REVIEW

Effects of chemotherapy during pregnancy on the maternal and fetal heart

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ABSTRACT

Objective The co-occurrence of cancer and pregnancy is more frequently diagnosed. The effects of cancer treatment on maternal and fetal outcomes are less well known. The cardiotoxic effects of chemotherapy are a specific concern for the mother and fetus. We wanted to review the existing literature, mainly consisting of case reports, case studies, and retrospective data.

Results Maternal effects Overall, the published data indicate that pregnancy is not an independent risk factor influencing cancer survival. There is no indirect evidence for an increased risk for maternal chemotherapy-related cardiotoxicity.

Fetal effects During the first trimester chemotherapy needs to be avoided because of teratogenic risks. The risks of chemotherapy during the second and third trimester are more controversial. It has been associated with intrauterine growth restriction and preterm delivery in some studies, while others did not find the same effect. Cardiotoxic fetal effects have been reported despite the limited transplacental passage of chemotherapy. In most patients this was transient and long-term data are generally reassuring.

Conclusion A specific strategy for monitoring fetal and maternal chemotherapy-induced cardiotoxicity is suggested. Prospective data are needed on the long-term effects of chemotherapy in both mother and child.

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INTRODUCTION

Especially in more industrialized countries, women tend to postpone pregnancy, increasing the proportion of pregnancies in women between 30 to 49 years of age. At the same time the incidence of cancer in this age group increases. Combining these two trends can explain why the diagnosis of cancer during pregnancy is made more frequently. Limited data are currently available on how chemotherapy during pregnancy influences maternal and fetal outcomes. Specific concerns are the cardiotoxic effects associated with certain chemotherapeutic agents like anthracyclines and trastuzumab on both the mother and the fetus. Pregnancy is a very specific physiologic state associated with significant cardiovascular changes and adaptations resulting in increased cardiac output and workload. These circulatory adaptations could result in increased sensitivity to cardiovascular side effects of cancer treatments. The first aim of our study is to summarize the current knowledge on maternal cardiotoxicity by first reviewing the general knowledge on cardiotoxicity and looking for evidence for a potential effect of pregnancy on maternal cardiovascular side effects of chemotherapy. A second aim is to study the effect on the fetus. First, data on the effect of cancer in pregnancy on overall fetal outcomes will be reviewed. Then, the study will zoom into the effects of cancer on the developing fetal heart. Data on early and long-term fetal outcomes will be summarized.

METHODS

Cohort series, case series, case reports, and reviews were identified using PubMed search for relevant articles from January 1989 to January 2011 using the following keywords: pregnancy, cancer, chemotherapy, anthracylines, trastuzumab, and cardiotoxicity. The search was limited to reports published in English and French. On the basis of this wide search we selected those papers on cardiotoxicity of chemotherapy in general and on chemotherapy during pregnancy more specifically. This was not intended as a systematic review because only very few papers on the specific topic of chemotherapy during pregnancy could be retrieved from the database.

Effect of pregnancy on cancer treatment outcomes

A first important question is whether pregnancy affects maternal outcomes of cancer treatment. A few studies have specifically focused on this question comparing the outcomes of different malignancies in pregnant versus nonpregnant women. A population-based study performed in Norway between 1967 and 2002 could identify 516 pregnant women on a total number of 42 511 women aged between 16 and 49 years diagnosed with cancer.[1] Interestingly the incidence of cancer diagnosed during pregnancy increased from about 20/100 000 pregnancies in the beginning of the study period to around 30 to 35/100 000 pregnancies at the end. The most common cancers diagnosed during pregnancy were breast cancer, malignant melanoma, and cervical cancer. The study results suggested that pregnancy did not affect maternal cancer survival with no increase in risk for cause-specific death. The problem with the population-based approach is that it is difficult to control for other risk factors. Because pregnant women are medically examined, certain cancers like breast and cervical cancer might be detected at earlier stages and thus a similar outcome compared with nonpregnant women could possibly indicate a negative effect of pregnancy on outcomes. Two larger multicenter studies suggested that maternal outcomes for different types of cancer were similar in pregnant women compared with nonpregnant women even when age and stage matched.[2–4] A recent systematic review analysis specifically looking at breast cancer prognosis suggested that the current evidence indicates that outcomes in pregnant women are comparable to age-matched nonpregnant women.[5] For other types of cancer, the data are more limited and warrant further careful assessment. Prospective studies are needed to answer the question particularly for the rarer forms of cancer. Apart from the effect on mortality, the multicenter studies suggested that the overall morbidity and side effects of cancer treatment were not significantly influenced by pregnancy apart from a higher frequency of nausea and vomiting when chemotherapy was given during pregnancy.[2–4] This could be related to hormonal changes associated with pregnancy but also to the different pharmacokinetics and pharmacodynamics of the chemotherapeutic agents used during pregnancy.

