

## CHEMOTHERAPY FOR BREAST CANCER DURING PREGNANCY AND *POSTPARTUM*: A RETROSPECTIVE DESCRIPTIVE STUDY

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### Abstract

As childbearing age increases, the incidence of cancer during pregnancy is rising. Herein we present a retrospective study of chemotherapy for breast cancer during pregnancy and *postpartum*. Among the four cases presented in our paper, two women received chemotherapy with doxorubicin/cyclophosphamide during pregnancy; one achieved a partial response and the other a complete response. Two women received chemotherapy with doxorubicin/cyclophosphamide and paclitaxel during the *postpartum* period. One of these patients died; she started treatment 3 months after diagnosis with an aggressive invasive ductal carcinoma. Three of the four patients achieved a favourable outcome, and are alive and free of disease 1 and 2 years after treatment. The 5 infants born showed normal development and cardiac assessment at 6 months and 1 year of age. We conclude that doxorubicin/cyclophosphamide chemotherapy can be safely administered during the second and third trimester of pregnancy and during *postpartum* period. While additional follow-up studies are needed to assess possible long-term toxicities, this pilot study can be seen as a first step toward changing medical opinion regarding the option of chemotherapy during pregnancy.

### Rezumat

Amânarea maternității la vârste avansate a dus la creșterea cazurilor de cancer depistate în timpul sarcinii. Prezentăm un studiu retrospectiv descriptiv despre administrarea chimioterapiei în sarcină și lăuzie. Articolul nostru descrie patru cazuri, din care 2 gravide cu protocolul doxorubicina/ciclofosfamidă în timpul sarcinii și utilizarea paclitaxelului în lăuzie. S-a înregistrat un singur deces la o pacientă cu o formă agresivă de carcinom ductal invaziv, la care tratamentul a debutat la 3 luni de la stabilirea diagnosticului. Trei dintre paciente au avut un răspuns favorabil și sunt în viață, fără semne de boală la 1 an și respectiv 2 ani de la terminarea tratamentului. Cei cinci copii născuți au avut o dezvoltare normală și o evaluare cardiacă la 6 luni și un an în limite normale. În concluzie, doxorubicina și ciclofosfamida pot fi administrate în siguranță în trimestrele 2 și 3 de sarcină și în *postpartum* și necesită o urmărire mai îndelungată. Studiul nostru pilot își propune să sensibilizeze opinia medicală care să ia în considerație, siguranța chimioterapiei administrată în timpul sarcinii pentru tratamentul cancerului de sân.

**Keywords:** chemotherapy, pregnancy, *postpartum*, breast cancer

### Introduction

The use of medication during pregnancy is controversial and debatable due to the potential for immediate or delayed adverse effects on the foetus. There is a lack of data from prospective randomized trials in pregnant patients. Drugs may cross the placenta, and, with the exception of vitamins, folic acid, and iron supplements, any other medication is questionable. Because of the lack of pregnant oncology patients in experimental trials, there is little data about oncological treatment of these patients, and, consequently, evidence-based guidance regarding benefit/risk drug therapy decisions does not address treatment during pregnancy, necessitating that an empirical approach

is used in these cases [7]. Studies conducted on animals report various adverse effects from medications used during pregnancy [16]. Pregnancy at an advanced maternal age increases the risk of diagnosis of a pregnancy-associated pathology such as cancer, which is ranked as a possible cause of mortality among women of reproductive age, after haemorrhage and eclampsia. Upon diagnosis, healthcare professionals, the patient, and the family face a difficult choice between delaying the treatment until after the birth or interrupting the pregnancy before starting the treatment or treating the pathology while weighing maternal benefit *versus* fetal risk. Although tumours found during pregnancy have previously been thought to be more biologically aggressive, recent data contradicted

this theory, demonstrating a similar response to therapy and prognosis among pregnant and non-pregnant patients with the same stage of cancer [21]. The first administration of chemotherapy (CMT) during pregnancy was accidental; in 1948 urethane was used to treat a patient who was not known to be pregnant at the time [6]. Since then, observational retrospective studies have been published based on data from the Cancer Registries from various countries [4, 12], and an international meeting of experts on gynaecological cancer during pregnancy was held in Europe in 2009 to seek consensus on the issues [1].

