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Review

Neurodevelopment of children exposed in utero to treatment of maternal malignancy

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Summary Cancer is the second most common cause of death during the reproductive years, complicating approximately 1/1000 pregnancies. The occurrence of cancer during gestation is likely to increase as a result of a woman's tendency to delay childbearing. Improved diagnostic techniques for malignancies increases detection of cancer during pregnancy. Malignant conditions during gestation are believed to be associated with an increase in poor perinatal and fetal outcomes that are often due to maternal treatment. Physicians should weigh the benefits of treatment against the risks of fetal exposure. To date, most reports have focused on morphologic observations made very close to the time of delivery with little data collected on children's long-term neurodevelopment following in utero exposure to malignancy and treatment. Because the brain differentiates throughout pregnancy and in early postnatal life, damage may occur even after first trimester exposure. The possible delayed effects of treatment on a child's neurological, intellectual and behavioural functioning have never been systematically evaluated. The goal of this report was to summarize all related issues into one review to facilitate both practitioners' and patients' access to known data on fetal risks and safety. © 2001 Cancer Research Campaign http://www.bjcancer.com

Keywords: malignancy; child development; antineoplastic medications; radiation; glucocorticoids; bromocriptine

METHODS

The data presented in this paper are based on a Medline search of the literature from 1966 to May 2001 and a Cancerlit search from 1983 to May 2001. Both searches were performed on Ovid Medline. The search strategy combined the following four concepts using available MeSH terms:

Concept 1 (exp pregnancy or exp pregnancy complication); and

Concept 2 (exp developmental disabilites or exp 'behaviour and behaviour mechanisms' or exp cognition disorders); and

Concept 3 (exp antibiotics, anthracycline or exp antibiotics, antineoplastic, exp antineoplastic agents, or antineoplastic agents, combined or exp antineoplastic agents, hormonal or exp antineoplastic and immunosuppressive agents or exp radioisotopes or exp anesthetics or prednisone or bromocriptine or glucocorticoids or exp estrogens); and

Concept 4 (exp neoplasms).

The search was not limited to specific languages, age groups or human studies. The studies were reviewed for details on fetal brain development evidenced postnatally by different physical, neurological and neurodevelopmental tests.

MATERNAL CANCER

Whether an association of maternal cancer with pregnancy has an undesirable effect on neurodevelopment in later childhood remains largely unknown. Metastasis to the placenta and/or fetus is very rare (Gililland and Weinstein, 1983; Potter, 1970). Melanoma is the most frequent of the few malignancies that do metastasize to the placenta and fetus (Gililland et al, 1983). Live born children exposed to such malignancies tend to die within a 1 day to 10 month period. Comprehensive reports about physical and mental health of the surviving children are not available.

The cancer patient has an increased tendency to experience febrile illnesses due to infections and/or as a result of the tumour itself. The relationship between hyperthermia, fetal brain development, and the incidence of impairment in human children has not been fully addressed. However, many human studies do support the hypothesis that maternal fever in early pregnancy is associated with an increased risk of NTDs and microphthalmia (Chambers et al, 1998; Miller et al, 1978; Layde et al, 1980; Clarren et al, 1979).

Malignancies may also be associated with maternal malnutrition and adverse neonatal outcome (Metcoff et al, 1981; Brown et al, 1981). Although animal studies have shown that severe maternal undernutrition can result in stillbirths and increased perinatal mortality, retrospective analyses of human data obtained during historical periods of starvation have shown little or no adverse fetal effects (Pritchard et al, 1985). Several studies have suggested that severe ketoacidosis due to dehydration or severe weight loss may pose an additional risk to the developing fetus (Naeye et al, 1981). On the other hand, analysis of males at age 19 born to mothers starved during pregnancy failed to document any differences in IQ score between these boys and the general male population (Stein et al, 1972).

