

Research into cancer during pregnancy:

Treating pregnant woman with chemotherapy has no detrimental effect on foetus.

Professor Frédéric Amant of the Katholieke Universiteit Leuven directs research into the treatment of cancer in pregnant women and the consequences of such treatment on foetal development. In her PhD dissertation on chemotherapy during pregnancy, Kristel Van Calsteren presents a number of new scientific discoveries.

Kristel Van Calsteren has concluded that there is no increased risk of congenital defects in children who are exposed to chemotherapy during pregnancy. Nor do these children suffer from any discernible negative effects in the long term.

The primary explanation for this reassuring discovery is that the placenta functions as a filter for most of the products researched and that it protects the foetus against the damaging effects of chemotherapy. A second important criterion is that chemotherapy is not administered during the first trimester, which is the most vulnerable period of a pregnancy. A team of paediatricians and psychologists intensively monitored 64 children. This is the very first time such research has been conducted.

Doctors in Flanders diagnose approximately 60 cases of cancer in pregnant women every year, while it is estimated that 3000 to 5000 pregnant women are confronted with cancer across Europe . Treatment is an enormous challenge under such circumstances considering that doctors have to consider both the recovery of the mother as well as the wellbeing of the unborn child. Nonetheless, current medical expertise and experience remains relatively limited.

A special research project was established in 2004 in order to acquire better insights into this complex issue.

- **The first part of this project** examined the treatments that are currently administered to pregnant women with cancer . Furthermore, it researched the influence of these therapies on foetal development and the health of the child at birth.

- **The second part** was of a pharmacological nature; it analysed the “pharmacokinetics” of chemotherapy drugs in pregnant women (i.e. the absorption, progression and distribution of the medication in the body) and the “transplacental transfer” of the medication (transfer through the placenta) to the foetus.

- **The third part** focused on the effects of prenatal exposure to chemotherapy on the general and neurological development of the child.

For the first part of the project , international co-operation was established between various hospitals. From their initial study, the researchers concluded that the same types of cancers

occur in women of the same age whether they are pregnant or not. Consequently, pregnancy is not a risk factor as such. It did appear, however, that half the pregnant women with cancer gave birth prematurely. In most cases, these deliveries were induced. This resulted in a high number of newborn babies being admitted to neonatal departments. Therefore, the researchers advocate the treatment of these mothers by a multidisciplinary team at a hospital with a department for 'high risk obstetrics' and neonatal care.

In cases of specific types of cancer and specific cancer treatments, growth retardation in the womb was observed, but the children made up for this delay after birth. However, the researchers' most important discovery is that the number and types of congenital defects are no different in cases where chemotherapy was administered to mothers. These reassuring findings will soon be published in the leading scientific periodical 'Journal of Clinical Oncology'.

The second phase of the doctoral research examined the "pharmacokinetics" of chemotherapy drugs during pregnancy, including the transfer of these drugs through the placenta. Pregnancies are characterised by important changes in the body, some of which influence the way in which medication is absorbed and distributed by the body. Pregnant women have increased blood volume and retain fluid more easily. Pregnancy also influences the functioning of the liver and kidneys. The effect this has on chemotherapy treatment had never been researched.

Kristel Van Calsteren's dissertation demonstrates that these physiological changes during pregnancy result in lower maximum concentrations of chemotherapy and in reduced exposure to chemotherapy. From the findings it appears that the medication is distributed over a greater volume and is also excreted more quickly by the body. Further research is necessary to determine whether this results in the medication having less impact on the tumour, and thus to evaluate whether chemotherapy is sufficiently efficacious when administered to pregnant women. Additional intensive research, both nationally and internationally, is necessary in order to determine the consequences on the chances of recovery and the health of mothers.

At the beginning of this project, the researchers had no notion of the quantity of chemotherapy that reaches unborn children. For this reason, the researchers closely examined the transfer of chemotherapy through the placenta in animals. The results indicated that this transfer differs significantly depending on the type of medication. Some medications barely penetrate the placenta, while in cases of other drugs the same concentration is found in both the mother and foetus. Depending on the specific properties of the chemotherapy drugs, regulatory systems in the placenta allow the medication to pass through to the foetus. It may also be possible to apply these findings to other medications that were not investigated in this study.

The research conducted indicates that the placenta acts as a filter for most tested chemotherapy drugs and thus reduces the foetus's exposure to chemotherapy. These discoveries are directive and reassuring. At this stage, however, they are too limited to make a definitive statement regarding wellbeing in the long term.

The third part researched the effect of chemotherapy on the neurological development of children. To this end, the researchers established international co-operation with the universities of Nijmegen in The Netherlands and Prague in the Czech Republic . The children were examined by pediatric neurologists and neuropsychologists in the same ways at the three centres. The results are based on the clinical examination of 64 children who were exposed to chemotherapy during pregnancy. The majority of them are under 6-years-old, while the oldest child is already 15.

This research indicated that most of the children were in a normal condition at birth. As they grew older, the children's development was in accordance with the expectations for their age. Specific tests of their memory and attentional functions did indicate increased impulsivity in these children, however. This has previously been described in children born prematurely and children exposed to their mothers' increased psychological stress during pregnancy. These factors also play a role in women to whom chemotherapy is administered during pregnancy.

For the very first time, children exposed to prenatal chemotherapy have been clinically and neurologically examined in a systematic manner. The first research results are very reassuring. However, in order to increase the accuracy of these findings in the long term, a greater number of children must be examined and longer check-up periods are also necessary. For these reasons, the research is being expanded further, both nationally and internationally.

Based on the new discoveries related to pharmacokinetics, the researchers are also committed to a further investigation of the efficiency of existing therapies for mothers.

Doctoral defence 'Chemotherapy during pregnancy: pharmacokinetics and the impact on foetal neurological development', K.U.Leuven, 22 October 2009 .