



The Effect of Chemotherapy in Pregnant Women on the Teeth of Offspring

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Abstract

No standardized therapeutic interventions have been reported for patients diagnosed with breast cancer during pregnancy. A high risk for malformations in the fetus has been claimed when chemotherapy is administered during the first trimester of the pregnancy. Tooth formation of the primary teeth begins at 11 to 14 weeks of fetal life and is completed postnatally. Therefore, the teeth may be affected by insults during the second and third trimesters of pregnancy, thus acting as a sensitive parameter of possible placental transfer of chemotherapy. The cases presented describe the dental status of 2 young children whose mothers received chemotherapy for cancer during the third trimester of their pregnancies (adriamycin or adriamycin and cytoxan). Both women gave birth to healthy babies, born with full hair, normal blood counts, and birth weights (3.200 and 3.100 kgs). Dental examinations of both children (at ages 18 and 30 months) revealed sound teeth. It seems that adriamycin and cytoxan for cancer chemotherapy do not affect the primary teeth when administered in the third trimester of pregnancy. (*Pediatr Dent.* 2003;25:601-604)

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Modern medicine is capable of preserving problematic pregnancies that would have been prematurely terminated in the past. Medicines given to the mothers during pregnancy have gained attention with regard to their effect on the fetus and his/her future life. The particular question is to what extent the placenta is a barrier to various drugs. With respect to dentistry, another important question is if drugs given during pregnancy may have an effect on the child's teeth.

The literature provides relatively large data regarding transplacental transfer of antibiotics and antihypertensive drugs. Most antibiotics can be used with relative safety during pregnancy. Moreover, none of the antibiotics to date has been shown to be teratogenic, although tetracycline may cause yellow to brown discoloration of the primary teeth (a fetal effect). Thus, antibiotics should not be withheld from the pregnant woman, especially when indicated for serious, life-threatening infections.^{1,2}

Antihypertensive drugs that are lipid soluble will pass through the placental barrier with ease, whereas the most polar ones will not. Placental transfer diminishes under

conditions that decrease the surface area or increase the thickness of the placenta. Highly protein-bound drugs form complexes which impair placental transfer, while unbound drugs cross the placenta easily. The ionized drug form is highly charged and cannot cross lipid membranes, while the nonionized form can easily cross the placenta.³⁻⁵

Cancer chemotherapy during pregnancy

Cancer is the second most frequent cause of death among women in reproductive age. Its frequency during pregnancy ranges between 0.07% to 0.1%, with breast cancer being the most prevalent malignancy followed by uterine, melanoma, lymphoma, ovary, thyroid and colon. Breast cancer during pregnancy accounts for 1% to 3% of all breast cancer cases.⁶ It is expected that the prevalence of malignancies during pregnancy will increase due to the tendency in the industrialized world to postpone the age of parenthood, thus breast cancer could potentially complicate 1 in 1,000 pregnancies.⁷

The standard treatment of breast cancer today includes tumor resection, radiation, chemotherapy, and hormonal

therapy. The combination and sequencing of these modalities depends on the stage and biology of the disease. No standardized therapeutic interventions have been reported for patients diagnosed with breast cancer during pregnancy. Due to the nature of the subject, one cannot expect a tremendous amount of reports. The literature provides some data regarding the various effects of cancer treatment modalities on the fetus and the newborn and future effects on the child.

High risk for malformations in the fetus, low birth weight, and stillbirth have been reported when chemotherapy is administered during the first trimester of pregnancy.^{8,9} When chemotherapy is administered during the second or third trimesters, relatively low risk for any effect on the fetus is expected.^{10,11}

Berry et al,¹² reported their experience with 24 pregnant patients with primary or recurrent cancer of the breast who were managed by outpatient chemotherapy or surgery. The chemotherapy included fluorouracil (1,000 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²), administered every 3 to 4 weeks after the first trimester of pregnancy. Premature labor was found in 12% of women, severe preeclampsia in 4%. No congenital malformations were found in the newborns. One baby was born preterm 2 days after chemotherapy with transient leukopenia. Two of the 24 babies had substantial hair loss. The authors concluded that breast cancer could be treated with chemotherapy during the second and third trimesters of pregnancy with minimal complications of labor and delivery. A possible risk for future carcinogenic effect is, however, uncertain.

