Short-term Effects on the Fetus and Long-term Outcome on Children Exposed to Maternal Chemotherapy

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Abstract
Ethical questions with regard to treatment arise when pregnant women are diagnosed with cancer. Does the health of the mother or the health of the fetus take priority? However, research suggests that concern over transplacental transfer should not deter those seeking treatments since avoidance of favorable transfer drugs can allow chemotherapy to be a viable option if properly administered. Doctors highly contraindicate the use of chemotherapeutic drugs in the first trimester due to high risks such as teratogenesis and fetal death. However, they reassure that treatment can be given in the final two trimesters. It presents minimal consequences as long as the drug is not favorably transferred, treatment is not given after thirty five weeks, and delivery is not less than three weeks after chemotherapy administration. Iatrogenic prematurity should also be avoided. Additionally, long term risks are minimal, but further research needs to be performed with longer follow ups and larger sample sizes in studies in order to obtain more conclusive data.

Introduction
There has been an increase in treating pregnant women with cancer and scientists suggest that the change in trend is due to older women conceiving. Reports indicate that cancer is diagnosed in approximately 1 in 1000-1500 pregnancies (Voulgaris, et al., 2011). If cancer treatment cannot be postponed until after birth, ethical concerns arise with regard to the health of the mother and fetus, and so the benefits and side-effects need to be discussed by patient, oncologist, and obstetrician. Factors that impact treatment include cancer type and stage, gestational age and consequences of treatment on the mother and fetus. In addition, risks, treatments and, if necessary, the option of abortion must be determined. The goal is to determine if and at what gestational age treatment should be given, whether cytotoxic drugs administered to the mother impacts the development of the fetus and results in long-term risks for the child.

Methods
Information and research was obtained through Ebsco, Proquest and Pubmed. Access was provided by Touro College library. Main key words included pregnancy, short-term, long-term, transplacental, in utero, fetus, and chemotherapy.

Discussion
Transplacental Transfer
To first address the impact of transplacental transfer, it is essential to determine if there is drug transfer between the mother and the fetus, and if so, to what extent. A mouse model using 40 pregnant mice was studied to determine the amount of transplacental transfer of chemotherapeutic agents, doxorubicin, epirubicin, cytarabine, paclitaxel, carboplatin and vinblastine. Due to the difference of drug metabolism in mice, the drugs were given at proportionately higher dosages than when given to humans. Fetal and maternal blood was collected on day eighteen and a half, during the phase of fetal development. The mice were delivered by caesarean section ninety minutes (an arbitrary amount of time) after chemotherapeutic drugs were intravenously given to the mother. At this point in time, an increase in plasma levels ensured drug detection and was the first phase of distribution after the drugs were intravenously administered. The drug levels in the maternal and fetal plasma were detected using two methods. High performance liquid chromatography determined the amount of the five chemotherapy drugs and Atomic absorption spectrometry determined carboplatin levels, based on the amount of platinum in the blood.

Plasma Drug Analysis
Paclitaxel was found in maternal plasma, but was not detected in fetal plasma. It has a high molecular weight, is highly protein bound and is a substrate of P—glycoprotein (ATP-binding cassette transporters) and multidrug resistance protein. P—glycoprotein is found in fetal-derived epithelial cells which forms the maternal-fetal blood exchange border and protects the fetus.

Vinblastine and anthracyclines, which includes epirubicin, a 4′-epimer of doxorubicin, and doxorubicin, only presents as a small transfer ratio due to being P-glycoprotein substrate, which protects the fetus against xenobiotics' harmful effects. Another factor is that it possesses pharmokinetic properties that contrast to the substances that cross the placenta. Thus, one can imply that vinblastine, anthacyclines and paclitaxel present a safe option for treatment when given in small dosages during the last two trimesters.

However, both carboplatin and cytarabine have high transfer rates and can penetrate the membranes barriers since they are slightly bound and have a low molecular weight. Therefore, researchers recommended, if possible, avoiding these drugs (Calsteren, et al., 2010; Van Calsteren et al., 2010)

The transplacental transfer is generally through passive diffusion and is typically penetrable. However, there are three factors that influence the maternal-fetal transfer. They are: (1) maternal and fetal circulation concentration gradient, (2) the placental blood flow, and (3) chemotherapy's drug properties. The pharmokinetics of chemotherapy that favor transplacental transfer are

uncharged, low molecular weight, lipid soluble, and unbound or low protein bound compounds (Calsteren, et al., 2011).

