GYNECOLOGY

How much platinum passes the placental barrier? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy

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OBJECTIVE: Cervical cancer is the most common solid cancer diagnosed in pregnancy. Platinum is an active drug in the treatment of patients with cervical cancer. In the second and third trimesters, platinum is used to prevent cancer progression until fetal maturity is reached. However, knowledge about the transplacental passage of platinum is very limited.

STUDY DESIGN: Between May 2008 and June 2014, platinum-based neoadjuvant chemotherapy was applied to 21 consecutive patients with cervical cancer diagnosed in their second trimester. At the time of delivery by cesarean delivery, synchronous samples from maternal blood, umbilical cord blood, and amniotic fluid were taken and analyzed for platinum concentrations.

RESULTS: The mean week of gestation at cancer diagnosis was 17 (13–23). On average 3 (range, 2–4) cycles of chemotherapy were applied. Cesarean deliveries were carried out between 30.4 and 36.5 weeks of gestation. Twenty-two healthy babies without renal, hepatic, auditory, or hematopoietic impairment were delivered. Platinum concentrations in umbilical cord blood and amniotic fluid were 23–65% and 11–42% of the maternal blood, respectively.

CONCLUSION: This series on in vivo measurement of platinum concentrations in the fetomaternal compartment observed that because of consistently lower platinum values in the fetoplacental unit, a placental filtration mechanism of platinum may be assumed.

Key words: cervical cancer, neoadjuvant chemotherapy, platinum concentration, pregnancy, transplacental transport

Cite this article as: Köhler C, Oppelt P, Favero G, et al. How much platinum passes the placental barrier? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. Am J Obstet Gynecol 2015;213:206.e1-5.

The diagnosis of cervical cancer in pregnancy is a very rare situation for the expectant mother as well as for medical staff. In addition to oncological questions, ethical, religious, philosophical, and legal issues also have to be considered by patient and physicians.[1] An interdisciplinary team of gynecological, medical, and pediatric oncologists, neonatologists, anesthesiologists, pathologists, radiooncologists, and psychologists is therefore mandatory to give best advice to the patient and her family and to create an individual treatment plan.

Cervical cancer is one of the most frequent solid carcinomas in pregnancy with an estimated incidence of 0.1-12 per 10,000 pregnancies.[2-8] Management of cervical cancer complicated by pregnancy depends on several factors, such as the stage of disease (tumor size), lymph node involvement, duration of pregnancy, histological subtype, the parent's wish to continue pregnancy, and future child-bearing desire.[9-11]

There are only a few available guidelines and reviews for the treatment of pregnant women with cervical cancer.[8-14] However, these recommendations are based on small retrospective cohort studies and few case reports and therefore are limited in their meaningfulness. In early cervical cancer,

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Received Oct. 18, 2014; revised Jan. 25, 2015; accepted Feb. 19, 2015.

A.S. is an adviser to Karl Storz, Germany, and received financial support for training fellows in gynecological oncology. The other authors report no conflict of interest.

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0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2015.02.022

postponing oncological therapy until fetal viability seems to be a safe option, whereas in locally advanced cancer, neoadjuvant platinum-based chemotherapy during the second and third trimesters is recommended to avoid rapid tumor progression until fetal maturity is reached.[1,8,10,11]

The feasibility and potential benefits of neoadjuvant chemotherapy derive from retrospective oncological and pediatric outcomes after its use in pregnancy. Although there are accumulating data in the literature concerning the administration of cisplatinum and carboplatinum during pregnancy, the safety of these molecules for the fetus remains uncertain.[2,15-17]

On the one hand, pregnancy is associated with physiological changes in plasma volume, placental passage, and hepatic and renal metabolism. These particular alterations may significantly affect pharmacokinetics of chemotherapy drugs. On the other hand, chemotherapy itself has the potential to adversely impact rapidly proliferating fetal cells.[18] Several pharmacokinetic studies on animals have confirmed these hypotheses.[19-21]

Despite the fact that platinum-based chemotherapy is the most frequently used systemic therapy in pregnant women with cervical cancer, only 1 small study and 1 case report have analysed maternofetal passage of cisplatinum.[22,23] It was therefore the intention of the present prospective study to extend the current literature data about the safety of chemotherapy during gestation and to reinforce our own results on in vivo measurement of platinum concentrations.