Cisplatin is a well-known cytostatic drug with high efficacy against several solid tumors, among which ovarian cancer can be included. A study showed that during pregnancy, the ability of the placental barrier to protect the fetal compartment from cisplatin was enhanced when the drug was coupled to cholyglycinate. This, of course, suggests the potential usefulness of this mode of drugs in the treatment of some tumors during pregnancy.¹³

Another study demonstrated the presence of DNA damage induced by cisplatin in multiple maternal and fetal rat tissues at tumorogenic doses of drug; the results were, therefore, consistent with the hypothesis that genotoxic mechanisms play an important role in the drug-induced tumor incidence.¹⁴

All these studies addressed the effect of transplacental transfer of the drugs on all the body organs of the fetus except for the teeth.

Tooth formation

Formation of the primary teeth begins at 11 to 14 weeks of fetal life and is completed postnatally.^{15,16} The initial phase consists of matrix formation, followed by calcification in utero. Since enamel is a relatively stable structure, defects involving its matrix secretion and/or maturation of the primary teeth can act as a permanent record of insults occurring pre- or perinatally. A wide range of conditions may contribute to these hypoplastic/hypomineralized den-

tal defects. Systemic maternal disorders associated with enamel hypoplasia of the dentition of the fetus/neonate include, among others, diabetes, kidney disease, and viral or bacterial infection.¹⁷ Teeth affected may be more susceptible to cariogenic insult. The hypoplastic lesions may be pronounced and clearly visible to the naked eye, appearing as defects in texture or as discoloration, forming an obvious basis for future dental caries.

A strong correlation between the appearance of early childhood caries (ECC) and a history of maternal complications during pregnancy has been demonstrated.¹⁸

Therefore, the teeth may be affected by insults during the second and third trimesters of pregnancy, thus acting as a sensitive parameter of possible placental transfer of chemotherapy.

The following cases describe the dental status of 2 young children whose mothers received chemotherapy for breast cancer during their pregnancies.

Case 1

A 42-year-old female, mother of 13 children, felt a mass in her right breast in her 24th week of pregnancy. Biopsy was positive for carcinoma, and on the 25th week she underwent right modified radical mastectomy. A 3.5 cm tumor was found with involvement of 9 lymph nodes out of 32. Pathological examination revealed infiltrating duct carcinoma, Grade II. Under normal circumstances chemotherapy would have been offered to the patient. Due to the pregnancy, the decision to administer treatment was controversial. On one hand, the immediate effect of the chemotherapy on the fetus during the third trimester is most probably minor since all systems have already been developed. Premature labor and preeclampsia might occur, but can be managed with modern medicine. On the other hand, the future carcinogenic effect is unknown as well as other future complications.

Abortion, of course, meant definite loss of the baby. Keeping the pregnancy with no chemotherapy would have seriously harmed the woman. A mutual decision by the woman and her doctors was made to keep the pregnancy and have the required chemotherapy for the breast cancer, with the leading thinking that the life of the mother was the most important since she had 13 other children to care for.

Radiation therapy, however, was postponed until after birth. Adriamycin was administered in the 27th week of the pregnancy at a total dose of 75 mg/m² every 3 weeks. Three courses of chemotherapy were administered until birth.

In the 36th week, delivery was induced and the woman gave birth to a baby girl. Birth weight was 3.200 kg. The child was born with a substantial amount of black hair and had a minor ventricular septal defect (VSD). The baby's blood counts were normal. The woman was advised not to breast-feed. After birth, 3 more courses of chemotherapy were administered to the woman, as well as radiation and hormonal therapy. The VSD closed spontaneously within 2 years. Medical records revealed that 2 of the woman's other children also suffered from VSD at birth, also with sponta-

neous closure. Table 1 summarizes the data regarding the drugs given during pregnancy and regarding the baby.

At age 30 months, the child was examined by a pediatric dentist. Anamnesis revealed no medical problems. The child was holding a bottle containing sweetened juice. Clinical examination revealed the following: Class I occlusion, spaced dentition, all incisors, canines, and the first molars were present. Only cuspal tips of all second molars were noted on the gingivae. All teeth were sound. A sound narrow white line on the buccal aspect of the upper incisors was noted. No hypoplastic defects were noticed, nor was any sign of discoloration on the teeth. A periapical radiograph of the incisors' area revealed normal appearance of the primary incisors and normal appearance of the tooth buds of the permanent central and lateral incisors. The parents and the child were given meticulous oral hygiene instructions and detailed diet counseling, and sodium fluoride gel was applied on the child's teeth. Clinical examination after 6 months demonstrated no change from the previous examination.

The woman is alive today, 45 months after diagnosis, with no evidence of disease activity.

Case 2

A 30-year-old woman, mother of 4, was presented with a mass in her breast in the 22nd week of pregnancy. Biopsy was positive for carcinoma. She underwent mastectomy in the 24th week. Examination revealed a 1.5 cm invasive duct carcinoma, Grade III, with foci of ductal carcinoma in situ. The same considerations for treatment that were described in the previous case were relevant in this case as well. It was decided by the woman and her doctors to keep the pregnancy and receive the required chemotherapy. From the 26th week of pregnancy, the woman received 3 courses of adriamycin 60mg/m² and cytoxan 600 mg/m² once every 3 weeks.

