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Review

Effects of prenatal exposure to cancer treatment on neurocognitive development, a review

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ABSTRACT

Due to the increasing incidence of cancer during pregnancy, the need to better understand long-term outcome after prenatal exposure to chemo- and/or radiotherapy has become more urgent. This manuscript focuses on the neurocognitive development after prenatal exposure to cancer treatment. We will review possible pathways for brain damage that could explain the subtle changes in neurocognition and behavior found after in utero exposure to cancer treatment. Contrary to radiation, which has a direct effect on the developing nervous system, chemotherapy has to pass the placental and blood brain barrier to reach the fetal brain. However, there are also indirect effects such as inflammation and oxidative stress. Furthermore, the indirect effects of the cancer itself and its treatment, e.g., poor maternal nutrition and high maternal stress, as well as prematurity, can be related to cognitive impairment. Although the available evidence suggests that cancer treatment can be administered during pregnancy without jeopardizing the fetal chances, larger numbers and longer follow up of these children are needed.

Contents

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1. Introduction

The incidence of cancer during pregnancy is increasing, most likely due to the fact that the age of pregnant women increases in combination with the increasing probability of cancer with age (Belgian Cancer Registry, 2016; Mathews and Hamilton, 2009). Today, approximately 1–2 in 2000 pregnancies are complicated with cancer. Most frequently it concerns breast cancer, hematological malignancies, melanoma and cervical cancer (Pavlidis, 2002), as is the case in non-pregnant women from the age range of 20–40 years old. Maternal treatment consists of chemotherapy, radiotherapy and/or surgery. The use of targeted therapy in the case of cancer in pregnancy is mostly contraindicated due to high fetal risks (Azim et al., 2010; Makol et al., 2011; Lambertini et al., 2015a).

Non-obstetric surgery during pregnancy exposes the fetus to a potential risk of not only the anesthetics, but also of surgical complications such as hypotension, hypoxia and a decreased utero-placental perfusion after prolonged supine positioning (Nulman et al., 2001). However, research has shown that most commonly used anesthetics are relatively safe to use (Nulman et al., 2001). Furthermore, a review of 12,452 women stated that there might be an increased of miscarriage when surgery was performed in the first trimester, but there was no evidence of an increased risk of maternal death, congenital malformation or long term neurodevelopmental issues (Cohen-Kerem et al., 2005; Walton and Prasad, 2011). Overall, surgery can be safely performed during pregnancy, given adequate monitoring of the mother and the use of anesthetics that have been previously used and proven safe during pregnancy.

The most commonly used chemotherapeutic agents are anthracyclines, cyclophosphamide and 5-fluorouracil (5-FU) for breast and hematological cancers; taxanes for breast, cervical and ovarian cancers; vinca alkaloids for hematological malignancies; and platinum agents for cervical, breast and ovarian cancer (Dekrem et al., 2013). All of these agents have their own specific working mechanism. Cyclophosphamides, 5-FU and platinum agents will interfere directly with the DNA and DNA-replication, whereas vinca alkaloids and taxanes will inhibit mitosis by disrupting microtubule function (Wiebe and Sipila, 1994). Drug toxicity is dose dependent. Important to note is that due to changes in physiology during pregnancy, the pharmacokinetics of drugs are affected. The most important changes are a decreased gastrointestinal motility, a significant increase in plasma volume and extracellular fluid, an increased glomerular filtration and tubular function, up- or downregulation of hepatic enzymes, an increased fat mass and the amniotic fluid which increases the distribution volume. These changes interfere with drug absorption, distribution, metabolism and excretion. van Hasselt et al. (2014) have recently shown that this leads to a decreased plasma volume of certain chemotherapeutic drugs such as docetaxel and paclitaxel in pregnant women (Bell and Kerr, 2015).

The use of radiotherapy during pregnancy is only indicated when it concerns tumors remote from the pelvis (breast cancer, brain tumors, lymphoma), especially during the first and second trimester of pregnancy when the uterine volume is smaller. It is important to carefully estimate the fetal dose from internal scatter and leakage radiation. A fetal exposure of maximum 100 mGy is considered to be acceptable with regard to fetal risk (Kal and Struikmans, 2005).

Of concern is the potential effect of cancer treatment on fetal development. Apart from the dose, the timing will determine the impact of prenatal chemo- and radiotherapy exposure. In the first two weeks after conception cells are omnipotent, thus administration of chemo-/radiotherapy in this stage will result in an all-or-nothing phenomenon depending on the amount of disrupted cells. From week 2 until 8 organogenesis takes place. Drug administration or radiation exposure in this organ development phase will result in malformations of mainly the heart, neural tube, limbs, palate and ears (Walton and Prasad, 2011; McCollough et al., 2007). However, organogenesis of the central nervous system (CNS) continues until well into the postnatal development. Therefore, even if the administration of anti-cancer drugs or radiation exposure occurs after 14 weeks of gestation, which is well after the end of the general organogenesis, the development of the brain can be influenced (Schull and Otake, 1999).

Recent studies in adults and children with cancer have shown that chemotherapeutic drugs can have an impact on cognitive functioning and brain regions responsible for memory (temporal area), attention and executive functions (frontal area). With advanced neuroimaging techniques, structural and functional changes in the brain have been reported in these patients after cytotoxic treatment (Deprez et al., 2012, 2011; Schuitema et al., 2013; Ahles et al., 2012; Wefel and Schagen, 2012). This raises the assumption that, if chemotherapeutic drugs and/or radiation reaches the fetus, similar effects could arise in the child.

In this paper we will review the current knowledge about the neurocognitive outcome after prenatal exposure to chemo- and radiotherapy and possible confounding factors.

2. Radiotherapy

2.1. Neurotoxic effect of radiotherapy

Although it is poorly documented, there is a general concern about the safety of radiotherapy during pregnancy. The International Commission on Radiological Protection reviewed the risks of medical irradiation of pregnant women (International Commission on Radiological Protection, 2000; Streffer et al., 2003). However, the results referred to are mostly derived from animal studies and human data from pregnancies during nuclear disasters and exposure to diagnostic X-rays (Streffer et al., 2003; Bromet et al., 2016). Based on these results the time- and dose-dependent deterministic risks are lethality, malformations, mental retardation and cancer induction.

The damage due to radiation can be caused directly to the DNA or cell components that are important in the signal transduction pathways involved in damage repair, or, as is mostly the case, indirectly through the formation of reactive oxygen species (ROS) (Verheyde and Benotmane, 2007). A significant increase in ROS will cause DNA damage, which in its turn can lead to a number of cellular responses, including cell cycle arrest (reduced level of neurogenesis), senescence, p53-mediated apoptosis and even tumor growth (Lehnert and Iyer, 2002; Verreet et al., 2015; Kokosova et al., 2015).