the management of pregnancy, labor and delivery.

As in other types of leukemia, management of APL in pregnancy cannot be based on evidence from clinical trials and relies on data from historical cases. A novel treatment strategy of APL was the introduction of All-Trans-Retinoic-Acid (ATRA). ATRA targets the fusion product of t(15;17). Pharmacological levels of ATRA lead to remission by differentiation of cells of the leukemic clone. By combining ATRA with induction and consolidation chemotherapy, APL has one of the more favorable outcomes (Sanz and Lo-Coco, 2011).

As with other vitamin A derivatives, ATRA exposure during the 1st trimester carries an 85% risk of teratogenicity, including severe neurological and cardiovascular malformations (Fadilah et al., 2001). ATRA appears to be reasonably safe and well tolerated if given outside the first trimester (Fadilah et al., 2001). A review of 15 cases of APL in pregnancy treated with ATRA did not reveal any fetal malformations that could be attributed to ATRA (Carradice et al., 2002; Fadilah et al., 2001; Giagounidis et al., 2006). However, close monitoring for fetal cardiac complications is mandatory throughout pregnancy (Yang and Hladnik, 2009). The most important maternal adverse effect of ATRA is the potentially lethal retinoic acid syndrome, which may be reversed with early administration of dexamethasone. The combination of ATRA with an anthracycline during the 2nd and 3rd trimesters has been reported in several case reports (Shapira et al., 2008). This regimen appears reasonably safe and is not associated with increased toxicity for either the pregnant woman or the fetus. Among 15 women receiving this regimen, 13 were diagnosed in late pregnancy and yielded live newborns, whereas 2 patients in 6th and 10th week of gestation at time of APL diagnosis had an abortion (Breccia et al., 2002).

The confirmation of diagnosis of APL in the 2nd and 3rd trimester should be followed by the initiation of ATRA with an anthracycline if the leukocyte count is less than 10,000/mm³. If the leukocyte count is greater than 10,000/mm³ an anthracycline alone is recommended to decrease the risk of ATRA syndrome. Arsenic trioxide is teratogenic and contraindicated in pregnancy (Rizack et al., 2009).

5.1.3 Acute Lymphoblastic Leukemia (ALL)

ALL is relatively rare among adults and only 21 cases of pregnant patients with ALL have been reported (Rizack et al., 2009). Because ALL is a highly aggressive disease, it is critical

that multiagent chemotherapy is administered immediately after the diagnosis. It has been shown that survival is significantly longer in patients whose induction therapy is started before delivery, than in those treated after delivery.

Methotrexate (a folate antagonist), a crucial component of most intensification protocols of ALL, is highly teratogenic and abortifacient when administered during the first trimester. Also the exposure to high dose methotrexate after the 1st trimester was associated with cranial dysostosis, delayed ossification, hypertelorism, wide nasal bridge, micrognathia, anomalies of external ears and cleft palate (aminopterin syndrome)(Ebert et al., 1997). The risk of fetal malformations diminishes as pregnancy advances (Ebert et al., 1997). Thereafter, termination of pregnancy is recommended for patients prior to the 20th week of gestation followed by the standard intensification chemotherapeutic ALL protocol. After the 20th week a modified anti ALL regimen that does not include methotrexate, may be used until the 3rd trimester (Rizack et al., 2009). Cyclophosphamide, vinca alkaloids, L-asparaginase, anthracyclines, cytarabine and steroids have been used in these regimens (Ali et al., 2009). However, all modified ALL protocols must be considered as “ bridging treatment” until the 3rd trimester. In the 3rd trimester treatment protocols as in non-pregnant women must be followed (Molkenboer et al., 2005). Close obstetric care and monitoring of the mother and fetus are essential to ensure the best possible outcome (Matsouka et al., 2008). Delivery after 32 weeks is suggested, simultaneous to a non-cytopenic period.

5.2 Chronic leukemia in pregnancy

5.2.1 Chronic Myelogenous Leukemia (CML)

The incidence of CML associated with pregnancy is estimated to be 1/75000 pregnancies (Celiloglu et al., 2000). The diagnostic approach is identical as in non-pregnant patients. The cytogenetic study reveals the Philadelphia chromosome and possibly additional chromosomal abnormalities of the clonal evolution. The disease is characterized by the presence of the bcr/abl fusion gene.

The introduction of imatinib mesylate, a tyrosine kinase inhibitor, has revolutionized the treatment of this disease. Pre-clinical models have suggested that imatinib may be teratogenic and therefore the present recommendation for women treated with imatinib is to use contraception (Azim et al., 2010). It has been reported that the concentration of imatinib and its active metabolite were higher in the placenta than in the maternal blood, while they were low or undetected in the umbilical cord. These findings suggest limited placental transfer of imatinib in late pregnancy (Russell et al., 2007).