Upon diagnosis of cancer during pregnancy, a multidisciplinary team of healthcare professionals is essential for the selection of the treatment approach. The team should include an obstetrician, a medical oncologist, an oncology surgeon, a haematologist, a paediatrician, a psycho oncologist and a radiotherapist, in order to best advise the patient about the treatment regimens available, the potential risks for both, mother and the foetus, the prognosis, and the necessity of long-term follow-up.

This study presents the use of CMT in a series of pregnant and *postpartum* patients receiving multimodal treatment for breast cancer at "Filantropia" Clinical Hospital in Bucharest.

The incidence of pregnancy-associated breast cancer is 1 in 3,000 pregnancies [10], or 15 to 35 cases in 100,000 deliveries [19, 25]. Food and Drug Administration classifies drugs in the following categories according to their safety during pregnancy: A, B, C, D, X. Classification is based on possible fetal pathologies that could be related to the medication, rather than the needs of the obstetrical practitioner. CMT drugs are included in the D and X categories. The consequent fear of drug-related fetal harm may explain the prevalence of elective termination of pregnancy upon cancer diagnosis. However, the hesitation to use medication during pregnancy may be lessening, as the use of four or more medications during the first trimester has increased threefold in recent years [15], including drugs in category D [24], such as aspirin, which is used for preventing preeclampsia. Longer delays in childbearing result in an increase in cancer-associated pregnancies. Affected families will have to make choices regarding the option of treatment during pregnancy. The international expert group that was assembled to evaluate issues related to gynaecologic and breast cancers that are found during pregnancy determined that CMT can be regarded as safe during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester, but that treatment contraindicates breastfeeding [1, 2]. There is limited information on the pharmacokinetics of various drugs in pregnant women. However, certain pregnancy-associated physiological changes, such as the increase in

plasma volume of up to 50%, the increase in renal clearance, the increase in hepatic oxidation [5], and the development of third-space fluid (the amniotic fluid) [9], are likely to decrease the plasma level of any drugs given. Pregnancy-associated decreased gastric motility can also impact the absorption of oral medications. On the other hand, decreased albumin serum levels may result in a large portion of potentially active medicine remaining unbound. The presence of P-glycoprotein, a multidrug resistance protein [13] that is found in both fetal tissue and decidua, appears to protect the foetus against possible effects of the CMT drugs that are given to the mother [20, 23]. Although data are insufficient to form a decisive conclusion, it is considered that any medication with a molecular weight of less than 600 kDa can cross the placental barrier. As most chemotherapeutic agents have molecular weights between 250 kDa and 400 kDa, all these molecules could potentially harm the foetus [17]. Evidence from preclinical studies conducted on test animals revealed that most chemotherapeutic agents have teratogenic effects [18, 25]. For example, anthracyclins were found to be mutagenic and carcinogenic when tested on virgin female Sprague-Dawley rats and can also cause oesophageal atresia, tracheoesophageal fistula, and axial alteration [14]. Placental transfer of anthracyclins was reported *in vitro* and *in vivo* in various animal models. In mice, the trans-placental passage of doxorubicin was observed to be  $5 \pm 0.2\%$ . In baboons, the fetal plasma concentrations of doxorubicin reach  $7.5 \pm 3.2\%$  and epirubicin reaches  $4 \pm 1.6\%$  compared with the maternal concentrations [22]. It should be noted that the doses used in clinical practice are lower than the test doses; therefore, extrapolation of these experimental findings to human therapeutic treatment may not be valid. Teratogenic effects depend on both the total given dose and on the gestational age. Exposure during the first trimester of pregnancy is associated with an increased risk of miscarriage, intrauterine growth restriction, low birth weight, prematurity, major birth defects, and fetal death [11, 26, 27], as the medication interferes with the development of various organs and systems. The foetus is most vulnerable to these effects between the 2<sup>nd</sup> and the 8<sup>th</sup> week of pregnancy, at the initiation of organogenesis. However, some organs and systems (e.g., eyes, central nervous system [CNS], genitalia, and hematopoietic system) can be harmed even after this period has passed [21].

