Paediatric outcomes following in utero exposure to the diagnosis and treatment of maternal malignancy

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Introduction

Cancer is the second leading cause of mortality in women during the reproductive years [1]. The incidence of pregnancies complicated by cancer increased from 1/1,560 in 1990 to 1/1,180 in 2004 [2], and is expected to continue to rise as women delay childbearing to later ages [3]. At present, approximately one per 1000 women will have cancer while pregnant [1,3–5], with breast, cervical, lymphoma, melanoma, and leukaemia most prevalent [6,7]. Almost all known types of cancer have been reported during pregnancy [4].

The presence of maternal malignancy during pregnancy is dauntingly stressful for all parties involved. Families and physicians are instantly thrown into an extremely challenging dilemma between optimal maternal care and fetal well-being. Often, treatment cannot be delayed until after delivery without significant maternal demise. This is especially true when dealing with aggressive cancers such as acute leukaemia or lymphoma [8]. The initiation of treatment, however, can have serious adverse consequences on the fetus, which must be considered. Treatment decisions become complicated by psychological, ethical, and religious considerations.

In all cases, decision makers must weigh the fetal risks of maternal cancer treatment against maternal risks if treatment is delayed. Unfortunately, the ability to ascertain the fetal risks is limited by several factors. Much information comes from case reports and studies that differ in methodology and are significantly underpowered, making their results difficult to interpret and generalise. Registries include a larger number of cases, but are limited by a lack of a denominator or control group, unknown treatment compliance, and possible selection and recall biases. Concomitant therapies and different treatment protocols make it difficult to understand individual drug effects. Outcomes are further confounded by the maternal disorder. Information regarding long-term follow-up after in utero exposure to maternal treatment is also scarce.

Despite these limitations, treatment decisions must be made. Knowledge and comprehension of available reports on the fetal risks associated with the management of maternal malignancy will assist healthcare providers to achieve an optimal balance between maternal care and fetal well-being.

The effects of teratogens

A teratogen is any substance, environmental hazard, or infection that can adversely affect fetal development. When pregnancy is complicated by cancer, several sources may cause teratogenicity, including the baseline maternal disorder, severe maternal stress, and the management of the cancer including diagnosis and treatment. Teratogenic effects of cancer therapy depend on the extent of its placental transfer, the timing of exposure, the dose administered, duration of exposure, and genetic variability in drug metabolism [9].

Teratogenic effects include death (miscarriage, stillbirth), congenital malformations, intrauterine growth restriction (IUGR) or macrosomia, organ dysfunction and long-term outcomes such as neurocognitive deficits, increased rates of malignancy, and problems with future fertility. The stage of development at the timing of exposure may determine the ultimate fetal outcome [9].

The most extreme teratogenic effect is death, which can occur at any stage of development. The conceptus is especially vulnerable to miscarriage during the first 8–14 days post-conception (known as the “all or none” period) as a teratogen may interrupt processes that facilitate implantation. However, if implantation is successful despite teratogenic exposure, then the fetus is expected to develop normally [10].

Congenital malformations, which are structural abnormalities of embryonic origin [11,12], can occur if the fetus is exposed to a teratogen in the

first trimester [13]. Major organ malformations are deficits that require surgical intervention and can have long-term consequences for the child's quality of life [14]. Exposure during gastrulation (weeks 3–5 post-conception), a period of major cell differentiation, is of particular importance to teratology as exposure during this time can adversely affect every system. Moreover, the mother is often unaware of the pregnancy at this time, heightening the conceptus' exposure to hazard. During organogenesis, there are specific times (critical windows of development) in which each organ is most sensitive to insult [10]. For example, the heart, neural tube, and limbs are affected earlier than the palate and ear [9]. Although organogenesis theoretically ends at week 8, some organs, including the kidney and palate continue to develop until week 10 [15]. Others, such as the eyes, genitalia, central nervous system (CNS), and haemopoietic system, remain vulnerable throughout the entire pregnancy [15,16]. Understanding the windows in which various organs develop can assist physicians in planning treatment accordingly.

Teratogenic exposure during the second and third trimesters mainly affects the growth, organ maturation, and CNS development of the fetus [10]. Treatment with carcinogenic and mutagenic agents at any time during gestation may alter the DNA of the fetus, presenting the possibility for future cancer or genetic mutations.

When assessing teratogenic risk, one must be mindful that even pregnancies in healthy, unexposed women have a baseline risk for aversive outcomes. The baseline incidence of miscarriage is up to 15% [4,17], with that of stillbirths being 0.5% [4]. Major malformations occur in approximately 2–3% of the population [4,17], and IUGR in approximately 4–8% [18]. The incidence of childhood cancer (i.e. cancer before the age of 19 years) is low at 0.3% [4,19].