Effects of cancer during pregnancy on overall fetal outcomes

Maternal illness during pregnancy can affect fetal well-being and outcomes. Apart from the direct maternal effect, there also is a potential influence of cancer treatment on fetal growth and development. Cardonick and Lacobucci published an elegant summary of all published case reports and case studies published prior to 2004.[6] They found reports on 321 fetuses exposed to chemotherapy. The published cases confirm that chemotherapy is to be avoided during the first trimester because of the teratogenic effect: in total, 9 of the 11 malformations occurred when chemotherapy was given in the first trimester. The two larger multicenter studies in North America[3] and Europe[4] suggested that the teratogenic effect seems negligible when chemotherapy is given after the first trimester. Table 1 summarizes the general fetal effect as reported by the systematic case review and the two larger multicenter studies. In total this contains data on 767 fetuses with 540 patients exposed to chemotherapy. The overall fetal demise associated with the treatment is low and similar between the different reports. Termination of pregnancy was higher in the European study suggesting a different approach. The most striking difference between the two studies was the high incidence of preterm delivery in the European study. The authors noted this was mainly due to iatrogenic preterm delivery. When cancer was detected in the third trimester, there was a tendency for early induction of delivery prior to starting chemotherapy in the European study. This high incidence of iatrogenic preterm deliveries leads to a high admission rate of neonates to the neonatal intensive care unit. There was also a significant difference in intrauterine growth restriction between the two registries with a higher incidence in the European registry (14.9%) compared with the North American (7.7%). The differences between the two groups require further study and more prospective data are required to determine the safety of maternal chemotherapy on fetal growth and development during the second and third trimester. The North American data seem to suggest that chemotherapy during the second and third trimester is relatively safe but more long-term prospective data are required.

Table 1 Fetal impact of chemotherapy during pregnancy

	Systematic case review[6]	North American Registry[3]	European Multicenter Study[4]
Total number included	321	231	215
Total number exposed to chemotherapy	321	157	62
Fetal demise	5.10%	6.4%	2.3%
Termination of pregnancy	N/A	5.6%	14%
Preterm delivery	5.10%	5.8%	54.2%
Intrauterine growth restriction	7.10%	7.7%	14.9%
Malformations	3.40%	3.8%	6.5%

For fetal medicine, the current data suggest that careful follow-up of fetal growth is required to detect intrauterine growth restriction and specific complications like hematological abnormalities (anemia) and cardiotoxicity. We suggest a baseline assessment prior to treatment, at the end of treatment and prior to delivery.

Chemotherapy and cardiotoxicity

Different chemotherapeutic agents are known to induce cardiovascular complications including heart failure, myocardial ischemia/infarction, thrombo-embolic complications and arrhythmia.[7–12] Table 2 summarizes the cardiovascular complications related to the different cardiotoxic agents. For maternal and fetal medicine especially anthracyclines and trastuzumab are important agents used during pregnancy. Anthracyclines are used in a wide variety of malignancies and are well-known for their cardiotoxic effects.[7–12] Multiple mechanisms are involved in anthracycline cardiotoxicity including oxidative damage,[10,13,14] changes in calcium metabolism and activation of apoptotic pathways.[8,13,15] In the acute phase these