Maternal- Fetal Transfer in a Baboon Model

The data obtained from the previous experiment, however, is limited in its clinical application due to the differences of human and mouse metabolism and permeability and formation of the placenta (Van Calsteren, et al., 2011). This elicited further investigation of the effects of maternal-fetal transfer of chemotherapeutic agents given in second and third trimesters. Two studies, using the same subjects, examined the results of different chemotherapeutic drugs on a group of nine pregnant baboons. Data more relevant to humans can be obtained from baboon models as compared to mice models due to the greater similarity of human and baboon embryological development, placental structure and function, reproductive physiology and endocrinology of pregnancy and drug metabolism. Based on the outcome, since only low levels were detected, the authors were reassured that the use of doxorubicin, epirubicin, vinblastine, taxanes (docetaxel and paclitaxel) and active metabolite of cyclophosphamide (4-OHPC) were not damaging to the fetus. However, they were concerned with the results of trastuzumab and carboplatin since they were transferred in large or complete amounts. The study was limited since there was no record of long term results, and it was suggested that further research needed to be performed (Calsteren, et al., 2010). Furthermore, other medical professionals contraindicate trastuzumab since it has been correlated with oligohydramnios, reduced production of amniotic fluid resulting from the drug binding to fetal renal receptors (Gziri, et al., 2012).

Placental Perfusion Model

As it would be unethical to perform human testing on pregnant women to determine whether there is maternal-fetal transfer due to fetal risk of fetal blood sampling from the umbilical cord known as cordocentesis, Van Calsteren et al. (2011) suggested that they can be applied to a single cotyledon models that have separate fetal and maternal circulations. Unfortunately, some complications with this proposal included difficulties obtaining absolute physiological conditions in a perfusion system, temporary status of tissue viability, and the differences in data between in vivo and placenta perfusion model with some drugs (Myllynen, Vhakangas, 2002; Van Calsteren, et al., 2011).

An attempt was made, however, to examine the effects of maternal-fetal transfer of taxanes (paclitaxel and docetaxel) to determine whether it can be a viable treatment option. The single cotyledons were taken from twelve placentas from uneventful pregnancies with each test group containing six models. The test groups were further divided into two groups of three, with one group containing high concentration of albumin (30 g/L) and the other group with low concentration of albumin (2 g/L). In the intervillous space two catheters were inserted to begin the perfusion and the twelve placentas were perfused for ninety minutes. The results indicated that taxanes have a low transplacental transfer due to their chemical properties and added that there was no difference in amount of drug transfer between paclitaxel and docetaxel. Furthermore, the outcome between the groups of high and low levels of albumin reinforced the theory that protein levels affect the maternal-fetal transfer. This was supported with the observation of less transfer of both docetaxel and paclitaxel with high levels of albumin. Although this reinforced previous studies of placental transfer, sample size was too small and further investigation should be performed (Berveiller, et al., 2012).

Factors and Effects of Chemotherapeutic Drugs

Based on research that positively indicated transplacental transfers of chemotherapeutic drugs, studies were initiated to determine the drug effect on the developing fetus. There are four main drugs that are typically administered to pregnant cancer patients. They are: anthracyclines (e.g., doxorubicin, epirubicin), platinum-based antineoplastics (e.g., cisplatin, carboplatin), cyclophosphamide and taxanes (e.g., paclitaxel, docetaxel). Anthracyclines result in cardiotoxicity and inhibit topoisomerase, interfering with DNA replication. Platinum based antineoplastics result in neurotoxicity and ototoxicity if given at high doses. It also allows for apoptosis to occur since it binds to and causes crosslinking of DNA. The effect of cyclophosphamide is permanent infertility if given at high dosage. Lastly, taxanes disrupt the microtubule function in cell division thereby inhibiting mitosis (Vandenbroucke, et al., 2014). The overall similarity between them is that they halt normal cell proliferation cycles which results in interrupting crucial cell processes. Studies on somatic cell mutations report that some adverse effects of chemotherapy are gene mutations, chromosomal breaks and rearrangements, and aneuploidy (Arnon, et al., 2001).