Maternal diagnostic imaging procedures and fetal risk

Radiation is used for important diagnostic procedures. Humans are constantly exposed to unavoidable environmental background radiation [17,19], which results in a cumulative fetal dose of approximately 0.1 cGy or less throughout an entire pregnancy [17]. Yet, there is a common misunderstanding that any amount of radiation is teratogenic [20], leading individuals to overestimate the risks associated with diagnostic tools [17,19–22]. Diagnostic imaging is vital to the early detection and treatment of maternal malignancy, and unnecessarily delaying such procedures can have devastating consequences. The risks of common procedures that use both ionising and non-ionising radiation are reviewed below.

Non-ionising radiation: ultrasounds and magnetic resonance imaging

Non-ionising radiation does not contain enough energy to ionise atoms. Rather, it may act as a teratogen through thermal and non-thermal (mechanical) effects [23]. Thermal effects result from a conversion of radiation energy into heat at the tissue level, with the tissue type and dose determining the temperature increase [23,24]. This can cause hyperthermia, a potential human teratogen [24]. Non-thermal (mechanical) effects may lead to the disturbance of nearby cells, presenting a theoretical human teratogenic effect [23].

Ultrasounds are used routinely in the field of obstetrics, with a mean of three ultrasounds performed per pregnancy [19,24]. Two large reviews by Salvesen and colleagues (who reviewed a total of 26 epidemiological studies) [25] and Houston and colleagues (who reviewed 55 studies, including 29 randomised controlled trials) [23] did not find an association between adverse fetal outcome and ultrasound exposure during gestation. Within these reviews, only four studies reported an association between ultrasounds and low birth weight. The association was mainly apparent after repeated ultrasounds were administered, thus the findings are confounded by the indication for ultrasound. Therefore standard ultrasounds are generally regarded as safe [19,20,23–26]. However, both authors caution that more research needs to be done on the safety of Doppler ultrasounds, which may exert a higher radiation output than standard tools [23,25].

Magnetic Resonance Imaging (MRI) is a powerful diagnostic tool, which uses electromagnetic and radiofrequency waves to create images of the body [20]. Although the Food and Drug Administration requires MRI machines to be marked that their safety has not yet been established in regard to fetal exposure [27], most research findings to date have not shown a teratogenic effect [28–32]. There is a theoretical concern of acoustic damage to the fetus due to noises generated by MRI coils [28]. However, a study by Baker and colleagues that followed 18 children after in utero exposure to echo planar imaging found no hearing impairments in 16 of the children at three years follow-up [33]. More research needs to be done to support these findings [28].

Table 1
Thresholds for deterministic effects[a]

Gestational stage	Time after conception	Fetal radiation threshold[b] (cGy)	Potential Effect
Pre-implantation	0–2 wk	5–20	Prenatal death due to failure to implant; surviving embryos should develop normally
Major organogenesis	1–8 wk	20–40	Growth retardation
	2–8 wk	10–25	Organ malformation (excluding the CNS)
	2–15 wk	20–25	Small head size; but exposure before 8 wk does not cause intellectual deficit
	8–15 wk	6–31	Most sensitive period for severe mental retardation
Rapid neuron development and migration	6–15 wk	>10	Small head size, seizures, decline in IQ
After organogenesis and rapid neuron development	16–25 wk	25–28	Severe mental retardation
	16 wk to term	>150	Fetal death

[a] Information from references [15,17,19–21,35,38].
[b] Threshold ranges determined by combining the opinions of several authors.

Many regulatory bodies discourage the use of gadolinium-based compounds during pregnancy for MRI contrast imaging (e.g. gladopentetate, gadodiamide, gadolinium DPTA), though available evidence suggests an unlikely fetal risk [30,34]. MRIs are an important diagnostic tool and should not be withheld because of pregnancy as they present low fetal risk [30].

Diagnostic procedures and ionising radiation

The use of imaging tests requiring ionising radiation increased 121 percent between 1997 and 2006 [27]. Thus, it is becoming increasingly important to clarify the fetal risk associated with such techniques, as they often raise unnecessary alarm when administered during pregnancy. Ionising radiation contains enough energy to convert atoms or molecules into free radicals [19]. These highly reactive charged species can then adversely affect other atoms in the body initiating a chain reaction.