Doll et al. showed that the risk of major defects associated with CMT is actually lower than predicted. Exposure to a single chemotherapeutic agent is reported to be associated with a 17% increase in the risk of birth defects, which can reach

up to 25% in cases exposed to a combination of cytostatic drugs [8]. Aviles et al. conducted a long-term study (22.4 years on average, between 3.8 and 32 years) of malignant haematological diseases of 54 individuals exposed to CMT during the first trimester of pregnancy, and reported that no birth defects were associated [3].

### Materials and Methods

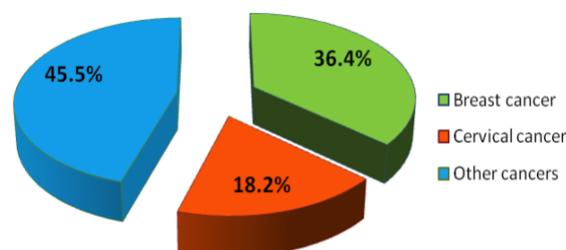
A retrospective descriptive study of pregnant women who were diagnosed with cancer during pregnancy and who chose to continue their pregnancy while receiving CMT was conducted between 30 June 2012 and 30 June 2014, with approval from the Hospital Ethics Committee and after the informed written consent of all of the patients. Data were collected from the hospital electronic registry and patients files. Complete data were obtained regarding monitoring of the pregnancies, multimodal cancer treatment and CMT administration, delivery of the babies, and assessment of the neonates at birth, in their first month, and subsequently every six months. The "Filantropia" Clinical Hospital in Bucharest has departments specialised in gynaecological oncology, obstetrics and maternal and fetal medicine, as well as a Level III neonatology service equipped to provide neonatal resuscitation, and a counselling psychologist.

Pregnancy-associated cancer was defined to include any cancer diagnosed during pregnancy or the first year *postpartum*. Decision-making regarding the cancer therapy in these cases was guided by treatment regimens developed for non-pregnant patients, but modified to take into account the stage of pregnancy and to omit radiotherapy during pregnancy. For breast malignant tumours greater than 2 cm in size (prior to surgical treatment), neoadjuvant CMT was given from the second trimester, which included the Adriamycin (doxorubicin)/cyclophosphamide (AC) regimen every 3 weeks, with 4 cycles during pregnancy, followed by paclitaxel. Doxorubicin was administered at a dose of 60 mg/m<sup>2</sup> and cyclophosphamide at 600 mg/m<sup>2</sup>. *Postpartum*, the patients were given taxanes. Patients treated in 2012 and 2013 were given 4 cycles of paclitaxel at a dose of 175 mg/m<sup>2</sup> every 3 weeks, and patients since 2014 received paclitaxel once weekly at 80 mg/m<sup>2</sup>.

### Results and Discussion

During the study period, 6,352 pregnant women with a total of 6,402 children were analysed, and 11 patients were diagnosed with pregnancy-associated cancers: 4 breast cancers (36.4%), 2 cervical cancers, 1 Hodgkin's lymphoma, 1 sarcoma of the

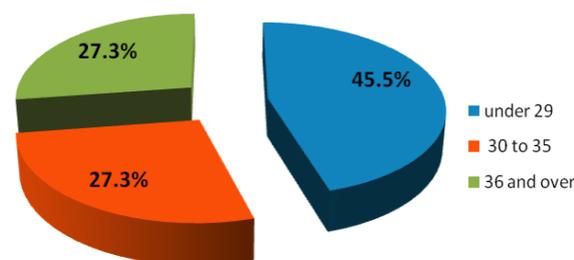
iliac bone, 1 head and neck cancer, 1 melanoma, and 1 thyroid cancer (Figure 1).