SURGERY

Surgical interventions may be required for the evaluation and treatment of malignancies diagnosed in pregnancy. Each year about 0.5% to 2% of pregnant women in North America undergo

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surgery for reasons unrelated to their pregnancy and approximately 7000 to 30 000 of these women are in the first trimester of pregnancy (Sylvester et al, 1994), a critical time for the development of the central nervous system (CNS) (Webster et al, 1988). This is also the time period when the woman may not be aware of her pregnancy. Some women are occupationally exposed to anaesthetics throughout gestation. Little is known about neurodevelopmental outcomes due to exposure in either surgical or occupational conditions. During surgery the fetus is exposed to a potential risk from the effects of anaesthetic agents in addition to complications that may arise during or as a result of maternal surgery. Surgery in pregnancy is often associated with hypotension, hypoxia, coagulation, metabolic disturbances, and decreased utero-placental perfusion secondary to prolonged maintenance in the supine position. Each of these conditions can threaten fetal well being (Doll et al, 1988).

There are studies that establish the safety of the most commonly used anaesthetic agents during pregnancy, including nitrous oxide, enflurane, barbiturates, and narcotics (Schardein, 1985). Friedman (1988) reviewed possible teratogenic effects of general anaesthetics, local anaesthetics, and occupational exposure to anaesthetic gases. He concluded that data available on these agents do not suggest a major teratogenic risk in humans.

Kallen and Mazze (1990), in a case control study, assessed the pregnancy outcome of 2252 infants born to women who had surgery in the first trimester. Six neonates (expected number = 2.5) had a definite diagnosis of neural tube defect (NTD). Five of these 6 mothers were operated on in the fourth and fifth weeks of gestation, the window of exposure in which NTDs may take place. Sylvester (1994), in a large population-based case-controlled study, evaluated whether exposure to maternal general anaesthesia is associated with an increase in fetal CNS abnormalities. Twelve of 694 mothers with infants who had CNS defects reported having first trimester surgery with anaesthesia. Thirty-four of the 2984 controls were exposed to general anaesthesia at the same time of gestation (OR = 1.7, 95% CI-0.8,3.3). The strongest association was observed between exposure to anaesthesia and hydrocephalus, as well as eye defects. Although available studies have indicated that the CNS is the most sensitive organ to surgical and anaesthetic damage, none of the studies have addressed later childhood neurodevelopment or cognition. Functional CNS abnormalities may exist even when structural abnormalities are not observed.

MEDICATIONS

Cytotoxic drugs

The common denominator of anti-cancer drugs is the ability to affect cell division adversely. Therefore, the same qualities that make those compounds desirable for cancer therapy, may also render them detrimental to the developing embryo. The dose of medication and time of exposure are critical during embryogenesis when susceptibility to teratogenic agents is high (Webster et al, 1988). A number of studies focused on congenital malformations at the time of delivery, and concluded that when chemotherapy is administered to women before conception or after the first trimester, in the majority of cases normal births are experienced (Harada, 1978; Gililland and Weinstein, 1983; Doll et al, 1988; Cantini and Yanes, 1984). These conclusions may not apply to the CNS, which develops throughout gestation and postnatally. Xenobiotics, including some heavy metals, ethanol and cocaine, are known to adversely affect CNS development during the second and third trimester (Koren et al, 1994; Harada, 1978).

Cognitive and behavioural functioning of children exposed in utero to chemotherapy at different periods of gestation remain largely undefined. Available data are based on small series and case reports. These reports suggest that gross and mental development of children exposed in utero to chemotherapy appears to be normal, but most authors did not conduct formal motor, cognitive and behavioural tests. As a result, they may have missed the opportunity to detect more subtle neurodevelopmental abnormalities. In case reports of women who were treated with a variety of chemotherapeutic agents and the developmental outcome was reported, the infants presented normal growth and developmental milestones at 3–21 months following delivery (Odom et al, 1990). However, Reynoso (1987) and Cantini (1984) reported 2 children with mental and or growth retardation born to mothers treated in pregnancy for acute leukaemia.