Two types of effects may result from exposure to ionising radiation: deterministic effects and stochastic effects. Deterministic effects result in multicellular injury or death and cause pregnancy loss, major malformations, growth retardation, and CNS abnormalities. These effects are characterised by a threshold dose of radiation, found by calculating the no-adverse-effect level (NOAEL). Below threshold dose no aversive outcomes result. Above the threshold, effects are dose-dependent whereby increased exposure results in an increased severity and incidence of negative outcomes [17,19,21]. Stochastic effects refer to the potential mutagenic outcomes associated with ionising radiation [19]. They are addressed later in this paper in the context of future childhood cancer.

The threshold dose for deterministic effects has been determined from animal studies, case reports of children exposed to diagnostic X-rays, and data from survivors who were in utero during nuclear explosions. Survivors from the 1945 atomic bombings in Hiroshima and Nagasaki, a group of about 2,800 pregnant women (500 of whom received a conceptus dose of more than 1 cGy) comprise the primary source of human data [35]. Based on this information several authors and authoritative committees, including the US National Council on Radiation Protection and Measurements, the American College of Obstetricians and Gynecologists, and the International Commission on Radiological Protection, have concluded that in utero exposure to less than 5 cGy is not associated with aversive fetal outcomes [4,17,19,20,35–40]. Most believe this is a conservative threshold, with an upper limit of 10–20 cGy unlikely to cause harm in clinical practice [4,19,21,41]. The thresholds for various deterministic effects according to timing of exposure can be seen in Table 1.

The estimated fetal ionising radiation dose from a single diagnostic procedure does not exceed the well-defined 5 cGy threshold for deterministic effects (see Table 2). The values in Table 2 are an estimated average amount of radiation per each exam. Actual fetal dose may vary depending on the dose delivered, where the fetus is positioned within the field being imaged (with exposure inversely related to distance from the radiation source to the power of two), and how internal radiation from radioisotope scans may concentrate in fetal tissue [17,38]. For example,

Table 2
Estimated fetal ionising radiation dose from common diagnostic imaging procedures

Test	Estimated fetal dose (cGy[a])
Computed Tomography (CT) Scan	
Abdomen (10 slices)	0.240–2.600
Abdomen and pelvis	0.640–4.000
Pelvis	0.730–4.600
Lumber spine	3.500
Chest	0.100–0.450
Head	<0.050
Radiography	
Abdomen (kidneys, ureter, bladder)	0.100–0.300
Pelvis	0.040–0.238
Urography (intravenous pyelography)	0.358–1.398
Upper gastrointestinal series (barium)	0.048–0.360
Hip and femur series	0.051–0.370
Cholecystography	0.005–0.060
Mammography	0.007–0.020
Lumbar spine	0.346–0.620
Chest (2 views)	<0.010
Retropyelography	0.800
Lower extremity	<0.001
Upper extremity	<0.001
Barium enema (fluoroscopic exam)	0.700–3.986
Position Emission Tomography (PET) Scan	
Bone scan	0.400–0.500
Whole-body PET scan	1.00–1.500
Thyroid scan	0.010–0.020
Other	
Ventilation-perfusion scan	0.060–1.000

[a] Information from references [17,19,27,35,38].

while short-lived radionucleotides (ex. technetium-99m) do not accumulate in fetal tissue, iodine for nuclear imaging is contraindicated as it can adversely affect the fetal thyroid leading to permanent hypothyroidism (especially if given after 10–12 weeks of gestation) [4,20,38]. The recent trend toward using PET-CT scans to monitor the staging and treatment of lymphomas should be avoided during pregnancy, as the radioisotope (FDG) used in this procedure may also impart high fetal radiation doses [1]. Before any radiation exposure occurs, an expert should calculate the cumulative dose to the fetus from all procedures and exposures should be kept as low as possible, while still achieving imaging goals [17,19,23,25].

Biopsies

Biopsies are a common diagnostic procedure, which may involve local anaesthesia. Commonly used local anaesthetics have not been found to be teratogenic [42].

Maternal cancer treatment and fetal risk

Treatment for maternal malignancy may include surgery, chemotherapy, radiotherapy, treatments with targeted agents, immunosuppressives and corticosteroids either separately or in combination with one another.

Surgery

Every year, approximately 0.5–2% of pregnant women in North America, including about 7,000–30,000 in their first trimester, undergo non-obstetric surgery [42–46]. This number excludes those who were unaware of the pregnancy at the time of the procedure [42]. Many commonly used anaesthetics including nitrous oxide, enflurane, barbiturates, and narcotics have been used safely in pregnancy [42,47,48]. Compiled data of over 12,107 fetuses exposed in utero to anaesthetics, with at least 2,439 occurring during the first trimester, did not show an increased risk of fetal malformations above baseline [49–54]. One such study that examined 5,405 pregnancy outcomes did not find an overall increased risk of malformations but did find a higher than baseline risk of neural tube defect in the subgroup of 572 women who underwent surgery during gestational weeks 4–5, the time of neural tube development (5 cases vs. 0.6 expected) [51,55]. However, the authors suggested that the association may be random and a subsequent investigation failed to find this effect [56].