It seems that administering imatinib during the first trimester is associated with a considerable risk of congenital anomalies and spontaneous abortions, while late exposure does not have the same impact. Nevertheless in patients diagnosed with CML during pregnancy, imatinib should not be the treatment of choice due to the limited experience (Shapira et al., 2008). Very limited data are available about the safety of second-generation oral tyrosine kinase inhibitors (dasatinib, nilotinib) during pregnancy and it is recommended that patients on these drugs should avoid pregnancy (Conchon et al., 2010).

Interferon-alpha (INF α), an immune modulator, does not cross the placenta to a great extent due to its high molecular weight (19kDa) and does not inhibit DNA synthesis. All reported cases of pregnant women with CML, treated with interferon, resulted in healthy babies and normal maternal outcomes. Given the available pre-clinical and clinical data, interferon can be safely administered throughout pregnancy and it is the treatment of choice for patients diagnosed with CML in pregnancy. Patients in the 2nd or 3rd trimester - who cannot tolerate or fail interferon therapy - may be treated with hydroxyurea or imatinib (Rizack et al., 2009).

Hydroxyurea is a cytotoxic drug, which inhibits DNA synthesis, and is capable of crossing the placenta. Several cases of hydroxyurea administration during pregnancy have been reported. Hydroxyurea treatment should be avoided in 1st trimester and could be given to patients who cannot tolerate interferon therapy during the 2nd or 3rd trimesters (Thauvin-Robinet et al., 2001).

5.2.2 Chronic Lymphocytic Leukemia (CLL)

CLL, a predominantly disease of the elderly, is very rarely associated with the reproductive period. Only five cases of CLL in pregnancy have been reported in literature (Chrisomalis and al., 1996; Baynes et al., 1996; Welsh and al., 2000; Gurman, 2002; Ali et al., 2004). In two of these cases placental infiltration has been described but with no impact on the fetus. Because CLL has an indolent clinical course, therapy of pregnant patients with CLL can usually be delayed until post partum. If intervention is required leukapheresis could be an option. Chlorambucil is contraindicated during the 1st trimester because of its teratogenicity and there are not enough data to recommend its use during late pregnancy. Fludarabine must be avoided in pregnancy. Autoimmune complications should be managed with corticosteroids as in non-pregnant patients (Rizack et al., 2009).

5.2.3 Hairy Cell Leukemia (HCL)

HCL is a type of chronic leukemia of late age at presentation with male predominance. Therefore it is extremely rare during pregnancy. Six cases of pregnancy-associated HCL have been reported and all pregnancies came to term without complications, resulting in delivery of healthy neonates (Shapira et al., 2008). When therapy is indicated in HCL during pregnancy, interferon-alpha is the treatment of choice (Baer et al., 1992).

5.2.4 Summary recommendations for the management of leukemia's in pregnancy

	1 st trimester	2 nd trimester	3 rd trimester
AML	pregnancy termination	Cytarabine-doxorubicin	cytarabine-doxorubicin
APL	pregnancy termination	ATRA & anthracycline	ATRA & anthracycline
ALL	pregnancy termination	>20w modified protocols	Standard protocols
CML	Interferon-alpha	Interferon-alpha	Interferon-alpha

Table 2. Recommendations for the management of leukemia's in pregnancy

6. Hodgkin disease in pregnancy

Hodgkin's disease (HD) is a unique malignant disorder, usually arising in lymph nodes and defined by the presence of the pathognomonic Reed-Sternberg 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. Although it represents only 0.5% of all cancers, it is not rare to diagnose HD in pregnant women, due to the peak incidence among young people. In these cases the incidence varies between 1:1,000 and 1:6,000 deliveries (Anselmo et al., 1999). It is curable even in advanced stages and ABVD (doxorubicin, bleomycin, vinblastin and dacarbazine) is considered the standard of care chemotherapy regimen in this disease (Connors, 2005).

6.1 Chemotherapy and Hodgkin disease in pregnancy

Based on the results of an extended literature review, we suggest that patients diagnosed with HD in pregnancy should be treated with the ABVD-regimen rather than with M-/COPP-regimen. ABVD outside the first trimester seems feasible and safe. Patients with early stage HD 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). Offering single agent vinblastine along with steroids is another option (Nisce et al., 1986), yet congenital anomalies and spontaneous abortions have been described with this approach. Patients diagnosed close to term could be good candidates for delivery anticipation to avoid any potential hazards to the fetus.