Presented below are the data concerning late effects of chemotherapy on children's neurodevelopment (Table 1). Blatt et al (1980) assessed retrospectively pregnancy outcome in patients who received aggressive moderate to high-dose combination chemotherapy for various oncologic diseases. Two patients conceived during treatment, which was continued for the first 2 months of gestation, and two other women started chemotherapy in the second and third trimester respectively. At the time of evaluation, the offspring ranged in age from several days to 12 years. Development was evaluated using the Denver Developmental Screening Test, and school performance was ascertained by history. Growth and development as well as school performance appeared to be normal in these children.

The peak incidence of Hodgkin's disease occurs during the reproductive years. Therefore, it is not surprising that there have been more reports on long-term follow-up for Hodgkin's disease than for other malignancies. Baisogolov and Shishkin (1985) reported on the pregnancy outcome of 78 retrospectively collected patients with Hodgkin's disease who delivered 89 children. The data were collected from the parents by local paediatricians. Twenty-one women conceived while undergoing chemotherapy. The psychomotor development of the case children was not different from that of the controls (children of healthy mothers). Seventeen out of 19 school-aged children were considered as 'good' or 'excellent' students. Twelve of these children were good in mathematics, 6 were in advanced programs to study foreign languages, 4 studied music, and 10 were good in sports. Another 7 children were gifted in other areas. A study conducted in Poland reported on the outcome of 20 pregnancies in 16 women with Hodgkin's disease (Balcewicz-Sablinska et al, 1990). In three pregnancies, cytostatic treatment was given after the first trimester. The course and labour of the observed pregnancies were normal. All babies were born healthy and were followed for a period of 6 years. The development of these children was reported to be normal, although formal psychological assessments were not performed.

The pregnancy outcome of women with haematologic malignancies, screened between 1970 and 1986, was presented by Aviles et al (1991). Forty-three children were born to 43 mothers who were treated with chemotherapy for non-Hodgkin's lymphoma, Hodgkin's disease, acute leukaemia, or chronic granulocytic leukaemia. Nineteen women received chemotherapy during the first trimester. The children's ages ranged from 3 to 19 years in 1989 at the time of testing. They were evaluated by

Table 1 In utero exposure to chemotherapeutic agents

Indication	Authors	Time of exposure in pregnancy	Study design	Sample size *n* = 111	Age assessed	Medications	Tests	Results
Different forms of malignancies	Blatt et al, 1980	Preconceptionally or 1st trimester	Retrospective	4	1 month to 12 years old	Combined chemotherapy	Denver Developmental Screening Test. School reports	Normal development and school performance
Hodgkin's disease	Baisogolov and Shishkin, 1985	–	Retrospective	19	1 to 14 years old	Combined chemotherapy	Parent and school reports	Normal development
Hodgkin's disease	Balcewicz-Sablinska et al, 1990	1st trimester	Retrospective	3	Up to age 6	MOPP	No formal testing	Normal development
Hodgkin's disease	Aviles et al, 1991	1st and 2nd trimesters	Retrospective, controlled	15	3 to 17 years	MOPP, ABVD	Wechsler and Bender-Gestalt cognitive tests. School report	Not different from controls
Haematological malignacies	Aviles et al, 1991	1st trimester, 2nd and 3rd trimester	Retrospective, controlled	43	3 to 19 years	Combination chemotherapy	Wechsler and Bender-Gestalt cognitive tests. School report	Not different from controls
Acute leukaemia	Aviles et al, 1988	1st trimester or sometime during pregnancy	Retrospective, controlled	17	4 to 22 years	Combination chemotherapy	Wechsler and Bender-Gestalt cognitive tests. School reports	Not different from controls
Rheumatic disease	Kozlowsky et al, 1990	1st trimester	Retrospective	5	3.7 to 16.7 years	Low-dose methotrexate	Parent reports	Normal development
Occupational exposure	Medkova 1991	Preconceptionally and/or during pregnancy	Retrospective, controlled	5	–	Low dose cytostatics	No formal testing	Normal development

physical and neurological examination in a 'blinded' manner. Evaluation of the children's school performance was obtained from their teachers. The Wechsler and Bender-Gestalt tests were administered to the children according to their ages, and the results were compared with those of 25 children of similar age and socio-economic class. The children in the study group were not different from their controls in any of the measured tests.