Anaesthetics have been associated with an increased incidence of miscarriages [57], and low birth weight [49–52,54]. However, a review by Cohen-Kerem and colleagues including 12,452 pregnant women (some from the aforementioned studies) found that the risk of miscarriage becomes comparable to baseline once appendectomies are excluded from the analysis [57]. Other authors have suggested that these aversive outcomes are more likely attributable to the causes for and conditions of surgery itself rather than the anaesthetics [47]. The potential complications of surgery, including maternal hypertension, hypoxia, or stress, pose a greater risk to the fetus than anaesthetic agents [4,42,47].

Overall, the data show that the fetal risk associated with surgery is minimal. If possible, it should be undertaken during the second trimester to minimise the risk of miscarriage or premature labour [4]. A complex situation occurs when surgery of the abdominal–pelvic region is required during advanced pregnancy or if it is indicated for cervical cancer. In these cases, it is best if surgery can be delayed until at least 34 weeks gestation, when the child can be safely delivered by cesarean section [1]. If surgery cannot be delayed, a multidisciplinary team of obstetricians, paediatricians, and anaesthesiologists should be involved, and treatments to assist fetal lung maturation should be given preoperatively to prepare for possible premature delivery [4].

Radiation therapy

The maternal dose of ionising radiation from radiotherapy is well above the threshold of 5–20 cGy, with exposure levels in the range of 3,000–7,000 cGy (an approximate 1,000-fold increase from that of diagnostic procedures) [15,58]. However, the fetal dose from radiation therapy depends on several factors including the cumulative dose, size of radiation fields, the distance from the edges of the fields to the fetus, and specifics of the radiation machine [1,15,59]. Unfortunately, much literature on this topic does not differentiate between maternal and fetal doses when describing thresholds. If the fetus is located at least 30 cm away from the field edges, the fetal dose may be no more than 4–20 cGy [1,58]. Thus, it may be possible to irradiate some areas of the mother, such as the head and neck, without exposing the fetus to dangerous doses [1,58]. Radiotherapy of cancers of the abdomen and pelvic regions is contraindicated due to the possibility of serious adverse affects to the fetus [4,38].

Therapeutic doses of radiation have been found to cause skeletal, eye, and brain anomalies in the human fetus, with the major defects being microcephaly, mental retardation, micropthalmia, cataracts, iridial defects, and skeletal anomalies [15]. The effects of radiation are time and dose dependent (see Table 1 for threshold doses). During the pre-implantation period, a higher risk of spontaneous abortion is associated with a radiation dose of more than 15–20 cGy [21]. According to Brent [21], during organogenesis, the risk of major malformations and growth retardation is increased at exposures of 20 cGy and 25–40 cGy, respectively. Both thresholds increase as pregnancy progresses, however, the precise thresholds are difficult to determine [21].

High fetal doses of radiation (between 100–200 cGy) are known to produce mental retardation and microcephaly [21], with a 40% risk of severe mental retardation at doses of 100 cGy [38]. The human brain is most sensitive to insult from ionising radiation between weeks 8 and 15, to a lesser extent between weeks 16 and 25, and is least susceptible prior to the 8th week and after the 26th week [15]. The reported threshold for these effects between 8 and 15 weeks is variable, with some reports indicating that a 6–10 cGy dose may result in a marked decrease in the child's intelligence quotient (IQ) [38]. During the most sensitive period, there is an approximate 21–30 point decrease in IQ per 100 cGy [21,38]. Between weeks 16 and 25, there is thought to be a 13 point decrease in IQ per 100 cGy, with a threshold of mental retardation at 25 cGy [38].

Ideally, radiation therapy should be delayed until after delivery to minimise adverse fetal outcome, however, it is not completely contraindicated. In some cases, distal tumours in the head, neck, and extremities can be treated with reduced fetal risk. If postponement is not possible and termination is not a viable option, fetal radiation exposure should be thoroughly assessed by a medical physicist. Action should be taken to protect the fetus against leakage radiation [38]. Abdominal shielding can lower fetal radiation exposure and should always be employed [59].

Chemotherapy

Despite the physiologic changes associated with pregnancy, both pregnant and non-pregnant women generally receive the same chemotherapy regimens [1,60]. These regimens combine different agents depending on the cancer type and stage [9]. Chemotherapeutic drugs may interrupt the growth, regulation, and division of rapidly dividing cells, and are therefore of risk to a developing fetus [4,8,9]. Almost all agents have a low enough molecular weight to cross the placenta, with most reaching the fetus in a significant concentration, heightening the teratogenic risk [9,15].