**Figure 1.**

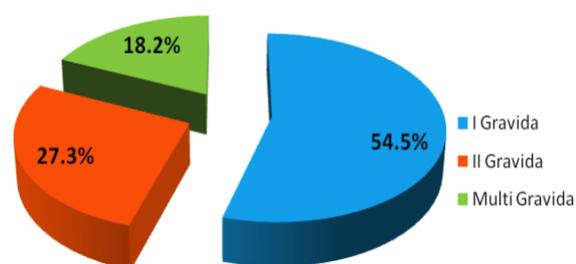
Incidence of cancer in pregnancy

The pregnancy-associated cancer incidence was 1.718% overall. The majority of patients was under 29 (Figure 2) and the average age of female patients with pregnancy-associated neoplasms was 30.82 years (20-38 years), with 54.50 % of the patients being *primigravida* (Figure 3).



**Figure 2.**

Age (years) of patients with pregnancy-associated cancer



**Figure 3.**

Gravidity of patients with pregnancy-associated cancer

The cancer diagnosis was established in the first trimester in 3 cases, in the second trimester in 5 cases, and in the third trimester in 3 cases.

A total of four cases were included in this study of CMT for breast cancer (invasive ductal carcinoma) associated with pregnancy. Two patients were given breast cancer CMT from the 2<sup>nd</sup> and 3<sup>rd</sup> trimester and into the *postpartum* period and two patients started CMT *postpartum*. Table I shows the characteristics of breast cancer patients who received CMT.

**Table I**

Characteristics of the diagnosed pregnant patients

No.	No of pregnancy	Age of the patient	Tumour site	Gestational time of tumour detection	Stage of breast carcinoma	Time at initiation of CMT
1	II	32 years	LIQ	20 weeks	T3N1M0	23 weeks
2	I	37 years	LOQ	23 weeks	T2N1M0	26 weeks and 3 days
3	VIII	36 years	LOQ	16 weeks	T4N1M0	<i>Postpartum</i>
4	I	38 years	CQ	37 weeks	T2N1M0	<i>Postpartum</i>

LIQ=lower inner quadrant; LOQ=lower outer quadrant; CQ=central quadrant

Oestrogen receptor (ER) and progesterone receptor (PR) were negative in 50% cases (case 3 and 4). HER2 (human epidermal receptor 2) was negative in 66% of cases. Based on the anatomic pathology findings and the cancer spread assessment, the following treatment regimens were selected and applied: CMT followed by surgical treatment (radical mastectomy and unilateral lymphadenectomy) and radiotherapy. The CMT regimen combined 4 cycles of AC and 4-12 cycles of taxanes *postpartum*, depending on the tumour response. The ventricular ejection fraction was assessed by echocardiography in all patients, and the two patients who were treated with CMT during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester were given serial ultrasounds to assess fetal morphology, biometry, and velocimetry. Mastectomy was not performed during pregnancy in any of the cases.

One breast cancer patient died (case 3). She started treatment 3 months after diagnosis with an aggressive invasive ductal carcinoma, Cerb2-positive, with no Trastuzumab exposure in the neoadjuvant setting. Three patients achieved a favourable response to CMT, and they were alive and free of disease 2 years and 1 year after completion of treatment, respectively. Breastfeeding was contraindicated in cases in which CMT had been given during pregnancy. The neonates whose mothers had received CMT during pregnancy showed outcomes similar to infants of the same age at birth and at 1 month, 6 months, and 1 year of age. No abnormalities were seen in the ventricular ejection fraction in infants of women who received CMT during pregnancy, as measured by serial echocardiography performed at 6 months and at 1 year of age, respectively. This small study group showed no fetal defects, intrauterine growth restriction, or intrauterine death. Deliveries occurred at full term, following obstetrical indications. In all cases, a cycle of corticotherapy was given at 28 weeks of pregnancy to promote fetal pulmonary maturation, and the last cycle of CMT treatment was given at 34 weeks. The CMT-related adverse events observed during pregnancy were similar to those in non-pregnant patients. No major complications were noted.