Leukaemia occurs in approximately one out of 100 000 pregnancies (Caligiuri and Mayer, 1989). Aviles and Niz (1988) examined 17 offspring of patients with acute leukaemia treated during pregnancy. Chemotherapy was given during the pregnancy in each case, including 11 cases during the first trimester. The treatment of acute leukaemia was not modified due to the pregnancy and these patients received at least 80% of the planned dose. Neurological, intellectual and visual-motor-perceptual assessments were performed on the offspring (who ranged in ages between 4 to 22 years), their siblings, and unrelated controls. All children were given the Wechsler or the Bender–Gestalt test according to their age. No differences were detected between the groups on any of the tests. Kozlowski et al (1990) reviewed retrospectively the outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. The duration of treatment ranged from 2 to 20 weeks of gestation. The women were given 7.5 to 10 mg methotrexate weekly. Five full-term live babies were born with a mean follow-up age of 11.5 years (range 3.7–16.7 years). All children reached normal growth and neurodevelopment. None of the children had learning disabilities. One child with speech impairment improved after speech therapy. Unfortunately, the methods of mental assessments were not reported.

The outcome of occupational chemotherapy exposure during pregnancy was addressed by Medkova (1991). The author reported on the pregnancy outcome and neurodevelopment of health personnel's children exposed to small doses of cytostatic medications. Sixty-one children were born to the healthcare workers on the oncology unit. In this group, exposure to antineoplastic agents was proven in five mothers and five fathers. Attention was paid to the children's physical development and possible incidence of dyslexia or dysgraphia. No abnormalities in these areas were found. Formal cognitive tests and statistical comparisons were not reported.

In summary, the data presented regarding late effects of chemotherapy on children's neurodevelopment are incomplete and are hampered by a lack of population-based, well designed studies. It is important to note that the paucity of neurobehavioural and cognitive studies in older children is due to limited late follow-up. The majority of available reports have focused on immediate maternal and fetal pregnancy outcomes, not considering later neurodevelopment as a primary end point, thus using a cross-sectional rather than longitudinal approach. The studies which did address long-term neurodevelopmental aspects typically used retrospective design in order to recruit a sufficient number of cases. Notwithstanding the limitations, these studies are very important as they represent the only existing source of information on the neurodevelopmental outcome of in utero exposure to cytotoxic therapy. The general impression, based on these reports, is that chemotherapy does not have a major impact on later child neurodevelopment. Methodologically, retrospective studies tend to show more adverse outcome than prospective studies, due to reporting bias (e.g.: parents of children with adverse outcome are more likely to report than those with normal outcome). Hence, negative retrospective studies are reassuring. With the increased use of cancer medications in nonmalignant conditions (e.g.: transplant, collagen diseases), it may be possible to recruit larger numbers of children for prospective, longitudinal studies and delineate abnormal outcomes induced by the malignancy itself.

Glucocorticoids

Glucocorticoids are part of the treatment protocol for many malignancies. They are also used as immunosupressive treatment in organ transplantation and for fetal lung maturation when preterm delivery is suspected. Most comprehensive studies on the neurodevelopmental effects of glucocorticoids were done in late pregnancy. Animal studies indicate that corticosteroids are associated with cognitive and behavioural abnormalities when administered during pregnancy. This has raised concerns about their use in humans (Trautman et al, 1995; Meaney et al, 1982; Angelucci et al, 1985). Table 2 presents the long-term effects of glucocorticoids used in gestation.