I. Pregnancy outcome following in utero chemotherapy by timing of exposure

Existing guidelines recommend that chemotherapy be avoided during the first trimester, but may be started during the second or third. Chemotherapy administered during the first trimester is associated with a heightened risk of pregnancy loss and major malformations [61]. When given during organogenesis, chemotherapy increases the risk of major malformations from 1–3% (baseline in population) to

10–20% [15], with rates as high as 25% for combination chemotherapy [62]. These malformations are of no specific pattern and reflect the gestational age at exposure and the drug type [9,15].

Early reports documented an association between chemotherapy administered during the second and third trimesters and an increased risk of miscarriages/stillbirths, intrauterine growth retardation (IUGR), and premature labour [9,15,18,63]. A review by Cardonick and Iacobucci published in Lancet Oncology in 2004 [9] summarised the outcomes of 376 fetuses exposed in utero to chemotherapy (from 1966 to 2004), most after organogenesis. Nineteen fetuses (5%) and four (1%) neonates died, with all but three deaths occurring with maternal haematological cancer. The rate of malformations was not increased above baseline when chemotherapy was given after the first trimester. Fifteen babies (4%) had transient myelosuppression, 18 (5%) were born spontaneously premature, and two (1.2%) cases of transient neonatal cardiomyopathy occurred after idarubicin exposure. No increased rate of IUGR was reported (7% born with IUGR). Based on these findings, the authors concluded that chemotherapy administered during the second and third trimester "seems to be safe" [9].

Subsequent reports have generally corroborated the relative safety of chemotherapy administered after the first trimester [18,64–66]. A 2005 report published in the Journal of Clinical Oncology, on the outcomes of 27 children exposed to chemotherapy for maternal breast cancer, did not find any cases of IUGR, malformations, or fetal/neonatal deaths [66]. The main adverse outcome reported in a 2006 study that examined the outcome of 57 pregnancies, was that six neonates were born with a birth weight of less than 2500 g [65]. However, it is unclear from the report whether or not this was low for their gestational ages [65]. Results from the Cancer and Pregnancy Registry published in the American Journal of Clinical Oncology that examined the outcomes of 157 fetuses did not find an increased risk of IUGR, or fetal death above baseline. This study did report a 0.7% rate of neonatal death, suggesting a slightly increased risk [18]. Although the overall pregnancy outcomes in a 2010 European collaborative study reporting on 62 neonates was good, there was an increased rate of IUGR (22.5% vs. 4–8% baseline), with most cases developing in mothers with haematological malignancies [64]. This study also reported a high rate of induced preterm labour with subsequent admission to neonatal intensive care units. Thus, the importance of interdisciplinary decision making on the timing of delivery was stressed by the authors as prematurity is associated with increased morbidity, mortality and poor neurocognitive outcomes [64]. Three of the aforementioned studies did show a slightly increased rate of malformations. However, as chemotherapy was not administered during the first trimester, these results may be attributable to other factors [18,64,65].

It is suggested that chemotherapy should be stopped 2–3 weeks before the planned delivery date to allow fetal bone marrow recovery, and minimise potential perinatal complications including fetal leukopenia, sepsis, haemorrhage and respiratory distress [8,56,67]. As the fetal renal and liver systems may not be fully matured, this also allots time for drugs to be eliminated prior to delivery [59].

The CNS develops throughout pregnancy, raising concern about the effects of chemotherapy exposure administered at anytime during gestation on fetal CNS development. Nulman and colleagues summarised the results of available studies on the long-term neurocognitive outcomes of 111 children exposed to chemotherapy in utero. The review did not support an association between exposure and significant aversive neurocognitive impairments (follow-up range of 1 month to 22 years) [3]. However, in many cases, formal psychological tests were not applied [3]. Aviles and Neri assessed 84 children exposed to chemotherapy for maternal haematological cancer for a period ranging from 6 to 29 years using the Wechsler Intelligence and Bender Gestalt cognitive tests [68]. These children did not differ from controls (unrelated matched children and unexposed siblings) on school performance or standardised intelligence tests results. Twelve second-generation children were also born within this cohort, suggesting that long-term fertility may be preserved [68].

II. Pregnancy outcome following first trimester exposure by drug type

The most commonly used chemotherapeutic agents are antimetabolites, alkylating agents, plant alkaloids, anthracyclines, and antibiotics. Separating the effects of these individual drugs is challenging, as results are confounded by exposure to other substances including radiation.