mechanisms are responsible for causing acute (mostly reversible) cardiac dysfunction sometimes resulting in heart failure during treatment in about 1% of all patients. Apart from acute effects on the heart, anthracyclines can cause late progressive and irreversible cardiac dysfunction. Cell death leads to a decreased number of myocardial cells affecting increasing the loading on the surviving muscle cells that are affected by the toxic exposure. In the surviving cells changes in mitochondrial function[16,17] and in sarcomeric protein gene expression have been observed.[13] Also, the normal cardiac repair mechanisms are affected and anthracycline exposure causes a depletion of cardiac stem cells.[18] These effects influence the function of the surviving cells and can cause a progressive deterioration in cardiac function. The incidence of heart failure in the general population is estimated at around 0.02/1000 between 25 and 45 years increasing up 11.6/1000 in the elderly population > 85 years.[19] Compared with this, a retrospective analysis of three different trials including patients treated with anthracyclines suggested that the incidence of heart failure in the anthracycline-treated group was around 26% with cumulative doses of 550 mg/m^2.[20] Mulrooney *et al.*[21] recently reported a 30-year cumulative incidence of congestive heart failure of around 4.1% in a large cohort of adult survivors of childhood and adolescent cancer and found that the relative hazard for developing congestive heart failure was 5.2-fold higher when the cumulative dose exceeded 250 mg/m^2. Anthracycline toxicity has been shown to be enhanced by the concomitant use of trastuzumab. This is a monoclonal antibody to ErbB2 that inhibits proliferation of cells that overexpress HER2 (human epidermal growth factor receptor tyrosine kinase). Around 25% of breast cancers express HER2 and recent clinical trials have proven a survival benefit of trastuzumab treatment in breast cancer patients with HER2+ disease.[22] However, an increased risk for heart failure and asymptomatic decline in systolic function was described in up to 4.0% of treated patients,[23] increasing to up to 25% when trastuzumab was administered concurrently with or shortly after anthracycline treatment.[24,25] There is an important synergistic effect of combining both treatments.

It is currently unknown how pregnancy affects the efficacy and the toxicity of the different chemotherapeutic agents. Registry data seem to suggest that the incidence of toxic side effects are not significantly increased during pregnancy and in the current literature there is no mention of an increased frequency of heart failure or left ventricular dysfunction during pregnancy.[2,4,6] The data are however very limited and different monitoring strategies have been used in different centers. No standard cardiac follow-up protocols are currently in place.[26] Toxicity of chemotherapeutic agents will be influenced by changes in pharmacokinetics and pharmacodynamics that occur during pregnancy. Our own data suggest that serum levels of chemotherapy, including anthracyclines, measured in pregnant women, were lower compared with those in nonpregnant women although the differences were not statistically significant.[27] These lower levels do not seem to affect oncologic outcomes, while they might have a beneficial effect on potential side effects. On the other hand, despite the lower serum levels, cardiotoxicity might have a more significant impact on the maternal cardiovascular system in a context of increased hemodynamic loading. The use of cardiotoxic medication during pregnancy requires further attention. Because no good data are currently available, it would seem reasonable to consider pregnant women at increased risk of developing heart failure. We suggest a clinical cardiac assessment and echocardiographic functional evaluation prior to starting chemotherapy and repeat the echocardiographic evaluation prior to every dose.[26] If changes in cardiac function are observed, less cardiotoxic treatments might be considered or cardioprotective agents could be used. Treatment of heart failure during pregnancy is challenging and requires close collaboration between different cardiology and obstetrics.