A prospective pilot study that investigated the long-term neurodevelopmental effects of prenatal exposure to dexamethasone (DEX) was conducted by Trautman et al (1995). The authors followed 26 children (ranging in age from 6 months to 5.5 years) whose mothers took DEX during pregnancy from weeks 1 to 21. The mothers took DEX for 2–29 weeks for the treatment of fetal risk for congenital adrenal hyperplasia (CAH). The offspring were compared with 14 children who were also at risk for CAH, but had not been exposed to DEX. The authors attempted to separate the effects of maternal disease by controlling for the same medical condition without treatment. The results indicated that DEX-exposed children were less likely to be cognitively delayed on a comprehension-conceptualization measure of development and that DEX-exposed 2- to 3-year-old children (n = 14) displayed more internalizing behaviour than unexposed children of the same age (n = 4). DEX-exposed children also exhibited a tendency to show higher avoidance behaviour and to be more shy and emotional and less sociable than unexposed children. No other significant differences were reported.

Pregnancy outcome and long-term follow-up with DEX used as an immunosuppressive agent taken throughout pregnancy for the treatment of lupus erythematosus (21 children) and heart transplant patients (29 children) were reported (Tincani et al, 1992; Wagoner et al, 1993). The authors indicated that the offspring were doing well at follow-up, but no formal cognitive or behavioural tests were conducted.

The literature on exposure to DEX in late pregnancy suggests that there are no significant cognitive differences between exposed and non-exposed children (MacArthur et al, 1982; Veszelovsky et al., 1981; Collaborative Group on Antenatal Steroid Therapy, 1984). The Collaborative Group on Antenatal Steroid Therapy (1984) was a prospective, randomized, placebo controlled, double-blinded study on the use of antenatal DEX for the prevention of respiratory distress syndrome in infants. The authors evaluated 200 children at 9, 18, and 36 months of age. The Bayley Scales and McCarthy Scales of Children's Abilities were used to assess cognitive and motor development. The results indicated that there were no significant differences in head circumference, cognitive, developmental or neurologic functioning between the placebo and the steroid treatment groups. The authors concluded that there were no detectable effects within the first 3 years of life in children who were exposed antenatally to DEX.

MacArthur et al (1982) conducted a double-blind, controlled study investigating the cognitive and psychosocial development of

Table 2 Children exposed in utero to glucocorticoids

Indication	Author	Time of exposure in pregnancy	Study design	Sample size *n* = 540	Age assessed	Substance	Duration of substance use	Tests	Results
Lung maturation **in Hungarian	Veszelovszky et al, 1981	3rd trimester	Retrospective, controlled	125	12–36 months	Dexamethasone		Neurological and psychological	No difference from the control group
Fetal lung maturation	MacArthur et al, 1981 and 1982	3rd trimester	Prospective, controlled	139	Age 4 and 6	Betamethasone		Stanford-Binet Intelligence Scale, Frostig Visual Perception Test, Vineland Social Maturity Scale, Illinois Test of Psycholinguistic Abilities, Peabody Vocabulary Test, Raven's Matrices, Bender-Gestalt Test	No difference from the control group
Fetal lung maturation	Collaborative Group on Antenatal Steroid Therapy (1984)	3rd trimester	Prospective, randomized, placebo controlled, double-blind	200	36 months	Dexamethasone		Bayley Scales, McCarthy Scales	No difference from the control group
Fetal lung maturation	NIH Consensus Conference, 1995	3rd trimester	Analysis of available data		up to age 12	Corticosteroids			No increased risk of long-term neurodevelopmental impairment
Maternal SLE	Tincani et al, 1992	Throughout pregnancy	Prospective	21	1–85 months	Fluocortolone plus aspirin and azathioprine (if needed)		No formal tests	No long-term consequences
Maternal heart transplants	Wagoner et al, 1993	During pregnancy	Prospective	29	3 months to 6.5 years	Corticosteroids plus other immunosuppresives		No formal tests	All children reported to be in good health
Fetal congenital adrenal hyperplasia	Trautman et al, 1995	Started from week 1 to 21 weeks of gestation	Porspective, controlled pilot study	26	6 months to 5.5 years	Dexamethasone	2–29 weeks	Denver Developmental Questionnaire, Minnesota Child Development Inventory, Child Behaviour Checklist, Temperament Questionnaire, EAS Temperament Survey	More shy, emotional, less sociable, and a trend for greater avoidance than control group. No differences in cognitive abilities.