Antimetabolites inhibit cellular metabolism by acting as false substrates during DNA or RNA synthesis [9,15,69]. Among the various antimetabolites, methotrexate, a folic acid antagonist, may present the highest risk to fetus during the first trimester [69]. It induces birth defects at doses as low as 10 mg per week, with a supposed critical period of 6–8 weeks post-conception [70], and presents a higher risk of fetal death [9]. Defects reported include CNS deficits

(hydrocephaly, cranial dysostosis with delayed ossification), facial anomalies (cleft palate, hypertelorism, ear anomolies), limb defects (syndactyly), IUGR, and mental retardation, all features of aminopterin syndrome [8,9]. These effects are time and dose dependent, as in more than 42 cases of methotrexate exposure (with more than 23 during the first trimester), both normal [9,67,70–74], and abnormal [74–86] pregnancy outcomes have been reported. Conversely, in 2004 Cardonick and Iacobucci [9] cited 49 cases of exposure to 6-mercaptopurine (6-MP), including 29 exposed during the first trimester, in which no malformations occurred. Two fetal deaths occurred but one involved a pregnancy complicated by pre-eclampsia and the other involved combination chemotherapy with daunorubicin. No congenital birth defects were found in a recent assessment of 27 children exposed to azathioprine throughout pregnancy for inflammatory bowel disease. The full scale IQ of these children was 109 (s.d. 8) and was not statistically significant from the control groups (Nulman I, personal communication, February 28, 2011).

Alkylating agents are postulated to be slightly less teratogenic than antimetabolites [9,15]. They function by cross-linking DNA strands, interrupting RNA and protein synthesis [15]. Cyclophosphamide is an integral part of several chemotherapy treatment regimens [9]. Exposure to cyclophosphamide has been extensively documented, and has been associated with both normal [9,15,71,75,87] and malformed infants [15,87–93] after first trimester exposure. Malformations documented in these infants included absent toes, cleft palate, abnormally shaped low set ears, and eye abnormalities [9].

Vinca alkaloids interrupt mitosis by binding tubulin and causing the dissociation of the microtubule apparatus [15]. They are highly protein bound and therefore may cross the placenta less easily than other agents, making them less teratogenic than the antimetabolties and the antibiotics [8,9,94,95]. Most human exposures have resulted in normal infants [15,95]. Of 29 in utero exposures to plant alkaloids during organogenesis reported by Cardonick and Iacobucci [9], only one resulted in a malformed infant after combination chemotherapy including vincristine. Other reports of adverse fetal outcomes after exposure have occurred but all involved combination therapy [63,75,96–100]. Some individual infants exposed to vinblastine have been followed long term (ranging from a few weeks to seven years) and have shown normal growth and development [101–109]. These agents do not seem to confer an increased risk of fetal anomalies [8,95].

Antracycline antibiotics are a group of agents that work by interposing between DNA [9]. A 2003 retrospective analysis by Germann and colleagues examined the outcome of 160 children exposed to anthracycline-containing regimens (i.e. doxorubicin, daunorubicin, epirubicin, idarubicin, and rubidazone) in utero [110]. Of those exposed during the first trimester (27 in total), 20 (74%) children were born normal, 3 (11%) had malformations, 2 (7%) were spontaneously aborted, 1 (4%) fetal death occurred, 1 (4%) had bone marrow depletion, and none were born premature or suffered cardiac toxicity. The malformations reported occurred during combination chemotherapy with antimetabolites or alkylating agents. When the dose of doxorubicin per cycle exceeded 70 mg/m^2, the risk of severe fetal toxicity increased 30-fold. However, the risk of toxicity was found to be relatively low when anthracyclines were administered after the first trimester and with doses of doxorubicin below 70 mg/m^2 [110]. An additional concern after anthracycline exposure is cardiotoxicity of the fetus, with reports of both no myocardial damage and transient or permanent cardiomyopathy [1,8]. A 2006 long-term cardiac evaluation of 81 children exposed in utero to chemotherapeutic agents including anthracyclines did not show any clinical or echocardiogram evidence of late cardiac toxicity [111].