The impact of chemotherapy on the fetus can vary due to physiologic changes in the pregnant patient. Some examples that may occur include an increase in glomerular filtration, which increases the amount of elimination or drug excreted by the kidney, and an increase of drug metabolization in the liver, which might impact the presence of active drugs. Additionally, there is an increase in entero-hepatic circulation in pregnant women. This causes active metabolites to return to the liver and then colon after being secreted from bile into the colon and reabsorbed by enterocytes. The circulation prolongs the drug exposure since it lengthens the time needed to eliminate the drug from the body because it returns to the blood stream. The amount of active drugs available can decrease due to an increase in protein binding which results in a greater impact of cytotoxic drugs. However, plasma levels of cytotoxic drugs may be reduced as a result of an increase in plasma concentration (Amant, et al., 2008). The third space that

develops in pregnant women resulting from an increase of amniotic fluid can also impact the distribution volume of chemotherapy, causing a slow release of drug which results in an increase of fetal chemotherapy exposure (Williams, Schilsky, 2000). Other factors that impact the maternal chemotherapy on the fetus are metabolic activity and excretion of the placenta, increase of body fat of the pregnant patient and pH difference between maternal and fetal fluids (Gedeon, Koren, 2006). When creating a treatment plan, these physiologic changes must be considered.

Various other factors can also result in teratogenic risks to the fetus. Although the placenta can excrete fetal waste products and assist in fetal drug elimination, some antineoplastic agents may not be eliminated from the fetus if drugs are administered close to delivery time. Additionally, due to the fetus's immature liver and kidney, the fetal metabolism and excretion of the chemotherapeutic drugs may be abnormal. This can result in an increase of chemotherapy exposure and acute toxicity (Williams, Schilsky, 2000).

Administration Variables

The effect on the fetus is not only dependent on drug type and performance, but is also based on dose, route and gestational age. Studies have proven higher toxicity can develop from short infusions, topically applied cytotoxic agents and intraperitoneal administration.¬ Drugs given orally may be absorbed less due to a decrease of elimination from the stomach and intravenous administration can result in fetal risks. As mentioned previously, prolonged drug elimination from the mother also impacts the toxicity on the fetus (Wiebe, et al., 1994).

Chemotherapy Exposure- Fertilization/ Implantation

To determine the effect of chemotherapy on the developing embryo and fetus, observations were performed during the three stages of pregnancy. The three phases of fetal development are fertilization/implantation, organogenesis, and the fetal phase. Chemotherapy is cytotoxic, thereby inhibiting cell growth. Therefore, exposure during the first ten days of pregnancy, the stage of fertilization/implantation, results in an all-or-nothing phenomenon. Cells are omnipotent and may develop into the three different embryological layers, ectoderm, mesoderm and endoderm. However, their ability to develop normally is dependent on the impact of maternal chemotherapy. If there is a sufficient amount of cells, the embryo will develop normally, but a miscarriage can occur if too many cells are destroyed by the chemotherapeutic drug (Reed, et al., 2010).

Chemotherapy Exposure- Organogenesis

During the first trimester, it is highly inadvisable to treat the mother with cytotoxic drugs. Voulgaris et al. reports (2011) that there is a 10-20% chance of teratogenicity, fetal malformation, occurring if agents are administered in the first trimester. An increase of embryonic death can occur if there is damage to the embryo in the first month of gestation resulting from chemotherapy exposure (Voulgaris, et al., 2011). Spontaneous abortion and major malformations are also possible risks that can occur. The fetus is more susceptible to malformations two to eight weeks after conception, the period of organogenesis. Specifically, the heart, neural tube, and limbs are more vulnerable, preceding the palate and ears of the fetus. If chemotherapy exposure continues after eight weeks, the eyes, genitalia, hematopoietic and central nervous system still remain at risk (Cardonick, Iacobucci, 2004). This strongly reinforces that maternal chemotherapy should be avoided in the first trimester.

Chemotherapy Exposure- Fetal Phase of Development

Based on observations of the fetus exposed to maternal chemotherapy during the final two trimesters, researchers have suggested that these exposed fetuses did not exhibit more congenital malformations than fetuses from untreated mothers. Nevertheless, intrauterine growth restriction, low birth weight and neonatal myelosuppression have been detected in neonates exposed to chemotherapy in the second and third trimester (Cardonick, Iacobucci, 2004; Van Calsteren, et al., 2011). From week eleven until delivery, functional damage will frequently occur as a result of cell death. In addition, some organs may later develop structural anomalies. For instance, the fetus can develop neuropsychological impairment since the central nervous system is progressing throughout gestation (Vandenbroucke, et al., 2014).