Herein we have described a small group of patients with cancers found during pregnancy, who decided

to continue the pregnancy while receiving CMT. Our pilot study examined cases of pregnancy-associated breast cancer that were treated with anthracycline and cyclophosphamide during pregnancy. In all cases, therapy was initiated during the second trimester. Patients who were diagnosed early and started treatment promptly are still alive and are free of disease. No birth defects, fetal intrauterine death or intrauterine growth restriction were observed. Deliveries occurred at full term, with no need to consider delivery before 37 weeks. However, one limitation of the study is due to the small number of cases and therefore insufficient for general conclusions to be drawn, and the infants will need to be monitored for longer periods of time to detect any possible long-term adverse effects.

### Conclusions

In conclusion, we find that some chemotherapeutic agents can be safely administered for the treatment of maternal cancer during pregnancy, starting in the second trimester of pregnancy, after carefully balancing the potential risks and benefits. The current regimens recommended for breast cancer treatment use anthracycline and cyclophosphamide. AC and taxanes can be administered *postpartum*. Our pilot study reports the outcomes of four cases in which breast cancer was found and treated during pregnancy, and these results can be seen as a start toward a change in medical opinion regarding the option of CMT during pregnancy. In our experience, it is unnecessary to risk iatrogenic prematurity caused by a rush to deliver the baby in order to start therapy with the patient in non-pregnant status, because it appears safe to administer cancer therapy during pregnancy. Infants of CMT-treated mothers will require extended follow-up to assess possible long-term effects of their exposure.

### References

1. Amant F., Van Calsteren K., Halaska M.J., Beijnen J., Lagae L., Hanssens M., Heyns L., Lannoo L., Ottevanger N.P., Vanden Bogaert W., Ungar L., Vergote I., du Bois A., Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. *Int. J. Gynecol. Cancer*, 2009; 19(1): S1-12.