children whose mothers were treated antenatally with betamethasone during preterm labour. A total of 250 children, 139 in the betamethasone group and 111 in the control group, were studied through to age 7. The authors used well-established measures of cognitive, academic, and psychosocial development. Their results suggested that there were no significant differences in the cognitive or psychosocial development between the two groups.

The NIH Consensus Conference in 1994 (Anonymous, 1995) summarized data on the effects of corticosteroids for fetal maturation and perinatal outcomes. The results from available studies did not indicate any evidence of adverse long-term outcomes associated with the use of single doses of glucocorticoids for lung maturation in the areas of motor, cognitive, language, memory, concentration, or scholastic achievement skills. There is however evidence that repeated doses, similar to what is encountered in cancer chemotherapy are associated with microcephaly and low birth weight.

The results of a prospective control study by French et al (1999) point to a reduction in head circumference when repeated courses of corticosteroids were given in late pregnancy. Although smaller head circumference may be associated with impaired cognitive outcome, the investigator did not report cognitive impairment.

In conclusion, although the literature on the impact of corticosteroids administration in pregnancy on fetal development is reassuring, more information is required on long-term effects of these substances on the CNS development.

Bromocriptine

Bromocriptine is an alkaloid that functions as a dopamine receptor agonist suppressing prolactine production and is the treatment of choice for pituitary tumours during pregnancy. Pregnancy outcome and children's functioning in long-term follow-up (up to age 9 years) in hundreds of children exposed in utero to bromocriptine were reported (Turkalj et al, 1982; Konopka et al, 1983; Nader, 1990) with no significant findings. However, no reports of formal tests of cognitive and behavioural functioning are available.

RADIATION

Radiation is widely used in the diagnosis and treatment of malignancies. Based on live birth rate statistics in the US, about 33 000 women each year are exposed to diagnostic abdominal radiation in early pregnancy (US Department of Health and Human Services, 1976). The developing embryo and fetus are extremely sensitive to ionizing radiation (Brent, 1980). Fetal structures exhibit various susceptibilities to ionizing radiation and the human brain seems to be the most sensitive organ. The CNS maintains its sensitivity to radiation throughout gestation and into the neonatal period, when morphological changes can still be observed. Ionizing radiation is a CNS teratogen and is a recognized cause of mental retardation. It has been suggested to be a more serious fetal risk than maternal cancer following in utero exposure (Hoel, 1987). The lowest dose of radiation that produces significant behavioural changes postnatally at any gestational day is 0.2 Gy (Schull et al, 1990).

Although radiation is one of the most studied environmental hazards in animal species, there are very few human studies available. Brent (1980) hypothesized that a radiation dose as low as 50 rad (0.5 Gy) in humans may be harmful to the fetus, especially to its CNS. Dekaban (1968), in a retrospective analysis, reported that 22 infants who were exposed to radiation in the third to twentieth week of gestation for treatment purposes, were microcephalic and/or mentally retarded. Woo et al (1992) reported results of 16 women treated for nodular sclerosing Hodgkin's disease. Seven women were treated during the first trimester, 10 in the second, and 8 in the third. Sixteen women received 35–40 Gy for supradiaphragmatic nodes. The uterus was shielded by a 4 to 5 hold-value layer of lead. The estimated dose to the mid-fetus ranged from 1.4 to 5.5 cGY for 6 MV photons and 10 to 13.6 cGY for cobalt 60. All 16 patients subsequently delivered full-term normal infants, who, at the time of assessment, were found to be physically and mentally normal. Formal cognitive tests were not reported.