Short-term Effects -Obstetric and Neonatal Outcomes

One study reported on 62 patients who were treated predominantly in the last two trimesters with chemotherapy alone or combined with other treatments, such as radiotherapy. These patients were part of a sample of 180 pregnant women who received various treatments for cancer. The results were analyzed to determine the fetal risks of treated and untreated mothers diagnosed with cancer.

Regarding patients treated with chemotherapy, there was a significant increase in preterm labor, but not in the rate of preterm premature rupture of membranes (PPROM) when compared to neonates not exposed to maternal chemotherapy. However, the only incidents of preterm labor and PPROM that occurred in the 180 cases analyzed involved patients treated with chemotherapy. Preterm labor can occur from the activation of hypothalamic-pituitary-adrenal axis of either the mother or fetus resulting from physical or psychological stress. Scientists propose that PPROM can result from apoptosis in amnion epithelial and chorion

trophoblast layers of the membranes after maternal chemotherapy exposure (Van Calsteren, et al., 2010).

The risks of preterm labor include intraventricular hemorrhage, bradycardia, apnea, respiratory insufficiency, necrotizing enterocolitis, sepsis, seizures, hypoglycemia, and feeding problems (Van Calsteren, et al., 2010). Additionally, Johnson (2007) reported that preterm births are associated with a decrease in IQ scores, cognitive delay, behavioral problems and higher risk for psychiatric disorders, primarily ADHD. Preterm labor in this research was preventable since several of the neonatal issues were iatrogenic. Therefore, researchers suggested that patients that can delay treatment until after delivery should do so to avoid prematurity (Van Calsteren, et al., 2010).

Data of small-for-gestational-age children was available for only 175 neonates. Regarding those treated with cytotoxic treatments (chemotherapy and/or radiotherapy), 16 of 66 children were small- for- gestational age as opposed to 10 of 109 children who were not exposed to maternal chemotherapy/radiotherapy.

The malformation outcome in comparison to normal pregnancies reveals that there was no significant increase in rate. The range of physical abnormalities of neonates exposed to maternal chemotherapy was still within normal range, with 2 of 66 (3.0%) inflicted with major malformations and 5 of 66 (7.5%) affected with minor malformations. The average rate of major and minor malformations was 4.1% to 6.9% and 6.5% to 35.8%, respectively. This suggests that the concern of malformation defects due to chemotherapy is not applicable and should not deter patients from avoiding treatment (Van Calsteren, et al., 2010).

Another fetal risk that may occur is transient neonatal myelosupression (TNM). Elburg et al. (2008) defined TNM as "leukopenia and/or neutropenia combined with anemia and/or thrombocytopenia, during the first weeks of life in newborns exposed to maternal chemotherapy during pregnancy." The disease is rare, potentially life-threatening and may not necessarily develop right after birth. Additionally, it may pose a risk for developing infections. The development of TNM may result from a short gap between chemotherapy administration and birth, maternal neutropenia at delivery, type of chemotherapy and maternal disease and dosage given. Treatments for TNM include thrombocyte and/or erythrocyte transfusions, bedside isolation, erythropoietin, and recombinant human granulocyte colony stimulating factors (G-CSF). In a study of fifteen neonates diagnosed with TNM, only one died due to infection resulting from TNM. However, the other fourteen neonates' physical and neurological developments were normal by the age of one and their TNM was resolved between two to ten weeks after birth. Generally, there is no difference detected in short term outcomes and survival rates between neonates exposed to chemotherapy that develop TNM and those not diagnosed with TNM. Researchers stated that this is true as long as the disease is recognized and aggressive treatment is given. However, the long-term consequences are still unknown (Udink ten Cate, et al., 2009).

Another study performed by Aviles et al. (1991) consisted of 43 infants exposed to maternal chemotherapy. The infants were examined from age three through nineteen years old and it was observed that only eight were pancytopenic at birth, which characterizes them as being deficient in red and white blood cells and platelets. However, the mothers of these neonates were treated with chemotherapy in the last three weeks prior to delivery which disputes the suggestion that a short gap between chemotherapy administration and delivery results in TNM. There were no congenital anomalies and neurological abnormalities reported and like the findings of the Udink ten Cate et al. (2009) study, the TNM resolved 2-10 weeks after birth. In addition, in a study of 62 patients, two children suffered postnatal hematologic toxicity (leukopenia and pancytopenia) when born ten days after maternal chemotherapy administration for acute lymphatic leukemia and required hematologic growth factors as treatment (Calsteren, et al., 2010). This study supports the theory, unlike Aviles et al. (1991) that a short interval between the chemotherapy administration and delivery can result in hematologic toxicity. As seen with these results, hematologic toxicity can present a slight concern for pregnant women with cancer, yet the risks are minimal if proper treatment is given.