2. Amant F., Deckers S., Van Calsteren K., Loibl S., Halaska M., Breppeels L., Beijnen J., Cardoso F., Gentilini O., Lagae L., Mir O., Neven P., Ottevanger N., Pans S., Peccatori F., Rouzier R., Senn H.J., Struikmans H., Christiaens M.R., Cameron D., Du Bois A., Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur. J. Cancer*, 2010; 46(18): 3158-3168.
3. Aviles A., Neri N., Nambo M.J., Haematological malignancies and pregnancy: Treat or no treat in the first trimester. *Int. J. Cancer*, 2012; 131(11): 2678-2683.
4. Cardonick E., Gilmandyar D., Somer R.A., Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. *Obstet. Gynecol.*, 2012; 120(6): 1267-1272.
5. Cardonick E., Iacobucci A., Use of chemotherapy during human pregnancy. *Lancet Oncol.*, 2004; 5(5): 283-291.
6. Creskoff A., Fitz-Hugh Tj., Urethane therapy in leukemia. *Blood*, 1948; 3: 896-910.
7. Doering P.L., Boothby L.A., Cheek M., Review of pregnancy labeling of prescription drugs: Is the current system adequate to inform of risks? *Am. J. Obstet. Gynecol.*, 2002; 187(2): 333-339.
8. Doll D.C., Ringenberg Q.S., Yarbrow J.W., Management of cancer during pregnancy. *Arch Intern. Med.*, 1988; 148(9): 2058-2064.
9. Doll D.C., Ringenberg Q.S., Yarbrow J.W., Antineoplastic agents and pregnancy. *Semin. Oncol.*, 1989; 16(5): 337-346.
10. du Bois A., Meerpohl H.G., Gerner K., Prömpeler H., Vach W., Aisslinger U., Breckwoldt M., Pfeleiderer A., Effect of pregnancy on the incidence and course of malignant diseases. *Geburtshilfe Frauenheilkd.*, 1993; 53(9): 619-624.
11. Leslie K.K., Koil C., Rayburn W.F., Chemotherapeutic drugs in pregnancy. *Obstet. Gynecol. Clin. North Am.*, 2005; 32: 627-640.
12. Loibl S., Han S.N., von Minckwitz G., Bontenbal M., Ring A., Giermek J., Fehm T., Van Calsteren K., Linn S.C., Schlehe B., Gziri M.M., Westenend P.J., Müller V., Heyns L., Rack B., Van Calster B., Harbeck N., Lenhard M., Halaska M.J., Kaufmann M., Nekljudova V., Amant F., Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol.*, 2012; 13(9): 887-896.
13. Nicolae A.C., Mitrea N., Arsene A.L., Constantinescu M.Z., Vuță V., Drăgoi C.M., *In vitro* P-glycoprotein inhibition assay on n2a murine cell line. *Farmacia*, 2013; 61(3): 481-491.
14. Menegola E., Broccia M.L., Di R.F., Histological study of timing and embryology of notochordal abnormalities in rat exposed *in utero* to Doxorubicin. *Histol. Histopathol.*, 2002; 17: 31-38.
15. Mitchell A.A., Gilboa S.M., Werler M.M., Kelley K.E., Louik C., Hernández-Díaz S., National Birth Defects Prevention Study. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am. J. Obstet. Gynecol.*, 2011; 205(1): 51.e1-e8.
16. Osz B.E., Vari C.E., Kolcsar M., Cotoi O.S., Marusteri M.S., Dogaru M.T., Are SSRI's equally safe in pregnancy? Fluoxetine and Citalopram experimental study. *Farmacia*, 2014; 5: 889-896.
17. Pacifici G.M., Nottoli R., Placental transfer of drugs administered to the mother. *Clin. Pharmacokinet.*, 1995; 28: 235-236.
18. Pop A., Lupu D., Drugan T.C., Loghin F., Slavcovici A., Kiss B., Endocrine disruptive effect of selected phytoestrogens from soy and green tea in case of individual and combined *in vitro* exposure. *Farmacia*, 2014; 62(6): 1126-1142.
19. Smith L.H., Danielsen B., Allen M.E., Cress R., Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am. J. Obstet. Gynecol.*, 2003; 189(4): 1128-1135.
20. Stevenson J., Giantonio B., Boyd R.L., Bruner J.A., Adjuvant chemotherapy for breast cancer in pregnancy: can recommendations be made with confidence. *Semin. Oncol.*, 1997; 24(2): xxv – xxxvi; discussion xxxvi, xxxix.
21. Surbone A., Peccatori F., Pavlidis N., Cancer and pregnancy. Berlin Heidelberg, Springer-Verlag, 2008: 21-38.
22. Van Calsteren K., Verbesselt R., Beijnen J., Devlieger R., De Catte L., Chai D.C., Van Bree R., Heyns L., de Hoon J., Amant F., Transplacental transfer of anthracyclines, vinblastine, and 4-hydroxy-cyclophosphamide in a baboon model. *Gynecol. Oncol.*, 2010; 119(3): 594-600.
23. van Kalken C.K., Giaccone G., van der Valk P., Kuiper C.M., Hadisaputro M.M., Bosma S.A., Scheper R.J., Meijer C.J., Pinedo H.M., Multidrug resistance gene (P-glycoprotein) expression in the human fetus. *Am. J. Pathol.*, 1992; 141(5): 1063-1072.
24. Weiner C.P., Buhimschi C., Drugs for pregnant and lactating women. Philadelphia: Churchill Livingstone, 2004: 51-52.
25. Woo J.C., Yu T., Hurd T.C., Breast cancer in pregnancy: a literature review. *Arch. Surg.*, 2003; 138(1): 91-98.
26. Zemlickis D., Lishner M., Degendorfer P., Panzarella T., Sutcliffe S.B., Koren G., Fetal outcome after *in utero* exposure to cancer chemotherapy. *Arch. Intern. Med.*, 1992; 152(3): 573-576.
27. Weisz B., Meirou D., Schiff E., Lishner M., Impact and treatment of cancer during pregnancy. *Expert Rev. Anticancer Ther.*, 2004; 4(5): 889-902.