Both the taxanes (e.g. paclitaxel) and the platinum-coordination complexes (e.g. cisplatin, carboplatin) are relatively novel chemotherapeutic agents and are often administered together. Less data is available on their effects, with our search revealing no documented exposures during the first trimester. However, the limited data published regarding second- or third-trimester exposures are reassuring. Out of 24 exposures that involved cisplatin and paclitaxel separately or in combination with one another (with at least 13 involving paclitaxel), 22 resulted in normal outcomes at up to age 36 months follow-up [86,112–125]. One abnormal outcome was significant ventriculomegaly with cerebral atrophy, however, this occurred after combination therapy of cisplatin (55 mg), bleomycin (30 mg), and etoposide (165 mg), as well as a premature birth [126]. The other was a child born with leukopenia, alopecia, and respiratory distress syndrome who developed sensorineural hearing loss at one year of age after exposure to cisplatin 6 days before delivery [127]. This child was born premature at 26 weeks and was treated postnatally with gentamycin, complicating the relationship between cisplatin and the child's outcomes [128]. Two cases of carboplatin exposure were located with both neonates healthy and developing normally [120,129]. Positive

outcomes despite exposure to taxanes have been attributed to the fact that taxanes are highly bound to plasma proteins, making it more difficult for them to cross the placenta than some other agents [117].

Novel targeted therapies

Targeted therapies are novel antineoplastic agents that interfere with specific molecules needed for the spread of cancer, rather than interfering with rapidly proliferating cells in general. There is limited fetal risk data available on these agents. Pereg and colleagues [1] summarised 23 cases of in utero exposure to imatinib mesylate (Gleevec) for the treatment of maternal chronic myeloid leukaemia. Five pregnancy losses were reported (1 therapeutic abortion and 4 spontaneous abortions during the first trimester), and the remaining 18 pregnancies resulted in normal outcomes. Limited reports on rituximab, an agent used for the treatment of intermediate non-Hodgkin's lymphomas, have not shown an increased risk of adverse fetal outcome after in utero exposure [1,59]. Trastuzumab (Herceptin), a treatment for breast cancer, has been associated with reversible anhydromnios when administered during the second trimester [130], and oligohydramnios (reduction of amniotic fluid), when administered in the second and third trimesters [131,132]. Two other case reports did not find any adverse outcome [133].

Hormonal therapy

Tamoxifen is used in the treatment of breast cancer, the most common malignancy in pregnancy [128]. It is believed to function by competing with oestrogen for binding sites in target tissues [109]. Barthelmes and Gateley's [128] review of seven reports, a cumulative total of 141 exposures, found 108 healthy babies (at least four exposed during the first trimester), 12 congenital anomalies (one child born with ambiguous genitalia and another born with Goldenhar's syndrome after first trimester exposure; two children born with craniofacial defects, time of exposure not documented). Eight pregnancies were terminated and the outcome of 13 was unknown [128]. Despite reassuring reports of tamoxifen exposures, more research is needed to address its safety. As healthy women are now using tamoxifen to reduce the risk of breast cancer, inadvertent in utero exposure to tamoxifen will likely become more prevalent [8].

Immunomodulators

Interferon alpha is an immunomodulator most commonly used in the treatment of leukaemia. It has not been shown to cross the placenta [134]. Briggs and colleagues [109] summarised the outcomes of 11 exposures during pregnancy for the treatment of hairy cell leukaemia and chronic myelogenous leukaemia (CML), including exposures during the first trimester. No adverse fetal outcomes were reported, with a follow-up of up to 44 months.

Cyclosporine

The treatment of certain cancers, such as leukaemia, lymphoma and myeloma, may require bone marrow transplant. In these cases, concomitant treatment with an immunosuppressive such as cyclosporine is necessary. A cohort study with matched controls by Nulman and colleagues evaluated the long-term neurodevelopmental outcomes of 39 children following in utero exposure to cyclosporine for maternal renal transplant [135]. Cyclosporine was not associated with long-term neurocognitive or behavioural development based on measures of intelligence, visuomotor abilities, and psychological adjustment [135]. However, within the cyclosporine group, children born premature achieved significantly lower scores on these measures.

Corticosteroids

Corticosteroids are part of many cancer treatment protocols. While several prospective cohort studies have not found an increased risk of congenital anomalies after in utero exposure [8], other retrospective reports have found a higher incidence of oral clefts [109,136,137]. To decipher these conflicting findings, Park-Wyllie and colleagues conducted a prospective cohort study that compared the outcomes of 187 children exposed in utero to prednisone with 188 controls, as well as a meta-analysis of the available epidemiological studies [138]. No significant increase in major malformations was found after exposure in either the prospective study or the meta-analysis. However, the meta-analysis did find a small increase in the risk of major malformations after first trimester exposure and a significant summary odds ratio for case–control studies examining oral clefts (3.35, 95% CI, 1.97–5.69). Repeated in utero exposure has also been associated with low birth weight [139–142]. Although there is an increased risk of oral cleft after first trimester exposure, the absolute risk remains very small as the incidence in the general population is about 0.1%. Moreover, clefting dysmorphology can be diagnosed in utero using 2-D or 3-D ultrasound. The benefits of maternal treatment should always be considered against the small absolute risk of clefting.