Cardonick and Iacobucci (2004) have studied the impact of chemotherapy given after the first trimester on 376 fetuses. Of the 376, nineteen of the fetuses and four of the neonates died, 28 neonates were born with intrauterine growth restriction and 18 were born prematurely (iatrogenic cases excluded). Additionally, two were diagnosed with transient neonatal cardiomyopathy due to maternal idarubicin treatment, fifteen neonates developed transient neonatal myelosuppression. Eleven malformations were also reported with the majority resulting from chemotherapy exposure in the first trimester.

Another study was performed which was composed of 61 patients receiving chemotherapy during the second and third trimesters. Of the 61 patients, 32 were treated with neoadjuvant chemotherapy and 2 received adjuvant chemotherapy. The 61 neonates that were exposed to maternal chemotherapy were examined and compared to 60 neonates who were born prematurely and were not exposed to maternal chemotherapy. Results suggested that there were no differences in birth weight, admissions to the NICU, and neonatal survival. No malformations were reported in either group. Nonetheless, one contrast between the groups was the considerable difference in Apgar score, which

tests the future neurobehavioral development first at one minute after birth, then five minutes after and after ten minutes after birth. The results favored the group of children not exposed to chemotherapy at one and five minutes, but there were no significant difference at ten minutes. Although it reflects positive short-term outcomes, it's limited in long-term follow up on these children and researchers suggest further studies need to be performed (Abdel-Hady, et al., 2012).

Fetal cardiotoxicity was also researched to determine whether it can develop from maternal chemotherapy and pose a threat to neonates. One study consisted of ten pregnant patients treated with anthracyclines in the last two trimesters to investigate whether these drugs, which are thought to cause fetal cardiotoxicity, can result in fetal cardiac abnormality. The results indicated that one fetus was diagnosed with fetal supraventricular tachycardia, but researchers believed it was unrelated to maternal chemotherapy. Additionally, differences in myocardial performance index and in the tricuspid inflow pattern were detected, but were considered clinically insignificant. The neurological development and weight, height, and clinical examination of the fetuses in the study group were within normal limits. Significant cardiac abnormality and intrauterine growth restriction were not detected, although low birth weight was observed. Although the researchers gathered data systematically, the study was small and therefore limited (Gziri, et al., 2012).

Long Term Effects

A concern of maternal chemotherapy is the long-term cardiotoxic effects on the fetus. A study used tissue Doppler and strain imaging to identify any specific changes in cardiac performances that might result from chemotherapeutic drug. The study focused on children exposed to anthracylines, a drug shown to cause cardiomyopathy and cardiac dysfunction. The children's ages ranged from 1-9 years old, with the mean age being 1.7 years old. Those exposed to anthracyclines were observed to have minor changes in left ventricular (LV) wall thickness that might have occurred from the effect of anthracycline's toxicity. Anthracycline is known to lead to loss of cardiac muscle. There was also indication that there might be a lower, but normal ejection fraction and left ventricular ejectional fractional shortening, which is not clinically important since there is no change in functionality. Since there were no differences in tissue Doppler and strain imaging between the control group and patients, researchers indicated that there was no change in myocardial function. They stated that changes recorded could have resulted from the fact that the majority of the neonates born were preterm. Overall, their observation showed that there was no significant change between the 62 patients and 62 age gender-matched controls. Researchers recommended further research to observe any future irregularities and suggested performing further studies with larger patient groups with proper follow up (Gziri, et. al., 2013).

Further research was performed to assess the neurodevelopment, cardiac function, and general health of 70 children who were exposed to chemotherapy in utero. Seventy children from 68 pregnancies (two twin pregnancies) were assessed at age 18 months and at ages 5–6, 8–9, 11–12, 14–15, or 18 years. The median gestational age at birth was 35.7 weeks, with a median follow-up period of 22.3 months. Most of the children had normal cognitive development. However, children who were born prematurely had lower cognitive development scores albeit within normal range of cognition. Moreover, for each additional month of gestation, the IQ score increased by an average 11.6 points. Therefore, iatrogenic preterm delivery is not suggested since it significantly impacts the cognitive development.