If advanced HD is diagnosed during the first trimester, termination of the pregnancy should be considered followed by appropriate staging and adequate doses of combination chemotherapy (Cannellos et al., 1992).

Treatment should not be delayed during pregnancy if patient presents with symptomatic (i.e. B symptoms), Bulky, subdiaphragmatic, or progressive HD after the first trimester.

Relapsed HL during pregnancy can be treated with chemotherapy, if the patient has been previously treated only with radiotherapy (Cannellos et al., 1992). Data in these cases are very rare.

6.2 Radiotherapy and Hodgkin Disease in pregnancy

Patients with HD stage I and II are treated mainly with polychemotherapy followed by radiotherapy (RT) given only to the originally involved sites (involved-field radiotherapy). In these cases, the average fetal exposure should not exceed 0.1–0.2 Gy, which is the threshold dose at which deterministic effects (e.g. mental retardation, organ malformation) can be expected (Kal and Struikmans, 2005). In stage III-IV disease, RT 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).

6.3 Possible decision tree for treatment of Hodgkin Disease in pregnancy

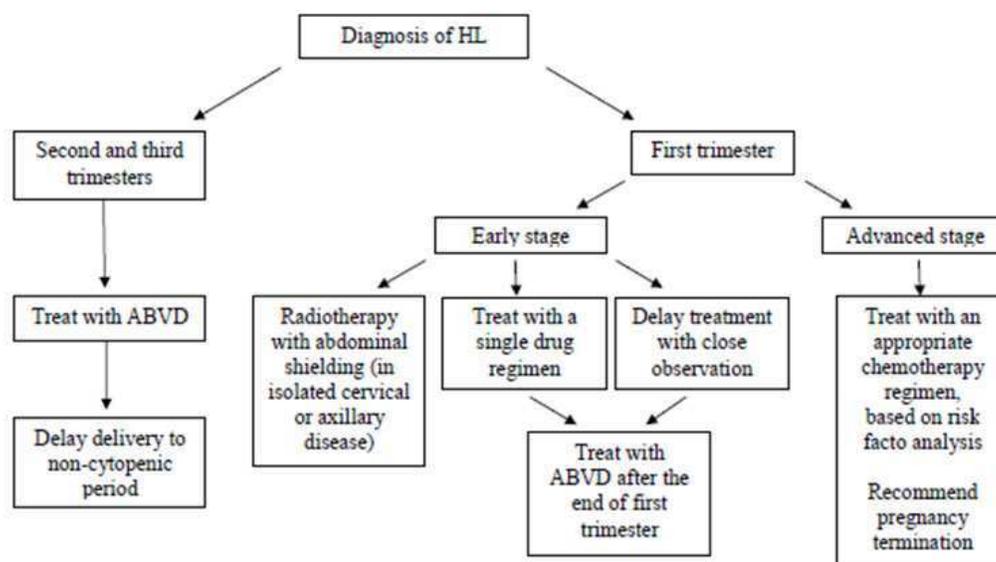


Fig. 1. Proposal of a possible algorithm for the treatment of pregnancy associated HD (Pereg, 2007)

7. Non-Hodgkin disease in pregnancy

Non-Hodgkin-lymphoma (NHL) forms a heterogeneous group of hematologic 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, but the occurrence of NHL during pregnancy is expected to increase due not only to the current trend to postpone pregnancy, but the increasing incidence of HIV-associated lymphoma in developing countries (Pereg et al., 2007). 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). Management of NHL varies significantly depending on the pathological subtype.

7.1 Indolent Non-Hodgkin Lymphoma

Indolent lymphomas are diseases of the elderly and have been rarely described during pregnancy. The exact incidence remains unknown as a significant proportion of the available reports lack a detailed pathological description. A large fraction of these tumors have an indolent course and thus could be safely watched during the course of pregnancy. In patients requiring active therapy, they could be offered regimens that have been shown to be safe in aggressive lymphomas (Nisce et al., 1986; Pereg et al., 2007).

7.2 Aggressive Non-Hodgkin Lymphoma

Treatment during the first trimester is complex and patients with aggressive disease should be counselled regarding therapeutic abortion, taking into consideration the fetal risk of staging and chemotherapy (Koren et al., 1990). Close observation or radiation therapy (Spitzer et al., 1991) during the first trimester could be considered in those patients presenting with early stage disease, low-volume disease, no B symptoms, and low international prognostic index (IPI) score. Patients with bulky disease or poorer prognostic indicators, such as high IPI score, B symptoms, or high Ki-67 in their biopsies should be treated immediately after pregnancy termination. Beyond the first trimester, standard chemotherapy should be instituted due to the poor prognosis of aggressive NHL without therapy.