Risk of childhood cancer

Concern has been raised regarding whether or not procedures used to diagnose and treat maternal cancer are carcinogenic to the fetus. The greatest concern is raised after exposure to ionising radiation.

Very high doses of ionising radiation can increase the risk of childhood cancer [21]. Data from those who were in utero at the time of the atomic bomb show that of those exposed to doses higher than 50 cGy, 7.1% developed solid tumours [21]. Although the stochastic effects of ionising radiation theoretically do not have a threshold, whether or not exposure to doses at low levels used for diagnostic purposes (<5 cGy) is carcinogenic is unclear [21,143]. Initial evidence came from the Oxford Survey of Childhood Cancers, a nationwide case–control study of deaths from leukaemia and other cancers in childhood. Between the years 1953 and 1981, 15,276 case–control pairs were examined, and an excess risk of childhood cancer after in utero exposure to maternal diagnostic abdominal radiation was found to be approximately 40% (odds ratio: 1.39, 95% confidence interval 1.30 to 1.49) [26,144]. Since these initial findings, several reports have been conflicting. Many studies (mostly case reports) support an increased risk, especially for childhood leukaemia, of about 1.6–3.0 times that above baseline [4,19,38,144]. However, some larger cohort studies and meta-analyses have not found a significant positive relationship [143].

A retrospective population-based study of 1.8 million maternal–child pairs in the province of Ontario between 1991–2008, examined the potential carcinogenic effect of major radiodiagnostic imaging on a fetus. The study included all children exposed in utero to either CT or radionuclide imaging up to two days before delivery. Of the mothers exposed (n = 5,590), four childhood cancers were detected (0.07%), whereas 2,539 cancers (0.14%) developed in the unexposed group (median follow-up 8.9 years) [145]. A subsequent case–control study of 305 children exposed in utero to diagnostic radiation (319 total procedures), found a slight non-statistically significant increase in risk for all cancers after in utero X-ray exposure (odds ratio 1.14, 95% confidence interval 0.90 to 1.45) and a separate non-statistically significant increase for leukaemia (1.36, 0.91–2.02) [26]. A 2008 systematic review that included 19 case–control and six cohort studies published between January 1990 and December 2006 did not find an association between prenatal exposures and leukaemia [146].

More research needs to be done on the relationship between low-level exposure to ionising radiation and cancer, and children should be monitored following exposure. However, the baseline risk of childhood cancer and leukaemia is low at about 2–3 per 1,000 [38]. Even if the risk is increased by 40% after exposure to 10 cGy, as authors have suggested, this would increase the incidence to 3–4 per 1,000 [38], and the absolute risk would still remain low.

Knowledge regarding the long-term of effect of future childhood malignancy after in utero chemotherapy exposure is even more limited due to the low baseline incidence of childhood cancer [15]. The aforementioned report by Aviles and Neri did not find an increased risk of childhood malignancy after in utero exposure to chemotherapy [68]. To date, only one published case report of malignancy in a child exposed to maternal chemotherapy has been reported [18]. This child developed thyroid cancer at age 11, followed by neuroblastoma at age 14. He was exposed to cyclophosphamide starting in the first trimester and also had several malformations. Curiously, his fraternal twin brother did not present with malformations or cancer [87].

Conclusion

The presence of cancer during pregnancy brings forth a challenging conflict between maternal care and fetal well-being. Knowledge on the optimal management of these cases is limited. However, cumulative research over the last decades has advanced our understanding. The risks associated with diagnostic procedures and surgery are negligible. Chemotherapy is associated with minimal teratogenic risk if administered after the first trimester, however serious concern should be given to iatrogenic prematurity, which is associated with increased child morbidity, mortality and neurocognitive impairments. Radiotherapy during pregnancy is not absolutely contraindicated if the tumour is localised far away from the fetus and appropriate fetal protection is employed. Although the available reports do not show long-term fetal neurotoxicity after in utero exposure to the treatment of maternal malignancy, research should focus on this outcome as it is a strong predictor of quality of life [3]. The risk of childhood cancer after in utero exposure to maternal cancer treatment needs to be clarified, and important distinctions must be made regarding the individual effects of chemotherapeutic agents. Further knowledge will assist physicians and families in making informed decisions that will save the life of the mother while minimising harm to the fetus.

Conflict of interest statement

I. Nulman has an interest in relation with one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this abstract. The relationships are summarised below:

(1) PI in a multicentre grant funded by the Canadian Breast Cancer Foundation
(2) Developing the first National Survey of Cancer in Pregnancy in Canada to investigate the long-term paediatric outcome.

H. Edell has no conflict of interest to declare.

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