Table 2 **Cardiovascular effects of chemotherapeutic agents**

Chemotherapeutic agent	Cardiovascular effect
Anthracyclines	Left ventricular dysfunction, dilated and restrictive cardiomyopathy, arrhythmia
Antimetabolites	
Capecitabine, Cytarabine and 5-fluorouracil	Ischemia (3–68%), pericarditis, thrombophlebitis
Cyclophosphamide	Heart failure (8–27%), pericarditis, myo-pericarditis
Anti microtubule agents	
Docetaxel	Heart failure (2.3–8%), ischemia (1–5%)
Paclitaxel	Bradycardia (1–31%)
Monoclonal antibodies	
Trastuzumab	Heart failure (2–28%)
Bevacizumab	Heart failure (1.7–3%), ischemia (0.6–1.5%), hypertension (4–35%)
Small molecule tyrosine kinase inhibitors	Heart failure (0.5–11%), ischemia (2–3%), hypertension (5–47%),
	QT prolongation (1–10%)

Fetal cardiac effects of maternal chemotherapy

Data on how maternal chemotherapy affects the fetal heart are limited. Surprisingly only limited experimental and clinical data on the transplacental passage of chemotherapeutic agents are currently available. Transplacental passage of anthracyclines has been studied both *in vitro* and in animal models. *In vitro* perfusion of the human placenta indicated that transplacental passage of doxorubicine is low and in the order of 2.96 ± 0.75% of plasma levels.[28] Transfer of epirubicine is comparable and estimated at 3.66 ± 1.07%.[29] Van Calsteren *et al.*[30] observed that plasma levels of doxorubicine in fetal mice reached 5.0 ± 0.2% of maternal plasma levels. In a baboon model, fetal plasma concentrations of doxorubicin and epirubicin were 7.5 ± 3.2% and 4.0 ± 1.6% of maternal concentrations. These data suggest a low transplacental transfer of anthracyclines. No *in vivo* human data are however currently available. A recent study looked at transplacental cisplatin transfer. Depending on the time between the chemotherapy and delivery, amniotic fluid concentration ranged between 13% to 42% of the maternal serum concentrations. Umbilical artery sample concentrations were up to 65%.[31]

Because of the lack of human data on transplacental passage, data on the direct effect on the fetus are currently the only alternative for assessing the fetal side effects. During the first trimester the potential effects of chemotherapy on early fetal development need to be considered as a strong contraindication to chemotherapy, but the maternal risks for postponing therapy in more advanced stages of cancer need to be taken into consideration. The risks and benefits of cancer treatment and continuation of pregnancy need to be discussed with the mother. Of the many possible fetal malformations associated with chemotherapeutic agents, craniofacial and limb abnormalities are the most common.[6,32,33] So far there have been no reports on an increased risk for congenital heart disease. Chemotherapy can be used during the second and third trimester without an increased risk for congenital malformations.[3,4]

Despite a low transplacental passage of chemotherapeutic agents, the pharmacodynamic effects of exposure of the fetal myocardium to low-dose cardiotoxic drugs could be different compared with a more mature myocardium. Fetal myocardium differs from adult myocardium because fetal myocytes are smaller; typically have a single nucleus compared with the multinuclear cells prevalent after birth. The myocytes also contain fewer sarcomeres per mass unit and different isoforms of contractile proteins are expressed.[34,35] Also, the sarcoplasmic reticulum is immature affecting excitation–contraction coupling and calcium metabolism. The myocytes contain lower numbers of mitochondria and the antioxidant pathways are still underdeveloped. All these factors might make the fetal myocardium more vulnerable to damage by chemotherapeutic agents. There might also be an effect on the fetal stem cell population that might influence cardiac repair mechanisms but no data are currently available.

Data on fetal cardiotoxicty are only based on case reports and retrospective case studies. The data are summarized in Table 3. These case reports seem to suggest that, despite low transplacental passage, chemotherapy can cause acute fetal cardiac dysfunction, which seems reversible in some cases. On the basis of these data, it seems reasonable to propose a fetal surveillance strategy and monitor cardiac function during and after fetal anthracycline exposure.