Additionally, because the CNS continues to develop after the first trimester, the possibility that maternal chemotherapy may adversely affect neurological development is a serious concern (Gziri, et al., 2012). However, only one set of twins of 70 children observed experienced severe neurodevelopmental delay. This cannot be completely attributed to the exposure to a chemotherapeutic drug (Amant, et al., 2012). The cortex of the fetal brain develops surface sulci and gyri at 14 weeks gestational age and doesn't remain the original smooth cerebral surface. The formation of polymicrogyria, in which the cerebral cortex develops abnormally before birth in the deeper layers and excessive gyri form, removes some of the probability that chemotherapy exposure after 15 weeks instigated the developmental delay observed in the twins (Amant, et al., 2012; Barkovich, et al., 2010). Yet, the researchers did acknowledge that although the neurodevelopment was normal in the overall researched group, subtle changes could occur and further research on longer follow-ups should be conducted.

Nonetheless, the average results of the children's behavior, general health, hearing, and growth were within the normal range, along with their cardiac dimensions and functioning. No increase in CNS morbidity was recorded. Although there were no congenital cardiac abnormalities detected, further study was recommended on the cardiac function since there were clinically small, but statistically significant changes in ejection fraction, fractional shortening and diastolic variables. They did detect, however, a higher incidence of disharmonic intelligence profiles. The results of the Wechsler test depicted a discrepancy between verbal and performance IQ values. This was seen in 39% of patients in comparison to 15% in the normal population. The discrepancy has been associated with several neurological disorders, learning problems and behavioral issues.

The study was limited due to the small sample size, short follow-up periods, and lack of children born at the same gestational age and similarly assessed, who were not prenatally exposed to

chemotherapy. Additionally, researchers could not predict if secondary malignancy and infertility would have developed due to time constraint of the experiment. Only one twin, who also had congenital malformation, was diagnosed with secondary malignancy and suffered from papillary thyroid cancer at age eleven and neuroblastoma at age fourteen.

Nonetheless, the researchers suggested that chemotherapy not be administered after 35 weeks since this can trigger spontaneous labor. Delivery, they stated, should be arranged to be no less than three weeks after the last chemotherapy cycle. This ensures that the bone marrow recuperates properly, prevents the development of fetal and maternal sepsis and hemorrhage and hematological toxicity. As mentioned, preterm delivery should be avoided due to the impact on cognitive development. Preterm neonates are limited in their capacity to metabolize and eliminate drugs since they have immature liver and kidneys. Therefore, if delivery can be postponed, the fetus can excrete the drug through the placenta instead.

The positive outcome led the researchers to conclude that there are three factors that may reduce the risks associated with maternal chemotherapy. First, is that maternal chemotherapy administration should be given after the first trimester, as this avoids the period of increased susceptibility of the fetus to toxicity. Secondly, they believe that the fetal blood brain barrier protects the brain from drug diffusion with tight junctions and decreases rates of transcytosis and expression of specialized influx and efflux transporters, such as P-glycoprotein. Furthermore, vascular permeability and CNS immune cell infiltration is decreased through the inhibition of pericytes. Lastly, they suggest that the fetus is protected since the plasma filters the chemotherapeutic drugs (Amant, et al., 2012).

The most reassuring study which demonstrated the safe use of maternal chemotherapy was the observation on the long-term effect on 84 children/adults with a follow-up period of 6-29 years. The mothers of these children were diagnosed with hematological malignancies, and were treated with intense chemotherapeutic agents given in adequate doses. The treatments, however, varied in which trimester the dosage was administered. Observations of the children/adults reported that the height, weight, birth and cytogenetic material were normal and that there was no evidence of cellular damage. Additionally, educational performance and neurological and psychological evaluations were on par with the general public. Furthermore, sixteen of patients were married, with twelve children born in total, who also did not suffer from any abnormalities. Although many doctors disagree, researchers in this study suggest that treatment can be given in the first trimester due to their positive results (Aviles, Neri, 2001). This gives positive encouragement to pregnant cancer patients since it provides concrete evidence that the fetus can escape harm and develop normally into a healthy accomplishing adult.

Conclusion

Overall, transplacental transfer of cytotoxic drug is not detected in all of the treatments and its impact varies based on the physiologic changes in pregnant women and the pharmokinetics of drugs administered. Many emphasize that chemotherapeutic agents should certainly be delayed and only be given after the first trimester since the fetus is highly vulnerable to teratogenicity. When given in the final two trimesters, risks can still persist. However, this should not prevent the mother from seeking treatments due to insignificant short-term and long-term effects.

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