Materials and Methods

After formal consultation with the Institutional Board Review of the Charité-Universitätsmedizin Berlin, official approval for the experiment and the prospective collection of data was considered unnecessary. The decision to participate in the study was taken on an individual basis and all included patients were extensively counseled about the oncological therapy and the proposed research. All women signed an informed consent allowing the experimentation and the publication of the data.

Neoadjuvant chemotherapy was indicated in 21 consecutive patients with cervical cancer in pregnancy and a strong wish to continue pregnancy between May 2008 and June 2014 at 5 gynaecological departments (Charité University Hospital Berlin, General Hospital Linz, University Hospital Cologne, University Hospital Bern, and University Hospital Jena). Prior to the application of neoadjuvant chemotherapy, the patients and their families were extensively counseled by gynecological, medical, and pediatric oncologists, neonatologists, psychologists, and anesthesiologists, and an interdisciplinary tumor conference recommendation was reached.

All patients underwent standardized obstetrical preventive examinations including fetal sonography every 4 weeks. To exclude rapid tumor progression during the course of the neoadjuvant chemotherapy, colposcopy and vaginal examinations during each cycle as well as pelvic magnetic resonance imaging scans were performed. Prior to elective caesarean delivery, 12 mg of betamethasone were given intramuscularly to prevent neonatal respiratory disease. The date of delivery was scheduled for each patient balancing oncological risk and fetal growth. At the time of the operation synchronous samples from maternal blood, umbilical cord blood, and amniotic fluid were taken and analyzed for platinum concentrations. Following informed consent, cesarean delivery was combined with different oncological operations according to the stage of the disease.

Results

Cervical cancer was diagnosed on average in the 17th week of gestation (range, 13−23 weeks) (Table). After histological confirmation and interdisciplinary tumor board conferences, laparoscopic pelvic lymphadenectomies were performed in all except 1 patient (number 13) as previously described.[24,25] One patient refused a lymphadenectomy because of her strong wish to continue pregnancy independent from the lymph node status.

Neoadjuvant platinum−based chemotherapy started between the 17th and 25th week of gestation. According to gestation time at diagnosis, on average 3 (range, 2−4) cycles of chemotherapy were applied. The neoadjuvant chemotherapy was monotherapy using cisplatin 20 mg/m^2 body surface area on days 1−3 every 3 weeks in 20 patients and using carboplatinum area under curve 5, every 3 weeks in 1 patient in combination with adequate supportive medication in all cases.

In consensus with neonatologists and anesthesiologists, the cesarean deliveries were carried out between 30.4 and 36.5 weeks of gestation after prophylactic application of betamethasone to the pregnant women. Cesarean delivery was combined with pelvic lymphadenectomy in 1 patient, simple hysterectomy in 1 other patient, and radical hysterectomy in 18 patients, respectively. Twenty-two healthy babies were delivered (including 1 set of twins).

After a follow-up period between 7 and 88 months, all children were without mental, renal, hepatic, auditory, or haematopoietic impairment. Platinum concentrations in maternal blood, umbilical cord and amniotic fluid samples taken during caesarean delivery were analysed in the same laboratory. The mean values of platinum concentrations in umbilical cord blood and amniotic fluid were 23-65% and 11-42% of the maternal blood, respectively (Figure).

In reference to the maternal oncological outcomes, no tumor progression was observed during the administration of the chemotherapy. One patient (number 6) was diagnosed with nodal metastasis (5%), and she was the sole subject who died by the disease. Consequently, the overall survival rate was 95.3% after a mean follow-up period of 33 months (range, 7−88 months).

Comment

Cervical cancer diagnosed in pregnant women is an oncological challenge. Therefore, patients should be counseled and treated in clinical institutions with interdisciplinary expert teams.[8,11] Individual treatment plans for all patients within this study were compiled in