Long-term outcomes after prenatal exposure to chemotherapy

A European multicentre observational cohort study suggests that prenatal exposure to chemotherapy may not harm development. Children of women exposed to chemotherapy while pregnant develop as well as children in the general population. However, given the small sample size, caution is advised when interpreting the results.

Overview: Cancer is estimated to complicate between 1 in 1000 and 1 in 2000 pregnancies, and its incidence is increasing. Chemotherapy for the treatment of maternal cancers during pregnancy has become more acceptable in the past decade. However, the effect of the malignancy and its treatment on fetal health remains a serious concern.

Current advice: There is no NICE guidance on the use of chemotherapy for the treatment of cancer during pregnancy. Breast cancer and haematological malignancies are the most common types of cancer during pregnancy. The Royal College of Obstetricians and Gynaecologists' green top guidelines on breast cancer state that systemic chemotherapy is contraindicated in the first trimester because of a high rate of fetal abnormality, but is safe from the second trimester and should be offered according to protocols defined by the risk of breast cancer relapse and mortality.

New evidence: A multicentre observational cohort study, across 3 European centres in Belgium, the Netherlands and Czech Republic, examined long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older, compared with children in the general population (Amant et al., 2012).

The study, which is still recruiting, assessed 68 pregnancies (producing 70 children), during which 236 cycles of chemotherapy were administered (on average 3 or 4 per pregnancy). The median gestational age at cancer diagnosis was 18 weeks. The children were born at a median of 36 weeks into pregnancy, with more than two-thirds of the women (69%, n=47) giving birth at less than 37 weeks.

The children assessed ranged in age from 1.5 to 18 years. Tests included clinical neurological examinations, tests of the general level of cognitive functioning (Bayley or intelligence quotient [IQ] test), electrocardiography and echocardiography, and a questionnaire on general health and development. For children aged 5 years or older, additional tests were performed: audiometry, the Auditory Verbal Learning Test, and subtasks of the Children's Memory Scale, and the Test of Everyday Attention for Children, and the child's parents also completed the 'Child Behavior Checklist'.

The authors found that although neurocognitive outcomes were within normal ranges, cognitive development scores were lower for children who were born preterm than for those born at full term. However, they emphasised that this difference is found in any group of children born prematurely, not just those in this study. When controlling for age, sex, and country, the score for IQ increased by an average 12 points for each additional month of gestation. The measurements of the children's behaviour, general health, hearing, and growth corresponded with those of the general population. Heart dimensions and function were within normal ranges.

Both children of a twin pregnancy presented with an important neurodevelopmental delay. This was not thought to be caused by prenatal exposure to chemotherapy, although this cannot be ruled out. The researchers can also not exclude an additional effect of chemotherapy and other drugs or radiation exposure on the children born preterm. Therefore, although the findings suggest that it is safe to administer chemotherapy from 14 weeks
gestational age onwards, longer follow-up in more children is needed to increase certainty that chemotherapy in pregnancy does not harm the health of the unborn child.

**Commentary:** The study by Amant et al. 2012 highlights the dilemma of how to weigh the potential long term harms to the child of maternal chemotherapy during pregnancy against the potential benefits of maternal survival. Adverse effects of chemotherapy on the brain and cardiac function are well-established in adults and children, but there are few studies of outcomes of prenatal exposure.

The study's strengths include standardised prospective assessments of cognition and cardiac function in children of mothers given chemotherapy in pregnancy. The major limitation of the study is the small sample size of 68 pregnancies with many babies born premature. Limitations also relate to potential selection biases affecting retrospective and prospective recruitment of children into the cohort from cancer referral centres, follow-up to different ages, and lack of a risk-adjusted comparison with children who were unexposed.

As the authors recognised, chemotherapy could adversely affect outcomes indirectly, through its effect on prematurity. The authors acknowledged the need for future studies to have a comparison group of unexposed children who were born premature and to account for the mediating effect of prematurity to from direct effects of chemotherapy.

It is very important that data like these are publicly available, not least for future systematic reviews. However, with a small study sample as in this study great caution needs to be taken in the interpretation of the study results. It may be too early to conclude that chemotherapy in second and third trimesters is not associated with the outcome examined. Large studies that link cancer registry data with healthcare data on mothers and their children and make risk-adjusted comparisons of chemotherapy-exposed and non-exposed pregnancies are needed to quantify other adverse effects of cancer and its treatment on pregnancy outcomes and subsequent morbidity. – Ruth Gilbert, Professor of Clinical Epidemiology Centre for Paediatric Epidemiology and Biostatistics, and MRC Centre of Epidemiology for Child Health Director, Centre for Evidence-based Child Health University College London.

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