Not only the acute cardiotoxicity is of concern, but also the chronic long-term effect of fetal exposure on cardiac function is important. Data from pediatric cancer survivors have shown that anthracycline exposure at a young age can result in progressive left ventricular dysfunction and clinical heart failure even more than 10 to 20 years after stopping chemotherapy.[21] Very few data are available on the long-term outcome of fetal exposure. Aviles reported results of follow-up echocardiographic data in 81 children aged between 9 and 29 years of age (mean 17.1 years) who received anthracycline treatment *in utero*.[36] Fractional shortening was reported to be normal in this patient group but the authors did not look at cardiac dimensions, wall thickness or diastolic functions, which are earlier markers of changes in cardiac function. Preliminary data from our group suggested that children exposed to chemotherapy *in utero* have mildly reduced ventricular wall thickness and reduced left ventricular mass index but this was based on a very small group of children and requires further study.[37]

There is only limited experience regarding the use of trastuzumab during pregnancy with only cases described in the literature.[38–42] No fetal cardiotoxicity was observed but the drug may have an important effect of fetal renal function. Trastuzumab could potentially block epidermal growth factor receptors in the fetal kidneys and alter their function and development. To date 15 pregnant patients were submitted to trastuzumab and nine fetuses developed oligoamnios or anhydramnios. One neonate born at 28 weeks died after multiorgan failure. Two other children prematurely born died after pulmonary and renal failure. In 11 cases trastuzumab was used during the first trimester of pregnancy. Long exposure (more than one trimester) to trastuzumab is associated to the highest risk of complications. On the basis of these observations, trastuzumab is currently contraindicated during pregnancy.[43–45]

Table 3 **Fetal cardiotoxicity after anthracyclines administration**

Study	Fetal cardiotoxicity
Germann *et al.*[47]	Two cases of cardiac dysfunction with one fetal death in the third trimester and one reversible heart dysfunction
Achtari and Hohlfeld[48]	One reversible biventricular dysfunction normalized 3 days after birth
Reynoso and Huerta[49]	One fetal death 3 days after idarubicin administration
Baumgartner *et al.*[50]	One reversible cardiac dysfunction at 24 weeks
Meyer-Wittkopf *et al.*[51]	One normal fetal follow-up after doxorubicin attested by ultrasound

CONCLUSION

Current data on the maternal and fetal cardiotoxic effects of chemotherapy during pregnancy are limited and based mainly on case reports and retrospective data collection. The data seem to suggest that overall treatment during the second and third trimester is relatively safe with some concerns for the development of fetal growth restriction and more direct effects on the developing fetal heart. Pregnancy as such does not seem to be a risk factor for the development of maternal cardiotoxicity but very limited data are currently available.

On the basis of the current data, we suggest a prospective monitoring of maternal and fetal cardiac function if chemotherapy is given during pregnancy. For the mother we suggest a cardiac evaluation including echocardiography, prior to chemotherapy and at least one repeat study after three doses of anthracyclines and/or prior to delivery. Ejection fraction can be used as the parameter for global cardiac function. More data are needed on the relationship between maternal cardiac effects and fetal growth. On the basis of current reports, *in utero* growth restriction, pancytopenia, and cardiotoxicity can occur after maternal chemotherapy. To monitor these effects, serial assessment of fetal growth, fetal Doppler measurements (umbilical artery, middle cerebral artery, and ductus venosus), and cardiac

function is recommended. For the assessment of cardiac function the cardiovascular scoring system can be used.[46] Depending on the cancer treatment, the frequency of fetal ultrasound may vary and no data are available to base any recommendations on. We suggest performing a fetal ultrasound within one to two weeks after every dose of cardiotoxic medication. After delivery, the newborn should be evaluated for hematologic and cardiac effects of prenatal exposure to chemotherapy. Hopefully, prospectively collected data will help to refine the treatment and monitoring strategies.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- This review emphasizes the limited data currently available on maternal and fetal risk of cardiotoxicity after chemotherapy administration.

WHAT DOES THIS STUDY ADD?

- This review summarizes the potential effects of anthracyclines and trastuzumab on the mother and the fetus. We propose a clinical follow-up protocol for pregnant women before and after chemotherapy exposure.

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