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.

Literature suggests that anti-metabolites (such as 6-MP) 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).

Overall it seems that offering standard regimens like CHOP or CHOP-like regimens (e.g. R-CHOP) is safe and feasible, certainly in 2nd and 3rd trimester.

7.3 Possible decision tree for treatment of Non-Hodgkin Disease in first trimester of pregnancy

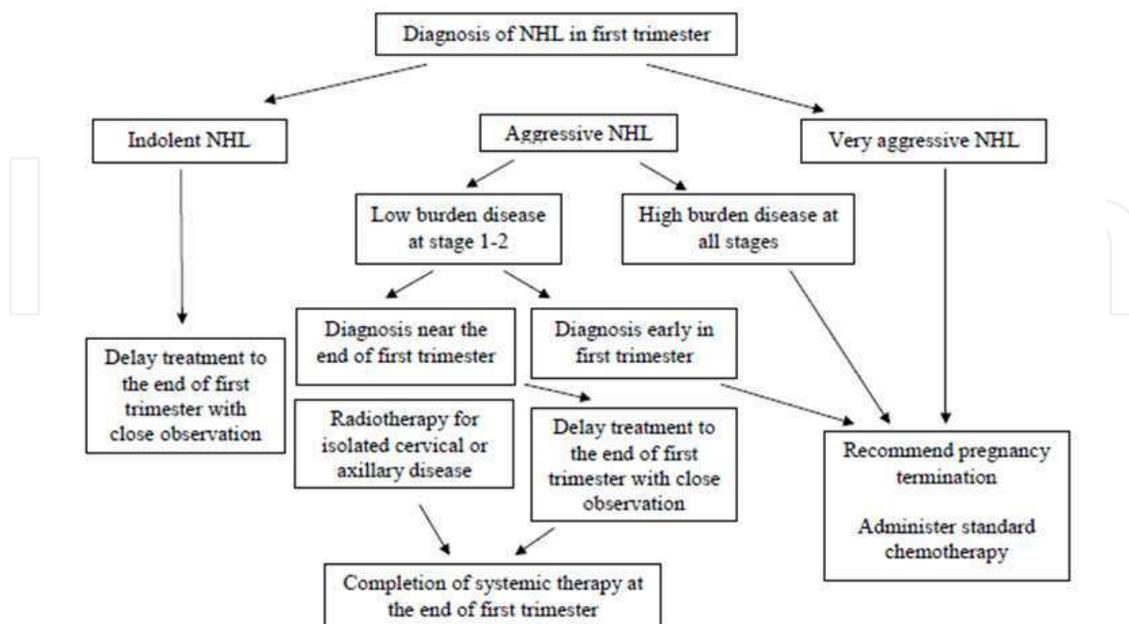


Fig. 2. Shows a possible algorithm for the treatment of first-trimester-associated NHL. Systemic therapy outside the first trimester (R-CHOP) seems to be safe for all forms of NHL (Pereg, 2007).

8. Summary and conclusion

Hematological malignancies are uncommon during pregnancy. Nevertheless, it includes a very complex medical, but also ethical and psychological problem. Delay in diagnosis and treatment will influence the prognosis for acute leukemia and aggressive/advanced lymphomas. Delay in treatment and even diagnostic delay may influence the prognosis for chronic leukemia and indolent non-Hodgkin lymphomas. In selected cases with limited disease of early stage Hodgkin's disease, treatment may be safely postponed until after delivery. The decision to use chemotherapy during pregnancy must be carefully weighed against the effect of treatment delay 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 relatively safe. Radiotherapy during pregnancy is possible, if the fetal exposure does not exceed the threshold dose of 10cGy. Seen the complexity of the decisions in treatment of pregnancy-associated cancer, this should be approached interdisciplinary and should be individually for each patient. Every decision should be made together with the patient, after careful balancing of both the risks and benefits.

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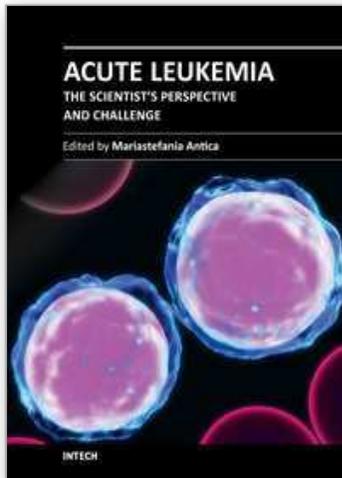
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Acute Leukemia - The Scientist's Perspective and Challenge

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This book provides a comprehensive overview of the basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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