Labor was induced in the 36th week. The woman gave birth to a 3.100 kg baby boy who was born with full hair and normal blood counts. The woman was advised not to breast-feed the baby. The data regarding the woman and the baby is summarized in Table 1.

At age 18 months, the boy was examined by a pediatric dentist. Anamnesis revealed no medical problems. The boy had a pacifier in his mouth. All teeth except for the second primary molars were present, and all were sound. The boy presented an open bite and spaced dentition. A periapical radiograph of the incisors' area revealed normal appearance of the primary incisors and normal appearance of the tooth buds of the permanent central and lateral incisors.

The woman is alive today, 36 months after diagnosis, with no evidence of active disease.

Discussion

A major concern in administering chemotherapy to a pregnant woman is the possible transfer of the drugs through the placenta and potential negative effects on the child, both developmental and carcinogenic. Administration of

chemotherapy during pregnancy has been associated with low birth weight, intrauterine growth retardation, spontaneous abortion, and premature birth.⁸ The effect of chemotherapy may be influenced by the timing of exposure to the chemotherapy, the duration and frequency of exposure, the ability of drugs to penetrate the placenta, maternal hyperproteinemia which increases the free drug concentration, and maternal obesity which may lead to sequestration of lipids soluble drugs.

Doll et al,⁸ claim that if chemotherapy is administered during the first 2 weeks after conception, either spontaneous abortion occurs or the fetus will be normal. Near-term administration is particularly dangerous since neonates cannot excrete and metabolize many drugs and myelosuppression may occur at the time of delivery.

In the cases described, both women received adriamycin and one of them received also cyclophosphamide. Both drugs are very potent in breast cancer.^{19,20} Their major toxicities include myelosuppression, nausea and vomiting, hair loss, cardiac toxicity and severe local injury upon extravasation (adriamycin only).¹⁹

In the cases described, the considerations regarding treatment were similar. The pros and cons of keeping the pregnancy with or without chemotherapy or discontinuing the pregnancies were thoroughly discussed by the doctors with their patients.

Although the long-term adverse effects on the child are not entirely well defined, some researchers claim that therapeutic abortion does not improve survival and that the general principle is to treat cancer and allow the pregnancy to proceed.⁷ Both women in the 2 cases described decided to keep the pregnancy and get the anti-cancer chemotherapy. Their decision was fully supported by their physicians.

Both babies were born in the 36th week after induction. Thus, had induction not been carried out, the babies would most probably have been born at term. The first sign that the administered chemotherapy did not penetrate the placenta significantly was that the babies were born with full hair and with normal blood counts. Had the drugs passed the placenta, the loss of the babies' hair would have been expected. The birth weight of both babies was normal.

The babies' teeth appeared relatively intact except for the white hard opacity around the marginal area of the upper incisors in the first case. This could be attributed to ad libitum use of a sugar-contained bottle by the child.²¹

Had the chemotherapeutic drugs passed the placenta during the early stages of tooth formation, major effects on the teeth would have been expected, among them abnormalities such as missing teeth or hypoplastic defects. At the time of examination, none were noted.

Conclusions

It seems that adriamycin and cytoxan for breast cancer chemotherapy when administered in the third trimester of pregnancy does not affect the primary teeth.

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ABSTRACT OF THE SCIENTIFIC LITERATURE



BIONATOR THERAPY

The aim of the study was to investigate the effects and optimal timing of Class II treatment with a bionator appliance. Lateral cephalograms from Class II patients who were treated with a bionator appliance were divided into 2 groups in which treatment was initiated before (13 patients) and during (10 patients) peak mandibular growth as determined by cervical vertebrae maturity (CVM). These cephalograms were compared to early and late control groups of untreated Class II subjects also based on cervical maturity. Differences between the late treatment and late control groups showed significant improvement in overjet, molar correction, and total mandibular length when compared to differences between the early treatment and early control groups. Treatment with a bionator should be initiated during the pubertal growth spurt when a concavity is evident at the lower borders of both the second and third cervical vertebrae (CVMS II).

Comments: This was a retrospective study of Class II bionator treatment with matched controls. A randomized clinical trial would offer a more effective direct comparison of the effects of using a bionator before and during the pubertal growth spurt. Cervical vertebrae maturation used in this article offers an alternative to the hand/wrist radiograph to assess growth status without additional radiation exposure. **LDK**

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