The experience at Hiroshima and Nagasaki is the most commonly sited source of knowledge considering long-term effects of radiation on the human embryo and fetus. These population based studies addressed relationships between dose of radiation and gestational age. Analysis of the data of survivors of the atomic bombings in Japan using refined estimates of the absorbed fetal dose demonstrated that the highest risk of brain damage occurred at 8–15 weeks of gestational age (Otake and Schull, 1984). These data were consistent with a linear dose-response model, which did not indicate the existence of a threshold level.

In contrast, the data collected for in utero exposures after the fifteenth week of gestation were not linearly related to dose, suggesting that a nonlinear model with a threshold dose for radiation effects best fits the data for this period of gestation. Radiation exposure before the eighth week of gestation and after the twenty-fifth week was not associated with an increased risk of mental retardation. Yoshimaru et al (1991) assessed school performance of prenatally exposed survivors of the atomic bombings using the DS86 dosimetry system and found that damage to the fetus exposed at 16–25 weeks after fertilization appeared similar to that seen in the 8–15 week group. Other studies of this population also suggest that radiation exposure in utero may affect intelligence test scores, with the greatest sensitivity during the eighth to fifteenth week of gestation (Mettler et al, 1985). One estimate of the dose-response relationship was a 20-point loss of IQ for each additional 1 Gy of exposure. The relationship between dose and intelligence test scores is not yet well-established, and the findings have to be refined to a demonstrable level of statistical significance or clinical relevance (Mettler et al, 1985). Jensh and Brent (1987) demonstrated a downward shift in the Gaussian distribution of IQ with an estimated probability coefficient indicating a loss of 30 IQ points per 1 Gy fetal dose at 8–15 weeks after conception. A similar, but smaller shift to lower intelligence was detectable following exposure at 6–25 weeks of gestation, but not at other periods of pregnancy. Several reports did not find mental retardation in 19 children exposed to 0.015 and 0.1 Gy and among 1458 children exposed to low diagnostic doses of radiation (Meyer and Tonascia, 1981). However, behavioural tests were not performed and these results should be interpreted with caution because of methodological limitations of the study design. Conversely, in a case control study, Granoth (1979) assessed the association of diagnostic X-ray examinations with the occurrence of CNS defects and found a significant increase in anencephaly, hydrocephaly, and microcephaly when the study group is compared with matched control infants. The cognitive and behavioural effects of low-dose prenatal diagnostic radiation has not been elucidated. As well, it is unknown whether there are behavioural sequelae due to exposure to radiation in the area of the electromagnetic spectrum. To date it is believed that fetal exposure to less than 0.05 Gy does not increase the teratogenic risk (Jensh and Brent, 1986).

In summary, ionizing radiation fulfills all of Wilson's criteria for a teratogen (Vorhees, 1986). Being neurotropic, radiation is capable of producing behavioural teratogenic effects that are demonstrable at doses below those causing obvious structural malformations (Vorhees, 1986).

In addition to the classic triad produced by a teratogenic substance, ionizing radiation was observed to cause obvious behavioural alternations in animals. As suggested by Jensh and Brent (1986) the inseparable radiation teratogenic effect on behaviour must be added to the triad thus creating a 'tetrad'.

CONCLUSION

Malignancy poses a difficult challenge to both patients and physicians, creating a conflict between optimal maternal therapy and fetal well-being. However, most malignant conditions are not absolute contraindications for pregnancy. Unfortunately, neurodevelopmental and behavioural effects, both important parts of the teratogenic spectrum regarding drug or treatment safety, have been only sparsely addressed. Mental health effects, which act as strong predictors of a child's quality of life, merit closer attention, as does the cognitive and behavioural effects of these drugs. At the present time little is known on the long term mental health effects in young children exposed in utero to treatment for maternal cancer. However, existing studies on cancer chemotherapy beyond the first trimester have failed to show neurotoxicity. In contrast, repeated doses of corticosteroids and radiation are definitely teratogenic. Further research is required to assess the behavioural teratology of cancer and its management.

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